J. Braz. Chem. Soc., Vol. 21, No. 11, 2088-2092, 2010.
Printed in Brazil - ©2010 Sociedade Brasileira de Química
0103 - 5053 $6.00+0.00

Article

PhSeBr-Catalyzed Selective Addition of Thiols to α,β-Unsaturated Carbonyl Compounds: Regioselective Synthesis of Thioacetals *vs*. β-Mercapto Ketones

Caroline C. Schneider,[a] Flávia Manarin,[a] Rodrigo B. Panatieri,[b] Olga S. R. Barros[c] and Gilson Zeni*,[a]

[a]*Laboratório de Síntese, Reatividade, Avaliação Farmacológica e Toxicidade de Organocalcogênios, CCNE, UFSM, 97105-900 Santa Maria-RS, Brazil*

[b]*Universidade Federal de Uberlândia, Faculdade de Ciências Integradas do Pontal-Ituiutaba, 38302-000 Ituiutaba-MG, Brazil*

[c]*Instituto de Química, Universidade Federal de Góias, 74001-970 Goiania-GO, Brazil*

Apresentamos aqui nossos resultados da adição de tióis, catalisada por PhSeBr, a compostos carbonílicos α,β-insaturados sob condições brandas para obter regiosseletivamente β-mercapto cetonas ou tioacetais com altos rendimentos e seletividade. A reação foi principalmente controlada pela temperatura, na qual os produtos de adição 1,4 foram obtidos à temperatura de –20 °C. Inversamente quando a reação foi realizada sob refluxo, tioacetais foram obtidos como único produto. O método admite diversos grupos funcionais, como alquilicos, benzilicos e arilicos com substituintes neutros, deficientes e ricos em elétrons no anel aromático.

We present herein results on the PhSeBr-catalyzed addition of thiols to α,β-unsaturated carbonyl compounds under mild conditions to afford regioselectivily β-mercapto ketones or thioacetals in high yields and selectivity. The reaction was highly controlled by the temperature in which, the 1,4-addition products were obtained when the temperature was –20 °C, conversely when the reaction was carried out at reflux, the thioacetals were obtained as a sole product. The developed protocol stands a wide range of functional groups, in which alkyl, benzyl and aryl with neutral, electron deficient and electron rich substituents on the aromatic ring.

Keywords: thioacetals, β-mercapto ketones, chalcogenides

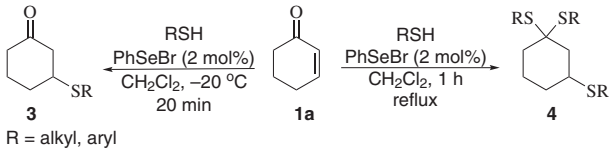
Introduction

Thioacetals are useful intermediates in organic synthesis and are often used as masked carbonyl groups, in particular α-lithiated thioacetals that are synthetic equivalents of carbonyl anions.[1,2] Thioacetals and thioketals are particularly attractive as carbonyl protecting groups in complex molecule synthesis because of their added stability to acidic conditions. In this view, there have been continued improvements in the thioacetal synthesis methods. Usually, these compounds are prepared by protic or Lewis acid-catalyzed condensation of carbonyl compounds with thiols. Lewis acid catalysts such as $ZnCl_2$,[3] $LnCl_3$,[4] $FeCl_3/SiO_2$,[5] $AlCl_3$,[6] $ZrCl_4/SiO_2$[7] $TeCl_4$,[8] $SnCl_2$,[9] $SiCl_4$,[10] $TiCl_4$,[11] BF_3•OEt_2[12] and others methods[13-15] have been used for this purpose. Despite those methods reported in the literature, some problems were found as, difficulties in work-up, isolation, requirement of inert atmosphere, harsh reaction conditions, expensive and stoichiometric reagents, incompatibility with other protecting groups and failure to protect desactivated and hindered substrates. In contrast, none of the reported methods describe the selective catalytic preparation of β-mercapto ketones or thioacetals from α,β-unsaturated carbonyl compounds with thiols, catalyzed by PhSeBr. Therefore, it would be of interest to define a method in order to prepare selectively β-mercapto ketones or thioacetals starting from α,β-unsaturated carbonyl compounds and thiols (Scheme 1).

