Final Report

การสังเคราะห์สารประกอบไนโตรเจนโดยปฏิกิริยาออกซิเดทีฟแอมมิเนชั่น

Synthesis of Nitrogen –Containing Compounds *via* Catalytic Oxidative Amination

By

Assistant Professor Dr. Sirilata Yotphan

Department of Chemistry, Faculty of Science

Mahidol University

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รหัสโครงการ: TRG5780148

โครงการ: การสังเคราะห์สารประกอบไนโตรเจนโดยปฏิกิริยาออกซิเดทีฟแอมมิเนชั่น

(Synthesis of Nitrogen –Containing Compounds via Catalytic Oxidative Amination)

นักวิจัย: ผศ.ดร.ศิริลตา ยศแผ่น ภาควิชาเคมี คณะวิทยาศาสตร์ มหาวิทยาลัยมหิดล

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ระยะเวลาโครงการ: 2 มิถุนายน 2557 – 1 มิถุนายน 2559

Abstract

Iodine-catalyzed oxidative coupling reactions for the syntheses of *N*-linked 2-(azol-1yl)indoles and sulfonamides were developed. These metal-free catalyzed reactions can be conveniently carried out under mild conditions using readily available non-halogenated starting materials and inexpensive catalytic-oxidant combinations, and give products in moderate to excellent yields, thereby providing efficient and sustainable synthetic approaches to access a variety of the biologically active *N*-linked 2-(azol-1yl)indoles and sulfonamides with good economic and environmental benefits.

Keywords iodine, catalysis, indole, sulfonamide, oxidative coupling

บทคัดย่อ

งานวิจัยนี้ได้ศึกษาและพัฒนากระบวนการสังเคราะห์ *N*-linked 2-(azol-1yl)indoles และ ซัลโฟนาไมด์ โดยใช้ไอโอดีนเป็นตัวเร่งปฏิกิริยา oxidative coupling ซึ่งปฏิกิริยานี้สามารถทำได้สะดวกโดยเริ่มต้นจากสารตั้งต้นที่ไม่มีฮาโลเจนเป็นส่วนประกอบและยังใช้ตัวเร่งปฏิกิริยาและออกซิแดนซ์ที่หาซื้อได้ในราคาไม่แพง อีกทั้งยังให้ผลิตภัณฑ์ในปริมาณที่มาก สอดคล้องกับการพัฒนาการสังเคราะห์อย่างยั่งยืนที่ดีต่อเศรษฐกิจและเป็นมิตรต่อสิ่งแวดล้อม

คำหลัก ไอโอดีน, การเร่งปฏิกิริยา, อินโดล, ซัลโฟนาไมด์, ออกซิเดทีฟคลัปปิง

Executive Summary

รหัสโครงการ: TRG5780148

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ความสำคัญและที่มา

สารประกอบไนโตรเจน เป็นสารที่พบในโครงสร้างทางเคมีของยา,สารที่มีฤทธิ์ทางชิวภาพและผลิตภัณฑ์ทางธรรมชาติ จึงมีนักวิทยาศาสตร์จำนวนมากให้ความสำคัญกับปฏิกิริยาและการสังเคราะห์สารเหล่านี้[1,2] เพราะจะก่อให้เกิดประโยชน์มากมายต่อการนำไปใช้ต่อในทางการแพทย์และทางชีววิทยา ดังนั้นการคิดค้นและพัฒนากระบวนการหรือวิธีในการสังเคราะห์สารประกอบไนโตรเจนให้มีประสิทธิภาพจึงเป็นสิ่งจำเป็นอย่างยิ่งต่อการนำเอาไปประยุกต์ใช้ ปฏิกิริยาoxidative amination เป็นปฏิกิริยามีประโยชน์ในการสร้างพันธะระหว่างคาร์บอนและไนโตรเจน โดยเฉพาะอย่างยิ่งการใช้ตัวเร่งปฏิกิริยาร่วมด้วย เพราะตัวเร่งปฏิกิริยาสามารถลดพลังงานก่อกัมมันต์อันจะทำให้ปฏิกิริยาเกิดได้ง่ายและรวดเร็วขึ้น[3] ดังนั้นการค้นพบและพัฒนาสภาวะของปฏิกิริยาที่ทำได้สะดวกจะเป็นประโยชน์อย่างยิ่งต่อการนำไปใช้ได้จริง

วัตถุประสงค์

1.เพื่อทำการหาสภาวะทีเหมาะสมในการเร่งปฏิกิริยา oxidative amination เพื่อสร้างพันธะคาร์บอนและไนโตรเจนในสารประกอบไนโตรเจนและอนุพันธ์อื่นๆที่มีมูลค่าที่สูงขึ้น อันจะนำไปสู่ค้นพบกระบวนการการสังเคราะห์ที่สะดวกและสามารถประยุกต์ใช้จริงได้

2.เพื่อศึกษากลไกการเกิดปฏิกิริยาอันนำไปสู่การพัฒนาความรู้ความเข้าใจในปฏิกิริยา oxidative amination

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(1) (a) Carey, J. S.; Laffan, D.; Thomson, C.; Williams, M. T. *Org. Biomol. Chem.* 2006, *4*, 2337. (b) Bashford, K. E.; Burton, M. B.; Cameron, S.; Cooper, A, L.; Hogg, R. D., Kane,

P. D.; MacManus, D. A.; Matrunola, C. A.; Moody, C. J.; Robertson, A. B.; Warne, M. R. *Tetrahedron Lett*. 2003, *44*, 1627.

(2) For reviews, see: (a) Mori, A.; Sugie, A. *Bull. Chem. Soc. Jpn.* 2008, *81*, 548. (b) Campeau, L. C.; Stuart, D. R.; Fagnou, K. *Aldrichimica Acta* 2007, *40*, 35. (c) Satoh, T.; Miura, M. *Chem. Lett.* 2007, *36*, 200. (d) Seregin, I. V.; Gevorgan, V. *Chem. Soc. Rev.* 2007, *36*, 1173.

(3) (a) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* 2007, *107*, 174. (b) Sezen, B.; Sames, D. *in Handbook of C-H Transformations* (Ed.: G. Dyker), Wiley-VCH, Weinheim, 2005, pp 3–10. (c) Fairlamb, I. J. S. *Annu. Rep. Prog. Chem. Sect. B* 2007, *103*, 68.

ระเบียบวิธีวิจัย

1 การศึกษาปฏิกิริยาและผลกระทบของตัวแปรต่างๆที่มีผลต่อปฏิกิริยา

เนื่องจากปฏิกิริยาออกซิเดทิฟแอมมิเนชั่นคือปฏิกิริยาการสร้างพันธะระหว่างคาร์บอนและไนโตรเจน (C—N bond) ดังนั้นโครงการวิจัยนี้เริ่มต้นจากการศึกษาในส่วนของปฏิกิริยาและการวิเคราะห์ปัจจัยต่างๆที่มีผลต่อการสังเคราะห์สารประกอบไนโตรเจนโดยใช้ตัวเร่งปฏิกิริยา ตัวแปรที่จะมีการศึกษาถึงผลกระทบต่อปฏิกิริยา เช่น ตัวเร่งปฏิกิริยา เบส ตัวทำละลาย รวมทั้งปริมาณของสารต่างๆที่ใช้ ซึ่งผู้วิจัยได้ใช้เทคนิคทาง Nuclear magnetic resonance (NMR) และ Gas chromatography (GC) ในการติดตามปฏิกิริยาและในการวิเคราะห์ในเชิงปริมาณและเชิงคุณภาพ และทำการประเมินผลเพื่อให้ได้สภาวะที่สะดวกและเหมาะสมต่อการเกิดปฏิกิริยา และได้สารผลิตภัณฑ์ในปริมาณมากที่สุด

2 การศึกษาขอบเขตและข้อจำกัดของปฏิกิริยา

ผู้วิจัยได้ศึกษาถึงขอบเขตและข้อจำกัดอื่นๆ ของปฏิกิริยา รวมทั้งการวิเคราะห์และประเมินผลกระทบต่อปฏิกิริยาเมื่อมีการเปลี่ยนแปลงโครงสร้างของสารตั้งต้นภายใต้สภาวะที่ค้นพบในขั้นตอนแรก เช่น การเปลี่ยนแปลงหมู่ฟังก์ชั่น การเพิ่มหมู่แทนที่และความเกะกะของสารตั้งต้น (electronic and steric effect) อีกทั้งยังมีการทดสอบความทนทานและเสถียรภาพของปฏิกิริยาและสารตั้งต้นต่างๆต่อน้ำ ความชื้นและอากาศ โดยจะมีการประเมินประสิทธิภาพทั้งทางปริมาณและทางคุณภาพของสารผลิตภัณฑ์ที่เกิดขึ้น เช่นความบริสุทธิ์ของสารที่แยกออกมาได้ โดยจะมีการพิสูจน์เอกลักษณ์ของสารด้วยเทคนิคทาง Nuclear Magnetic Resonance Spectroscopy (NMR), Infrared

Spectroscopy (IR) และ Mass Spectroscopy (MS) อีกทั้งยังจะศึกษาความเป็นไปได้ในการนำเอาวิธีที่ค้นพบนี้ไปใช้ในการสังเคราะห์สารประกอบไนโตรเจนต่างๆที่ต้องการ ทั้งนี้สารที่สังเคราะห์ทุกตัวได้นำไปเปรียบเทียบกับข้อมูลรายงานทาง Literature ที่เกี่ยวข้อง

3 การศึกษากลไกของปฏิกิริยา

ศึกษาโดยการติดตามปฏิกิริยาอย่างใกล้ชิดและมีการแยกสารตัวกลางหรือสารต่างๆที่เกิดขึ้นในระหว่างที่ปฏิกิริยาดำเนินอยู่เพื่อวิเคราะห์ว่าคือสารอะไรบ้าง เพื่อที่จะทราบรายละเอียดที่เกี่ยวข้องกับปฏิกิริยาได้ และสรุปเป็นวัฏจักรของตัวเร่งปฏิกิริยา (catalytic cycle) ที่คาดว่าน่าจะเป็นไปได้

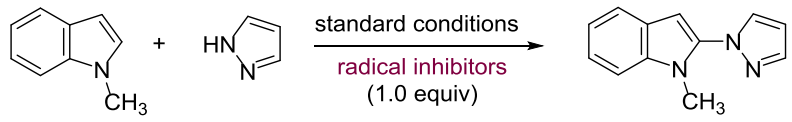
ผลการทดลอง

1. การสังเคราะห์ *N*-linked indole โดยใช้ปฏิกิริยา I_2-catalyzed oxidative coupling

เนื่องจาก สาร indole เป็น *N*-heterocycle ที่พบมากโดยทั่วไปใน natural products และยังมีการใช้ค่อนข้างมากในการวิจัยเพื่อศึกษาการออกฤทธิ์ต่าง อีกทั้งยังไม่ค่อยมีการศึกษาด้านการสังเคราะห์ *N*-linked indole derivatives จากกระบวนการ catalytic direct coupling ของ indole โดยตรง งานวิจัยนี้ได้มีการนำเอาหลักการทาง catalysis เข้ามาใช้ และพบว่าเมื่อใช้ Iodine (I_2) เป็นตัวเร่งปฏิกิริยา สามารถเกิดผลิตภัณฑ์ ที่สามารถเกิด direct coupling ระหว่าง indole และ azole ได้โดยตรงโดย อีกทั้งยังพบว่าหากใช้ TBHP เป็นสาร oxidant จะสามารถสังเคราะห์ *N*-linked indole จาก indole และ azole ได้ในปริมาณที่น่าพอใจ โดยที่สภาวะที่เหมาะสมในปฏิกิริยาและ scope ของปฏิกิริยานี้ แสดงใน Table 1

Scope ของปฏิกิริยาค่อนข้างดี มี percent yield ของ product ที่สูง และปฏิกิริยายังเกิดแบบ regio- and chemoselective reaction ซึ่งผลจากการค้นพบในส่วนนี้เรายังได้มีการขยายงานไปในส่วนที่ 2 คือทดสอบ I_2 เป็นตัวเร่งปฏิกิริยาอื่นๆ

สำหรับการศึกษาอื่นๆ พบว่า



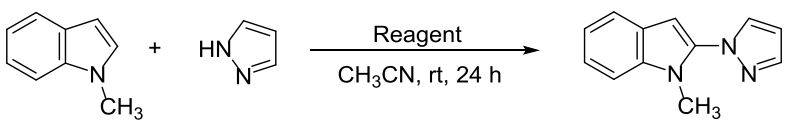
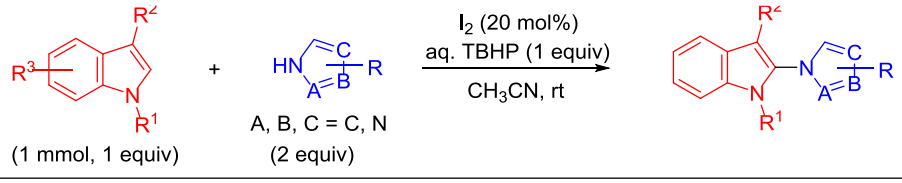
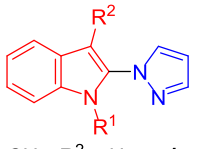


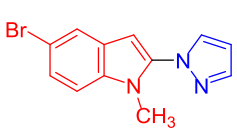
Table 1. **Synthesis of *N*-Linked Indole from Indole and Azole via Iodine-Catalyzed Reaction.**



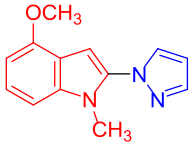
(1 mmol, 1 equiv) (2 equiv)



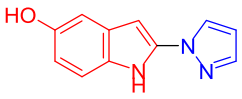
R^1 = CH_3, R^2 = H **$1a_1$** (90%)
R^1 = H, R^2 = CH_3 **$1a_2$** (85%)
R^1 = H, R^2 = H **$1a_3$** (91%)



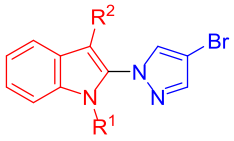
1b (44%)



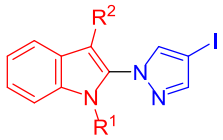
1c (86%)



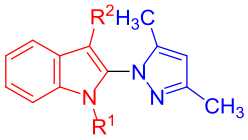
1d (79%)



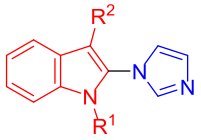
R^1 = CH_3, R^2 = H **$2a_1$** (59%)
R^1 = H, R^2 = CH_3 **$2a_2$** (91%)



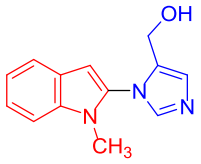
R^1 = CH_3, R^2 = H **$2b_1$** (54%)
R^1 = H, R^2 = CH_3 **$2b_2$** (69%)



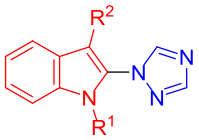
R^1 = CH_3, R^2 = H **$2c_1$** (52%)
R^1 = H, R^2 = CH_3 **$2c_2$** (71%)



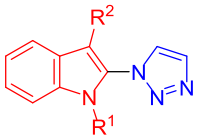
R^1 = CH_3, R^2 = H **$2d_1$** (91%)
R^1 = H, R^2 = CH_3 **$2d_2$** (97%)



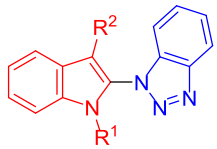
2e (50%)



R^1 = CH_3, R^2 = H **$2f_1$** (63%)
R^1 = H, R^2 = CH_3 **$2f_2$** (86%)
R^1 = H, R^2 = H **$2f_3$** (65%)

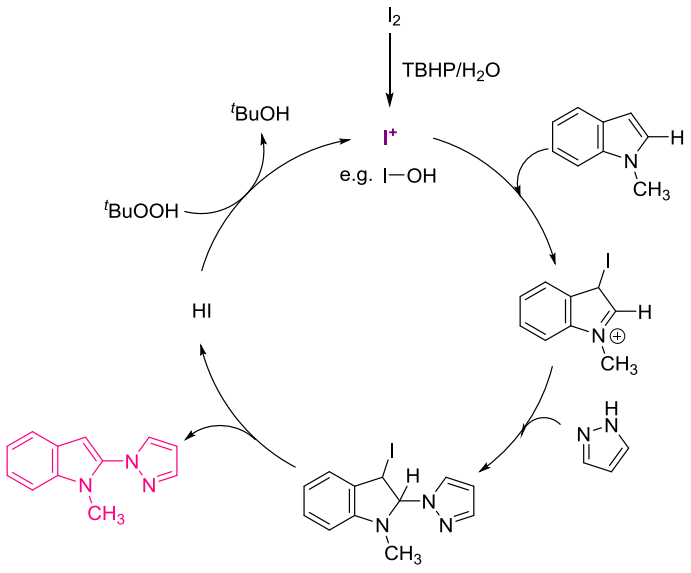


R^1 = CH_3, R^2 = H **$2g_1$** (93%)
R^1 = H, R^2 = CH_3 **$2g_2$** (86%)
R^1 = H, R^2 = H **$2g_3$** (53%)



R^1 = CH_3, R^2 = H **$2h_1$** (92%)
R^1 = H, R^2 = CH_3 **$2h_2$** (95%)
R^1 = H, R^2 = H **$2h_3$** (58%)

กลไกของปฏิกิริยาน่าจะมีแนวโน้มดังนี้

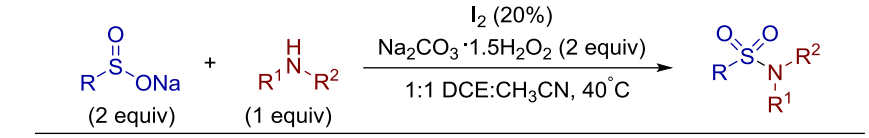


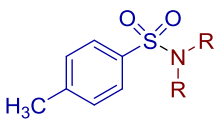
2. การสังเคราะห์ sulfonamide โดยใช้ปฏิกิริยา I_2-catalyzed oxidative amination/coupling

สืบเนื่องมากจากผลการทดลองในส่วนแรก เรายังพบว่า iodine ยังสามารถเป็นตัวเร่งปฏิกิริยาในการสังเคราะห์ sulfonamide ซึ่งเป็นสารที่ใช้มากในทางการวิจัยทางการแพทย์และเภสัชได้เช่นกัน โดยเริ่มต้นจากสารตั้งต้นที่เสถียรและหาซื้อได้ง่าย คือ amine และ sodium sulfonate

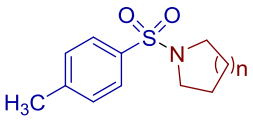
จากการศึกษาเกี่ยวกับสภาวะของปฏิกิริยา ปฏิกิริยาระหว่าง amine และ sodium sulfonate เพื่อใช้สังเคราะห์ sulfonamide นั้น สามารถใช้ I_2 เป็นตัวเร่งปฏิกิริยาเมื่อใช้สาร oxidant ที่เหมาะสมคือ $Na_2CO_3{\cdot}1.5H_2O_2$ (sodium percarbonate) ซึ่งจากการศึกษาปัจจัยต่างๆที่มีผล พบว่าสภาวะที่เหมาะสมสำหรับปฏิกิริยาและ scope ที่กว้าง ดังแสดงในตารางที่ 2 ดังนี้

Table 2. Synthesis of Sulfonamide via Iodine-Catalyzed Oxidative Amination.

