

สัญญาเลขที่ PDF/36/2543

รายงานวิจัยฉบับสมบูรณ์

โครงการการพัฒนาวิธีเตรียมสารประกอบไดไฮโดรอัลคอลลีอินต่างๆ

โดย นายเทียนทอง ทองพันธ์ และคณะ

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สนับสนุนโดยสำนักงานกองทุนสนับสนุนการวิจัย

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บทคัดย่อ

ส่วนที่ 1 งานวิจัยนี้เป็นการศึกษาและพัฒนาวิธีการสังเคราะห์สารประเภทบิสอัลคิลไฮโดรเอรีน ซึ่งพบว่าสามารถทำได้ในขั้นตอนเดียว วิธีการดังกล่าวสามารถนำมาใช้ในการเตรียมสารประกอบออกซิเจนและซัลเฟอร์เฮเทอโรไซเคิลได้อย่างมีประสิทธิภาพ

ส่วนที่ 2 งานวิจัยนี้เกี่ยวข้องกับการพัฒนาวิธีการสังเคราะห์สารอาร์ทิมิสิทิน ซึ่งเป็นสารดั้งเดิมที่สำคัญในการเตรียมอนุพันธ์ของสารต้านเชื้อมาลาเรีย โดยวิธีการใหม่นี้ สามารถทำได้ในขั้นตอนเดียวและเป็นวิธีที่ปลอดภัยต่อสิ่งแวดล้อมและเหมาะสมที่จะนำไปพัฒนาในกระบวนการผลิตยาต่อไป

Abstract

Part I. An efficient one-pot synthesis of bisalkylthioarenes is described. Its application in the synthesis of oxygen and sulfur heterocycles is also demonstrated.

Part II. An environmentally friendly one-pot synthesis of artemisitene is described.

Executive Summary

ชื่อโครงการ

ส่วนที่ 1 การพัฒนาวิธีเตรียมสารประกอบไดไธโออัลคิลเอรีนต่างๆ

ส่วนที่ 2 การพัฒนาวิธีการเตรียมสารอาร์เทมิซิทีนโดยวิธีที่ปลอดภัยต่อ

สิ่งแวดล้อม

Part I An Alternative, Simple Method for the Preparation of

Dithioalkylarenes.

Part II An Environmentally Friendly, Low Cost, One-Pot

Synthesis of Artemisitene.

หัวหน้าโครงการ

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ปัญหาที่ทำการวิจัยและความสำคัญของปัญหา

Bisalkylthioarenes and their derivatives are of great interest due to their potential applications as precursors in organic synthesis or as components in the study of new organic materials. However, the utilization of this type of compounds are still scarce because of the limited variety and availability. Although the syntheses of these compounds are known, some required harsh conditions or applied several steps leading to high production cost and low overall yields. Therefore a new and efficient synthesis of bisalkylthioarenes from more readily available starting materials is well worth investigation.

Malaria continues to be a major endemic infectious disease in many developing countries, especially in Africa, Asia and South America. Lately the problem has been further complicated by the emergence of drug resistant strain of *Plasmodium falciparum*, the life threatening form of *Plasmodium* sp. parasites. The above problems make it imperative to quest for new drugs both from synthesis and natural products.

Artemisinin and its derivatives form a group of new drugs currently in use in many malaria infected countries. Artemisitene, the oxidized form of artemisinin, bears an exocyclic α,β -unsaturated lactone moiety which is most suitable for the nucleophilic attack in a 1,4- addition fashion. Reports revealed that such reaction provided C-16 derived artemisinins, some of which showed dramatic improvement on antimalarial activities. However, owing to the fact that artemisitene coexists with artemisinin in rather low and variable quantities and also its isolation and purification from the crude extract are not straightforward, artemisitene has so far been underutilized.

Although the synthesis of artemisitene has already been described, the process involve the use of either environmentally hazardous chlorinated solvent or toxic selenium reagent. Indeed, further development of promising antimalarial candidates, obtained from manipulation of artemisitene which was prepared accordingly has been rejected on the ground of good manufacturing practice (GMP). Thus it is essential to find an alternative procedure, yet equally efficient, to prepare artemisitene in order to meet the acceptable pharmaceutical standard.

วัตถุประสงค์

1. To develop a simple and convenient method for the preparation of dithioalkylarenes from the corresponding dihydroxyarenes.
2. To develop an efficient and environmentally friendly method for the synthesis of artemisitene.

