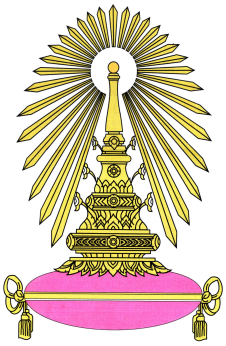

รายงานวิจัยฉบับสมบูรณ์

Synthesis of Functional Acetylenic Compounds from Calcium carbide and their Application in Fluorescence Chemosensor

โดย สัมฤทธิ์ วัชรสินธุ์ และคณะ

พฤษภาคม / 2560

สัญญาเลขที่ RSA57800055

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ผู้วิจัย

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สังกัด

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จุฬาลงกรณ์ มหาวิทยาลัย

สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

และจุฬาลงกรณ์มหาวิทยาลัย

(ความเห็นในรายงานนี้เป็นของผู้วิจัย สกว. ไม่จำเป็นต้องเห็นด้วยเสมอไป)

บทคัดย่อ

รหัสโครงการ : RSA5780055
ชื่อโครงการ : Synthesis of Functional Acetylenic Compounds from Calcium carbide and their Application in Fluorescence Chemosensor
ชื่อนักวิจัย : รศ.ดร. สัมฤทธิ์ วัชรสินธุ์
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ระยะเวลาโครงการ : 15 มิถุนายน 2557 – 15 มิถุนายน 2560

บทคัดย่อ:

งานวิจัยนี้แบ่งออกเป็นโครงการย่อย 4 โครงการ สองโครงการแรกเป็นการนำแคลเซียมคาร์ไบน์มาใช้แทนแก๊ซอะเซธีลีนเพื่อนำไปเตรียมอนุพันธ์อเซธิลีนต่างๆ แม้ว่าแก๊ซอะเซธีลีนจะหาง่าย มีราคาถูกแต่มันมีความอันตรายสูงเนื่องจากเป็นแก๊ซที่ไวไฟ กลุ่มวิจัยของเราจึงสนใจที่จะปรับปรุงกระบวนการต่างๆในอุตสาหกรรมเคมีที่ใช้แก๊ซอะเซธีลีนเป็นสารตั้งต้นให้มีความปลอดภัยมากขึ้นและมีช่วยลดต้นทุนการผลิตสารเหล่านี้ ในงานิจัยนี้เราใช้แคลเซียมคาร์ไบน์มาผลิตสารสองตัวคือเอริลไพโรล์และไวนิลอินโดว์ กระบวนการผลิตนี้มีประสิทธิภาพสูงหรือเทียบเท่ากระบวนการผลิตแบบเก่าที่ใช้แก๊ซอะเซธีลีน ในงานวิจัยนี้เราได้ระบุสภาวะเหมาะสมในการใช้แคลเซียมคาร์ไบน์มาทำปฏิกิริยากับออกซีมไปเป็นเอริลไพโรล์ และใช้อินโดว์เปลี่ยนมาเป็นไวนิลอินโดว์ซึ่งกระบวนการนี้จะให้ความเข้ากันกับหมู่แทนที่ต่างๆของสารตั้งต้นที่สูงและมีความสะดวกในการทำมากกว่าวิธีดั้งเดิม

ในงานวิจัยชิ้นที่สาม กลุ่มวิจัยของเราใช้แสงเป็นตัวหนี่ยวนำให้เกิดปฏิกิริยาคลัปปลิงแบบออกซิเดชันของไทออลเป็นไดซัลไฟด์โดยมีสารย้อมโรสเบงกอลเป็นตัวเร่งปฏิกิริยาซึ่งสารชนิดนี้มีราคาถูกและไม่เป็นพิษต่อสิ่งแวดล้อม เราพบว่าในสภาวะที่เหมาะสมนั้น ภายใต้แสงตาที่ตาเปล่ามองเห็นและที่อุณหภูมิห้อง เราสามารถเปลี่ยนไทออลเป็นไดซัลไฟด์ได้อย่างมีประสิทธิภาพ ซึ่งข้อดีหลักของปฏิกิริยานี้คือ ไม่จำเป็นต้องใช้โลหะ ราคาถูกและใช้ได้อย่างสะดวกเช่น ทำได้ในอุณหภูมิห้อง เปิดฝาทำปฏิกิริยาได้ ตัวทำละลายไม่จำเป็นต้องแห้งอีกทั้งกระบวนทำบริสุทธิ์สารผลิตภัณฑ์นั้นง่ายมาก เพียงสกัดธรรมดา

ในงานิจัยชิ้นสุดท้ายของโครงการนี้ เป็นการพัฒนาตัวตรวจวัดไซยาไนด์แบบสังเกตุด้วยตาเปล่าควบคู่ไปกับการวาวแสง โพรบตรวจวัดในงานวิจัยนี้ชื่อ **GSB** ซึ่งประกอบด้วย bipyrrole-methene (BODIPY) ที่มีหมู่ salicylaldehyde โพรบนี้จะแสดงการเปลี่ยนสีอย่างจำเพาะกับไซยาไนด์จากส้มเป็นไม่มีสีและจะมีวาวแสงแบบเพิ่มสัญญาณที่ความยาวคลื่น 504 นาโนเมตร มีประสิทธิภาพการตรวจวัดในระดับ 0.88 ไมโครโมลาร์ในน้ำดื่มซึ่งต่ำกว่ามาตรฐานขององค์การอนามัยโลก (WHO) และโพรบตัวนี้สามารถผ่านเซลล์สิ่งมีชีวตไปตอบสนองกับไซยาไนด์และสามารถสร้างภาพในเซลล์สิ่งมีชีวิตได้

คำหลัก : เซนเซอร์ทางเคมี, แคลเซียมคาร์ไบน์, ไซยาไนด์, บอดิพี

Abstract :

This work consists of four projects. The first two projects involve the use of calcium carbide as acetylene surrogate to prepare acetylene based chemicals. Although acetylene gas is widely available and inexpensive, its highly flammable gaseous nature poses a serious disadvantage. To achieve an industrial safety improvement without additional cost, a less hazardous and more economical starting material is highly desirable. In this work we demonstrate the use of calcium carbide to prepare acetylenic derivatives such as arylpyroles and N-vinyl indoles. The processes provide high yields of arylpyroles and N-vinyl indoles in comparable or better yields than conventional methods. In the presence of solid caclium carbide as acetylene source under the optimized condition, oxime can be converted into arylpyrole while indole can be vinylated into the corresponding N-vinyl indoles in high yields with great functional group compatibility. It is also less complicate and cheaper to carry out.

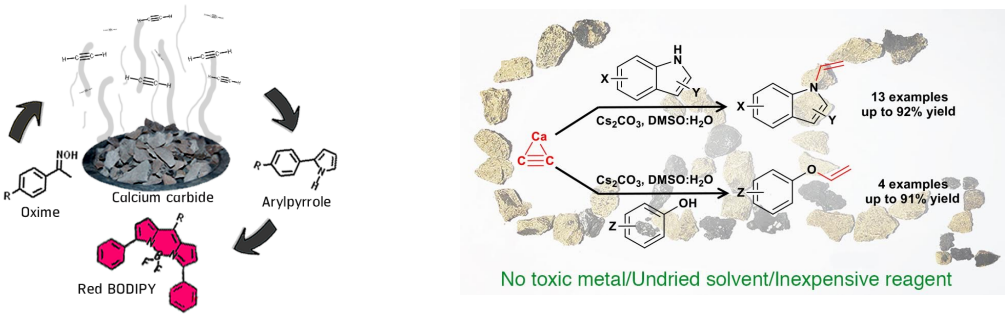
For the third project, we develop a visible light induced oxidative coupling of thiols into the corresponding disulfides in a process catalyzed by an inexpensive and non hazardous Rose Bengal dye. Our optimization study reveals that the use of Rose Bengal catalyst under irradiation with visible light at room temperature can convert a variety of thiols into their corresponding disulfides in good to excellent yields. The key benefits of this reaction include the use of metal-free, low cost Rose Bengal catalyst and practical operation (room temperature, open flask, undried solvents and simple work up procedure by extraction).

The last project focus on the development of a new colorimetric and fluorescent probe for cyanide detection. Probe is based on boron dipyrrole-methene (BODIPY) containing salicylaldehyde called **GSB** which undergoes exclusive colorimetric change from orange to colorless and exhibits selective fluorescence turn-on at 504 nm upon the addition of cyanide. Detection limit of the new cyanide-sensing **GSB** is 0.88 uM, which is below World Health Organization (WHO) recommended level in drinking water and cell imaging studies demonstrated that **GSB** is compatible and capable of sensing cyanide anion in living cells.

Keywords : chemical sensor, calcium carbide, BODIPY, cyanide

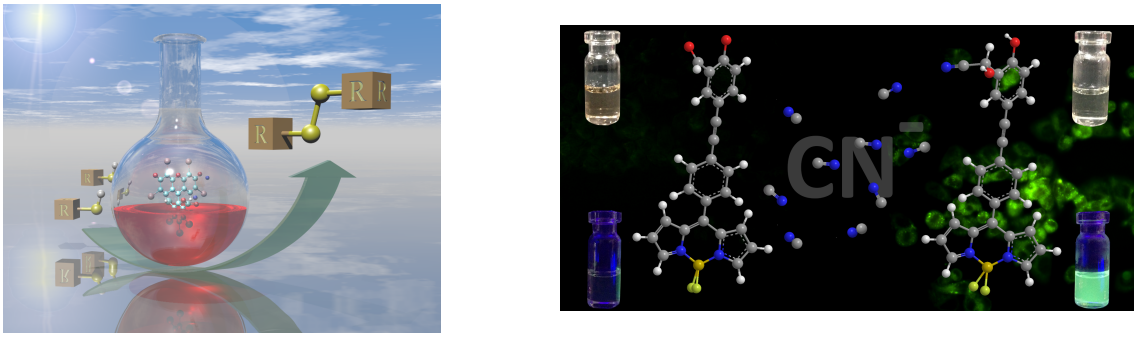
บทสรุปผู้บริหาร

งานวิจัยในโครงการนี้สามารถดำเนินเป็นไปได้ตามความคาดหมาย โดยมีงานวิจัยย่อย 4 โครงการ โดยทั้งหมดได้ตีพิมพ์ในวารสารนานาชาติ 4 ฉบับโดยใน 2 โครงการแรกเกี่ยวข้องนำสารตั้งต้นชนิดใหม่ที่ประหยัดและปลอดภัยมาทดแทนการใช้แก๊สอะเซทิลีน ซึ่งปรกติจะใช้เป็นสารต้นกำเนิดในการสร้างสารกลุ่ม acetylene based compounds กลุ่มวิจัยของเราสามารถใช้แคลเซียมคาร์ไบน์ซึ่งมีราคาถูกและหาง่ายมาใช้เป็นสารตั้งต้นในการเตรียมสารกลุ่มนี้สองชนิดคือ เอริลไพโรล์ และ ไวนิลอินโด ดังรูปที่ 1 ซึ่งได้ตีพิมพ์ในวารสาร **Green Chemmistry 2015, 17, 460** และ **European Journal of Organic Chemistry 2016, 4347**



รูปที่ 1

ในงานวิจัยที่ 3 เราคิดค้นวิธีที่มีประสิทธิภาพและเป็นมิตรต่อสิ่งแวดล้อมในการออกซิไดซ์สารกลุ่มไทออลเป็นไดซัลไฟด์ โดยใช้ตัวเร่งปฏิกิริยาอินทรีย์ในสภาวะที่ใช้แสงที่ตามองเห็นซึ่งใน เราพบว่าการใช้โรสเบงกอลเป็นตัวเร่งเชิงแสงในและฉายแสงด้วย LED สามารถใช้สังเคราะห์ไดซัลไฟด์จากไธออลต่างๆได้อย่างมีประสิทธิภาพ ประโยชน์ของการพัฒนาวิธีการสังเคราะห์นี้คือ ไม่ใช้ตัวเร่งโลหะ ทำปฏิกิริยาที่อุณหภูมิห้องและแยกผลิตภัณฑ์จากปฏิกิริยาด้วยการสกัดอย่างง่าย (รูปที่ 2 ซ้าย) ซึ่งงานวิจัยได้รับการตีพิมพ์ในวารสาร **Tetrahedron 2016, 77, 788** ในงานวิจัยที่ 4 ได้สร้างตัวตรวจวัดไซยาไนด์ที่สามารถสังเกตุการเปลี่ยนแปลงทางสีและการวาวแสง เราได้เตรียมสารกลุ่ม BODIPY ที่มีหมู่ซาลิซัลดีไฮด์เป็นตัวจับไซยาไนด์ ซึ่งสารที่เตรียมขึ้นจะเกิดการเปลี่ยนสีจากส้มเป็นใส พร้อมทั้งมีการเพิ่มขึ้นของสัญญาณเมื่อได้รับไซยาไนด์ เราพบว่ามีค่าการตรวจวัดต่ำสุดที่ 0.88 ไมโคโมลาร์ และยังสามารถใช้ในการตรวจสอบไซยาไนด์ในเซลล์สิ่งมีชีวิตได้อีกด้วย ดังแสดงใน (รูปที่ 2 ขวา) ซึ่งได้ตีพิมพ์ในวารสาร **Journal of Hazardous Materials 2016, 344, 277**



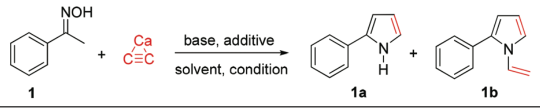
รูปที่ 2

เนื้อหางานวิจัย

<u>โครงการที่ 1</u> การสังเคราะห์อัลริลไพโรล์จากแคลเซียมคาร์ไบน์โดยตรง

ออกซีม **1** ทำปฏิกิริยากับแคลเซียมคาร์ไบน์ในสภาวะต่างๆกลายเป็นไพโรล์ **1a** และไวนิลไพโรล์ **1b** ตามตารางที่ 1 เราพบว่าเมื่อเปลี่ยนเบสชนิดต่างเราพบว่า KOH จะให้ไพโรล์ **1a** ได้ดีที่สุดถึง 58% และเมื่อเติม phase trasfer catalyst เช่น 18 crown 6 ลงไปในปฏิกิริยาจะทำให้ได้ **1a** เพิ่มมา 65 % ซึ่งเป็นเพราะมันช่วยให้ KOH ละลายใน DMSO ได้ดียิ่งขึ้น และเพื่อเพิ่มการปลดปล่อยก๊าซอะเซทิลีน เราจึงทดลองเติมน้ำที่ปริมาณต่างๆลงไปในปฏิกิริยา พบว่าน้ำที่ 2% จะทำให้สามารถเตรียมไพโรล์ **1a** ถึง 73% และไม่มีผลิตภัณฑ์ไวนิลไพโรล์ 1b เกิดขึ้น ซึ่งจะเป็นสภาวะที่ดีที่สุดในการเตรียมไพโรล์ จากผลของการหาสภาวะที่เหมาะสม เราจึงนำใช้ทดลองกับออกซีมชนิดต่างๆ ทั้งหมด 10 ชนิดดังแสดงในตารางที่ 2 พบว่า สามารถเตรียมไพโรล์ต่าง **1-10a** ที่มีประสิทธิภาพการสังเคราะห์ถึง 38-88% โดยมีไวนิลไพโรล์ **1-10c** เป็นผลิตภัณฑ์ข้างเคียงในช่วง 0-5%

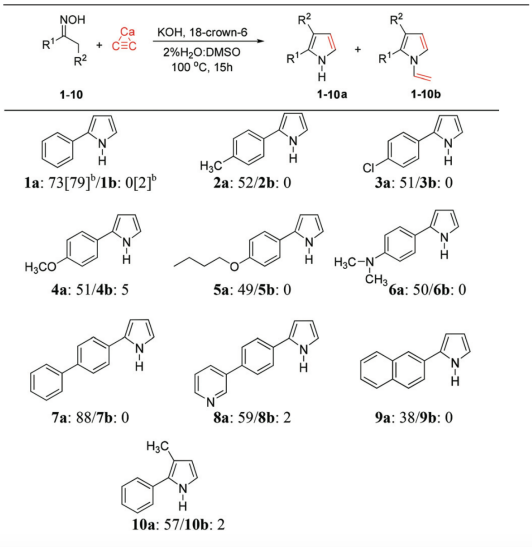
ตารางที่ 1



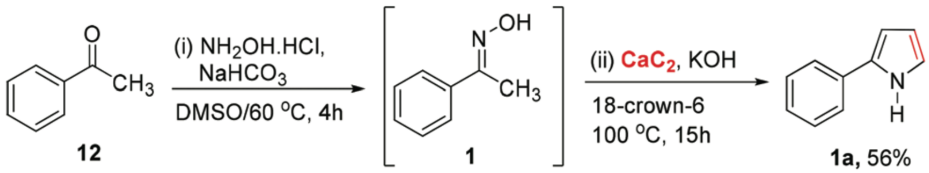
Entry[a]	Additive	Base [equiv.]	Solvent	Yield[b] **1a** [%]	Yield[b] **1b** [%]
1	—	KOH [1.5]	DMSO	58	3
2[c]	—	KOH [1.5]	DMF	0	0
3	—	NaOH [1.5]	DMSO	44	0
4	—	CsOH [1.5]	DMSO	48	0
5[d]	—	KOH [1.5]	DMSO	44	8
6	18-crown-6	KOH [1.5]	DMSO	65	8
7[e]	18-crown-6	KOH [3.0]	DMSO	32	12
8	—	KOH [1.5]	2% H_2O–DMSO	60	0
9	—	KOH [1.5]	10% H_2O–DMSO	32	0
10	18-crown-6	KOH [1.5]	2% H_2O–DMSO	73	0

[a] Acetophenone oxime (1 equiv.), CaC_2 (6 equiv.), 18-crown-6 (3 mol%) and solvent (0.074 M) were heated at 100 °C in a sealed tube for 15 h. [b] Isolated yields after purified by column chromatography on neutral alumina. [c] Starting material was recovered in 50% yield. [d] The reaction was heated to 120 °C. [e] Large excess (10 equiv.) of CaC_2 was added.

ตารางที่ 2

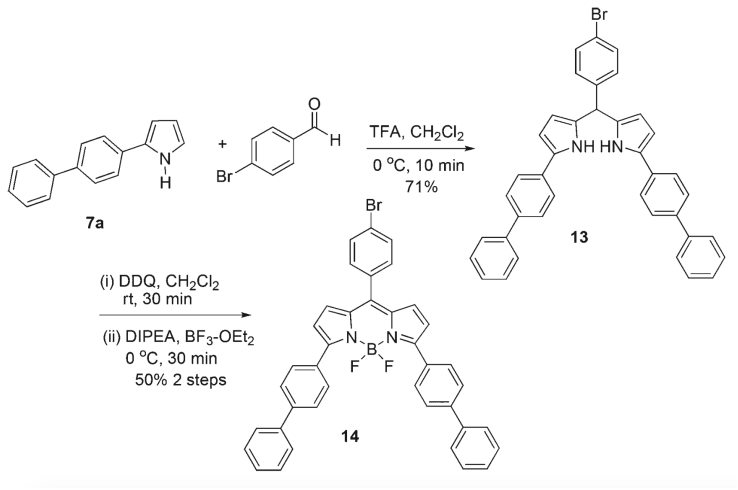


นอกจากนี้แล้วเรายังสามารถเตรียมไพโรล์โดยตรงจากคีโตนได้ โดยคีโตน **12** สามารถเปลี่ยนไปเป็นออกซีมและทำปฏิกิริยากับแคลเซียมคาร์ไบน์ได้ในขั้นตอนเดียว เกิดเป็นไพโรล์ **1a** ถึง 56% ดังแสดงในแผนภาพที่ 1



แผนภาพที่ 1

อัลริลไพโรล์ที่เตรียมขึ้น **7a** สามารถนำมาใช้เป็นสารตั้งต้นในการเตรียม BODIPY ได้อีก เมื่อนำอัลริลไพโรล์ **7a** ทำปฏิกิริยากับอัลดีไฮด์ตามด้วย DDQ และ BF_3OEt_2 จะได้ BODIPY **14** ดังแสดงใน แผนภาพที่ 2 ซึ่งสารตัวนี้จะมีการเรืองแสงเป็นสีแดงเนื่องจากหมู่ไพโรล์มีคอนจูเกตที่ยาวขึ้นจากหมู่อัลริลที่แทนที่บนวงไพโรล์



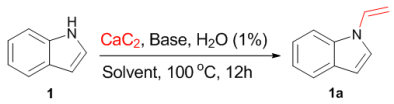
แผนภาพที่ 2

จากผลการทดลองนี้จะทำให้เราสามารถสร้างสารกลุ่มเอริลไพโรล์ได้สะดวกกว่าวิธีที่มีอยู่ ซึ่งจะต้องใช้แก๊สอะเซธิลีนหรืออนุพันธ์อื่นๆของอะเซธิลีนแก๊ส ที่มีความยุ่งยากและอันตรายกว่าวิธีที่เราคิดค้นขึ้นมา

<u>โครงการที่ 2</u> การทำปฏิกิริยาไวนิลเลชันของอินโดลและฟีนอลโดยใช้แคลเซียมคาร์ไบน์เป็นแหล่งกำเนิดแก๊ซอะเซธิลีน

งานวิจัยนี้เริ่มต้นจากการหาสภาวะที่เหมาะสมของการเตรียมไวนิลอินโดล (**1a**) จากการทำปฏิกิริยาระหว่างอินโดลและแคลเซียมคาร์ไบน์ในสภาวะต่างๆ ตามตารางที่ 3 พบว่าเมื่อเปลี่ยนเบสและตัวทำละลายเป็นชนิดต่างจะให้ผลิตภัณฑ์ **1a** ที่แตกต่างกันโดยเบสและตัวทำละลายที่มีประสิทธิภาพการสังเคราะห์มากที่สุดคือ เมื่อใช้เบสเป็น ซีเซียมคาร์บอเนตในตัวทำละลาย DMSO เป็นเวลา12 ชั่วโมงที่ 100 องศาเซลเซียสทั้งนี้อาจเนื่องมากจากการเป็นตัวทำละลายที่ดีของ DMSO และความสามารถในการเกิดขั้วของซีเซียมไอออนรวมทั้งปรากฏการณ์ “cesium effect” ที่ช่วยให้ไนโตรเจนอะตอมบนอินโดลสามารถเกิดปฏิกิริยาได้ดีขึ้นอีกด้วยจากผลของการหาสภาวะที่เหมาะสมเราจึงนำมาใช้ทดลองกับอนุพันธุ์ของอินโดลชนิดต่างๆทั้งหมด 14 ชนิดดังแสดงในตารางที่ 4 พบว่าสามารถเตรียมไวนิลอินโดลต่างๆ **2a-15a** ที่มีประสิทธิภาพการสังเคราะห์ถึง 65-91% ยกเว้นพวกที่มีหมู่ดึงอิเล็กตรอนเป็นองค์ประกอบไม่สามารถทำให้เกิดสารผลิตภัณฑ์ได้ นอกจากนี้จากผลการทดลองยังพบว่าตัว **15a** สามารถเกิด *O*-vinylation ได้อีก

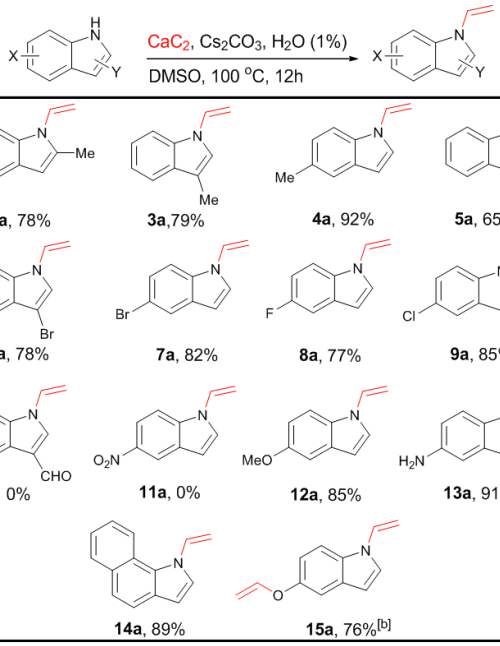
ตารางที่ 3



Entry	Solvent	Base	Yield[b] (%)
1[c]	DMSO	Cs_2CO_3	48
2	DMSO	Cs_2CO_3	85
3[d]	DMSO	Cs_2CO_3	60
4	DMSO	KOH	46
5	DMSO	K_2CO_3	21
6	DMSO	DBU	7
7	DMSO	NaOMe	0
8[e]	DMSO	Cs_2CO_3	60
9	THF	Cs_2CO_3	13
10	Toluene	Cs_2CO_3	5
11	^{i}PrOH	Cs_2CO_3	7
12	DMF	Cs_2CO_3	26
13	NMP	Cs_2CO_3	21
14	DMSO	-	0
15[f]	DMSO	Cs_2CO_3	44

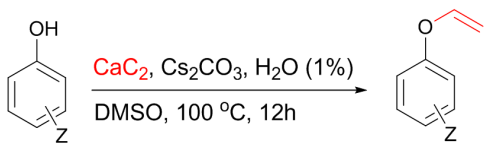
[a] Reaction condition: indole (1.0 equiv.), CaC_2 (6.0 equiv.) and base (1.5 equiv.) in 1 %water–solvent (0.2 M) at 100 °C for 12 h. [b] Isolated yield after silica gel chromatography. [c] The reaction was performed for 6 h. [d] Dried

ตารางที่ 4



[a] Reaction condition: indole derivatives (1.0 equiv.), CaC_2 (6.0 equiv.) and Cs_2CO_3 (1.5 equiv.) in 1 %water–DMSO (0.2 M) at 100 °C for 12 h. [b] CaC_2 (12.0 equiv.) and Cs_2CO_3 (3.0 equiv.) were used.

