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CuCl-catalyzed cleavage of *S*-triphenylmethyl thioether: a new detritylation method for thio group

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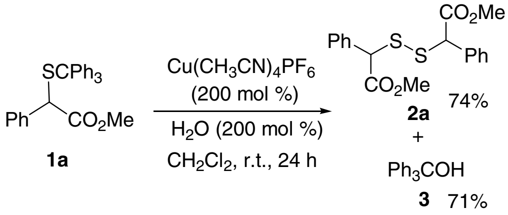
Abstract—A new method for the deprotection of trityl thioethers using CuCl as the catalyst under ultrasonic conditions is described.

Triphenylmethyl (trityl) is a common *S*-protecting group used to avoid disulfide formation and prevent the thiol group from reacting with other sensitive functional groups.[1] Thus, the methods that are able to cleave the *S*-trityl group under mild conditions are very important for the thiol group containing molecules. Classical ways for detritylation usually employ acidic conditions, either with protonic acid[2] (e.g., hydrogen chloride, hydrogen bromide, trifluoroacetic acid) or Lewis acid[3] (e.g., $AlBr_3$). Besides, some oxidative protocols have been developed for the deprotection of trityl thioethers.[4–8] Among them, iodinolysis in a protic solvent such as methanol is most commonly used.[7,8] On the other hand, due to the affinity of sulfur atom with heavy metals, such as mercury(II) and silver(I), the *S*-trityl group can be removed easily with heavy metal salts at room temperature.[9–12] Obviously, these methods suffer some drawbacks such as strongly acidic conditions and heavy metal pollutions.[13] Herein we report a new and efficient detritylation method for thioethers, in which CuCl is utilized as an efficient catalyst under ultrasonic conditions.

During our study on [2,3]-σ rearrangement of sulfur ylide generated from Cu(I) carbene,[14] we unexpectedly found that the reaction of trityl thioether **1a** and $Cu(CH_3CN)_4PF_6$ (200 mol %) at room temperature in CH_2Cl_2 containing H_2O (200 mol %) afforded disulfide **2a** in a 74% yield, together with triphenylmethol in a 71% yield (Scheme 1).



Scheme 1.

Following this primary result, we proceeded to examine other copper salts with **1a** as the substrate. The data are collected in Table 1. It was concluded that $Cu(CH_3CN)_4PF_6$ and CuCl similarly mediated detritylation reactions (entries 1 and 2). However, with other copper salts, such as CuBr, CuI, and $CuSO_4$, the detritylation did not proceed well (entries 3–5).

To further improve the reaction, we studied the reaction of thioether **1b** with CuCl under different conditions

Table 1. Effect of different copper salts on the reaction of **1a**

Entry	Copper salt[a]	Reaction time (h)	Yield[b] (%)
1	$Cu(CH_3CN)_4PF_6$	24	74
2	CuCl	24	86
3	CuBr	24	Trace
4	CuI	24	NR[c]
5	$CuSO_4·5H_2O$	24	NR

[a] 2.0 equiv of copper salt was used.
[b] Isolated yield by column chromatography.
[c] No reaction occurred as judged by TLC.

Keywords: Deprotection; Thiol; CuCl-catalyzed; Trityl.
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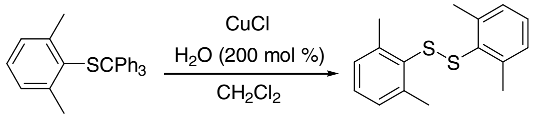
Table 2. Detritylation of **1b** using CuCl under various conditions



1b **2b**

Entry	Reaction condition	Copper salt (mol %)	Reaction time[b] (h)	Yield[a] (%)
1	rt	200	18	83
2	rt ~ reflux	200	16	85
3	Ultrasonic rt ~ 30 °C[c]	200	3	89
4	Ultrasonic rt ~ 30 °C	50	3	93
5	Ultrasonic rt ~ 30 °C	20	3	88

[a] Isolated yield after column chromatography.

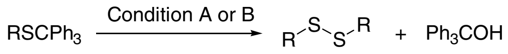
[b] Thioether **2b** completely disappeared by TLC.

[c] The water bath was used and the temperature of the water bath kept 30 °C during ultrasonic irradiation.

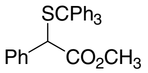
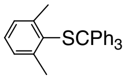
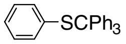
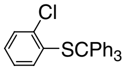
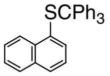
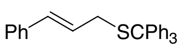
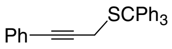
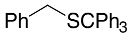
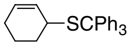
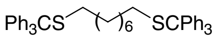
(Table 2). The results demonstrated that the reaction could be only slightly accelerated by raising the reaction temperature (entry 2). To our delight, under ultrasonic conditions, the reaction could complete within 3 h (entry 3). Furthermore, the amount of CuCl could be reduced to 20 mol % under ultrasonic conditions. Thus, the detritylation could be performed with catalytic CuCl.

