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Benzyl chloroformate (CbzCl) synthesis using carbon monoxide as a carbonyl source

Takumi Mizuno,[a,*] Junko Takahashi[b] and Akiya Ogawa[b]

[a]*Osaka Municipal Technical Research Institute, 1-6-50, Morinomiya, Joto-ku, Osaka 536-8553, Japan*
[b]*Department of Chemistry, Faculty of Science, Nara Women's University, Kitauoyanishi-machi, Nara 630-8506, Japan*

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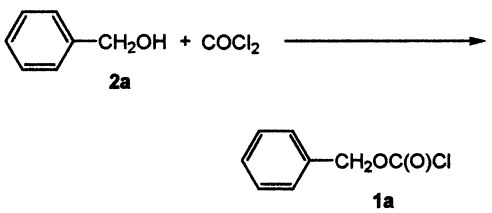
Abstract—A novel non-phosgene synthetic method for benzyl chloroformate (CbzCl) was established. *S*-Methyl *O*-benzyl carbonothioates were prepared by the carbonylation of benzyl alcohols with carbon monoxide and sulfur (or carbonyl sulfide) in the presence of DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) followed by esterification using methyl iodide in good yields. Then, CbzCl derivatives were successfully synthesized by the chlorination of *S*-methyl *O*-benzyl carbonothioates using sulfuryl chloride in excellent yields.

1. Introduction

Benzyl chloroformate (CbzCl) (**1a**) was introduced by Bergmann and Zervas in 1932 for an *N*-protective reagent for amino group in peptide synthesis,[1] as well as di-*tert*-butyl dicarbonate which is a reagent for the preparation of *t*-Boc protected amines. CbzCl (**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 CbzCl (**1a**), the synthetic methods for **1a** are limited to ones using toxic phosgene as a raw material. The reaction of benzyl alcohol with phosgene only remains the practical synthetic process for CbzCl (**1a**) (Eq. (1)).[1,5,6] However, because of high toxicity and legal restriction of phosgene, use of this synthetic method is considerably limited for industrial large-scale production of CbzCl (**1**).



(1)

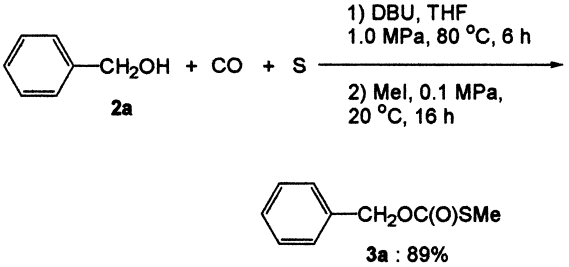
Therefore, in our strategy, we explored a new and efficient non-phosgene route to CbzCl (**1a**) synthesis.[11]

We report here the full results of our investigation on a facile synthesis of CbzCl (**1**) using carbon monoxide or carbonyl sulfide as a carbonyl source, which is much less toxic compared with phosgene.

2. Results and discussion

Our breakthrough for a novel synthesis of CbzCl (**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 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and the chlorination of thus 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)).[12]



(2)

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

* Corresponding author. Tel.: +81-6-6963-8051; fax: +81-6-6963-8049; e-mail: tmizuno@omtri.city.osaka.jp.

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Table 1. Effect of bases on synthesis of **1a**

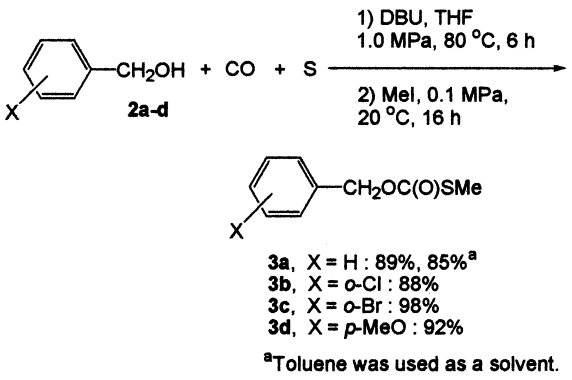
Entry	Base	Yield (%)
1	DBU[a]	89
2	DBN[b]	14
3	K_2CO_3	0
4	Et_3N	0
5	None	0

[a] 1,8-Diazabicyclo[5.4.0]undec-7-ene.
[b] 1,5-Diazabicyclo[4.3.0]non-5-ene.

The effect of bases on this sulfur-assisted carbonylation of benzyl alcohol (**2a**) with carbon monoxide was examined (Table 1). In contrast to the excellent effect of DBU, the use of other bases (DBN (1,5-diazabicyclo[4.3.0]non-5-ene), Et_3N, K_2CO_3, and none) in place of DBU gave the poor results (entries 2–5). Unchanged benzyl alcohol (**2a**) was recovered.

The present carbonylation reaction was performed under milder conditions (1.0 MPa) by using less amount of sulfur (1.5 equiv.) and DBU (1.5 equiv.), compared with those of our previous report[14] for the synthesis of carbonothioate (**3**) by the sulfur-assisted carbonylation with carbon monoxide (3.0 MPa, 3.0 and 5.0 equiv., respectively).