จากการทดลองในตารางที่ 4 พบว่าสามารถใช้แคลเซียมคาร์ไบน์ทำปฏิกิริยา *O*-vinylation ของสารประกอบฟีนอลได้ ดังนั้นเราจึงทดสอบปฏิกิริยากับสารประกอบฟีนอลชนิดต่างๆ เราพบว่าจำเป็นอย่างยิ่งที่ต้องมีหมู่ให้อิเล็กตรอนเป็นองค์ประกอบเช่น หมู่อะมิโน เราพบว่าสามารถเตรียม ฟีนิลไวนิลอีเธอร์ **17a-20a** (67-91%) โดยใช้อคลเซียมคาร์ไบน์ทำปฏิกิริยากับสารประกอบฟีนอลชนิดต่างๆ ตามแผนภาพที่ 3

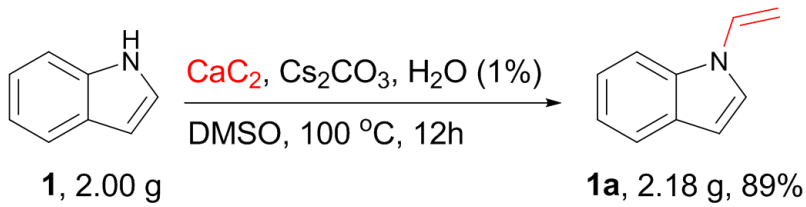


16-20

16a; Z = H; 0%
17a; Z = *o*-NH_2; 67%
18a; Z = *m*-NH_2; 82%
19a; Z = *p*-NH_2; 91%
20a; Z = 2,3-dimethoxy, 65%[b]

แผนภาพที่ 3

นอกจากนี้เราได้ทดลองปฏิกิริยาการสังเคราะห์ไวนิลอินโดลในระดับหน่วย กรัมสเกล ซึ่งพบว่าให้ประสิทธิภาพการสังเคราะห์ไม่ต่างจากการสังเคราะห์ระดับมิลลิกรัม ได้สารไวนิลอินโดล 1a 89% ดังแผนภาพที่ 4

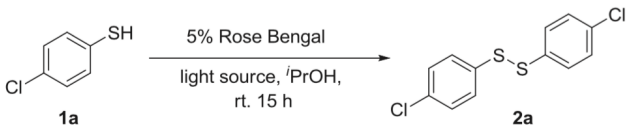


แผนภาพที่ 4

<u>โครงการที่ 3</u> การใช้สารอินทรีย์เป็นตัวเร่งเชิงแสงในการสังเคราะห์ไดซัลไฟด์จากไธออล

เราได้ศึกษาหาสภาวะที่เหมาะสมของการสังเคราะห์ไดซัลไฟด์ (**2a**) โดยใช้ตัวเร่งเชิงแสงและแหล่งกำเนิดแสงชนิดต่างๆ ดังตารางที่ 5 และตัวทำละลายชนิดต่างๆ ดังตารางที่ 6 จากการติดตามปฏิกิริยาด้วย NMR เราพบว่าแหล่งกำเนิดแสงที่ดีและเหมาะสมที่สุดคือ white LED ในขณะที่ ตัวทำลายนั้น เกือบทุกตัวทำละลายเหมาะสมดับปฏิกิริยาสามารถเปลี่ยนไทออลเป็นไดซัลไฟด์ อย่างไรก็ตามเราได้ตัดสินใจเลือก ไอโซโพพานอลและน้ำเป็นตัวทำละลายที่จะใช้ในการศึกษาต่อไป เนื่องจากเป็นตัวทำละลายที่มีความเป็นพิษน้อย

ตารางที่ 5

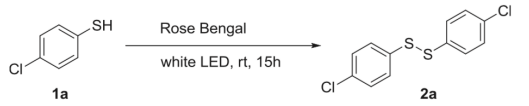


1a **2a**

Entry	Light source	Yield(%)[b]
1	White LED	90
2	Blue LED	93
3	Green LED	93
4	Red LED	18[c]
5	—	0[d]

[a] Reaction were carried at 0.5 mmol of 1a with 5 mol% of Rose Bengal in ^{i}PrOH 10 mL.
[b] Isolated by extraction.
[c] Isolated by column chromatography.
[d] Vessel was covered with aluminum foil.

ตารางที่ 6



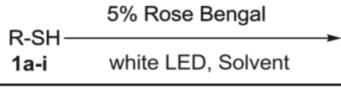
1a **2a**

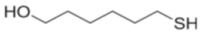
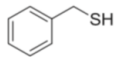
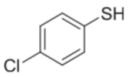
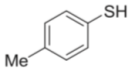
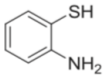
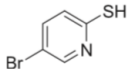
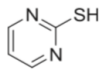
Entry	mol%	Solvent	Conversion (%)[b]
1	5	Acetonitrile	100
2	5	DMF	100
3	5	Toluene	100
4	5	^{i}PrOH	100
5	1	^{i}PrOH	25
6	0	^{i}PrOH	0
7	5	Water	100

[a] Reaction were carried on a 0.5 mmol of **1a** with 5 mol% of Rose Bengal in 10 mL solvent.
[b] Determined by ^{1}H NMR.

จากผลของการหาสภาวะที่เหมาะสมเราจึงนำมาใช้ทดลองกับไธออลชนิดต่างๆ ทั้งหมด 9 ชนิดดังทั้ง aliphatic aromatic และ heterocyclic (**1a-1i**) ดังแสดงในตารางที่ 7 พบว่าสามารถเตรียมไดซัลไฟด์ต่างๆ **2a-2i** ที่มีประสิทธิภาพการสังเคราะห์ถึง 75-94% ซึ่งสามารถทำปฏิกิริยาได้ในทั้งน้ำและไอโซโพรพานอล

ตารางที่ 7

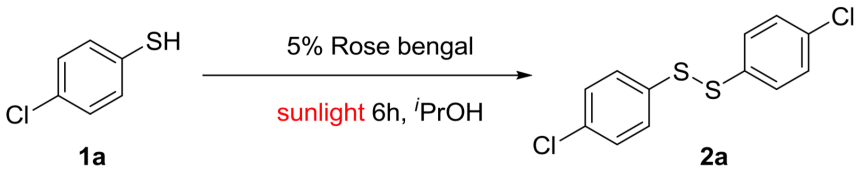


Entry		Thiols	T (h)	Yields (%)[b]
1	**1b**		15	94
2	**1c**		15 (24)	89 (84)
3	**1d**		15	77[c]
4	**1a**		6 (9)	90 (81)
5	**1e**		6 (9)	86 (92)
6	**1f**		15	75[c]
7	**1g**		3 (6)	92 (88)
8	**1h**		3	86
9	**1i**		3	81

[a] Reaction conditions: thiol (0.5 mmol), Rose Bengal (5 mol%) in ^{i}PrOH 10 mL under 1.5 W white LED; numbers in parentheses are the yields and reaction time when carried the reaction in water.
[b] Isolated yield by extraction.
[c] Isolated by silica gel chromatography.

นอกจากนี้ไดซัลไฟด์ (**2a**) ถูกสังเคราะห์ขึ้นจาก ไธออล (**1a**) โดยใช้โรสเบงกอลเป็ นตัวเร่งเชิงแสงใน ตามแผนภาพที่ 5 ภายใต้แสงอาทิตย์ที่ระเบียงของห้องปฏิบัติการของเรา พบว่าปฏิกิริยาสามารถเกิดสมบูรณ์ได้ใน

ตัวทำละลายไอโซโพรพานอล โดยสามารถตรียมสารในระดับเสกล 50 มิลิกรัมถึง 1 กรัมในปฏิกิริยาแบบกะ (batch reaction)



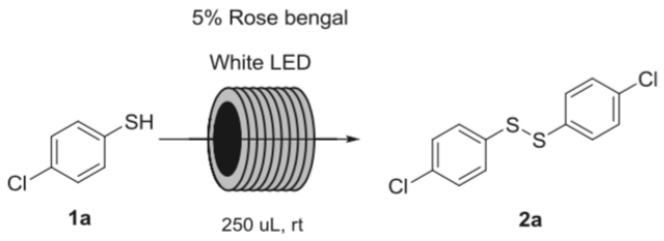
1a **2a**

	%Conv.	% Yield
50 mg	100	90
1 g	95	86

แผนภาพที่ 5

นอกจากนี้ไดซัลไฟด์ (**2a**) สามารถสังเคราะห์ขึ้นมาจาก ไธออล (**1a**) โดยใช้ปฏิกิริยาแบบไหลต่อเนื่อง (continuous flow reaction) เราสามารถใช้เครื่อง micro flow reaction มีแผ่นที่ประกอบไปด้วยท่อขนาด 250 uL และฉายแสง LED ในขณะทำปฏิกิริยา ซึ่งความสามารถในการเกิดปฏิกิริยาจะแปรผกผันกับอัตราการไหลของระบบ ตามตารางที่ 8 ที่ความเข้มข้น 0.05 M ต้องปรับอัตราการไหลเป็น 8.3 uL/min ถึงจะเกิดเป็นปฏิกิริยาสมบูรณ์

ตารางที่ 8

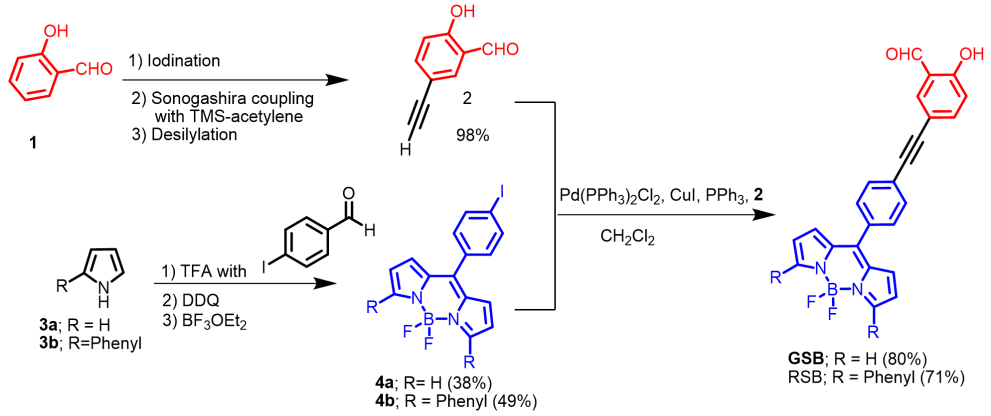


Entry	Conc (M)	Flow rate (μL/min)	Residence time (min)	Conversion (%)[b]
1	0.01	8.3	30	100
2	0.01	50	5	100
3	0.05	8.3	30	100
4	0.05	50	5	39

[a] Reaction were performed using microflow reactor from Syriss FRXTM with 250 μL chip equipped with a panel of 24 small white LEDs (1.5 W, Fig. S3).
[b] Determined by ^{1}H NMR.

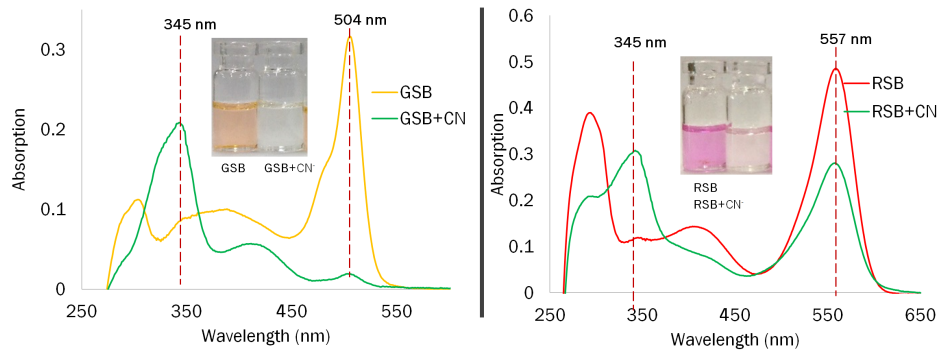
<u>โครงการที่ 4</u> ตัวตรวจวัดไซยาไนด์ที่สามารถสังเกตุการเปลี่ยนแปลงทางสีและการวาวแสงจาก BODIPY

ตัวตรวจวัดไซยาไนด์ **GSB** และ **RSB** ได้ถูกสังเคราะห์ขึ้นดัง แผนภาพที่ 6 ซึ่งจะประกอบด้วยหมู่ที่ให้สัญญาน (signaling unit) คือ BODIPY และส่วนหมู่จับ (receptor) คือ ซาลิซัลดีไฮด์ เราได้ทำการประกอบส่วนทั้งสองจาก BODIPY **4a** และ **4b** เข้ากับ อัลไคลน์ **2** ผ่านปฏิกิริยาโซโนกาชิราคลัปปลิง ซึ่งสารทั้งสองตัวได้รับการยืนยันโครงสร้างด้วยเทคนิค NMR และ Mass spectroscopy



แผนภาพที่ 6

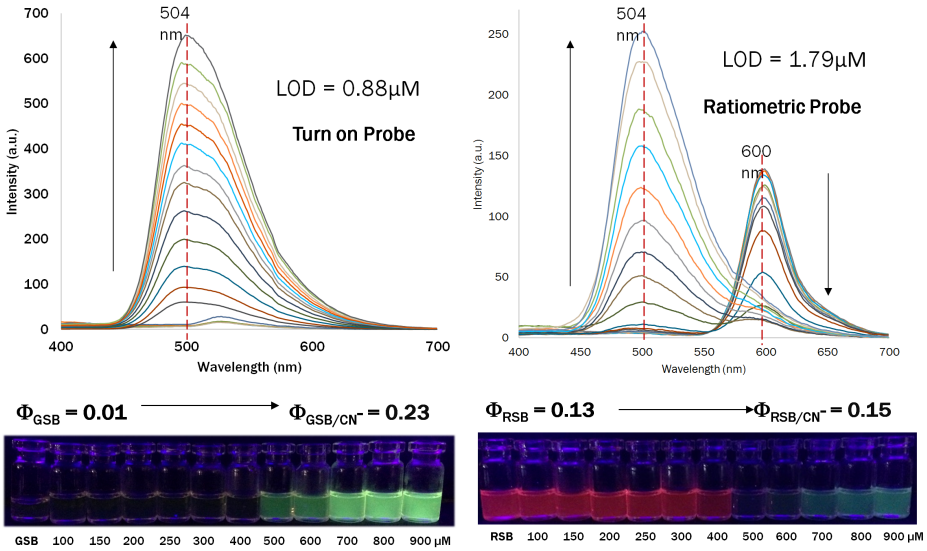
สารทั้งสองตัวเมื่อได้รับไซยาไนด์จะเกิดการเปลี่ยนสี โดยเมื่อเติมไซยาไนด์ลงไป 0.9 มิลลิโมลาร์ จะทำให้ **GSB** เปลี่ยนจากสีส้มเป็นไม่มีสีในขณะที่ **RSB** จากสีแดงเป็นไม่มีสีดังแสดงในรูปที่ 3 ซึ่งการเปลี่ยนแปลงเหล่านี้ยังสามารถตรวจสอบโดยใช้เครื่องยูวีเสปกโตรมิเตอร์ พบว่าในกรณีของ **GSB** นั้นค่าการดูดกลืนแสงสูงสุดที่ 504 nm จะลดลงและเกิดพีคใหม่บริเวณ 345 nm ขณะที่ RSB ค่าการดูดกลืนแสงสูงสุดที่ 554 nm จะลดลงและเกิดพีคใหม่บริเวณ 345 nm



รูปที่ 3

การเปลี่ยนสัญญาณการคายแสงของ **GSB** และ **RSB** กับไซยาไน์ได้ตรวจสอบด้วยเครื่องฟลูออร์เรสเซนต์ดังแสดงในรูปที่ 4 **GSB** จะมีการคายแสงเพิ่มขึ้นที่สัญญาณพีคที่ 504 nm พร้อมกับการคายแสงสีเขียวที่มากขึ้น โดยพบว่ามีค่าการตรวจสอบต่ำสุดที่ 0.88 ไมโคโมลาร์และค่า quantum efficiency เปลี่ยนจาก 0.01 เป็น 0.23

ในขณะที่ **RSB** มีการเปลี่ยนสัญญาณคายแสงที่ต่างออกไป **RSB** จะมีการลดลงของสัญญาณพีคการคายแสงสูงสุดที่ 600 nm และจะมีค่าการคายแสงเพิ่มขึ้นที่สัญญาณพีคที่ 504 nm พร้อมกับการคายแสงสีเขียวที่มากขึ้น โดยพบว่ามีค่าการตรวจสอบต่ำสุดที่ 1.79 ไมโครโมลาร์และค่า quantum efficiency เปลี่ยนจาก 0.13 เป็น 0.15 เราจึงสรุปได้ว่าทั้ง **GSB** และ **RSB** สามารถใช้เป็นตัวตรวจวัดไซยาไนด์โดยสังเกตุการเปลี่ยนสีและการเปลี่ยนสัญญาณฟลูออร์เรสเซนต์



รูปที่ 4

RSB และ **GSB** ได้ถูกนำมาทดสอบการแอนไอออนชนิดอื่นๆ อีก 14 ชนิดในสภาวะเดียวกับการทดสอบกับไซยาไนด์ดังแสดงในรูปที่ 7 เราพบว่าทั้ง **RSB** และ **GSB** ไม่เกิดการเปลี่ยนแปลงกับแอนไอออนชนิดอื่นๆ ทั้งจากการสังเกตุได้ด้วยตาเปล่าภายใต้แสงปกติและหลอดยูวี ซึ่งแสดงให้เห็นถึงความเจาะจงของ **RSB** และ **GSB** ต่อไซยาไนด์แอนไอออน

รูปที่ 5

จากผลการทดลองสรุปได้ว่า **GSB** และ **RSB** สามารถใช้เป็นตัวตรวจวัดไซยาไนด์ได้อย่ างเฉพาะเจาะจงกับไซยาไนด์เท่านั้นโดย **GSB** มีการเปลี่ยนสัญญาณการคายแสงแบบเพิ่มขึ้น (turn on mode) ในขณะที่ **RSB** จะ

มีการเปลี่ยนสัญญาณการคายแสงไปที่ตำแหน่งใหม่ (ratiometric mode) นอกจากนี้แล้วความเข้มข้นต่ำสุดที่วิธีนี้จะหาไซยาไนด์ได้ (LOD) มีค่าต่ำกว่ามาตราฐานของ WHO ในน้ำดื่ม ที่ 1.78 ไมโครโมลาร์

ผลลัพธ์ที่ได้จากโครงการ

1. ผลงานวิจัยที่ตีพิมพ์ในระดับนานาชาติ (แนบในภาคผนวก)

1) Kaewchangwat, N., Sukato, R., Vchirawongkwin, V., Vilaivan, T., Sukwattanasinitt, M., Wacharasindhu, S. Direct synthesis of aryl substituted pyrroles from calcium carbide: An underestimated chemical feedstock (2015) Green Chemistry, 17 (1), pp. 460-465

2) Sukato, R., Sangpetch, N., Palaga, T., Jantra, S., Vchirawongkwin, V., Jongwohan, C., Sukwattanasinitt, M., Wacharasindhu, S. New turn-on fluorescent and colorimetric probe for cyanide detection based on BODIPY-salicylaldehyde and its application in cell imaging (2016) Journal of Hazardous Materials, 314, pp. 277-285.

3) Tankam, T., Poochampa, K., Vilaivan, T., Sukwattanasinitt, M., Wacharasindhu, S. Organocatalytic visible light induced S-S bond formation for oxidative coupling of thiols to disulphides (2016) Tetrahedron, 72 (6), pp. 788-793.

4) Rattanangkool, E., Vilaivan, T., Sukwattanasinitt, M. Wacharasindhu, S. Atom-economic approach for vinylation of indoles and phenols using calcium carbide as acetylene surrogate (2016) European Journal of Organic Chemistry, 2016 pp. 4347

2.กิจกรรมอื่นๆที่เกี่ยวข้อง : นำเสนอผลงาน

2.1) Direct Synthesis of Acetylenic Compounds from Calcium Carbide: A New Sustainable Chemical Feedstock" Pure and Applied Chemistry Conference 2015 (PACCON2015) 21 - 23 January 2015 Amari Watergate Hotel, Bangkok, Thailand

2.2) Direct Colorimetric Sensor From Polydiacetylenes: JSPS-DST Asian Academic Seminar and School 2015 Spectroscopy, Theoretical Chemistry and Chemistry of Materials March 6–10, 2015, Kolkata, India

2.3) Direct Synthesis of Acetylenic Compounds from Calcium Carbide: A New Sustainable Chemical Feedstock Chemistry in The Asian CORE Program (ACP) (ICCEOCA-9) 11-15 December 2014, Malaysia

2.4) Synthesis of acetylenic derivatives from calcium carbide: a new sustainable Chemical feedstock at PACCON2016 Bangkok, 9-11 February 2016

2.5) Direct Colorimetric Sensor From Polydiacetylenes at PACCON2016 Bangkok, 9-11 February 2016

2.6) Synthesis of acetylene-based chemicals from calcium carbide: an underestimated chemical feedstock , 20th Annual Green Chemistry & Engineering Conference, 14-16 June 2016, Portland Oregon USA.

3. การเชื่อมโยงกับต่างประเทศหรือรางวัลที่ได้รับ

2015 Wiley-CST Green Chemistry Award. The award was presented at the Pure and Applied Chemistry International Conference (PACCON 2015) at the Amari Watergate Hotel, Bangkok, Thailand, on January 21, 2015.

2014 Asian CORE Program (ACP) Lectureship Awards to Japan and Taiwan. The award presented at the 9th International Conference on Cutting-Edge Organic Chemistry in Asia (ICCEOCA-9), Malasia (11-15 December 2014)

2014 TRF-CHE-SCOPUS Researcher Award for Chemical & Pharmaceutical Sciences

20616 CST Citation Award 2015. The award was presented at the Pure and Applied Chemistry International Conference (PACCON 2016) at the BITEC, Bangkok, Thailand, on February 9, 2016.

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Direct synthesis of aryl substituted pyrroles from calcium carbide: an underestimated chemical feedstock†

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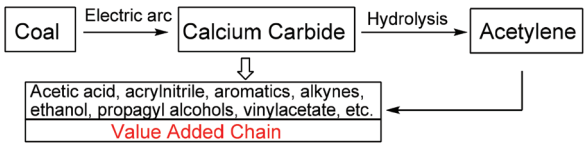
In this work, a novel synthetic methodology for the preparation of aryl pyrroles directly from the reaction of calcium carbide with oxime is reported. Various pyrrole derivatives are generated from the corresponding oximes in satisfactory yields (49–88%) under the optimized conditions. The one-pot synthesis of aryl pyrrole from widely available ketone is also successfully developed. A new near-infrared fluorescent BODIPY dye containing a phenyl substitution at the C-3 position is expediently prepared from the aryl pyrrole derived from this methodology. The key benefit of this methodology is the use of an inexpensive and less hazardous primary chemical feedstock, calcium carbide, in a wet solvent without any metal catalysts. This process offers a novel cost-efficient route for the synthesis of functionalized pyrrole.

Introduction

One of the key conversion routes along the value added chain in the petrochemical industry is the formation of calcium carbide from an electric arc furnace of coke and lime. The hydrolysis of calcium carbide produces acetylene gas as one of the major primary chemical feedstocks for downstream products in the chemical industry such as acetic acid, ethanol, aromatics, vinyl acetate, *etc.* (Scheme 1).[1] Although acetylene gas is widely available and inexpensive, its highly flammable gaseous nature poses a serious disadvantage in requiring an extra level of operation control, and a higher cost to prevent leakage and explosion. To achieve an industrial safety improvement without additional cost, a less hazardous and more economical starting material is highly desirable.[2] As a main source of acetylene gas, solid calcium carbide is a promising candidate for a safer and cheaper alternative to acetylene gas, for the production of acetylene-derived chemicals.



Scheme 1 Conversion of coal to commodity chemicals.

