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Original article

Efficient synthesis of unsymmetrical diaryl thioethers *via* TBAF-mediated denitrative substitution of nitroarenes with PhSTMS under mild and neutral conditions

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ABSTRACT

Tetrabutylammonium fluoride (TBAF) effectively facilitated a denitrative substitution reaction of electron-deficient nitroarenes with phenylthiotrimethylsilane (PhSTMS) under mild and base-free neutral conditions at room temperature, providing a practical and efficient synthesis of useful unsymmetrical diaryl thioethers. Nitroarenes bearing *ortho-* and *para*-positioned electron-withdrawing groups are the most reactive substrates, indicating that this reaction most possibly proceeded *via* the nucleophilic aromatic substitution (S_NAr) mechanism.

1. Introduction

The formation of carbon-heteroatom bonds *via* arylation reactions has attracted much interest in recent years. These methods have also been applied in diaryl thioether synthesis since they are also a class of useful intermediates in synthesis and key building blocks in natural products and biologically and pharmaceutically active compounds [1,2]. One common method for diaryl thioether preparation is the classic, copper-assisted Ullmann reactions [3–5]. However, this method usually requires a high reaction temperature and large amounts of copper reagent, which may lead to the generation of undesirable wastes and other problems upon scaling-up of the reactions. Thus, in recent years to overcome these limitations, various new methods have been developed for the reactions of aryl halides and sulfur nucleophiles, such as the palladium-catalyzed reactions [6,7], improved copper-catalyzed Ullmann reactions [4,5,8–10], as well as iron [11], nickel [12] and other transition metal-catalyzed methods. Despite the advances in metal-catalyzed methods, nucleophilic aromatic substitution (S_NAr) reactions of electron-deficient aryl halides are still attractive alternatives in synthesis of thioethers and other C-heteroatom compounds due to the relatively milder conditions and environmentally benign features of the reactions [13–16]. In comparison with the reactions of the corresponding aryl halides, the C-heteroatom bond formation *via* S_NAr reactions of the readily available nitroarenes by displacement of the nitro groups were much less known processes [17]. Recently, Oshima [18], Beier [19], and Wu [20] independently reported C–O, C–S and C–C coupling reactions of electron-deficient nitroarenes with thiols, alkali alkoxides, alkane thiolates, and arylboronic acids. However, drawbacks still remain because these methods usually use excess amounts of nucleophiles, large amounts of base resulting in strong basic conditions, high reaction temperatures, and the generation of large amounts of wastes. In our previous studies, we have developed a mild and efficient method for the synthesis of diaryl thioethers by tetrabutylammonium fluoride (TBAF)-catalyzed S_NAr reactions of aryl fluorides and phenylthiotrimethylsilane (PhSTMS) under base-free neutral conditions [21,22]. In comparison with conventional S_NAr reactions [13–16], the advantages of using TBAF as the catalyst and trimethylsilyl-activated PhSTMS as the sulfur nucleophile include comparatively lower reaction temperatures (*e.g.*, at room temperature), base-free neutral conditions, and high tolerance of the reactive functional groups, which also implied that this method may have broader applications in synthesis. Herein we continue to report on a mild and efficient TBAF-mediated denitrative substitution reaction of electron-deficient nitroarenes with PhSTMS, providing a simple and practical alternative for the synthesis of useful unsymmetrical diaryl thioethers.

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2. Experimental

Unless otherwise noted, reactants and catalyst were purchased and used without further purification. In reactions carried out under air, commercial solvents were directly used. In reactions carried out under N_2, degassed solvents were used. The reactions were then monitored by TLC. Products were purified by column chromatography on silica gel using petroleum ether and ethyl acetate as eluent. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker Avance-III 500 instrument (500 MHz for ^{1}H NMR and 125.4 MHz for ^{13}C NMR spectroscopy) or a Bruker Avance 300 instrument (300 MHz for ^{1}H NMR and 75 MHz for ^{13}C NMR spectroscopy) using $CDCl_3$ as the solvent with tetramethylsilane (TMS) as the internal standard. IR spectra were recorded on a Bruker Vector-55 instrument. Mass spectra were measured on a Shimadzu GC-MS-QP2010 Plus spectrometer (EI). HRMS (EI) analysis was performed by the Analytical Center at the Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences.

