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ARTICLE TYPE

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

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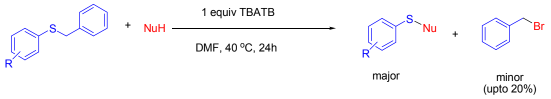
An efficient TBATB mediated debenzylative cross coupling of aryl benzyl sulfides with electron rich compounds has been providing diarylsulfides in moderate to excellent yield. The salient features of the present protocol are simplicity, high efficiency and this reaction is compatible with various electron rich compounds.

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

Recently, Jianyou Mao and co workers[8] developed an efficient methodology for construction of diarylsulfides from aryl benzyl sulfide as sulfur source. In this context 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-napthol, α-napthol, phenol, pyridine and thiophene etc.



Scheme 1 Synthesis of arylsulfide

In our initial work, we reported a general method for transition-metal-free C-S cross couplings of nitro phenylbenzylsulfide (**1a**) and indole (**b**) 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 source. When 2-nitrophenylbenzylsulfide 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 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 the decrease in temperature to room temperature (58%, Table1, 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-napthol, α-napthol and phenol. As shown in Table 2, that arylbenzylsulfide containing strong deactivating group gave maximum yield 87% (**3a**), whereas, strong activating group gave poor yield 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 (SI). The low yields of amino substrates could be attributed to the amine itself reacting with the brominating agent to form N-Br compound, which would be hydrolysed on work up. It was noted that due to presence of strong deactivating group in ortho position of aryl ring favoured the bromination at sulphur end more readily and formation of reactive sulfenyl bromide which reacted with electron rich aromatic ring to give the product in high yield.

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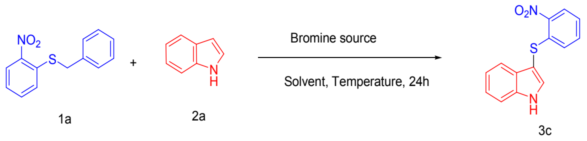
Table 1 Optimization of the reaction conditions.[a]



Entry	Bromine source	Temperture	Solvent	Yield(%)[b]
1	-------	120 °C	DMF	No
2	TBATB (1equiv)	50 °C	DMF	75
3	TBATB(1equiv)	40°C	DMF	81
4	TBATB(1equiv)	rt	DMF	58
5	TBATB(1equiv)	40 °C	Toluene	20
6	TBATB(1equiv)	60 °C	THF	64
7	TBATB(0.5equiv)	40 °C	DMF	45
8	NBS(1equiv)	40 °C	CH_3CN	59
9[c]	TBATB(2 equiv)	40 °C	H_2O	trace
10	Br_2(1equiv)	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]Isolate yield
[c]36 hours reaction

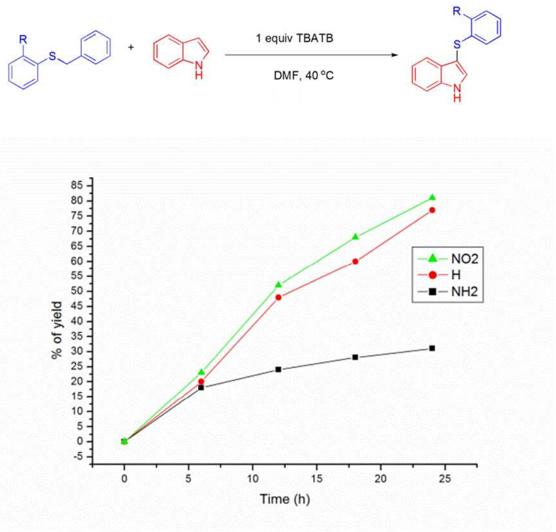
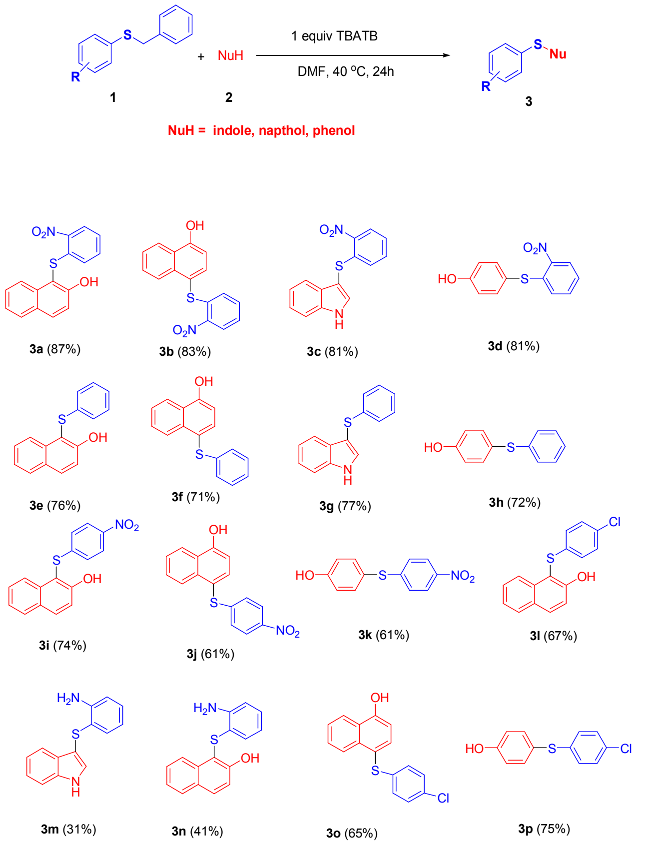


