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Graphical Abstract

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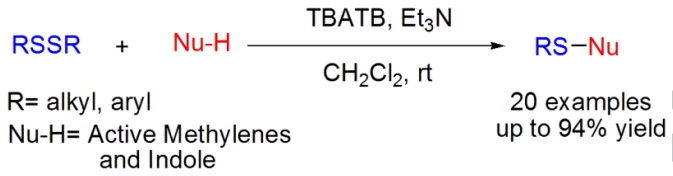

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Metal free sulfenylation of active methylene compounds and indole: TBATB mediated synthesis

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ABSTRACT

The present work addresses a development of metal free one pot direct method for sulfenylation of active methylene compounds and indole. The reaction might proceed through sulfenyl bromide as an intermediate, which initiates the C-S bond formation. The reaction was performed using tetrabutylammonium tribromide (TBATB) as a brominating agent, CH_2Cl_2 as a solvent at room temperature.

1. Introduction

Over the past few decade, there has been much attention for C-S bond formation because of their presence in many pharmaceutically and biologically important molecules.[1] Because of their greater therapeutic value in the treatment of HIV, cancer, cardiovascular and bacterial diseases sulfenylated indole moieties have increased importance in organosulfur chemistry.[2] Many organosulfur compounds are used as an intermediate for the synthesis of various types of sulfur containing compounds.[3] The C-S cross coupling between electrophilic carbon and nucleophilic sulfur species has been broadly accepted.[4] However, the C-S cross coupling between a nucleophilic carbon centre and a nucleophilic sulfur species is generally not feasible. But when the sulfur atom is attached to a halogen or heterocyclic compounds, it acts as an electrophilic centre and reacts with various types of nucleophilic compounds such as ketones,[5] amines,[6] active methylenes,[7] indoles,[8] oxindoles[9] etc. Because the halogen or heterocyclic atom acts as a good leaving group, the yield of the product increases dramatically.[10] In most of the sulfenylation reactions, the sulfur sources are either difficult to prepare, or they are expensive, hazardous or moisture and air sensitive. In 2008 Liang and Liu *et al*. reported that reaction between disulfide and active methylene was not possible after a long period of reaction time though it was possible between active methylene and carbon disulfide as well as thiol under harsh reaction conditions.[11]

In 2004, Shimizu *et al*. reported reactions of organosulfur compounds with active methylene compounds, but they used only one type of organosulfur moiety in strongly basic conditions.[12] Next, M. Arisawa *et al*. described a rhodium-catalyzed sulfenylation of diethyl malonate, but the product formation is very much low and long time needed for completion of the reactions.[13]

In this communication we have reported an efficient protocol in mild reaction conditions without using any transition metal for sulfenylation of active methylene compounds and indole with diaryl disulfide through sulfenyl bromide as an intermediate. We used TBATB as a brominating agent, which was synthesized using a simple method.[14] TBATB is a solid source of bromine.[15] The sulfenyl bromide is formed in situ in the reaction mixture, this step is the key step as it makes the sulfur atom a good electrophilic centre. The sulfenyl bromide is attacked by an active methylene or indole via S_N2 type of reaction to give the product.

2. Result and discussion

At first we examined a model reaction between o-nitrosulfenyl bromide and acetyl acetone for optimizing the reaction condition. The reaction was carried out in various solvents such as DMSO, EtOH, DMF, CH_2Cl_2, THF, toluene and CH_3OH. Among them CH_2Cl_2 was the best solvent for the sulfenylation reaction. The effect of the base was then examined. We examined number of

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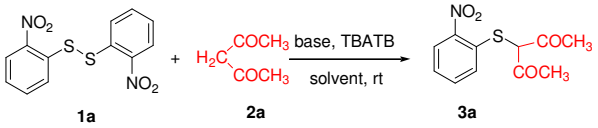
bases such as Et_3N, NaOH, KOH, Na_2CO_3 and K_2CO_3; it was observed that Et_3N provided the desired product in high yield when used in stoichiometric amount. There was no reaction product obtained without using triethylamine.

