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Synthesis of di(hetero)aryl sulfides by directly using arylsulfonyl chlorides as a sulfur source†

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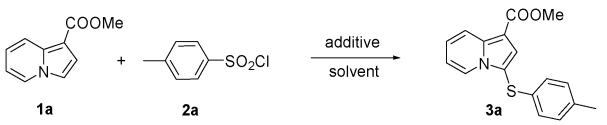
A new, efficient protocol for the synthesis of di(hetero)aryl sulfides is described. Cheap and easily available arylsulfonyl chlorides as a sulfur source reductively couple with electron-rich (hetero)arenes (*e.g.*, indolizines, indoles, electron-rich benzenes, *etc.*) in the presence of triphenylphosphine to afford di(hetero)aryl thioethers in good yields.

Di(hetero)aryl sulfides are important building blocks for creating molecules of medicinal interest, natural products and functional materials. In the last decade, transition metal-catalyzed Ullmann condensation and modified reactions of aryl donors (*e.g.*, aryl halides, aryl boronic acids, *etc.*) with S-containing nucleophiles have been well developed, and become one of the most powerful and reliable protocols for the synthesis of di(hetero)aryl thioethers.[1] An alternative approach to di(hetero)aryl thioethers is the electrophilic substitution of (hetero)arenes (especially electron-rich (hetero)-arenes) by diverse sulfenylating agents such as quinone mono-*O*,*S*-acetals,[2] disulfides,[3] sulfenyl halides,[4,5] *N*-thioaryl-phthalimides,[6] and thiols in combination with *N*-chlorosuccinimide, Selectfluor™ or iron (III) chloride.[7–9] Despite significant progress, the development of a new, direct and facile sulfenyl-ation of (hetero)arenes to forge di(hetero)aryl thioethers is still a highly desirable objective.

Arylsulfonyl chlorides have been widely used as the protecting groups, sulfonylating agents,[10] and leaving groups in C–C bond formation.[11,12] Quite recently, Beller and co-workers reported a novel palladium-catalyzed synthesis of diaryl sulfides *via* the direct C–H functionalization of electron-rich arenes with arylsulfonyl cyanides.[13] Due to an interest in the palladium-catalyzed arylation of heteroarenes with sulfonyl chloride as a leaving group, we herein accidentally discovered that inexpensive and easily available arylsulfonyl chlorides can directly serve as a sulfur source for sulfenylation of (hetero)arenes. More surprisingly, this type of transformation even works well in the absence of a transition metal catalyst. To the best of our knowledge, there are no examples describing metal-free synthesis of di(hetero)aryl sulfides by directly using sulfonyl chlorides as a sulfur source (Fig. 1).

Indolizines have been widely explored due to their biological and pharmaceutical importance. In particular, 3-sulfenyl-indolizines are ligands of the CRTH2 receptor, and valuable in treatment of various respiratory diseases. Furthermore, these sulfenyl-containing compounds can be subjected to oxidation to form sulfone derivatives, which act as a foothold in a variety of target bioactive molecules.[14] Following our interest in direct C–H functionalization of heteroarenes, we herein would like to focus on sulfenylation of indolizines with arylsulfonyl chlorides, which affords a variety of 3-sulfenyl-indolizines.



(1)

In our initial work, we surprisingly observed that *N*-methyl-morpholine (NMM) did mediate the reductive coupling of *p*-tolylsulfonyl chloride **2a** with methyl indolizine-1-carboxylate **1a** to afford methyl 3-(*p*-tolylthio)indolizine-1-carboxylate **3a** in 50% yield in the absence of a transition metal catalyst (see ESI†, Table S1) (eqn (1)). We assumed that NMM might function as a reductive reagent in the sulfenylation process. Inspired by these preliminary findings, we further screened a series of other additives (*e.g.*, *i*-Pr_2NEt, Ph_3N, *n*-Pr_3N, DBU,

