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Thiolate-Initiated Synthesis of Dibenzothiophenes from 2,2′-Bis(methylthio)-1,1′-Biaryl Derivatives through Cleavage of Two Carbon–Sulfur Bonds

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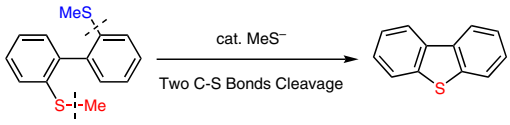

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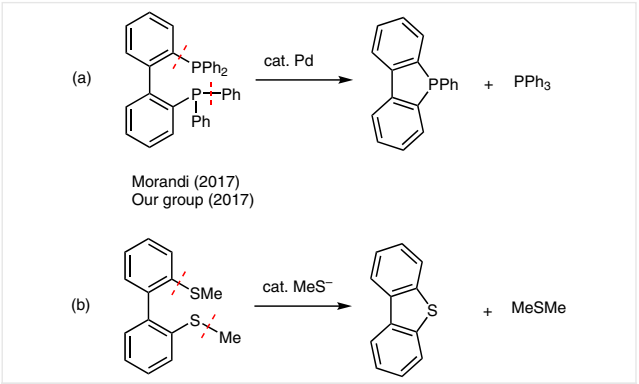
Abstract A catalytic reaction involving the cleavage of two carbon–sulfur bonds in 2,2′-bis(methylthio)-1,1′-biaryl derivatives is reported. This reaction does not require a transition-metal catalyst and is promoted by a thiolate anion. Notably, based on DFT calculations, the product-forming cyclization step is shown to proceed through a concerted nucleophilic aromatic substitution (CS_NAr) mechanism.

Key words C–S cleavage, C–O cleavage, metathesis, thiophene

Given the fact that heteroatom analogues of cyclopentadiene, such as siloles,[1] phospholes,[2] and thiophenes,[3] which are referred as heteroles,[4] have emerged as privileged scaffolds in the field of organic materials and pharmaceuticals, the development of synthetic methods for preparing these compounds has attracted considerable interest. In this context, we have been investigating the synthesis of heteroles that proceed through cleavage of a carbon–heteroatom bond.[5] Morandi and our group both independently reported on a palladium-catalyzed method for the synthesis of phosphole derivatives from bisphosphines through the formal metathesis of carbon–phosphorus bonds (Scheme 1a).[6] These reactions allow for the rapid, efficient construction of a range of elaborate phosphole derivatives by using commercially available bisphosphines as substrates. We report herein on a sulfur variant of this reaction and its use in the synthesis of thiophenes (Scheme 1b).

We hypothesized that 2,2′-bis(methylthio)-1,1′-biphenyl (**1a-Me**) could be cyclized by palladium catalysis to give the dibenzothiophene (**2a**) through a mechanism similar to that reported for the corresponding bisphosphines.[6a] Consistent with this expectation, the desired product was obtained in 97% yield.[7] To our surprise, **2a** was formed, even in the absence of a palladium catalyst (Table 1).[8] For example, the reaction of **1a-Me** in the presence of a catalytic amount of KO^{t}Bu (20 mol%) in *N*,*N*-dimethylformamide (DMF) at 160 °C for 4 h afforded **2a** in 56% yield (entry 3).

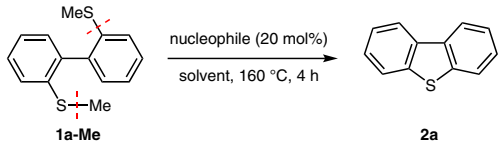


Scheme 1 Synthesis of heteroles through the formal metathesis of carbon–heteroatom bonds

Screening a series of bases led to an improvement in the yield of **2a**, with NaSMe being the most effective, giving **2a** in 87% isolated yield[9] (Table 1, entry 5). The use of a polar aprotic solvent, such as DMF, was essential for the success of this reaction (entries 6–8), suggesting that this cyclization reaction proceeded through a nucleophilic substitution process. Having established that NaSMe is the optimal initiator for this reaction, we proceeded to explore the effect of the leaving groups on the sulfur atoms (Table 2). Increasing the steric bulk on the sulfur substituent led to a dramatic decrease in yield, which would be predicted based on the assumption that an S_N2 mechanism is involved in the C(alkyl)–S bond cleavage process. Although the desired cyclization of substrates having ethyl and phenethyl groups took place with low efficiency, it was possible to improve the yields by changing the reaction conditions (entries 1 and 2).

