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Non-phosgene synthesis of benzyl chloroformate (CbzCl)

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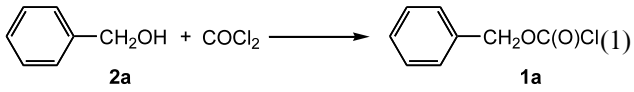
Abstract—A novel synthetic method for benzyl chloroformate (CbzCl) using carbon monoxide or carbonyl sulfide as a carbonyl source was established. Benzyl chloroformate was successfully synthesized by the chlorination using sulfuryl chloride of *S*-methyl *O*-benzyl carbonothioate, which was prepared by the carbonylation of benzyl alcohol with carbon monoxide and sulfur (or carbonyl sulfide) in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) followed by esterification using methyl iodide.

Benzyl chloroformate (CbzCl) (**1a**) was introduced by Bergmann and Zervas about 70 years ago for a *N*-protective reagent for amino group in peptide synthesis.[1] Benzyl chloroformate (**1a**) smoothly reacts with an amino group of amino acids in aqueous solution under weak basic conditions, and the *N*-protective Cbz group can be removed either by hydrogenolysis or by treatment with hydrogen bromide in acetic acid.[2–4] The reagent (**1a**) still affords the widely useful means of *N*-protection in peptide synthesis,[5–7] isolation of amines,[8,9] and *N*-protection of uracils.[10]

In spite of the remarkable importance of benzyl chloroformate (**1a**), the synthetic methods for **1a** are limited to using toxic phosgene as a raw material. The reaction of benzyl alcohol with phosgene only remains the practical synthetic process for benzyl chloroformate (**1a**) (Eq. (1)).[1,5,6] Therefore, in our strategy, we explored a new and efficient non-phosgene route to benzyl chloroformate synthesis.



(1)

Herein, we wish to report a facile synthesis of benzyl chloroformates (**1**) using carbon monoxide or carbonyl sulfide as a carbonyl source.

Our breakthrough for a novel synthesis of benzyl chloroformate (**1a**) is based on the combination of the carbonylation of benzyl alcohol (**2a**) with carbon monoxide and sulfur or carbonyl sulfide in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene), and the chlorination of formed *S*-methyl *O*-benzyl carbonothioate (**3a**) using sulfuryl chloride.

At the outset, our trial showed a successful result of the sulfur-assisted carbonylation of benzyl alcohol (**2a**) with carbon monoxide. Benzyl alcohol (**2a**) easily reacted with carbon monoxide and sulfur at 1.0 MPa, 80°C for 6 h in the presence of DBU in THF. The resulting carbonothioate salt in THF solution was esterified by methyl iodide under an ambient pressure, at 20°C for 16 h. Finally, *S*-methyl *O*-benzyl carbonothioate (**3a**) was given in 89% yield (Eq. (2)).[11]

The present carbonylation reaction was performed under milder conditions (1.0 MPa) and using a less amount of sulfur (1.5 equiv.) and DBU (1.5 equiv.), compared with those of our previous report[12] for the synthesis of carbonothioate (**3**) by the sulfur-assisted carbonylation with carbon monoxide (3.0 MPa, 3.0 and 5.0 equiv., respectively). Furthermore, the use of other bases in place of DBU gave the poor results (DBN (1,5-diazabicyclo[4.3.0]non-5-ene): 14%, Et_3N: 3%, K_2CO_3: 0%, none: 0%).

Several *S*-methyl *O*-benzyl carbonothioates (**3a–d**) were synthesized similarly in excellent yields from the corresponding benzyl alcohols (**2a–d**) substituted by halogen groups or methoxy group.

Keywords: benzyl chloroformate; carbobenzoxy chloride; carbon monoxide; sulfur; carbonyl sulfide; carbonylation.
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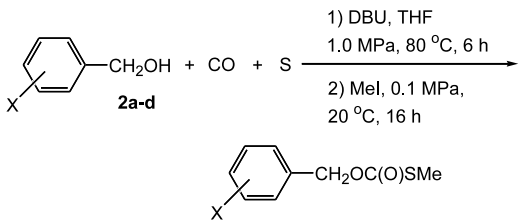
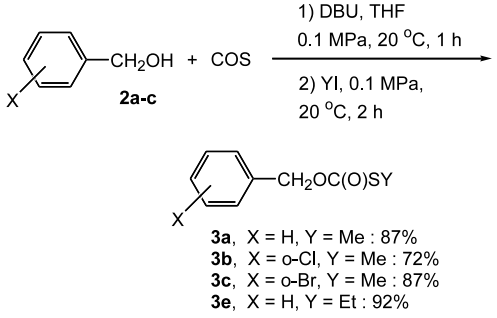


(2)

3a, X = H : 89%, 85%[a]
3b, X = o-Cl : 88%
3c, X = o-Br : 98%
3d, X = p-MeO : 92%
[a]Toluene was used as a solvent.

