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Carbon Tetrabromide-Mediated Carbon−Sulfur Bond Formation via a Sulfenyl Bromide Intermediate

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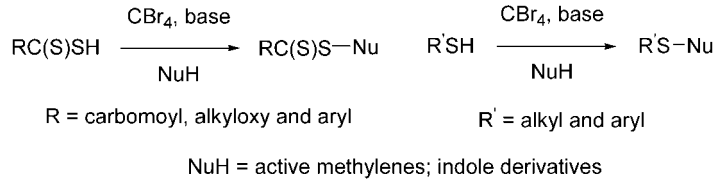
ABSTRACT



In the presence of carbon tetrabromide, a variety of dithiocarbamates, xanthates, dithioesters, and thioethers were prepared in one pot by reacting the corresponding dithioic acids or thiols with active methylene compounds/indole derivatives under mild conditions. The formation of a sulfenyl bromide intermediate is proposed as the key step, which initiates the C−S bond formation.

Carbon−sulfur bond formation is a fundamental approach to introduce sulfur into organic compounds and has received much attention due to the occurrence of this bond in many molecules that are of biological, pharmaceutical, and material interest.[1,2] For C−S cross-coupling, a nucleophilic displacement reaction by a sulfur nucleophile with a carbon electrophile has been widely accepted.[3] However, the C−S cross-coupling between a nucleophilic sulfur species and a nucleophilic carbon component is generally regarded as impossible. During our research on ketene dithioacetal chemistry,[4] we found that the C−S cross-coupling of an active methylene compound with a thiolate, a dithiocarbamate, a xanthate, or a benzodithioate can be achieved in the presence of carbon tetrabromide and the results are thus presented in this communication.

Carbon tetrabromide, as a commercially available and cheap reagent, has found many applications in organic synthesis,[5] for example, the bromination reaction of benzene hydrocarbons,[6a] terminal acetylenes,[6b,c] alkanes, or arylalkanes,[5a,6d] and active methylenes.[6] The known Appel[7] and Corey−Fuchs[8] reactions represent another typical ap-

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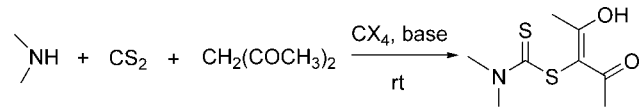
plication of CBr_4 in organic synthesis, which involve the initial formation of triphenylphosphine bromide (TPPB) or analogue via a S_N2 type attacking of the phosphorus atom of PPh_3 at a bromine atom of CBr_4. In this work, the initial studies were focused on the investigation of the C−S cross-coupling of a dithiocarbamate, which was derived from the reaction of an amine and carbon disulfide,[9] with an active methylene compound in the presence of CBr_4. The design was based on the consideration that the C−S coupling might occur through a transient (dialkylamino(thiocarbonyl))-sulfenyl bromide intermediate[10] which, similar to Appel agents,[7,8] could be formed in situ by the nucleophilic attack of a dithiocarbamate anion on a bromine atom of CBr_4, and then trapped by an active methylene compound to form an organic dithiocarbamate.

A model reaction between dimethylamine **1a**, carbon disulfide, acetylacetone **2a** and CBr_4 was first examined under various conditions. Among the solvents tested, CH_2Cl_2 proved to be the most efficient (Table 1, entry 6). After optimization, in open air at ambient temperature, the mixture comprising **1a** (1.0 equiv), CS_2 (1.0 equiv), **2a** (1.2 equiv), CBr_4 (1.0 equiv), and triethylamine (1.2 equiv, as the base) for 2.0 h gave the C−S bond formation product, 2,4-dioxopentan-3-yl dimethylcarbamodithioate **3aa** in 96% yield (Table 1, entry 9). The structure of **3aa** was characterized on the basis of its spectra and analytical data, as well as X-ray diffraction (Figure S1, Supporting Information).[11] Comparatively, in the absence of CBr_4, **3aa** could not be obtained at all (Table 1, entry 1) and catalytic amount of CBr_4 was not enough to drive the reaction to completion (Table 1, entry 10). The reactivity of CCl_4 was also examined concerning this C−S bond-forming reaction, but proved to be inactive under otherwise the same conditions (Table 1, entry 11).