ระเบียบวิธีวิจัย

Part I First a general procedure for the transformation will be established. Spectroscopic techniques will be applied for product identification. Then scope of the reaction will be determined. Finally application of this reaction in organic synthesis will be surveyed. If feasible, mechanism of the reaction will be proposed and investigated.

Part II A variety of methods for the generation of α,β -unsaturated ester will be applied in the synthesis of artemisitene from artemisinin. Purification and spectroscopic techniques will be used in order to identify products from each reaction. Optimal condition will finally be determined.

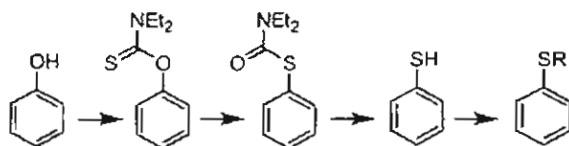
Part I

A Convenient One-Pot Synthesis of Bisalkylthioarenes

Due to the fact that sulfur and oxygen, although are in the same column in the periodic table, differ in terms of electron donating ability,¹ sulfur containing molecules have thus received much attention as potential candidates in the development of new organic materials.²

Alkylthioarenes or arylsulfides, precursors for the synthesis of aromatic sulfoxides, sulfones and other sulfur heterocycles, could be synthesized from the coupling reaction between alkyl or aryl halides with thiols or vice versa.³ The method however suffers from limitation of types of aromatic thiols or halides, as well as requirement of high temperature and long reaction time. The elegant Newman-Karnes' procedure⁴ (exemplified in scheme 1) avoided such substrate limitations by converting the readily and more variably available hydroxyarene to the corresponding thiocarbamate which then underwent consecutive thermal rearrangement, hydrolysis and subsequent alkylation to afford the desired alkylthioarenes.

Scheme 1. Newman-Kwart's synthesis of bisalkylthioarenes



We are interested in charge transfer complexation between electron deficient molecules and organosulfur analogs of bisalkoxyarenes and thus required an efficient, straightforward method to obtain a variety of bisalkylthioarenes. Furman, *et al.*⁵

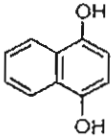
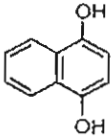
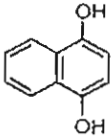
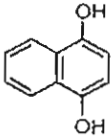
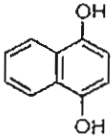
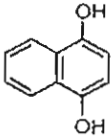
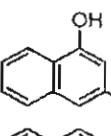
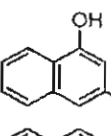
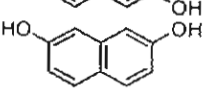
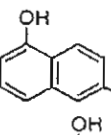
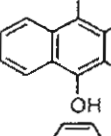
reported the acid mediated synthesis of naphthylsulfide from the reaction of 2-naphthol with various alkylmercaptans. Similarly the nucleophilic replacement of phenolic hydroxy group with mercaptans in strong acid at high temperature was also accomplished.⁶ In addition Nakazawa, *et al.*⁷ succeeded in using similar reaction, 50°C in neat trifluoromethane-sulfonic acid, in the preparation of 1,5 ; 1,6 ; 2,6 and 2,7 bisalkylthionaphthalenes. Here we wish to report the expansion of the scope of this transformation and to establish a practical procedure for the preparation of compounds in this class.

Laastch⁸ reported the regioselective monomethylation⁹ of 1,4-dihydroxynaphthalene derivatives using saturated hydrogen chloride in methanol; the process previously described by Russig.¹⁰ 1,4-dihydroxynaphthalene was then chosen to be a subject for our model study. However, due to the difficulty in accessing and handling of gaseous hydrogen chloride, *p*-toluenesulfonic acid was then used throughout the course of this work.¹¹ Thus treatment of 1,4-dihydroxynaphthalene¹² with a variety of thiols in refluxing benzene in the presence of *p*-toluenesulfonic acid¹³ for 1 h provided 1,4-bisalkylthionaphthalenes¹⁴ whose yields are summarized in Table 1 (entries 1-6).

It is of great interest to note that, under this rather mild reaction condition, none of the monoalkylthionaphthalene was observed. Reaction with 1° thiol (entry 1) apparently proceeds to give 1,4-bisalkylthionaphthalene with higher yield in relative to 2° (entry 3) and 3° thiols (entry 4) respectively, reflecting the effect of steric crowding of the mercapto group in the reaction.

