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# TBATB mediated debenzylative cross-coupling of aryl benzyl sulfides with electron rich compounds: synthesis of diaryl sulfides†

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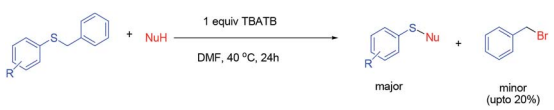
An efficient TBATB mediated debenzylative cross coupling of aryl benzyl sulfides with electron rich compounds provides diaryl sulfides in moderate to excellent yield. The salient features of the present protocol are simplicity, high efficiency and compatibility of the reaction with various electron rich compounds.

Aryl sulfide moieties are a common functionality present in a large number of natural products, bioactive molecules, agrochemicals, functional materials, and pharmaceuticals.[1] Various synthetic methodologies have been developed to prepare aryl sulfides among which transition-metal-catalyzed reactions such as Cu,[2] Ni,[3] Pd,[4] Co,[5] and Fe[6] cross-coupling reactions between organohalides and thiol reagents are predominant in classical organic synthesis. Over the past few years, chemists have discovered a C–S coupling reaction involving C–H sulfenylation reactions using thiols or disulfides as the sulfur source.[7] However; these methods suffer from some inevitable drawbacks such as the employment of sensitive organometallic reagents or expensive metal catalysts and are limited to indoles or phenols only. In addition, transition metal impurities in the products are also unavoidable using this method.

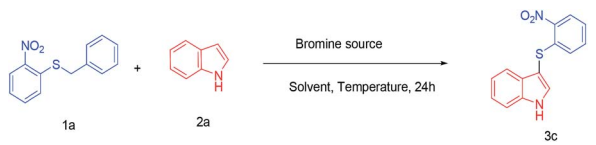
Recently, Jianyou Mao and co-workers[8] developed an efficient methodology for the construction of diaryl sulfides from aryl benzyl sulfides as the sulfur source. In this context the present reaction mode is a normal electrophilic substitution of aromatic compounds *via* addition–elimination (Scheme 1). The main advantage of the present protocol is that it is tolerated by various electron rich aromatic compounds such as indoles, β-naphthol, α-naphthol, phenol, pyridine and thiophene *etc.*




Scheme 1 Synthesis of aryl sulfides.

In our initial work, we investigated a general method for transition-metal-free C–S cross couplings of 2-nitrophenyl benzyl sulfide (**1a**) and indole (**2a**) in DMF. It was chosen as a model reaction for the optimization of reaction conditions (Table 1). The initial experiments were carried out to screen different solvents and bromine sources. When 2-nitrophenyl benzyl sulfide reacted with 1 equiv. of indole in the absence of any bromine source, the desired product **3c** was not obtained. The results showed that, TBATB (tetrabutylammonium tribromide) in DMF at 40 °C, could efficiently initiate the cross-coupling reaction, and turned out to be optimal with the

Table 1 Optimization of the reaction conditions[a]




| Entry | Bromine source | Temperature | Solvent | Yield[b] (%) |
|---|---|---|---|---|
| 1 | — | 120 °C | DMF | No |
| 2 | TBATB (1 equiv.) | 50 °C | DMF | 75 |
| 3 | TBATB (1 equiv.) | 40 °C | DMF | 81 |
| 4 | TBATB (1 equiv.) | rt | DMF | 58 |
| 5 | TBATB (1 equiv.) | 40 °C | Toluene | 20 |
| 6 | TBATB (1 equiv.) | 60 °C | THF | 64 |
| 7 | TBATB (0.5 equiv.) | 40 °C | DMF | 45 |
| 8 | NBS (1 equiv.) | 40 °C | $CH_3CN$ | 59 |
| 9[c] | TBATB (2 equiv.) | 40 °C | $H_2O$ | Trace |
| 10 | $Br_2$ (1 equiv.) | 40 °C | DMF | 53 |

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol) and bromine source (0.5 to 2 mmol) in 2 mL of solvent 24 h. The purity of **1a** is 99.99%. [b] Isolated yield. [c] 36 h reaction.