Next, under the optimized conditions as above (Table 1, entry 9), a range of reactions of various amines with acetylacetone and CS_2 in the presence of CBr_4 were investigated. The reactions with secondary aliphatic amines, such as dimethylamine **1a**, diethylamine **1b**, dibutylamine **1c**, morpholine **1d**, and piperidine **1e** proceeded efficiently

Table 1. Reaction of Dimethylamine **1a** with Acetylacetone **2a** under Different Conditions



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

entry	**1a**/CS_2/**2a**/CX_4	CX_4	base	solvent	yield (%)[a]
1	1.0/1.0/7.5/0	CBr_4	−	neat	−[b]
2	1.0/1.0/1.0/1.0	CBr_4	−	CH_3CN	18
3	1.0/1.0/1.0/1.0	CBr_4	−	C_2H_5OH	25
4	1.0/1.0/1.0/1.0	CBr_4	−	THF	31
5	1.0/1.0/1.0/1.0	CBr_4	−	DMF	36[c]
6	1.0/1.0/1.0/1.0	CBr_4	−	CH_2Cl_2	50
7	1.0/1.0/1.0/1.0	CBr_4	Et_3N (1.0)	CH_2Cl_2	56
8	1.0/1.0/1.0/1.0	CBr_4	Et_3N (1.2)	CH_2Cl_2	72
9	1.0/1.0/1.2/1.0	CBr_4	Et_3N (1.2)	CH_2Cl_2	96
10	1.0/1.0/1.2/0.5	CBr_4	Et_3N (1.2)	CH_2Cl_2	49
11	1.0/1.0/1.2/1.0	CCl_4	Et_3N (1.2)	CH_2Cl_2	−[b]

[a] Isolated yields. [b] No reaction. [c] Thiuram disulfide was found to be the main product.

and the corresponding dithiocarbamates **3aa**−**ea** were obtained in high to excellent yields (Table 2, entries 1−5).[12] Then the reactions of amines and CS_2 with other active methylenes were examined in the following work. Under identical conditions as described above, the reactions of diethylamine **1b**, CS_2 with ethyl acetoacetate **2b**, 3-oxo-*N*-phenylbutanamide **2c**, *N*-(4-cholorophenyl)-3-oxobutanamide **2d**, 4-chlorobenzoylacetone **2e**, and diethyl malonate **2f** were carried out. All reactions proceeded smoothly to afford the desired products **3bb**−**bf** in high yields (Table 2, entries 6−10).[13] Other active methylenes such as malonitrile and ethyl nitroacetate were examined, but proved to be inefficient to afford the corresponding C−S bond formation products. Additionally, the reaction of sodium ethoxide with CS_2 and acetylacetone, and the reaction of dithiobenzoic acid with acetylacetone were performed. In the presence of CBr_4, both reactions proceeded efficiently, giving xanthate[14] **4** and dithioester **5** in 77 and 81% yield, respectively (Scheme 1). Obviously, this protocol provides a simple and efficient route to dithiocarbamates **3**, xanthates **4**, and dithioesters **5**. These compounds are valuable synthetic intermediates[15] and have

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(11) X-ray diffraction data for **3aa** has been deposited in the Cambridge Crystallographic Data Centre with supplementary publication number of CCDC 616702.

(12) In our experiment, it was found that the secondary aromatic amines were inert to this C−S bond formation reaction, probably due to their weaker nucleophilicity. For primary aliphatic amines, the resulting products were not the desired C−S bond formation products. Instead, thioureas were obtained based on the spectra data.

(13) In some cases, the S−S coupling products could be detected. In the absence of the carbon nucleophiles, the thiuram disulfides would be produced via S−S coupling. The CBr_4-promoted S−S coupling reaction will be reported seperately, along with the results mentioned in ref 12.