Results and Discussion

Our initial studies have focused on the development of an optimum set of reaction conditions to obtain β-mercapto ketones in the absence of thioacetals. In

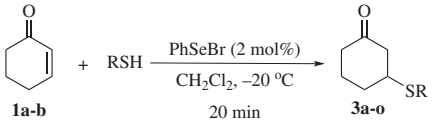
*e-mail: gzeni@pq.cnpq.br



Scheme 1. General scheme.

this way, cyclohex-2-enone **1a** and benzenethiol **2a** were used as standard substrates and the variation in the temperature, time, presence or absence of catalyst were investigated. At first, the reaction was tested under room temperature, using CH_2Cl_2 as solvent in the presence of PhSeBr (2 mol%); thus after 10 min the product of 1,4-addition was obtained in 65% yield. However, under this reaction condition traces of the thioacetal were also obtained. In attempt to avoid the thioacetal by-product and to select the β-mercapto ketones, as a sole product, we carried out the reaction at 0 and –20 °C. At 0 °C a mixture of both β-mercapto ketone and thioacetal was yet obtained, but changing the temperature to –20 °C, after 20 min, the desired product in 79% yield was found with no mixture. Regarding the influence of the catalyst, neither β-mercapto ketones nor thioacetals

Table 1. Addition of thiols in the carbonyl group; synthesis of β-mercapto ketones



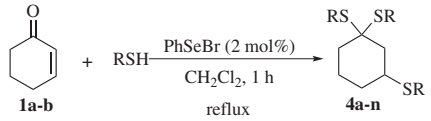
Entry	Ketone	Thiol	Product	Yield (%)
1	**1a**	**2a**	**3a**	79
2	**1a**	**2b**	**3b**	74
3	**1a**	**2c**	**3c**	63
4	**1a**	**2d**	**3d**	74
5	**1a**	$C_{12}H_{25}SH$ **2e**	**3e**	76
6	**1a**	**2f**	**3f**	61
7	**1a**	**2g**	**3g**	95
8	**1a**	**2h**	**3h**	75
9	**1a**	**2i**	**3i**	84
10	**1a**	**2j**	no product	N.R.
11	**1a**	**2k**	**3k**	71
12	**1b**	**2i**	**3l**	78
13	**1b**	**2a**	**3m**	62
14	**1b**	**2k**	**3n**	56
15	**1b**	**2g**	**3o**	50

N.R.: no reaction.

were obtained when the reactions was carried out in the absence of PhSeBr. Thus, the analysis of the optimized reaction conditions demonstrated that the optimal ones for this procedure were the addition of cyclohex-2-enone **1a** (1 mmol), benzenethiol **2a** (1.1 mmol), PhSeBr (2 mol%) and CH_2Cl_2 (1 mL) as a solvent. After the addition, the reaction was stirred for 20 min at –20 °C and the product **3a** was obtained in 79% yield. These reactions conditions were systematically applied to other substrates to demonstrate the efficiency of this method, and the results are summarized in Table 1.

Inspections of Table 1 show that in general, all of the reactions proceeded smoothly with good yields. Most importantly, the addition turned out to be general with respect to a diverse array of functional thiol sources. Our experiments showed that the reaction with thiols having aryl and aryl substituted, was sensitive to the electronic nature of functional groups present in the aromatic ring. Electron donating group such as metoxy gave the conjugated addition product in high yield 95%, in contrast to this, electron withdrawing group decrease the yield (Table 1, entries 7, 8 and 11). We also observed that hindered and non-hindered alkyl thiols gave the desired products in good yields (Table 1; entries 2, 4 and 6). As shown in Table 1, bulky carbonyl ketone afforded the 1,4-addition product in moderated yields (Table 1, entries 13-15). A limitation

Table 2. Addition of thiols in the carbonyl group; synthesis of thioacetals Aqui corrigir só o 1 h



1a-b **4a-n**

Entry	ketone	Thiol	Product	Yield (%)
1	**1a**	**2a**	**4a**	81
2	**1a**	**2b**	**4b**	83
3	**1a**	**2c**	**4c**	95
4	**1a**	**2d**	**4d**	N.R.
5	**1a**	$C_{12}H_{25}SH$ **2e**	**4e**	88
6	**1a**	**2f**	**4f**	60
7	**1a**	**2g**	**4g**	86
8	**1a**	**2i**	**4h**	82
9	**1a**	**2j**	no product **4i**	N.R.
10	**1a**	**2k**	**4j**	N.R.
11	**1b**	**2i**	**4k**	76
12	**1b**	**2c**	**4l**	89
13	**1b**	**2g**	**4m**	92
14	**1b**	**2b**	**4n**	78

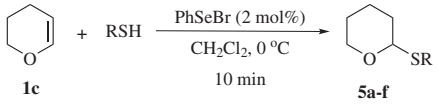
N.R.: no reaction.

in this methodology was observed when oxazolethiol derivative **2j** was used as thiol source. In this case no product was obtained, even under long reaction time, probably due to steric effects.