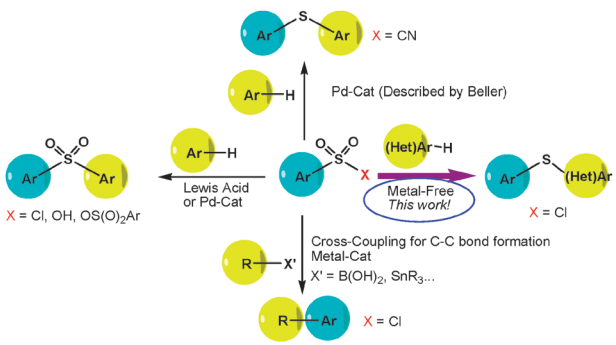


Fig. 1 Scope of application of arylsulfonyl derivatives.

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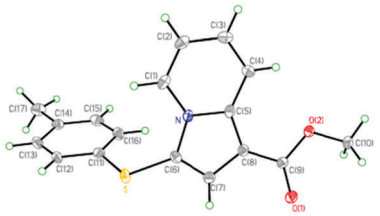
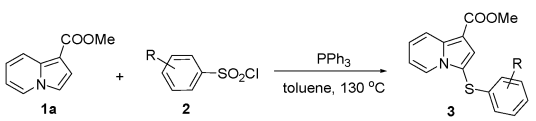


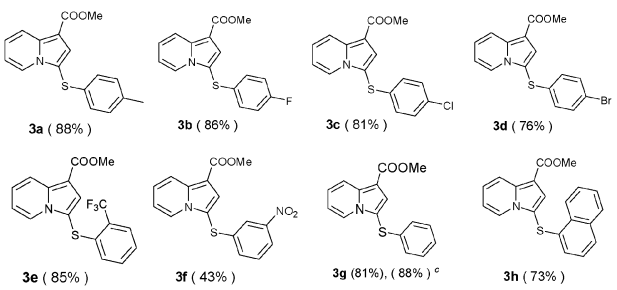
Fig. 2 ORTEP diagram of **3a**. Thermal ellipsoids are shown at the 50% probability level.

NMI, Me_3SiCl, $HP(OPh)_2$, $P(OEt)_3$, PPh_3, *etc.*). Among the additives investigated, inexpensive triphenylphosphine proved to be more effective. Although NMI, *i*-Pr_2NEt and *n*-Pr_3N gave slightly higher yields at 120 °C, the substrate **1a** was consumed completely in 24 h (Table S1, entries 2, 4, 6 and 10, ESI†). The yield of **3a** could be greatly improved up to 88% by elevating the reaction temperature to 130 °C in the presence of PPh_3 (Table S1, entry 15, ESI†). Subsequently, a set of solvents were explored, and toluene turned out to be the best choice. Furthermore, we attempted to shorten the reaction time and reduce the amount of triphenylphosphine and *p*-tolylsulfonyl chloride, but the results were disappointing (Table S1, entries 18–20, ESI†). Finally, the cross-coupling reaction proceeded well when 3.0 equiv. of triphenylphosphine and 3.0 equiv. of *p*-tolylsulfonyl chloride were employed in toluene at 130 °C for 24 h. An X-ray analysis of single crystals of **3a** confirmed the selective sulfenylation at the C3-position of **1a** rather than the sulfonylation (Fig. 2).[15]

With optimized conditions now in hand, we first investigated the scope of this protocol with respect to arylsulfonyl chlorides as shown in Table 1. No matter if the substituents on the aromatic ring were electron-withdrawing (except the nitro group), electron-donating, or sterically bulky, all of them afforded good to excellent yields. It was noteworthy that our method could be applied to arylsulfonyl chlorides with the chloro and bromo groups on the aromatic ring, which provided a complementary platform for further functionalizations through transition metal catalyzed-coupling reactions to create more complex bioactive molecules (Table 1, **3c–d**).[14b]