Reactions between a variety of dihydroxyarenes with *n*-propanethiol were then pursued to determine the scope of this transformation (entries 7-14 in Table 1). Remarkably this reaction was also found to be very effective with various dihydroxy-

Table 1. Reaction of dihydroxyarenes with thiols.¹⁵

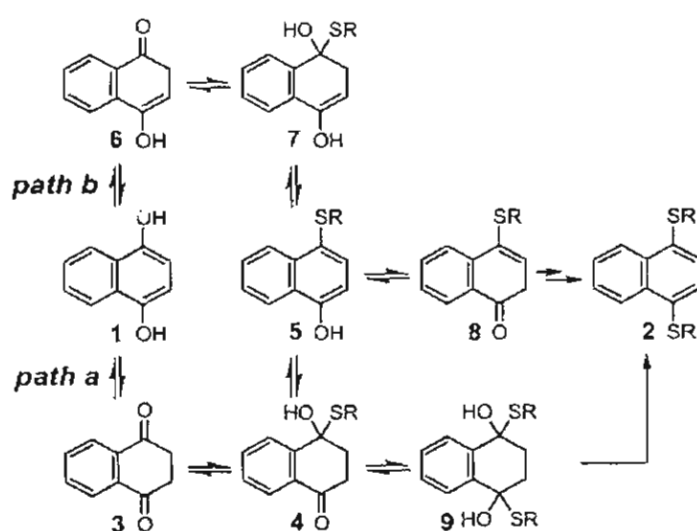
$\text{Ar}(\text{OH})_2 + \text{RSH}$		$\xrightarrow[\text{benzene, reflux, 1 h.}]{p\text{-TsOH}}$	$\text{Ar}(\text{SR})_2$
Entry	$\text{Ar}(\text{OH})_2$	R	% Yield
1		$-\text{CH}_2\text{CH}_2\text{CH}_3$	96
2		$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	84
3		$-\text{CH}(\text{CH}_3)_2$	56
4		$-\text{C}(\text{CH}_3)_3$	-
5		$-\text{CH}_2\text{Ph}$	51
6		$-\text{CH}_2\text{CH}_2\text{SH}$	96
7		$-\text{CH}_2\text{CH}_2\text{CH}_3$	98
8			46
9			94
10			97
11			77
12			59
13			4
14			-

naphthalenes including 1,3-; 2,3-; 2,7-; and 1,6-dihydroxynaphthalenes (entries 7-10, respectively). Comparatively low yield in the case of 2,3- derivative may result from the sterically hindered ortho-dihydroxy group. 9,10-Dihydroxy-anthracene (entry 11) was also affected with this transformation with good yield. For dihydroxy-benzene, however, only 1,3- derivative (entry 12) gave the desired bisthioalkyl products

whereas merely small amount of product was observed from the reaction of thiol with 1,4- analog (entry 13) and none in the case of 1,2- (entry 14).

Mechanism of this transformation is yet unknown but is believed to occur via enol-keto tautomerization^{16,17} as depicted in either path *a* or *b* (scheme 2). In path *a*, the mechanism is similar to that of the Russig-Laastch reaction, *i.e.* acid catalyzed enol-keto tautomerization of phenolic groups would provide the diketo intermediate **3**^{8,18} which could then undergo nucleophilic attack by the mercapto group at the quasi-stable carbonyl center to form monohemithioacetal **4**.^{16a} This intermediate could then dehydrate and rearomatize to provide monosulfide **5** after which repetitive enol-keto tautomerization followed by hemithioacetal formation and subsequent dehydration would furnish bisalkylthioarene **2**. It is also possible that **4** could react with another equivalent of thiol to form bishemithioacetal **9**, which after dehydration would yield bisalkylthionaphthalene **2**.

Scheme 2.



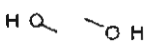
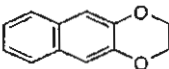
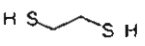
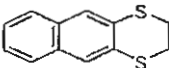
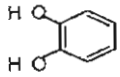
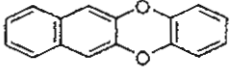
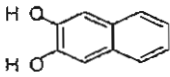
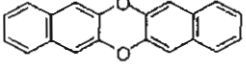
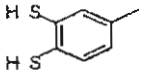
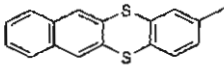
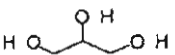
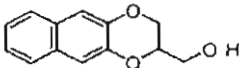
Alternatively tautomerization could occur to give monoketo- intermediate **6** (path *b*). Hemithioacetal formation followed by dehydration then yielded intermediate

5, which could later transform to compound 2 in a similar manner to that previously described.