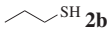
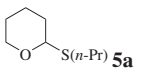
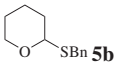
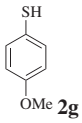
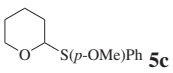
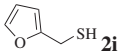
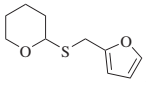
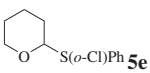
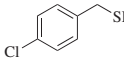
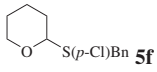
It was gratifying to discover the use of cyclohex-2-enone **1a** and benzenethiol **2a** as standard substrates and the simply changing in the temperature from -20 °C to reflux, in the procedure described to obtaine β-mercapto ketones **3**, had a dramatic effect. Thus, the reaction of cyclohex-2-enone **1a** (1 mmol), benzenethiol **2a** (4.0 equiv.) with PhSeBr (2 mol%) in CH_2Cl_2 (1 mL) at reflux, gave thioacetal **4a** as the sole product in 85% yield. Using the optimized reaction conditions, a wide variety of thiols containing useful functional groups can be successfully used as substrate (Table 2). The results revealed that the aryl, alkyl and benzyl thiols, gave the product efficiently under these conditions. The exception was the bulky thiols **2d**, **2J** and **2k**, which did not gave the desired product, even changing the reaction conditions.

The fact that the protection of thiols has found widespread applications in the organic transformations[16] associated with the simple preparation, low cost and easy handling of PhSeBr, prompted us to study its application on the thiol reaction with dihydropyrane. Thus, the standard reaction condition applied to prepare the β-mercapto ketones **3** was also tested for the reaction of thiols and dihydropyrane. In this way, the reaction of dihydropyrane **1c** (1 mmol), benzenethiol **2a** (1.1 mmol), PhSeBr (2 mol%) and CH_2Cl_2 (1 mL) as a solvent, at 0 °C for 10 min gave THP thioether in 75% yield. The scope and limitations of this protection are summarized in Table 3.

Table 3 Addition of thiols in dihydropyrane; synthesis of thioethers



1c **5a-f**

Entry	Thiol	Produt	Yield (%)
1	 **2b**	 **5a**	75
2	**2c**	 **5b**	91
3	 **2g**	 **5c**	87
4	 **2i**	 **5d**	61
5	 **2k**	 **5e**	85
6	 **2f**	 **5f**	90

The results showed that the reaction is not sensitive to the electronic effect at aromatic ring in the thiol. For example, both arylthiol bearing electron-donating (OMe) and electron-withdrawing (Cl) group gave the product in good yields. Differentiation in the reactivity between chlorine and sulfur atoms of thiol can also be seen by the reaction of thiols **2k** and **2f** to provide only the THP thioether products in 85 and 90% yields, respectively, without any side-product observed. In this case, the chlorine substituent was not affected.

Conclusions

We described herein an efficient method for PhSeBr-mediated addition of thiols to α,β-unsaturated carbonyl compounds providing a versatile and regioselective synthesis of 1,4-addition products or thioacetals. The reaction was highly controlled by the temperature in which, the 1,4-addition products were obtained when the temperature was –20 °C; conversely when the reaction was carried out at reflux thioacetals were obtained as a sole product. With this protocol, we were also able to prepare THP thioethers under mild conditions in fair to excellent yields demonstrating the versatility of the PhSeBr in this catalytic system. The advantages of this method include, the use of cheap, easy and handle catalyst, non anhydrous reaction conditions, non aqueous work-up and ease of product isolation, besides short reaction times and high yields. This reaction associated with the ease in which the protect group can be removed from thiol, can contribute to an interesting alternative route for preparation of more functionalized organothiols.

Supplementary Information

Experimental details and spectra are available free of charge at http://jbcs.sbq.org.br, as PDF file.

Acknowledgments

We are grateful to Conselho Nacional de Desenvolvimento Científico e Tecnológico, Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (SAUX) and Fundação de Amparo à Pesquisa do Estado do Rio Grande do Sul, for the fellowships and financial support (PRONEX-10-0005-1).