In the case of an isopropyl group, no desired product was formed (entry 3). When a benzyl-substituted substrate was used, dibenzothiophene was successfully formed in 78% yield, along with dibenzyl sulfide (71%) (entry 4). These results suggest that the benzyl thiolate, which is generated after the cyclization reaction via a C(aryl)–S bond cleavage, also functions as a nucleophile in the cleavage of the C(alkyl)–S bond.

Table 1 Optimization of Reaction Conditions[a]

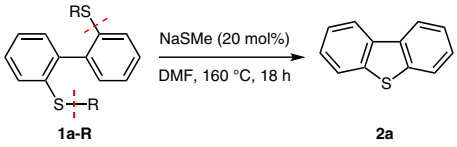


1a-Me **2a**

Entry	Nucleophile	Solvent	NMR yield of **2a** (%)
1	LiO^{t}Bu	DMF	0
2	NaO^{t}Bu	DMF	3
3	KO^{t}Bu	DMF	56
4	NaOMe	DMF	16
5	NaSMe	DMF	99 (87[b])
6	NaSMe	toluene	0
7	NaSMe	1,4-dioxane	0
8	NaSMe	^{t}Amyl-OH	0

[a] *Reaction conditions*: **1a-Me** (0.20 mmol) and the nucleophile (0.04 mmol) in DMF (1.0 mL) at 160 °C for 4 h.
[b] Isolated yield.

Table 2 Effect of the Leaving Groups[a]

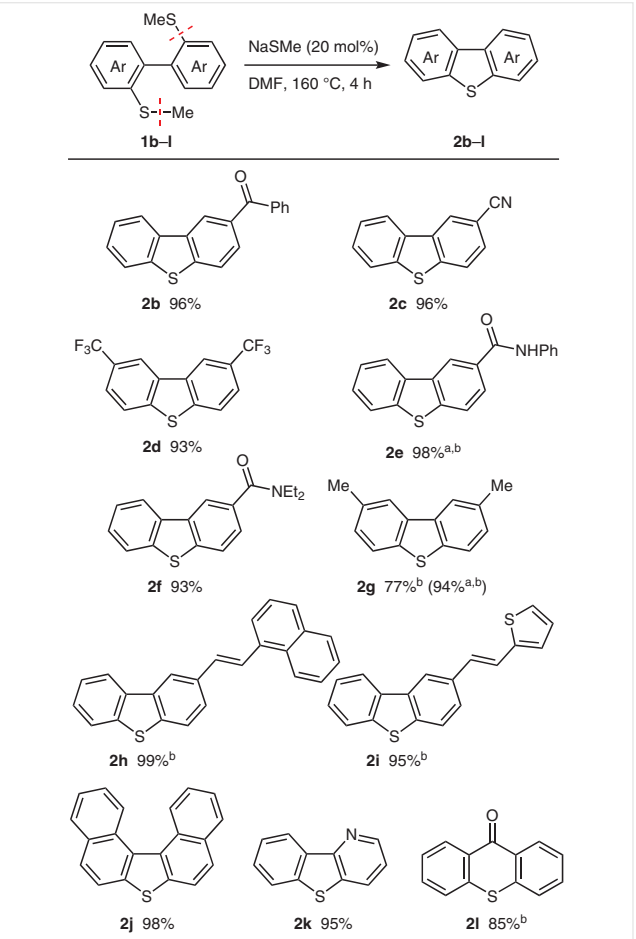


1a-R **2a**

Entry	R	Isolated yield of **2a** (%)
1	Et	16 (79[b])
2	Phenylethyl	39 (87[c])
3	^{i}Pr	0 (15[c])
4	Benzyl	78[d]

[a] *Reaction conditions*: **1a-R** (0.20 mmol) and NaSMe (0.04 mmol) in DMF (1.0 mL) at 160 °C for 18 h.
[b] NaSMe (0.08 mmol) was used.
[c] NaO^{t}Bu (0.40 mmol) was used instead of NaSMe.
[d] Dibenzyl sulfide was also obtained (71% isolated yield).

We next investigated the scope of the reaction with respect to SMe-substituted biaryl substrates (Scheme 2). Gratifyingly, this method allowed us to synthesize various biaryl substrates containing a range of functional groups, including ketone (**2b**), cyano (**2c**), trifluoromethyl (**2d**), and amide (**2e** and **2f**) groups. Interestingly, the introduction of an electron-donating group, such as a methyl group at the *para*-position to the SMe group was tolerated, with the cyclized product **2g** being formed in 94% yield. Our formal metathesis method also allowed us to incorporate alkenes (**2h** and **2i**), naphthalenes (**2j**) and a pyridine ring (**2k**) into the molecule, resulting in the synthesis of a variety of π-extended thiophenes. Pleasingly, it was also possible to prepare six-membered rings (**2l**) by using this method.