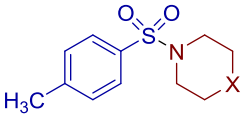




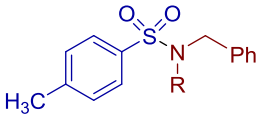
R = ethyl **3a$_1$** (81%)
R = *n*-propyl **3a$_2$** (59%)
R = H **3a$_3$** (78%)



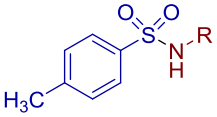
n = 1 **3b$_1$** (42%)
n = 2 **3b$_2$** (59%)
n = 3 **3b$_3$** (56%)



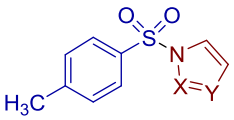
X = O **3c$_1$** (72%)
X = S **3c$_2$** (74%)
X = NH **3c$_3$** (73%)
X = NCH$_3$ **3c$_4$** (84%)
X = NBoc **3c$_5$** (50%)



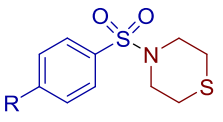
R = Bn **3d$_1$** (49%)
R = Me **3d$_2$** (62%)
R = H **3d$_3$** (68%)



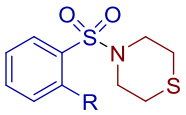
R = cyclohexyl **3e$_1$** (76%)
R = *i*-propyl **3e$_2$** (52%)
R = *t*-butyl **3e$_3$** (58%)
R = *n*-butyl **3e$_4$** (40%)



X = N Y = CH **3f$_1$** (46%)
X = CH Y = N **3f$_2$** (60%)



R = H **3g$_1$** (70%)
R = Cl **3g$_2$** (65%)
R = Br **3g$_3$** (63%)
R = OCH$_3$ **3g$_4$** (69%)
R = NO$_2$ **3g$_5$** (45%)



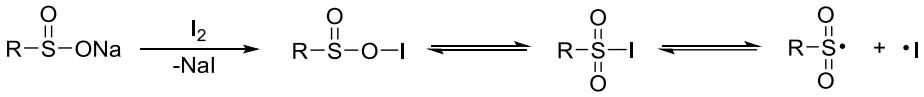
R = CH$_3$ **3h$_1$** (68%)
R = Br **3h$_2$** (35%)

X = O **3i$_1$** (76%)
X = S **3i$_2$** (72%)

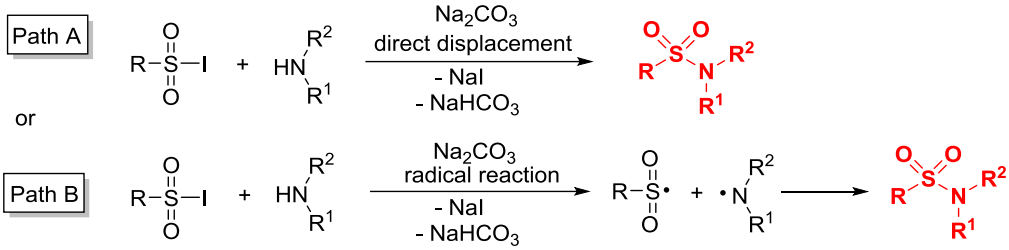
จะเห็นได้ว่าปฏิกิริยา oxidative coupling ของ amine และ sodium sulfonate ในการสังเคราะห์ sulfonamide มี scope ที่กว้าง สามารถใช้ได้กับทั้ง amine ชนิด primary และ secondary รวมถึง heteroaromatic amine และ หมู่ function หลายๆ หมู่ที่อยู่บน amine และ sodium sulfonate ก็ยัง compatible กับสภาวะของปฏิกิริยาด้วย

ในส่วนของกลไกการเกิดปฏิกิริยาน่าจะเกิดผ่าน radical ดังนี้

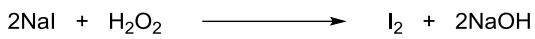
Step 1 : *In situ* formation of sulfonyl iodide



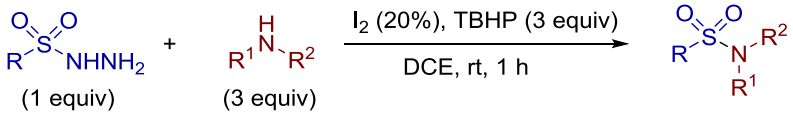
Step 2 : Sulfonamide formation



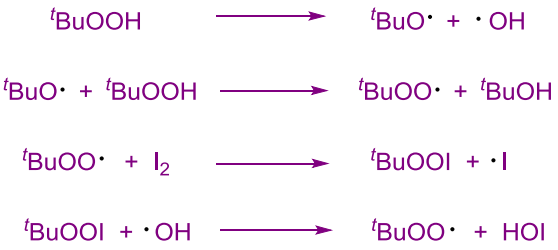
Step 3 : Oxidation



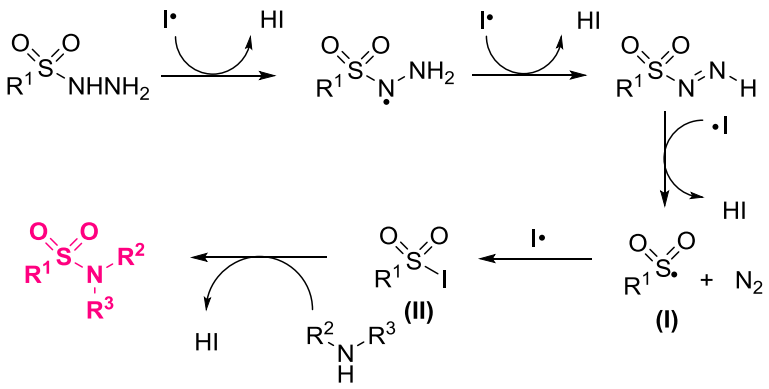
นอกเหนือจากนั้นปฏิกิริยา iodine-catalyzed oxidative coupling ระหว่าง sulfonyl hydrazide และ amine ก็สามารถเกิดผลิตภัณฑ์เป็น sulfonamides ได้เช่นกัน ซึ่งได้มีการยืนยันลักษณะโครงสร้างโดยใช้เทคนิคทาง NMR Spectroscopy และ Mass Spectroscopy และสภาวะที่เหมาะสมกับปฏิกิริยาคือ 20% I_2, TBHP oxidant, room temperature, DCE ได้ สำหรับทดสอบ substrate scope ซึ่งได้ผลดังแสดงในตารางที่ 3 และมีความเป็นไปได้ที่จะเกิดผ่าน radical pathway ดังนี้



Step 1: Generation of reactive species



Step 2: Sulfonamide formation



Step 3: Regeneration of I_2

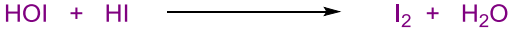
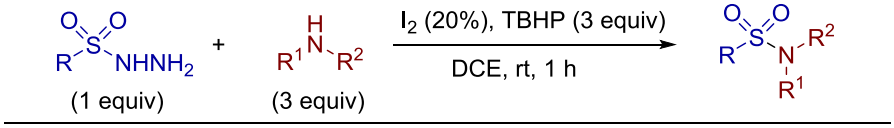
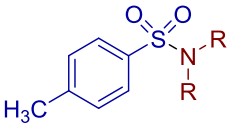
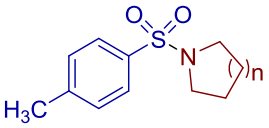


Table 3. **Synthesis of Sulfonamide from Sulfonyl Hydrazide and Amine.**

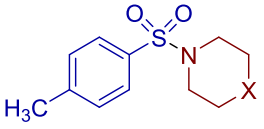




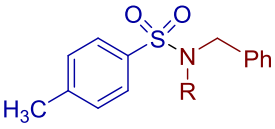
R = ethyl **4a$_1$** (84%)
R = H **4a$_2$** (66%)



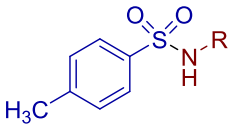
n = 1 **4b$_1$** (86%)
n = 2 **4b$_2$** (86%)
n = 3 **4b$_3$** (85%)



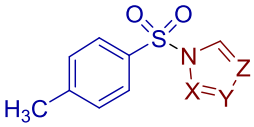
X = O **4c$_1$** (87%)
X = S **4c$_2$** (83%)
X = NCH_3 **4c$_4$** (87%)
X = NBoc **4c$_5$** (90%)



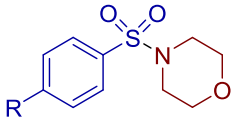
R = Bn **4d$_1$** (70%)
R = Me **4d$_2$** (89%)



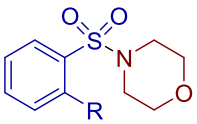
R = cyclohexyl **4e$_1$** (84%)
R = *t*-butyl **4e$_2$** (58%)
R = *n*-butyl **4e$_3$** (79%)



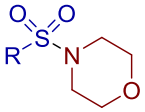
X = N Y = CH Z = CH **4f$_1$** (78%)
X = N Y = CH Z = N **4f$_2$** (59%)



R = H **4g$_1$** (82%)
R = Cl **4g$_2$** (80%)
R = Br **4g$_3$** (86%)
R = OCH_3 **4g$_4$** (89%)
R = NO_2 **4g$_5$** (87%)



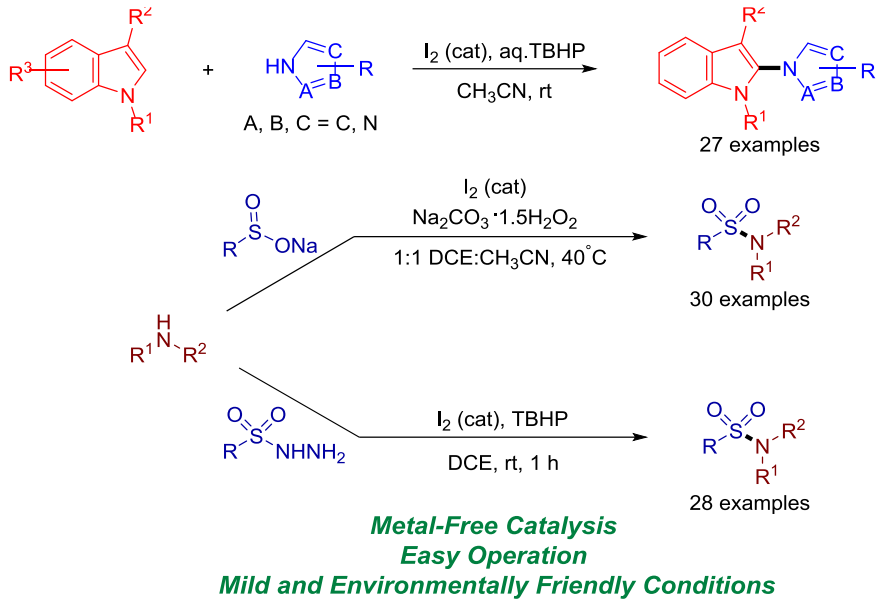
R = CH_3 **4h$_1$** (90%)
R = Br **4h$_2$** (84%)



R = mesitylene **4i$_1$** (82%)
R = quinoline **4i$_2$** (75%)
R = thiophene **4i$_3$** (41%)

อภิปรายและสรุปผลการทดลอง

We have discovered practical protocols for the synthesis of *N*-heterocycles such as *N*-linked-indoles and sulfonamides *via* metal-free catalyzed reactions. We employed molecular iodine (I_2) as catalyst in the oxidative coupling transformations. These reactions show good substrate scope, tolerate a wide range of functionalities and offer facile synthetic routes to access a variety of *N*-linked-indoles and sulfonamides, which are employed widely in medicinal chemistry and other related applications. Further efforts to expand the synthetic utility of this chemistry and to construct complex molecules are currently under investigation.



Output

International Journal Publication

(1) Iodine-Catalyzed Oxidative Cross-Coupling of Indoles and Azoles: Regioselective Synthesis of N-Linked 2 -(Azol-1 -yl)indole Derivatives. Danupat Beukeaw, Kwanchanok Udomsasporn, Sirilata Yotphan*. *J. Org. Chem.* **2015**, *80*, 3447. (Q1; IF(2014) = 4.721)

(2) Iodine-Catalyzed Oxidative Amination of Sodium Sulfinates: A Convenient Approach to the Synthesis of Sulfonamides under Mild Conditions. Chonchanok Buathongjan, Danupat Beukeaw, Sirilata Yotphan*. *Eur. J. Org. Chem.* **2015**, 1575. (Q1; IF(2014) = 3.065)

(3) Iodine-Catalyzed Expeditious Synthesis of Sulfonamides from Sulfonyl Hydrazides and Amines. Sirilata Yotphan*, Ladawan Sumunnee, Danupat Beukeaw, Chonchanok Buathongjan, Vichai Reutrakul. *Org. Biomol. Chem.* **2016**, *14*, 590. (Q1; IF(2014) = 3.562)

Appendix

JOC The Journal of Organic Chemistry

Article

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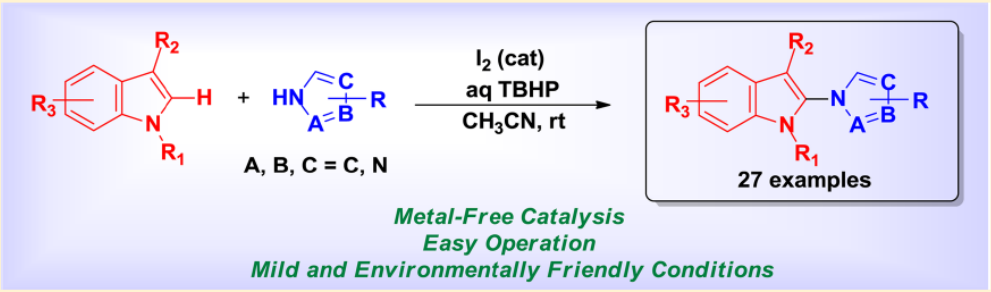
Iodine-Catalyzed Oxidative Cross-Coupling of Indoles and Azoles: Regioselective Synthesis of *N*-Linked 2-(Azol-1-yl)indole Derivatives

Danupat Beukeaw, Kwanchanok Udomsasporn, and Sirilata Yotphan*

Center for Catalysis and Center of Excellence for Innovation in Chemistry (PERCH−CIC), Department of Chemistry, Faculty of Science, Mahidol University, Bangkok 10400, Thailand

Supporting Information



ABSTRACT: A highly efficient iodine-catalyzed regioselective oxidative cross-coupling of an indole C−H bond and azole N−H bond is described. This metal-free reaction can be easily carried out at room temperature under mild and environmentally friendly conditions and provides a series of *N*-linked 2-(azol-1-yl)indole derivatives in moderate to excellence yields.

INTRODUCTION

Indoles are structural motifs prevalent in a number of biologically active natural products. They are employed widely in medicinal chemistry, pharmacological research, and material applications.[1] As a consequence of their importance, the development of efficient methodologies for the preparation and functionalization of various indole derivatives has been a subject of intense research efforts. Among many synthetic strategies available, direct C−H bond functionalization/C−C bond and C−N bond formations of indoles have received considerable attention.[2] Over the past decade, a number of studies have reported the synthesis of indoles via direct C−H bond functionalization/C−C bond construction approaches.[3] However, there are a few reports on a direct C−H bond functionalization/C−N bond formation of indole derivatives due to the lack of control over chemo- and regioselectivity in the reactions.[4]

2-(Azol-1-yl)indoles, *N*-substituted derivatives of indoles at the C-2 position, exhibit interesting pharmaceutical properties. This substituted indole moiety is present in some biologically active compounds, such as melatonin derivatives (with cardioprotective activity)[5] and celogentin and moroidin families of natural antimitotics (potent inhibitors for tubulin polymerization).[6] A general method for the synthesis of novel 2-(azol-1-yl)indoles is nucleophilic displacement on 2-halogenated indole derivatives bearing an electron-withdrawing group at the C-3 position (Scheme 1).[7] Another way to build up the 2-(azol-1-yl)indole core was reported by Poirier and Beaulieu using a thermal or microwave-mediated reaction of azoles and halogenated indoles.[8] A direct C−N bond formation of indole−azole linkage from nonactivated indole and azole was reported by Castle and co-workers.[9a] This method employed a stoichiometric amount of *N*-chlorosuccinimide (NCS) as the oxidant in the oxidative coupling reaction. The utility of this methodology was later demonstrated in the total synthesis of Celogentin C.[9b,c]

Recently, Huang and co-workers also reported an efficient protocol for the preparation of a series of 2-(azol-1-yl)indole derivatives from nonprefunctionalized indoles and azoles via iodine-mediated selective C−N bond formation in aqueous solution.[10] We envisioned that a catalytic version of this transformation should become feasible and provide an eco-friendly synthetic option because a number of recent studies have demonstrated the utility of iodine catalysis in oxidative coupling reactions.[11] The combination of catalytic amounts of iodine or iodide salts and readily available oxidants such as *tert*-butyl hydroperoxide (TBHP) or hydrogen peroxide (H_2O_2) has proven to be a versatile and powerful liaison for the successful carbon−carbon and carbon−heteroatom bond formation in many catalytic oxidative coupling methods.[12] Herein, we report regioselective C−N bond formation at the C-2 position of indoles with azoles via the I_2-catalyzed direct oxidative C−H and N−H coupling strategy. Our catalytic approach offers a facile synthesis of 2-(azol-1-yl)indole derivatives with several advantages, including metal-free regioselective catalysis, mild and environmentally benign

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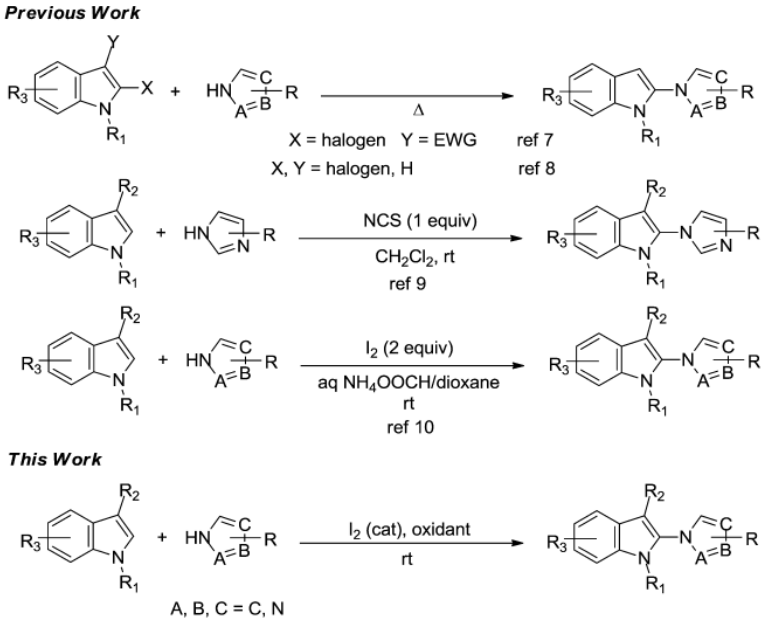
Scheme 1. Synthetic Strategies for *N*-linked 2-(Azol-1-yl)indoles

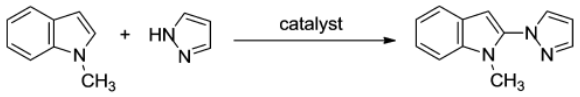


conditions, accommodation of a broad range of substrates, and avoiding the generation of toxic byproducts.

RESULTS AND DISCUSSION

We initiated this study by examining the oxidative C−H and N−H coupling reaction of 1-methylindole (**1a**) with pyrazole (**2a**) under various catalytic conditions; selected results are summarized in Table 1.[13] When the reaction of **1a** and **2a** was carried out in the presence of I_2 (20%), aq TBHP (1 equiv) in H_2O at room temperature, *N*-linkage at the C-2 position of indole (**3a**) was achieved in a promising 47% yield (Table 1, entry 1). Screening of solvents revealed that CH_3CN is the optimal solvent, in which the desired product **3a** can be generated in excellent yield (91%, entry 2). Dichloromethane (CH_2Cl_2) and 1,2-dichloroethane (DCE) are also viable solvents for this reaction (88−89%, entries 3 and 4). Other polar and nonpolar solvents are less effective (entries 5−10). Employing H_2O_2 as the oxidant gave lower yield of product (entry 11). Increasing the amount of TBHP led to a decrease in yield and caused unwanted side reactions, and incomplete conversion was observed when using less than 1 equiv of TBHP.[13] Further attempts to drive the reaction to completion by increasing temperature were unsuccessful; lower yield of product was found as temperature increased.[13] The combinations of TBHP with other forms of iodine/iodide (e.g., KI, TBAI, and NIS) showed much lower or no catalytic activity (entries 12−14, respectively). Additionally, no reaction was observed in the absence of I_2 (entry 15), and only 15% yield of product **3a** could be attained when the oxidant was omitted from the reaction (entry 16). These results indicated that both the I_2 catalyst and the TBHP oxidant play pivotal roles for this catalytic transformation.

