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Selective mono protection of diols, diamines, and amino alcohols using cesium bases

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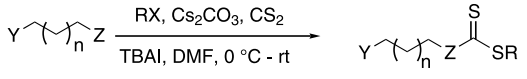
Abstract—Efficient synthetic methods were developed for the synthesis of mono xanthates, as well as mono dithiocarbamates of diamines and amino alcohols. This protocol utilizes the three component coupling of diols, diamines, and amino alcohols using alkyl bromides and carbon disulfide in the presence of a cesium base and tetrabutylammonium iodide (TBAI).

Selective monoderivatization of two chemically-equivalent functional groups within the same molecule is a difficult synthetic transformation.[1] While ample efforts to desymmetrize symmetrical diols or diamines have been developed, a statistical mixture of products is usually obtained, with poor selectivity for the desired monosubstituted product.[2] Keeping these challenges in mind, we herein provide an efficient method to selectively protect one functionality of both symmetric and unsymmetrical bifunctional molecules.

Dithiocarbonyl-containing compounds such as xanthates and dithiocarbamates have enjoyed much success as important synthetic precursors[3] and held considerable biological and medicinal interest.[4] However, we found that to date, few efficient methods were reported regarding the monodithiocarbonylation of diols, and monothiocarbamation of diamines and amino alcohols.[5] In addition, current methods are hampered by overalkylations,[6] product decomposition,[7] or more commonly, cyclization products.[8]

Recently, we reported an efficient synthesis of dithiocarbonates and dithiocarbamates via a three-component coupling of an alcohol or amine with an alkyl halide and carbon disulfide in the presence of cesium carbonate and tetrabutylammonium iodide (TBAI).[9] Furthermore, we have also developed an efficient protocol for selective mono alkylation of diamines.[10] Based on these results, we decided to initiate a project on a cesium based chemoselective mono-dithiocarbonylation of diols as well as mono-dithiocarbamation of diamines and amino alcohols. Success in this area would aid in the exploration of peptidomimetic synthesis using the dithiocarbamate moiety as a potentially novel linker. These linkers would complement our studies into carbamatoids (carbamate linked amino acids), which were formed via three component coupling of an amine, alkyl bromide, and carbon dioxide in the presence of cesium carbonate.[11]

As per our previously reported method, various diols **1**, diamines **2**, and amino alcohols **3** were smoothly incorporated into carbon disulfide upon stirring in *N*,*N*-dimethylformamide at room temperature in the presence of a cesium base and TBAI (Scheme 1). The reaction mixture was subsequently cooled to 0°C, and a slight excess of an alkyl halide was added dropwise over a half hour yielding the monodithiocarbonate **4** or monodithiocarbamate (**5** or **6**), respectively, along with accompaniment of starting material. Bis-alkylation products were detected in trace amounts only in a few cases. It is strongly believed that the dithiocarbonate or dithiocarbamate anion forms a weakly coordinated species with the cesium ion (e.g. 'naked anions'), thereby



1, (Y = Z = OH)
2, (Y = Z = NH_2)
3, (Y = OH, Z = NH_2)

4, (Y = OH, Z = O)
5, (Y = NH_2, Z = NH)
6, (Y = OH, Z = NH)

Scheme 1.

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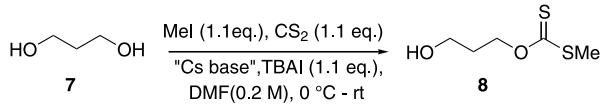
exhibiting enhanced nucleophilicities to effect nucleophilic attack on alkyl halide at room temperature.[12] Although the reactions proceeded smoothly with high degree of selectivity in the case of diamines and amino alcohols, the reaction was somewhat sluggish with diols.

In an effort to optimize the conditions, we studied the effect of bases on the reaction. Use of cesium carbonate as per our previous protocol led to incomplete conversions and longer reaction times. In sharp contrast, reaction of diols with cesium hydroxide as a base led to much shorter reaction times, but accompanied by higher amounts of overalkylated product. Adding the electrophile in portions easily circumvented this problem, furnishing the mono-protected alcohol **8** in high yield (Scheme 2).



Base (1.1 eq.)	time	8
Cs_2CO_3	7 h	81%
$CsOH{\cdot}H_2O$[a]	1.5 h	92%

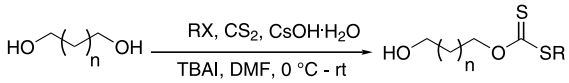
a: MeI was added in 3 portions over a period of 60 mins.

Scheme 2. Effect of base on mono-dithiocarbonylation of diols.