Accordingly, considering the aromatic character of benzene, in comparison to naphthalene and anthracene, it is not of our surprise to find that the acid catalyzed enol-keto tautomerization of either naphthalene or anthracene should occur much faster than that of benzene, a consequence of less energetic penalty from dearomatization process. However it is still unclear why only reaction with 1,3-dihydroxybenzene, but 1,2- and 1,4-, is effective. This observation is, however, related to that reported by Wiberg^{16b} in the study of acid catalyzed formation of enol ethers.

This reaction should serve as a versatile tool in the preparation of a wide variety of bisalkylthioarene derivatives. For example, it is found that treatment of 2,3-dihydroxynaphthalene with various 1,2-diols or 1,2-dithiols provided the dioxins or dithiins derivatives in moderate to excellent yields as summarized in **Table 2**.

Table 2. Reactions between 2,3-dihydroxynaphthalene with diols and dithiols.

Entry	Nucleophile	Product	%
1			61
2			91
3			63
4			30
5			50
6			44

Applications of this method in the preparation of electron donating species in charge transfer complexation are currently under active investigation.

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11. An expensive trifluoromethanesulfonic acid can also be used with similar results. Concentrated sulfuric acid can also be used but is less miscible with organic solvents and frequently gives water-soluble by-products.
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13. *p*-Toluenesulfonic acid was purified by recrystallization from ethyl acetate and dried under vacuum. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd edition, Pergamon Press, Oxford, p 291.
14. *General procedure*: To a round bottom flask containing dihydroxyarene (1 mmol) and *p*-toluenesulfonic acid (0.5 mmol) was added, at room temperature, benzene (5 ml) and thiol (12 mmol) respectively. The mixture was allowed to reflux for 1 h. Normal work up followed by silica gel chromatography using ethyl acetate/hexane as a mobile phase yielded 1,4-bisalkylthionaphthalene.
15. Values represent purified yields and do not necessarily represent the optimal conditions.
16. A) Oae, S.; Fukumoto, T.; Kiritani, R. *Bull. Chem. Soc. Jpn.* **1963**, *36*, 346. b) Wiberg, K. B.; Saegebarth, K. A. *J. Org. Chem.* **1960**, *25*, 832.
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Part II

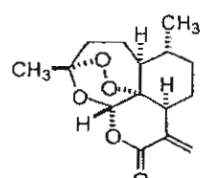
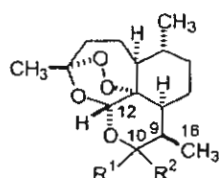
AN ENVIRONMENTALLY FRIENDLY, LOW COST, ONE-POT SYNTHESIS OF ARTEMISITENE

During the course of our study on sulfur chemistry, we are challenged by the problem on how to prepare artemisitene, the key intermediate for the synthesis of potent antimalarial artemisinin derivatives, without using environmentally toxic chlorinated solvents or selenium reagents. We have found that sulfur chemistry we are currently investigated may provide a new approach to overcome such obstacle and would allow a new synthesis that is certified for the good manufacturing practice, GMP. The followings are adapted from the manuscript submitted to the journal – *Synthetic Communications*. The manuscript has already been accepted for publication.

Malaria continues to be a major endemic infectious disease in many developing countries, especially in Africa, Asia and South America. Lately the problem has been further complicated by the emergence of drug resistant strain of *Plasmodium falciparum*, the life threatening form of *Plasmodium* sp. parasites. Also, the ease of communication and mobility of population to and from the infected areas resulted in the spreading of the disease to new grounds where they were hitherto unknown. The above problems make it imperative to quest for new drugs both from synthesis and natural products.¹

Since its discovery by the Chinese group,² artemisinin **1a**, a naturally occurring endoperoxide-containing sesquiterpene lactone from *Artemisia annua* Linn., and its derivatives (**1b–1e**), form a group of new drugs currently in use in many

malaria infected countries.³ Although the parent compound artemisinin and compounds **1b–1e**, the semi-synthetic products derived from chemical manipulation at C-10 lactone carbonyl moiety of **1a**, are very active against drug resistant malarial parasites, the search for new derivatives continues in order to find more potent candidates for future clinical use.