*General procedure for the synthesis of unsymmetrical diaryl thioethers (**3**) by denitrative substitution reaction of nitroarenes (**2**) with PhSTMS (**1**):* The mixture of nitroarene **2** (1.0 mmol), PhSTMS **1** (1.2 mmol, 1.2 equiv.), and TBAF (1.2 mmol, 1.2 equiv.) in degassed acetonitrile (2 mL) was stirred at room temperature under N_2 for 2 h and the reaction was monitored by TLC. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue purified by flash column chromatography on silica gel to give **3**.

*6-(Phenylthio)benzo-[1,3]dioxole-5-carbaldehyde (**3c**):* ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.30 (s, 1H), 7.29 (s, 1H), 7.23–7.18 (m, 5H), 6.67 (s, 1H), 5.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 189.7, 152.9, 148.2, 135.6, 135.5, 130.7, 129.5, 127.5, 112.9, 108.3, 102.4; IR (KBr, cm^{-1}): ν 3717, 2910, 1683, 1582, 1472, 1252, 1037; MS (EI): *m/z* (%) 258 (M$^+$), 241, 199, 171, 148, 120, 95, 69, 51; HRMS Calcd. for $C_{14}H_{10}O_3S$: 258.0351; found: 258.0353. *2,4-Bis(phenylthio)-benzaldehyde (**3d**):* ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.22 (s, 1H), 7.68 (d, 1H, J = 8.2 Hz), 7.38–7.28 (m, 10H), 7.00 (d, 1H, J = 8.2 Hz), 6.61 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.4, 147.6, 143.3, 134.7, 134.1, 132.7, 131.6, 130.1, 129.8, 129.4, 128.9, 125.9, 123.4; IR (KBr, cm^{-1}): ν 3747, 3430, 2801, 1683, 1575, 1205, 752, 691; MS (EI): *m/z* (%) 322 (M$^+$), 244, 212, 184, 152, 109, 77, 51; HRMS Calcd. for $C_{19}H_{14}OS_2$: 322.0486; found: 322.0483.

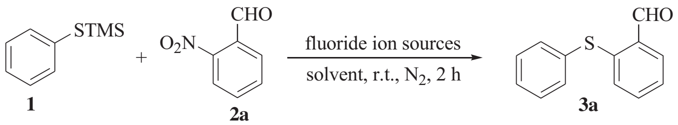
For the known products, their spectral data are in agreement with the literature [21–27].

3. Results and discussion

In previous studies [21,22], we noticed that contrary to the usual behavior of halo-substituted nitroarenes, those nitroarenes bearing electron-withdrawing groups (EWGs), such as formyl, as substrate, the formyl-retained and nitro-displaced product could be obtained under similar conditions. This interesting result encouraged us to further explore the denitrative reactions of nitroarenes with PhSTMS in detail. Thus, the reaction of PhSTMS (**1**) and 2-nitrobenzaldehyde (**2a**) was investigated to optimize the reaction conditions (Table 1). As in the previous studies, the reaction was initially carried out under atmospheric conditions using 1.2 equiv. of both **1** and TBAF in acetonitrile. The reaction proceeded rapidly even at room temperature (2 h), but only with a moderate yield of product **3a** (entry 1). No higher yield of the product could be achieved despite large excessive amounts of **1** and TBAF (2 equiv.) under the identical condition (entry 2). During the study, we noticed that variant amounts of diphenyl disulfide (PhSSPh) and other unidentified byproducts were detected in the reactions under air. Realizing that oxygen may oxidize **1** to PhSSPh and **2a** to the corresponding acid when the reaction was conducted under air, we next performed the reaction under nitrogen and degassed solvents. Thus, by carrying out the reaction under nitrogen, 1.2 equiv. of **1** and TBAF could successfully afford a high yield of target **3a** (entry 3). To further optimize the reaction conditions, various solvents such as toluene, THF, DMF, DMSO, dioxane (entries 4–8) and fluoride salts (entries 9–11) were screened under the same condition, indicating acetonitrile was the best solvent and TBAF the most effective fluoride salt for the reaction (entry 3).