Scheme 2 Substrate Scope. *Reaction conditions*: **1b-1l** (0.20 mmol) and NaSMe (0.04 mmol) in DMF (1.0 mL) at 160 °C for 4 h. Isolated yields are shown. [a] 180 °C. [b] 18 h.

To get insights into the mechanism, we used DFT calculations to further investigate the cyclization of **1a-Me** with an SMe anion (Figure 1).[10] The energy changes at the B3LYP/6-311+G* level of theory [SCRF (pcm, solvent=*N*,*N*-dimethylformamide)] are shown in kcal/mol (Figure 1). An exothermic reaction pathway with two transition states (**TS1** and **TS2**) was obtained. The first step is the cleavage of a C(alkyl)–S bond via an S_N2 mechanism and the calculated Gibbs energy of activation ($\Delta G^{\ddagger}$) was estimated to be 33.4 kcal/mol. The calculations also indicate that the second step

proceeds through a concerted nucleophilic aromatic substitution reaction (CS_NAr)[11] pathway with a $\Delta G^{\ddagger}$ of 35.0 kcal/mol,[12] which is the rate-determining step. Notably, a Meisenheimer type intermediate could not be obtained by intrinsic reaction coordinate (IRC) calculations at **TS2**. Since the negative charge in the **TS2** is also dispersed at the sulfur atoms in addition to the arene ring, the reaction would be expected to be less sensitive to the electronic effect of the arene ring, compared with a pathway that proceeds through a classical S_NAr mechanism involving a Meisenheimer intermediate, in which the negative charge is accommodated over the aromatic ring. The involvement of a CS_NAr mechanism is consistent with the successful cyclization of the electron-rich substrate **1g** (Scheme 2).

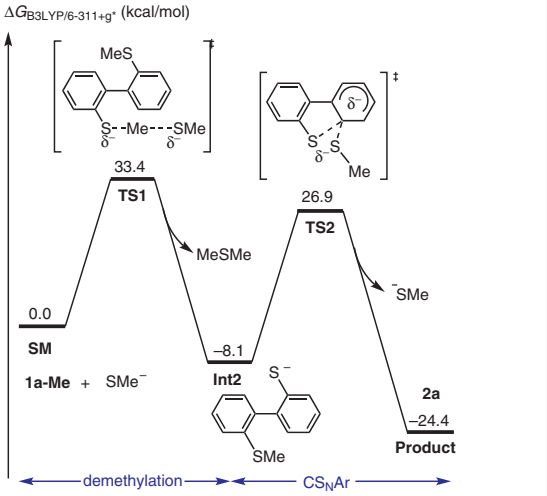
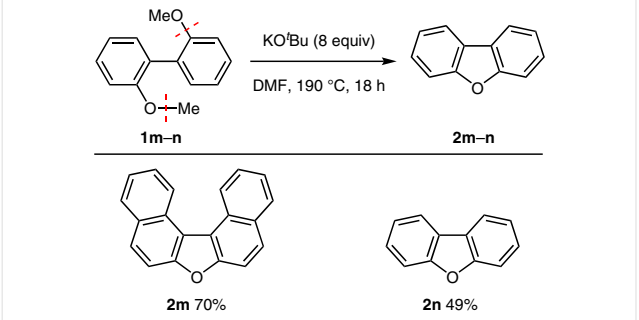


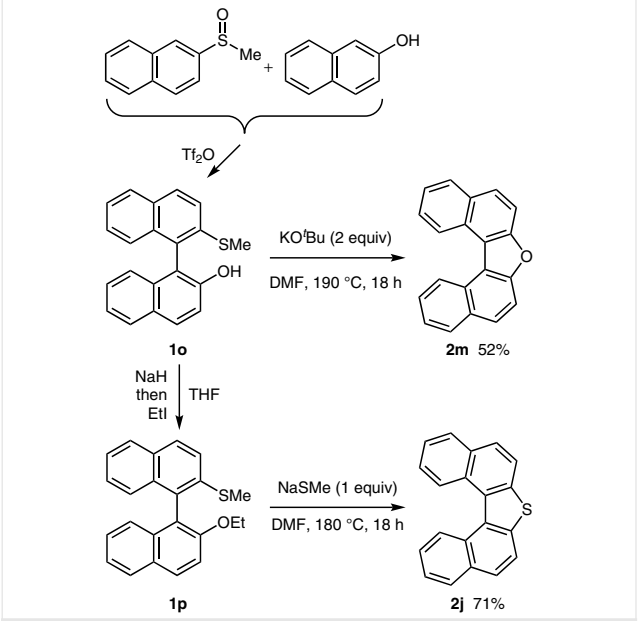
Figure 1 Reaction pathways for carbon–sulfur bond metathesis