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

entry	catalyst	oxidant	solvent	yield (%)[b]
1	I_2	TBHP	H_2O	47
2	**I_2**	**TBHP**	**CH_3CN**	**91**
3	I_2	TBHP	CH_2Cl_2	88
4	I_2	TBHP	DCE	89
5	I_2	TBHP	MeOH	63
6	I_2	TBHP	DMSO	13
7	I_2	TBHP	DMF	14
8	I_2	TBHP	THF	56
9	I_2	TBHP	1,4-dioxane	42
10	I_2	TBHP	toluene	41
11	I_2	H_2O_2	CH_3CN	54
12	KI	TBHP	CH_3CN	0
13	TBAI	TBHP	CH_3CN	0
14	NIS	TBHP	CH_3CN	5
15		TBHP	CH_3CN	0
16	I_2		CH_3CN	15

[a]Conditions: **1a** (0.5 mmol, 1 equiv), **2a** (1 mmol, 2 equiv), catalyst (0.1 mmol, 0.2 equiv), aq TBHP in water (0.5 mmol, 1 equiv), CH_3CN (2 mL), rt, 24 h. [b]GC yield.

Overall, the optimal conditions for I_2-catalyzed direct C−N bond coupling was established (Table 1, entry 2; 1 equiv of indole, 2 equiv of azole, 20 mol % of I_2, 1 equiv of aq TBHP, CH_3CN, rt, 24 h). This catalytic method employs readily available nonactivated substrates, avoids the use of excessive amounts of I_2 and TBHP oxidant, generates a minimal amount of waste, and can be conveniently carried out under mild conditions. Thus, our protocol offers good economic and environmental benefits and can be an alternative substitution for the stoichiometric I_2-mediated oxidative cross-coupling reaction or other previously reported methods.

We next explored the generality and functional group compatibility of this transformation under the established conditions. Reactions between many indole substrates and

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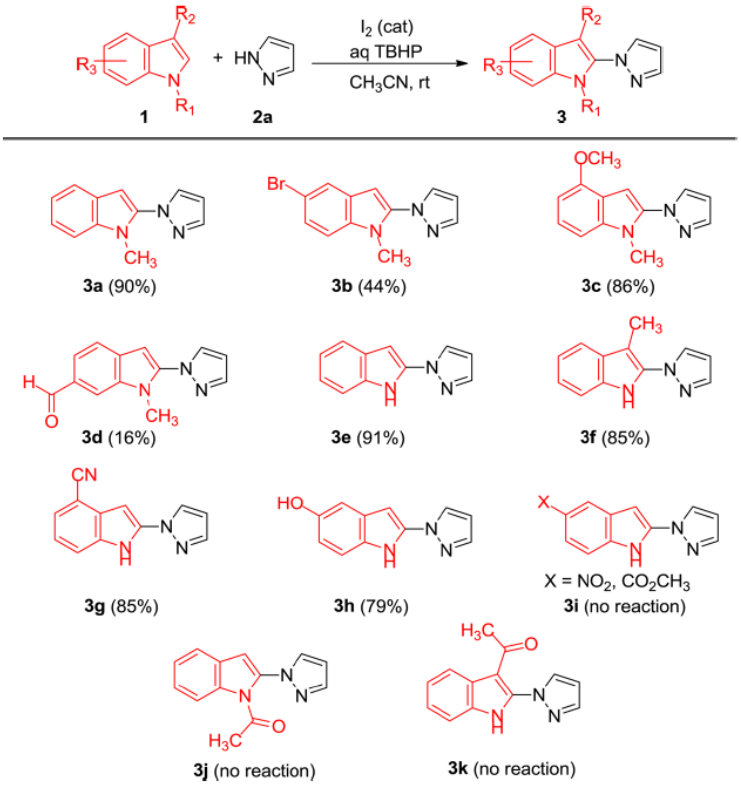
Table 2. Scope of Indoles[a]



[a]Conditions: indole (1 mmol, 1 equiv), 2a (2 mmol, 2 equiv), I_2 (0.2 mmol, 0.2 equiv), aq TBHP (1 mmol, 1 equiv), CH_3CN (4 mL), rt, 24 h. In parenthesis: isolated yields after chromatography purification.

pyrazole 2a were tested, and the results were summarized in Table 2 (3a−3h). The presence of halogen (bromo) at the C-5 position of 1-methylindole does not appear to interrupt the reaction. This 5-bromo-1-methylindole substrate gave the C−N coupling product 3b in 44% isolated yield. Gratifyingly, the electron-rich 4-methoxyl-1-methylindole substrate reacted with pyrazole to provide product 3c in decent yield. On the other hand, the presence of the electron poor formyl group at the C-6 position has a negative impact on the transformation; the corresponding product 3d was obtained in considerably low yield (16%). Apart from 1-methylindole, we also examined the reaction scope of other free indole (N−H) substrates. To our delight, free N−H indole underwent smooth coupling with pyrazole (2a), affording product 3e in excellent yield (91%). A self-coupling product between the C−H bond and the N−H bond of free indole was not observed. A reaction of 3-methylindole and pyrazole also furnished high yield of indole product 3f. These outcomes from the successful formation of products 3e and 3f thus emphasized the usefulness of this catalytic method for regioselective C−N bond coupling at the C-2 position of indole.

The electronic effects of substitutents on indole substrates were also evaluated. The indole substrate bearing an electron-poor cyano group substituted at the C-4 position delivered product 3g in very good yield. However, electronic variations in the C-5 position of indole substrates have a dramatic effect on the efficiency of the reaction. In the case of the electron-donating group (such as a hydroxyl group), good yield of product 3h can be achieved (79% isolated yield). Conversely, no reaction was observed in the case of indole substrates bearing an electron-withdrawing substituent at C-5 position (nitro and methylcarboxylate groups; 3i). In addition, 1- and 3-acetylindole do not react under optimal conditions, indicating that electronic effects from substituents on indole substrates play essential roles in this transformation.

The reactions between indoles and a variety of azoles were also examined under optimal conditions. As illustrated in Table 3, both 1-methylindole (1a) and N−H free indoles (indole and 3-methylindole) showed a tolerance toward many azole coupling partners, and the oxidative cross-coupling reactions can be achieved without any difficulties, allowing facile preparation of 2-(azol-1-yl)indoles in moderate to excellent yields. As anticipated, the reactions of these indole substrates and halogen-substituted pyrazoles (e.g., 4-bromopyrazole or 4-iodopyrazole) proceeded smoothly, affording the desired products $4a_1$, $4a_2$, $4b_1$, and $4b_2$ in reasonable to excellent quantities (54−91%). Notably, sterically hindered pyrazole (3,5-dimethylpyrazole) also gave products $4c_1$ and $4c_2$ in modest amounts. In the case of the imidazole coupling partner, the *N*-linked C-2 indole products $4d_1$ and $4d_2$ could be generated in excellent yields. It is noteworthy that reactions of indoles with 1,2,3-triazole and 1,2,4-triazole resulted in 2-(1-triazolyl)indole isomer exclusively, and the products $4e_1$, $4e_2$, $4e_3$, $4f_1$, $4f_2$, and $4f_3$ could be collected in good to excellent yields. Other regioisomers were not observed under our established coupling conditions. Benzimidazole and benzotriazole are also effective substrates for this direct C−H and N−H oxidative cross-coupling reaction (4g, $4f_1$, $4f_2$, and $4f_3$).

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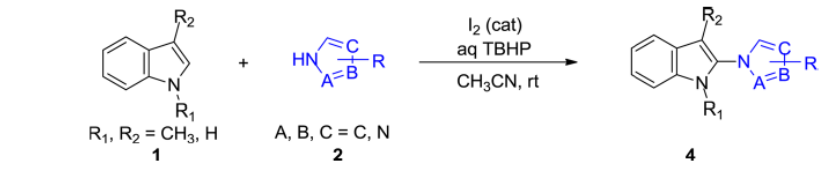
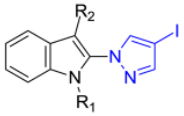
Table 3. Scope of Azoles[a]

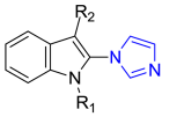


$R_1 = CH_3, R_2 = H$ **4a$_1$** (59%)
$R_1 = H, R_2 = CH_3$ **4a$_2$** (91%)

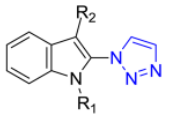


$R_1 = CH_3, R_2 = H$ **4b$_1$** (54%)
$R_1 = H, R_2 = CH_3$ **4b$_2$** (69%)

$R_1 = CH_3, R_2 = H$ **4c$_1$** (52%)
$R_1 = H, R_2 = CH_3$ **4c$_2$** (71%)

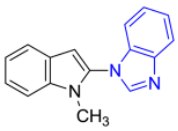


$R_1 = CH_3, R_2 = H$ **4d$_1$** (91%)
$R_1 = H, R_2 = CH_3$ **4d$_2$** (97%)

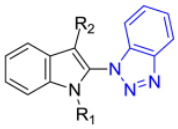


$R_1 = CH_3, R_2 = H$ **4e$_1$** (93%)
$R_1 = H, R_2 = CH_3$ **4e$_2$** (86%)
$R_1 = H, R_2 = H$ **4e$_3$** (53%)

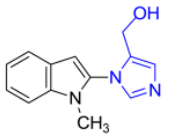
$R_1 = CH_3, R_2 = H$ **4f$_1$** (63%)
$R_1 = H, R_2 = CH_3$ **4f$_2$** (86%)
$R_1 = H, R_2 = H$ **4f$_3$** (65%)



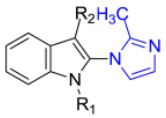
4g (78%)



$R_1 = CH_3, R_2 = H$ **4h$_1$** (92%)
$R_1 = H, R_2 = CH_3$ **4h$_2$** (95%)
$R_1 = H, R_2 = H$ **4h$_3$** (58%)



4i (50%)



$R_1 = CH_3, R_2 = H$ **4j$_1$** (trace)
$R_1 = H, R_2 = CH_3$ **4j$_2$** (trace)
$R_1 = H, R_2 = H$ **4j$_3$** (trace)

[a]Conditions: indole (1 mmol, 1 equiv), azole (2 mmol, 2 equiv), I_2 (0.2 mmol, 0.2 equiv), aq TBHP (1 mmol, 1 equiv), CH_3CN (4 mL), rt, 24 h. In parenthesis: isolated yields after chromatography purification.

Interestingly, the azole substrate containing an oxidant-sensitive hydroxyl group is compatible with the reaction conditions. The C−N coupling product **4i** was formed selectively in one regioisomer without impacting the hydroxyl group, demonstrating the mild nature of our protocol. The regiochemistry of the isolated coupling product (**4i**) was confirmed by the two-dimensional NOESY spectrum (see the Supporting Information), which exhibits the through-space correlations between indole-hydrogen at the C-3 position and imidazole-CH_2OH at the C-5 position as well as an indole methyl (CH_3) group at the N-1 position and imidazole-hydrogen at the C-2 position.[13] Nonetheless, 2-methylimidazole is unable to couple with indoles under these conditions; only trace amounts of products **4j$_1$**, **4j$_2$**, and **4j$_3$** were detected by GCMS. These results suggested that the steric hindrance from the methyl group at the C-2 position of imidazole could interfere with product formation.

To gain insight into the reaction mechanism, a series of control experiments were conducted (Scheme 2). When a radical inhibitor was employed in the reaction of indole **1a** and azole **2a**, no inhibition was observed under optimal conditions (Scheme 2a). The product can be obtained in 60, 96, and 94% in the presence of TEMPO, BHT, and hydroquinone, respectively. Therefore, these results suggested that the reaction is not likely to involve a radical pathway. To provide further evidence regarding the role of iodine and TBHP, the reaction was carried out without the use of an oxidant. The yield of product **3a** was significantly reduced when subjecting **1** or **2** equiv of I_2 to this reaction (Scheme 2b), which implied that I_2 is not likely to be the catalytic active species. These results are different from that reported by Huang and co-workers (2012), who showed that a stoichiometric amount (1−2 equiv) of I_2 can be utilized to mediate the oxidative C−N coupling reaction in a saturated aqueous ammonium salt solution. Under our standard conditions, however, the I_2 precatalyst could likely be converted to another active intermediate prior to entering the catalytic cycle. In the absence of TBHP, excess I_2 would presumably directly react with the starting material and lead to unwanted side reactions.[13]

Although the combination of a catalytic amount of iodide anion (I^-) and TBHP oxidant was insufficient to elaborate successful formation of the *N*-linked indole product (Table 1, entries 12 and 13), the reaction of indole **1a** and pyrazole **2a** in the presence of catalytic HI (hydroiodic acid) and TBHP

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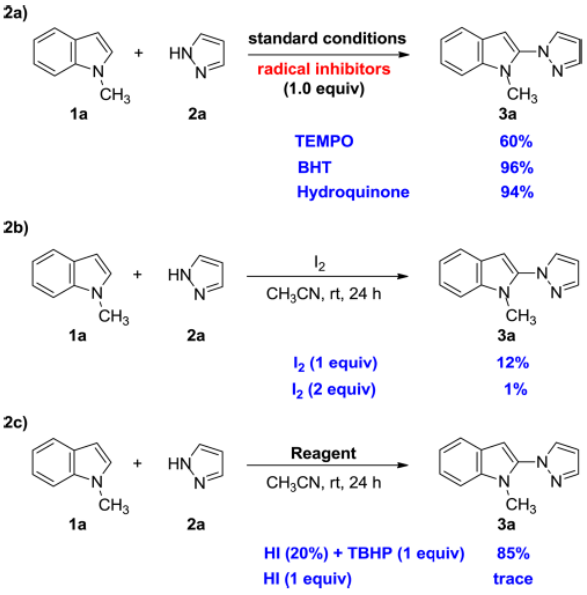
Scheme 2. Control Experiments



oxidant afforded product 3a in 85% yield (Scheme 2c). This result implied that a catalytic amount of acid might be required for conversion of an iodide anion to an active species in this reaction. We also speculated that H^+ and I^- (HI) are possibly involved in the catalytic cycle. To verify whether HI could facilitate product formation, the reaction of **1a** and **2a** was treated with only a stoichiometric amount of HI. In this case, no product was obtained. This outcome underlined the necessity of TBHP oxidant to convert not only I_2, but also HI (iodide anion in acidic medium) to the active catalytic species in this transformation.

On the basis of the results described above and relevant literature,[9−12] a plausible mechanism for this transition-metal-free oxidative coupling is proposed using 1-methylindole **1a** and pyrazole **2a** as the model substrates. Under the optimal reaction conditions, the initial process could involve *in situ* iodination, giving an electrophilic iodine species ("I^+"), such as hypoiodous (HIO) or iodous acid (HIO_2).[11b,14,15] Then, nucleophilic attack of this "I^+" species by indole will generate either active iodonium ion **A** or 3-iodo iminium intermediate **B**.[4f,10] This intermediate can be trapped by a nucleophilic azole, leading to the formation of key intermediate **C**.[8,9a] Subsequent elimination of HI would furnish the corresponding 2-(azol-1-yl)indole product. Further oxidation of HI by TBHP would reproduce the "I^+" species to resume the catalytic cycle as depicted in Scheme 3.

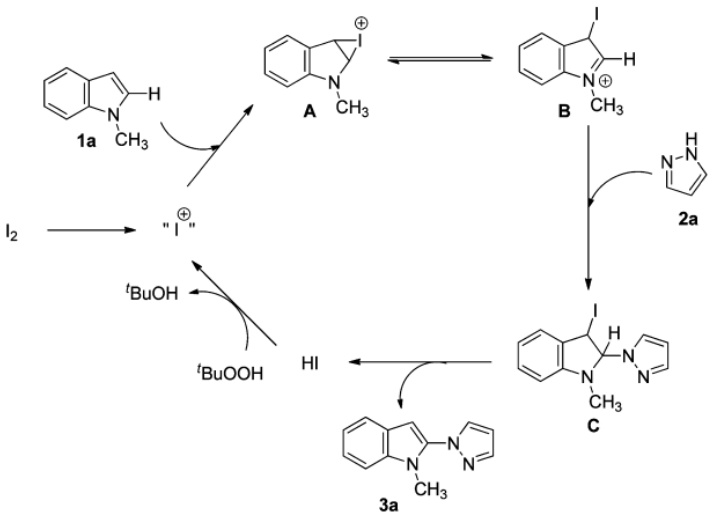
CONCLUSION

In summary, we have disclosed an expedient metal-free catalytic protocol for regio- and chemoselective C−N bond formation of indoles with azoles. This iodine-catalyzed oxidative coupling reaction can be carried out at room temperature under mild conditions with good scope using a ubiquitous and inexpensive catalytic combination. This catalytic transformation provides a convenient synthetic route with good economical and environmental advantages to access a series of *N*-linked 2-(azol-1-yl)indole derivatives, which have potential applications in medicinal chemistry. Mechanistic studies and further extension of this methodology to other substrates are currently under investigation.

EXPERIMENTAL SECTION

General Information. Unless otherwise specified, all experiments were carried out under air atmosphere. All reagents were obtained from commercial suppliers and used without further purification. Oven-dried glassware was used in all cases. Column chromatography was performed over silica gel (SiO_2; 60 Å silica gel, 70−230 Mesh). GC experiments were carried out with a GC-FID on a chromatograph equipped with an HP-1 polysiloxane column (24.5 m × 0.32 mm ID × 0.17 μm). ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz in $CDCl_3$ or DMSO-d_6 solution. NMR chemical shifts are reported in ppm and were measured relative to $CHCl_3$ (7.24 ppm for ^{1}H and 77.00 ppm for ^{13}C) or DMSO (2.51 ppm for ^{1}H and 39.51 ppm for ^{13}C). IR spectra were recorded on an FT-IR spectrometer, and only partial data are listed. High resolution mass spectroscopy (HRMS) data were analyzed by a high-resolution micrOTOF

Scheme 3. Tentative Reaction Mechanism



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instrument with electrospray ionization (ESI). The structures of known compounds were corroborated by comparing their ^{1}H and ^{13}C NMR data with values from the literature.[9]

General Procedure for the Synthesis of Compounds 3a−3h and 4a−4i. A 20 mL oven-dried scintillation vial equipped with a magnetic stir bar was charged with a mixture of indole substrate (1.00 mmol, 1.00 equiv), azole (2.00 mmol, 2.00 equiv), iodine (I_2, 51 mg, 0.20 mmol, 0.20 equiv), TBHP in water (1.00 mmol, 1.00 equiv), and acetonitrile (CH_3CN) (4.00 mL). The vial was capped, and the reaction mixture was stirred at room temperature for 24 h. Upon completion, saturated $Na_2S_2O_3$ (5 mL) and distilled deionized H_2O (12 mL) was added, and the mixture was extracted with ethyl acetate (EtOAc) (2 × 25 mL). The combined organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography to afford the desired *N*-linked 2-(azol-1-yl)indole product.

1-Methyl-2-(1H-pyrazol-1-yl)-1H-indole (**3a**).[10] Following the general procedure, the product was isolated as a white solid in 177.5 mg (90%) by column chromatography (4:1 hexanes/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 1.2 Hz, 1H), 7.72 (d, J = 2.4 Hz, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.36−7.34 (m, 1H), 7.31−7.27 (m, 1H), 7.19−7.15 (m, 1H), 6.51 (s, 1H), 6.47 (t, J = 2.0 Hz, 1H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.8, 135.7, 132.4, 126.0, 122.6, 121.0, 120.4, 109.6, 106.8, 95.9, 29.9. HRMS (ESI+, m/z): [M + H]$^+$ calcd for $C_{12}H_{12}N_3$, 198.1026; found, 198.1031.

5-Bromo-1-methyl-2-(1H-pyrazol-1-yl)-1H-indole (**3b**).[10] Following the general procedure, the product was isolated as a white solid in 121.1 mg (44%) by column chromatography (6:1 hexanes/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (d, J = 1.6 Hz, 1H), 7.73−7.72 (m, 2H), 7.37−7.34 (m, 1H), 7.22−7.20 (m, 1H), 6.47 (t, J = 2.0 Hz, 1H), 6.44 (s, 1H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.1, 136.6, 134.4, 132.3, 127.7, 125.5, 123.4, 113.6, 111.2, 107.1, 95.2, 30.2. HRMS (ESI+, m/z): [M + H]$^+$ calcd for $C_{12}H_{11}BrN_3$, 276.0131; found, 276.0130.