Also, carbonyl sulfide[13] played the role of an effective reagent for this carbonylation reaction. The carbonylation of benzyl alcohol (**2a**) with carbonyl sulfide occurred under an ambient pressure, at 20°C for 1 h in the presence of DBU in THF. The formed carbonothioate salt was quenched by methyl iodide at 0°C, and the resulting mixture was stirred under an ambient pressure, at 20°C for additional 2 h, to provide *S*-methyl *O*-benzyl carbonothioate (**3a**) in 87% yield (Eq. (3)).[17]



(3)

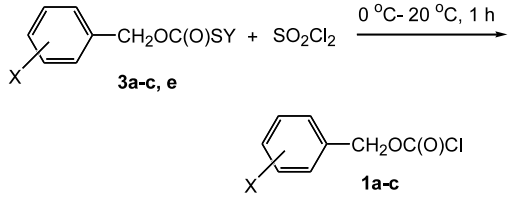
3a, X = H, Y = Me : 87%
3b, X = o-Cl, Y = Me : 72%
3c, X = o-Br, Y = Me : 87%
3e, X = H, Y = Et : 92%

Several *S*-alkyl *O*-benzyl carbonothioates (**3a**–**c**,**e**) were prepared by the carbonylation of benzyl alcohols (**2a**–**c**) with carbonyl sulfide in good yields. In this carbonylation using carbonyl sulfide, DBU similarly worked as an excellent base to give *S*-methyl *O*-benzyl carbonothioate (**3a**) in good yield (87%). However, other bases (Et_3N or K_2CO_3) were not effective for this carbonylation, and the product (**3a**) was not formed at all.

Next, the chlorination of *S*-methyl *O*-benzyl carbonothioate (**3a**) by sulfuryl chloride was successfully performed under mild conditions. The slow addition of sulfuryl chloride to *S*-methyl *O*-benzyl carbonothioate (**3a**) at 0°C and vigorous stirring at 20°C for 1 h gave benzyl chloroformate (CbzCl) (**1a**) in quantitative yield as an almost pure form (Eq. (4)).[18] Further purification by vacuum distillation afforded **1a** in 72% yield, accompanied with a partial decomposition.[20] However, thionyl chloride ($SOCl_2$) which works for the preparation of acid chlorides, did not give **1a** under the same reaction conditions.

Several benzyl chloroformates (**1a**–**c**) were satisfactorily provided in excellent yields from the corresponding *S*-methyl *O*-benzyl carbonothioate (**3a**–**c**,**e**) with sulfuryl chloride under very mild reaction conditions.

The chlorination of carbonothioates (**3**) by sulfuryl chloride was reported in the literature. However, these results are only limited to the reaction of acyloxymethyl carbonothioates with sulfuryl chloride,[22] or the use of high temperature reaction conditions which is not applicable to the present chlorination.[23]



(4)

1a from **3a**, X = H, Y = Me : 100%, 72%[a]
1a from **3e**, X = H, Y = Et : 81%[a]
1b, X = o-Cl, Y = Me : 100%
1c, X = o-Br, Y = Me : 100%
[a]Purified by vacuum distillation.

In conclusion, a useful and efficient synthetic method which is a non-phosgene route for benzyl chloroformate (**1a**) was developed, in which CbzCl (**1a**) was synthesized by the carbonylation of benzyl alcohol (**2a**) with carbon monoxide using elemental sulfur or carbonyl sulfide and the esterification using methyl iodide, followed by the chlorination with sulfuryl chloride.

From the viewpoint of application to actual industrial production of benzyl chloroformate (**1a**) as an *N*-protective reagent for amino groups in peptide synthesis, the present method for synthesis of CbzCl (**1a**) in the absence of phosgene is very significant, in terms of the use of easily available carbon monoxide or carbonyl sulfide as carbonyl source, and industrially acceptable reaction conditions.

References

1. Bergmann, M.; Zervas, L. *Ber*. **1932**, *65*, 1192–1201.
2. Ben-Ishai, D.; Berger, A. *J. Org. Chem*. **1952**, *17*, 1564–1570.
3. Boissonnas, R. A.; Preitner, G. *Helv. Chim. Acta* **1953**, *36*, 875–886.
4. Sokolovsky, M.; Wilchek, M.; Patchornik, A. *J. Am. Chem. Soc*. **1964**, *86*, 1202–1206.
5. Carter, H. E.; Frank, R. L.; Johnston, H. W. *Org. Syn., Coll*. **1955**, *3*, 167–169.
6. Farthing, A. C. *J. Chem. Soc*. **1950**, 3213–3217.
7. Schumann, I.; Boissonnas, R. A. *Helv. Chim. Acta* **1952**, *35*, 2237–2241.
8. Greig, C. G.; Leaback, D. H.; Walker, P. G. *J. Chem. Soc*. **1961**, 879–883.
9. Dutcher, J. D.; Walters, D. R.; Wintersteiner, O. *J. Org. Chem*. **1963**, *28*, 995–999.
10. Nagase, T.; Seike, K.; Shiraishi, K.; Yamada, Y.; Ozaki, S. *Chem. Lett*. **1988**, 1381–1384.
11. Typical procedure for the synthesis of *S*-methyl *O*-benzyl carbonothioate (**3a**) from carbon monoxide and sulfur is as follows. In a 100 mL stainless steel autoclave, benzyl

