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An efficient one-pot synthesis of bisalkylthioarenes ☆

Porntip Charoonniyomporn,[a] Tienthong Thongpanchang,[a,*] Suteera Witayakran,[a] Yodhathai Thebtaranonth,[a] Karen E. S. Phillips[b] and Thomas J. Katz[b]

[a]Department of Chemistry, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400, Thailand
[b]Department of Chemistry, Columbia University in the City of New York, New York, NY 10027, USA

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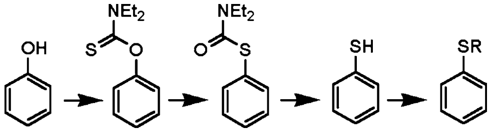
Abstract—Bisalkylthioarenes can be prepared efficiently from reactions between dihydroxyarenes and thiols under acidic conditions.

The procedure most commonly used in a number of studies[1] to synthesize aryl sulfides has been the coupling of aryl halides and thiols.[2] However, there are other ways to prepare such structures. Particularly useful, if it could be carried out easily and generally, would be to replace the hydroxyl groups in phenols with alkylthio groups.

Newman and Karnes developed a procedure[3] (shown in Scheme 1) that works for a variety of phenols. The process however takes four steps to achieve, and one of them is a high-temperature rearrangement. Much easier is the direct displacement of phenolic hydroxyls by thiols under the influence of strong acid. Such transformations were first demonstrated in 1960 by Furman et al., who heated naphthols and thiols to 110–120 °C for a day with very large amounts of *p*-toluenesulfonic acid and little or no solvent.[4,5] Subsequently, some examples were described in which the acid was 12 M HCl, the temperature was 180 °C, and the reaction times were 2–3 days.[6] Another was described in which the reaction medium was pure trifluoromethanesulfonic acid[7] with reaction temperature at 50 °C, and the reaction time was 3 h. Here we report, with a number of examples employing dihydroxyarenes, a practical procedure for carrying out such transformations and some factors that affect the yields.



Scheme 1. The Newman–Karnes alkylthioarene synthesis.

1,4-Dihydroxynaphthalene was used for initial studies following Russig[8] and Laatsch,[9] who reported that its derivatives were regioselectively mono *O*-methylated by methanol saturated with hydrogen chloride. However, because it is easier to handle than gaseous hydrogen chloride, *p*-toluenesulfonic acid was used.[10] It was found that when 1,4-dihydroxynaphthalene[11] was refluxed in benzene for 1 h with *p*-toluenesulfonic acid[12] with a variety of thiols, 1,4-bisalkylthionaphthalenes[13] were obtained in the yields summarized in Table 1 (entries 1–6). These yields are higher when the thiols are primary (entries 1 and 2) than when they are branched (entries 3 and 4).

The reactions of a variety of dihydroxyarenes and *n*-propanethiol were then pursued to determine the scope of the transformation (entries 7–14, Table 1). It was found that 1,3-, 2,7-, and 1,6-dihydroxynaphthalenes (entries 7, 9 and 10) and 9,10-dihydroxyanthracene (entry 11) all gave good yields.[14] 2,3-Dihydroxynaphthalene gave a lower yield (entry 8), and catechol (entry 14) gave none of the expected product. In fact, of the

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Keywords: Bisalkylthioarenes; Arylsulfides; Phenols; Thiols; Sulfides; Displacement.

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* Corresponding author. Tel./fax: +66-2201-5139; e-mail: tettp@mahidol.ac.th

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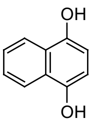
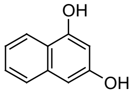
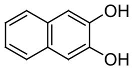
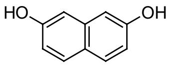
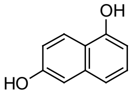
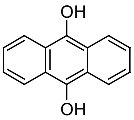
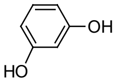
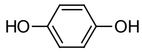
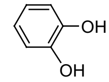
Table 1. Formation of bisalkylthioarenes by the reactions of diols with thiols[a]

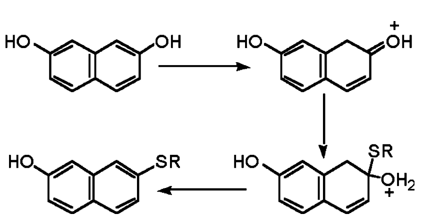
$$\mathrm{Ar(OH)_2 + RSH} \xrightarrow[\text{benzene, reflux 1 h}]{p\text{-TsOH}} \mathrm{Ar(SR)_2}$$

Entry	Ar(OH)$_2$	R	Yield (%)
1		–$CH_2CH_2CH_3$	96
2		–$CH_2CH(CH_3)_2$	84
3		–$CH(CH_3)_2$	56
4		–$C(CH_3)_3$	—
5		–CH_2Ph	51
6		–CH_2CH_2SH	96
7		–$CH_2CH_2CH_3$	98
8			46
9			94
10			97
11			77
12			59
13			4
14			—

[a] Yields are those of purified materials, but they are not optimized. The procedure is given in Ref. 13.

dihydroxybenzenes, only the 1,3-derivative (entry 12) gave an appreciable yield of the bisalkylthio product.

The mechanisms by which the phenolic hydroxyl groups are replaced by alkylthio groups, like analogous replacements by alkoxy- and amino groups,[5] probably involve additions of thiols to the keto tautomers of the phenols as outlined in Scheme 2. However, notably different in the reactions described here is that while aromatic diols with alcohols give *mono* alkyl ethers,[15] with thiols they give bisthioethers. This could reflect the greater nucleophilicities of thiols compared to alcohols.[16]



Scheme 2.

The different reactivities illustrated by the yields in Table 1 can be explained if the reactions require the carbonyl groups of the carbon-protonated phenols to be conjugated with either a benzene ring or a β-alkoxy- (or alkylthio-) substituted double bond. Accordingly, the only benzenediols that reacted with thiols, like those that react with alcohols, are those that have hydroxyl groups *meta* to one another.[17]

It should be possible to apply the procedure reported here to prepare a variety of bisalkylthioarenes and a variety of sulfur-containing heterocyclic compounds. Research towards these goals is currently in progress.

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12. *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 ed.; Pergamon: Oxford; p 291.
13. *General procedure*: Dihydroxyarene (1 mmol), *p*-toluenesulfonic acid (0.5 mmol) and thiol (12 mmol) in benzene (5 mL) were refluxed for 1 h. After aqueous workup, the product was chromatographed on silica gel. Ethyl acetate/hexane eluted the bisalkylthioarene.
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