4-Methoxy-1-methyl-2-(1H-pyrazol-1-yl)-1H-indole (**3c**). Following the general procedure, the product was isolated as a white solid in 194.6 mg (86%) by column chromatography (4:1 hexanes/ethyl acetate). Mp 82.3−83.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 1.2 Hz, 1H), 7.71−7.70 (m, 1H), 7.23−7.19 (m, 1H), 6.97 (d, J = 8.0 Hz, 1H), 6.60−6.57 (m, 2H), 6.45−6.44 (m, 1H), 3.95 (s, 3H), 3.65 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 153.5, 141.8, 137.0, 134.3, 132.4, 123.4, 116.6, 106.7, 103.0, 100.2, 93.3, 55.4, 30.2. IR (neat, cm^{-1}): 3145, 2929, 2838, 1889, 1569, 1501, 1463, 1388, 1355, 1250, 1104, 929, 624. HRMS (ESI+, m/z): [M + Na]$^+$ calcd for $C_{13}H_{13}N_3NaO$, 250.0951; found, 250.0949.

1-Methyl-2-(1H-pyrazol-1-yl)-1H-indole-6-carbaldehyde (**3d**). Following the general procedure, the product was isolated as a white solid in 35.4 mg (16%) by column chromatography (4:1 hexanes/ethyl acetate). Mp 117.9−119.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.07 (s, 1H), 7.93 (s, 1H), 7.83 (d, J = 1.2 Hz, 1H), 7.78 (d, J = 2.0 Hz, 1H), 7.72−7.67 (m, 2H), 6.55 (d, J = 0.8 Hz, 1H), 6.51 (t, J = 2.0 Hz, 1H), 3.84 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 192.1, 142.4, 139.4, 135.5, 132.0, 131.4, 131.3, 121.9, 121.1, 112.2, 107.5, 95.7, 30.6. IR (neat, cm^{-1}): 3114, 2922, 1674, 1570, 1468, 1369, 1221, 930, 811, 756, 627. HRMS (ESI+, m/z): [M + H]$^+$ calcd for $C_{13}H_{12}N_3O$, 226.0980; found, 226.0975.

2-(1H-Pyrazol-1-yl)-1H-indole (**3e**).[10] Following the general procedure, the product was isolated as a brown solid in 166.7 mg (91%) by column chromatography (4:1 hexanes/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.41 (br s, 1H), 7.95 (d, J = 2.4 Hz, 1H), 7.71 (d, J = 1.6 Hz, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.19−7.10 (m, 2H), 6.48 (t, J = 2.0 Hz, 1H), 6.41−6.40 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 140.8, 135.5, 133.5, 127.8, 127.6, 122.0, 120.6, 120.3, 111.0, 108.0, 87.1. HRMS (ESI+, m/z): [M + H]$^+$ calcd for $C_{11}H_{10}N_3$, 184.0869; found, 184.0870.

3-Methyl-2-(1H-pyrazol-1-yl)-1H-indole (**3f**).[10] Following the general procedure, the product was isolated as an off-white solid in 167.2 mg (85%) by column chromatography (4:1 hexanes/ethyl acetate). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.33 (br s, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.75 (d, J = 1.5 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.22−7.13 (m, 2H), 6.51 (t, J = 2.0 Hz, 1H), 2.42 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 140.6, 132.9, 131.4, 129.3, 128.6, 122.4, 119.9, 118.7, 110.9, 107.3, 98.1, 8.6. HRMS (ESI+, m/z): [M + H]$^+$ calcd for $C_{12}H_{12}N_3$, 198.1026; found, 198.1031.

2-(1H-Pyrazol-1-yl)-1H-indole-4-carbonitrile (**3g**). Following the general procedure, the product was isolated as a white solid in 177.0 mg (85%) by column chromatography (4:1 hexanes/ethyl acetate). Mp 203.6−203.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.10 (s, 1H), 8.02 (d, J = 2.4 Hz, 1H), 7.75 (d, J = 1.2 Hz, 1H), 7.51 (d, J = 7.6 Hz, 1H), 7.48−7.45 (m, 1H), 7.21−7.16 (m, 1H), 6.61 (d, J = 1.2 Hz, 1H), 6.56−6.55 (m, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.7, 137.6, 132.9, 130.0, 127.8, 125.8, 121.6, 118.6, 115.5, 108.9, 102.6, 85.7. IR (neat, cm^{-1}): 3211, 3123, 2349, 2219, 2013, 1573, 1367, 1195, 1046, 772, 604. HRMS (ESI+, m/z): [M + Na]$^+$ calcd for $C_{12}H_8N_4Na$, 231.0641; found, 231.0646.

2-(1H-Pyrazol-1-yl)-1H-indol-5-ol (**3h**). Following the general procedure, the product was isolated as a pale-white solid in 158.1 mg (79%) by column chromatography (1:1 hexanes/ethyl acetate). Mp 188.3−189.8 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.54 (br s, 1H), 8.80 (s, 1H), 8.35 (d, J = 2.4 Hz, 1H), 7.77 (d, J = 1.4 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H), 6.61−6.59 (m, 1H), 6.56−6.55 (m, 1H), 6.41 (d, J = 1.2 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, DMSO): δ 151.4, 140.9, 136.2, 128.5, 128.3, 128.2, 112.0, 111.3, 107.8, 104.1, 87.2. IR (neat, cm^{-1}): 3436, 3069, 2920, 1645, 1511, 1476, 1318, 1201, 1052, 792, 740, 641. HRMS (ESI+, m/z): [M + Na]$^+$ calcd for $C_{11}H_9N_3NaO$, 222.0638; found, 222.0640.

2-(4-Bromo-1H-pyrazol-1-yl)-1-methyl-1H-indole (**4a$_1$**). Following the general procedure, the product was isolated as a white solid in 163.6 mg (59%) by column chromatography (10:1 hexanes/ethyl acetate). Mp 131.1−131.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.78 (s, 1H), 7.74 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.37−7.30 (m, 2H), 7.22−7.18 (m, 1H), 6.52 (s, 1H), 3.67 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 142.4, 135.7, 134.7, 132.2, 125.8, 122.9, 121.1, 120.6, 109.7, 96.3, 94.9, 29.9. IR (neat, cm^{-1}): 3137, 2938, 1699, 1480, 1454, 1337, 953, 775,755, 609. HRMS (ESI+, m/z): [M + H]$^+$ calcd for $C_{12}H_{11}BrN_3$, 276.0131; found, 276.0134.

2-(4-Bromo-1H-pyrazol-1-yl)-3-methyl-1H-indole (**4a$_2$**). Following the general procedure, the product was isolated as a white solid in 250.6 mg (91%) by column chromatography (10:1 hexanes/ethyl acetate). Mp 71.0−71.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.83 (s, 1H), 7.91 (s, 1H), 7.68 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 1H), 7.23−7.20 (m, 1H), 7.18−7.14 (m, 1H), 2.40 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 141.2, 132.8, 130.6, 129.2, 128.4, 122.9, 120.2, 119.0, 110.9, 99.0, 95.4, 8.6. IR (neat, cm^{-1}): 3364, 3244, 3113, 2920, 1718, 1584, 1451, 1381, 950, 736, 576. HRMS (ESI+, m/z): [M + H]$^+$ calcd for $C_{12}H_{11}BrN_3$, 276.0131; found, 276.0138.

2-(4-Iodo-1H-pyrazol-1-yl)-1-methyl-1H-indole (**4b$_1$**). Following the general procedure, the product was isolated as an off-white solid in 173.6 mg (54%) by column chromatography (10:1 hexanes/ethyl acetate). Mp 156.3−157.5 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.80 (s, 1H), 7.76 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.36−7.29 (m, 2H), 7.20−7.16 (m, 1H), 6.51 (s, 1H), 3.66 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 146.8, 136.5, 135.7, 134.5, 125.8, 122.9, 121.1, 120.6, 109.7, 96.3, 58.2, 29.9. IR (neat, cm^{-1}): 3130, 2921, 2337, 1563, 1454, 1334, 1165, 953, 855, 776, 610. HRMS (ESI+, m/z): [M + Na]$^+$ calcd for $C_{12}H_{10}IN_3Na$, 345.9812; found, 345.9816.

2-(4-Iodo-1H-pyrazol-1-yl)-3-methyl-1H-indole (**4b$_2$**). Following the general procedure, the product was isolated as a white solid in 221.5 mg (69%) by column chromatography (10:1 hexanes/ethyl acetate). Mp 61.7−62.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.62 (s, 1H), 7.94 (s, 1H), 7.72 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.32 (d, J = 8.0 Hz, 1H), 7.22−7.20 (m, 1H), 7.18−7.14 (m, 1H), 2.41 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 145.5, 133.4, 132.8, 130.5, 128.4, 122.9, 120.1, 119.0, 110.9, 99.0, 58.6, 8.7. IR (neat, cm^{-1}): 3277, 3139, 2917, 1714, 1595, 1505, 1452, 1019, 939, 737. HRMS (ESI+, m/z): [M + H]$^+$ calcd for $C_{12}H_{11}IN_3$, 323.9992; found, 323.9999.

2-(3,5-Dimethyl-1H-pyrazol-1-yl)-1-methyl-1H-indole (**4c$_1$**). Following the general procedure, the product was isolated as a yellow solid in 116.3 mg (52%) by column chromatography (9:1 hexanes/ethyl acetate). Mp 45.7−46.3 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63

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(d, J = 8.0 Hz, 1H), 7.34−7.26 (m, 2H), 7.18−7.14 (m, 1H), 6.51 (d, J = 0.8 Hz, 1H), 6.01 (s, 1H), 3.48 (s, 3H), 2.31 (s, 3H), 2.16 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.1, 142.7, 135.5, 133.6, 126.1, 122.5, 121.1, 120.1, 109.5, 106.0, 98.4, 29.2, 13.6, 11.4. IR (neat, cm^{-1}): 3053, 2924, 2349, 1563, 1451, 1393, 1345, 1314, 1119, 1030, 783, 730, 656. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{14}H_{16}N_3$, 226.1344; found, 226.1342.

*2-(3,5-Dimethyl-1H-pyrazol-1-yl)-3-methyl-1H-indole (**4c$_2$**).* Following the general procedure, the product was isolated as a white solid in 159.7 mg (71%) by column chromatography (9:1 hexanes/ethyl acetate). Mp 173.9−174.9 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.48 (s, 1H), 7.57 (d, J = 7.6 Hz, 1H), 7.30−7.28 (m, 1H), 7.22−7.20 (m, 1H), 7.16−7.12 (m, 1H), 5.97 (s, 1H), 2.26 (s, 3H) 2.18−2.17 (m, 6H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 150.3, 142.4, 133.7, 129.3, 127.7, 123.0, 119.7, 119.3, 111.0, 106.1, 105.9, 13.6, 11.2, 8.5. IR (neat, cm^{-1}): 3057, 2917, 2349, 1629, 1452, 1300, 1131, 1037, 778, 735. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{14}H_{16}N_3$, 226.1344; found, 226.1354.

*2-(1H-Imidazol-1-yl)-1-methyl-1H-indole (**4d$_1$**).*[10] Following the general procedure, the product was isolated as a yellow solid in 179.2 mg (91%) by column chromatography (1:4 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.35−7.29 (m, 2H), 7.25−7.24 (m, 1H), 7.21−7.17 (m, 1H), 7.14 (s, 1H), 6.53 (s, 1H), 3.52 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 138.7, 135.6, 132.1, 130.0, 125.9, 123.0, 121.3, 121.1, 120.8, 109.7, 97.8, 29.2. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{12}H_{12}N_3$, 198.1026; found, 198.1031.

*2-(1H-Imidazol-1-yl)-3-methyl-1H-indole (**4d$_2$**).*[8] Following the general procedure, the product was isolated as a white solid in 191.3 mg (97%) by column chromatography (1:4 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 11.14 (s, 1H), 7.69 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.30−7.25 (m, 2H), 7.23−7.19 (m, 1H), 7.15 (s, 1H), 2.29 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 137.3, 133.7, 128.5, 127.8, 127.7, 122.8, 120.7, 119.8, 119.0, 111.2, 103.3, 7.9. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{12}H_{12}N_3$, 198.1026; found, 198.1040.

*1-Methyl-2-(1H-1,2,3-triazol-1-yl)-1H-indole (**4e$_1$**).*[10] Following the general procedure, the product was isolated as a yellow solid in 184.3 mg (93%) by column chromatography (2:1 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 7.87 (dd, J = 5.2, 0.8 Hz, 2H), 7.65 (d, J = 8.0 Hz, 1H), 7.39−7.32 (m, 2H), 7.22−7.18 (m, 1H), 6.62 (s, 1H), 3.66 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 135.9, 133.5, 131.4, 126.5, 125.7, 123.4, 121.3, 120.8, 109.9, 97.3, 30.0. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{11}H_{11}N_4$, 199.0978; found, 199.0984.

*3-Methyl-2-(1H-1,2,3-triazol-1-yl)-1H-indole (**4e$_2$**).*[8] Following the general procedure, the product was isolated as a white solid in 170.6 mg (86%) by column chromatography (2:1 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 9.03 (s, 1H), 8.04 (d, J = 1.0 Hz, 1H), 7.88 (d, J = 1.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.30−7.26 (m, 1H), 7.21−7.17 (m, 1H), 2.40 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 134.1, 133.4, 127.9, 127.5, 123.7, 123.5, 120.4, 119.4, 111.3, 101.7, 8.5. IR (neat, cm^{-1}): 3170, 2917, 2349, 1626, 1504, 1417, 1231, 1027, 766, 742. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{11}H_{11}N_4$, 199.0978; found, 199.0992.

*2-(1H-1,2,3-Triazol-1-yl)-1H-indole (**4e$_3$**).*[10] Following the general procedure, the product was isolated as a white solid in 96.9 mg (53%) by column chromatography (2:1 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 9.35 (s, 1H), 8.06 (s, 1H), 7.85 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.29−7.25 (m, 1H), 7.19−7.16 (m, 1H), 6.58−6.57 (m, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 134.5, 133.8, 131.4, 127.0, 123.5, 121.7, 121.2, 121.0, 111.4, 90.5. HRMS (ESI+, m/z): $[M + Na]^+$ calcd for $C_{10}H_8N_4Na$, 207.0641; found, 207.0650.

*1-Methyl-2-(1H-1,2,4-triazol-1-yl)-1H-indole (**4f$_1$**).*[10] Following the general procedure, the product was isolated as a yellow solid in 124.9 mg (63%) by column chromatography (1:2 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.38 (s, 1H), 8.19 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.38−7.31 (m, 2H), 7.22−7.18 (m, 1H), 6.61 (s, 1H), 3.66 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 153.2, 145.5, 136.0 131.2, 125.6, 123.4, 121.4, 120.8, 109.8, 97.5, 29.9. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{11}H_{11}N_4$, 199.0978; found, 199.0986.

*3-Methyl-2-(1H-1,2,4-triazol-1-yl)-1H-indole (**4f$_2$**).* Following the general procedure, the product was isolated as a white solid in 169.9 mg (86%) by column chromatography (1:1 hexanes/ethyl acetate). Mp 125.2−125.5 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 8.96 (s, 1H), 8.52 (s, 1H), 8.14 (s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.0 Hz, 1H), 7.28−7.25 (m, 1H), 7.23−7.16 (m, 1H), 2.39 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.1, 142.8, 133.3, 128.0, 127.5, 123.5, 120.4, 119.3, 111.1, 101.6, 8.5. IR (neat, cm^{-1}): 3117, 2916, 1721, 1509, 1334, 1144, 983, 962, 729, 666. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{11}H_{11}N_4$, 199.0978; found, 199.0988.

*2-(1H-1,2,4-Triazol-1-yl)-1H-indole (**4f$_3$**).*[10] Following the general procedure, the product was isolated as a white solid in 119.8 mg (65%) by column chromatography (1:1 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 9.29 (s, 1H), 8.61 (s, 1H) 8.12 (s, 1H), 7.61 (d, J = 8.0 Hz, 1H), 7.38 (dd, J = 8.0, 0.8 Hz, 1H), 7.26−7.22 (m, 1H), 7.19−7.15 (m, 1H), 6.58 (d, J = 1.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 152.2, 141.4, 133.6, 131.3, 127.2, 123.1, 121.1, 120.9, 111.3, 90.0. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{10}H_9N_4$, 185.0822; found, 185.0824.

*1-(1-Methyl-1H-indol-2-yl)-1H-benzo[d]imidazole (**4g**).* Following the general procedure, the product was isolated as a white solid in 193.4 mg (78%) by column chromatography (1:2 hexanes/ethyl acetate). Mp 144.4−145.1 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.98 (s, 1H), 7.87−7.85 (m, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.36−7.26 (m, 4H), 7.22−7.16 (m, 2H), 6.60 (s, 1H), 3.43 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.6, 143.2, 135.9, 135.4, 130.3, 126.2, 124.3, 123.2, 123.1, 121.2, 120.7, 120.6, 110.5, 109.8, 99.1, 29.4. IR (neat, cm^{-1}); 3113, 2923, 1581, 1454, 1399, 1220, 751, 733, 659. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{16}H_{14}N_3$, 248.1188; found, 248.1180.

*1-(1-Methyl-1H-indol-2-yl)-1H-benzo[d][1,2,3]triazole (**4h$_1$**).* Following the general procedure, the product was isolated as a pale-yellow solid in 227.7 mg (92%) by column chromatography (4:1 hexanes/ethyl acetate). Mp 158.0−158.7 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.99 (d, J = 8.0 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.40−7.36 (m, 2H), 7.30−7.26 (m, 2H), 7.21−7.17 (m, 1H), 7.07−7.03 (m, 1H), 6.58 (s, 1H), 3.46 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 145.4, 136.0, 134.7, 130.2, 128.9, 126.1, 124.7, 123.4, 121.4, 120.8, 120.2, 110.2, 109.9, 98.2, 29.9. IR (neat, cm^{-1}): 3053, 2930, 1561, 1451, 1318, 1286, 1035, 788, 744, 651. HRMS (ESI+, m/z): $[M + Na]^+$ calcd for $C_{15}H_{12}N_4Na$, 271.0954; found, 271.0963.

*1-(3-Methyl-1H-indol-2-yl)-1H-benzo[d][1,2,3]triazole (**4h$_2$**).* Following the general procedure, the product was isolated as a yellow gel, 235.9 mg (95%) by column chromatography (4:1 hexanes/ethyl acetate). ^1H NMR (400 MHz, $CDCl_3$): δ 8.49 (s, 1H), 8.14 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.58−7.54 (m, 1H), 7.51−7.48 (m, 1H), 7.47−7.42 (m, 2H), 7.34 (td, J = 8.0, 1.2 Hz, 1H), 7.26−7.22 (m, 1H), 2.27 (s, 3H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 145.4, 134.3, 133.9, 128.7, 127.9, 125.8, 124.6, 123.9, 120.4, 120.3, 119.7, 111.3, 110.3, 106.8, 8.60. IR (neat, cm^{-1}): 3209, 2919, 1920, 1722, 1452, 1278, 1048, 1004, 782, 739. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{15}H_{13}N_4$, 249.1135; found, 249.1149.

*1-(1H-Indol-2-yl)-1H-benzo[d][1,2,3]triazole (**4h$_3$**).* Following the general procedure, the product was isolated as a white solid in 135.3 mg (58%) by column chromatography (4:1 hexanes/ethyl acetate). Mp 166.1−166.3 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 9.57 (s, 1H), 8.14 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.70−7.68 (m, 1H), 7.64−7.60 (m, 1H), 7.51−7.44 (m, 2H), 7.31−7.26 (m, 1H), 7.22−7.18 (m, 1H), 6.78 (d, J = 1.6 Hz, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 146.2, 133.7, 131.4, 131.2, 129.0, 127.4, 125.0, 123.2, 121.0, 120.9, 120.4, 111.3, 110.8, 91.0. IR (neat, cm^{-1}): 3363, 1561, 1445, 1296, 1061, 766, 748, 738, 648, 548. HRMS (ESI+, m/z): $[M + Na]^+$ calcd for $C_{14}H_{10}N_4Na$, 257.0803; found, 257.0815.