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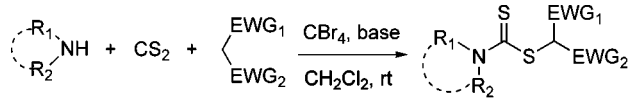
Table 2. Reactions of Amines **1** with CS_2 and Active Methylenes **2** in the Presence of CBr_4[a]



1 **2** **3**

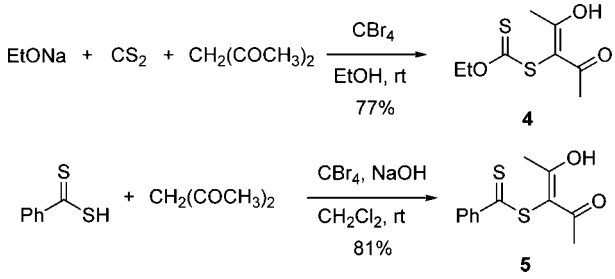
entry	amine **1**	substrate **2**	EWG_1	EWG_2	base	t (h)	product **3**	yield (%)[b]
1	dimethylamine (**1a**)	**2a**	MeCO	MeCO	Et_3N	1.5	**3aa**	96
2	diethylamine (**1b**)	**2a**	MeCO	MeCO	Et_3N	1.5	**3ba**	92
3	dibutylamine (**1c**)	**2a**	MeCO	MeCO	Et_3N	1.5	**3ca**	95
4	morpholine (**1d**)	**2a**	MeCO	MeCO	Et_3N	2.5	**3da**	85
5	piperidine (**1e**)	**2a**	MeCO	MeCO	Et_3N	2.5	**3ea**	93
6	diethylamine (**1b**)	**2b**	MeCO	EtOCO	NaOH	2.5	**3bb**	65
7	diethylamine (**1b**)	**2c**	MeCO	PhNHCO	Et_3N	2.5	**3bc**	76
8	diethylamine (**1b**)	**2d**	MeCO	4-ClPhNHCO	Et_3N	4.5	**3bd**	81
9	diethylamine (**1b**)	**2e**	EtOCO	4-ClPhCO	NaOH	5.5	**3be**	78
10	diethylamine (**1b**)	**2f**	EtOCO	EtOCO	NaOH	4.5	**3bf**	70

[a] Amine (1.0 equiv), CS_2 (1.0 equiv), active methylene compounds (1.2 equiv), carbon tetrabromide (1.0 equiv), base (1.2 equiv). [b] Isolated yields.

shown wide applications as pesticides, fungicides in agriculture, sulfur vulcanization in rubber manufacturing,[16] and radical chain transfer agents in the reversible addition fragmentation chain transfer (RAFT) polymerizations.[17]

The sulfenylation reaction is one of the particularly effective methods in the introduction of a thio group into various organic compounds.[18] With the aim to further explore

Scheme 1



the scope of the sulfur components in the cross-coupling reaction, the reaction of benzylthiol **6a** with CBr_4 and active methylene compounds was thus carried out at ambient temperature. To our delight, with NaOH as the base, the reactions of **6a** and a range of active methylene compounds including acetylacetone, ethyl acetylacetate and 3-oxo-*N*-4-chlorophenylbutanamide gave the corresponding C−S bond-forming products **7aa**, **7ab**, and **7ag** in good to excellent yields (entries 1−3, Table 3). It should be noted that even 2-methyl-3-oxo-*N*-phenylbutanamide also gave satisfactory result (entry 4). The reaction of 4-methylphenylthiol **6b** with CBr_4 and acetyl acetone under the identical conditions proceeded smoothly, giving **7ba** in 70% yield (entry 5). The reaction of **6b** with 3-oxo-*N*-phenylbutanamide or ethyl acetoacetate also furnished the sulfides **7ba** and **7bc**, but the yields were low (entries 6 and 7). On the basis of the above results, it was concluded that the reaction is general to a wide range of thiols or their equivalents.

To clarify the possible mechanism, some supplementary experiments were carried out. Under otherwise identical conditions, the mixture of the corresponding disulfides including 1,2-diphenyldisulfide, 1,2-dibenzyldisulfide, and 1,2-bis(dimethylamino)disulfide gave no reaction, which ruled out the possible mechanism of first formation of the disulfides and then the substitution of the disulfides by carbon nucleophiles.[19] On the basis of the above results, a possible mechanism for the formation of **3**−**5**, and **7** was proposed, as depicted in Scheme 2. Initially, a nucleophilic attack of a sulfur anion **I** (or **I′**) at a bromine atom of CBr_4 leads to the formation of sulfur-centered electrophile **II** (or **II′**).[10,20] Then, the reactive intermediate **II** (or **II′**) would be trapped in situ by a carbon nucleophile, giving the C−S bond-forming product, dithiolates **3**−**5** or sulfides **7**. Bromoform has been detected as a byproduct. It is noteworthy, as the key step of