1a (artemisinin)	$R^1 = R^2 = O$	2 (artemisitenone)
1b (artemether)	$R^1 = H, R^2 = OMe$	
1c (arteether)	$R^1 = H, R^2 = OEt$	
1d (sodium artesunate)	$R^1 = H, R^2 = OOCCH_2CH_2COONa$	
1e (sodium artelinate)	$R^1 = H, R^2 = OCH_2-C_6H_4-COONa$	

Artemisitene **2**, the oxidized form of artemisinin **1a**, exists as a minor constituent in an American variant of *Artemisia annua*.⁴ Structural feature of **2**, bearing an exocyclic α,β -unsaturated lactone moiety, is most suitable for the nucleophilic attack in a 1,4- addition fashion⁵ and, indeed, reports revealed that such reaction provided C-16 derived artemisinins,^{6,7} some of which showed dramatic improvement on antimalarial activities.⁸ However, owing to the fact that **2** coexists with **1a** in rather low and variable quantities and also its isolation and purification from the crude extract are not straightforward, artemisitene **2** has so far been underutilized. A semisynthesis of **2** from the cheap and naturally abundant **1a** would provide a solution to overcome this drawback. Consequently, El-Feraly, *et al.*⁹ reported an elegant four step, 53% overall yield, synthesis of artemisitene from **1a** employing the methylene blue-sensitized photo-oxygenation of anhydrodihydro-artemisinin as the key transformation step. Thereafter a convenient one-pot synthesis

of **2** from **1a** involving an anionic [2,3]-sigmatropic selenoxide elimination route was described by Paitayatat, *et al.*⁵

Although the latter synthesis described by Paitayatat, *et al.* has proved efficient and straightforward providing high yield of the required artemisitene, the process involves the use of either environmentally hazardous chlorinated solvent or toxic selenium reagent. Indeed, further development of promising antimalarial candidates, obtained from manipulation of artemisitene which was prepared according to Paitayatat's method,⁵ has been rejected on the ground of good manufacturing practice (GMP). Thus it is essential to find an alternative procedure, yet equally efficient, to prepare artemisitene in order to meet the acceptable pharmaceutical standard.

The use of di-2-pyridyl disulfide, reported by Dubs in 1978¹⁰ and successfully utilized by Nagao and Roush research groups in their syntheses of natural products,^{11,12} as reagent for the introduction of a double bond α,β to the carbonyl group seemed attractive. However, we have found that conversion of artemisinin to artemisitene employing di-2-pyridyl disulfide under conditions reported¹⁰⁻¹² was not entirely satisfactory. Thus, addition of the disulfide to the anion derived from lithium diisopropylamide treatment of **1a** followed by oxidation with MCPBA and subsequent elimination provided **2** only in poor yield (<50% in each run).

The use of methyl 2-pyridinesulfinate as reagent for sulfinylation-dehydrosulfinylation in the preparation of α,β -unsaturated ketone was reported by Trost.¹³ We were encouraged to note that a modified Trost's methodology employing, instead of methyl 2-pyridinesulfinate, the readily available *p*-toluenesulfinyl chloride could successfully be used in the conversion reaction of **1a** to **2**. Thus, treatment of the lithium anion derived from **1a** with freshly prepared *p*-

that temperature for 1 h after which the reaction temperature was raised to 0°C where the mixture was stirred for an additional 2 h. The reaction mixture was then quenched with saturated aqueous ammonium chloride and the solution was extracted with EtOAc. The combined organic extract was washed with brine, dried over MgSO₄, filtered and, finally, evaporated to dryness. The crude product was then subjected to silica gel chromatographic purification using EtOAc : hexane = 1 : 3 as an eluent to give, after recrystallization with hexane and small amount of EtOAc, the desired product **2** (0.2602 g, 86% yield, 100% conversion). Spectroscopic data of the product are identical in all respects to those previously described.^{4,5,9}

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ผลที่ได้รับ

Part I Manuscript entitled '*A Convenient One-Pot Synthesis of Bisalkylthioarenes*' is in preparation. It will be submitted to the journal *Organic Letters* (Impact Factor 2001 = 3.67).

Part II Manuscript entitled '*An Environmentally Friendly One-Pot Synthesis of Artemisitene*' was already accepted for publication in the journal *The Synthetic Communications* (Impact Factor 2001 = 0.912).