alcohol (**2a**) (1.03 mL, 10 mmol), powdered sulfur (481 mg, 15 mmol), DBU (2.24 mL, 15 mmol), and THF (10 mL) were placed with a magnetic stirring bar under an argon atmosphere. The autoclave was then flushed three times with carbon monoxide and finally charged with carbon monoxide at 1.0 MPa at 20°C. The reaction was carried out at 80°C for 6 h with vigorous stirring. After cooling down and evacuation of carbon monoxide, methyl iodide (0.93 mL, 15 mmol) was added at 0°C under an argon atmosphere. The reaction mixture was stirred for an additional 16 h under ambient pressure, at 20°C. Then, the resulting mixture was poured into 1N HCl (100 mL) and extracted with *t*-butyl methyl ether (100 mL, 3×50 mL). After evaporation of solvents and purification by short-column chromatography (silica gel, toluene:AcOEt = 1:1), *S*-methyl *O*-benzyl carbonothioate (**3a**) was afforded in an 89% yield (1.62 g). *S*-Methyl *O*-benzyl carbonothioate (**3a**): IR (neat) 1710, 1135 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 3H), 5.24 (s, 2H), 7.36 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 68.9, 128.3, 128.4, 128.5, 135.2, 171.6; MS (*m*/*z*, %) 182 (M^+, 69), 92 (48), 91 (100), 77 (27), 65 (36); exact MS calcd for $C_9H_{10}O_2S$: 182.0402. Found: 182.0368.

12. Mizuno, T.; Nishiguchi, I.; Hirashima, T.; Ogawa, A.; Kambe, N.; Sonoda, N. *Tetrahedron Lett*. **1988**, *37*, 4767–4768.
13. Carbonyl sulfide is a useful synthetic agent for the introduction of the thiocarbonyl functionality into various organic molecules.[14] Generally, carbonyl sulfide is produced from carbon monoxide and sulfur at high temperature.[15] We also developed the carbonyl sulfide synthesis using carbon monoxide with sulfur in the presence of selenium catalyst under mild conditions.[16]
14. Mori, K.; Shimizu, M.; Kanazawa, T. *J. Syn. Org. Chem. Jpn*. **1971**, *29*, 609–615.
15. Nakayama, Y.; Sano, H.; Okamura, S.; Hirao, K. Japanese Patent 131993, 1977. *Chem. Abstr*. **1978**, *88*, 63801.
16. Mizuno, T.; Nishiguchi, I.; Hirashima, T.; Sonoda, N. *Heteroatom Chem*. **1990**, *1*, 157–159.
17. Typical procedure for the synthesis of *S*-methyl *O*-benzyl carbonothioate (**3a**) by the carbonylation with carbonyl sulfide is as follows. A THF solution (50 mL) containing benzyl alcohol (**2a**) (10.3 mL, 100 mmol) and DBU (22.4 mL, 150 mmol) was vigorously stirred under carbonyl sulfide (0.1 MPa) at 20°C for 1 h. Into the THF solution of carbonothioate salt, methyl iodide (7.5 mL, 120 mmol) was added slowly at 0°C under an argon atmosphere. The reaction mixture was stirred for an additional 2 h at 20°C. The resulting mixture was then poured into 1N HCl (100 mL) and extracted with *t*-butyl methyl ether (3×100 mL). After evaporation of solvents and purification by vaccum distillation, *S*-methyl *O*-benzyl carbonothioate (**3a**) was obtained in an 87% yield (15.76 g).
18. General procedure for the synthesis of benzyl chloroformate (**1a**) by the chlorination of **3a** with sulfuryl chloride is as follows. Into neat *S*-methyl *O*-benzyl carbonothioate (**3a**) (3.64 g, 20 mmol), sulfuryl chloride (2.41 mL, 30 mmol) was added slowly at 0°C under an argon atmosphere. The reaction mixture was stirred for an additional hour at 20°C. After evaporation of volatile compounds (SO_2Cl_2 and MeSCl), benzyl chloroformate (CbzCl) (**1a**) was given in a 100% yield (3.41 g) as an almost pure form. After further purification by vacuum distillation accompanied with a partial decomposition, **1a** was obtained in a 72% yield (2.47 g). Benzyl chloroformate (CbzCl) (**1a**): IR (neat) 1780, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (s, 2H), 7.40 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 73.4, 128.8, 128.9, 129.3, 133.3, 150.6; MS (*m*/*z*, %) 172 (28), 170 (M^+, 80), 91 (100), 90 (35).[19]
19. Identification of benzyl chloroformate (CbzCl) (**1a**) was performed by comparison of the spectra of **1a** with those of commercially available authentic sample.
20. Thermal instability of benzyl chloroformate (**1a**) to decompose into benzyl chloride and carbon dioxide is well known.[21]
21. Merck Index, **1996**, *12*, 1848.
22. Folkmann, M.; Lund, F. J. *Synthesis* **1990**, 1159–1166.
23. Gilligan, W. H.; Stafford, S. L. *Synthesis* **1979**, 600–602.