Pergamon

Tetrahedron Letters 42 (2001) 2055–2058

TETRAHEDRON LETTERS

Mild and efficient synthesis of thiocarbonates and thiocarbamates via a three-component coupling utilizing Cs_2CO_3 and TBAI

Ralph N. Salvatore,[a] Suma Sahab[a] and Kyung Woon Jung[a,b,*]

[a]*Department of Chemistry, University of South Florida, 4202 E. Fowler Avenue, Tampa, FL 33620-5250, USA*
[b]*Drug Discovery Program, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612-9497, USA*

Received 12 December 2000; accepted 22 January 2001

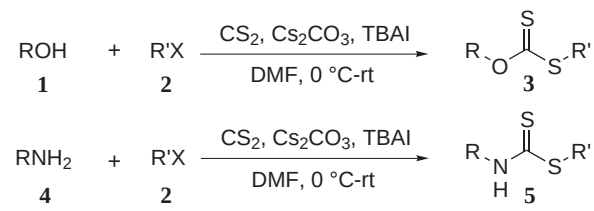
Abstract—The presence of cesium carbonate and tetrabutylammonium iodide (TBAI) facilitated efficient thiocarbonylation of alcohols, and thiocarbamation of amines, using carbon disulfide with alkyl halides. This protocol was mild, chemoselective, and efficient, compared to the existing methods. © 2001 Published by Elsevier Science Ltd.

Thiocarbonates (xanthates) and thiocarbamates[1] have received much attention due to their interesting technological,[2] biological,[3] and synthetic applications.[4] Typically, the thiocarbonyl moiety has been utilized ubiquitously as a protecting group,[5] and as an intermediate in further synthesis.[6] Their formation employs harsh reaction conditions such as the use of strong bases, high temperatures, and long reaction times.[7] In addition, modifications have been reported to use thiophosgene,[8] chlorothioformates,[1c] and isothiocyanates,[1c] which are costly and toxic reagents. Thus, we were prompted to embark on improved procedures. Recently, we reported a highly efficient cesium base-promoted solution phase synthesis of alkyl carbonates and carbamates,[9] which utilizes non-toxic reagents under mild conditions. This protocol has been successfully applied to peptidomimetic synthesis as well as solid phase synthesis.[10] As a complementary approach, this procedure has been extended to the formation of thiocarbonates and thiocarbamates using carbon disulfide.

In the presence of cesium carbonate and tetrabutylammonium iodide (TBAI), various alcohols and amines smoothly coupled with carbon disulfide at ambient temperatures to produce the incipient thiocarbonate (or thiocarbamate) anions in *N*,*N*-dimethylformamide. Subsequent addition of an alkyl halide at 0°C exclusively produces thiocarbonate **3** or thiocarbamate **5**, respectively, upon gentle warming to room temperature (Scheme 1).

Under the explored standard conditions (Table 1), various primary alcohols were found to react efficiently with active halides such as methyl iodide to provide the corresponding methyl thiocarbonates in high yields (entries 1–3). However, the thiocarbonate analog of tertiary alcohol **10** offered low yield (entry 4). Sterically hindered secondary alcohols, including pantolactone **11** and menthol **12**, underwent three way couplings with carbon disulfide and methyl iodide, delivering the methyl xanthates in high yields. A noteworthy feature is that our developed protocol averts common side reactions such as elimination (Chugaev reaction), permitting a wide range of applications.

As representatively depicted in Scheme 2, unreactive bromides including **13** were compatible with the reac-

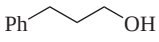
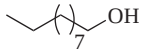
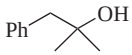
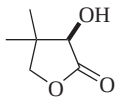


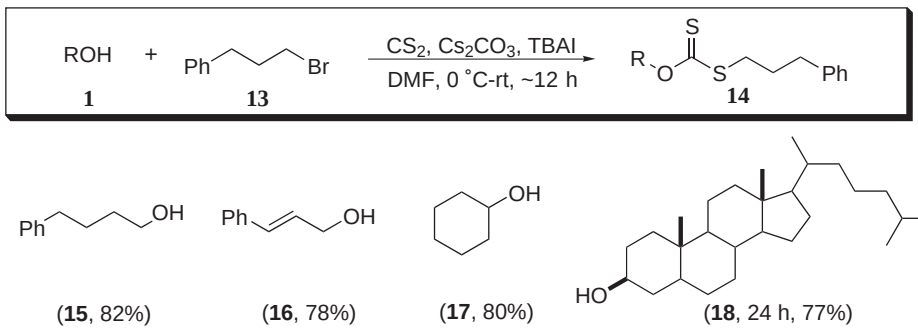
Scheme 1.