After optimization in open air at room temperature, the mixture comprising **1a** (0.5 equiv), **2a** (1.2 equiv), TBATB (1 equiv), and triethylamine (1.2 equiv) gave the sulfenylated product **3a** in 90 % yield. Other bromine sources like NBS, Br_2 were evaluated but not effective like TBATB (Table 1, entries 17, 18,). The product was characterized on the basis of FT-IR, ^{1}H-NMR and ^{13}C-NMR spectral and analytical data.

Table 1. Optimization of the reaction conditions[a]

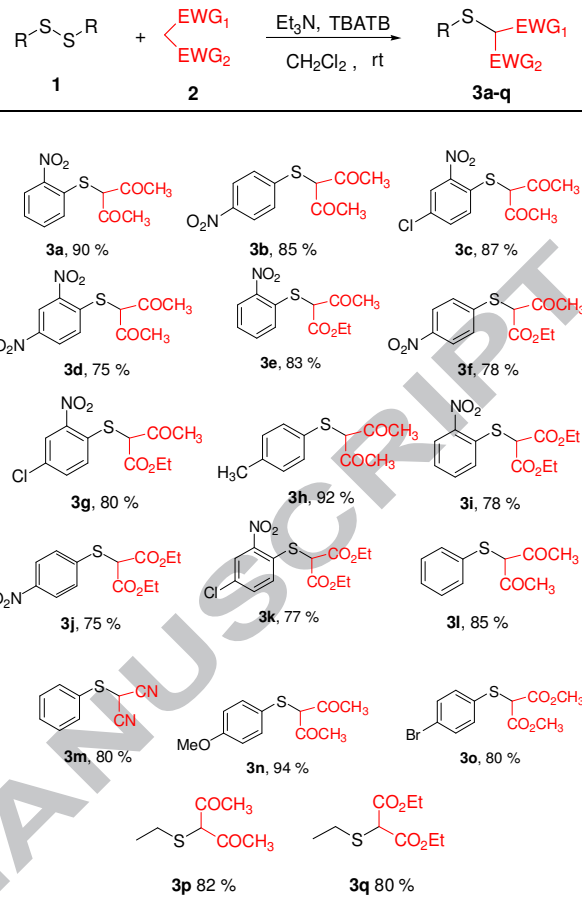


1a **2a** **3a**

Entry	**1a/2a** (equiv)	Bromine source (equiv)	Base (equiv)	Solvent	Yield (%)[b]
1	0.5/1.0	TBATB (1.0)	-	-	NR
2	0.5/1.0	TBATB (1.0)	Et_3N (1.0)	-	trace
3	0.5/1.0	TBATB (1.0)	Et_3N (1.0)	DMSO	40
4	0.5/1.0	TBATB (1.0)	Et_3N (1.0)	EtOH	35
5	0.5/1.0	TBATB (1.0)	Et_3N (1.0)	DMF	50
6	0.5/1.0	TBATB (1.0)	Et_3N (1.0)	CH_3OH	20
7	0.5/1.0	TBATB (1.0)	Et_3N (1.0)	THF	40
8	0.5/1.0	TBATB (1.0)	Et_3N (1.0)	Toluene	45
9	0.5/1.0	TBATB (1.0)	Et_3N (1.0)	CH_2Cl_2	65
10	0.5/1.0	TBATB (1.0)	Et_3N (1.2)	CH_2Cl_2	75
11	0.5/1.2	TBATB (1.0)	Et_3N (1.2)	CH_2Cl_2	90
12	0.5/1.2	TBATB (0.5)	Et_3N (1.2)	CH_2Cl_2	45
13	0.5/1.2	TBATB (1.0)	NaOH (1.2)	CH_2Cl_2	70
14	0.5/1.2	TBATB (1.0)	KOH (1.2)	CH_2Cl_2	72
15	0.5/1.2	TBATB (1.0)	Na_2CO_3 (1.2)	CH_2Cl_2	65
16	0.5/1.2	TBATB (1.0)	K_2CO_3 (1.2)	CH_2Cl_2	74
17	0.5/1.2	NBS (1.0)	Et_3N (1.2)	CH_2Cl_2	25
18	0.5/1.2	Br_2 (1.0)	Et_3N (1.2)	CH_2Cl_2	65