*(1-(1-Methyl-1H-indol-2-yl)-1H-imidazol-5-yl)methanol (**4i**).* Following the general procedure, the product was isolated as a white solid in 113.6 mg (50%) by column chromatography (1:9 methanol/ethyl acetate). Mp 156.0−157.2 °C. ^1H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.0 Hz, 1H), 7.47 (s, 1H), 7.34−7.28 (m, 2H), 7.18−7.14 (m,

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1H), 7.06 (s, 1H), 6.58 (s, 1H), 4.44 (s, 2H), 3.42 (s, 3H), 3.02 (br s, 1H). $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 139.7, 135.7, 133.7, 129.8, 128.5, 125.9, 123.2, 121.2, 120.7, 109.8, 99.8, 53.5, 29.1. IR (neat, cm^{-1}): 3770, 3591, 3140, 2783, 1670, 1562, 1562, 1467, 1098, 1030, 926, 752, 661. HRMS (ESI+, m/z): $[M + H]^+$ calcd for $C_{13}H_{14}N_3O$, 228.1131; found, 228.1130.

■ ASSOCIATED CONTENT

Supporting Information

^1H and ^{13}C spectra and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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FULL PAPER

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Iodine-Catalyzed Oxidative Amination of Sodium Sulfinates: A Convenient Approach to the Synthesis of Sulfonamides under Mild Conditions

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Keywords: Iodine / Sulfonamides / Sodium sulfinates / Amines / Oxidative amination

The iodine-catalyzed oxidative amination of sodium sulfinates in the presence of sodium percarbonate as the oxidant has been developed. The reaction shows good substrate scope and tolerates a wide range of functionalities in both amine and sodium sulfinate substrates. Aliphatic amines, heteroaromatic amines and hydrochloride salts of amines can be employed as the amine sources in this transformation. Mechanistic studies indicated that a radical pathway might be involved in the reaction process. This transition-metal-free protocol offers an alternative and convenient approach for a preparation of a series of sulfonamides in moderate to good yields under mild conditions.

Introduction

Sulfonamides are a privileged class of pharmaceutical compounds with a broad spectrum of activities.[1] They are employed widely in medicinal chemistry as essential structural motifs for the development of new therapeutic agents. Sulfonamide drugs have various clinical applications, including as antibacterials, diuretics, anticonvulsants, and HIV protease inhibitors.[2] Examples of important sulfonamide drugs are azosemide (diureatic), piroxicam (anti-inflammatory drug), sumatriptan (anti-migraine agent), and amprenavir (protease inhibitor for treatment of HIV infection). Other applications of sulfonamides include their use as nitrogen protecting groups and incorporation into organic dyes to improve stability and lubrication.[3] Because of their significance, a number of advancements in sulfonamide synthesis have been developed, in order to provide the sulfonamide products in decent yields and with high selectivity and good functional group compatibility.[4] Examples of effective methods for sulfonamide formation include the traditional synthesis from sulfonyl chlorides and amino compounds,[5] catalytic cross-coupling of sulfonamides with halides,[6] oxidation of sulfinamides,[7] and aminosulfonation of hydrocarbons.[8] Despite their potential utility, many of these methods have some limitations such as vigorous conditions, side reactions, tedious isolation procedures, poor functional group tolerance, difficulty in handling, and problems with long-term storage.

Recently, Jiang and co-workers reported a new route to sulfonamide synthesis through Cu-catalyzed oxidative coupling of amines and the bench-stable, nonhygroscopic sodium sulfinates.[9,10] This study offered a method for the preparation of sulfonamides in good yields and with excellent chemoselectivity; however, a high temperature is required to facilitate product formation. Inspired by this work, we became interested in exploring the possibility of replacing the copper catalyst by employing the transition-metal-free catalyzed oxidative coupling strategy. In particular, catalysis involving molecular iodine (I_2) and its salts attracted our attention, due to the ease of handling, low toxicity, commercial availability, and mild reactivity of the reagents. A number of recent studies have demonstrated the utility of iodine catalysis as an efficient and powerful tool for formation of carbon–carbon and carbon–heteroatom bonds.[11] The combination of catalytic amounts of iodine or iodide salts and oxidants such as *tert*-butyl hydroperoxide (TBHP) or hydrogen peroxide (H_2O_2) has proven to provide versatile oxidation conditions for many oxidative coupling transformations.[12]

Herein we report a method for the formation of sulfonamides by I_2-catalyzed oxidative amination of sodium sulfinates. Readily available sodium percarbonate – $Na_2CO_3 \cdot 1.5H_2O_2$, a solid carrier of hydrogen peroxide[13] – is an effective oxidant for this transformation. Our approach has several advantages, including being transition-metal-free, using bench-stable reagents, involving simple handling under mild and air-stable conditions, accommodating a broad scope of substrates, and avoiding the generation of toxic byproducts.

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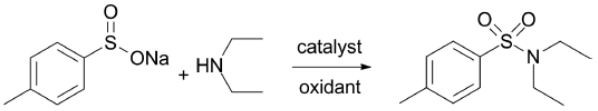
Results and Discussion

Optimization of Reaction Conditions

We initiated the studies by examining the reaction between sodium *p*-toluenesulfinate (**1a**) and diethylamine (**2a**) under various conditions, and selected results are summarized in Table 1. When the reaction between **1a** and **2a** was carried out in the presence of I_2 (20 mol-%) and sodium percarbonate (2 equiv.) in 1,2-dichloroethane (DCE) at room temperature, the product **3a** could be obtained in 57% yield (Table 1, Entry 1). To our delight, a better yield (71%) could be achieved upon heating the reaction mixture at 40 °C (Entry 2). Further attempts to drive the reaction to completion by increasing the temperature to 50 or 60 °C were unsuccessful; lower yields of product were obtained and some unidentified byproducts were observed as the temperature increased (Entries 3 and 4). Our results agree with previous reports according to which sodium percarbonate is not an effective oxidant at high temperature.[13a,14] Replacing I_2 catalyst with NIS provided product **3a** in 55% yield (Entry 5), whereas use of other iodide sources such as LiI, NaI, KI, and TBAI did not result in product formation (Entries 6–9). Employing H_2O_2 or TBHP as the oxidant gave lower levels of conversion (Entries 10 and 11). It is possible that H_2O_2 or TBHP might be too reactive for our reactions. The molecular I_2 catalyst could presumably have converted into other iodine species in higher oxidation states in the presence of the reactive H_2O_2 or TBHP as oxidant; as a result, lower yields of product might have been obtained. Furthermore, either increasing or decreasing the amount of sodium percarbonate led to a decrease in yield (Entries 12 and 13). In the absence of sodium percarbonate, only a 16% yield of product **3a** was isolated (Entry 14). In addition, no product was detected when I_2 was excluded from the reaction (Entry 15). These results indicated that both I_2 catalyst and peroxide oxidant are required for this catalytic reaction.

We suspected that the relatively low solubility of sodium percarbonate in DCE could have an impact on the reaction, so the effect of solvent was evaluated with the goal of improving the yield of sulfonamide product (Table 2). A variety of polar and nonpolar solvents were screened: the reaction in DCE still showed the highest catalytic activity (Entry 1), whereas the others (in H_2O, CH_3OH, DMF, DMSO, dioxane, THF, CH_3CN, toluene, and CH_2Cl_2) were less effective (Entries 2–10). Then the DCE solvent was mixed with other solvents such as H_2O, CH_3OH, and CH_3CN (Entries 11–15). A combination of 1:1 (*v*/*v*) of CH_3CN and DCE afforded the sulfonamide **2a** in 81% yield.[15]

Table 1. Optimization of reaction conditions.[a]

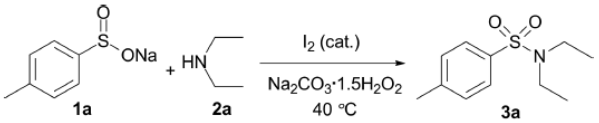


1a **2a** **3a**

Entry	Catalyst	Oxidant [equiv.]	Temp. [°C]	Yield[b] [%]
1	I_2	$Na_2CO_3{\cdot}1.5H_2O_2$ (2)	room temp.	57
2	**I_2**	**$Na_2CO_3{\cdot}1.5H_2O_2$ (2)**	**40**	**71**
3	I_2	$Na_2CO_3{\cdot}1.5H_2O_2$ (2)	50	37
4	I_2	$Na_2CO_3{\cdot}1.5H_2O_2$ (2)	60	24
5	NIS	$Na_2CO_3{\cdot}1.5H_2O_2$ (2)	40	55
6	LiI	$Na_2CO_3{\cdot}1.5H_2O_2$ (2)	40	33
7	NaI	$Na_2CO_3{\cdot}1.5H_2O_2$ (2)	40	10
8	KI	$Na_2CO_3{\cdot}1.5H_2O_2$ (2)	40	13
9	TBAI	$Na_2CO_3{\cdot}1.5H_2O_2$ (2)	40	14
10	I_2	H_2O_2 (3)	40	13
11	I_2	TBHP (3)	40	60
12	I_2	$Na_2CO_3{\cdot}1.5H_2O_2$ (1)	40	46
13	I_2	$Na_2CO_3{\cdot}1.5H_2O_2$ (3)	40	68
14	I_2	–	40	16
15	–	$Na_2CO_3{\cdot}1.5H_2O_2$ (2)	40	0

[a] Conditions: **1a** (1.0 mmol, 2 equiv.), **2a** (0.5 mmol, 1 equiv.), oxidant (1–3 equiv.), catalyst (0.1 mmol, 20 mol-%), solvent (2 mL), 24 h. [b] Isolated yield based on **2a**.

Table 2. Optimization of solvents.[a]



1a **2a** **3a**

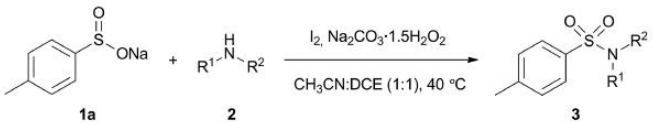
Entry	Solvent	Yield[b] [%]
1	DCE	71
2	H_2O	19
3	CH_3OH	14
4	DMF	44
5	DMSO	17
6	1,4-dioxane	54
7	THF	50
8	CH_3CN	46
9	toluene	30
10	CH_2Cl_2	58
11	H_2O/DCE (1:4, *v*/*v*)	20
12	CH_3OH/DCE (1:4, *v*/*v*)	66
13	CH_3CN/DCE (1:4, *v*/*v*)	75
14	CH_3CN/DCE (4:1, *v*/*v*)	74
15	**CH_3CN/DCE (1:1, *v*/*v*)**	**81**

[a] Conditions: **1a** (1.0 mmol, 2 equiv.), **2a** (0.5 mmol, 1 equiv.), $Na_2CO_3{\cdot}1.5H_2O_2$ (1.0 mmol, 2 equiv.), catalyst (0.1 mmol, 20 mol-%), solvent (2 mL), 40 °C, 24 h. [b] Isolated yield based on **2a**.

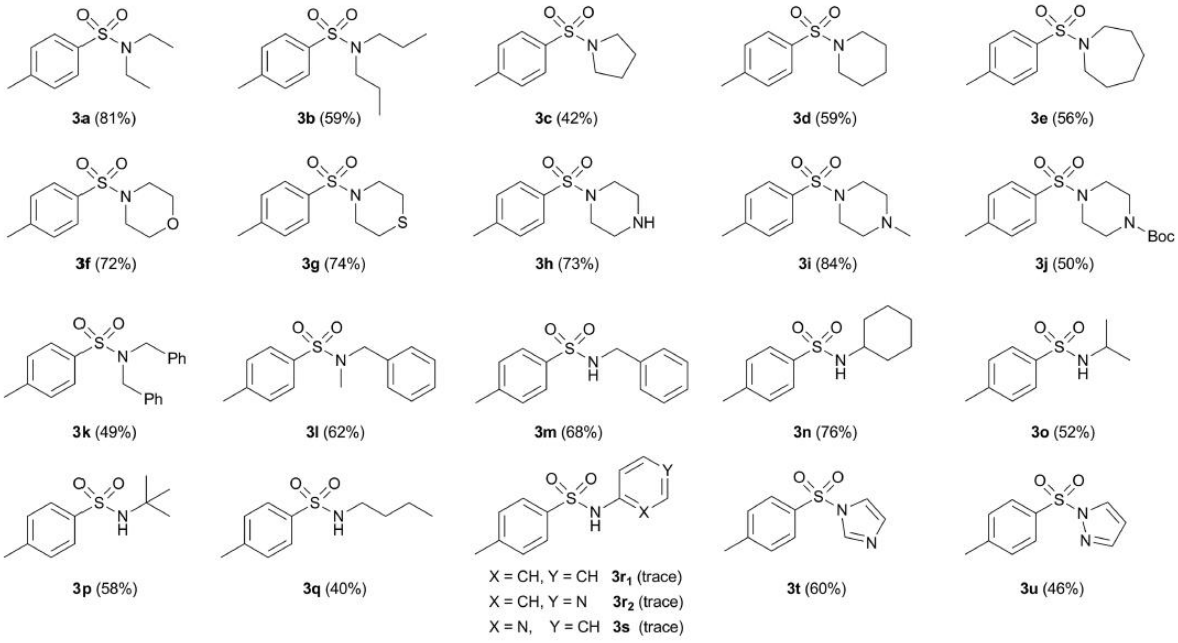
Substrate Scope and Limitation

We tested the generality and limitation of this protocol under the optimized conditions (1 equiv. of amine, 2 equiv. of sodium sulfinate, 20 mol-% of I_2, 2 equiv. of sodium percarbonate in CH_3CN/DCE 1:1, *v*/*v* at 40 °C). The reaction scope with respect to a variety of amines is quite broad, allowing facile preparation of sulfonamides from primary and secondary aliphatic amines in moderate to good yields (Table 3, compounds **3a**–**3q**). Both acyclic and cyclic secondary amines were suitable substrates for the iodine-catalyzed oxidative amination (compounds **3a**–**3e**). An additional oxygen or sulfur heteroatom in the amine was tolerated, as shown by the successful reactions with morpholine or thiomorpholine in this transformation (compounds

Table 3. Substrate scope of amines.[a]



1a 2 3

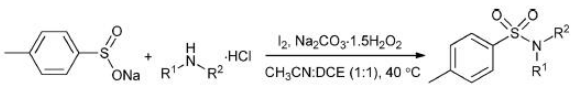


[a] Conditions: **1a** (2.0 mmol, 2 equiv.), **2** (1.0 mmol, 1 equiv.), Na_2CO_3·1.5 H_2O_2 (2.0 mmol, 2 equiv.), I_2 (0.2 mmol, 20 mol-%), CH_3CN/DCE (1:1, *v*/*v*, 4 mL), 40 °C, 24 h. Isolated yields after chromatography.

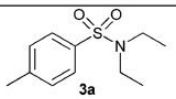
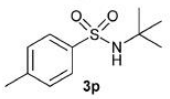
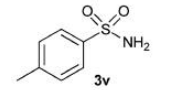
3f and **3g**). In the cases of piperazine and 1-methylpiperazine, good reactivity was observed and the sulfonamide products **3h** and **3i** were isolated in good quantities. Boc and benzyl protecting groups on nitrogen were also compatible (compounds **3j**–**3m**). Moreover, reactions with primary amines proceeded smoothly and yielded only single products under the optimal conditions (compounds **3m**–**3q**). Notably, the sterically bulky *tert*-butylamine also gave sulfonamide **3p** in moderate yield (58%). On the other hand, *n*-butylamine showed lower efficiency (compound **3q**, 40%). We observed no reaction when less nucleophilic aromatic amines were employed (compounds $\mathbf{3r_1}$, $\mathbf{3r_2}$, and **3s**) under these conditions. However, reasonable amounts of sulfonamide products **3t** and **3u** were obtained (60% and 46%, respectively) on subjecting imidazole and pyrazole to this transformation. These results suggested that nucleophilic character of an aromatic amine could have an influence on the reaction.

Thanks to the relatively mild basic conditions, hydrochloride salts of amines could be employed as alternative amine sources in this transformation (Table 4). Salts of both secondary and primary amines (diethylamine hydrochloride

Table 4. Reactions of amine hydrochloride salts.[a]



1 2 3

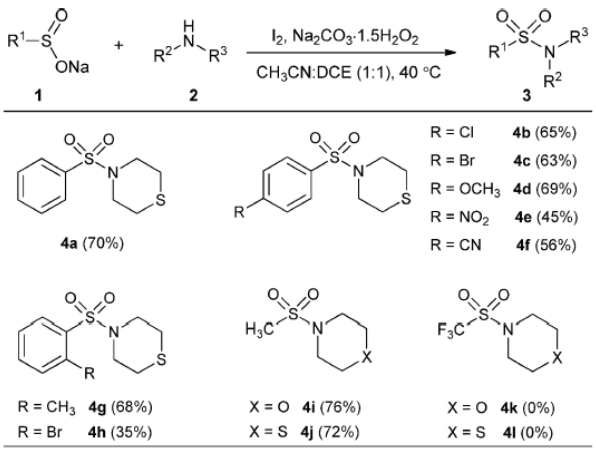
Entry	Amine hydrochloride salt	Product	Yield[b] [%]
1	Et_2NH•HCl	 **3a**	77
2	$^tBuNH_2$•HCl	 **3p**	50
3	NH_4Cl (NH_3•HCl)	 **3v**	78

[a] Conditions: **1** (2.0 mmol, 2 equiv.), **2** (1.0 mmol, 1 equiv.), Na_2CO_3·1.5 H_2O_2 (2.0 mmol, 2 equiv.), I_2 (0.2 mmol, 20 mol-%), CH_3CN/DCE (1:1, *v*/*v*, 4 mL), 24 h. [b] Isolated yields after chromatography.

and *tert*-butylamine hydrochloride) were compatible, giving sulfonamide products **3a** and **3p** in yields comparable to those from reactions of normal amine substrates. Interestingly, ammonium chloride (NH_4Cl) was also a viable substrate under these conditions. The corresponding *p*-toluenesulfonamide **3v** could be obtained as the sole product in decent yield (78%).

We also explored the reaction scope with regard to the sodium sulfinates. As shown in Table 5, sodium phenylsulfinate reacted with thiomorpholine smoothly, to afford sulfonamide **4a** in 70% yield. Halogen-substituted benzenesulfinates (e.g., Cl, Br) were tolerated well under the optimal conditions and provided the desired products **4b** and **4c** in satisfactory quantities. Benzenesulfinate substrates bearing electron-donating (methoxy group) or -withdrawing (nitro and cyano groups) substituents also delivered sulfonamides **4d**–**4f** in modest yields. An *ortho*-methyl-substituted benzenesulfinate substrate underwent oxidative amination to give the corresponding product **4g** in 68% yield; however, in the case of a 2-bromo-substituted benzenesulfinate a much lower yield of sulfonamide **4h** was obtained. It is noteworthy that sodium methanesulfinate could be converted into sulfonamides **4i** and **4j** in good yields (76% and 72%). Nonetheless, sodium trifluoromethanesulfinate was not an effective substrate (**4k** and **4l**), which indicated that the nature of the sodium sulfinate might have an effect on product formation.[9]

Table 5. Substrate scope of sodium sulfinates.[a]

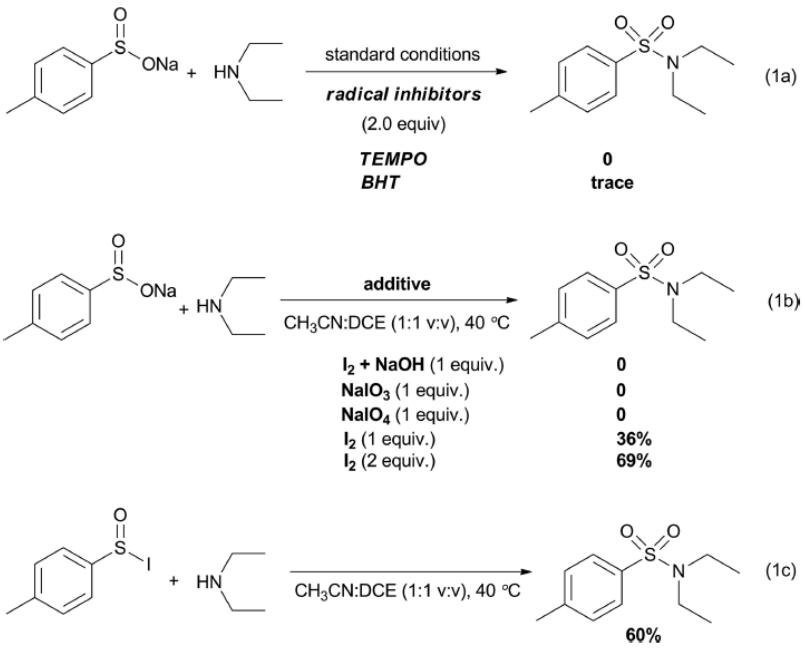


[a] Conditions: **1** (2.0 mmol, 2 equiv.), **2** (1.0 mmol, 1 equiv.), $Na_2CO_3{\cdot}1.5\,H_2O_2$ (2.0 mmol, 2 equiv.), I_2 (0.2 mmol, 20 mol-%), CH_3CN/DCE (1:1, *v*/*v*, 4 mL), 24 h. Isolated yields after chromatography.