Exploring the generality of these conditions, we proved that the mono-dithiocarbonylation of symmetrical diols were successful using the newly developed method. 1,3-propanediol (**7**) reacted efficiently with benzyl chloride (**9**) in high yield (Table 1, entry 1). In addition, desymmetrization of 2-butene-1,4-diol (**10**) with an unactive electrophile **11** also proved successful, converting exclusively to its corresponding mono-dithiocarbonate in good yield (entry 2). As depicted in entry 3, 2,2-dimethyl-1,3-propanediol (**12**) was subjected to the same mild conditions using MeI (**13**) to afford its respective mono-methylated xanthate. In comparison, we found that the monofunctionalization of symmetrical secondary diols also gave high selectivity (entry 4). Unlike these examples, diols like *cis* 1,2-cylohexanedimethanol failed to give isolable monoalkylated product. This is because of propensity of mono-dithiocarbonate to cyclize into thioketone derivative. In most cases, symmetrical diols were efficiently desymmetrized to afford mono-dithiocarbonate product exclusively, along with recovery of the starting diol, which accounts for the mass balance. Also, it is noteworthy to mention that bis-alkylation products did not exceed 5% of the total yield.

The protocol was further tested on unsymmetrical 1,2-diols. Reactions of a diol containing the bulky *t*-butyl group with CS_2 and benzyl chloride (**9**) led to the formation of dithiocarbonate at the primary alcoholic position exclusively (Table 2, entry 1). Likewise, reaction of methyl iodide (**13**) and carbon disulfide with 1-phenyl-1,2-ethanediol gave mono-dithiocarbonate derivative of less sterically congested primary alcohol, leaving alcohol at benzylic position intact (entry 2).

Table 1. Mono-dithiocarbonylation of symmetrical diols



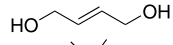
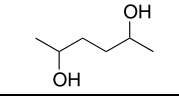
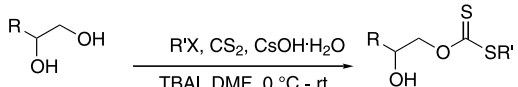
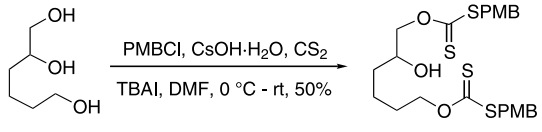
entry	diol	halide (RX)	time	yield
1	**7**	BnCl (**9**)	1.6 h	93%
2	 (**10**)	$Ph(CH_2)_3Br$ (**11**)	2 h	80%
3	 (**12**)	MeI (**13**)	2.4 h	78%
4	 (**14**)	**13**	2.5 h	80%

Table 2. Mono-dithiocarbonylation of unsymmetrical diols



entry	R	halide (R'X)	time	16
1	*t*-Bu	BnCl (**9**)	1.5 h	85%
2	Ph	MeI (**13**)	1.5 h	90%

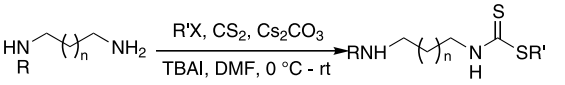
To test the potential of this protocol to the full extent, 1,2,6-hexanetriol (**17**) was coupled with carbon disulfide (2.0 equiv.) and *p*-methoxybenzyl chloride (2.0 equiv.) to selectively give bis-dithiocarbonate **18** at primary alcoholic positions as a major product along with other water soluble dithiocarbonates (Scheme 3).

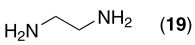
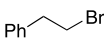
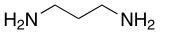
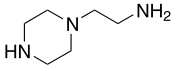


Scheme 3.

To further investigate the scope of this method, diamines were next examined for desymmetrization using our newly developed protocol. We soon discovered that unlike diols, diamines reacted rapidly in the presence of cesium carbonate as a base. Equilibration of primary aliphatic diamines of varying chain lengths with cesium carbonate, TBAI and carbon disulfide for 15 minutes, followed by the addition of halide over 20 min under ice bath led to the formation of mono-dithiocarbamate in optimum yield. Symmetrical diamines including ethylenediamine (**19**) and 1,3-diaminopropane (**21**) reacted readily, providing the mono-alkylated dithiocarbamates in satisfactory yields

Table 3. Mono-dithiocarbamation of diamines



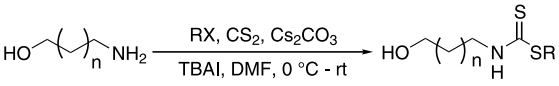
entry	diamine	R'X	time	yield
1	 (**19**)	 **20**	0.5 h	65%
2	 (**21**)	**13**	0.5 h	68%
3	Tryptamine (**22**)	**20**	0.5 h	65%
4	 (**23**)	**13**	0.5 h	68%

within minutes (Table 3, entries 1 and 2). However, mono *N*-alkylated side products accounted for the remainder of mass balance (15–20%) to produce mono secondary amine. Primary amino groups of diamines **22** and **23** reacted regioselectively to furnish mono-dithiocarbamates as the major product, leaving secondary amines intact (entries 3–4).