* Corresponding author.

0040-4039/01/$ - see front matter © 2001 Published by Elsevier Science Ltd.
PII: S0040-4039(01)00132-0

Table 1.

entry	alcohol		halide	time	yield
1		(**6**)	MeI (**7**)	8 h	94%
2		(**8**)	**7**	12 h	96%
3	BnOH	(**9**)	**7**	3 h	90%
4		(**10**)	**7**	12 h	57%
5		(**11**)	**7**	12 h	72%
6	menthol	(**12**)	**7**	12 h	77%



Scheme 2.

tion conditions illustrated in Scheme 1. Aliphatic alcohol **15** and unsaturated alcohol **16** gave similar yields, whereas more sterically hindered secondary substrates encompassing cyclohexanol **17** and dihydrocholesterol **18** were also facile and pragmatic.

As delineated in Table 2, the techniques were applicable for various amines, which offered efficient thiocarbamate syntheses. Primary amines (**19**–**26**) gave high yields and short reaction times. These amines contained diverse alkyl moieties including primary and secondary alkyls (**19**–**22**) as well as cyclic and heterocyclic skeletons (**23**–**26**). Secondary amines (**27**–**29**) were also found to incorporate easily into CS_2, which in turn ligated with benzyl chloride **20**. Aromatic amines (**30**–**32**) were examined, offering the organic thiocarbamates exclusively in high yields as well.

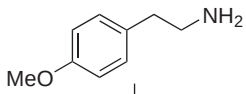
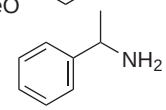
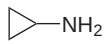
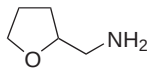
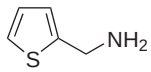
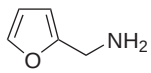
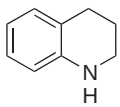
In comparison, we applied our thiocarbamation techniques using halide **13** with various primary and secondary amines (Scheme 3). Activated primary amines including allyl amine **34** and sterically hindered *tert*-butyl amine **35** were found to progress smoothly under the developed conditions. Secondary amine, 1-(3-chlorophenyl)piperazine **36**, reacted expeditiously while a chiral template, such as L-leucine methyl ester **37**, also gave a satisfactory result. In our thiocarbamation processes, side products such as isothiocyanates, stemming from hydrolysis or decomposition, were not detected in any cases.

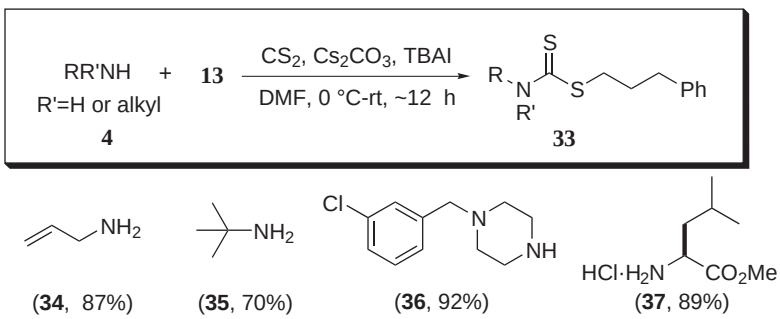
In conclusion, we have developed a convenient and efficient protocol for a one-pot, three-component coupling of various alcohols or amines with an alkyl halide via a CS_2 bridge using cesium carbonate and TBAI. Our highly chemoselective reactions generate the corresponding thiocarbonates or thiocarbamates exclusively in moderate to high yields without direct *N*- or *O*-alkylations. Furthermore, our explored methods exhibit substrate versatility, mild reaction conditions, and experimental convenience. These synthetic protocols developed in our laboratories are believed to offer a more general method for the formation of carbon–sulfur bonds, essential to numerous organic syntheses.