ภาคผนวก

กิจกรรมที่เกี่ยวข้องกับการเสนอผลงาน

1. เสนอผลงานแบบโปสเตอร์ในการประชุม วทท. ครั้งที่ 27 ที่จังหวัดสงขลา
2. เสนอผลงานแบบโปสเตอร์ในการประชุม วทท. ครั้งที่ 28 ที่กรุงเทพมหานคร

A Convenient One-Pot Synthesis of Bisalkylthioarenes

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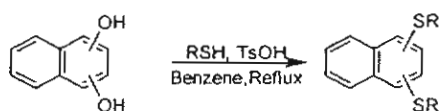
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ABSTRACT



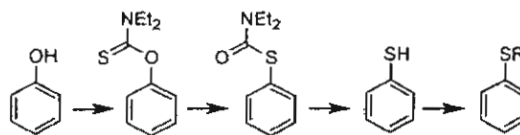
Bisalkylthioarenes could efficiently be prepared from corresponding dihydroxyarenes.

Due to the fact that sulfur and oxygen, although are in the same column in the periodic table, differ in terms of electron donating ability,¹ sulfur containing molecules have thus received much attention as potential candidates in the development of new organic materials.²

Alkylthioarenes or arylsulfides, precursors for the synthesis of aromatic sulfoxides, sulfones and other sulfur heterocycles, could be synthesized from the coupling reaction between alkyl or aryl halides with thiols or vice versa.^{1a,3} The method however suffers from limitation of types of aromatic thiols or halides, as well as requirement of high temperature and long reaction time. The elegant

Newman-Karnes' procedure⁴ (exemplified in scheme 1) avoided such substrate limitations by converting the readily and more variably available hydroxyarene to the corresponding thiocarbamate which then underwent consecutive thermal rearrangement, hydrolysis and subsequent alkylation to afford the desired alkylthioarenes.

Scheme 1. Newman-Kwart's synthesis of bisalkylthioarenes



We are interested in charge transfer complexation between electron deficient molecules and organosulfur analogs of bisalkoxyarenes and thus required an efficient,

¹ a) Tagaki, W. In *Organic Chemistry of Sulfur*, Oae, s., Ed.; Plenum Press: New York, 1977, p 265. b) Brown, H. C.; Okamoto, Y. *J. Am. Chem. Soc.* 1958, 80, 4979

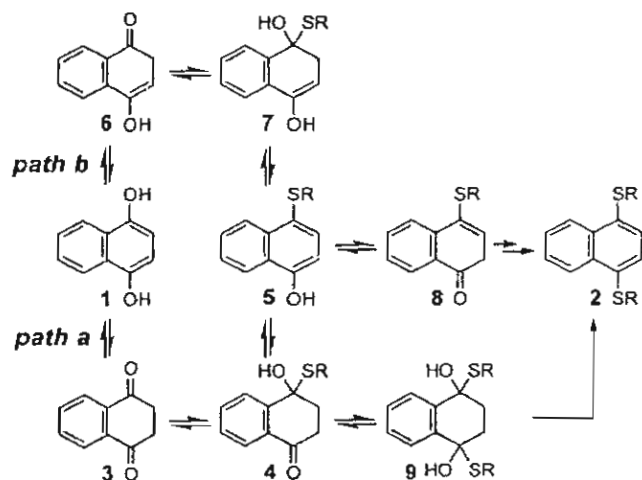
² For some selected examples, see a) Cox, S. D.; Dirk, C. W.; Moraes, F.; Wellman, D. E.; Wudl, F.; Soltis, M.; Strouse, C. *J. Am. Chem. Soc.* 1984, 106, 7131. b) MacNicol, D. D.; Mallinson, P. R.; Robertson, C. D. *J. Chem. Soc., Chem. Commun.* 1985, 23, 1649. c) Miyamoto, H.; Yui, K.; Otsubo, T.; Ogura, F. *Tetrahedron Lett.* 1986, 27, 2011.

³ a) Campbell, J. R. *J. Org. Chem.* 1964, 29, 1830. b) Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* 1979, 44, 2642. c) Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* 1980, 21, 3099. d) Pastor, S. D. *Helv. Chim. Acta* 1988, 71, 859.