The scope of the detritylation procedure is demonstrated by the reaction with a series of thioether substrates **1a**–**k** (Table 3). For comparison, the data both for reactions under ultrasonic conditions with catalytic amount of CuCl and the reactions under non-ultrasonic conditions with 200 mol % CuCl were collected in the table. The data indicate a remarkable increase in the rate of the reactions under ultrasonic conditions in general. A complete detritylation of thioethers **1a**–**h** under ultrasonic conditions (Condition B) took 2.5–7 h, and the yields

Table 3. Detritylation of thioethers **1a**–**k** with CuCl[15]



1a-k **2a-k**

Entry		Thioether **1**	Condition A[a]		Condition B[b]	
			Reaction time	Yield[c] (%)	Reaction time (h)	Yield (%)
1	**1a**		3 days	90	4	89
2	**1b**		18 h	83	3	88
3	**1c**		12 h	85	2.5	90
4	**1d**		18 h	83	3	94
5	**1e**		12 h	86	3.5	88
6	**1f**		3 days	88	5	89
7	**1g**		3 days	86	5	90
8	**1h**		5 days	78	7	83
9	**1i**		36 h	76	—[d]	—[d]
10	**1j**	$CH_3(CH_2)_8CH_2SCPh_3$	5 days	63	—	—
11	**1k**		5 days	57[e]	—	—

[a] Condition A: 200 mol % CuCl, 200 mol % H_2O, CH_2Cl_2, rt.

[b] Condition B: 20 mol % CuCl, 200 mol % H_2O, CH_2Cl_2, ultrasonic, rt ~ 30 °C.

[c] Isolated yield after column chromatography when thioether **1** completely disappeared by TLC.

[d] Reaction gave complex mixture.

[e] Yield of a mixture of dimer and trimer.

of the isolated disulfide products ranged from 83% to 94% (Table 3, entries 1–8). The reaction under condition A (200 mol % CuCl, non-ultrasonic), gave comparable yields. However, the reaction took much longer time. The detritylation was found to be general. In addition to aryl thioethers, the thio ether substrates containing benzyl, allyl, and propargyl group all worked well and gave the corresponding disulfides in good yields. Thioether substrates **1i**–**k**, which contain alkyl substituents, also worked well under non-ultrasonic conditions (Condition A). However, under ultrasonic conditions the reaction resulted in a complex mixture (entries 9–11).

In summary, we have developed a mild and efficient reaction for the deprotection of trityl thioethers to their corresponding disulfide compounds with CuCl. Because the conditions is virtually neutral, acid-sensitive groups could tolerate the reaction. Although the reaction mechanism is not clear at present, it is likely that the reaction proceeds through electron-transfer process with radical species as a reactive intermediate.

Acknowledgements

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References and notes

1. For comprehensive reviews on protecting groups, see: (a) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 2nd ed.; Wiley: New York, 1991; (b) Kocieński, P. J. *Protecting Group*, 3rd ed.; Georg Thieme Verlag: Stuttgart, 2005.
2. (a) Zervas, L.; Photaki, I. *J. Am. Chem. Soc.* **1962**, *84*, 3887; (b) Photaki, I.; Taylor-Papadimitriou, J.; Sakarellos, C.; Mazarakis, P.; Zervas, L. *J. Chem. Soc. C* **1970**, 2683; (c) Hiskey, R. G.; Mizoguchi, T.; Igeta, H. *J. Org. Chem.* **1966**, *31*, 1188.
3. Tarbell, D. S.; Harnish, D. P. *J. Am. Chem. Soc.* **1952**, *74*, 1862.
4. Gregg, D. C.; Hazelton, K.; McKeon, T. F., Jr. *J. Org. Chem.* **1953**, *18*, 36.
5. Gregg, D. C.; Blood, C. A., Jr. *J. Org. Chem.* **1951**, *16*, 1255.
6. Schreiber, K. C.; Fernandez, V. P. *J. Org. Chem.* **1961**, *26*, 2478.
7. Kamber, B.; Rittel, W. *Helv. Chim. Acta* **1968**, *51*, 2061.
8. Li, K. W.; Wu, J.; Xing, W. N.; Simon, J. A. *J. Am. Chem. Soc.* **1996**, *118*, 7237.
9. Maltese, M. *J. Org. Chem.* **2001**, *66*, 7615.
10. Carroll, F. I.; Dickson, H. M.; Wall, M. E. *J. Org. Chem.* **1965**, *30*, 33.
11. Gregg, D. C.; Iddles, H. A.; Stearns, P. W., Jr. *J. Org. Chem.* **1951**, *16*, 246.
12. Hiskey, R. G.; Adams, J. B. *J. Org. Chem.* **1966**, *31*, 2178.
13. Other methods for detritylation of trityl thioethers, see: (a) Hiskey, R. G.; Mizoguchi, T.; Smithwick, E. L. *J. Org. Chem.* **1967**, *32*, 97; (b) Mairanovsky, V. G. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 281; (c) Pearson, D. A.; Blanchette, M.; Baker, M. L.; Cuindon, C. A. *Tetrahedron Lett.* **1989**, *30*, 2739.
14. Ma, M.; Peng, L.; Li, C.; Zhang, X.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 15016.
15. *General procedure for the detritylation of thioethers to disulfides under condition B.* Thioether **1** (60 mg, 0.16 mmol) was dissolved in CH_2Cl_2 (1.5 mL), and to this solution was successively added CuCl (3 mg, 0.03 mmol) and H_2O (6 mg, 0.32 mmol), then the reaction bottle was sealed with a rubber plug. The reaction was conducted under ultrasonic irradiation for 3–7 h until detritylation was complete as judged by TLC. Removal of the solvent afforded a crude product, which was purified by column chromatography to give pure disulfide product **2**.