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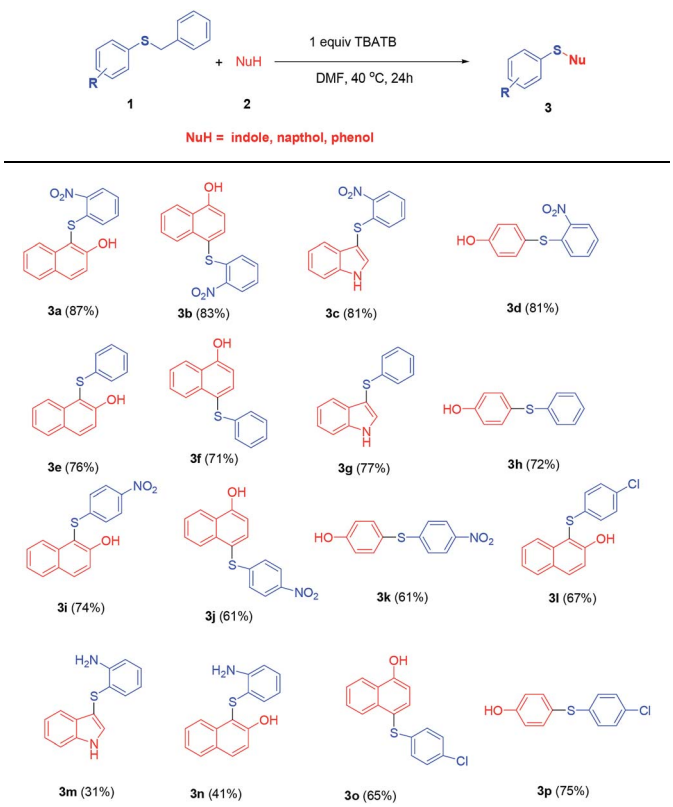
highest yield (81%, Table 1, entry 3). Other different brominating sources including NBS and $Br_2$ were then tested with no fruitful result. Reducing the amount of TBATB also caused a decreased yield of **3c** (45%, Table 1, entry 7). The yield decreased with a decrease in temperature to room temperature (58%, Table 1, entry 4).

With the optimized reaction conditions (Table 1, entry 3) in hand, the scope and generality of the debenzylative coupling reaction was investigated using several diverse indoles, β-naphthol, α-naphthol and phenol. As shown in Table 2, an aryl benzyl sulfide containing a strong deactivating group gave the maximum yield of 87% (**3a**), whereas, a strong activating group gave a poor yield of 31% (**3m**). A plot of time *versus* yield shows a rapidly progressing reaction for highly activated substrates (Fig. 1). The reactivity order is as $NO_2$ > H > $NH_2$ (ESI†). The low yields of amino substrates could be attributed to the amine itself reacting with the brominating agent to form an N–Br compound, which would be hydrolysed on work up. It is noted that the presence of a strong deactivating group at the *ortho* position of the aryl ring favoured bromination at the sulfur end more readily and formation of reactive sulfenyl bromide which reacted with the electron rich aromatic ring to give the product in high yield.

Table 2 Formation of diaryl sulfide: from aryl benzyl sulfide[a]




[a] Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol) and TBATB (0.5 mmol) in 2 mL of DMF for 24 h.

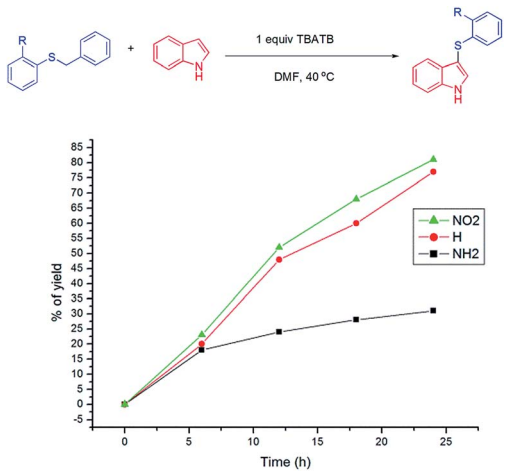



Fig. 1 Progress of the reaction comparing when R = $NO_2$, H, $NH_2$.