Reaction Mechanism for Sulfonamide Formation

To aid understanding of the reaction mechanism, the reaction between sodium sulfinate **1a** and diethylamine (**2a**) was conducted under the optimal conditions in the presence of radical scavenger such as TEMPO or BHT (Scheme 1, a). These two radical scavengers inhibited the reaction and only trace amounts of the sulfonamide product were observed in these control experiments, suggesting that the reaction probably proceeds via a radical intermediate.

To provide further evidence of the roles of iodine and the oxidant, the reaction was carried out in the absence of sodium percarbonate. Mixtures of **1a** and **2a** were treated with iodized salts of different oxidation states (Scheme 1, b). No

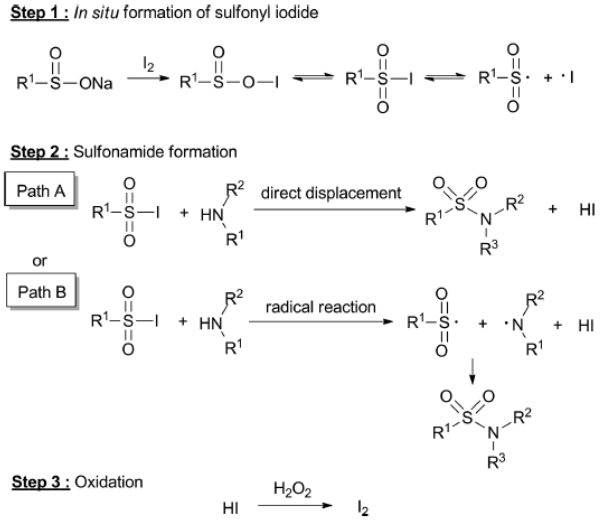


Scheme 1. Mechanistic studies and control experiments.

product was detected when mixtures of I_2 with NaOH,[16] sodium periodate ($NaIO_3$), or sodium iodate ($NaIO_4$) were used. Conversely, when 1 and 2 equivalents of I_2 were applied in this reaction, the desired product **3a** could be obtained in 36% and 69% yields, respectively. It was thus implied that molecular iodine (I_2) was the active species in the catalytic cycle; this was also supported by the result shown in Entry 14 in Table 1 (I_2 catalyst gave a 16% yield of product in the absence of oxidant).

It has long been known that the reaction between sodium sulfinate and molecular iodine can generate the relatively unstable sulfonyl iodide,[17] so *p*-toluenesulfonyl iodide (TsI) was prepared[18] and utilized in the subsequent experiment. The reaction between TsI and amine **2a** provided the corresponding sulfonamide **3a** in 60% yield (Scheme 1, c). This result suggested that the sulfonyl iodide is likely to be the intermediate in this transformation.

On the basis of our results and literature precedence,[11,12] a plausible mechanism is proposed in Scheme 2. An initial reaction between iodine (I_2) and sodium sulfinate could lead to in situ formation of the relatively unstable sulfonyl iodide intermediate through homolytic cleavage.[17] The decomposition of this sulfonyl iodide species would yield a sulfonyl radical. Next, either a direct displacement of iodide by the amine (path A) or a radical substitution (at a nitrogen-centered radical, path B) might be involved in the S–N bond-formation process. Lastly, the HI generated in the previous step could undergo further oxidation with H_2O_2, regenerating I_2 to resume the catalytic cycle.[12,14]



Scheme 2. Proposed mechanism for iodine-catalyzed oxidative amination.

Conclusions

We have discovered an expedient protocol for formation of sulfonamides from sodium sulfinates and amines through an I_2-catalyzed oxidative amination strategy. Sodium percarbonate, a dry carrier of hydrogen peroxide, is employed as the oxidant in this reaction, allowing for convenient reaction setup and handling. The reaction shows good substrate scope and tolerates a wide range of functionalities both in the amine and the sodium sulfinate substrates. Additionally, hydrochloride salts of amines are also viable substrates under the optimal conditions. This transformation offers a facile synthetic route to access a variety of sulfonamides, which are employed widely in medicinal chemistry and other related applications. Further efforts to study the mechanism and to expand the synthetic utility to construct complex molecules are currently under investigation.

Experimental Section

General Information: Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. All experiments were carried out under air, and oven-dried glassware was used in all cases. Column chromatography was performed over silica gel (SiO_2, 60 Å silica gel, Merck Grade, 70–230 mesh). GC experiments were carried out with an Agilent 6890N GC-FID chromatograph equipped with an Agilent column (HP-1, polysiloxane, 24.5 m × 0.32 mm ID × 0.17 μm). ^1H and ^{13}C NMR spectra were recorded with Bruker AV 400 spectrometers in $CDCl_3$ solution at 400 and 100 MHz, respectively. NMR chemical shifts are reported in ppm and were measured relative to $CHCl_3$ (δ = 7.24 ppm for ^1H and 77.23 ppm for ^{13}C). IR spectra were recorded with a Bruker FT-IR Spectrometer Model ALPHA (neat), and only partial data are listed. Melting points were determined with a Buchi Melting Point M-565 apparatus. High-resolution mass spectrometry (HRMS) data were analyzed with a high-resolution micrOTOP instrument and use of electrospray ionization (ESI). The structures of known compounds were corroborated by comparing their ^1H NMR and ^{13}C NMR spectroscopic data with those in the literature.

General Procedure for the Synthesis of Sulfonamides 3a–3v and 4a–4j from Sodium Sulfinates and Amines: The amine (1.00 mmol, 1.00 equiv.), the sodium sulfinate (2.00 mmol, 2.00 equiv.), sodium percarbonate ($Na_2CO_3 \cdot 1.5\,H_2O_2$, 314.0 mg, 2.00 mmol, 2.00 equiv.), iodine (51.0 mg, 0.20 mmol, 0.20 equiv.), and CH_3CN/DCE (1:1, *v*/*v*, 4 mL) were placed in an oven-dried screw cap reaction vial containing a magnetic stirrer bar. The vial was then capped, and the mixture was stirred at 40 °C for 24 h. The reaction mixture was quenched by addition of saturated aqueous $Na_2S_2O_3$ (10 mL), followed by extraction with EtOAc (3 × 10 mL). The combined organic extracts were washed with H_2O (2 × 10 mL) and brine (5 mL), then dried with anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by SiO_2 column chromatography to afford the corresponding sulfonamide product.

***N*,*N*-Diethyl-4-methylbenzenesulfonamide (3a):**[9] White solid. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.67 (d, *J* = 8.2 Hz, 2 H), 7.26 (d, *J* = 8.0 Hz, 2 H), 3.20 (q, *J* = 7.2 Hz, 4 H), 2.39 (s, 3 H), 1.10 (t, *J* = 7.2 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.1, 137.6, 129.8, 127.2, 42.2, 21.7, 14.3 ppm. HRMS (ESI): calcd. for $C_{11}H_{17}NO_2SNa$ [M + Na]$^+$ 250.0872; found 250.0876.

4-Methyl-*N*,*N*-dipropylbenzenesulfonamide (3b): Yellow oil. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 8.2 Hz, 2 H), 7.29 (d, *J* = 8.2 Hz, 2 H), 3.06 (t, *J* = 7.7 Hz, 4 H), 2.42 (s, 3 H), 1.60–1.51 (m, 4 H), 0.88 (t, *J* = 7.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 137.3, 129.7, 127.2, 50.2, 22.2, 21.6, 11.4 ppm. IR: $\tilde{\nu}$ = 2966, 2875, 1599, 1494, 1336, 1241, 1153, 727 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{21}NO_2SNa$ [M + Na]$^+$ 278.1185; found 278.1189.

1-Tosylpyrrolidine (3c):[9] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.69 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 3.22 (t, J = 6.8 Hz, 4 H), 2.41(s, 3 H), 1.74–1.71 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5, 134.1, 129.8, 127.8, 48.1, 25.4, 21.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{17}NO_2SNa$ [M + Na]$^+$ 248.0716; found 248.0727.

1-Tosylpiperidine (3d):[19] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.1 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 2.94 (t, J = 5.4 Hz, 4 H), 2.40 (s, 3 H), 1.64–1.58 (m, 4 H), 1.41–1.35 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5, 133.4, 129.7, 127.9, 47.1, 25.4, 23.7, 21.7 ppm. HRMS (ESI): calcd. for $C_{12}H_{17}NO_2SNa$ [M + Na]$^+$ 262.0872; found 262.0869.

1-Tosylazepane (3e):[19] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.64 (d, J = 8.2 Hz, 2 H), 7.25 (d, J = 8.1 Hz, 2 H), 3.24–3.21 (m, 4 H), 2.39 (s, 3 H), 1.68–1.67 (m, 4 H), 1.56–1.53 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.0, 136.8, 129.8, 127.1, 48.4, 29.3, 27.1, 21.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{17}NO_2SNa$ [M + Na]$^+$ 276.1029; found 276.1031.

4-Tosylmorpholine (3f):[9] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.59 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.2 Hz, 2 H), 3.69 (t, J = 4.6 Hz, 4 H), 2.94 (t, J = 4.6 Hz, 4 H), 2.40 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.1, 132.2, 129.9, 128.0, 66.2, 46.1, 21.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}NO_3SNa$ [M + Na]$^+$ 264.0665; found 264.0666.

4-Tosylthiomorpholine (3g):[20] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 3.31–3.28 (m, 4 H), 2.69–2.67 (m, 4 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.0, 134.0, 130.0, 127.7, 48.1, 27.5, 21.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{15}NO_2S_2Na$ [M + Na]$^+$ 280.0436; found 280.0434.

1-Tosylpiperazine (3h): White solid, m.p. 96.2–97.1 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.2 Hz, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 2.94–2.88 (m, 8 H), 2.40 (s, 3 H), 1.57 (s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 132.7, 129.8, 128.1, 47.1, 45.5, 21.7 ppm. IR: $\tilde{\nu}$ = 3331, 2911, 2851, 1597, 1495, 1442, 1335, 1158, 1092, 722 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}N_2O_2S$ [M + H]$^+$ 241.1005; found 241.1007.

1-Methyl-4-tosylpiperazine (3i):[21] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.61 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 2.99 (br., 4 H), 2.46–2.43 (m, 4 H), 2.40 (s, 3 H), 2.24 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.9, 132.5, 129.8, 128.1, 54.3, 46.2, 45.9, 21.7 ppm. HRMS (ESI): calcd. for $C_{12}H_{19}N_2O_2S$ [M + H]$^+$ 255.1162; found 255.1165.

***tert*-Butyl 4-Tosylpiperazine-1-carboxylate (3j):** White solid, m.p. 150.0–151.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.60 (d, J = 8.2 Hz, 2 H), 7.31 (d, J = 8.0 Hz, 2 H), 3.49–3.46 (m, 4 H), 2.94–2.92 (m, 4 H), 2.41 (s, 3 H), 1.38 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.2, 143.9, 132.5, 129.8, 127.8, 80.4, 45.9, 43.0, 28.3, 21.5 ppm. IR: $\tilde{\nu}$ = 2973, 1694, 1596, 1416, 1345, 1164, 1126, 938, 720 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{24}N_2O_4SNa$ [M + Na]$^+$ 363.1349; found 363.1348.

***N*,*N*-Dibenzyl-4-methylbenzenesulfonamide (3k):**[19] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.20–7.19 (m, 6 H), 7.04–7.02 (m, 4 H), 4.29 (s, 4 H), 2.43 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.5, 138.0, 135.9, 129.9, 128.8, 128.6, 127.8, 127.5, 50.7, 21.8 ppm. HRMS (ESI): calcd. for $C_{21}H_{21}NO_2SNa$ [M + Na]$^+$ 374.1185; found 374.1187.

***N*-Benzyl-*N*,4-dimethylbenzenesulfonamide (3l):**[22] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, J = 8.0 Hz, 2 H), 7.34 (d, J = 8.0 Hz, 2 H), 7.32–7.27 (m, 5 H), 4.10 (s, 2 H), 2.56 (s, 3 H), 2.44 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.7, 135.9, 134.5, 130.0, 128.8, 128.6, 128.1, 127.7, 54.4, 34.5, 21.8 ppm. HRMS (ESI): calcd. for $C_{15}H_{17}NO_2SNa$ [M + Na]$^+$ 298.0872; found 298.0877.

***N*-Benzyl-4-methylbenzenesulfonamide (3m):**[9] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.74 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.26–7.17 (m, 5 H), 4.64 (br., 1 H), 4.10 (d, J = 6.2 Hz, 2 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 137.1, 136.5, 130.0, 128.9, 128.2, 128.1, 127.4, 47.5, 21.8 ppm. HRMS (ESI): calcd. for $C_{14}H_{15}NO_2SNa$ [M + Na]$^+$ 284.0716; found 284.0717.

***N*-Cyclohexyl-4-methylbenzenesulfonamide (3n):**[21] Yellow solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.0 Hz, 2 H), 7.26 (d, J = 8.0 Hz, 2 H), 4.87–4.85 (m, 1 H), 3.08–3.07 (m, 1 H), 2.39 (s, 3 H), 1.72–1.45 (m, 5 H), 1.19–1.05 (m, 5 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.2, 138.7, 129.8, 127.1, 52.7, 34.0, 25.3, 24.8, 21.7 ppm. HRMS (ESI): calcd. for $C_{13}H_{19}NO_2SNa$ [M + Na]$^+$ 276.1029; found 276.1036.

***N*-Isopropyl-4-methylbenzenesulfonamide (3o):** White solid, m.p. 45.0–46.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.75 (d, J = 8.2 Hz, 2 H), 7.26 (d, J = 8.1 Hz, 2 H), 4.79 (br., 1 H), 3.44–3.35 (m, 1 H), 2.39 (s, 3 H), 1.03 (d, J = 6.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.3, 138.3, 129.8, 127.2, 46.2, 23.9, 21.7 ppm. IR: $\tilde{\nu}$ = 3276, 2974, 1598, 1424, 1301, 1140, 1091, 813, 660 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{15}NO_2SNa$ [M + Na]$^+$ 236.0716; found 236.0718.

***N*-(*tert*-Butyl)-4-methylbenzenesulfonamide (3p):**[9] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, J = 8.2 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 5.06 (br., 1 H), 2.43 (s, 3 H), 1.22 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 142.9, 140.8, 129.6, 127.2, 54.7, 30.3, 21.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{17}NO_2SNa$ [M + Na]$^+$ 250.0872; found 250.0873.

***N*-Butyl-4-methylbenzenesulfonamide (3q):**[9] Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.73 (d, J = 8.2 Hz, 2 H), 7.26 (d, J = 8.0 Hz, 2 H), 4.97 (br., 1 H), 2.89–2.85 (m, 2 H), 2.38 (s, 3 H), 1.43–1.35 (m, 2 H), 1.28–1.19 (m, 2 H), 0.79 (t, J = 7.3 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.4, 137.1, 129.8, 127.2, 43.0, 31.6, 21.6, 19.8, 13.7 ppm. HRMS (ESI): calcd. for $C_{11}H_{17}NO_2SNa$ [M + Na]$^+$ 250.0872; found 250.0877.

1-Tosyl-1*H*-imidazole (3t):[23] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.98 (s, 1 H), 7.80 (d, J = 8.4 Hz, 2 H), 7.33 (d, J = 8.2 Hz, 2 H), 7.26 (s, 1 H), 7.06 (s, 1 H), 2.42 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.5, 136.8, 135.1, 131.6, 130.6, 127.6, 117.6, 21.9 ppm. HRMS (ESI): calcd. for $C_{10}H_{11}N_2O_2S$ [M + H]$^+$ 223.0536; found 223.0544.

1-Tosyl-1*H*-pyrazole (3u):[24] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–8.08 (m, 1 H), 7.87 (d, J = 8.3 Hz, 2 H), 7.70 (s, 1 H), 7.30 (d, J = 8.2 Hz, 2 H), 6.37–6.36 (m, 1 H), 2.39 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 145.4, 134.2, 131.3, 130.2, 128.4, 108.9, 21.9 ppm. HRMS (ESI): calcd. for $C_{10}H_{11}N_2O_2S$ [M + H]$^+$ 223.0536; found 223.0542.

4-Methylbenzenesulfonamide (3v):[25] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 8.3 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 4.91 (s, 2 H), 2.41 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 143.8, 139.3, 129.9, 126.7, 21.7 ppm. HRMS (ESI): calcd. for $C_7H_9NO_2S$ [M + Na]$^+$ 194.0246; found 194.0253.

4-(Phenylsulfonyl)thiomorpholine (4a): White solid, m.p. 110.6–111.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72–7.70 (m, 2 H), 7.60–7.57 (m, 1 H), 7.53–7.50 (m, 2 H), 3.32–3.30 (m, 4 H), 2.69–

2.67 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.0, 133.1, 129.4, 127.6, 48.0, 27.5 ppm. IR: $\tilde{\nu}$ = 2922, 2846, 1474, 1336, 1161, 891, 733 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{13}NO_2S_2Na$ [M + Na]$^+$ 266.0280; found 266.0281.

4-[(4-Chlorophenyl)sulfonyl]thiomorpholine (4b): White solid, m.p. 147.2–147.8 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.6 Hz, 2 H), 7.50 (d, J = 8.7 Hz, 2 H), 3.33–3.31 (m, 4 H), 2.70–2.68 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.7, 135.6, 129.8, 129.0, 48.1, 27.5 ppm. IR: $\tilde{\nu}$ = 2913, 1587, 1449, 1338, 1161, 1094, 896, 760, 608 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{12}ClNO_2S_2Na$ [M + Na]$^+$ 299.9890; found 299.9898.

4-[(4-Bromophenyl)sulfonyl]thiomorpholine (4c): White solid, m.p. 145.2–146.0 °C ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.66 (d, J = 8.7 Hz, 2 H), 7.58 (d, J = 8.0 Hz, 2 H), 3.32–3.31 (m, 4 H), 2.70–2.68 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1, 132.7, 129.1, 128.2, 48.1, 27.5 ppm. IR: $\tilde{\nu}$ = 2913, 1574, 1449, 1338, 1159, 1092, 898, 747, 663 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{12}BrNO_2S_2Na$ [M + Na]$^+$ 343.9385; found 343.9389.

4-[(4-Methoxyphenyl)sulfonyl]thiomorpholine (4d): White solid, m.p. 81.8–82.4 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.9 Hz, 2 H), 6.97 (d, J = 8.9 Hz, 2 H), 3.85 (s, 3 H) 3.30–3.28 (m, 4 H), 2.69–2.67 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.3, 129.7, 128.5, 114.5, 55.8, 48.1, 27.5 ppm. IR: $\tilde{\nu}$ = 2914, 1594, 1496, 1331, 1258, 1151, 1090, 891, 711 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}NO_3S_2Na$ [M + Na]$^+$ 296.0386; found 296.0394.

4-[(4-Nitrophenyl)sulfonyl]thiomorpholine (4e): Yellow solid, m.p. 160.0–161.0 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.37 (d, J = 8.8 Hz, 2 H), 7.92 (d, J = 8.8 Hz, 2 H), 3.40–3.38 (m, 4 H), 2.72–2.70 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.4, 143.3, 128.7, 124.7, 48.1, 27.5 ppm. IR: $\tilde{\nu}$ = 2921, 1526, 1348, 1159, 1088, 906, 851, 736, 687 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{12}N_2O_4S_2Na$ [M + Na]$^+$ 311.0131; found 311.0134.

4-(Thiomorpholinosulfonyl)benzonitrile (4f): White solid, m.p. 190.6–191.7 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.83 (s, 4 H), 3.37–3.35 (m, 4 H) 2.71–2.68 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.7, 133.4, 133.2, 128.1, 117.4, 116.9, 48.1, 27.5 ppm. IR: $\tilde{\nu}$ = 2955, 2236, 1449, 1359, 1159, 898, 842, 704, 621 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}N_2O_2S_2Na$ [M + Na]$^+$ 291.0232; found 291.0230.