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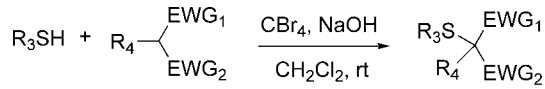
Table 3. Reactions of Thiols **1** with Active Methylene Compounds **2** in the Presence of CBr_4



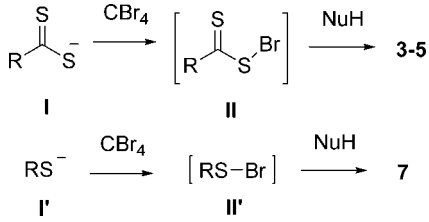
6 **2** **7**

entry	substrate **6**	R_3	R_4	EWG_1	EWG_2	t (h)	product **7**	yield (%)[a]
1	**6a**	Bn	H	MeCO	MeCO	1.2	**7aa**	95
2	**6a**	Bn	H	MeCO	COOEt	1.5	**7ab**	71
3	**6a**	Bn	H	MeCO	4-ClC_6H_4NHCO	1.5	**7ad**	81
4	**6a**	Bn	Me	MeCO	C_6H_5NHCO	1.5	**7ag**	72
5	**6b**	4-MePh	H	MeCO	MeCO	2.0	**7ba**	70
6	**6b**	4-MePh	H	MeCO	COOEt	2.0	**7bb**	29
7	**6b**	4-MePh	H	MeCO	C_6H_5NHCO	2.5	**7bc**	28

[a] Isolated yields.

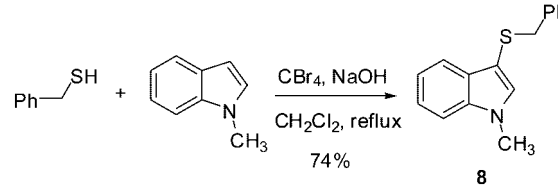
the new C−S cross-coupling reaction, the original nucleophilic sulfur atom is converted into an electrophilic site assisted by CBr_4. The overall process can be understood as

Scheme 2. Proposed Mechanism for the C−S Cross-Coupling Reaction



a formal umpolung of sulfur anions. Umpolung strategy has been demonstrated to facilitate the construction of organic molecules in unusual ways.[21] K. Schlosser et al. reported the reaction of indole derivatives with *N*-chlorosucnimide and thiols, in which a transient formation of the sulfenyl chloride intermediate was proposed.[20b] Comparatively, we succeeded the reaction of acetylacetone with NBS and benzylthiol. The control experiment indicated that the mechanism shown in Scheme 2 was reasonable.

Inspired by Schlosser's work mentioned above, *N*-methyl indole was subjected to the CBr_4-mediated C−S coupling reaction. As a result, 3-benzylthio-*N*-methylindole **8** was obtained in 74% yield (eq 1). In this case, heating to reflux in CH_2Cl_2 is required to accomplish this reaction. The scope of the carbon components in this CBr_4-mediated C−S cross-coupling reaction was extended. Further work is ongoing in our laboratory.



(1)

In conclusion, a new route to dithiocarbamates, xanthates, dithioesters and thioethers was developed by reacting the corresponding sulfur components with active methylenes/indole derivatives. It uses unusual umpolung reactivity created from the reaction of the thiol and equivalents with CBr_4 which leads to a reactive sulfenyl bromide. Such species are highly electrophilic and rather unstable, but the advantage of this chemistry is that they are generated and used in situ. The C−S bond-forming reaction is characterized as a wide range of substrates, multicomponent one-pot procedure, mild conditions, and metal-catalyst-free.

Acknowledgment. Financial support of this research by NSFC (20672019) is greatly acknowledged.

Supporting Information Available: Experimental details, characterization data, ORTEP drawing, and CIF data for **3aa**. This material is available free of charge via the Internet at http://pubs.acs.org.

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