Fig.1 Progress of reaction comparing when R= NO_2, H, NH_2

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

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.

Table 3 Formation of Diaryl sulfide: from Aryl acetyl sulfide

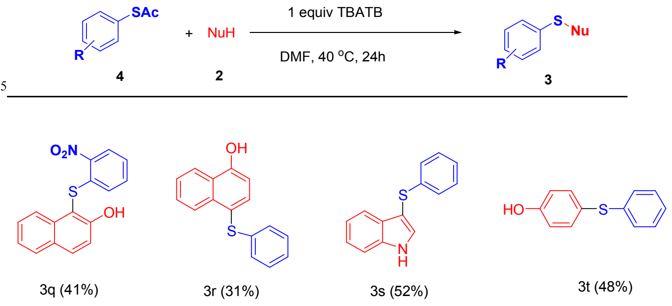


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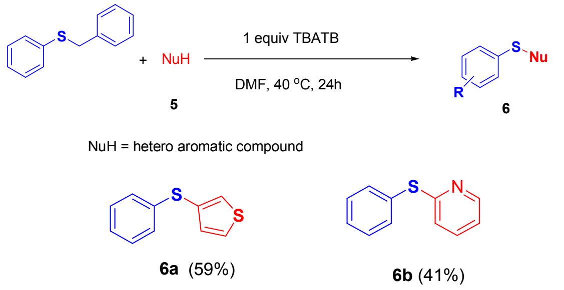
Table 4 Formation of Diaryl sulfide: from heteroaromatic compound



The possible 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, arylbenzylsulfide reacts with insitu generation of Br_2 to form an electrophilic species RSBr (A). The reactive sulfenyl bromide can react with indole moiety to form intermediate (B) which on further deprotonation forms the desired product 3c (Fig. 2).

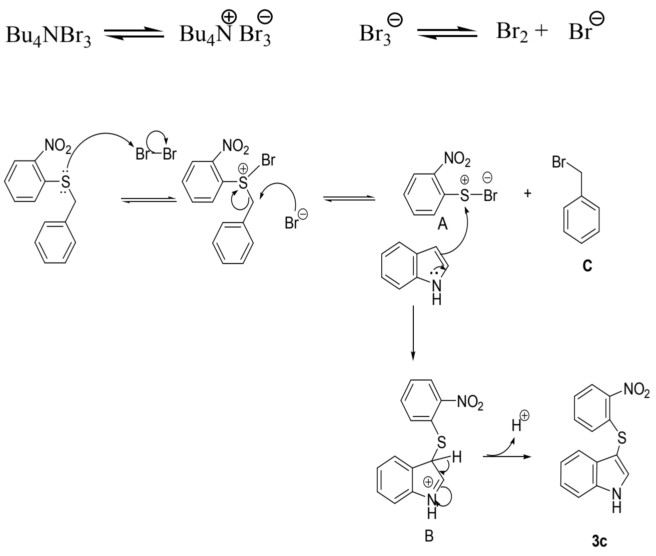


Fig. 2 Proposed mechanism

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

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Notes and references

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Electronic Supplementary Information (ESI) available

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