4-(*o*-Tolylsulfonyl)thiomorpholine (4g): Yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.86–7.84 (m, 1 H), 7.46–7.42 (m, 1 H), 7.31–7.28 (m, 2 H), 3.50–3.47 (m, 4 H), 2.68–2.65 (m, 4 H) 2.58 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.9, 136.6, 133.1, 133.0, 130.2, 126.4, 47.3, 27.6, 20.8 ppm. IR: $\tilde{\nu}$ = 2913, 1595, 1453, 1316, 1284, 1155, 1068, 895, 717 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{16}NO_2S_2$ [M + H]$^+$ 258.0617; found 258.0612.

4-[(2-Bromophenyl)sulfonyl]thiomorpholine (4h): Colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08–8.06 (m, 1 H), 7.74–7.72 (m, 1 H), 7.45–7.36 (m, 2 H), 3.59–3.57 (m, 4 H), 2.69–2.66 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.3, 136.0, 133.9, 132.5, 127.8, 120.5, 47.8, 27.6 ppm. IR: $\tilde{\nu}$ = 2914, 1574, 1329, 1158, 904, 742, 683 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{12}BrNO_2S_2Na$ [M + Na]$^+$ 343.9385; found 343.9383.

4-(Methylsulfonyl)morpholine (4i):[9] White solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78–3.75 (m, 4 H), 3.20–3.18 (m, 4 H) 2.77 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 66.5, 46.1, 34.2 ppm. HRMS (ESI): calcd. for $C_5H_{11}NO_3SNa$ [M + Na]$^+$ 166.0532; found 166.0530.

4-(Methylsulfonyl)thiomorpholine (4j): White solid, m.p. 132.6–132.9 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.50–3.48 (m, 4 H), 2.76 (s, 3 H), 2.72–2.70 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 47.8, 36.0, 27.7 ppm. IR: $\tilde{\nu}$ = 2923, 1457, 1319, 1281, 1145, 1064, 899, 775 cm^{-1}. HRMS (ESI): calcd. for $C_5H_{11}NO_2S_2Na$ [M + Na]$^+$ 204.0123; found 204.0124.

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Iodine-catalyzed expeditious synthesis of sulfonamides from sulfonyl hydrazides and amines†

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A new synthesis of sulfonamides has been developed *via* an iodine-catalyzed sulfonylation of amines with arylsulfonyl hydrazides. This metal-free strategy employs readily accessible and easy to handle starting materials, catalysts and oxidants, and can be easily conducted under mild conditions, providing a convenient access to a wide range of sulfonamides in moderate to excellent yields within a short reaction time.

Introduction

Sulfonamides are prominent structural motifs found in numerous bioactive molecules, pharmaceuticals, and natural products. They exhibit a broad spectrum of biological activities and are employed extensively in various medicinal and pharmaceutical applications, for example as antibacterials, anticonvulsants, HIV protease inhibitors, antitumor and antifungal agents.[1] Pharmaceutically important examples of sulfonamides include the analgesic celecoxib, sildenafil for erectile dysfunction and the HIV protease inhibitors darunavir and amprenavir (Fig. 1).[2] In addition, sulfonamides are important functional groups with wide utility in herbicides, dyes and organic materials.[3] They are also used as amine protecting groups with easy removability under mild conditions.[4]

The traditional method for sulfonamide formation involves a reaction of amines with sulfonyl chlorides in the presence of a base.[5] Other examples for the synthesis of sulfonamides (Scheme 1) include a transition metal-catalyzed cross-coupling of *N*-unsubstituted/*N*-monosubstituted sulfonamides with organohalides or boronic acids,[6] a copper-catalyzed Chan-Lam type coupling using sulfonyl azides and boronic acids,[7] an oxidation reaction of sulfenamides/sulfinamides,[8] and an oxidative coupling reaction of sulfinate salts with amines.[9] Although many of these available methods can form sulfonamides successfully, they are still limited by some drawbacks such as using non-stable, hazardous and mutagenic starting materials (*e.g.* sulfonyl chlorides and organic azides), generating a large quantity of toxic waste, difficulty in handling and storing, poor functional group tolerance, and the requirement of harsh conditions and a prolonged reaction time. Therefore, an alternative and facile catalytic methodology to construct sulfonamides efficiently is highly desirable from a synthetic viewpoint.

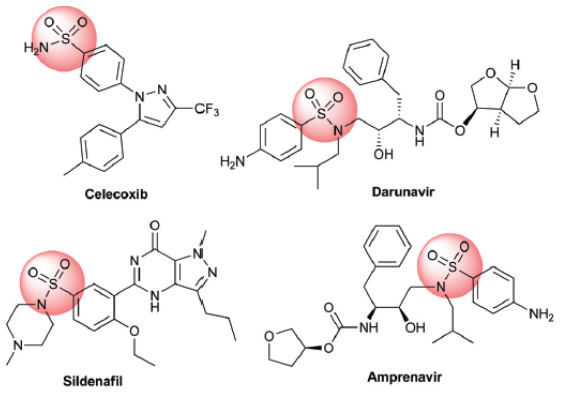

Fig. 1 Examples of important sulfonamide drugs.

During the past few years, molecular iodine and its salts have emerged as efficient catalysts in modern synthetic chemistry because of the ease of handling, commercial availability, low toxicity, mild reactivity and versatile nature of the reagents. A number of studies have demonstrated impressive advancements of iodine- and iodide-catalyzed carbon–carbon and carbon–heteroatom bonds formation.[10] Our group was also interested in exploring a metal-free catalytic approach for the synthesis of biologically active nitrogen-containing compounds.[11] We recently reported a convenient synthesis of sulfonamides *via* an iodine-catalyzed oxidative coupling reaction of

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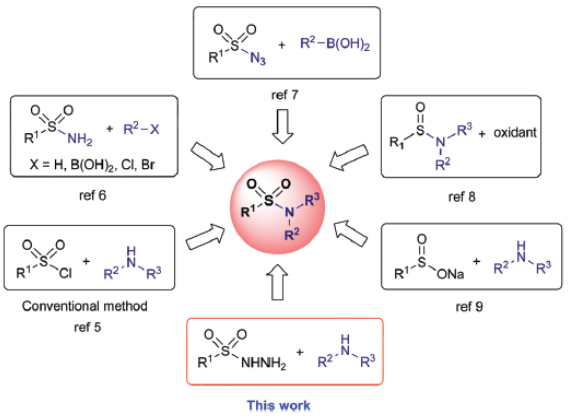


Scheme 1 Approaches for the synthesis of sulfonamides.

sodium sulfonates and amines.[9c] The combination of a catalytic amount of iodine and *tert*-butyl hydroperoxide (TBHP) or hydrogen peroxide (H_2O_2) has provided an expedient liaison for our successful transformations.

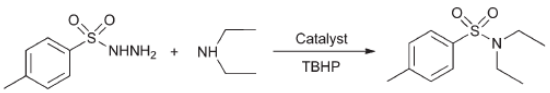
Recently, the readily accessible sulfonyl hydrazides have received considerable attention as excellent synthons for many organic transformations. They have been used as odourless and easy to handle sulfonyl sources,[12] sulfenylating reagents (aryl thiol surrogates),[13] and arylating precursors.[14] Depending upon the nature of the reaction conditions, sulfonyl hydrazides can act as nucleophiles or electrophiles. Compared with other sulfur reagents, sulfonyl hydrazides are not sensitive to air and moisture, exhibit high reactivity and versatility under relatively mild conditions, and give eco-friendly byproducts (water and N_2). However, to the best of our knowledge, the formation of sulfonamides from sulfonyl hydrazides and amines has not been explored so far. With our continuing efforts towards the development of improved catalytic methods for sulfonamide preparation, herein, we wish to report a new route to synthesize sulfonamides *via* iodine-catalyzed sulfonylation of amines with arylsulfonyl hydrazides. The present method is metal-free, features a simple experimental procedure, accommodates a broad scope of substrates, generates clean by-products, and can be a good synthetic tool to access a number of sulfonamide products in reasonable to excellent yields at room temperature within a short reaction time.

Results and discussion

To evaluate the feasibility of sulfonamide formation *via* a catalytic sulfonylation of amines from sulfonyl hydrazide precursors, we initiated our investigation by studying a coupling reaction between *p*-toluenesulfonyl hydrazide (1a) and diethylamine (2a) as a model reaction. After screening several combinations of catalysts (metals and non-metals) and oxidants (see ESI†), the reaction proceeded in high yield when 20 mol% of molecular iodine (I_2) was employed in combination with TBHP (3.0 equiv.) in 1,2-dichloroethane (DCE) solvent at room temperature. Moreover, the reaction was essentially complete after 1 hour[15] and gave the corresponding sulfonamide product 3a in 85% yield (Table 1, entry 5). The combination of TBHP with other forms of iodine or iodide salts showed lower catalytic activities (entries 1–4). Encouraged by these results, various solvents were screened and dichloromethane (CH_2Cl_2) could also be used as a viable alternative to DCE (entry 6; 80%). Other polar or non-polar solvents were less efficient (entries 7–14). Further attempts to drive the reaction to completion by increasing the temperature were unsuccessful; there was no improvement in yield through our efforts and a slight decrease in product yield was found as the temperature increased (entries 15–17).[16] Screening a range of additives (acid, base, *etc.*) and oxidants such as H_2O_2, di-*tert*-butyl peroxide (DTBP) revealed that other reagents were ineffective for this transformation.[16] In addition, no reaction was observed in the absence of I_2 catalyst (entry 18), and only a trace amount of the product was obtained when TBHP was omitted from the reaction (entry 19). These results highlight the importance of both the I_2 catalyst and TBHP for this catalytic reaction.

Overall, the optimal conditions for the I_2-catalyzed sulfonylation of amines were established (Table 1, entry 5; 1 equiv. of sulfonyl hydrazide, 3 equiv. of amine, 20 mol% of I_2, 3 equiv. of TBHP, DCE, rt, 1 h). With these conditions in hand, we sought to expand the substrate scope that is applicable for the current reaction. Therefore, the sulfonylation reaction between

Table 1 Optimization of reaction conditions[a]



1a 2a 3a

Entry	Catalyst	Solvent	*T* (°C)	Yield[b] (%)
1	NIS	DCE	rt	67
2	KI	DCE	rt	36
3	NH_4I	DCE	rt	64
4	TBAI	DCE	rt	45
5	I_2	DCE	rt	85
6	I_2	CH_2Cl_2	rt	80
7	I_2	Toluene	rt	49
8	I_2	MeCN	rt	46
9	I_2	MeOH	rt	20
10	I_2	H_2O	rt	Trace
11	I_2	DMSO	rt	Trace
12	I_2	DMF	rt	Trace
13	I_2	THF	rt	73
14	I_2	1,4-Dioxane	rt	70
15	I_2	DCE	40	80
16	I_2	DCE	60	80
17	I_2	DCE	80	76
18	—	DCE	rt	0
19	I_2	DCE	rt	Trace[c]

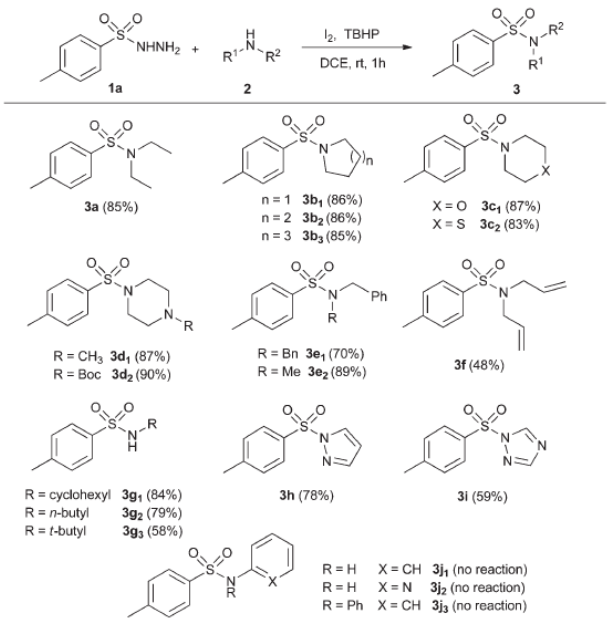
[a] Conditions: 1a (0.5 mmol), 2a (1.5 mmol), TBHP in decane (1.5 mmol), catalyst (0.1 mmol; 20 mol%), solvent (4 mL), 1 h. [b] Isolated yield. [c] No TBHP added.

p-toluenesulfonyl hydrazide (**1a**) and different types of amines were tested under the established conditions and the results are summarized in Table 2 (**3a–3i**). A range of secondary aliphatic amines, including acyclic and cyclic amines, were suitable for this I_2-catalyzed sulfonylation reaction and they delivered the expected products in good to excellent yields (**3a–3f**). Additional oxygen or sulfur heteroatom in the amine was tolerated, as shown by the successful sulfonylation reactions with morpholine or thiomorpholine in this transformation ($3c_1$ and $3c_2$). Delightfully, 1-methyl piperazine and 1-boc-piperazine exhibit relatively high reactivity toward the sulfonylation reaction and the sulfonamide products $3d_1$ and $3d_2$ were achieved in excellent quantities (87 and 90%, respectively). Benzyl protecting groups on nitrogen were also compatible with the standard conditions, affording good to high yields of the desired products $3e_1$ and $3e_2$. In the case of diallylamine, the sulfonamide product **3f** could be collected in moderate quantity (48%). We next turned our attention toward the reactions of primary amines in which sulfonylation reactions also proceeded readily and yielded only single products under the optimal conditions ($3g_1$–$3g_3$). Moreover, modest to good amounts of sulfonamide products (**3h** and **3i**) were obtained upon examining sulfonylation reactions of heterocyclic amines (pyrazole and triazole). On the other hand, we observed no reaction when less nucleophilic aromatic amines were employed under these conditions. These results suggested that the nucleophilic character of amines could play a crucial role in a product formation.

The scope of this reaction with a variety of sulfonyl hydrazides was also investigated as illustrated in Table 3. Various types of arylsulfonyl hydrazides are compatible with standard conditions, affording the desired sulfonamide products (**4a–4e**) in moderate to excellent quantities. Arylsulfonyl hydrazides with halogen-substituents (Cl and Br) could serve as practical substrates for the I_2-catalyzed sulfonylation reaction and the sulfonamide products $4a_2$ and $4a_3$ were obtained in 80% and 86% yields respectively. The electron-rich (methoxy) and electron-deficient (nitro) substituents on the aryl ring of arylsulfonyl hydrazides also underwent a successful transformation, leading to the formation of products $4a_4$ and $4a_5$ in decent yields. Notably, arylsulfonyl hydrazides bearing substituents at the *ortho* position (*o*-CH_3 and *o*-Br) could be converted to their corresponding sulfonamide products $4b_1$ and $4b_2$ in very high yields (90 and 84%, respectively). Additionally, the mesitylenesulfonyl hydrazide substrate was an effective substrate for this reaction, furnishing the product **4c** in 82% yield. Remarkably, the heteroarylsulfonyl hydrazides were also tolerated under these conditions as exemplified by the successful reaction using 2-thiophene- and 8-quinolinesulfonyl hydrazide substrates (**4d** and **4e**). Nevertheless, none or a trace amount of the desired product was obtained when aliphatic sulfonyl hydrazides such as butylsulfonyl hydrazide and benzylsulfonyl hydrazide were employed. In this regard, it could be due to instability of the reaction intermediates generated from alkylsulfonyl hydrazide substrates.

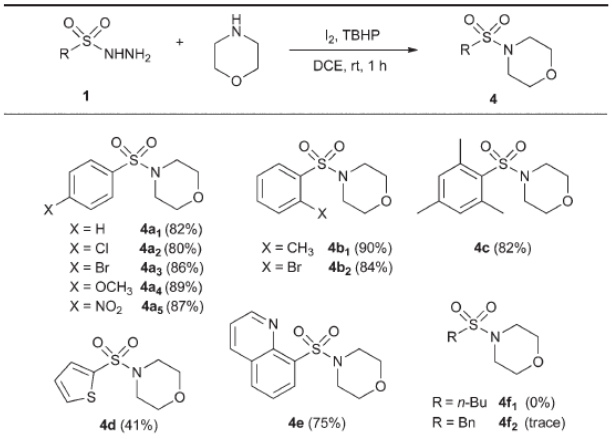
It is noteworthy that the synthesis of sulfonamide *via* this iodine-catalyzed sulfonylation of amine could be effectively scaled up to the gram scale (10 mmol) with similar efficacy. As shown in Scheme 2, *p*-toluenesulfonyl hydrazide (**1a**) and morpholine were reacted with each other under the standard

Table 2 Reaction of sulfonyl hydrazide 1a with various amines[a]

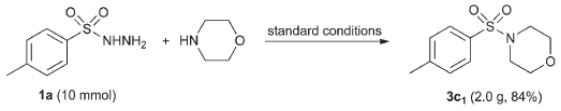


[a] Conditions: **1a** (1.0 mmol), **2** (3.0 mmol), TBHP in decane (3.0 mmol), I_2 (0.2 mmol; 20 mol%), DCE (8 mL), rt, 1 h. Isolated yield.

Table 3 Substrate scope with various sulfonyl hydrazides[a]



[a] Conditions: **1** (1.0 mmol), morpholine (3.0 mmol), TBHP in decane (3.0 mmol), I_2 (0.2 mmol, 20 mol%), DCE (8 mL), rt, 1 h. Isolated yield.

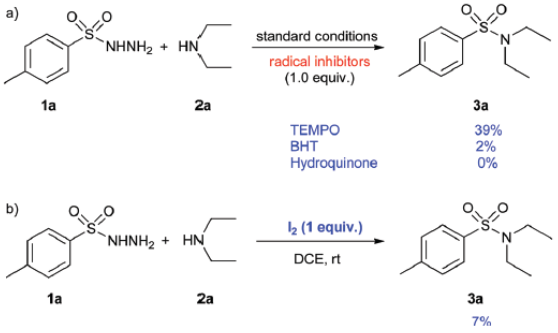


Scheme 2 Gram scale reaction.

conditions and generated sulfonamide $3c_1$ in 84% yield (2.0 gram), which might suggest a potential application in industry.

The utility of this protocol was further extended to the sulfonylation of amine hydrochloride salt. Unfortunately, a trace amount of product was detected. Thus, we added a stoichiometric amount of Na_2CO_3 base for neutralization and increasing the solubility of the amine salt. In the presence of an added base, sulfonylation reactions of diethylamine hydrochloride and *t*-butylamine hydrochloride gave the sulfonamide products in comparable yields to those from the reactions of normal amine substrates (Table 4, entries 1 and 2). Interestingly, when ammonium chloride (NH_4Cl) was used as an amine source, the corresponding product **3k** was produced in 66% yield.

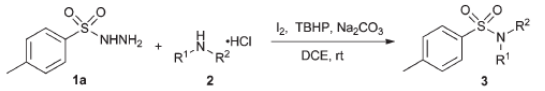
In comparison with previous approaches using other synthetic precursors (*e.g.* sulfonyl chloride, sulfonyl azide, sodium sulfinate), sulfonyl hydrazides have proven to be particularly useful and attractive substrates for the preparation of sulfonamides due to their commercial availability and synthetic accessibility, their stability in air and moisture at ambient temperature, their good solubility in organic solvents, and their high reactivity under I_2/TBHP-catalyzed reaction. Therefore, this method greatly enriches the current N–S bond formation chemistry with several advantages including metal-free catalysis, mild conditions, simple experimental procedure, using easy to handle and readily available reagents, generating clean by-products, and can be carried out at room temperature within a short reaction time with reliable scalability as well as broad substrate scope, which make this synthetic strategy highly valuable for future applications.

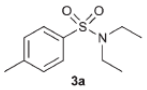
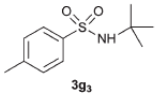
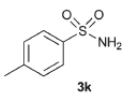


Scheme 3 Control experiments.