Table 1

Condition optimization for denitrative substitution of 2-nitrobenzaldehyde with PhSTMS.[a]



Entry	Fluorides (equiv.)	PhSTMS (equiv.)	Solvent	Yield of **3a** (%) [b]
1[c]	TBAF (1.2)	1.2	CH_3CN	73
2[c]	TBAF (2.0)	2.0	CH_3CN	83
3	TBAF (1.2)	1.2	CH_3CN	95
4	TBAF (1.2)	1.2	Toluene	Trace
5	TBAF (1.2)	1.2	THF	Trace
6	TBAF (1.2)	1.2	Dioxane	Trace
7	TBAF (1.2)	1.2	DMF	55
8	TBAF (1.2)	1.2	DMSO	61
9	CsF (1.2)	1.2	CH_3CN	48
10	KF (1.2)	1.2	CH_3CN	15
11	NaF (1.2)	1.2	CH_3CN	trace

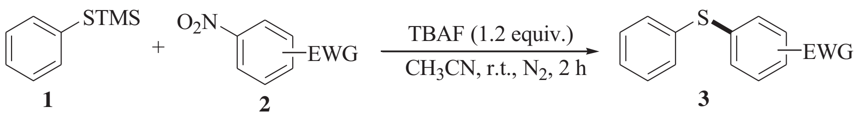
[a] Unless otherwise specified, the reactions were carried out using **1**, **2a** (1 mmol), and a fluoride source in a degassed solvent (2 mL) under N_2 at room temperature (25–30 °C). The reactions were monitored by TLC.

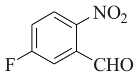
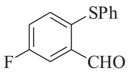
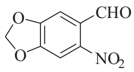
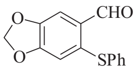
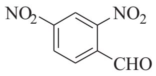
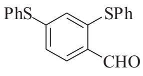
[b] Isolated yields.

[c] The reactions were conducted under air.

The optimized condition was then employed to investigate the utility of the method. As shown in Table 2, the reaction of nitroarene analogs bearing EWGs, such as formyl, acetyl, benzoyl, and cyano groups at *ortho*- or *para*-positions similar to **2a** (entry 1), usually proceeded efficiently to give high yields of the nitro-displaced, unsymmetrical diaryl thioethers (entries 2–11). However, *ortho*-acetyl- and *ortho*-benzoyl nitrobenzenes **2 g** and **2i** did not react under this condition (entries 7 and 9). Since the *para*-isomers of **2g** and **2i** (**2f** and **2h** in entries 6 and 8) and another *ortho*-substituted nitrobenzene **2j** (entry 10) bearing the smaller cyano group, all reacted efficiently to give high yields of the corresponding products, the reason for the failure of **2g** and **2i** to react may be attributed to steric hindrance of the *ortho*-acetyl and -benzoyl groups, because these bulky groups may prevent the similarly bulky phenylthio group from approaching the *ortho*-nitro groups. In the case of 5-fluoro-2-nitrobenzaldehyde **2b**, the fluoro is usually regarded as a better leaving group than nitro group [13,17,28], possibly because the nitro group is activated by both the *ortho*-formyl and *para*-fluoro groups while the fluoro is only activated by the *para*-nitro group, the nitro group, another good leaving group, accordingly become more reactive than fluoro, and thus the reaction finally gave the fluorine-retained, but nitro-replaced product 5-fluoro-2-(phenylthio)benzaldehyde **3b** (entry 2). For dinitrobenzene **2d**, a double-sulfenylated product **3d** could result as the major product in high yield when an excess of 2.4 equiv. of **1** and TBAF was used (entry 4). As shown in Table 2, the reactions under nitrogen (results outside the parentheses) were always more efficient than those under air (results in

Table 2
TBAF-mediated denitrative substitution reactions of various nitroarenes with PhSTMS