⁴ Newman, M. S.; Karnes, H. A. *J. Am. Chem. Soc.* 1966, 88, 3980.

depicted in either path *a* or *b* (scheme 2). In path *a*, the mechanism is similar to that of the Russig-Laastch reaction, i.e. acid catalyzed enol-keto tautomerization of phenolic groups would provide the diketone intermediate **3**^{8,18} which could then undergo nucleophilic attack by the mercapto group at the quasi-stable carbonyl center to form monohemithioacetal **4**.^{16a} This intermediate could then dehydrate and rearomatize to provide monosulfide **5** after which repetitive enol-keto tautomerization followed by hemithioacetal formation and subsequent dehydration would furnish bisalkylthioarene **2**. It is also possible that **4** could react with another equivalent of thiol to form bishemithioacetal **9**, which after dehydration would yield bisalkylthionaphthalene **2**.

Scheme 2.



Alternatively tautomerization could occur to give monoketo- intermediate **6** (path *b*). Hemithioacetal formation followed by dehydration then yielded intermediate **5**, which could later transform to compound **2** in a similar manner to that previously described.

Accordingly, considering the aromatic character of benzene, in comparison to naphthalene and anthracene, it is not of our surprise to find that the acid catalyzed enol-keto tautomerization of either naphthalene or anthracene should occur much faster than that of benzene, a consequence of less energetic penalty from dearomatization process.

However it is still unclear why only reaction with 1,3-dihydroxybenzene, but 1,2- and 1,4-, is effective. This observation is, however, related to that reported by Wiberg^{16b} in the study of acid catalyzed formation of enol ethers.

This transformation should serve as a versatile tool in the preparation of a wide variety of bisalkylthioarene derivatives. Applications of this reaction in the synthesis of sulfur-containing heterocyclic compounds are currently in progress and will be reported elsewhere.

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Supporting Information Available: Characterization of products (¹H and ¹³C NMR, IR, MS and melting point). This material is available free of charge via the internet at <http://pubs.acs.org>.

¹⁶ A) Oae, S.; Fukumoto, T.; Kiritani, R. *Bull. Chem. Soc. Jpn.* 1963, 36, 346. b) Wiberg, K. B.; Saegbarth, K. A. *J. Org. Chem.* 1960, 25, 832.

¹⁷ Other examples of enol-keto tautomerization of phenolic compounds, see a) Forsen, S.; Nilson, M. In *The chemistry of the Carbonyl Group*, Vol. 2; Zabicky, J., Ed.; Interscience: New York, 1970; pp 168-183. b) Vagedes, D.; Frohlich, R.; Erker, G. *Angew. Chem. Int. Ed.* 1999, 38, 3362 and references in footnote 2 therein.

¹⁸ Pearson, M. S.; Jensky, B. J.; Greer, F. X.; Hagstrom, J. P.; Wells, N. M. *J. Org. Chem.* 1978, 43, 4617.

straightforward method to obtain a variety of bisalkylthioarenes. Furman, *et al.*⁵ reported the acid mediated synthesis of naphthylsulfide from the reaction of 2-naphthol with various alkylmercaptans. Similarly the nucleophilic replacement of phenolic hydroxy group with mercaptans in strong acid at high temperature was also accomplished.⁶ In addition Nakazawa, *et al.*⁷ succeeded in using similar reaction, 50°C in neat trifluoromethanesulfonic acid, in the preparation of 1,5 ; 1,6 ; 2,6 and 2,7 bisalkylthionaphthalenes. Here we wish to report the expansion of the scope of this transformation and to establish a practical procedure for the preparation of compounds in this class.

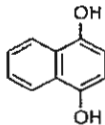
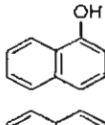
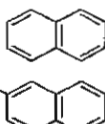
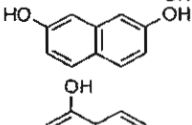
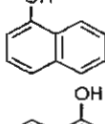
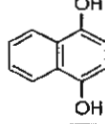
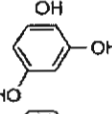
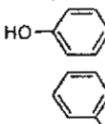
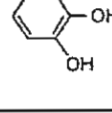
Laatsch⁸ reported the regioselective monomethylation⁹ of 1,4-dihydroxynaphthalene derivatives using saturated hydrogen chloride in methanol; the process previously described by Russig.¹⁰ 1,4-dihydroxynaphthalene was then chosen to be a subject for our model study. However, due to the difficulty in accessing and handling of gaseous hydrogen chloride, *p*-toluenesulfonic acid was then used throughout the course of this work.¹¹ Thus treatment of 1,4-dihydroxynaphthalene¹² with a variety of thiols in refluxing benzene in the presence of *p*-toluenesulfonic acid¹³ for 1 h provided 1,4-bisalkylthionaphthalenes¹⁴ whose yields are summarized in Table 1 (entries 1-6).