The same reaction condition was also applied for the removal of an acetyl group (Table 3), but found to be not very useful because the C–S bond in aryl nitrobenzyl sulfide is very weak[9] and debenzylation occurs more easily. Further, the reaction conditions were also used to synthesize hetero-aromatic sulfides (**6a** and **6b**) which resulted in intermediate yields (Table 4).

The proposed mechanism of formation is very simple. The facility of bromination of the C–S bond in sulfides is determined primarily by the nature of the leaving group, the structure of the initial sulfide, and the bromination conditions.[10] Initially, aryl benzyl sulfide reacts with *in situ* generated $Br_2$ to form an electrophilic species RSBr (A). The reactive sulfenyl bromide can react with the indole moiety to form intermediate (B) which on further deprotonation forms the desired product **3c** (Fig. 2).

In summary, we have developed a simple and efficient protocol to generate diaryl sulfides by a TBATB mediated coupling reaction of aryl benzyl sulfide with electron rich compounds. The tolerance of various aromatic and hetero aromatic compounds such as indole, β-naphthol, α-naphthol, phenol, pyridine and thiophene is an important and useful aspect of the methodology.

Table 3 Formation of diaryl sulfide: from aryl acetyl sulfides

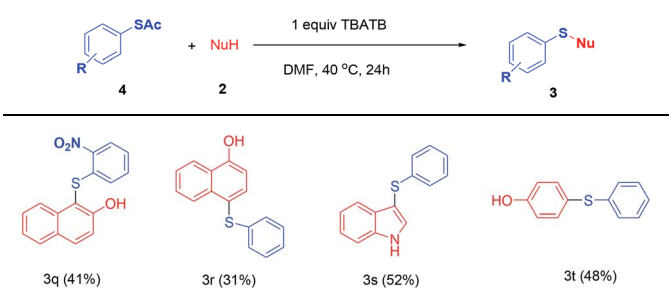
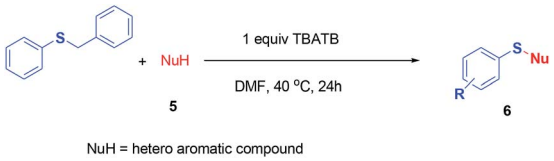


Table 4 Formation of diaryl sulfide: from heteroaromatic compounds





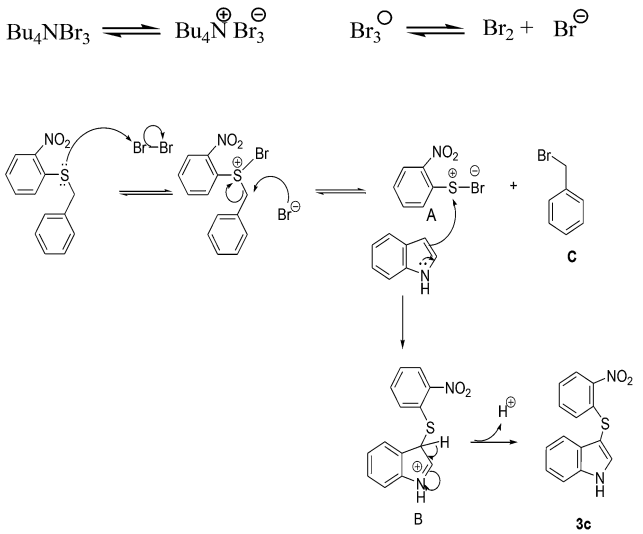



Fig. 2 Proposed mechanism.

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