In 2006, Zhang *et al.* reported the use of calcium carbide as a C–C triple bond moiety for the synthesis of diarylethynes *via* a Sonogarshira coupling reaction.[3] Following this work, our group and others recently developed methodologies for the direct use of calcium carbide in the synthesis of C≡C-containing compounds, such as diarylethynes,[4] poly(*p*-phenyleneethynylene)s (PPEs),[5] polyenynes,[6] propagylamine,[7] enaminones[8] and acetylenic alcohols.[9] All reported processes rely on the slow release of acetylene gas from calcium carbide which then turns into the corresponding anion (C_2^{2-} anion). Subsequently, the reactive intermediate acts as either a coupling partner for a metal-catalyzed reaction or as a nucleophile for a carbonyl addition.

One of the highest value compounds that can be obtained from acetylene is 2-aryl pyrrole. It is a basic building block for pharmaceuticals[10] and fluorescent dyes (BODIPY).[11] Current methods for the preparation of 2-aryl pyrrole involve using either unsubstituted pyrrole or ketoxime (Scheme 2). The first method involves a metal-catalyzed reaction to introduce the aryl group to C2-halogenated pyrroles.[12] In addition, direct C–H activation of pyrrole has recently been developed.[13] The drawbacks of these methods are the requirement of a precious metal catalyst and additional protection/deprotection steps in some cases. Moreover, direct arylation of *N*-substituted pyrroles with aryl iodides in the presence of lithium *tert*-butoxide, without use of a transition metal catalyst, has also been reported.[14]

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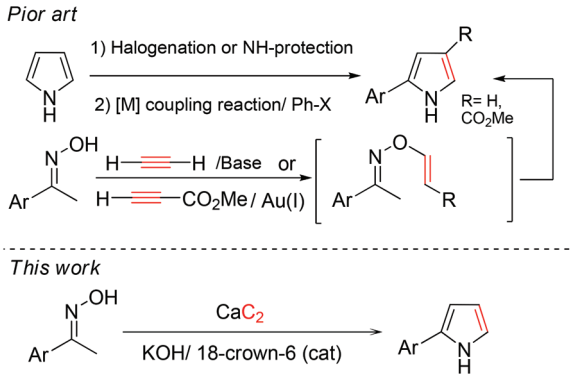
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c4gc01615g



Scheme 2 Synthetic approaches for 2-aryl pyrrole.

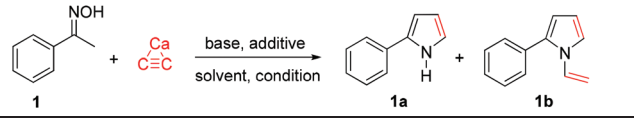
On the other hand, the readily and inexpensively available ketoxime can be converted to 2-aryl pyrrole in one step by a reaction with substituted alkynylcarbonyl compounds or acetylene gas. The former uses a reagent metal catalyst such as Au and Ni to activate the triple bond.[15] The latter (the so-called Trofimov reaction) uses acetylene gas, bubbled into the reactor in the presence of a strong base.[16] The Trofimov reaction is the preferred method for 2-aryl pyrrole synthesis, because metal is not required in the transformation and the product is directly obtained without an additional deprotection step.

In this study, we propose a novel process for the direct transformation of calcium carbide into 2-aryl pyrroles (Scheme 2). This is not only an unprecedented application of calcium carbide as an electrophile precursor in a vinylation reaction to produce vinylic derivatives, but also its first utilization in heterocycle synthesis. Our methods successfully overcome the challenges of the poor solubility of calcium carbide in organic solvent and the unpolarized nature of the acetylenic triple bond, to achieve excellent product yields. The developed method uses economical starting materials (ketoximes) and avoids the handling of gaseous acetylene. The use of heavy metal is eliminated, and overall process is significantly shortened in terms of the number of steps. Therefore it can be considered a convenient, safe, and more environmentally conscious, green and sustainable process. Moreover, our process can be easily applied in large scale manufacturing in the chemical industries as well as for routine laboratory synthesis.

Results and discussion

To design the reaction conditions for the calcium carbide we considered the main problems; these are the low solubility of calcium carbide, and the poor electrophilic nature of acetylene gas, which limits its application in organic synthesis. However, previous work by Trofimov *et al.* demonstrated that the use of a superbase can promote the O-alkylation of oximes by acetylene gas.[16] Moreover, our work has shown that the use of a wet polar aprotic solvent can slowly hydrolyze the calcium carbide into acetylene *in situ*.[4] Therefore, we began our optimization study by reacting acetophenone oxime (**1**) with calcium carbide in the presence of a base to provide *NH*-2-aryl pyrrole (**1a**) along with *N*-vinyl pyrrole (**1b**); the results are depicted in Table 1. Among several bases studied, including KOH, NaOH and CsOH (Table 1, entries 1, 3–4), the best results were obtained with KOH, providing the desired pyrrole **1a** in 58% yield along with the vinylation product **1b** in 3% yield. Switching from DMSO to DMF resulted in no reaction occurring (Table 1, entry 2). In order to drive the reaction forward, the temperature was raised from 100 to 120 °C for 24 hours; however, the yield of the pyrrole **1a** decreased along with an increase in the vinylation product **1b** (Table 1, entry 5). Therefore, controlling the temperature and reaction time are vital for the reaction conditions. To increase the base strength, we therefore added a catalytic amount of 18-crown-6 as a catalyst (3% mol) to the reaction mixture. The yields of both pyrroles (**1a** and **1b**) increased to 65% and 8%, respectively (Table 1, entry 6). It should be noted that under these conditions, the crude NMR indicated that the oxime was completely consumed, and no hydrolysis product (acetophenone) was detected in the reaction mixture. The slightly low yield of pyrrole **1a** is perhaps due to its sensitivity to air, meaning that some decomposition may have occurred during chromatographic purification.

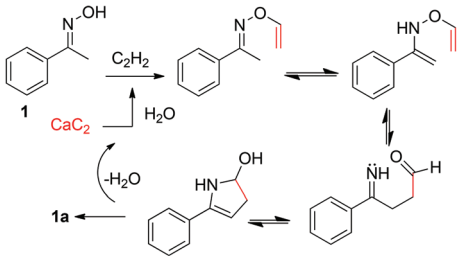
Table 1 Effect of various parameters on the yield of aryl pyrroles



Entry[a]	Additive	Base [equiv.]	Solvent	Yield[b] **1a** [%]	Yield[b] **1b** [%]
1	—	KOH [1.5]	DMSO	58	3
2[c]	—	KOH [1.5]	DMF	0	0
3	—	NaOH [1.5]	DMSO	44	0
4	—	CsOH [1.5]	DMSO	48	0
5[d]	—	KOH [1.5]	DMSO	44	8
6	18-crown-6	KOH [1.5]	DMSO	65	8
7[e]	18-crown-6	KOH [3.0]	DMSO	32	12
8	—	KOH [1.5]	2% H_2O–DMSO	60	0
9	—	KOH [1.5]	10% H_2O–DMSO	32	0
10	18-crown-6	KOH [1.5]	2% H_2O–DMSO	73	0

[a] Acetophenone oxime (1 equiv.), CaC_2 (6 equiv.), 18-crown-6 (3 mol%) and solvent (0.074 M) were heated at 100 °C in a sealed tube for 15 h. [b] Isolated yields after purified by column chromatography on neutral alumina. [c] Starting material was recovered in 50% yield. [d] The reaction was heated to 120 °C. [e] Large excess (10 equiv.) of CaC_2 was added.

All reactions mentioned above were performed in the undried solvent. In order to increase the liberation of acetylene, we added a small amount of water to the reaction (Table 1, entries 8–10). The presence of water at 2% w/w with 18-crown-6 gave the best yield of the product **1a** (73%) and this has been used as the optimized conditions for further studies. The deliberate addition of water can suppress the formation of vinyl pyrrole, and only trace amounts were detected in the crude ^{1}H NMR spectra. In the presence of water, N-vinylation is sluggish due to the reduction of the basic strength of the KOH in DMSO by the so-called "leveling effect". However, too



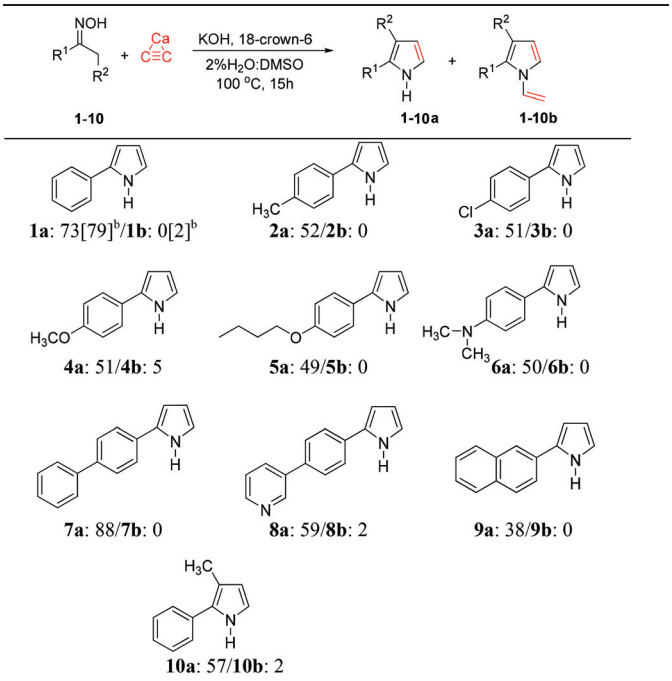
Scheme 3 Proposed mechanism for the synthesis of pyrrole **1a** from oxime **1**.

much added water (10%) gave a significantly lower yield of **1a**, perhaps due to the hydrolysis of the calcium carbide occurring too fast, and making acetylene escape from the system faster than it could react with the oxime; it could also be due to the leveling effect lowering the KOH–DMSO basic strength. Importantly, in comparison with the original Trofimov reaction, our reaction based on calcium carbide gave a comparable efficiency, offering an alternative synthesis of 2-aryl pyrroles that is both convenient and safer to perform. The proposed mechanism of the reaction between calcium carbide and oxime is presented in Scheme 3. The added water initially hydrolyzed the calcium carbide to liberate the acetylene gas. The reaction then proceeded as in the standard Trofimov reaction, which involves addition to acetylene followed by tautomerization to generate an enamine.[1c] Next, the enamine underwent a sigmatropic rearrangement to form an aldehyde–imine intermediate. The desired aryl pyrrole **1a** was finally obtained following a tautomerization-addition-dehydration sequence of the aldehyde–imine intermediate.

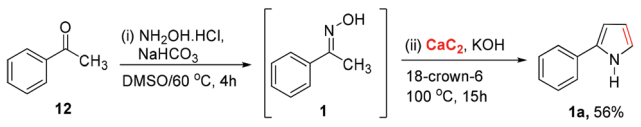
With the optimized conditions in hand, we next expanded the scope of this reaction by subjecting a variety of oximes (**2–11**) to the reaction conditions (Table 1). These oxime substrates were easily prepared from commercially available ketones using hydroxylamine hydrochloride, and were purified by recrystallization. A panel of acetophenone oximes (**2–6**) bearing methyl, chloro, methoxy, butoxy and dimethylamino were successfully transformed into aryl pyrroles (**2a–6a**) in moderate yields, along with small amounts of vinylation products (**2b–6b**) of less than 6% yields. The oxime-containing bicyclic structures such as **7–9** were also tested in the optimized conditions and generated highly conjugated pyrroles **7a–9a** in fair-to-good yields. The scope of the reaction also extends to preparation of highly substituted pyrroles. Propiophenone oxime **10** was reacted with calcium carbide under the described conditions to afford the 2,3-disubstituted pyrrole **10a** in 57% yield along with the corresponding vinylpyrrole **10b** in 2% yield (Table 2).

Although oxime can be prepared easily, an additional oxime preparation step is still required. On the other hand, the use of ketone (the precursor of oxime) as the starting material is preferred because it allows the convenient one-pot preparation of 2-arylpyrroles. Here, we successfully developed such one-pot pyrrole synthesis directly from ketone, which combines oxime formation with the Trofimov reaction, as shown in Scheme 4. The ketone **12** was reacted with hydroxylamine hydrochloride in DMSO at 60 °C in the presence of a base ($NaHCO_3$). Addition of calcium carbide and catalytic amounts of 18-crown-6 to the reaction mixture led to the formation of aryl pyrrole (**1a**) in 56% yield as the sole product. This one-pot process is comparable to the two-step transformation in terms of isolated yield, but is shorter and more convenient to perform.

Table 2 Substrate scope of oxime in the reaction with calcium carbide[a]



[a] Oxime (1 equiv.), CaC_2 (6 equiv.), and 18-crown-6 (3 mol%) in 2% water–DMSO (0.074 M) were heated at 100 °C in a sealed tube for 15 h and purified by column chromatography on neutral alumina. [b] GC yield from the Trofimov reaction.[16e]

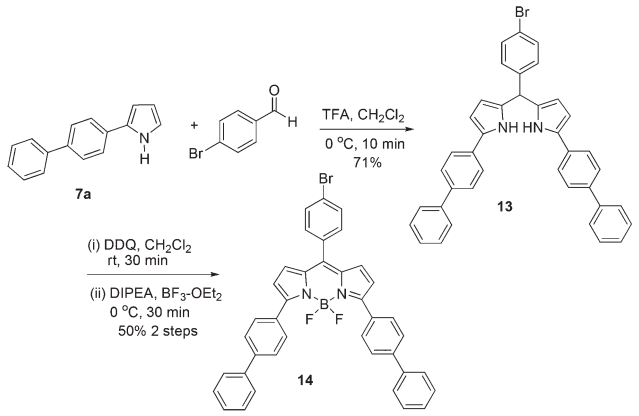


Scheme 4 One-pot synthesis of 2-phenyl pyrrole **1a** from acetophenone **12**.

To demonstrate an application of our methodology, we next synthesized 3-substituted BODIPY (4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene) using the aryl pyrrole prepared by our methods. Fluorescent BODIPY dyes are widely used as sensors, for optoelectronic materials and in imaging applications.[11b,17] In recent years, near-infrared (NIR) dyes have attracted much interest for *in vivo* imaging applications[18] because they allow bioimaging with low interference from the tissues. The high penetration power and the low energy of the light also causes less cell damage. To make NIR BODIPY, post-structural modification of the BODIPY scaffold by an extension of the π-conjugation, such as an alkenyl or aryl substitution at the

3-position, is generally employed.[11b] The 3-alkenyl substituted BODIPY is obtained from the Knoevenagel reaction of 3-methyl BODIPY.[11a] The preparation of 3-aryl substituted BODIPY usually involves a metal-catalyzed cross-coupling reaction of the halo-substituted BODIPY, which not only requires additional steps but also causes the partial decomposition of the BODIPY during the coupling reaction.[19]

With the readily accessible 2-aryl pyrroles in hand, we have the opportunity to perform the direct synthesis of a BODIPY fluorophore containing an aromatic substitutent at the C-3 position. Using the standard method,[20] the synthesis was accomplished *via* a two-step procedure presented in Scheme 5. Initially, the condensation of biphenyl-substituted pyrrole **7a** with 4-bromobenzaldehyde led to the formation of the dipyrrane **13** in 71% yield (Scheme 5). The oxidation of **13** using DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone), followed by complexation with $BF_3{\cdot}OEt_2$, gave the desired BODIPY **14** with a biphenyl substitution at the C-3 position in 50% yield. The peripheral bromobenzene moiety at the C-5 position of **14** provides an opportunity for further probe attachment for fluorescence sensing applications. The absorption and emission spectra of the BODIPY **14** are shown in Fig. 1. The maximum absorption and emission wavelengths are at 582 and 632 nm, respectively. It is apparent that the conjugation extension of the BODIPY scaffold by installation of additional phenyl groups can shift both absorption and emission maxima into the far red region.



Scheme 5 The synthesis of BODIPY **14** from pyrrole **7a**.

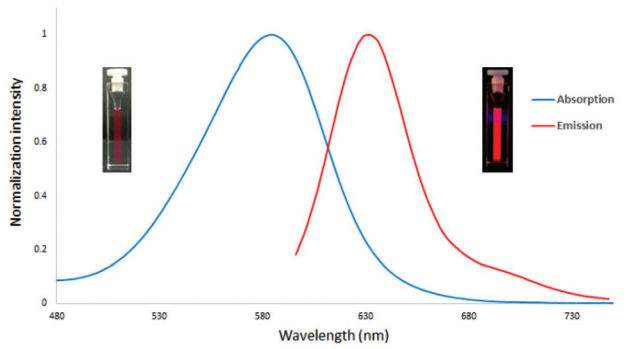


Fig. 1 UV-vis absorption and fluorescence emission spectra of BODIPY **14** in THF. λ_{ex} = 582 nm.

Materials and methods

All chemicals were obtained from commercial suppliers (Sigma Aldrich), and were used without further purification. All solvents were used directly without drying, except for dimethyl sulfoxide (DMSO), which was dried over 4 Å molecular sieves. Calcium carbide was ground before use. Analytical thin-layer chromatography (TLC) was performed on Kieselgel F254 pre-coated plastic TLC plates from EM Science. Visualization was performed with a 254 nm ultraviolet lamp. Column chromatography was carried out with aluminium oxide (90 active neutral, 70–230 mesh) from Merck and silica gel (60, 230–400 mesh) from ICN Silitech. The ^1H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 or Bruker Avance 400 for ^1H (400 MHz) and Bruker Avance 400 for ^{13}C (100 MHz) in $CDCl_3$ or $(CD_3)_2SO$ solution. Mass spectrometry was performed with a Micromass Quattro micro TM API and triple quadrupole GC/MS from Agilent technologies. The UV-visible absorption spectra were obtained with a Varian Cary 50 UV-Vis spectrometer and the fluorescence emission spectra were recorded on a Varian Cary Eclipse spectrofluorometer.

General procedure for synthesis of 2-arylpyrroles

A mixture of calcium carbide (6.0 equiv.), ketone oxime (1.0 equiv.), potassium hydroxide (1.5 equiv.) and 18-crown-6 (3.0 mol%) was suspended in 10 mL of (50 : 1) DMSO–H_2O in a sealed tube. The reaction mixture was stirred at 100 °C overnight. The reaction was cooled to room temperature and diluted by the dropwise addition of H_2O (10 mL). The reaction mixture was filtered and the solution was extracted with ether (5 × 30 mL). The combined extracts were washed with brine (2 × 30 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product, which was further purified by column chromatography on alumina (eluted with ethyl acetate–hexanes = 1 : 3) to afford the desired compound.

General procedure for one-pot synthesis of 2-phenylpyrrole (1a)

Hydroxylamine hydrochloride (0.83 mmol, 57 mg) was dissolved in DMSO (10 mL) in a sealed tube with a magnetic stirrer bar, and then $NaHCO_3$ (0.83 mmol, 93 mg) and acetophenone (0.83 mmol, 100 mg) were added. The reaction mixture was stirred at 60 °C for 4 h. After completion of the reaction, calcium carbide (4.98 mmol, 319 mg), potassium hydroxide (1.25 mmol, 70 mg) and 18-crown-6 were added and the mixture was heated to 100 °C overnight. The reaction was cooled to room temperature and diluted by the dropwise addition of H_2O (10 mL). The reaction mixture was filtered and the solution was extracted with ether (5 × 30 mL). The combined extracts were washed with brine (2 × 30 mL), dried over $MgSO_4$ and evaporated under reduced pressure to give the crude product, which was further purified by column chromatography on alumina (eluted with ethyl acetate–hexanes = 1 : 3)

to afford the corresponding 2-phenylpyrrole as a purple solid (66 mg, 56% yield).

2-Phenylpyrrole (1a).[21] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.45 (br, 1H, NH), 7.36 (d, J = 8.0 Hz, 2H, Ar–H), 7.36 (t, J = 8.0 Hz, 2H, Ar–H), 7.11 (1H, d, J = 8.0 Hz, Ar–H), 6.87 (s, 1H, CH), 6.53 (s, 1H, CH), 6.31 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 132.8, 132.2, 128.9, 126.2, 123.7, 118.9, 110.1, 106.0. ESI-MS calculated for $C_{10}H_9N$: 143.07, found at 143.01.

2-*p*-Tolylpyrrole (2a).[12c] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.41 (br, 1H, NH), 7.37 (d, J = 8.0 Hz, 2H, Ar–H), 7.17 (d, J = 8.0 Hz, 2H, Ar–H), 6.84 (s, 1H, CH), 6.47 (s, 1H, CH), 6.28 (s, 1H, CH), 2.35 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 135.9, 132.3, 130.1, 129.5, 123.9, 118.4, 110.0, 105.4, 21.1; GC-Ms: m/z: 157.1.

2-(4-Chlorophenyl)pyrrole (3a).[12c] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.84 (br, 1H, NH), 7.40 (d, J = 8.6 Hz, 2H, Ar–H), 7.33 (d, J = 8.5 Hz, 2H, Ar–H), 6.88 (s, 1H, CH), 6.52 (d, J = 5.6 Hz, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 131.8, 131.3, 131.0, 129.0, 125.0, 119.2, 110.4, 106.5; GC-Ms: m/z: 177.1.

2-(4-Methoxyphenyl)pyrrole (4a).[13c] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.24 (br, 1H, NH), 7.30 (d, J = 8.4 Hz, 2H, Ar–H), 6.82 (d, J = 8.5 Hz, 2H, Ar–H), 6.72 (s, 1H, CH), 6.32 (s, 1H, CH), 6.19 (s, 1H, CH), 3.73 (s, 3H, OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 158.3, 132.2, 126.0, 125.3, 118.2, 114.4, 109.9, 104.9, 55.35; GC-Ms: m/z: 173.1.

2-(4-Butoxyphenyl)pyrrole (5a). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.33 (br, 1H, NH), 7.39 (d, J = 8.6 Hz, 2H, Ar–H), 6.90 (d, J = 8.3 Hz, 2H, Ar–H), 6.83 (s, 1H, CH), 6.40 (s, 1H, CH), 6.27 (s, 1H, CH), 3.97 (t, J = 6.5 Hz, 2H, OCH_2), 1.82–1.73 (m, 2H, CH_2), 1.50 (q, J = 8.0 Hz, 2H, CH_2), 0.98 (t, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 157.9, 132.3, 130.6, 125.8, 125.3, 118.1, 115.0, 109.9, 104.8, 67.8, 31.4, 19.3, 13.3; GC-Ms: m/z: 215.2.

***N*,*N*-Dimethyl-4-(pyrrol-2-yl)aniline (6a).**[12d] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.31 (br, 1H, NH), 7.37 (d, J = 8.7 Hz, 2H, Ar–H), 6.80 (s, 1H, CH). 6.77 (d, J = 8.5 Hz, 2H, Ar–H), 6.36 (s, 1H, CH), 6.28 (s, 1H, CH), 2.97 (s, 6H, N–CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 149.3, 132.9, 125.1, 125.1, 122.0, 117.5, 113.0, 109.7, 103.9, 40.6; GC-Ms: m/z: 186.2.

2-(Biphenyl-4-yl)pyrrole (7a).[12c] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.48 (br, 1H, NH), 7.62 (d, J = 8.3 Hz, 4H, Ar–H), 7.55 (d, J = 8.4 Hz, 2H, Ar–H), 7.45 (t, J = 7.6 Hz, 2H, Ar–H), 7.34 (t, J = 7.4 Hz, 1H, Ar–H), 6.90 (s, 1H, CH), 6.58 (s, 1H, CH), 6.32 (s, 1H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 140.7, 138.9, 131.8, 128.8, 127.5, 127.2, 126.8, 124.2, 118.9, 110.3, 106.2; GC-Ms: m/z: 219.1.

3-(4-(Pyrrol-2-yl)phenyl)pyridine (8a). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 9.40 (br, 1H, NH), 8.94 (s, 1H,), 8.85 (1H, d, J = 5.2 Hz), 8.58 (1H, s), 8.41 (1H, d, J = 4.6 Hz) 7.96 (1H, d, J = 8.0 Hz), 7.81 (1H, d, J = 9.2 Hz), 7.30 (2H, d, J = 4.0 Hz), 6.93 (1H, d, J = 1.9 Hz), 6.59 (1H, d, J = 1.1 Hz), 6.31 (1H, d, J = 2.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 152.5, 149.2, 147.1, 146.1, 144.7, 133.7, 133.2, 131.6, 129.4, 128.4, 123.9, 123.4, 120.4, 110.3, 107.4.

2-(Naphthalen-2-yl)pyrrole (9a).[12c] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.61 (br, 1H, NH), 7.85 (s, 1H, Ar–H), 7.84–7.78 (m, 3H, Ar–H), 7.67 (dd, J = 8.4, 1.6, 2H, Ar–H), 7.52–7.36 (m, 2H, Ar–H), 6.93 (s, 1H, CH), 6.66 (s, 1H, CH), 6.35 (s, 1H, CH). ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 133.8, 132.2, 132.1, 130.2, 128.6, 127.8, 127.7, 126.5, 125.4, 123.3, 121.1, 119.2, 110.3, 106.7; GC-Ms: m/z: 193.2.