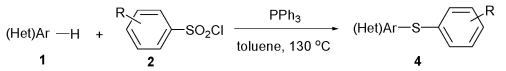
Table 1 Scope of arylsulfonyl chlorides[a,b]

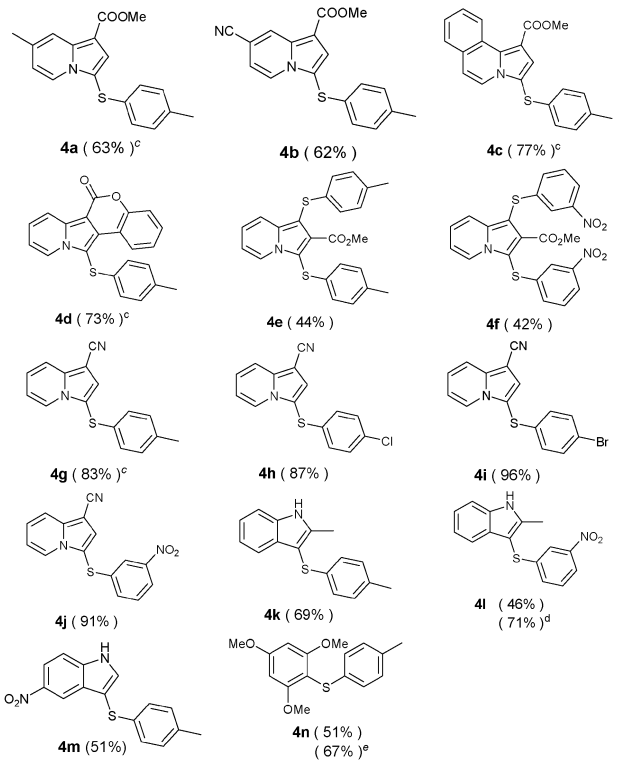




[a] Reactions were carried out using indolizine **1a** (0.25 mmol), arylsulfonyl chloride **2** (0.75 mmol), and PPh_3 (0.75 mmol) in toluene (1.5 mL) at 130 °C for 24 h. [b] Isolated yield based on **1a**. [c] 140 °C.

Table 2 Synthesis of di(hetero)aryl sulfides with sulfonyl chlorides[a,b]





[a] Reactions were carried out using **1** (0.25 mmol), **2** (0.75 mmol), and PPh_3 (0.75 mmol) in toluene (1.5 mL) at 130 °C for 24 h. [b] Isolated yield based on **1**. [c] 140 °C. [d] *N*-Pivaloyl-2-methylindole was used as substrate. [e] $FeCl_3$ (20 mol%) was added.

It was gratifying to find that a variety of indolizines could couple with diverse arylsulfonyl chlorides in satisfactory yields (Table 2). For example, the C1-substituted indolizines smoothly furnished the sulfenylation of indolizines at the C3 position in good yields (**4a–d**, and **4g–j**), whereas the C2-occupied ones gave 1,3-bis-*S*-arylated products (**4e–f**). In addition to indolizines, various indoles proceeded well under optimized conditions (**4k–m**). Particularly noteworthy is that the free (NH)-indole could be sulfenylated with arylsulfonyl chlorides. Interestingly, the protection of indole with the pivaloyl group could dramatically improve the yield of sulfenylindole from 46% to 71%, but gave the free (NH)-indole derivative **4l**, which might be attributed to hydrochloride generated during the transformation. We next determined that our protocol was applicable to not only heteroarenes, but also electron-rich arenes to some extent. For example, trimethoxybenzene gave the diaryl sulfide **4n** in an acceptable yield. Notably, the addition of extra $FeCl_3$ (20 mol%) could raise the yield of **4n** up to 67%.