[a]Reaction conditions: 1a (0.5 mmol), 2a (1.2 mmol), base (1.2 mmol), TBATB (1 mmol), solvent (10 mL) stirred for 1.5 h (monitored by TLC) at room temperature.
[b]Yield of isolated product after column chromatography 90 %.
NR= no reaction.

With the optimized reaction condition (Table 1 entry 11), a series of sulfenylated compounds were synthesized between diaryl disulfides and active methylenes. All the substrate reacted smoothly and gave the respective products with excellent yields. In general, the disulfides with electron donating groups provided products in better yields than those with electron withdrawing groups. Halogens (-Cl, -Br) containing disulfides afforded the corresponding desired products with high yields without any difficulties. The disulfides with electron donating groups like –Me produced the desired products with high yields. The results in scheme 1 show that the reaction has a high degree of functional group tolerance with a broad substrate scope.

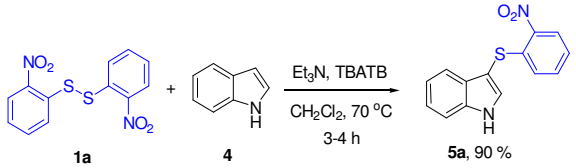


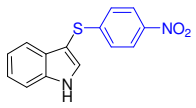
The reactions were carried out on a 1 mmol scale using 0.5 mmol of diaryl disulfide, 1.2 mmol of active methylene compounds, 1.2 mmol of Et_3N, and 1 mmol of TBATB in 10 mL of CH_2Cl_2 stirred for 1.5 h (monitored by TLC) at room temperature. Yield of isolated product 75-94 %.

Scheme 1. Scope of substrates

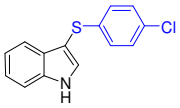
The NMR spectra of compounds **3a**, **3b**, **3e**, **3f**, **3g** and **3p** in $CDCl_3$ showed that they exist as the enol isomers. The ^{1}H-NMR spectrum the assigned peak of O-H peak of the enol displayed a singlet at downfield δ = 13-15. In some compounds the O-H peak was not assigned but the absence of the methylene proton strongly suggested that the compounds were in the enol form. In the ^{13}C-NMR spectra, a low field peak at δ_c = 90-100 indicated that the Sp3 carbon atom of the active methylenes transformed to a Sp2 carbon.

We have also investigated the reaction between diaryl disulfide and indole under the same reaction condition. However, in this case some sort of heat was necessary for completion of the reactions. So many processes have been developed for sulfenylation of indole, but in our case we used TBATB as a brominating agent and disulfides as a sulfenylating agent. The protocol for sulfenylation of indole is environmental friendly; excellent yield with short reaction time. We have done sulfenylation of unsubstituted indole only; sulfenylation of substituted indoles are ongoing in our laboratory.





5b, 85 %

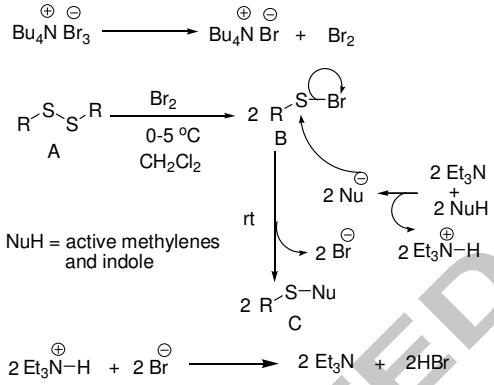


5c, 83 %

The reactions were carried out on a mmol scale using 1 mmol of indole, 0.5 mmol of diaryl disulfide, 1.2 mmol of Et_3N, and 1 mmol of TBATB in 10 mL of CH_2Cl_2 stirred for 3-4 h (monitored by TLC) at room temperature. Yield of isolated product 83-90 %.