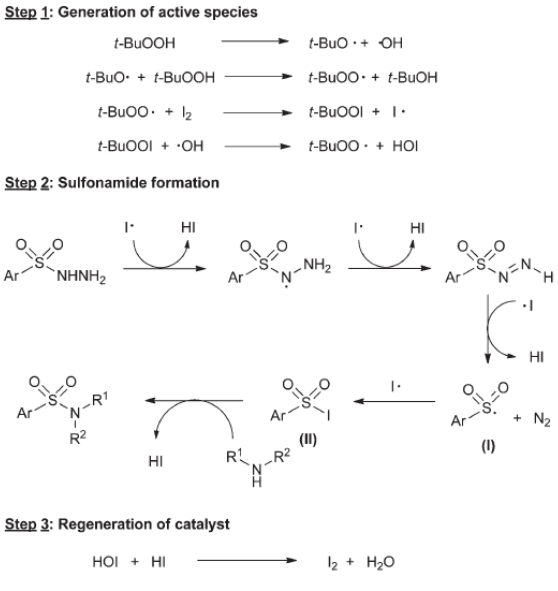
To elucidate the reaction mechanism of sulfonamide formation, several control experiments were conducted (Scheme 3).[16] A reaction of sulfonyl hydrazide **1a** and amine **2a** in the presence of a radical scavenger under the standard conditions resulted in a decrease in product yield. Sulfonamide **3a** was obtained in 39%, 2% and 0% in the presence of TEMPO (2,2,6,6-tetramethylpiperidine-*N*-oxyl), BHT (2,6-di-*tert*-butyl-4-methylphenol), and hydroquinone, respectively (Scheme 3a).

Table 4 Sulfonylation of amine hydrochloride salts[a]



Entry	Amine hydrochloride salt	Product	Yield[b] (%)
1	Et_2NH·HCl	 **3a**	80
2	*t*-$BuNH_2$·HCl	 **3g₃**	54
3	$NH_2Cl(NH_3$·HCl)	 **3k**	66[c,d]

[a] Conditions: **1a** (1.0 mmol), **2** (3.0 mmol), Na_2CO_3 (3.0 mmol), TBHP in decane (3.0 mmol), I_2 (0.2 mmol; 20 mol%), DCE (8 mL), rt, 1 h. [b] Isolated yield. [c] Isolated yield after 16 h. [d] Product **3k** was obtained in 30% yield after 1 h of reaction.



Scheme 4 Possible mechanism.

These results indicated that the reaction was inhibited by a radical scavenger; thus, the reaction pathway is likely to involve a radical process.

To understand the role of iodine, this reaction was carried out in the absence of TBHP. Upon subjecting to 1 equivalent of I_2, a small amount of the product was observed at 1 h and 24 h (Scheme 3b). This outcome implies that I_2 does not react with substrates directly during this transformation. The I_2 pre-catalyst, therefore, is likely to be converted to another intermediate in the presence of TBHP prior to reacting with sulfonyl hydrazide or amine.

Based on the aforementioned results and relevant literature,[10,17] a plausible mechanism for the I_2-catalyzed sulfonylation of an amine is proposed in Scheme 4. This transformation presumably involves an initial reaction of I_2 and TBHP to form a reactive iodine radical species through a radical process.[17c] Then, the sequential N–H abstraction by the iodine radical would lead to the formation of sulfonyl radical (**I**). This resulting sulfonyl radical could subsequently combine with the iodine radical and yield a sulfonyl iodide (**II**). A direct displacement of the sulfonyl iodide (**II**) by amine would furnish the sulfonamide product and release HI species. Further transformation of HI under standard conditions could regenerate I_2 to resume the catalytic cycle.[16,18]

Conclusions

In summary, we have developed a new protocol for the synthesis of sulfonamides *via* an iodine-catalyzed sulfonylation of amines with sulfonyl hydrazides. In this work, for the first time sulfonyl hydrazides were used for the preparation of a variety of sulfonamides at room temperature and provided moderate to excellent yields of products within a short reaction time. This method utilizes inexpensive and readily available reagents, features a simple experimental procedure, generates non-toxic by-products, demonstrates good functional group compatibility and proves to be versatile for a range of arylsulfonyl hydrazides and various types of amines such as primary and secondary aliphatic amines, heteroaromatic amines and amine hydrochloride salts. Further mechanistic investigation and expansion of the synthetic application of this chemistry are currently under exploration in our laboratory.

Experimental section

General information

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. All experiments were carried out under an air atmosphere, and oven-dried glassware was used in all cases. Column chromatography was performed over silica gel (SiO_2; 60 Å silica gel, Merck Grade, 70–230 Mesh). GC experiments were carried out with an Agilent 6890N GC-FID chromatograph equipped with an Agilent column (HP-1, polysiloxane, 24.5 m × 0.32 mm ID × 0.17 μm). ^{1}H and ^{13}C NMR spectra were recorded on Bruker-AV400 spectrometers in $CDCl_3$ solution, at 400 and 100 MHz, respectively. NMR chemical shifts are reported in ppm, and were measured relative to $CHCl_3$ (7.24 ppm for ^{1}H and 77.00 ppm for ^{13}C). IR spectra were recorded on a Bruker FT-IR Spectrometer Model ALPHA by neat method, and only partial data are listed. Melting points were determined on Buchi Melting Point M-565 apparatus. High resolution mass spectroscopy (HRMS) data were analysed by a high-resolution micrOTOF instrument with electrospray ionization (ESI). The structures of known compounds were corroborated by comparing their ^{1}H NMR and ^{13}C NMR data with those in the literature.

Typical procedure for the synthesis of sulfonamides 3a–3i, 3k and 4a$_1$–4e

To a 20 ml oven-dried scintillation vial equipped with a magnetic stir bar, sulfonylhydrazide substrate (1.00 mmol, 1.00 equiv.), iodine (I_2) (51 mg, 0.20 mmol, 0.20 equiv.), 1,2-dichloroethane (DCE) (8.00 mL), amine (3.00 mmol, 3.00 equiv.), and TBHP in decane (3.00 mmol, 3.00 equiv.) were added. The reaction mixture was stirred at room temperature for 1 h. Upon completion, distilled deionized H_2O (10 mL) and saturated $Na_2S_2O_3$ (10 mL) were added, and the mixture was extracted with ethyl acetate (EtOAc) (2 × 20 mL). The combined organic layer was washed with saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by SiO_2 column chromatography to afford a desired sulfonamide product.

***N*,*N*-Diethyl-4-methylbenzenesulfonamide** (3a).[9c] White solid (192 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (d, J = 8.2 Hz, 2H), 7.24 (d, J = 8.2 Hz, 2H), 3.18 (q, J = 7.0 Hz, 4H), 2.37 (s, 3H), 1.11 (t, J = 7.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 137.3, 129.5, 126.9, 41.9, 21.4, 14.1; HRMS (ESI): calcd for $C_{11}H_{17}NO_2SNa$ $[M + Na]^+$ 250.0872, found 250.0871.

1-Tosylpyrrolidine (3b$_1$).[9c] White solid (194 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, J = 8.2 Hz, 2H), 7.29 (d, J = 8.2 Hz, 2H), 3.22–3.18 (m, 4H), 2.40 (s, 3H), 1.73–1.70 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.3, 133.8, 129.6, 127.5, 47.9, 25.2, 21.5; HRMS (ESI): calcd for $C_{11}H_{15}NO_2SNa$ $[M + Na]^+$ 248.0716, found 248.0729.

1-Tosylpiperidine (3b$_2$).[9c] White solid (206 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.59 (m, 2H), 7.28 (d, J = 8.0 Hz, 2H), 2.92 (t, J = 5.6 Hz, 4H), 2.39 (s, 3H), 1.62–1.57 (m, 4H), 1.40–1.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 133.1, 129.5, 127.6, 46.9, 25.1, 23.4, 21.4; HRMS (ESI): calcd for $C_{12}H_{17}NO_2SNa$ $[M + Na]^+$ 262.0872, found 262.0877.

1-Tosylazepane (3b$_3$).[9c] White solid (215 mg, 85% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 3.21 (t, J = 5.8 Hz, 4H), 2.38 (s, 3H), 1.68–1.66 (m, 4H), 1.55–1.52 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.8, 136.5, 129.5, 126.9, 48.1, 29.0, 26.8, 21.4; HRMS (ESI): calcd for $C_{13}H_{19}NO_2SNa$ $[M + Na]^+$ 276.1029, found 276.1032.

4-Tosylmorpholine (3c$_1$).[9c] White solid (211 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.2 Hz, 2H), 7.31 (d,

J = 8.2 Hz, 2H), 3.70 (t, J = 4.8 Hz, 4H), 2.94 (t, J = 4.8 Hz, 4H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.9, 131.9, 129.7, 127.8, 66.0, 45.9, 21.5; HRMS (ESI): calcd for $C_{11}H_{15}NO_3SNa$ $[M + Na]^+$ 264.0665, found 264.0679.

4-Tosylthiomorpholine (**3c$_2$**).[9c] White solid (213 mg, 83% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 3.28–3.26 (m, 4H), 2.67–2.64 (m, 4H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.7, 133.6, 129.7, 127.3, 47.7, 27.2, 21.4; HRMS (ESI): calcd for $C_{11}H_{15}NO_2S_2Na$ $[M + Na]^+$ 280.0436, found 280.0442.

1-Methyl-4-tosylpiperazine (**3d$_1$**).[9c] White solid (221 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.58 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 2.96 (br, 4H), 2.43–2.41 (m, 4H), 2.37 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 132.1, 129.5, 127.8, 53.9, 45.9, 45.6, 21.4; HRMS (ESI): calcd for $C_{12}H_{19}N_2O_2S$ $[M + H]^+$ 255.1162, found 255.1167.

***tert*-Butyl 4-tosylpiperazine-1-carboxylate** (**3d$_2$**).[9c] White solid (307 mg, 90% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.59 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 3.46 (t, J = 5.0 Hz, 4H), 2.91 (t, J = 5.0 Hz, 4H), 2.40 (s, 3H), 1.36 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 143.9, 132.3, 129.7, 127.7, 80.3, 45.8, 43.2, 28.2, 21.5; HRMS (ESI): calcd for $C_{16}H_{24}N_2O_4SNa$ $[M + Na]^+$ 363.1349, found 363.1352.

***N*,*N*-Dibenzyl-4-methylbenzenesulfonamide** (**3e$_1$**).[9c] White solid (245 mg, 70% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.22–7.18 (m, 6H), 7.05–7.02 (m, 4H), 4.29 (s, 4H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 137.7, 135.6, 129.7, 128.5, 128.4, 127.6, 127.2, 50.4, 21.5; HRMS (ESI): calcd for $C_{21}H_{21}NO_2SNa$ $[M + Na]^+$ 374.1185, found 374.1191.

***N*-Benzyl-*N*,4-dimethylbenzenesulfonamide** (**3e$_2$**).[9c] White solid (246 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.71 (d, J = 8.0 Hz, 2H), 7.35–7.25 (m, 7H), 4.10 (s, 2H), 2.56 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.4, 135.6, 134.2, 129.7, 128.6, 128.3, 127.8, 127.4, 54.1, 34.3, 21.5; HRMS (ESI): calcd for $C_{15}H_{17}NO_2SNa$ $[M + Na]^+$ 298.0872, found 298.0878.

***N*,*N*-Diallyl-4-methylbenzenesulfonamide** (**3f**).[19] Colorless oil (121 mg, 48% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68 (d, J = 8.0 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 5.63–5.53 (m, 2H), 5.14–5.09 (m, 4H), 3.77 (d, J = 6.4 Hz, 4H), 2.40 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.2, 137.3, 132.6, 129.6, 127.1, 118.9, 49.3, 21.5; HRMS (ESI): calcd for $C_{13}H_{17}NO_2SNa$ $[M + Na]^+$ 274.0872, found 274.0880.

***N*-Cyclohexyl-4-methylbenzenesulfonamide** (**3g$_1$**).[9c] Dark yellow solid (213 mg, 84% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75 (d, J = 8.8 Hz, 2H), 7.25 (d, J = 8.8 Hz, 2H), 4.97–4.96 (m, 1H), 3.08–3.06 (m, 1H), 2.39 (s, 3H), 1.71–1.68 (m, 2H), 1.60–1.56 (m, 2H), 1.47–1.43 (m, 1H), 1.19–1.07 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.0, 138.4, 129.5, 126.9, 52.5, 33.7, 25.1, 24.5, 21.4; HRMS (ESI): calcd for $C_{13}H_{19}NO_2SNa$ $[M + Na]^+$ 276.1029, found 276.1037.

***N*-Butyl-4-methylbenzenesulfonamide** (**3g$_2$**).[9c] Colorless oil (180 mg, 79% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 5.10 (br s, 1H), 2.88–2.83 (m, 2H), 2.37 (s, 3H), 1.40–1.35 (m, 2H), 1.26–1.20 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.1, 136.8, 129.5, 127.0, 42.8, 31.4, 21.4, 19.6, 13.4; HRMS (ESI): calcd for $C_{11}H_{17}NO_2SNa$ $[M + Na]^+$ 250.0878, found 250.0878.

***N*-(*tert*-Butyl)-4-methylbenzenesulfonamide** (**3g$_3$**).[9c] White solid (131 mg, 58% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (d, J = 8.0 Hz, 2H), 7.24 (d, J = 8.0 Hz, 2H), 5.02 (br, 1H), 2.38 (s, 3H), 1.17 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.7, 140.5, 129.4, 126.9, 54.4, 30.1, 21.4; HRMS (ESI): calcd for $C_{11}H_{17}NO_2SNa$ $[M + Na]^+$ 250.0878, found 250.0894.

1-Tosyl-1*H*-pyrazole (**3h**).[9c] White solid (173 mg, 78% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08–8.07 (m, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.69–7.68 (m, 1H), 7.29 (d, J = 8.0 Hz, 2H), 6.36–6.35 (m, 1H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 145.8, 145.1, 133.9, 131.0, 130.0, 128.0, 108.7, 21.6; HRMS (ESI): calcd for $C_{10}H_{10}N_2O_2SNa$ $[M + Na]^+$ 245.0355; found 245.0365.

1-Tosyl-1*H*-1,2,4-triazole (**3i**).[20] White solid (131 mg, 59% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.72 (s, 1H), 7.98 (s, 1H), 7.93 (d, J = 8.6 Hz, 2H), 7.36 (d, J = 8.6 Hz, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 154.1, 147.2, 144.4, 132.6, 130.3, 128.6, 21.8; HRMS (ESI): calcd for $C_9H_9N_3O_2SNa$ $[M + Na]^+$ 246.0313; found 223.0323.

4-Methylbenzenesulfonamide (**3k**).[9c] White solid (113 mg, 66% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.79 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 4.92 (s, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 143.6, 139.0, 129.7, 126.4, 21.5; HRMS (ESI): calcd for $C_7H_9NO_2SNa$ $[M + Na]^+$ 194.0246, found 194.0252.

4-(Phenylsulfonyl)morpholine (**4a$_1$**).[9e] White solid (187 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.73–7.70 (m, 2H), 7.61–7.57 (m, 1H), 7.54–7.50 (m, 2H), 3.69 (t, J = 4.8 Hz, 4H), 2.95 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.9, 133.0, 129.0, 127.7, 66.0, 45.9; HRMS (ESI): calcd for $C_{10}H_{13}NO_3SNa$ $[M + Na]^+$ 250.0508, found 250.0514.

4-((4-Chlorophenyl)sulfonyl)morpholine (**4a$_2$**).[9b] White solid (210 mg, 80% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (dt, J = 8.8, 2.4 Hz, 2H), 7.50 (dt, J = 8.8, 2.4 Hz, 2H), 3.71 (t, J = 4.8 Hz, 4H), 2.96 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 139.6, 135.6, 129.4, 129.2, 66.0, 45.9; HRMS (ESI): calcd for $C_{10}H_{12}ClNO_3SNa$ $[M + Na]^+$ 284.0119, found 284.0125.

4-((4-Bromophenyl)sulfonyl)morpholine (**4a$_3$**).[9e] White solid (263 mg, 86% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.68–7.65 (m, 2H), 7.60–7.56 (m, 2H), 3.70 (t, J = 4.8 Hz, 4H), 2.95 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 134.1, 132.4, 129.2, 128.1, 65.9, 45.8; HRMS (ESI): calcd for $C_{10}H_{12}BrNO_3SNa$ $[M + Na]^+$ 327.9613, found 327.9617.

4-((4-Methoxyphenyl)sulfonyl)morpholine (**4a$_4$**).[9e] White solid (229 mg, 89% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dt, J = 9.6, 2.4 Hz, 2H), 6.97 (dt, J = 9.6, 2.4 Hz, 2H), 3.84 (s, 3H), 3.69 (t, J = 4.8 Hz, 4H), 2.93 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 163.1, 129.9, 126.4, 114.2, 66.0, 55.6, 45.9; HRMS (ESI): calcd for $C_{11}H_{15}NO_4SNa$ $[M + Na]^+$ 280.0614, found 280.0619.

4-((4-Nitrophenyl)sulfonyl)morpholine (**4a$_5$**).[9e] Yellow solid (236 mg, 87% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (dt, J = 9.2, 2.0 Hz, 2H), 7.92 (d, J = 9.2, 2.0 Hz, 2H), 3.72 (t, J = 4.8 Hz, 4H), 3.02 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 141.2, 128.9, 124.4, 65.9, 45.8; HRMS (ESI): calcd for $C_{10}H_{12}N_2O_5SNa$ $[M + Na]^+$ 295.0359, found 295.0365.

4-(*o*-Tolylsulfonyl)morpholine (4b$_1$). White solid (218 mg, 90% yield); m.p. 79.8–89.1 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.86–7.84 (m, 1H), 7.44 (td, J = 7.2, 0.8 Hz, 1H), 7.32–7.28 (m, 2H), 3.68 (t, J = 4.8 Hz, 4H), 3.11 (t, J = 4.8 Hz, 4H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.1, 134.8, 133.0, 132.8, 130.3, 126.1, 66.2, 45.2, 20.8; IR (neat, cm^{-1}): ν 2860, 1447, 1337, 1261, 1158, 1114, 942, 728; HRMS (ESI): calcd for $C_{11}H_{15}NO_3SNa$ $[M + Na]^+$ 264.0665, found 264.0670.

4-((2-Bromophenyl)sulfonyl)morpholine (4b$_2$). White solid (256 mg, 84% yield); m.p. 127.2–128.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.05–8.02 (m, 1H), 7.73 (dd, J = 7.6, 1.2 Hz, 1H), 7.45–7.36 (m, 2H), 3.70–3.67 (m, 4H), 3.26–3.24 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 137.0, 135.8, 133.8, 132.3, 127.5, 120.4, 66.3, 45.6; IR (neat, cm^{-1}): ν 2860, 1573, 1344, 1262, 1166, 1113, 942, 761, 532; HRMS (ESI): calcd for $C_{10}H_{12}BrNO_3SNa$ $[M + Na]^+$ 327.9613, found 327.9618.

4-(Mesitylsulfonyl)morpholine (4c).[21] White solid (220 mg, 82% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.93 (s, 2H), 3.67–3.65 (m, 4H), 3.13–3.10 (m, 4H), 2.60 (s, 6H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 142.9, 140.6, 131.9, 130.7, 66.1, 44.3, 22.9, 20.9; HRMS (ESI): calcd for $C_{13}H_{19}NO_3SNa$ $[M + Na]^+$ 292.0978, found 292.0985.

4-(Thiophen-2-ylsulfonyl)morpholine (4d).[22] White solid (106 mg, 41% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.63 (dd, J = 4.8, 1.2 Hz, 1H), 7.51 (dd, J = 4.0, 1.2 Hz, 1H), 7.14 (dd, J = 4.8, 4.0 Hz, 1H), 3.74 (t, J = 4.8 Hz, 4H), 3.03–3.00 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 135.1, 132.7, 132.5, 127.7, 65.9, 45.9; HRMS (ESI): calcd for $C_8H_{11}NO_3S_2Na$ $[M + Na]^+$ 256.0073, found 256.0081.

4-(Quinolin-8-ylsulfonyl)morpholine (4e).[9e] White solid (208 mg, 75% yield); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.03 (dd, J = 4.0, 1.6 Hz, 1H), 8.44 (dd, J = 7.6, 1.2 Hz, 1H), 8.22 (dd, J = 8.4, 1.6 Hz, 1H), 8.02 (dd, J = 8.4, 1.2 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.52–7.49 (m, 1H), 3.68 (t, J = 4.8 Hz, 4H), 3.41 (t, J = 4.8 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 151.2, 144.1, 136.4, 136.3, 133.6, 133.3, 128.9, 125.4, 122.0, 66.8, 46.3; HRMS (ESI): calcd for $C_{13}H_{14}N_2O_3SNa$ $[M + Na]^+$ 301.0617, found 301.0620.

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16 See the ESI† for details.

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