3-Methyl-2-phenylpyrrole (10a).[22] ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.15 (br, 1H, NH), 7.46–7.32 (m, 5H, Ar–H), 7.26 (s, 1H, CH), 6.78 (s, 1H, CH), 6.16 (s, 1H, CH), 2.29 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 133.8, 128.7, 126.4, 126.0, 123.0, 117.3, 116.2, 112.2, 12.5; GC-Ms: m/z: 156.1.

Synthesis of BODIPY 14

4-Bromobenzaldehyde (0.28 mmol, 52 mg) and 2-(biphenyl-4-yl)pyrrole (**7a**) (0.558 mmol, 122 mg) were dissolved in dichloromethane (30 mL) in a round bottomed flask with a magnetic stirrer bar. The reaction mixture was stirred at room temperature for 5 minutes, then a few drops of trifluoroacetic acid were added and the reaction was stirred for another 5 minutes. The reaction was washed with water (3 × 30 mL), dried over $MgSO_4$, and the solvent was removed under reduced pressure. Purification by column chromatography on silica gel (dichloromethane–hexanes = 1 : 2) gave compound **13** as a dark red solid (240 mg, 71% yield). The intermediate **13** (0.196 mmol, 119 mg) and DDQ (0.196 mmol, 45 mg) were dissolved in dichloromethane (10 mL) in a round bottomed flask with a magnetic stirrer bar under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 30 minutes. Then *N*,*N*-diisopropylethylamine (1.97 mmol, 0.34 mL) and boron trifluoride diethyl etherate (2.36 mmol, 0.30 mL) were added at 0 °C and the mixture was stirred for 30 minutes. The reaction was washed with saturated $NaHCO_3$ (3 × 30 mL) and brine (3 × 30 mL), dried over $MgSO_4$ and the solvent was removed under reduced pressure. The residue was purified by column chromatography on silica gel (dichloromethane–hexanes = 1 : 2) to give the product as a red solid (129 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 8.00 (d, J = 8.4 Hz, 4H, Ar–H), 7.73–7.61 (m, 10H, Ar–H), 7.52–7.42 (m, 6H, Ar–H), 7.37 (d, J = 7.4 Hz, 2H, Ar–H), 6.89 (d, J = 4.4 Hz, 2H, CH), 6.72 (d, J = 4.2 Hz, 2H, CH); ^{13}C NMR (100 MHz, $CDCl_3$): δ ppm 142.4, 140.5, 136.4, 133.3, 132.0, 131.7, 131.4, 130.5, 130.0, 130.0, 129.9, 128.8, 127.6, 127.2, 127.0, 124.7, 121.2. HRMS (ESI) calculated for $[M + Na]^+$: 673.1238, found at 673.1232.

Conclusions

In summary, a practical synthesis of 2-arylpyrroles from calcium carbide and oximes was successfully developed. The reaction was carried out in wet solvent without the use of toxic metals. Moreover, the process was extended to preparing 2-arylpyrroles in a one-pot manner starting from acetophenone and hydroxylamine. The resulting aryl pyrroles prove to be excellent building blocks for NIR-BODIPY fluorophores. These novel synthetic methods provide an opportunity to establish calcium carbide as a sustainable and cost effective carbon source in modern chemical industries.

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Organocatalytic visible light induced S–S bond formation for oxidative coupling of thiols to disulfides

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ABSTRACT

In this work, we developed a visible light induced oxidative coupling of thiols into the corresponding disulfides in a process catalyzed by an inexpensive and non hazardous Rose Bengal dye. Our optimization study revealed that the use of Rose Bengal catalyst under irradiation with visible light in either 2-propanol or water at room temperature can convert a variety of thiols into their corresponding disulfides in good to excellent yields. Natural sunlight can be applied as a light source to prepare disulfide in high yield at gram-scale quantity. Our photochemical reaction can be performed in a continuous flow reactor, demonstrating a short residence time. The key benefits of this reaction include the use of metal-free, low cost Rose Bengal catalyst and practical operation (room temperature, open flask, undried solvents and simple work up procedure by extraction).

1. Introduction

Solar light is an attractive way to initiate chemical transformations as it is renewable, environmentally friendly, safe and scalable. Classically, photochemical reactions are performed under UV irradiation although this often leads to decomposition and side reactions due to its high energy. The lack of visible light absorption by most organic molecules has limited the general utility of photochemical reactions under visible light. Fortunately, a break-through discovery of photoredox catalysis by Macmillan and Yoon has made visible light sensitization possible.[1,2] The reports has drawn significant attention from the synthetic chemist communities and since then many elegant chemical transformations under visible light irradiation were reported.[3–5] Most reactions utilized metal-based photosensitizers such as ruthenium, rhenium, iron and iridium as a photoredox catalyst due to their high activity and stability.[6–10] However, high cost and high toxicity have limited their applications. On the other hands, organic dyes could serve as a promising catalyst in the field of visible light reactions because they are inexpensive, widely available through the entire visible spectrum range and have low toxicity.[11–14]

The formation of S–S bonds plays an important role in the stabilization and folding of proteins in biological systems.[15] Disulfides also serve as a protecting group for drug delivery systems.[16] In rubber and textile industry, it is the basis of the well-known vulcanizing process.[17] In particular, organic disulfides are common intermediates for organic transformations[18] and have found broad applications in pharmaceutical,[19,20] and material science.[21] Common methods for preparing disulfides include the stoichiometric or catalytic oxidation of thiols using a metal catalyst such as Fe, Pb, Ce, Mn, Co, Cr, Cu, or Al (Scheme 1).[22,23] Other commonly used stoichiometric oxidizing agents include halogen (I_2, Br_2), hydrogen peroxide, azo compounds, DDQ or sodium nitrite.[24,25] Recently, the use of purely organic stoichiometric hypervalent iodine (III) reagent[26] or enzyme catalyst such as laccase[27] to perform oxidative coupling of thiols were reported. However, except for the use of enzymes, the high toxicity and cost of the reagents combined with harsh reaction conditions, long reaction time and risk of over-oxidation represent significant disadvantages.

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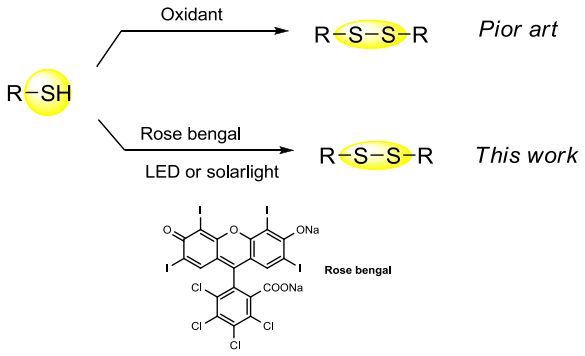


Scheme 1. Oxidation of thiols into disulfides.

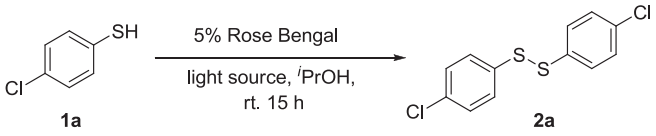
Recently, there were several emerging reports on the oxidation of thiols into disulfide mediated by visible light. In 2010, Ando first reported the use of diaryl tellurides under photosensitized conditions for thiol oxidation.[28] Later, an iron phthalocyanine immobilized on graphene was used as a photosensitizer for the conversion of thiols into disulfides.[29] More recently, Wu also demonstrated the oxidative coupling of thiols using recyclable CdSe quantum dots in the presence of $NiCl_2$ to generate disulfide and hydrogen gas.[30] However, these reports required the use of toxic metal-based catalysts or strong oxidants. Therefore, metal-free photocatalytic systems for thiol oxidation into disulfide under visible light are highly desirable. During the preparation of this manuscript, an elegant work using Eosin Y dye for oxidation of thiols to disulfides under visible-light has been reported.[31] The application of such organic dyes is less toxic comparing with the heavy metal containing catalysts. We have investigated the reaction based on a similar approach using an inexpensive organic dye, Rose Bengal as a photocatalyst and found that it is very efficient for conversion of thiols into disulfides under visible or sunlight at ambient temperature (Scheme 1). In addition, Rose Bengal is also highly water soluble, allowing the reaction to be performed in water and the catalyst can be removed by simple aqueous extraction from the organodisulfide products.

2. Results and discussion

2.1. Reaction optimization

Various Light Emitting Diodes (LEDs, 1.5 W) were used as a light source for oxidative coupling of 4-chlorothiophenol (**1a**) in the presence of 5 mol% Rose Bengal (Table 1, Fig. S1). Bearing the concept of green chemistry in mind, all tested reactions were conducted in undried 2-propanol, which is one of the preferable organic solvent choices in the pharmaceutical industries[32] at room temperature in open air for 15 h. Even though Rose Bengal has absorption maxima at around 550 nm, most of LED sources including white, blue and green are compatible with this photocatalytic reaction giving the desired disulfide product (**2a**) in 90–93% yields (Table 1, entries 1–3). We would like to point out that the starting material **1a** was completely consumed without over oxidized by-product such as sulfoxide, sulfone or sulfonic acid detected. Importantly, because no additional base or oxidant was used in the reaction, the product **2a** can simply be purified by aqueous extraction using 1M NaOH solution to remove the Rose Bengal (Fig. S2a). However, under Red LED irradiation, only 18% of **2a** was obtained (Table 1, entry 4). This is perhaps due to the low energy of the light source. Also, in the absence of light, the oxidative coupling of thiol was unable to proceed (Table 1, entry 5), suggesting that the reaction is indeed a photocatalyzed reaction. Due to the wide availability of white LED, we thus decided to use it for further studies.

Table 1
Effect of light source in photocatalytic oxidation of thiols[a]

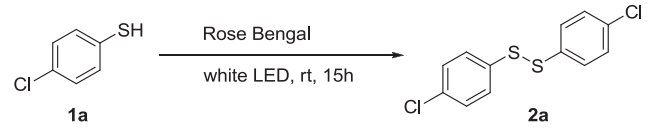


Entry	Light source	Yield(%)[b]
1	White LED	90
2	Blue LED	93
3	Green LED	93
4	Red LED	18[c]
5	—	0[d]

[a] Reaction were carried at 0.5 mmol of 1a with 5 mol% of Rose Bengal in ^{i}PrOH 10 mL.
[b] Isolated by extraction.
[c] Isolated by column chromatography.
[d] Vessel was covered with aluminum foil.

With the results of light source screening in hand, we next studied the effects of solvent and catalytic amounts of Rose Bengal for oxidation of 4-chlorothiophenol (**1a**). Acetonitrile, DMF, toluene and 2-propanol were screened as a solvent for the photocatalytic oxidation of thiols in the presence of 5 mol% of Rose Bengal (Table 2, entries 1–4). All reactions were monitored by ^{1}H NMR showing complete conversion into the corresponding disulfide **2a** after 15 h. Lowering the amount of Rose Bengal to 1 mol% resulted in incomplete reaction (Table 2, entry 5), while in the absence of catalyst, the reaction did not proceed (Table 2, entry 6). To our surprise, performing the reaction in water gave complete conversion even though the thiols **1a** was poorly soluble in water (Table 2, entry 7). These results suggested the broad solvent compatibility and high efficiency of Rose Bengal as photocatalyst for oxidation of thiols.

Table 2
Effects of solvent and amounts of Rose Bengal in photocatalytic oxidation of thiols[a]



Entry	mol%	Solvent	Conversion (%)[b]
1	5	Acetonitrile	100
2	5	DMF	100
3	5	Toluene	100
4	5	^{i}PrOH	100
5	1	^{i}PrOH	25
6	0	^{i}PrOH	0
7	5	Water	100

[a] Reaction were carried on a 0.5 mmol of **1a** with 5 mol% of Rose Bengal in 10 mL solvent.
[b] Determined by ^{1}H NMR.

Based on the above results, the ability to perform the reaction in water under open-flask conditions prompted us to investigate the reaction rate of reactions from the entries 4 and 7 (Table 2). In ^{i}PrOH under open-flask conditions required only 6 h to complete. Switching the solvent from ^{i}PrOH to water, it required a longer time required to complete the conversion (ca. 9 h, Figure 1). This is due to the formation of heterogeneous reaction mixture. Even though the longer reaction time in water system is necessary, the fact that it is the most preferable solvent system for green synthesis encouraged

us to further investigate the reactions of various substrates in both ^{i}PrOH and water).

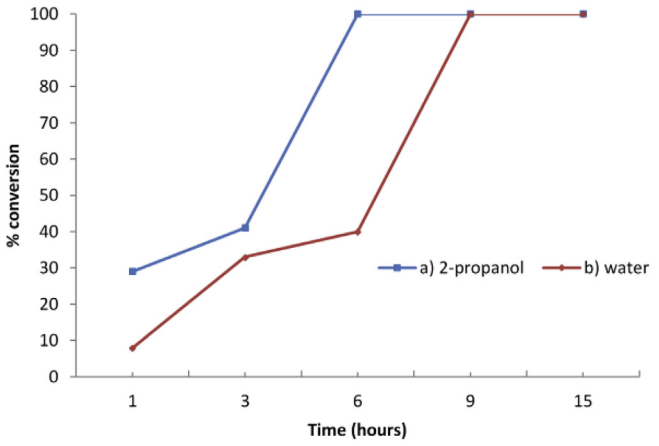
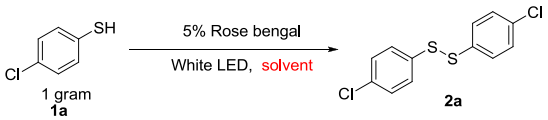


Fig. 1. Photocatalytic oxidation of thiols **1a** irradiated by white LED in a) ^{i}PrOH; b) water under open air. % Conversion was determined from ^{1}H NMR.

2.2. Scalability

To investigate scalability of the photolytic oxidation reaction, one gram-scale reactions were carried out under optimized condition using white LED in both ^{i}PrOH and water (Table 3). The monitoring by ^{1}H NMR revealed the complete consumption of thiol **1a** within 6 h in ^{i}PrOH and disulfide **2a** was isolated in excellent yield after aqueous extraction (Table 3, entry 1). The reaction time required in this reaction is similar to a small scale batch (50 mg), suggesting a high potential for industry scale-up. On the other hands, when the reaction in water was performed under one gram-scale, a longer reaction time was required (15 h) in order to convert all starting **1a** into **2a** (Table 3, entry 2). Carrying out the reaction in water, the disulfide **2a** was also obtained in good yield after extraction with NaOH.

Table 3
Gram-scale photocatalytic oxidation of thiol[a]



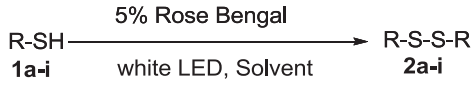
Entry	Solvent	t(h)	Conversion(%)[b]	Yields(%)[c]
1	^{i}PrOH	6	100	91
2	Water	15	100	89

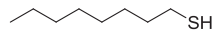
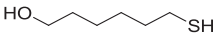
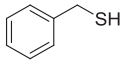
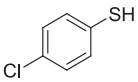
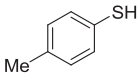
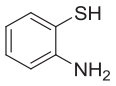
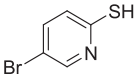
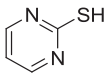
[a] Reaction conditions: thiol (6.91 mmol, 1.0 g), Rose Bengal (5 mol %) in solvent 50 mL under 1.5 W white LED.
[b] Determined by ^{1}H NMR.
[c] Isolated yield by extraction.

2.3. Functional group compatibility

With the optimized conditions in hand, we explored the generality and scope of this reaction by using a variety of aliphatic, aromatic, and heteroaromatic thiols. Eight thiols were subjected to the optimized oxidation conditions using either 2-propanol or water as the solvent (Table 3). In 2-propanol, the oxidative coupling of all thiols proceeded smoothly and the desired disulfides **2b**–**i** were isolated in good to excellent yields (Table 4). The reactions of aromatic thiols especially for nitrogen-containing heteroaromatic thiols (**1g**–**1i**) generally required shorter reaction times. Based on these results, the reaction mechanism might involve the formation of thiol radical. Therefore, the faster conversion observed in aromatic substrate is perhaps governed by the stability of the thiol radical intermediate whereby arylthio radicals are more stable than alkylthio radicals.[33] To demonstrate the ability to perform the reaction in water, **1a**, **1c**, **1e** and **1g** were selected as representative substrates for the present photocatalytic oxidative coupling reaction in water. In all cases, longer irradiation time were required comparing to ^{i}PrOH, but good to high yields of disulfides **2a**, **2c**, **2e** and **2g** (81–92%) were obtained (Table 4, entries 2, 4, 5 and 7). TLC monitoring suggested that, in all cases, the starting thiols were completely consumed without other side-products formation. Therefore, the product can be purified simply by extraction with NaOH to remove the Rose Bengal catalyst. This reaction is thus not only highly functional group tolerant but also shows high atom economy and generates low waste, making it applicable for modern green organic reactions.

Table 4
Photocatalytic oxidation of various thiols[a]



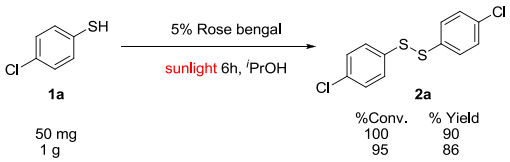
Entry	Thiols	T (h)	Yields (%)[b]
1	**1b** 	15	94
2	**1c** 	15 (24)	89 (84)
3	**1d** 	15	77[c]
4	**1a** 	6 (9)	90 (81)
5	**1e** 	6 (9)	86 (92)
6	**1f** 	15	75[c]
7	**1g** 	3 (6)	92 (88)
8	**1h** 	3	86
9	**1i** 	3	81

[a] Reaction conditions: thiol (0.5 mmol), Rose Bengal (5 mol %) in ^{i}PrOH 10 mL under 1.5 W white LED; numbers in parentheses are the yields and reaction time when carried the reaction in water.
[b] Isolated yield by extraction.
[c] Isolated by silica gel chromatography.

2.4. Reaction under sunlight

Nowadays, a foremost scientific challenge is to harness the energy from the sun. Therefore, we attempted our reaction in open round-bottomed flask under sunlight (Scheme 2, Fig. S2a). When carrying out the reaction in 50 mg scale, the thiols **1a** were totally consumed within 6 h and 90% of the disulfide **2a** was isolated.

Moreover, when 1 g of the thiol **1a** was subjected to the above reaction condition (6 h), small starting material remained (ca. 5%) and 86% of disulfide **2a** was isolated after extraction. These results suggested the possibility for a large scale synthesis of disulfide using Rose Bengal as a photocatalyst under natural sunlight.

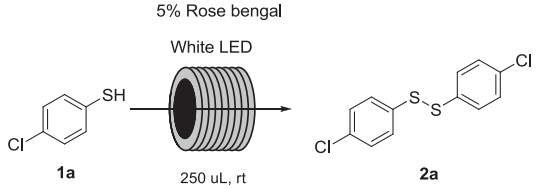


Scheme 2. Photocatalytic oxidation of thiol under sunlight.

2.5. Continuous flow reaction

It is well-known that in large scale-batch reactions, the efficiency of the photocatalyst will decrease because the penetration ability of light decreases exponentially with the path length according to the Beer–Lambert law. In order to overcome this problem, many research groups demonstrated the use of continuous flow reactors mediated by visible-light-active photoredox catalysts to achieve high surface area and minimal path length.[34–36] Notably, flow chemistry also provides several advantages in the aspect of green chemistry such as safety, low waste generation, reducing solvent usage and the possibility of a continuous 24/7 production.[37,38] We used a commercial continuous microflow reactor with a 250 μL chip assembled with 35 white LEDs to test our reaction (see Supplementary Fig. S3). To further understand of this transformation, we conducted a systematic study of two reaction variables: flow rate and reaction concentration (Table 5). Performing the oxidation of **1a** under dilute condition (0.01 M) afforded a complete conversion within 5 min of residence time (Table 5, entries 1 and 2). However, when the reaction concentration was the same as batch reaction (0.05 M, Table 5, entries 3 and 4), only 39% conversion were obtained at 5 min residence time. Gratifyingly, a complete conversion was observed at 30 min residence time. Even though the concentration of the thiol crucially affected the reaction efficiency, the present catalytic visible-light reaction of thiol into disulfide in a flow reactor can lower the reaction time when compared to the batch reaction.

Table 5
Photocatalytic oxidation of thiols using a micro flow reactor[a]

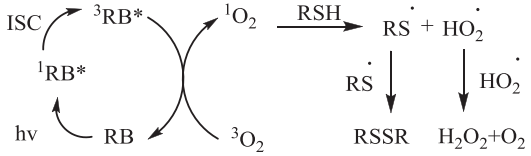


Entry	Conc (M)	Flow rate (μL/min)	Residence time (min)	Conversion (%)[b]
1	0.01	8.3	30	100
2	0.01	50	5	100
3	0.05	8.3	30	100
4	0.05	50	5	39

[a] Reaction were performed using microflow reactor from Syriss FRXTM with 250 μL chip equipped with a panel of 24 small white LEDs (1.5 W, Fig. S3).
[b] Determined by ^{1}H NMR.

2.6. Proposed mechanism

A plausible mechanism is outlined in Scheme 3. Based on previous work on the use of Rose Bengal as a photocatalyst, we hypothesize that the reaction involves the formation of singlet oxygen and thiol radical.[33,39] The singlet excited state of rose Bengal (^{1}RB*) is converted into a triplet state (^{3}RB*) via intersystem crossing (ISC). This phenomenon transfers the energy to triplet oxygen from air to generate singlet oxygen, which later became an active oxidizing agent. Then singlet oxygen oxidizes thiol into the corresponding thiol radical which undergoes homocoupling to provide the disulfide. The faster conversion of aromatic than aliphatic thiol substrates (Table 4) is consistent with the proposed reaction mechanism.



Scheme 3. A plausible mechanism for photocatalytic oxidation of thiols using Rose Bengal.

3. Conclusion

In summary, we have developed a photocatalytic method using Rose Bengal dye as a photocatalyst under visible light for oxidative coupling of thiols into disulfides. The method offers high selectivity, high functional group compatibility and produces disulfides in high yields under mild reaction conditions. The reactions are operationally simple and can be performed at room temperature in an open air system. The reaction can be performed in environmentally benign solvents such as water or isopropanol. Importantly, the use of Rose Bengal as a photocatalyst eliminates the need for additional oxidant other than air, and thus simplifies the work up.

4. Experimental section

4.1. General information

All chemicals were obtained from commercial suppliers (Sigma Aldrich), Fluka (Switzerland) or Merck (Germany) and were used without further purification. All solvents were used directly without drying. Analytical thin-layer chromatography (TLC) was performed on Kieselgel F254 pre-coated plastic TLC plates from EM Science. Visualization was performed with a 254 nm ultraviolet lamp. Column chromatography was performed by using Merck and silica gel (60,230–400 mesh) from ICN Silitech. The ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury 400 or Bruker Avance 400 for ^{1}H (400 MHz) and Bruker Avance 400 for ^{13}C (100 MHz) in $CDCl_3$ or CD_3OD solution. White, Blue, Green and Red LED reactors were made from a 250 mL beaker lined with a commercial belt LED (1.5 W×228). Flow reaction was performed in a Microflow reactor (Syriss, FRXTM Model) with Asia microreactor chip (volume 250 μL). Low-resolution mass spectra was obtained from triple quadrupole GC/MS Agilent technology. Fourier transform infrared spectra were acquired on Nicolet 6700 FTIR spectrometer equipped with a mercury-cadmium telluride (MCT) detector (Nicolet, USA).

4.2. General procedure A for synthesis of disulfides in ^{i}PrOH

To a mixture of thiol (0.35 mmol) in ^{i}PrOH in a 10 mL vial, Rose Bengal (0.05 equiv) were added and the reaction mixture was

stirred at room temperature under white LED irradiation. The reaction mixture was quenched by addition of saturated aqueous NaOH (10 mL), extracted with Et_2O (3×10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give the desired product.

4.3. General procedure B for synthesis of disulfides in water

To a mixture of thiol (0.35 mmol) in water in 10 mL vial, Rose Bengal (0.05 equiv) were added and the reaction mixture was stirred at room temperature under white LED irradiation. The reaction mixture was quenched by saturated NaOH (10 mL), extracted with Et_2O (3×10 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give the desired product.

4.4. General procedure C for synthesis of disulfides in gram scale (Table 3)

To a 100 mL of round bottom flask, 4-chlorothiophenol (1.00 g, 6.91 mmol) was dissolved in ^{i}PrOH (50 mL) and Rose Bengal (0.05 equiv 0.40 g, 0.40 mmol) were added and the reaction mixture was stirred at room temperature under white LED irradiation for 6 h until 4-chlorothiophenol disappeared as detected by TLC. Then the reaction was quenched by saturated NaOH (100 mL). The product was extracted with Et_2O (5×30 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give the desired product **2a** (0.912 g, 3.19 mmol, 91%).