It is of great interest to note that, under this rather mild reaction condition, none of the monoalkylthionaphthalene was observed. Reaction with 1° thiol (entry 1) apparently proceeds to give 1,4-bisalkylthionaphthalene with higher yield in relative to 2° (entry 3) and 3° thiols (entry 4) respectively, reflecting the effect of steric crowding of the mercapto group in the reaction.

Reactions between a variety of dihydroxyarenes with *n*-propanethiol were then pursued to determine the scope of this transformation (entries 7-14 in Table 1). Remarkably this reaction was also found to be very effective with various dihydroxynaphthalenes including 1,3-; 2,3-; 2,7-; and 1,6-dihydroxynaphthalenes (entries 7-10, respectively). Comparatively low yield in the case of 2,3- derivative may

result from the sterically hindered ortho-dihydroxy group. 9,10-Dihydroxy-anthracene (entry 11) was also affected with this transformation with good yield. For dihydroxybenzene, however, only 1,3- derivative (entry 12) gave the desired bithioalkyl products whereas merely small amount of product was observed from the reaction of thiol with 1,4-analog (entry 13) and none in the case of 1,2- (entry 14).

Table 1. Reaction of dihydroxyarenes with thiols.¹⁵

Entry	Ar(OH) ₂	R	% Yield
	$\text{Ar(OH)}_2 + \text{RSH} \xrightarrow[\text{benzene, reflux 1 h.}]{p\text{-TsOH}}$	Ar(SR)_2	
1		-CH ₂ CH ₂ CH ₃	96
2		-CH ₂ CH(CH ₃) ₂	84
3		-CH(CH ₃) ₂	56
4		-C(CH ₃) ₃	-
5		-CH ₂ Ph	51
6		-CH ₂ CH ₂ SH	96
7		-CH ₂ CH ₂ CH ₃	98
8			46
9			94
10			97
11			77
12			59
13			4
14			-

Mechanism of this transformation is yet unknown but is believed to occur via enol-keto tautomerization^{16,17} as

¹⁵ Values represent purified yields and do not necessarily represent the optimal conditions.

⁵ Furman, F. A.; Thelin, J. H.; Hein, D. W.; Hardy, W. B. *J. Am. Chem. Soc.* 1960, 82, 1450.

⁶ Oae, S.; Kiritani, R. *Bull. Chem. Soc. Jpn.* 1965, 38, 1381.

⁷ Nakazawa, T.; Hirose, N.; Itabashi, K. *Synthesis* 1989, 955.

⁸ Laatsch, H. *Liebigs Ann. Chem.* 1980, 140.

⁹ For selected applications of this transformation, see a) Laatsch, H. *Liebigs Ann. Chem.* 1980, 1321. b) Dreher, S. D.; Paruch, K.; Katz, T. J. *J. Org. Chem.* 2000, 65, 806. c) Dreher, S. D.; Katz, T. J.; Lam, K.-C.; Rheingold, A. L. *J. Org. Chem.* 2000, 65, 815.

¹⁰ Russig, F. *J. Prakt. Chem.* 1900, 62, 30.

¹¹ An expensive trifluoromethanesulfonic acid can also be used with similar results. Concentrated sulfuric acid can also be used but is less miscible with organic solvents and frequently gives water-soluble by-products.

¹² a) Oatis, Jr., J. E.; Walle, T.; Daniell, H. B.; Gaffney, J. E.; Knapp, D. R. *J. Med. Chem.* 1985, 28, 822. b) ref. 8.

¹³ *p*-Toluenesulfonic acid was purified by recrystallization from ethyl acetate and dried under vacuum. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd edition, Pergamon Press, Oxford, p 291.

¹⁴ **General procedure:** To a round bottom flask containing dihydroxyarene (1 mmol) and *p*-toluenesulfonic acid (0.5 mmol) was added, at room temperature, benzene (5 ml) and thiol (12 mmol) respectively. The mixture was allowed to reflux for 1 h. Normal work up followed by silica gel chromatography using ethyl acetate/hexane as a mobile phase yielded 1,4-bisalkylthionaphthalene.

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