Scheme 2. Extension of substrate scope to indole

On the basis of the above reactions, a plausible mechanism for the formation of the compounds was proposed in Scheme 3. Initially, formation of the arylsulfenyl bromide (B) occurs from the diaryl disulfide (A). The brominating agent TBATB liberates Br_2, which brominates the disulfide to the corresponding sulfenyl bromide. The formation of sulfenyl bromide is the key step, where the nucleophilic sulfur atom is converted to an electrophilic centre. In the next step, electrophilic sulfur atom is attacked by the nucleophiles, which leads to the formation of the desired product (C). The whole process can be understood by umpolung strategy.[16]



Scheme 3. Plausible mechanism for the C-S bond formation

Conclusions

We have developed a fast and efficient method for sulfenylation of active methylene compounds and indole with a metal free, one pot, simple and mild reaction conditions. This new process afforded the desired products in good to excellent yields. The reaction might proceeds through in situ formation of a sulfenyl bromide intermediate.[11,15a] The process is carried out using brominating agent TBATB and CH_2Cl_2 as solvent at the room temperature. The developed process is not air or moisture sensitive.

Experimental Section

General Information

All reagents were purchased from commercially available sources and used without further purification unless otherwise noted. When necessary, solvents and reagents were dried prior to use. CH_2Cl_2 was distilled from CaH_2. All experiments were monitored by analytical thin layer chromatography (TLC) by a pre-coated plate. Column chromatography was performed with a 200-300 mesh, packed as slurry in hexane and ethyl acetate (9:1) solvent system. Proton nuclear magnetic resonance and carbon nuclear magnetic resonance spectra were recorded on Bruker 500 MHz and 125 MHz FT NMR spectrometer respectively. All chemical shift resonance are referenced by the solvent resonance peak δ 7.26 ($CDCl_3$) for ^{1}H NMR and δ 77.00 ($CDCl_3$) for ^{13}C NMR Spectra. The following abbreviations are used to classify the multiplicity of the protons s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet. ^{1}H NMR data are represented as follows: chemical shift, multiplicity, coupling constant in Hz and number of protons.

Typical procedure for the preparation of 3 (**3a** as an example): A mixture of diaryl disulfide **1a** (0.5 mmol, 154 mg), TBATB (1 mmol, 482 mg) and Et_3N (1.2 mmol, 0.17 mL) in anhydrous CH_2Cl_2 (10 mL) were stirred for a 30 minutes in an ice water bath. After 30 minute **2a** (1.2 mmol, 0.12 mL) was added and the reaction mixture was stirred for additional 1.5 hour at room temperature. After completion of the reaction monitored by TLC the reaction mixture was diluted by distilled water. The mixture was extracted with CH_2Cl_2. The organic layer was separated, dried over Na_2SO_4, and concentrated under vacuum. The reaction mixture was purified by column chromatography on silica gel using hexane/ethyl acetate (9:1) to give the desired **3a** (228 mg, 90 %) as a yellow solid. m.p. 110-113 °C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ = 11.87 (s, 1H), 8.36-8.35 (dd, J = 8.5 Hz and 1.5 Hz, 1H), 7.87-7.85 (dd, J = 8.5 Hz and 1 Hz, 1H), 7.62-7.58 (m, 1H), 7.44-7.40 (m, 1H), 2.31 (s, 3H), 1.71 (s, 3H). ^{13}CNMR ($CDCl_3$, 125 MHz) δ = 198.6, 146.0, 138.0, 134.5, 127.2, 127.0, 126.39, 125.5, 100.6, 24.2, 8.59; anal. calcd. for $C_{11}H_{11}NO_4S$: C 52.16, H 4.38, N 5.53 %; found: C 52.18, H 4.39, N 5.54 %.

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Notes and References

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Supplementary Material

Supplementary material is available with a separate file.