4.5. General procedure D for synthesis of disulfides in micro flow reaction (Table 5)

To a solution of 4-chlorothiophenol 144 mg (1.00 mmol) in 100 mL ^{i}PrOH (0.01 M) was added Rose Bengal (0.05 equiv 0.05 mmol, 51 mg) and the mixture was stirred for 30 s in 250 mL Erlenmeyer flask). At the same time the Syriss flow reactor was equipped with Asia microreactor chip (250 μL volume, 1 min residence time at 250 μL/min flow rate) and a panel of small White LEDs (1.5 W × 35) were attached in front of the chip (Fig. S3). The system was first primed with ^{i}PrOH. Then a flow rate of 8.3 μL/min (30 min residence time) were selected and the process were started. At that point, inlet tube was switched from the solvent reservoir to the 250 mL flask containing the reaction mixture. The first 5 mL of reaction mixture was collected from the outlet. The mixture was added saturated NaOH (5 mL) and extracted with Et_2O (3×5 mL) and solvent was evaporated under reduced pressure. The reaction conversion was determined using ^{1}H NMR.

*4.5.1. 1,2-Bis(4-chlorophenyl)disulfane (**2a**).*[40] [CAS: 1142-19-4]: Synthesized according to procedure A using 4-chlorothiophenol (50 mg, 0.345 mmol), Rose Bengal (18 mg, 0.018 mmol) in ^{i}PrOH (10 mL) for 6 h to afford **2a** (45.0 mg, 0.159 mmol, 90%) as a yellow solid.

Synthesized according to procedure B using 4-chlorothiophenol (50 mg, 0.345 mmol), Rose Bengal (18 mg, 0.018 mmol) in water (10 mL) 9 h to afford **2a** (40.6 mg, 0.141 mmol, 81%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.40 (d, *J*=8.7 Hz, 4H), 7.27 (d, *J*=8.7 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 135.1, 133.6, 129.3, 129.3; GC–MS: *m*/*z*: 285.8; IR (ATR, cm^{-1}): 3081, 2920, 1473, 1387.

*4.5.2. 1,2-Dioctyldisulfane (**2b**).*[41] [CAS: 822-27-5]: Synthesized according to procedure A using 1-octanethiol (50 mg, 0.342 mmol), Rose Bengal (18 mg, 0.018 mmol) in ^{i}PrOH (10 mL) for 15 h to afford **2b** (47.1 mg, 0.161 mmol, 94%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 400 MHz): 2.67 (m, 4H), 1.69 (m, 4H), 1.29 (m, 20H), 0.9 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz):δ 39.3, 31.8, 29.2, 28.6, 22.6, 14.1; GC–MS: *m*/*z*: 289.9; IR (ATR, cm^{-1}): 2955, 2922, 2852, 1452.

*4.5.3. 6,6-Disulfanediyldihexan-1-ol (**2c**).*[42] [CAS: 80901-86-6]: Synthesized according to procedure A using 6-mercapto-1-hexanol (50 mg, 0.372 mmol), Rose Bengal (20 mg, 0.020 mmol) in ^{i}PrOH (10 mL) for 15 h to afford **2c** (44.1 mg, 0.165 mmol, 89%) as a yellow oil.

Synthesized according to procedure B using 6-mercapto-1-hexanol (50 mg, 0.372 mmol), Rose Bengal (20 mg, 0.020 mmol) in water (10 mL) for 24 h to afford **2c** (42.6 mg, 0.159 mmol, 84%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=3.64 (t, *J*=6.6 Hz, 4H), 2.69 (m, 4H), 1.70 (m, 4H), 1.56 (m, 4H), 1.41 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 62.8, 39.0, 32.6, 29.1, 28.2, 25.4; GC–MS: *m*/*z*: 266.0; IR (ATR, cm^{-1}): 3326, 2926, 2854, 1046.

*4.5.4. 1,2-Dibenzyldisulfane (**2d**).*[28] [CAS: 150-60-7]: Synthesized according to procedure A using benzyl mercaptan (50 mg, 0.402 mmol), Rose Bengal (20 mg, 0.020 mmol) in ^{i}PrOH (10 mL) for 15 h to afford **2d** (38.5 mg, 0.155 mmol, 77%) as white solid. ^{1}H NMR ($CDCl_3$, 400 MHz):δ 7.28 (m, 10H), 3.63 (s, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.2, 129.3, 128.5, 127.4, 43.3; GC–MS: *m*/*z*: 246.0; IR (ATR, cm^{-1}): 3064, 3091, 2927, 2847, 1491, 1459.

*4.5.5. 1,2-Di-p-tolyldisulfane (**2e**).*[28] [CAS: 103-19-5]: Synthesized according to procedure A using 4-methyl thiophenol (50 mg, 0.402 mmol), Rose Bengal (20 mg, 0.020 mmol) in ^{i}PrOH (10 mL) for 6 h to afford **2e** (42.7, 0.173 mmol, 86%) as a yellow solid.

Synthesized according to procedure B using 4-methyl thiophenol (50 mg, 0.402 mmol), Rose Bengal (20 mg, 0.020 mmol) in water (10 mL) for 9 h to afford **2e** (45.7 mg, 0.185 mmol, 92%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.36 (d, *J*=8.4 Hz, 4H), 7.07 (d, *J*=8.4 Hz, 4H), 2.33 (s, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.4, 133.9, 129.7, 128.5, 21.1; GC–MS: *m*/*z*: 245.8; IR (ATR, cm^{-1}): 3013, 2917, 2866, 1489.

*4.5.6. 2,2-Disulfanediyldianiline (**2f**).*[43] [CAS: 1141-88-4]: Synthesized according to procedure A using 2-aminothiophenol (50 mg, 0.399 mmol), Rose Bengal (20 mg, 0.020 mmol) in ^{i}PrOH (10 mL) for 16 h to afford **2f** (37.5 mg, 0.150 mmol, 75%) as a yellow solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ=7.18 (t, *J*=11.0 Hz, 4H), 6.75 (m, 2H), 6.61 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 148.6, 136.8, 131.6, 118.8, 118.3, 115.3; GC–MS: *m*/*z*: 247.9; IR (ATR, cm^{-1}): 3358, 2915, 2845, 1603, 1471.

*4.5.7. 1,2-Di(pyridine-2-yl)disulfane (**2g**).*[28] [CAS: 2127-03-9]: Synthesized according to procedure A using 2-mercaptopyridine (50 mg, 0.450 mmol), Rose Bengal (20 mg, 0.020 mmol) in ^{i}PrOH (10 mL) for 3 h to afford **2g** (46.2 mg, 0.202 mmol, 92%) as a yellow oil.

Synthesized according to procedure B using 2-mercaptopyridine (50 mg, 0.450 mmol), Rose Bengal (20 mg, 0.020 mmol) in water (10 mL) 6 h to afford **2g** (43.8 mg, 0.199 mmol, 88%) as a yellow oil.

^{1}H NMR ($CDCl_3$, 400 MHz): δ=8.47 (d, *J*=8.1 Hz, 2H), 7.63 (m, 4H), 7.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 158.9, 149.6, 137.4, 121.2, 119.9; GC–MS: *m*/*z*: 219.8; IR (ATR, cm^{-1}): 3046, 2987, 1571, 1412.

*4.5.8. 1,2-Bis(5-bromopyridin-2-yl)disulfane (**2h**).*[44] [CAS: 872273-36-4]: Synthesized according to procedure A using 5-bromopyridine-2-thiol (50 mg, 0.263 mmol), Rose Bengal (13 mg, 0.013 mmol) in ^{i}PrOH (10 mL) for 3 h to afford **2h** (43.0 mg, 0.110 mmol, 86%) as a white solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.55 (d, *J*=2.4 Hz, 2H), 7.77 (dd, *J*=8.5, 2.4 Hz, 2H), 7.50 (d, *J*=8.5 Hz, 2H); ^{13}C NMR ($CDCl_3$,

100 MHz): δ=157.7, 150.0, 139.8, 121.0, 118.4; GC–MS: *m*/*z*: 377.7; IR (ATR, cm^{-1}): 3041, 2959, 2922, 2852, 1433.

*4.5.9. 1,2-Di(pyrimidin-2-yl)disulfane (**2i**).*[45] [CAS: 15718-46-4]: Synthesized according to procedure A using 2-mercaptopyrimidine (50 mg, 0.445 mmol), Rose Bengal (20 mg, 0.02 mmol) in ^{i}PrOH (10.0 mL) for 3 h to afford **2i** (40.5 mg, 0.181 mmol, 81%) as a yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.59 (d, *J*=4.8 Hz, 4H), 7.13 (t, *J*=4.8 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.8, 158.0, 118.1; GC–MS: *m*/*z*: 221.8; IR (ATR, cm^{-1}): 3115, 3029, 2961, 2919, 1547.

Acknowledgments

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Supplementary data

Supplementary data (Experimental setup and images of ^{1}H, ^{13}C NMR and Mass spectrum of all disulfides are available in the Supplementary data.) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2015.12.036.

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New turn-on fluorescent and colorimetric probe for cyanide detection based on BODIPY-salicylaldehyde and its application in cell imaging

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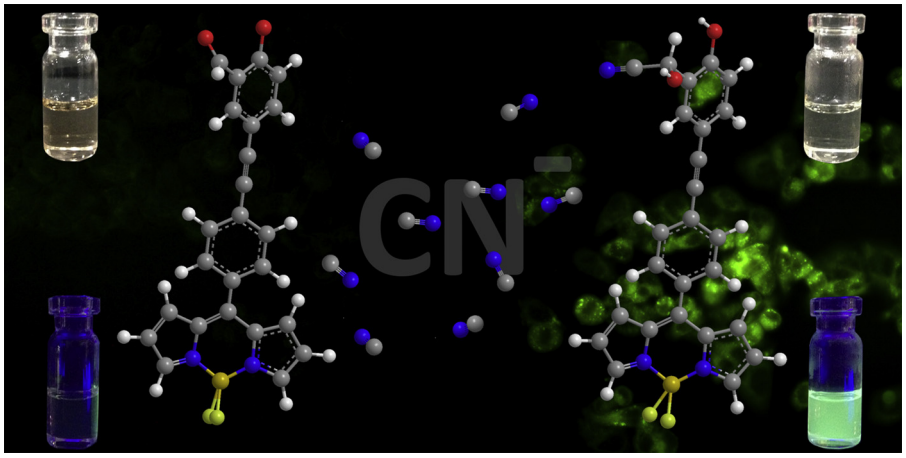
HIGHLIGHTS

- A novel salicylaldehyde-BODIPY fluorescent sensor is prepared.
- The sensor shows dual colorimetric & turn-on fluorescence response to cyanide ion.
- Detection limit is 0.88 μM (below WHO standard for drinking water).
- It is effective for cyanide detection an in vitro cellular system.

GRAPHICAL ABSTRACT



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ABSTRACT

Development of cyanide sensor is important as the anion is harmful to human health and the environment. Herein, a new colorimetric and fluorescent probe **GSB** based on boron dipyrrole-methene (BODIPY) containing salicylaldehyde group for cyanide detection has been reported. **GSB** undergoes exclusive colorimetric change from orange to colorless and exhibits selective fluorescence turn-on at 504 nm upon the addition of cyanide. Other 13 anions give almost no interference under physiological condition. Detection limit of the new cyanide-sensing **GSB** is 0.88 μM, which is below World Health Organization (WHO) recommended level in drinking water. A calculation by density functional theory (DFT) shows suppression of photoinduced electron transfer (PET) mechanism along with the interruption of π-conjugation between salicylaldehyde and BODIPY core by cyanide anion. Cell imaging studies demonstrated that **GSB** is compatible and capable of sensing cyanide anion in living cells.

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1. Introduction

In recent years, the design and synthesis of anion receptors have played an important role in advancement of chemical and biochemical analysis [1–3]. Among the analytes of interest, cyanide ion is one of the most concerned due to its high toxicity to the environment, animals and humans [4]. Because of the widespread use of cyanide in industry, risk of contamination is high. Uptake of cyanide into the body affects visual, vascular, metabolic functions and the nervous systems. Only 0.5–3.5 mg of cyanide per kilogram of body weight can cause death in humans [5,6]. Traditional methods for cyanide detection, namely potentiometry and titration, are laborious and time consuming [7–9]. Thus, a sensitive and selective sensing system for rapid detection of cyanide contamination is needed.

Recently, development of fluorescence and colorimetric sensors for highly sensitive and selective naked eyes detection has gained much attention due to their user-friendly nature suitable for on-site analysis, such as simple operation, portability, versatile adaptation and low cost [10–13]. Among fluorescent probes, borondipyrromethene (BODIPY) has unique advantages such as high fluorescence quantum yield, narrow emission bandwidth, large molar absorptivity, high photostability and tunable fluorescence characteristic [14–17]. Fluorescent BODIPY has been extensively developed for metal ion sensing and fluorescent cell imaging, but there is little development in anion detection [11,18–29]. Design of cyanide fluorescent probes generally relies on the nucleophilic attack of cyanide anion on the electrophilic functional group such as dicyano-vinyl [30–35], aldehyde [36–40], indolium [41–47] and trifluoroacety group [48–50], causing changes in π conjugated system and thus the fluorescent properties. This allows high sensitivity and selectivity for cyanide detection. However, there are several drawbacks such as narrow pH working range, low sensing ability in aqueous solution, inability to perform cellular imaging, lack of colorimetric change and creation of turn-off instead of turn-on fluorescent. Therefore, development of a colorimetric and turn-on fluorescence chemosensor for cyanide detection with high sensitivity and cell penetrating ability would be highly desirable. Along this line, we herein report a novel green fluorescent salicylaldehyde-BODIPY (**GSB** in Fig. 1) as a highly specific and sensitive colorimetric and fluorescent sensor for cyanide anion. The salicylaldehyde group was incorporated via CC triple bond to BODIPY as a cyanide receptor. The aldehyde moiety acts as an electron withdrawing group while the hydroxyl moiety acts as an electron donating group, causing fluorescence weakening by intramolecular charge transfer (ICT). Nucleophilic attack by cyanide anion at the aldehyde group stops the ICT process, thus creating the turn-on fluorescent signal. The salicylaldehyde moiety not only serves as the probe for cyanide anion but also facilitates the photoinduced electron transfer (PET) to the BODIPY core and weakens the fluorescence intensity of the initial fluorophore. This provides a strategy to construct a turn-on fluorescent probe by the PET initially blocking the emission from the BODIPY core. Furthermore, to show the role of BODIPY and salicylaldehyde units, a simple phenyleneethynylene containing salicylaldehyde (**PE**) and BODIPY probe without salicylaldehyde group (**I-BOD**) were synthesized as comparing models.

2. Experimental

2.1. Apparatus, reagents and chemicals

All reagents were purchased from Sigma-Aldrich, Fluka® (Switzerland) or Merck® (Germany) and used without further purification. Analytical thin-layer chromatography (TLC) was performed on Kieselgel F-254 pre-coated plastic TLC plates from EM Science. Visualization was performed under a 254 nm ultraviolet lamp. Column chromatography was carried out with silica gel (60, 230–400 mesh) from ICN Silitech.

2.2. Analytical instruments

The ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury NMR spectrometer operating at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei (Varian, USA). Mass spectra were recorded on a Microflex MALDI-TOF mass spectrometer (Bruker Daltonics) using doubly recrystallized α-cyano-4-hydroxy cinnamic acid (CCA) and dithranol as a matrix. The absorption spectra were recorded by a Varian Cary 50 UV–vis spectrophotometer. The fluorescence spectra were obtained from a Varian Cary Eclipse spectrofluorometer.

HepG2 culture-HepG2 cells were maintained in RPMI 1640 (Hyclone, Logan, UT, USA) supplemented with 10% (v/v) fetal bovine serum (Hyclone), 1% (w/v) sodium pyruvate (Hyclone), 1% (w/v) HEPES (Hyclone), penicillin and streptomycin (M&H Manufacturing Co. Ltd., Bangkok, Thailand). Cultures were maintained at 37 °C under a humidified atmosphere containing 5% CO_2. The florescent images were acquired by Olympus DP71 microscope equipped with a digital camera with an objective lens ×40.

2.3. Synthesis of *PE*, *I-BOD* and *GSB*

2.3.1. 3,5-Diiodosalicylaldehyde (*2*)

CAS Registry Number: 2631-77-8: To a solution of iodine (38.10 g, 150.06 mmol) in a 100 mL of pyridine and dioxane (1:1) was added salicylaldehyde (5.24 mL, 50.86 mmol) at 0 °C and kept stirring for overnight at room temperature. The reaction mixture was diluted with water, extracted with CH_2Cl_2 (3 × 20 mL), washed with saturated $Na_2S_2O_3$ (3 × 30 mL) and concentrated under reduced pressure. The crude product was recrystallized by CH_2Cl_2 to give **2** as yellow solid (5.18 g, 28% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 11.75 (s, 1H), 9.69 (s, 1H), 8.31 (s, 1H), 7.84 (s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 194.77, 160.04, 152.82, 142.16, 121.84, 87.37, 81.39.

2.3.2. 2-Hydroxy-3,5-bis(phenylethynyl)benzaldehyde (*PE*)

25 mL of round bottom flask was charged with 3,5-diiodosalicylaldehyde (100.0 mg, 0.264 mmol), $Pd(PPh_3)_2Cl_2$ (3.30 mg, 0.013 mmol), CuI (5.0 mg, 0.026 mmol) and PPh_3 (6.90 mg, 0.026 mmol) in nitrogen atmosphere. Dried THF (5 mL) was added at room temperature followed by TEA (2.5 mL) and phenylacetylene (**3**) (0.086 mL, 0.780 mmol). The mixture was kept stirred for overnight and concentrated under reduced pressure. The crude product was then purified by silica gel column chromatography (10% EtOAc:hexane) to give **PE** as yellow solid (37.3 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.56 (s, 1H), 7.98 (d, J = 7.4 Hz, 2H), 7.93 (d, J = 7.2 Hz, 2H), 7.56 (d, J = 3.3 Hz, 2H), 7.50 (t, J = 7.4 Hz, 2H), 7.43 (d, J = 7.3 Hz, 1H), 7.41–7.34 (m, 3H), 7.09 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 187.45, 158.33, 153.57, 131.66, 131.18, 129.50, 128.94, 128.45, 125.24, 123.02, 120.88, 118.73, 100.48, 89.26, 88.40. IR(ATR): 3356, 3073, 2843, 2160, 1686 cm^{-1}. HRMS m/z Calcd. For $C_{23}H_{14}O_2$ $[M+Na]^+$ 345.0891; Found 345.0897.

2.3.3. *I-BOD*

4-Iodobenzaldehyde (1.00 g, 4.31 mmol), pyrrole (0.58 g, 8.620 mmol) were dissolved in dried CH_2Cl_2 (40 mL). Trifluoroacetic acid (TFA) (2 drops) was added dropwise and the reaction was kept stirring for 10 min at room temperature. The reaction mixture was concentrated under reduced pressure, redissolved in CH_2Cl_2 (30 mL), washed with water (3 × 30 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure.

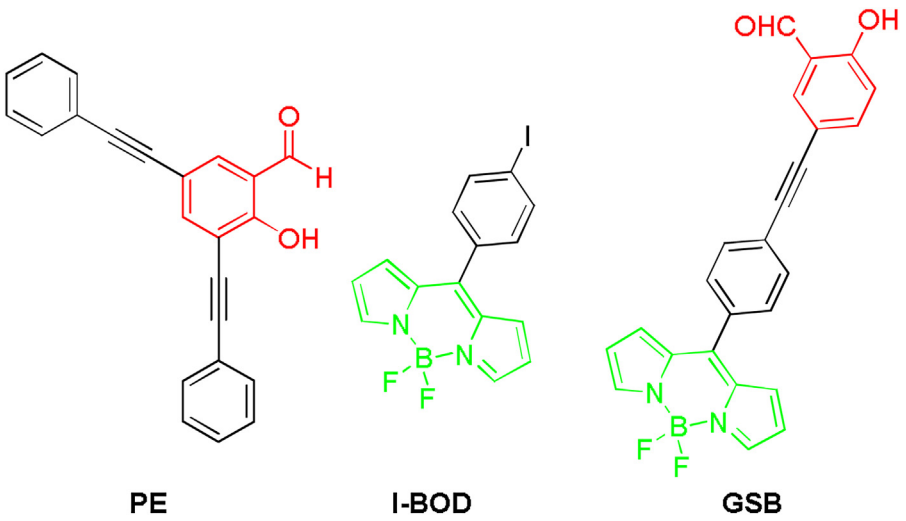


Fig. 1. Structure of **PE**, **I-BOD** and **GSB**.

The crude product was purified by silica gel column chromatography (30% CH_2Cl_2:hexane) to give the dipyrrole intermediate (0.39 g, 1.135 mmol). To a solution of crude dipyrrole intermediate (0.39 g, 1.135 mmol) in dried CH_2Cl_2 (20 mL), 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (0.26 g, 1.135 mmol) was added at 0 °C on the ice bath followed by *N*,*N*-diisopropylethylamine (1.03 g, 8.000 mmol) and boron trifluoride diethyl etherate (1.62 g, 11.420 mmol) and the reaction was kept stirred for 30 miniutes. The reaction was quenched by saturated $NaHCO_3$ (30 mL), extracted with CH_2Cl_2 (3 × 30 mL), and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (30% CH_2Cl_2 in hexane) to give **I-BOD** as orange solid (570 mg, 38% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.23 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 3.4 Hz, 1H), 6.49 (d, J = 2.3 Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$): δ ppm 145.89, 144.57, 137.77, 134.64, 133.21, 131.87, 131.30, 118.80, 97.44. IR(ATR): 3139, 3102, 1563, 1529 cm^{-1}. HRMS *m*/*z* Calcd. For $C_{15}H_{10}BF_2IN_2$ $[M+Na]^+$ 416.9847; Found 416.9849.

2.3.4. 5-Ethynyl-2-hydroxybenzaldehyde (*4*)

CAS Registry Number: 252771-08-7: A mixture of salicylaldehyde (5.00 g, 0.041 mol), acetic acid (3.00 g, 0.05 mol) and iodine monochloride (8.12 g, 0.05 mol) at room temperature was stirred for 18 h. The reaction was quenched by water (30 mL), extracted with CH_2Cl_2 (3 × 30 mL), washed with saturated $NaHCO_3$ (2 × 30 mL) and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel column chromatography (30% CH_2Cl_2:hexane) to provide the product, 2-hydroxy-5-iodobenzaldehyde **3** in (2.72 g, 27%) as white solid. (CAS Registry Number: 38170-02-4): ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.93 (d, J = 1.0 Hz, 1H), 9.81 (d, J = 0.7 Hz, 1H), 7.83 (d, J = 2.0 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 6.78 (d, J = 8.8 Hz, 1H).

To a solution of **3** (1.00 g, 4.03 mmol), bis(triphenylphosphine)palladium(II)dichloride (85.0 mg, 0.121 mmol), CuI (23.0 mg, 0.121 mmol), PPh_3 (21.3 mg, 0.081 mmol) and trimethylsilylacetylene (594.0 mg, 6.05 mmol) in THF (30 mL), TEA (5 mL) was added slowly at room temperature under nitrogen atmosphere and the reaction was kept stirring for additional 18 h. After removal of solvent under reduced pressure, the crude product was purified by column chromatography on silica gel to give 2-hydroxy-5-((trimethylsilyl)ethynyl)benzaldehyde as a white solid (864.0 mg, 98%): ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.85 (s, 1H), 9.83 (s, 1H), 7.68 (s, 1H), 7.58 (d, J = 6.8 Hz, 1H), 6.92 (d, J = 8.6 Hz, 1H), 0.23 (s, 9H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 196.08, 161.63, 140.22, 137.43, 120.46, 118.05, 115.25, 103.24, 93.92, 0.00. To a solution of 2-hydroxy-5-((trimethylsilyl)ethynyl)benzaldehyde (0.85 g, 2.910 mmol) in 45 mL of CH_2Cl_2/MeOH mixture (2:1), K_2CO_3 (1.40 g, 17.46 mmol) were slowly added in at room temperature and the reaction was kept stirring for 18 h. The reaction was quenched by water (30 mL), dried over anhydrous $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (30% CH_2Cl_2:hexane) to give **4** as white solid (308.0 mg, 54% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.12 (s, 1H), 9.85 (s, 1H), 7.70 (s, 1H), 7.61 (d, J = 8.6 Hz, 1H), 6.94 (d, J = 8.4 Hz, 13H), 3.02 (s, 12H), 1.63-1.59 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 195.92, 161.78, 140.19, 137.50, 120.42, 118.14, 114.02, 81.88, 77.32. IR(ATR): 3270, 2750, 2849, 2149, 1660 cm^{-1}.