References

1. Greene, T. W.; Wuts, P. G. M.; *Protecting Groups in Organic Synthesis*, 3rd ed.; John Wiley & Sons: New York, 1999, pp. 297-348.
2. Cordes, E. H.; Bull, H. G.; *Chem. Re*v. **1974**, *74*, 581.
3. Truce, W. E.; Roberts, F. E.; *J. Org. Chem.* **1963**, *28*, 961.
4. Garlaschelli, L.; Vidari, G.; *Tetrahedron Lett*. **1990**, *31*, 5815.
5. Patney, H. K.; *Tetrahedron Lett*. **1991**, *32*, 2259.
6. Ong, B. S.; *Tetrahedron Lett*. **1980**, *21*, 4225.
7. Patney, H. K.; Margan, S.; *Tetrahedron Lett*. **1996**, *37*, 4621.
8. Tani, H.; Masumoto, K.; Inamasu, T.; *Tetrahedron Lett*. **1991**, *32*, 2039.
9. Das, N. B.; Nayak, A.; Sharma, R. P.; *J. Chem. Res. (S)* **1993**, 242.
10. Ku, B.; Oh, D. Y.; *Synth. Commun*. **1989**, *19*, 433.
11. Kumar, V.; Dev, S.; *Tetrahedron Lett*. **1983**, *24*, 1289.
12. Fieser, L. F.; *J. Am. Chem. Soc*. **1954**, *76*, 1945.
13. Khurana, J. M.; Agrawal, A.; Kumar, S.; *J. Braz. Chem. Soc*. **2009**, *20*, 1256.
14. Lenardão, E. J.; Trecha, D. O.; Ferreira, P. C.; Jacob, R. G.; Perin, G.; *J. Braz. Chem. Soc.* **2009**, *20*, 93.
15. Almeida, Q. A. R.; Pereira, M. L. D. O.; Coelho, R. B.; *J. Braz. Chem. Soc*. **2008**, *19*, 894
16. Masaki, Y.; Tanaka, N.; Miura, T.; *Tetrahedron Lett.* **1998**, *39*, 5799.
17. *General procedure for β-mercapto ketones formation:* To a Schlenck tube, under air atmosphere containing an appropriate α,β-unsaturated carbonyl compound (0.50 mmol) in CH_2Cl_2 (2.0 mL), was added the thiol (0.6 mmol). In the resulting solution was added PhSeBr (2 mol%) and the reaction mixture was allowed to stir for 20 min at –20 °C. After that, the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. *3-(Phenylthio)cyclohexanone (**3a**):* Yield 0.162 g (79%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.43-7.40 (m, 2H), 7.33-7.25 (m, 3H), 3.46-3.37 (m, 1H), 2.68 (d, *J* 9.7 Hz, 1H), 2.40-2.25 (m, 3H), 2.17-2.08 (m, 2H), 1.80-1.63 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 208.63, 133.09, 132.88, 128.95, 127.66, 47.63, 45.98, 40.75, 31.09, 23.90. HRMS calc. for $C_{12}H_{24}OS$: 206.0765. Found: 206.0769.
18. *General procedure for thioacetals formation:* To a Schlenck tube, under air atmosphere containing an appropriate α,β-unsaturated carbonyl compounds (0.50 mmol) in CH_2Cl_2 (2.0 mL), was added the thiol (2.0 mmol). In the resulting solution was added PhSeBr (2 mol%) and the reaction mixture was allowed to stir for 1 h under reflux. After that, the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. *1,1,3-tris(Phenylthio)cyclohexane (**4a**):* Yield 0.330 g (81%). ^{1}H NMR ($CDCl_3$, 200 MHz), δ: 7.70-7.65 (m, 2H), 7.54-7.50 (m, 2H), 7.35-7.20 (m, 11H), 3.56 (tt, *J* 12.0/3.5 Hz, 1H), 2.28-2.19 (m, 1H), 2.03-1.75 (m, 3H), 1.69-1.50 (m, 3H), 1.16-0.94 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 137.33, 136.11, 133.67, 132.63, 130.90, 130.72, 129.16, 128.96, 128.77, 128.61, 128.55, 127.08, 65.05, 43.37, 42.73, 36.12, 32.15, 22.66. HRMS calc. for $C_{24}H_{24}S_3$: 408.1040. Found: 408.1043.
19. *General procedure for thioethers formation*: To a Schlenck tube, under air atmosphere containing an appropriate dihydropyrane (0.50 mmol) in CH_2Cl_2 (2.0 mL), was added the thiol (0.6 mmol). In the resulting solution was added PhSeBr (2 mol%) and the reaction mixture was allowed to stir for 20 min at 0 °C. After this, the mixture was concentrated under vacuum. The residue was purified by flash chromatography on silica gel using ethyl acetate/hexane as the eluent. *2-(Propylthio)-tetrahydro-2H-pyran (**5a**)***:*** Yield 0.120 g (75%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.16-3.71 (m, 2H), 3.53-3.36 (m, 1H), 2.72-2.49 (m, 2H), 1.92-1.51 (m, 8H), 0.99 (t, *J* 7.20 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 98.80, 67.26, 62.26, 51.81, 35.98, 29.21, 25.44, 19.59. HRMS calc. for $C_8H_{16}OS$: 160.0921. Found: 160.0918.

Submitted: March 30, 2010
Published online: July 8, 2010