The sulfonyl chlorides as electrophilic reagents have been described, especially in the presence of a Lewis acid or

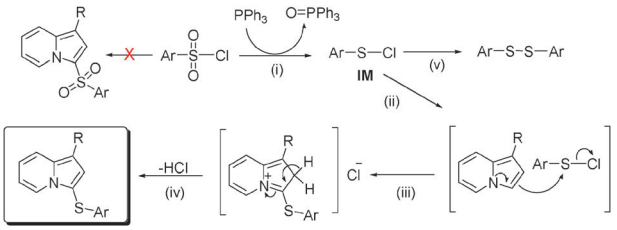
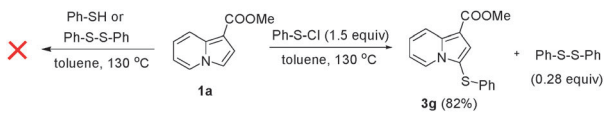


Fig. 3 Proposed mechanism for sulfenylation of (hetero)arenes.

transition-metal catalyst.[10] It is noteworthy that no sulfonylating product was observed. In order to get some mechanistic insights, the reaction mixture was further investigated. Under the standard conditions, the coupling of **1a** with **2a** produced **3a** in 88% yield with a concomitant quantitative amount of triphenylphosphine oxide (Ph_3PO) and 0.30 equiv. of 1, 2-di-*p*-tolyldisulfide (based on **1a**). These results suggested that arylsulfonyl chloride was subjected to reduction by triphenylphosphine, which abstracted oxygen from arylsulfonyl chloride to generate the corresponding RS^+ equivalent (Fig. 3).

A point worthy of note is that the reduction of sulfonyl chlorides with triphenylphosphine or other reductive reagents to yield sulfenyl chlorides,[12] arylthiols[16] or disulfides through a possible ArSX (X = Cl, I) intermediate[17] is known in the literature (for extra experimental data, see ESI†, VI), and sulfenyl chlorides, disulfides and arylthiols may all serve as effective sulfenylating agents.[3–5] Fortunately, the controlled experiments gave the direct evidence of the plausible mechanism (eqn (2)). Benzenesulfenyl chloride (PhSCl) coupled with **1a** to give the desired product **3g** in 82% yield with 0.28 equiv. of diaryldisulfide as the side product under the standard conditions, whereas both diphenyl disulfide (PhSSPh) and arylthiol (ArSH) failed to react with **1a**. In the absence of indolizine, benzenesulfenyl chloride coupled to each other to form diphenyl disulfide as a competitive reaction in 85% yield in toluene at 130 °C for 24 h (see ESI†, VI).[17,18] These results implied that sulfenyl chlorides might act as a selective source of RS^+ equivalents.



(2)

In addition, the ICP-MS and/or AAS analysis indicated that the contents of Pd and Cu were less than the detection limits of 1.0 ppb in the samples of **1a**, **2a**, and Ph_3P, and the contents of Fe were less than 30 ppb, which indicated that the reactions observed could be considered as a metal-free process (ESI†, Table S2).

Although the mechanism was not well understood at this stage, on the basis of the above observations, we proposed that a plausible mechanism could consist of (i) reduction of sulfonyl chloride with Ph_3P to **IM**, and (ii) electrophilic attack of **IM** on the electron-rich (hetero)arene to give di(hetero)aryl sulfide with the release of the acidic HCl gas that was detected at the end of the reaction (Fig. 3).[5b] The diaryl disulfide observed in the reaction system could be attributed to the coupling of reactive sulfenyl chloride to each other.[17]

In conclusion, we have developed a new, efficient organo-mediated-sulfenylation of (hetero)arenes (*e.g.*, indolizines, indoles, electron-rich benzenes, *etc.*) to prepare di(hetero)aryl thioethers by directly using inexpensive and easily available arylsulfonyl chlorides as an alternative sulfur source in combination with cheap triphenylphosphine. We believe that this methodology would provide a useful complement for the sulfenylation of electron-rich (hetero)arenes.

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