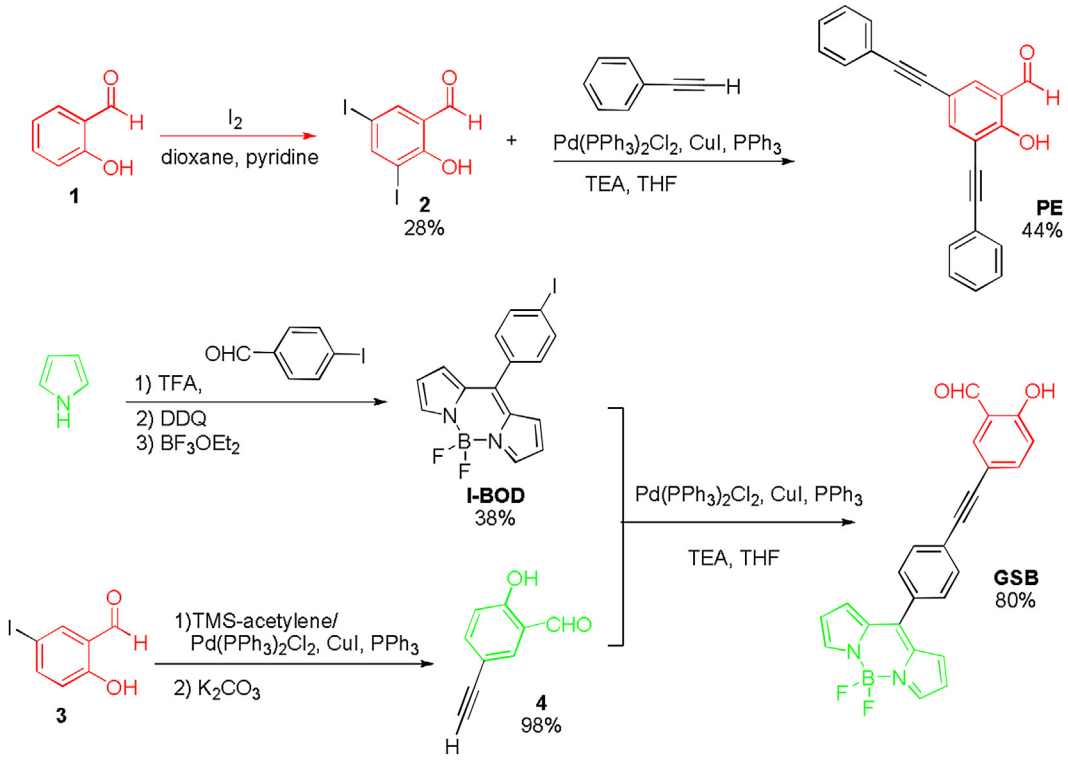
2.3.5. GSB

A mixture of **I-BOD** (54.00 mg, 0.137 mmol), 5-ethynyl-2-hydroxybenzaldehyde (**4**) (40.0 mg, 0.274 mmol), bis(triphenylphosphine)palladium(II) dichloride (14.0 mg, 0.020 mmol), CuI (3.81 mg, 0.020 mmol) and PPh_3 (2.9 mg, 0.011 mmol) were dissolved in 18 mL of TEA/THF mixture (1:5) (3 mL) and stirred at ambient temperature for 18 h. The reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (30 mL), washed with saturated NH_4Cl (3 × 30 mL), water (3 × 30 mL), dried with $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (30% CH_2Cl_2:hexane) to give **GSB** as dark green solid (45 mg, 80% yield): ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.17 (s, 1H), 9.91 (s, 1H), 7.94 (s, 2H), 7.80 (s, 2H), 7.74–7.51 (m, 7H), 7.01 (d, J = 8.3 Hz, 1H), 6.93 (s, 2H), 6.55 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ ppm 195.97, 161.84, 146.32, 144.41, 139.86, 137.09, 134.74, 133.62, 131.47, 131.38, 130.60, 125.86, 120.61, 118.73, 118.38, 114.62, 90.44, 87.93. IR(ATR): 3126, 2758, 2849, 2207, 1657, 1556 cm^{-1}. HRMS *m*/*z* Calcd. For $C_{24}H_{15}BF_2N_2O_2$ $[M+Na]^+$ 435.1092; Found 435.1086.

3. Results and discussion

3.1. Preparation of *PE*, *I-BOD* and *GSB*

The synthetic routes for **PE** and **I-BOD** as well as target **GSB** are outlined in Scheme 1. The **PE** probe was successfully prepared by the Sonogashira cross coupling reaction between 3,5-diiodosalicylaldehyde (**2**) with phenylacetylene in the presence of



Scheme 1. Synthesis of **PE**, **I-BOD** and **GSB**.

Table 1
Photophysical properties of **PE1**, **I-BOD** and **GSB** in 90% DMSO/Tris buffer pH 7.4.

Compounds	Color in visible light	Color in fluorescent black light	λ_{ab} (nm)	λ_{em} (nm)	$\varepsilon \times 10^4$ ($cm^{-1}\,M^{-1}$)	(Φ_F) (%)
PE			301,350	450	4.44	N/A
I-BOD			504	526	4.80	5
GSB			504	529	4.44	1

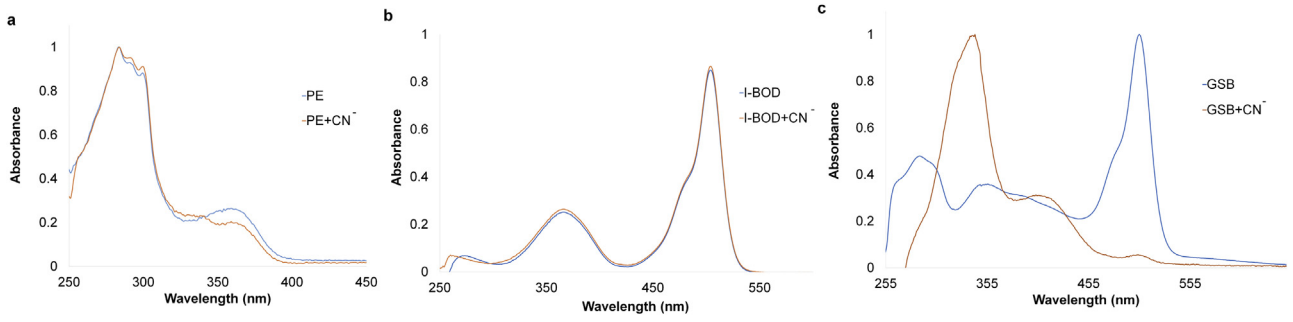


Fig. 2. The absorption of (a) **PE** (b) **I-BOD** and (c) **GSB** at 10 μM before and after addition of CN^- (1 mM) in 90% DMSO/Tris buffer pH 7.4 measured after 60 min of mixing.

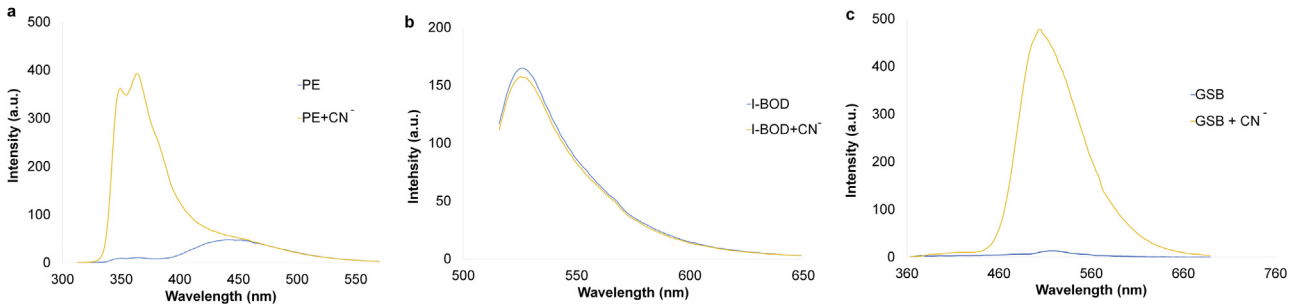


Fig. 3. The emission of (a) **PE** (λ_{ex} = 301 nm), (b) **I-BOD** (λ_{ex} = 504 nm) and (c) **GSB** (λ_{ex} = 350 nm) at 10 μM in 90% DMSO/Tris buffer pH 7.4 before and after addition of CN^-.

$Pd(PPh_3)_4$/CuI in THF as the solvent to give **PE** in 44% yield. For **I-BOD**, it was synthesized from the condensation reaction between the commercially available pyrrole with 4-iodobenzaldehyde in the presence of TFA followed by the oxidation with DDQ and complexation with boron trifluoride diethyl etherate in moderate yield. The receptor 5-ethynyl-2-hydroxybenzaldehyde (**4**) was obtained from the Sonogashira coupling reaction between **2** and trimethylsilylacetylene followed by a desilylation. Consequently, the synthesis of **GSB** was accomplished via the Sonogashira coupling reaction between alkyne **4** and **I-BOD** in excellent yield.

3.2. Optical properties of *PE*, *I-BOD* and *GSB*

The photophysical properties of **PE**, **I-BOD** and **GSB** were studied in an aqueous DMSO solution and summarized in Table 1. **PE** exhibited the absorption maxima at 301 and 350 nm while **I-BOD** and **GSB** showed the same λ_{max} of 504 nm. The absorption maxima of **I-BOD** and **GSB** are in the visible region suggesting that both compounds may be used in detection via visualization and optical imaging. Under black light, **PE** displayed weak blue emission (λ_{em} = 363). The Stokes shift of **PE** implied the involvement of the ICT process in its excited state of their fluorophore [39]. On the other hand, **I-BOD** and **GSB** demonstrated the green emission under black light with λ_{em} of 526 and 529 nm, respectively.

I-BOD and **GSB** also showed high molar absorptivity around $4.64–4.80 \times 10^4\ cm^{-1}\ M^{-1}$. The fluorescence quantum yields (Φ_F) of **I-BOD** and **GSB** determined in dilute DMSO solution, using quinine sulfate (Φ_F = 0.546 in 0.5 N H_2SO_4) as the standard, were 0.05 and 0.01, respectively. These low quantum yields are perhaps contributed by the heavy atom effect from an iodide substituent in the case of **I-BOD** [51] while the photo induced electron transfer (PET) and ICT processes from salicylaldehyde moiety may be the main causes in the case of **GSB** [39].

3.3. Optical responses of *PE*, *I-BOD* and *GSB* toward cyanide

To evaluate the prepared fluorophores as the colorimetric cyanide sensors, the addition of CN^- to **PE**, **I-BOD** and **GSB** solutions in 90% DMSO/water were performed and recorded by UV–vis absorption spectrometer. There was no significant change in the absorption spectra of **PE** and **I-BOD** before and after the addition of CN^- (Fig. 2a and b). On the other hand, the absorption peak of **GSB** at 504 nm decreased with a new peak at 342 nm (Fig. 2c). These results corresponded to the observation by naked eye displaying the decolorization of the orange solution of **GSB** into pale yellow upon the addition of CN^-. Next, we studied the fluorescence responses of **GSB** to CN^- in comparison with the model compounds **PE** and **I-BOD**. Upon the addition of CN^- to **PE**, the fluorescence signal at 351 nm increased significantly (Fig. 3a) but there was no fluorescence response for **I-BOD** after the addition of CN^- (Fig. 3b). This suggested that salicylaldehyde can indeed act as a probe for CN^- and the BODIPY moiety is stable to CN^-. For **GSB**, the addition of CN^-, led to a dramatic enhancement of the emission at 529 nm upon the excitation at 345 nm (Fig. 3c). The results from UV–vis and fluorescence spectroscopy suggested that **GSB** may be used as either colorimetric or fluorometric analysis of CN^-. The salicylaldehyde group acts as the cyanide probe while the BODIPY moiety allows the detection in the visible range, including naked eye detection.

3.4. Sensitivity of *GSB* toward cyanide

We next investigated the cyanide concentration dependence of the absorption and emission of **GSB**. The gradual increase of the CN^- concentration added to **GSB** caused a rise of a new absorption peak at 342 nm with the expense of the peak at 504 nm (Fig. 4a). The plot of A_{342}/A_{504} absorbance ratio against CN^- concentration gave an S curve with a sharp rise in the range of 400–700 μM (Fig. 4a inset). The plot of the emission enhancement ratio (I/I_0) at 503 nm of **GSB** against the CN^- concentration also gave the similar S curve with slightly wider dynamic response range (Fig. 4b inset). At 900 μM of cyanide, the time dependence of fluorescence intensity showed saturation at 60 min indicating the time required for reaching the equilibrium (Fig. S10). We would like to note here that the sensing time could be reduced with an increase in temperature. When we perform an experiment by mixing the cyanide ion with **GSB** probe at 60 °C, a strong fluorescence emission was observed within 15–20 min. This evidence suggested the sensing mechanism is a reaction mode. Under room temperature, the addition of cyanide increased the fluorescence quantum efficiency (Φ_F) by 220-fold from 0.01 to 0.22. At the lower cyanide concentration (<300 μM), the 60 min time allowed was unlikely to be adequate for the reaction to reach the equilibrium. The measurement under such a kinetic condition, in the low concentration range, still consistently gave a satisfactory linear calibration line for quantitative determination of cyanide concentration (Fig. S11). The detection limit was calculated with the following equation:

$$\text{Detectionlimit} = 3\sigma/S$$

where σ is the standard deviation of the blank and S is the slope of the calibration curve. The detection limit was then calculated to be 0.88 μM (Fig. S11). This level of the detection is significantly lower than the maximum cyanide concentration of 1.9 μM limited in drinking water by the World Health Organization (WHO).

Even though the sensing experiments conducted at the physiological pH of 7.4 seem logical, our investigation of pH effect on the fluorescence properties of **GSB** gave insight understanding of photophysical mechanism governing its fluorescence responses (Fig. 5). **GSB** itself showed low fluorescence emission due to the multiple non-radiative pathways, including PET, ICT, intersystem crossing, affected by the carbonyl group. It is also interesting to note that **GSB** has lower emission (I_0) in basic pH due to the favorable PET and ICT process from the phenolate anion. The conversion of phenolate anion to phenol, in lower pH range, resulted in the suppression of PET. The addition of the cyanide converted the aldehyde group

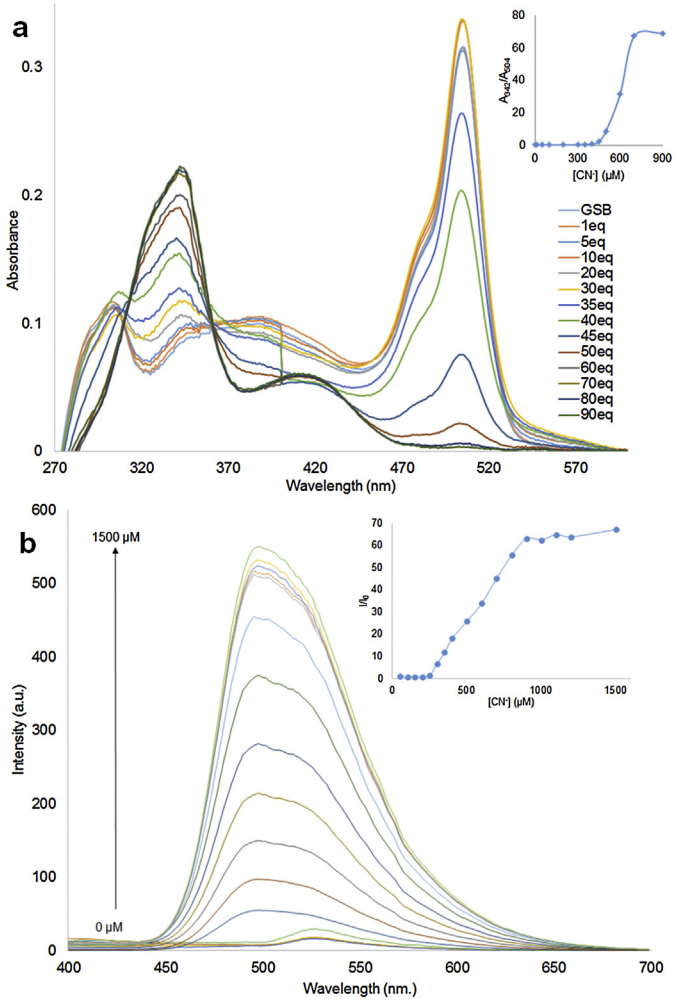


Fig. 4. (a) Absorption and (b) emission spectrum of **GSB** (10 μM in 90% DMSO/Tris buffer pH 7.4) upon the addition of CN^- at various concentration (inset: plots of absorbance ratio (A_{342}/A_{504}) and fluorescence ratio (I/I_0) against CN^- concentration) measured after 60 min of mixing.

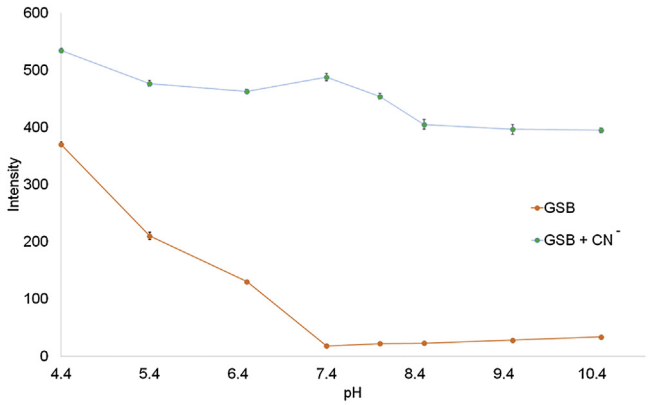


Fig. 5. The emission of **GSB** (10 μM) before and after addition of CN^- (900 μM) in 90% DMSO/water at various pH.

to the corresponding cyanohydrin resulting in the fluorescence enhancement. The emission intensity of **GSB** after the addition of cyanide was also pH dependence. The drop in the fluorescence intensity of the **GSB**-CN adduct was observed at a little higher pH that was probably due to the increase of pK_a value of the phenolic group, upon conversion of the aldehyde to cyanohydrin group.

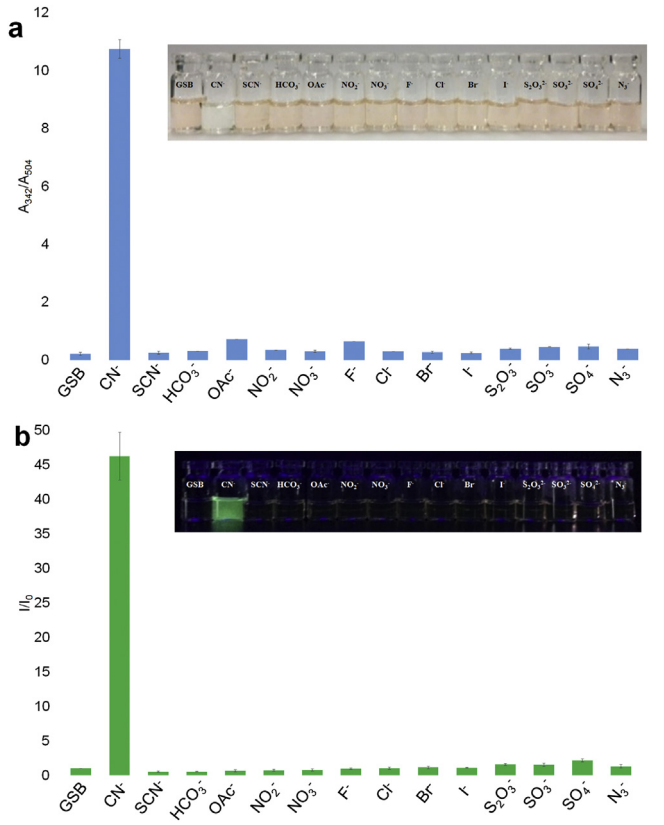


Fig. 6. Ratio of (a) absorbance (A_{342}/A_{504}) and (b) fluorescence intensity (I/I_0) of **GSB** (10 μM) upon addition of other anions (1 mM) in 90% DMSO/Tris buffer pH 7.4 (inset: photograph of **GSB** solutions before and after addition of anions under natural and black light).

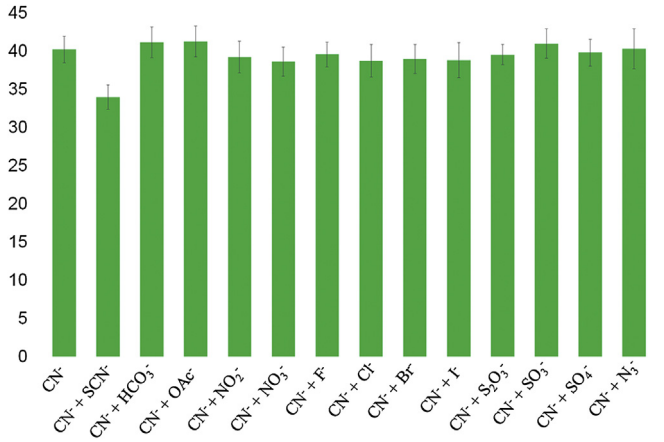


Fig. 7. Fluorescence enhancement ratio (I/I_0) of GSB (10 μM) upon addition of CN^- (500 μM) and other anions (1500 μM) in 90% DMSO/Tris buffer pH 7.4.

Serendipitously, among all pH tested, the sensing test at pH 7.4 also gave the highest fluorescence enhancement ratio (I/I_0).

To support the addition mechanism of cyanide ion to aldehyde group in **GSB** probe, we performed the NMR measurement of **GSB** upon the addition of cyanide (Fig. S16). We observed the disappearance of peak at 11.26 ppm along with the new peak at 5.68 ppm which is corresponding to the hydrogen attached to cyanohydrin group [39]. Moreover, to show the ability to detect cyanide in real sample, we replaced the buffered aqueous (10:90/tris buffer:DMSO) tab water. Upon the increasing concentration of the cyanide, the **GSB** probe displayed stronger fluorescence intensity

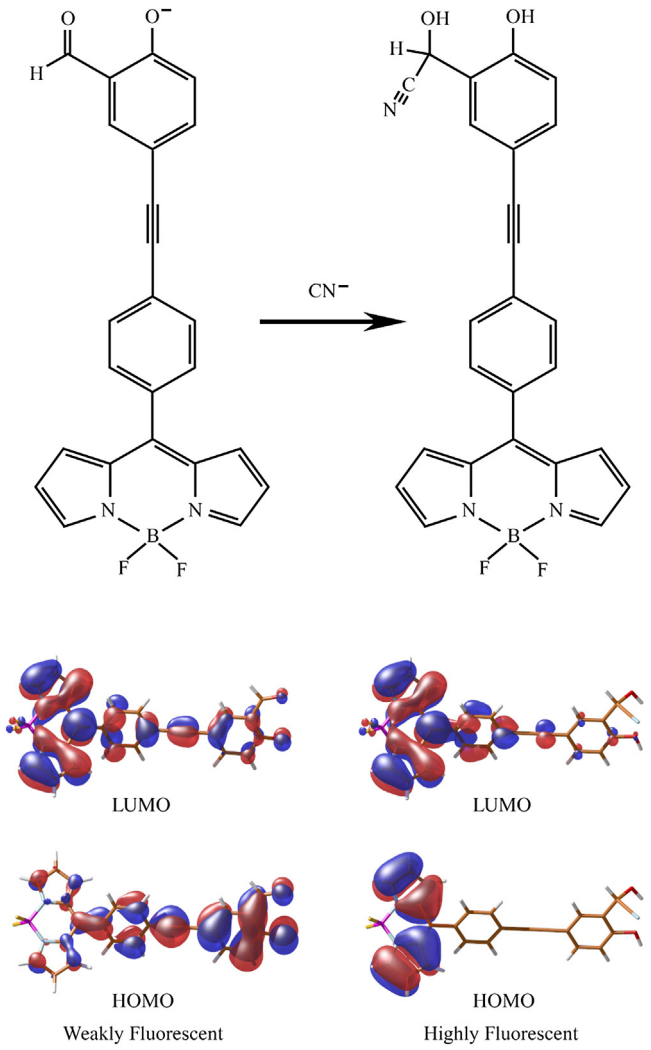


Fig. 8. Calculated geometries and HOMO-LUMO interfacial plot of orbitals for deprotonated **GSB** (left) and cyanohydrin-**GSB** (right).

same as in aqueous buffer system (Fig. S17a) suggesting that it can also be used for detecting cyanide in tab water. However, the fluorescence enhancement ratio (I/I_0) is not as high as in aqueous buffer system due to stronger fluorescence emission at the initial state of **GSB** probe in tab water (Fig. S17b).