Entry	Nitroarenes	Products	Yield %[a]
1	*o*-$NO_2C_6H_4CHO$ (**2a**)	*o*-$PhSC_6H_4CHO$ (**3a**)	95 (73)
2	 (**2b**)	 (**3b**)	98 (74)
3	 (**2c**)	 (**3c**)	93 (23)
4[b]	 (**2d**)	 (**3d**)	93 (30)
5	*p*-$NO_2C_6H_4CHO$ (**2e**)	*p*-$PhSC_6H_4CHO$ (**3e**)	91 (31)
6	*p*-$NO_2C_6H_4COCH_3$ (**2f**)	*p*-$PhSC_6H_4COCH_3$ (**3f**)	94 (91)
7	*o*-$NO_2C_6H_4COCH_3$ (**2g**)	*o*-$PhSC_6H_4COCH_3$ (**3g**)	–
8	*p*-$NO_2C_6H_4COPh$ (**2h**)	*p*-$PhSC_6H_4COPh$ (**3h**)	89 (50)
9	*o*-$NO_2C_6H_4COPh$ (**2i**)	*o*-$PhSC_6H_4COPh$ (**3i**)	–
10	*o*-$NO_2C_6H_4CN$ (**2j**)	*o*-$PhSC_6H_4CN$ (**3j**)	96 (85)
11	*p*-$NO_2C_6H_4CN$ (**2k**)	*p*-$PhSC_6H_4CN$ (**3k**)	95 (81)
12[c]	*p*-$NO_2C_6H_4CO_2CH_3$ (**2l**)	*p*-$PhSC_6H_4CO_2CH_3$ (**3l**)	34 (27)
13[c]	*p*-$NO_2C_6H_4CO_2C_2H_5$ (**2m**)	*p*-$PhSC_6H_4CO_2C_2H_5$ (**3m**)	37 (35)
14	*m*-$NO_2C_6H_4CHO$ (**2n**)	*m*-$PhSC_6H_4CHO$ (**3n**)	–
15	$C_6H_5NO_2$ (**2o**)	C_6H_5SPh (**3o**)	–
16	*p*-$NO_2C_6H_4CH_3$ (**2p**)	*p*-$PhSC_6H_4CH_3$ (**3p**)	–

[a] Isolated yield from reactions under nitrogen were shown outside the parentheses (yields obtained from reactions under air were shown in the parentheses).
[b] 2.4 equiv. of **1** and TBAF were used.
[c] The reaction was conducted at 75 °C.

parentheses) (entries 1–11), especially in the case of **2c**–**e** (entries 3–5), which afforded much higher product yields under nitrogen. Worth noting is that, under the current mild, TBAF-mediated, base-free neutral conditions, the reactive formyl, acetyl, benzoyl, and cyano groups can be retained. For comparison, under conventional strong basic conditions using less reactive protonic nucleophiles, side reactions of these reactive functional groups usually occur to give undesired byproducts.

In contrast with above efficient reactions, the reactions of methyl- and ethyl-4-nitrobenzoates were ineffective under the standard conditions. When heated at an elevated temperature of 75 °C, low yields of the target products were obtained, and the reactions under nitrogen failed to yield much better results (entries 12–13). In these reactions, some unidentified byproducts were observed both under air and under nitrogen, but the reasons are still not clear at present.

In addition, *meta*-formyl nitrobenzene (**2n**), unsubstituted nitrobenzene (**2o**), and a substituted nitrobenzene with an electron-donating group at the *para*-position (**2p**) were also investigated (Table 2, entries 14–16). However, no reaction occurred at all and no target product could be detected under the standard condition. Based on the great difference of these inert substrates to the previous reactive ones, it can be concluded that the present reaction is a nucleophilic aromatic substitution (S_NAr) reaction, in which the leaving nitro group is activated by the *para*- or *ortho*-EWGs, as with the aryl halides in our previous systems. Therefore, the present reactions most possibly proceeded *via* a typical S_NAr mechanism.

4. Conclusion

In summary, we have developed a mild and efficient TBAF-mediated denitrative substitution reaction of electron-deficient nitroarenes with PhSTMS for the synthesis of useful unsymmetrical diaryl thioethers. Due to the wide availability of the nitroarenes, high tolerance of the reactive functional groups under the base-free neutral conditions, fast transformation under the mild conditions, and higher efficiency of the reactions than those of the corresponding aryl halides [21,22], the present method may provide a potentially useful alternative for the synthesis of unsymmetrical diaryl thioether from nitroarenes.

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