Acknowledgements

The authors gratefully acknowledge financial support from the H. Lee Moffitt Cancer Center & Research Institute and the American Cancer Society (Institutional Research Grant #032). The authors also wish to thank Dr. Seok-In Kim for initial efforts on this project.

Table 2.

entry	amine		halide	time	yield
1		(**19**)	BnCl (**20**)	6 h	93%
2		(**21**)	**20**	8 h	82%
3	$BnNH_2$	(**22**)	**20**	4 h	92%
4		(**23**)	**20**	5 h	89%
5		(**24**)	**20**	7 h	84%
6		(**25**)	**20**	5 h	84%
7		(**26**)	**20**	6 h	81%
8		(**27**)	**20**	4 h	97%
9	1-Benzylpiperazine	(**28**)	**20**	3 h	98%
10	4-Benzylpiperidine	(**29**)	**20**	4 h	80%
11	Aniline	(**30**)	**7**	3 h	83%
12	*o*-Nitroaniline	(**31**)	**20**	10 h	65%
13	2-Aminopyridine	(**32**)	**20**	7 h	72%



Scheme 3.

References

1. For reviews on thiocarbonate formation, see: (a) Rao, S. R. *Xanthates and Related Compounds*; Marcel Dekker: New York, 1971; (b) Yokoyama, M.; Immamoto, T. *Synthesis* **1984**, 797; For thiocarbamate syntheses, see: (c) Walter, W.; Bode, K.-D. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 281.
2. (a) Raichle, K.; Rossing, L.; Zorn, H. *Ger. Pat.* 840239, 1952 (Badische Anilin- & Soda-Fabrik); *Chem. Abstr.* **1953**, *47*, 1732; (b) American Cyanamid Co. *Br. Pat.* 700334, 1953; *Chem. Abstr.* **1955**, *49*, 2492.
3. (a) Alexander, B. H.; Gertler, S. I.; Oda, T. A.; Bown, R. T.; Ihndris, R. W.; Beroza, M. *J. Org. Chem.* **1960**, *25*, 626; (b) Thorn, G. D.; Ludwig, R. A. *The Dithiocarbamates and Related Compounds*; Elsevier: Amsterdam, 1962.
4. Nice, H. R. *Org. React.* **1962**, *12*, 57 and references cited therein.
5. Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; Wiley-Interscience: New York, 1999; pp. 484–486.
6. For a comprehensive overview using the thiocarbonyl functionality as an intermediate in organic syntheses, see:

Dunn, A. D.; Rudorf, W.-D. *Carbon Disulphide in Organic Chemistry*; Ellis Horwood: Chichester, UK, 1989; pp. 226–367.
7. (a) Lee, A. W. M.; Chan, W. H.; Wong, H. C.; Wong, M. S. *Synth. Commun.* **1989**, *19*, 547; (b) Degani, I.; Fochi, R. *Synthesis* **1978**, 365.
8. Burke, Jr., T. R.; Bajwa, B. S.; Jacobson, A. E.; Rice, K. C.; Streaty, R. A.; Klee, W. A. *J. Med. Chem.* **1984**, *27*, 1570.
9. For our cesium-promoted carbonylations, see: (a) Kim, S.-I.; Chu, F.; Dueno, E. E.; Jung, K. W. *J. Org. Chem.* **1999**, *64*, 4578; (b) Chu, F.; Dueno, E. E.; Jung, K. W. *Tetrahedron Lett.* **1999**, *40*, 1847; For our cesium-promoted carbamations, see: (c) Salvatore, R. N.; Shin, S. I.; Nagle, A. S.; Jung, K. W. *J. Org. Chem.* **2001**, *66*, 1035.
10. For our solid-phase carbonylation and carbamation protocols, see: Salvatore, R. N.; Flanders, V. L.; Ha, D.; Jung, K. W. *Org. Lett.* **2000**, *2*, 2797.