3.5. Selectivity and interference of *GSB*

To evaluate the selectivity of **GSB**, 14 anion species (CN^-, SCN^-, HCO_3^-, OAc^-, NO_2^-, NO_3^-, F^-, Cl^-, Br^-, I^-, $S_2O_3^{2-}$, SO_3^{2-}, SO_4^{2-} and N_3^-) were tested with **GSB** using absorption and fluorescence spectroscopy (Fig. 6). Clearly, only CN^- induced about 10-fold increase in absorbance ratio (A_{342}/A_{504}) of **GSB** (Fig. 6a) along with decolorization of the original orange color (Fig. 6a inset). Similarly, the fluorescence enhancements by other anions were less than 0.5 folds while in the case of cyanide was *ca.* 45 folds (Fig. 6b). These results demonstrated that **GSB** had specific colorimetric and fluorogenic response towards cyanide ions.

In the interference test, a competition experiment was performed in which the **GSB** probe (10 μM) was added to the mixture of CN^- (500 μM) and other anions (1500 μM). The results showed that there was no significant interference from most anions (Fig. 7). However, SCN^- posed a significant interference in which our investigation has not yielded a good rational for the mechanism of this interference.

3.6. DFT calculation

In an attempt to gain more insight information of the fluorescence response, structural optimization of deprotonated **GSB** and cyanohydrin-**GSB** were carried out by DFT calculation in B3LYP/6-31+G** level as depicted in Fig. 8 (below). The optimized structure of **GSB** revealed an extended π-conjugation between BODIPY core and salicylaldehyde group through the CC triple bond linkage. HOMO of **GSB** localizes on salicylaldehyde while LUMO delocalizes on BODIPY core. These suggested that there is a strong photoinduced electron transfer (PET) process between BODIPY and salicylaldehyde unit resulting in the fluorescence quenching of initial **GSB**. The attacking of CN^- generates cyanohydrin in which the electron situated on BODIPY unit in both of LUMO and HOMO (Fig. 8, below right). Therefore, the attack of cyanide ion not only causes the change in pK_a of phenolic group, but also interrupts the π-conjugation leading to the fluorescence enhancement of **GSB**.

3.7. Detection of cyanide in living cell

Fluorescent dyes in cellular biology have recently become one of the most popular biological analysis as it is a non-destructive way of tracking and analyzing biological molecules [13]. Therefore, we tested the **GSB** as a fluorescent dye for the detection of cyanide in living cells (Fig. 9). HepG2 cells were chosen as a representative cell line and fluorescent images were recorded under fluorescence microscope. Incubation of HepG2 cells with either NaCN or **GSB** alone resulted in almost no fluorescence emission under green field as seen in Fig. 9a and b, respectively. On the other hand, when NaCN was added to HepG2 cell and further incubated with **GSB**, a strong green emission in the cytoplasm of HepG2 cell was clearly observed (Fig. 9c). These results suggested the ability to use the **GSB** as dye for visualizing CN^- in living cell.

4. Conclusions

In summary, we successfully prepared a robust colorimetric and fluorescent turn-on sensor, **GSB**, for the detection of cyanide in aqueous media. The incorporation of salicylaldehyde group onto the BODIPY can effectively suppress the emission whereas the addition of cyanide caused the formation of cyanohydrin resulting in exclusive "turn-on" green emission. This sensor also exhibited lower detection limit than the WHO regulation for safety in drinking water. The ICT and PET inhibition sensing mechanism of **GSB** probe was confirmed by density functional theory (DFT) calculation. Moreover, **GSB** was successfully extended to the intracellular cyanide detection in HepG2 cell lines which was confirmed by fluorescence microscopy imaging. The outcome of this research suggested that **GSB** will make a great tool for cyanide detection in an aqueous and living cell system as well as provide key information for future fluorescent probe design.

Acknowledgements

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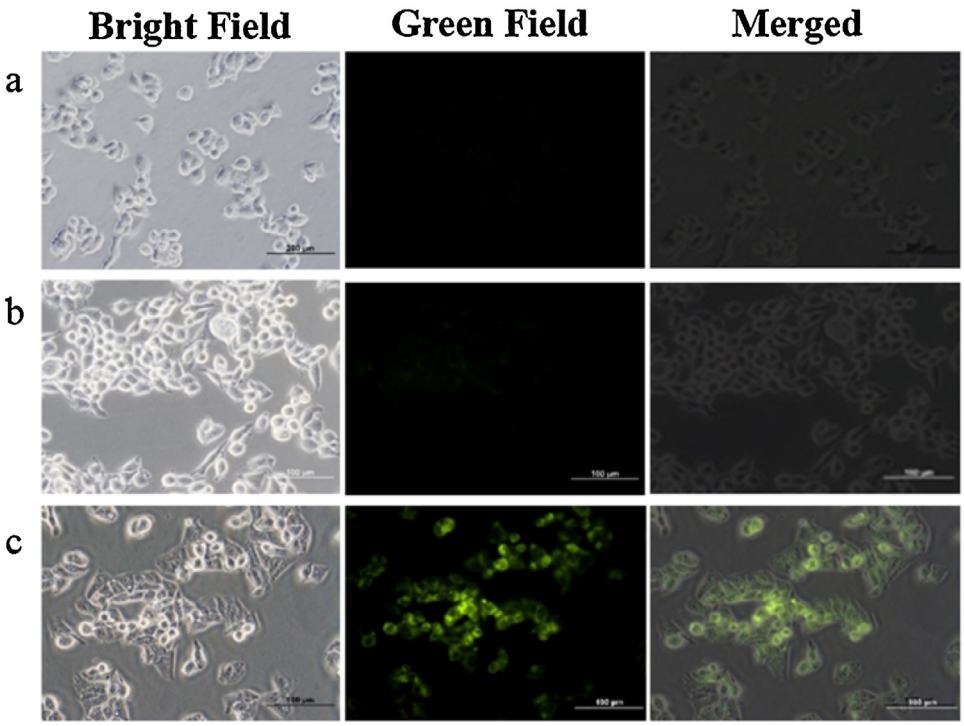

Fig. 9. Bright and fluorescence microscope images of living HepG2 cells (a) treated with sodium cyanide (1 mM) for 60 min, (b) incubated with **GSB** (0.5 μM) for 30 min and (c) treated with sodium cyanide (1 mM) for 60 min followed by incubation with **GSB** (0.5 μM) for 30 min.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jhazmat.2016.04.001.

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Vinylation Chemistry

An Atom-Economic Approach for Vinylation of Indoles and Phenols Using Calcium Carbide as Acetylene Surrogate

Eakkaphon Rattanangkool,[a] Tirayut Vilaivan,[a] Mongkol Sukwattanasinitt,[b] and Sumrit Wacharasindhu*[b]

Abstract: An efficient *N*-vinylation of indoles and *O*-vinylation of phenols to give *N*-vinyl indoles and phenyl vinyl ethers is reported. The vinylated products can be produced in satisfactory to excellent yields (65–92 %) upon treatment of indoles or phenols with calcium carbide in wet solvents in a standard laboratory setup. Key features of this reaction include the use of calcium carbide as a safe and inexpensive slow released acetylene source for *N*- and *O*-vinylation under simple reaction conditions without the need for metal catalyst or halogenated substrates.

Introduction

Since the discovery of its production in the late 1800s via hydrolysis of calcium carbide, itself prepared by a reaction between coke and lime in an electric furnace, acetylene has become a basic raw material for the production of a wide range of industrial chemicals. For example, acrylonitrile, vinyl acetate, acetaldehyde, 1,2-dichloroethene, vinyl methyl ether and vinyl carbazole have been produced from simple addition reactions between the triple bond of acetylene and hydrogen cyanide, acetic acid, water, chlorine, methanol or carbazole, respectively.[1] These addition reactions are very economical from an atom perspective as all atoms in the reactants are incorporated into the final products. However, an important drawback from the direct use of acetylene gas is one of operator safety due to acetylene's gaseous and highly flammable nature. These liabilities necessitate an extra level of operator control as well as higher costs needed to prevent leakage and explosion.[2] As a main source of acetylene gas, solid calcium carbide stands as a potential candidate for a safer and cheaper alternative to acetylene gas, for the production of acetylene-based chemicals.

Zhang first reported the use of calcium carbide as a C≡C equivalent for the synthesis of diarylethynes via a Sonogarshira coupling reaction.[3] Following this work, our group and others have developed methodologies[4] relying on a slow release of acetylene gas from calcium carbide to utilize calcium carbide as an acetylene or acetylide anion (HC_2^- and C_2^{2-}) equivalent for the synthesis of diarylethynes,[5] poly(*p*-phenyleneethynylene) species (PPEs),[6] polyenynes,[7] propargylamine,[8] enaminones,[9] and acetylenic alcohols.[10] Recently, calcium carbide was used as an electrophilic precursor in a vinylation reaction to produce vinylic derivatives such as *O*-vinyloximes, which could further cyclize into 2-arylpyrroles.[11] Calcium carbide has similarly been used in the generation of vinyl thioesters from *S*-vinylated thiophenols[12] as well as vinyl alcohols from *O*-vinylated aliphatic alcohols.[13]

N-Vinylindole derivatives are widely used as monomers for polymeric[14] and photoactive[15] materials. Moreover, it is a core structure for numerous natural products and biologically active compounds.[16] On the other hand, aryl vinyl ethers serve as i) valuable intermediates in various reactions,[17] ii) precursors for polymeric materials,[18] and iii) as phenolic protecting groups[19] in organic synthesis. Current methods for preparing *N*-vinylindole involve the metal-catalyzed reaction between an indole and coupling partner[20] such as trimethoxyvinylsilane,[21] vinyl bromide,[22] vinyl acetate[23] and ethylene,[24,25] (Scheme 1, left side). An alternative method for *N*-vinylation of indoles involves the use of 1,2-dichloroethane in the presence of phase transfer catalyst.[26] Acetylene gas has also been used as a vinylating agent with KOH in the presence of an iron catalyst.[27] Similarly, aryl vinyl ethers are prepared from the metal-catalyzed reaction between phenol and various coupling partners such as vinyl acetate,[28] ethyl vinyl ether,[29] and tetravinyl tin[30] (Scheme 1, right side). Also, vinylation using acetylene gas in the presence of KOH has been reported recently.[31] However, the above mentioned methods for the synthesis of *N*-vinylpyrole and aryl vinyl ether have some drawbacks. These limitations include: i) high cost of reagents and/or catalysts, ii) low product yields, iii) the requirement for metal or halogenated substrates, iv) production of toxic waste, and v) the requirement for harsh conditions such as in pressurized reactor.

In this study, we propose a new process for the synthesis of *N*-vinylindole and phenyl vinyl ether using solid calcium carbide as a vinylating agent. Our method avoids the direct handling of highly flammable gaseous acetylene and overcomes the un-

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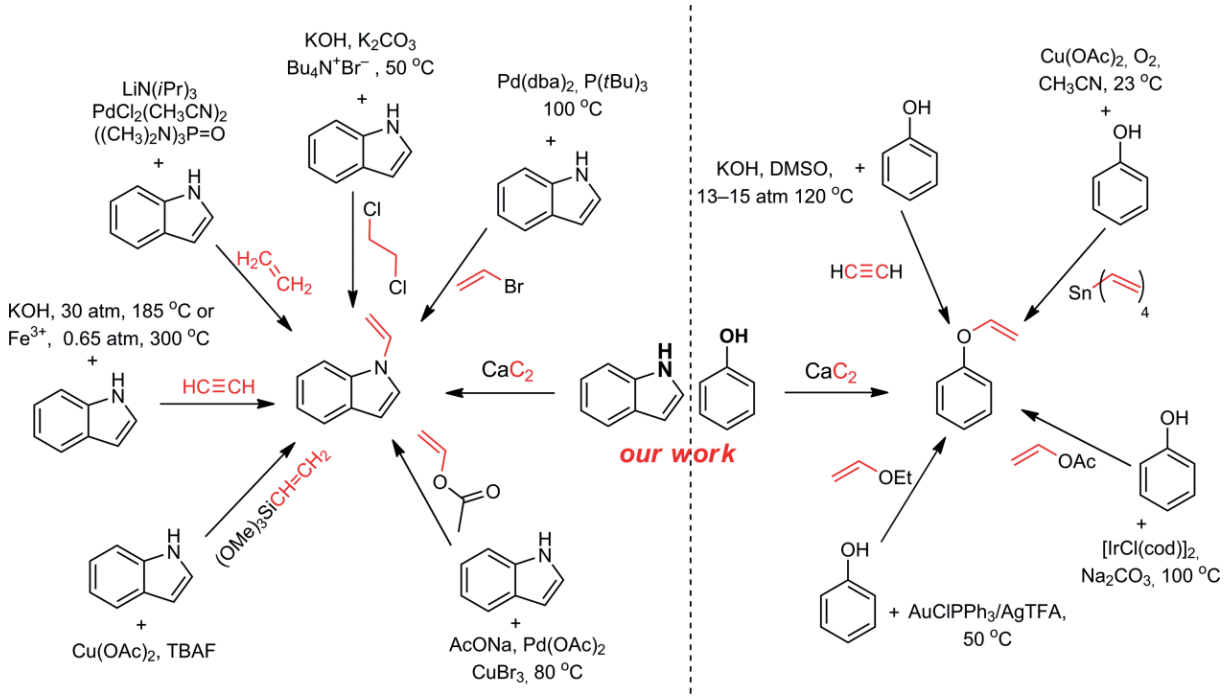


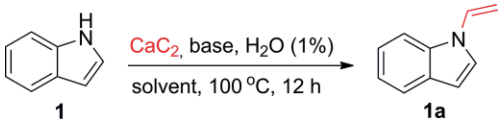
Scheme 1. Synthetic routes to *N*-vinylindoles and phenyl vinyl ethers.

polarized nature of the acetylenic triple bond, enabling excellent yields of the desired products. The key features of the developed method include: i) the simplicity of the reaction conditions which is compatible with gram scale synthesis, ii) the use of calcium carbide as a safe and low cost alternative to acetylene gas, iii) the ability to control the stoichiometry of the reactants more precisely, and iv) the absence of metal catalyst or halogenated substrates together with the atom economy which lead to low levels of waste production.

Results and Discussion

The reaction conditions (i.e. temperature, base, solvent and reagent amount for *N*-vinylation of indole) were optimized using the unsubstituted 1*H*-indole (**1**) as a model substrate and the results are summarized in Table 1. Our preliminary work suggested that the presence of water is essential for efficient acetylene generation.[5] Consequently, reactions were carried out in wet DMSO (containing 1 % H_2O) using freshly ground calcium carbide. In the presence of Cs_2CO_3 as a base, the reaction gave 48 % of the corresponding vinyl indole in 6 h but the yield drastically improved to 85 % upon increasing the reaction time to 12 h (Table 1, Entries 1 and 2). It is important to note that freshly ground calcium carbide in powder form is a key factor to the success of this reaction. The use of calcium carbide in the pelleted form or powder form that has been stored for days tended to give slower reactions. This may be attributed to calcium carbide deactivation via hydrolysis enabled by atmospheric moisture; the product, calcium hydroxide, coats the calcium carbide presumably limiting its availability for reaction. A lower yield of *N*-vinyl indole was obtained when dried DMSO was used in place of the undried DMSO (Table 1, Entry 3). This result confirms the need for a certain amount of water for the hydrolysis of calcium carbide and slow generation of acetylene gas, keeping in mind the presence of indole substrate. Among several bases tested, including KOH, K_2CO_3, DBU, NaOMe and Cs_2CO_3 (Table 1, Entries 2, 4–7), the best results were obtained

Table 1. Optimization of the reaction conditions for the synthesis of *N*-vinylindole.[a]



1 **1a**

Entry	Solvent	Base	Yield[b] [%]
1[c]	DMSO	Cs_2CO_3	48
2	DMSO	Cs_2CO_3	85
3[d]	DMSO	Cs_2CO_3	60
4	DMSO	KOH	46
5	DMSO	K_2CO_3	21
6	DMSO	DBU	7
7	DMSO	NaOMe	0
8[e]	DMSO	Cs_2CO_3	60
9	THF	Cs_2CO_3	13
10	Toluene	Cs_2CO_3	5
11	*i*PrOH	Cs_2CO_3	7
12	DMF	Cs_2CO_3	26
13	NMP	Cs_2CO_3	21
14	DMSO	–	0
15[f]	DMSO	Cs_2CO_3	44

[a] Reaction conditions: indole (1.0 equiv.), CaC_2 (6.0 equiv.) and base (1.5 equiv.) in 1 %water/solvent (0.2 M) at 100 °C for 12 h. [b] Isolated yield after silica gel chromatography. [c] The reaction was performed for 6 h. [d] Dried DMSO was used and no water was added. Starting material was recovered in 32 % yield. [e] 4.0 equiv. of CaC_2 was used. [f] 0.5 equiv. of Cs_2CO_3 was used.

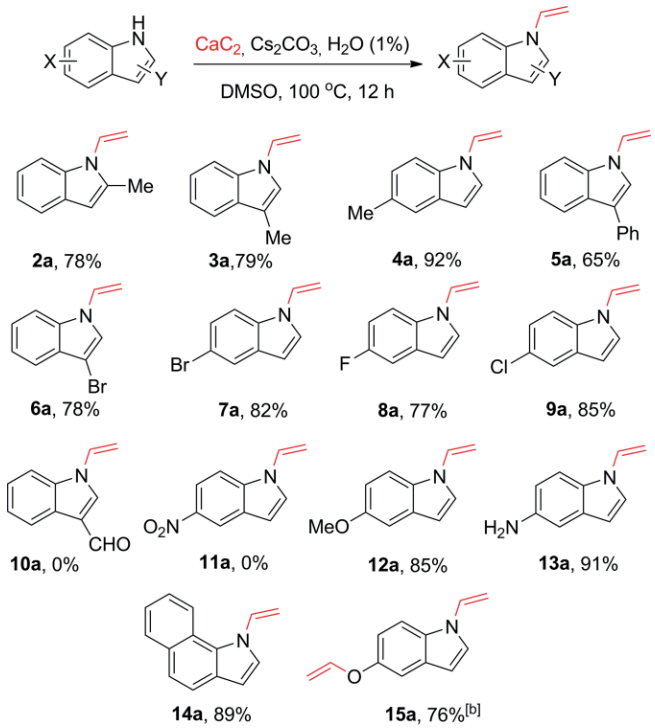
with Cs_2CO_3, which provided desired *N*-vinyl indole in 85 % yield (Table 1, Entry 2); this reaction component, considered to be optimized, was employed throughout subsequent studies. The superior activity of Cs_2CO_3, relative to other bases, can be explained by its good solubility in DMSO and the large polarizability of the cesium ion. The latter, so called "cesium effect", may facilitate nucleophilic addition of the indole N atom across the triple bond of acetylene.[32] Switching the solvent from DMSO to THF, toluene, 2-propanol, DMF and NMP, resulted in incomplete reactions and much lower yields of the desired *N*-vinyl indole (Table 1, Entries 9–13). When the reaction was performed in the absence of Cs_2CO_3, only starting material **1** was obtained (Table 1, Entry 14). Moreover, when 0.5 equiv. Cs_2CO_3 was used, product **1a** was produced in only 44 % yield along with unreacted indole **1** in 38 % yield (Table 1, Entry 15). These results suggest that a stoichiometric amount of Cs_2CO_3 is required during vinylation.

With the optimized reaction conditions now in hand, we next expanded the scope of this transformation by subjecting a variety of indole derivatives (**2**–**15**) to the reaction under the optimized conditions (Table 2). Representative results are reported in Table 2. Simple substituted indoles bearing methyl or phenyl groups were successfully transformed into desired *N*-vinylindoles (**2a**–**5a**) in good to excellent yields (65–92 %). Halogenated indoles such as **6**–**9** were also vinylated successfully and the corresponding products (**6a**–**9a**) were isolated in excellent yields. However, attempts to react indoles bearing electron-withdrawing groups such as aldehyde and nitro moieties (**10** and **11**) under the same conditions were unsuccessful and only starting materials were recovered. The presence of electron-withdrawing groups reduces electron density on the indole nitrogen correlating to diminished nucleophilicity and hence, poor vinylation yields.

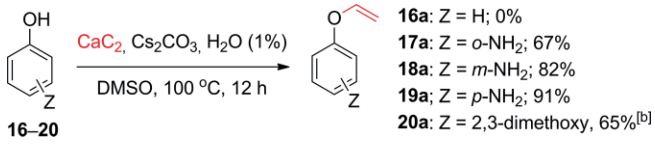
On the other hand, indole substrates bearing an electron-donating groups (as in **12**–**14**) smoothly reacted to provide the desired products in high yields. Interestingly, the vinylation of 5-hydroxyindole (**15**) generated the *N*,*O*-divinylated product **15a** in 76 % yield. This result suggested the possibility that calcium carbide might serve also as an effective acetylene source for the *O*-vinylation of phenolic substrates.

The vinyl ether bond is often represented in many important precursors employed in the polymer field[18] and is prevalent in assorted intermediates in organic synthesis.[17a,17c,30,33] Supported by these realizations, this functional group's far-reaching importance prompted us to investigate the *O*-vinylation of phenolic substrates using calcium carbide as the acetylene source. Therefore, a variety of phenol derivatives were treated with calcium carbide in the presence of Cs_2CO_3 in wet DMSO (Scheme 1). Surprisingly, the use of phenol (**16**) as a substrate, gave no reaction, even when using reaction temperatures as high as 150 °C. This is probably due to the low nucleophlicity of unsubstituted phenol. On the other hand, satisfactory results were obtained using phenol derivatives possessing one or more electron-donating groups. Aminophenol derivatives **17**–**19** and 2,3-dimethoxyphenol **20** underwent smooth *O*-vinylation to provide the corresponding phenyl vinyl ethers in good yields (67–91 %) (Scheme 2).

Table 2. Substrate scope of indole vinylation.[a]

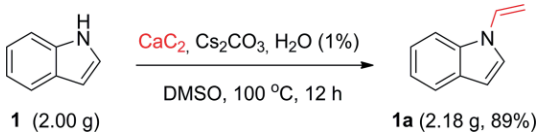


[a] Reaction conditions: indole derivatives (1.0 equiv.), CaC_2 (6.0 equiv.) and Cs_2CO_3 (1.5 equiv.) in 1 %water/DMSO (0.2 M) at 100 °C for 12 h. [b] CaC_2 (12.0 equiv.) and Cs_2CO_3 (3.0 equiv.) were used.



Scheme 2. *O*-vinylation of substituted phenol substrates. [a] Reaction conditions: phenol derivative (1.0 equiv.), CaC_2 (6.0 equiv.) and Cs_2CO_3 (1.5 equiv.) in 1 % water/DMSO (0.2 M) at 100 °C for 12 h. [b] Reaction was performed at 150 °C.

In order to demonstrate the practical application of this method on a larger synthetic scale, *N*-vinylation of indole was carried out (Scheme 3). The reaction was performed using 2.0 g of indole and a commensurate quantity of CaC_2 in a 100 mL reactor to afford **1a** in almost the same yield as had been previously obtained in the milligram scale (Table 1, Entry 2).



Scheme 3. Gram-scale synthesis of *N*-vinylindole (**1a**).

As mentioned above, when the reaction was carried out in anhydrous DMSO, targeted product **1a** was isolated in only 60 % yield along with recovery starting material in 32 % yield (Table 1, Entry 3). This result suggested that water plays a crucial role in this reaction. Accordingly, we investigated the effect

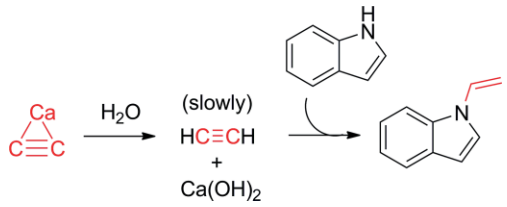
of water on the *N*-vinylation reaction of indole (Table 3). The addition of water (between 1 and 3 %) led to the complete conversion of indole **1** into **1a** (Table 3, Entries 1 and 2). On the other hand, increasing the amount of water in DMSO solution to greater than 5 % lowered yields of *N*-vinylation product and led to incomplete consumption of the indole substrate (Table 3, Entries 3–5).

Table 3. Optimization of the reaction conditions for the synthesis of *N*-vinylindole.[a]

Entry	H_2O added to dried DMSO [%]	Yield[b] **1a**/**1** [%]
1	1	85:0
2	3	86:0
3	5	81:7
4	10	72:12
5	20	54:32

[a] Reaction condition: indole (1.0 equiv.), CaC_2 (6.0 equiv.) and Cs_2CO_3 (1.5 equiv.) in water/DMSO (0.2 M) at 100 °C for 12 h. [b] Isolated yield.

On the basis of these data, in which a small amount of water is clearly needed during vinylation reactions, we suggest the importance of in situ acetylene gas generation from CaC_2 prior to the addition step as proposed in Scheme 4. When larger amounts of water were added, the reaction yields decreased gradually along with a corresponding increase in recovered, unreacted starting material. This indicates that controlling the rate of calcium carbide hydrolysis is essential to keeping acetylene gas in the reaction solution for subsequent nucleophilic addition. The success of this synthetic method thus relies on balancing of the rates of calcium carbide hydrolysis and acetylene addition.