A variety of amino alcohols were then examined for the selective formation of dithiocarbamates. Various amino alcohols encompassing primary amino groups reacted efficiently with different electrophiles to give dithiocarbamate in high yields (Table 4; entries 1–3). These conditions work equally well with less nucleophilic aromatic amines like **29** to give dithiocarbamate exclusively. Also, it is noteworthy to mention that the crude reaction mixtures were devoid of side products and did not require chromatographic purification.

We then examined amino alcohols possessing sterically hindered secondary amino groups. As depicted in Table 5, various ethanolamines were subjected to dithiocarbamation with side chains of different bulkiness. *N*-Methyl-2-aminoethanol (**30**) reacted smoothly with

Table 4. Mono-dithiocarbamation of amino alcohols with primary amino groups



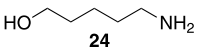
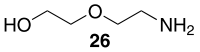
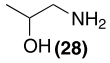
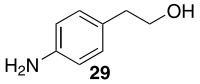
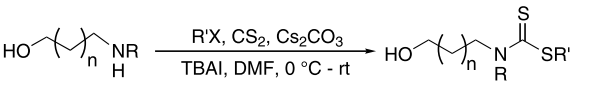
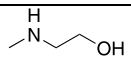
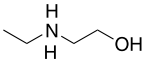
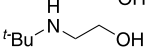
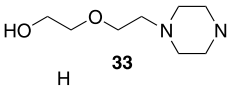
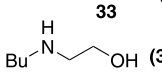
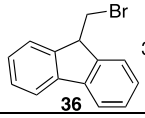
entry	amino alcohol	halide (RX)	time	yield
1	 **24**	 **25**	15 mins	94%
2	 **26**	PMBCl **27**	20 mins	95%
3	 (**28**)	**9**	15 mins	91%
4	 **29**	**13**	15 mins	98%

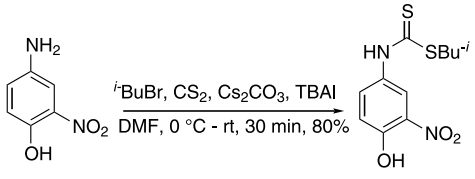
Table 5. Mono-dithiocarbamation of amino alcohols with secondary amino groups



entry	amino alcohol	halide (R'X)	time	yield
1	 (**30**)	**9**	15 mins	95%
2	 (**31**)	**13**	15 mins	95%
3	 (**32**)	**13**	20 mins	94%
4	 **33**	^{i}BuBr (**34**)	30 mins	89%
5	 (**35**)  **36**		30 mins	45%

benzyl chloride to afford dithiocarbamate exclusively (entry 1). *N*-Ethyl-2-aminoethanol (**31**) coupled uneventfully with methyl iodide (**13**) to give the desired product in high yield. The presence of bulky groups did not hinder in the presence of active and inactive electrophiles, both yielding mono-dithiocarbamate exclusively with no dithiocarbonate product was detected (entries 3 and 4). In order to prove the mildness of the protocol, we subjected base labile fluorene derivative **36** to dithiocarbamation conditions.[13] The use of stoichiometric amount of bromide led to the formation of the desired product in 45% yield along with alkene derived from **36**.

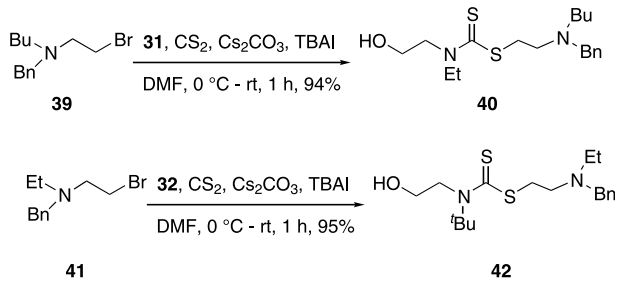
With this viable protocol in hand, the scope of the reaction was further probed using an amino phenol in the same context. To our delight, 2-nitro-4-aminophenol (**37**) underwent smooth mono-dithiocarbamation to give **38** in 80% yield. We believe this is the first example of dithiocarbamation of amino phenol reported (Scheme 4).



37 **38**

Scheme 4.

Therefore, we decided to broaden the scope of applications by carrying out the synthesis of short dimeric analogs, which contain the dithiocarbamate as the skeletal backbone without a protection–deprotection sequence. 2-(Ethylamino)ethanol (**31**) and 2-(*tert*-butylamino)ethanol (**32**) underwent facile dithiocarbamations using two unactivated amino bromides **39** and **41**, which were prepared using our previously reported bromination techniques,[14] to afford dithiocarbamates **40** and **42**, respectively, in high yields (Scheme 5).



Scheme 5.

Conclusion

In conclusion, a three way coupling was performed to combine diols, diamines, and amino alcohols with carbon disulfide and halides in the presence of a cesium base and TBAI, leading to the synthesis of dithio derivatives. Due to its simplicity and mildness, this mono-alkylation protocol is anticipated to find wide application in synthetic organic chemistry based on its ability to mono-protect or desymmetrize bifunctionalized compounds.

Acknowledgements

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