We subsequently investigated the possibility of extending the C–S bond metathesis reaction to the corresponding C–O bonds. A C(sp^2)–O bond is typically an inert bond and transition metals are normally required to activate them.[13] It should be noted, however, that nucleophilic aromatic substitution reactions in which an OMe group serves as a leaving group have recently been reported. However, the use of substrates bearing strong electron-withdrawing groups, such as cyano groups at *ortho*- or *para*-positions are required for such reactions to proceed.[14,15] We initially examined the reaction of 2,2′-dimethoxy-1,1′-binaphthalene (**1m**) in the presence of NaSMe (400 mol%) at 160 °C for 18 h, but the expected dibenzofuran derivative **2m** was not formed. The lower reactivity of **1m** compared with **1j** can be attributed to the lower nucleophilicity of the phenoxide anion and poorer leaving ability[11c] of an OMe group compared to an SMe group. Optimization of the reaction of **1m** led us to discover that when 8 equivalents of KO^{t}Bu were used as a base at 190 °C, **2m** was produced in 70% yield (Scheme 3). These conditions can also be used for the cyclization of the more challenging biphenyl-based substrate **1n**. DFT calculations revealed that the cyclization of **1m** and **1n** proceeds via a Meisenheimer intermediate,[16] probably because the OMe is a poorer leaving group than an SMe group.



Scheme 3 Synthesis of dibenzofurans via metathesis of carbon-oxygen bonds. *Reaction conditions*: **1m–n** (0.10 mmol) and KO^{t}Bu (0.80 mmol) in DMF (1.0 mL) at 190 °C for 18 h. Isolated yields are shown.

We also investigated substrates bearing both carbon–sulfur and carbon–oxygen bonds (Scheme 4). Treatment of the biaryl substrate **1o**, which is readily accessible from simple naphthalene derivatives,[17] with a stoichiometric amount of KO^{t}Bu gave the dibenzofuran derivative **2m** selectively in a yield of 52%. The selective O-cyclization of **1o** is not surprising given that the OH group is a far poorer leaving group than the SMe group. In contrast, selective S-cyclization is possible by the reaction of the ethylated biaryl **1p** under our conditions to form the dibenzothiophene derivative **2j** in 71% yield. The selectivity for the cyclization of



Scheme 4 Chemoselective ring closure via formal C-O/C-S metathesis

1p is determined by the initial de-alkylation step, in which a less hindered methyl group reacts more rapidly than an ethyl group.

In summary, we report herein on the thiolate-initiated formal double carbon–sulfur bonds metathesis for use in the synthesis of dibenzothiophene derivatives. The C(aryl)–S bond cleavage process was found to proceed through a concerted nucleophilic aromatic substitution (CS_NAr) pathway. Furthermore, this metathesis protocol enables the method to be expanded to double carbon–oxygen bonds and carbon–oxygen/carbon–sulfur metathesis.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1611974.

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(8) Treatment of **1j** with a stoichiometric amount of NaSMe was reported to give a demethylated compound, along with a small amount of **2j** (11%). However, this was not investigated in detail. See: Furia, F. D.; Licini, G.; Modena, G.; Valle, G. *Bull. Soc. Chim. Fr.* **1990**, 134.

(9) **Dibenzothiophene (2a) [CAS: 132-65-0]; Typical Procedure**
An oven-dried 5 mL screw-capped vial was charged with **1a-Me** (49.2 mg, 0.20 mmol), NaSMe (2.8 mg, 0.04 mmol), and DMF (1 mL) under a gentle stream of nitrogen. The vessel was then sealed and heated at 160 °C for 4 h. The mixture was cooled to r.t. and filtered through a short pad of silica gel, eluting with EtOAc. The eluent was evaporated to give a residue, which was purified by flash chromatography (R_f 0.43, hexane) to give **2a** as a white solid (49 mg, 87%). ^{1}H NMR ($CDCl_3$, 399.78 MHz): δ = 7.44-7.47 (m, 4 H), 7.84–7.87 (m, 2 H), 8.15–8.17 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100.53 MHz): δ = 121.7, 122.9, 124.5, 126.8, 135.7, 139.6. HRMS (EI): *m*/*z* calcd for $C_{12}H_8S$: 184.0347; found: 184.0349.

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