Scheme 4. Proposed mechanism for the *N*-vinylation of indole.

Conclusions

In summary, we have developed a convenient method for preparing *N*-vinylindoles that involves the addition reaction between indole and acetylene generated in situ from calcium carbide in wet DMSO; the method does not require the use of any toxic metals. This process can also be extended to *O*-vinylation of activated phenols enabling the synthesis of vinyl ethers of the electron-rich phenols. The low cost and high degree of commercial availability of calcium carbide make this protocol suitable not only for small scale laboratory synthesis but also for industrial applications calling for large scale construction of vinyl indoles and phenyl vinyl ethers. Efforts to apply this reaction to broader sets of nucleophiles such as other *N*-heterocycles and electron-deficient phenol derivatives are under investigation and will be reported in due course.

Experimental Section

General Remarks: All reagents were purchased from Sigma–Aldrich, Fluka (Switzerland) or Merck (Germany) and used without further purification. All reactions were carried out under an air atmosphere. DMSO was dried with molecular sieves (4 Å) for 15 h and other solvents were used without distillation. MS (ESI) and HRMS (ESI) were obtained with a micrOTOF Bruker mass spectrometer. ^1H and ^{13}C NMR spectra were recorded in [D_6]DMSO at 400 MHz and 100 MHz, respectively, with a Varian Mercury 400 NMR or Bruker Avance 400 NMR spectrometers. Analytical thin-layer chromatography (TLC) was performed with precoated Merck silica gel 60 F_{254} plates (thick layer, 0.25 mm) and visualized by 254 nm using an ultraviolet lamp or by staining with aqueous potassium permanganate solution as the detecting agent. Column chromatography was performed using Merck silica gel 60 (70–230 mesh). A gram scale reaction was performed in 100 mL PARR reactor (mini bench top reactor model 4565).

General Procedure for the Synthesis of *N*-Vinyindoles 1a–13a and Phenyl Vinyl Ethers 17a–20a Derivatives (General Procedure A): A mixture of calcium carbide (6.0 equiv.), indole derivatives (1.0 equiv.) and cesium carbonate (1.5 equiv.) was suspended in (100:1) DMSO/H_2O (0.2 M) in a sealed tube. The reaction mixture was stirred at 100 °C for 12 h. The reaction was cooled to room temperature and diluted by dropwise addition of H_2O (5 mL). The reaction mix was filtered and the filtrate was extracted with EtOAc (3 × 20 mL). The combined extracts was washed with brine (2 × 30 mL), dried with Na_2SO_4 and evaporated under reduced pressure to give the crude product, which was further purified by column chromatography (eluted with ethyl acetate/hexanes) to afford the desired compound.

1-Vinyl-1*H*-indole (1a) [CAS: 1557-08-0]: Synthesized according to **General Procedure A** using calcium carbide (328 mg, 5.12 mmol), indole (100 mg, 0.854 mmol) and cesium carbonate (452 mg, 1.28 mmol) in wet DMSO (4.20 mL) to afford **1a** (103.9 mg, 0.726 mmol, 85 %) as a colorless oil; ^1H NMR (400 MHz, [D_6]DMSO): δ = 7.81 (d, J = 4.0 Hz, 1 H), 7.68 (d, J = 8.0 Hz, 1 H), 7.57 (d, J = 4.0 Hz, 1 H), 7.49 (dd, J = 16.0, 12.0 Hz, 1 H), 7.20 (t, J = 8.0 Hz, 1 H), 7.09 (t, J = 8.0 Hz, 1 H), 6.64 (d, J = 4.0 Hz, 1 H), 5.37 (d, J = 16.0 Hz, 1 H), 4.74 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 135.1, 129.9, 128.6, 124.0, 122.4, 120.7, 120.5, 110.0, 104.7, 96.5 ppm. IR (neat): $\tilde{\nu}$ = 3049, 2951, 2917, 2850, 1637, 1436, 1346, 1230, 1096, 1014, 954, 739 cm^{-1}. HRMS: m/z 143.0731 [M] (calcd for [$C_{10}H_9N$] 143.0735).

2-Methyl-1-vinyl-1*H*-indole (2a) [CAS: 21476-60-8]: Synthesized according to **General Procedure A** using calcium carbide (294 mg, 4.58 mmol), 2-methylindole (100 mg, 0.763 mmol) and cesium carbonate (402 mg, 1.14 mmol) in wet DMSO (3.80 mL) to afford **2a** (93.5 mg, 0.595 mmol, 78 %) as a yellow oil; ^1H NMR (400 MHz, [D_6]DMSO): δ = 7.65 (d, J = 8.0 Hz, 1 H), 7.47 (d, J = 8.0 Hz, 1 H), 7.23 (dd, J = 16.0, 12.0 Hz, 1 H), 7.14 (t, J = 8.0 Hz, 1 H), 7.07 (t, J = 8.0 Hz, 1 H), 6.35 (s, 1 H), 5.42 (d, J = 16.0 Hz, 1 H), 5.06 (d, J = 8.0 Hz, 1 H), 2.46 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 136.4, 135.5, 130.3, 128.5, 121.5, 120.4, 119.5, 110.9, 102.7, 102.5, 13.4 ppm. IR (neat): $\tilde{\nu}$ = 3052, 2950, 2920, 2851, 1638, 1461, 1386, 1350, 1230, 731 cm^{-1}. HRMS: m/z 158.0968 $[M + H]^+$ (calcd for $[C_{11}H_{12}N]^+$ 158.0970).

3-Methyl-1-vinyl-1*H*-indole (3a) [CAS: 21476-61-9]: Synthesized according to **General Procedure A** using calcium carbide (294 mg, 4.58 mmol), 3-methylindole (100 mg, 0.763 mmol) and cesium carbonate (402 mg, 1.14 mmol) in wet DMSO (3.80 mL) to afford **3a** (94.7 mg, 0.602 mmol, 79 %) as a colorless oil; ^1H NMR (400 MHz,

[D$_6$]DMSO): δ = 7.65 (d, J = 8.0 Hz, 1 H), 7.60 (s, 1 H), 7.53 (d, J = 8.0 Hz, 1 H), 7.45 (dd, J = 16.0, 8.0 Hz, 1 H), 7.22 (t, J = 8.0 Hz, 1 H), 7.11 (t, J = 8.0 Hz, 1 H), 5.25 (d, J = 16.0 Hz, 1 H), 4.66 (d, J = 8.0 Hz, 1 H), 2.28 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 135.4, 129.7, 129.0, 122.5, 121.2, 120.0, 118.8, 113.5, 109.7, 94.9, 9.4 ppm. IR (neat): $\tilde{\nu}$ = 3052, 2956, 2923, 2852, 1638, 1461, 1345, 1231, 734 cm^{-1}. HRMS: m/z 158.0970 [M + H]$^+$ (calcd for [$C_{11}H_{12}N$]$^+$ 158.0970).

5-Methyl-1-vinyl-1*H*-indole (4a) [CAS: 328123-83-7]: Synthesized according to **General Procedure A** using calcium carbide (294 mg, 4.58 mmol), 5-methylindole (100 mg, 0.763 mmol) and cesium carbonate (402 mg, 1.14 mmol) in wet DMSO (3.80 mL) to afford **4a** (110 mg, 0.702 mmol, 92 %) as a pale yellow solid; ^{1}H NMR (400 MHz, [D$_6$]DMSO) : δ = 7.76 (d, J = 4.0 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.45 (dd, J = 16.0, 8.0 Hz, 1 H), 7.36 (s, 1 H), 7.04 (d, J = 8.0 Hz, 1 H), 6.57 (d, J = 4.0 Hz, 1 H), 5.34 (d, J = 16.0 Hz, 1 H), 4.72 (d, J = 8.0 Hz, 1 H), 2.38 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 133.5, 130.1, 129.2, 128.9, 124.0, 123.9, 120.4, 109.7, 104.3, 96.0, 20.9 ppm. IR (neat): $\tilde{\nu}$ = 3013, 2953, 2920, 2851, 1638, 1482, 1386, 1314, 1242, 952, 848, 785, 713 cm^{-1}. HRMS: m/z 158.0971 [M + H]$^+$ (calcd for [$C_{11}H_{12}N$]$^+$ 158.0970).

3-Phenyl-1-vinyl-1*H*-indole (5a): Synthesized according to **General Procedure A** using calcium carbide (176 mg, 2.74 mmol), 3-phenylindole (100 mg, 0.456 mmol) and cesium carbonate (241 mg, 0.684 mmol) in wet DMSO (2.30 mL) to afford **5a** (142 mg, 0.296 mmol, 65 %) as a colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.20 (s, 1 H), 7.99 (d, J = 8.0 Hz, 1 H), 7.79 (d, J = 8.0 Hz, 1 H), 7.75 (d, J = 8.0 Hz, 2 H), 7.59 (dd, J = 16.0, 8.0 Hz, 1 H), 7.48 (t, J = 8.0 Hz, 2 H), 7.32 (q, J = 8.0 Hz, 2 H), 7.22 (t, J = 8.0 Hz, 1 H), 5.54 (d, J = 16.0 Hz, 1 H), 4.84 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 136.0, 134.3, 129.5, 128.8, 127.0, 126.3, 126.1, 122.9, 121.6, 121.3, 119.6, 118.9, 110.4, 97.2 ppm. IR (neat): $\tilde{\nu}$ = 3130, 3018, 2951, 2917, 2847, 1635, 1479, 1315, 1235, 952, 791, 758, 716 cm^{-1}. HRMS: m/z 220.1125 [M + H]$^+$ (calcd for [$C_{16}H_{14}N$]$^+$ 220.1126).

3-Bromo-1-vinyl-1*H*-indole (6a): Synthesized according to **General Procedure A** using calcium carbide (197 mg, 3.08 mmol), 3-bromoindole (100 mg, 0.513 mmol) and cesium carbonate (271 mg, 0.770 mmol) in wet DMSO (2.50 mL) to afford **6a** (88.4 mg, 0.400 mmol, 78 %) as a yellow oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.13 (s, 1 H), 7.76 (d, J = 4.0 Hz, 1 H), 7.53–7.43 (m, 2 H), 7.31 (t, J = 8.0 Hz, 1 H), 7.22 (t, J = 8.0 Hz, 1 H), 5.46 (d, J = 16.0 Hz, 1 H), 4.49 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 134.6, 129.3, 127.0, 123.8, 123.4, 121.5, 118.6, 110.5, 97.7, 93.5 ppm. IR (neat): $\tilde{\nu}$ = 3061, 3034, 2962, 2926, 2845, 1644, 1473, 1398, 1281, 1236, 1210, 955, 755, 728 cm^{-1}. HRMS: m/z 221.9920 [M + H]$^+$ (calcd for [$C_{10}H_9BrN$]$^+$ 221.9918).

5-Bromo-1-vinyl-1*H*-indole (7a): Synthesized according to **General Procedure A** using calcium carbide (197 mg, 3.08 mmol), 5-bromoindole (100 mg, 0.513 mmol) and cesium carbonate (271 mg, 0.770 mmol) in wet DMSO (2.50 mL) to afford **7a** (93.0 mg, 0.421 mmol, 82 %) as a white powder; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.83 (d, J = 4.0 Hz, 1 H), 7.72 (s, 1 H), 7.64 (d, J = 12.0 Hz, 1 H), 7.43 (dd, J = 16.0, 8.0 Hz, 1 H), 7.27 (d, J = 8.0 Hz, 1 H), 6.59 (d, J = 4.0 Hz, 1 H), 5.37 (d, J = 16.0 Hz, 1 H), 4.75 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 133.8, 130.4, 129.8, 125.6, 124.9, 123.0, 113.0, 112.1, 104.2, 97.6 ppm. IR (neat): $\tilde{\nu}$ = 3110, 3072, 3005, 2923, 1634, 1517, 1457, 1277, 1226, 957, 859, 795, 755 cm^{-1}. HRMS: m/z 221.9926 [M + H]$^+$ (calcd for [$C_{10}H_9BrN$]$^+$ 221.9918).

5-Fluoro-1-vinyl-1*H*-indole (8a): Synthesized according to **General Procedure A** using calcium carbide (285 mg, 4.44 mmol), 5-fluoroindole (100 mg, 0.740 mmol) and cesium carbonate (392 mg, 1.11 mmol) in wet DMSO (3.70 mL) to afford **8a** (124 mg, 0.570 mmol, 77 %) as a white solid; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.92 (d, J = 4.0 Hz, 1 H), 7.74 (dd, J = 8.0, 4.0 Hz, 1 H), 7.51 (dd, J = 12.0, 8.0 Hz, 1 H), 7.37 (dd, J = 12.0, 4.0 Hz, 1 H), 7.08 (td, J = 8.0, 8.0, 4.0 Hz, 1 H), 6.66 (d, J = 4.0 Hz, 1 H), 5.41 (d, J = 16.0 Hz, 1 H), 4.79 (d, J = 12.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 157.6 (d, $^1J_{CF}$ = 233.0 Hz), 131.8, 129.5 (d, $^3J_{CF}$ = 88.0 Hz), 128.9, 125.8, 111.1 (d, $^3J_{CF}$ = 9.0 Hz), 110.4 (d, $^2J_{CF}$ = 25.0 Hz), 105.6 (d, $^2J_{CF}$ = 23.0 Hz), 104.6 (d, $^4J_{CF}$ = 5.0 Hz), 97.0 ppm. IR (neat): $\tilde{\nu}$ = 3110, 2948, 2926, 2853, 1641, 1473, 1235, 1115, 947, 849, 748, 716 cm^{-1}. HRMS: m/z 161.0645 [M] (calcd for [$C_{10}H_8FN$] 161.0641).

5-Chloro-1-vinyl-1*H*-indole (9a): Synthesized according to **General Procedure A** using calcium carbide (255 mg, 3.97 mmol), 5-chloroindole (100 mg, 0.662 mmol) and cesium carbonate (350 mg, 0.993 mmol) in wet DMSO (3.30 mL) to afford **9a** (99.7 mg, 0.563 mmol, 85 %) as a pale yellow solid; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.91 (s, 1 H), 7.74 (d, J = 4.0 Hz, 1 H), 7.65 (s, 1 H), 7.50 (dd, J = 16.0, 8.0 Hz, 1 H), 7.23 (d, J = 8.0 Hz, 1 H), 6.66 (d, J = 4.0 Hz, 1 H), 5.43 (d, J = 16.0 Hz, 1 H), 4.82 (d, J = 12.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 133.6, 129.8, 129.8, 125.7, 125.1, 122.3, 120.0, 111.6, 104.3, 97.5 ppm. IR (neat): $\tilde{\nu}$ = 3112, 3078, 2914, 1638, 1452, 1386, 1276, 1228, 952, 857, 758, 722 cm^{-1}. HRMS: m/z 178.0428 [M + H]$^+$ (calcd for [$C_{10}H_9ClN$]$^+$ 178.0424).

5-Methoxy-1-vinyl-1*H*-indole (12a): Synthesized according to **General Procedure A** using calcium carbide (258 mg, 4.02 mmol), 5-methoxyindole (100 mg, 0.670 mmol) and cesium carbonate (356 mg, 1.01 mmol) in wet DMSO (3.30 mL) to afford **12a** (98.7 mg, 0.567 mmol, 85 %) as a white powder; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.74 (d, J = 4.0 Hz, 1 H), 7.58 (d, J = 8.0 Hz, 1 H), 7.44–7.38 (dd, J = 16.0, 8.0 Hz, 1 H), 7.07 (s, 1 H), 6.82 (dd, J = 8.0, 4.0 Hz, 1 H), 6.55 (d, J = 4.0 Hz, 1 H), 5.30 (d, J = 16.0 Hz, 1 H), 4.69 (d, J = 12.0 Hz, 1 H), 3.75 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 154.3, 130.2, 129.2, 124.6, 112.1, 110.8, 104.4, 102.8, 95.9, 55.3 ppm. IR (neat): $\tilde{\nu}$ = 3114, 2962, 2938, 2830, 1638, 1482, 1320, 1248, 1150, 1021, 958, 842, 755, 725 cm^{-1}. HRMS: m/z 174.0987 [M + H]$^+$ (calcd for [$C_{11}H_{12}NO$]$^+$ 174.0919).

5-Amino-1-vinyl-1*H*-indole (13a): Synthesized according to **General Procedure A** using calcium carbide (292 mg, 4.55 mmol), 5-aminoindole (100 mg, 0.758 mmol) and cesium carbonate (402 mg, 1.14 mmol) in wet DMSO (3.80 mL) to afford **13a** (109 mg, 0.690 mmol, 91 %) as a brown solid; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.55 (s, 1 H),7.35 (d, J = 8.0 Hz, 1 H), 7.29 (dd, J = 16.0, 8.0 Hz, 1 H), 6.69 (s, 1 H), 6.57 (d, J = 8.0 Hz, 1 H), 6.35 (d, J = 4.0 Hz, 1 H), 5.19 (d, J = 16.0 Hz, 1 H), 4.64 (br. s, 2 H), 4.59 (d, J = 12.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 142.7, 130.1, 129.7, 128.7, 123.8, 112.4, 110.2, 103.8, 103.6, 94.6 ppm. IR (neat): $\tilde{\nu}$ = 3392, 3309, 3105, 2953, 2920, 1631, 1473, 1323, 1248, 964, 839 cm^{-1}. HRMS: m/z 159.0924 [M + H]$^+$ (calcd for [$C_{10}H_{11}N_2$]$^+$ 159.0922).

1-Vinyl-1*H*-benzo[*g*]indole (14a) [CAS: 107607–38–5]: Synthesized according to **General Procedure A** using calcium carbide (230 mg, 3.59 mmol), 1*H*-benzo[*g*]indole (100 mg, 0.599 mmol) and cesium carbonate (317 mg, 0.899 mmol) in wet DMSO (3.00 mL) to afford **14a** (103 mg, 0.533 mmol, 89 %) as a colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 8.43 (d, J = 8.0 Hz, 1 H), 8.01–7.93 (m, 2 H), 7.72 (d, J = 8.0 Hz, 1 H), 7.65 (s, 1 H), 7.58 (m, 2 H), 7.47 (t, J = 8.0 Hz, 1 H), 6.78 (d, J = 4.0 Hz, 1 H), 5.58 (d, J = 12.0 Hz, 1 H), 5.19 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 134.2, 131.2, 129.0, 128.4, 126.2, 125.9, 125.8, 123.7, 122.4, 121.6, 121.2, 120.8, 105.0, 104.8 ppm. IR (neat): $\tilde{\nu}$ = 3132, 3100, 3050, 2955, 2920, 1638, 1505, 1318, 868, 805, 729 cm^{-1}. HRMS: m/z 194.0969 [M + H]$^+$ (calcd for [$C_{14}H_{12}N$]$^+$ 194.0970).

1-Vinyl-5-(vinyloxy)-1*H*-indole (15a): Synthesized according to **General Procedure A** using calcium carbide (578 mg, 9.02 mmol), 5-hydroxyindole (100 mg, 0.752 mmol) and cesium carbonate (797 mg, 2.26 mmol) in wet DMSO (3.80 mL) to afford **15a** (106 mg, 0.571 mmol, 76 %) as a white powder; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.85 (d, J = 4.0 Hz, 1 H), 7.70 (d, J = 12.0 Hz, 1 H), 7.48 (dd, J = 16.0, 8.0 Hz, 1 H), 7.24 (s, 1 H), 6.95 (d, J = 8.0 Hz, 1 H), 6.84 (dd, J = 16.0, 4.0 Hz, 1 H), 6.63 (d, J = 4.0 Hz, 1 H), 5.38 (d, J = 16.0 Hz, 1 H), 4.76 (d, J = 8.0 Hz, 1 H), 4.63 (d, J = 12.0 Hz, 1 H), (d, J = 12.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 150.1, 149.8, 131.7, 130.0, 129.2, 125.3, 113.5, 111.0, 107.8, 104.6, 96.6, 93.5 ppm. IR (neat): $\tilde{\nu}$ = 3022, 2956, 2917, 2848, 2367, 1640, 1482, 1314, 1236, 1183, 791 cm^{-1}. HRMS: m/z 186.0916 [M + H]$^+$ (calcd for [$C_{12}H_{12}NO$]$^+$ 186.0919).

2-(Vinyloxy)aniline (17a) [CAS: 7707-00-8]: Synthesized according to **General Procedure A** using calcium carbide (352 mg, 5.50 mmol), 2-aminophenol (100 mg, 0.917 mmol) and cesium carbonate (485 mg, 1.38 mmol) in wet DMSO (4.60 mL) to afford **17a** (83.0 mg, 0.614 mmol, 67 %) as a yellow oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.84 (t, J = 8.0 Hz, 2 H), 6.73–6.68 (m, 2 H), 6.53 (td, J = 8.0, 8.0, 4.0 Hz, 1 H), 4.84 (br. s, 2 H), 4.56 (dd, J = 12.0, 4.0 Hz, 1 H), 4.36 (dd, J = 8.0, 4.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 149.3, 142.3, 138.9, 124.1, 117.1, 116.1, 115.2, 93.1 ppm. IR (neat): $\tilde{\nu}$ = 3457, 3358, 1600, 1582, 1489, 1283, 1181, 990, 947, 763 cm^{-1}. HRMS: m/z 136.0767 [M + H]$^+$ (calcd for [$C_8H_{10}NO$]$^+$ 136.0762).

3-(Vinyloxy)aniline (18a) [CAS: 1005-42-1]: Synthesized according to **General Procedure A** using calcium carbide (352 mg, 5.50 mmol), 3-aminophenol (100 mg, 0.917 mmol) and cesium carbonate (485 mg, 1.38 mmol) in wet DMSO (4.60 mL) to afford **18a** (111 mg, 0.752 mmol, 82 %) as a yellow-brown oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.96 (d, J = 8.0 Hz, 1 H), 6.73 (dd, J = 12.0, 8.0 Hz, 1 H), 6.23 (td, J = 28.0, 24.0, 8.0 Hz, 3 H), 5.19 (br. s, 2 H), 4.66 (d, J = 16.0 Hz, 1 H), 4.39 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 157.3, 150.3, 148.4, 129.8, 109.0, 103.7, 101.9, 94.3 ppm. IR (neat): $\tilde{\nu}$ = 3449, 3367, 2920, 1600, 1582, 1489, 1283, 1181, 1156, 993, 839 cm^{-1}. HRMS: m/z 136.0768 [M + H]$^+$ (calcd for [$C_8H_{10}NO$]$^+$ 136.0762).

4-(Vinyloxy)aniline (19a) [CAS: 1005-63-6]: Synthesized according to **General Procedure A** using calcium carbide (352 mg, 5.50 mmol), 4-aminophenol (100 mg, 0.917 mmol) and cesium carbonate (485 mg, 1.38 mmol) in wet DMSO (4.60 mL) to afford **19a** (113 mg, 0.834 mmol, 91 %) as a brown oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 6.74 (d, J = 8.0 Hz, 2 H), 6.66 (dd, J = 12.0, 8.0 Hz, 1 H), 6.54 (d, J = 8.0 Hz, 2 H), 4.86 (br. s, 2 H), 4.48 (d, J = 12.0 Hz, 1 H), 4.25 (d, J = 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 150.3, 146.8, 144.8, 118.2, 114.7, 92.1 ppm. IR (neat): $\tilde{\nu}$ = 3449, 3379, 2956, 2920, 2844, 1600, 1582, 1492, 1283, 1178, 1155, 990, 836, 772 cm^{-1}. HRMS: m/z 136.0769 [M + H]$^+$ (calcd for [$C_8H_{10}NO$]$^+$ 136.0762).

1,2-Dimethoxy-3-(vinyloxy)benzene (20a): Synthesized according to **General Procedure A** using calcium carbide (249 mg, 3.89 mmol), 2,3-dimethoxyphenol (84.6 µL, 0.649 mmol) and cesium carbonate (343 mg, 0.974 mmol) in wet DMSO (3.20 mL) to afford **20a** (76.0 mg, 0.422 mmol, 65 %) as a colorless oil; ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.04 (t, J = 8.0 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 6.75 (dd, J = 12.0, 8.0 Hz, 1 H), 6.69 (d, J = 8.0 Hz, 1 H), 4.61 (dd, J = 12.0, 4.0 Hz, 1 H), 4.40 (dd, J = 4.0, 4.0 Hz, 1 H), 3.80 (s, 3 H), 3.70 (s, 3 H) ppm. ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 153.6, 149.6, 149.4, 123.8, 110.9, 108.3, 93.6, 60.4, 55.9 ppm. IR (neat): $\tilde{\nu}$ = 2959, 2917, 2851, 1640, 1589, 1470, 1246, 1156, 1087, 734 cm^{-1}. HRMS: m/z 181.0885 [M + H]$^+$ (calcd for [$C_{10}H_{13}O_3$]$^+$ 181.0865).

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