Similarly, several *S*-methyl *O*-benzyl carbonothioates (**3a–d**) were synthesized in excellent yields from the corresponding benzyl alcohols (**2a–d**) substituted by halogen groups or methoxy group at the *ortho*- and *para*-position (Eq. (3)).

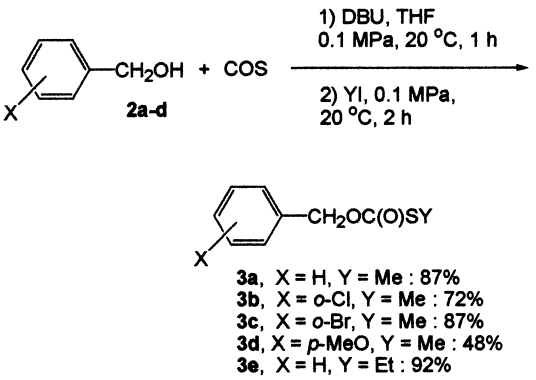


3a, X = H : 89%, 85%[a]
3b, X = *o*-Cl : 88%
3c, X = *o*-Br : 98%
3d, X = *p*-MeO : 92%

[a]Toluene was used as a solvent. (3)

Also, carbonyl sulfide played the role of an effective reagent for this carbonylation reaction.[15] 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. 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. (4)).

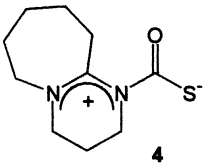
Several *S*-alkyl *O*-benzyl carbonothioates (**3a–c**, **e**) were prepared by the carbonylation of benzyl alcohols (**2a–c**) substituted by halogen groups with carbonyl sulfide in good yields. However, substitution of methoxy group led to the formation of **3d** in moderate yield, and *p*-methoxybenzyl alcohol (**2d**) was also recovered.



3a, X = H, Y = Me : 87%
3b, X = *o*-Cl, Y = Me : 72%
3c, X = *o*-Br, Y = Me : 87%
3d, X = *p*-MeO, Y = Me : 48%
3e, X = H, Y = Et : 92% (4)

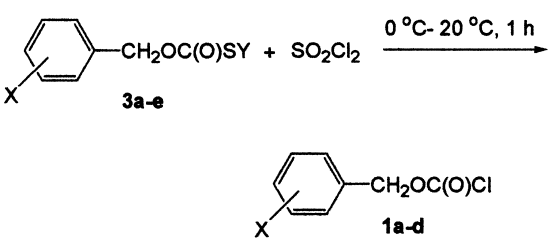
In this carbonylation using carbonyl sulfide, DBU similarly worked as an excellent base to give *S*-methyl *O*-benzyl carbonothioate (**3a**) in good yield (87%). However, other bases (Et_3N or K_2CO_3) were not effective for this carbonylation, and the desired product (**3a**) was not formed at all.

Furthermore, we found that introduction of carbonyl sulfide into the DMF solution of DBU at room temperature, afforded white solid, which was thermally unstable and regenerated carbonyl sulfide on warming to 45°C. This solid which is assumed to be a COS–DBU complex (**4**), is considered to be an active species for the present carbonylation.[18,19]



4

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 CbzCl (**1a**) in quantitative yield in an almost pure form (Eq. (5)). Further purification by vacuum distillation afforded **1a** in 72% yield, accompanied with a partial decomposition.[21] However, thionyl chloride ($SOCl_2$) which works for the preparation of acid chlorides from carboxylic acids, did not give **1a** under the same reaction conditions.



1a
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%
1d, X = *p*-MeO, Y = Me : 0%

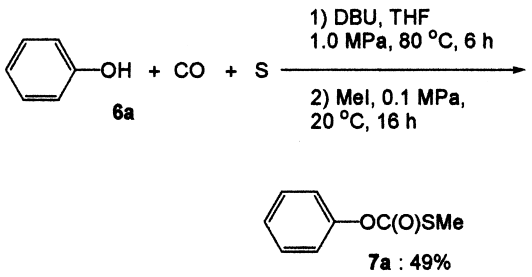
[a]Purified by vacuum distillation. (5)

Several CbzCl derivatives (**1a**–**c**) were satisfactorily provided in excellent yields from the corresponding *S*-methyl *O*-benzyl carbonothioates (**3a**–**c**, **e**) with sulfuryl chloride under mild reaction conditions. However, *p*-methoxybenzyl chloroformate (**1d**) from *S*-methyl *O*-*p*-methoxybenzyl carbonothioate (**3d**) was not obtained under the reaction conditions, because of thermal instability of **1d**.

The chlorination of carbonothioates (**3**) by sulfuryl chloride was reported in the literatures. However, these results are only limited to the reaction of acyloxymethyl carbonothioates with sulfuryl chloride,[23] or the use of high temperature reaction conditions which is not applicable to the present chlorination.[24]

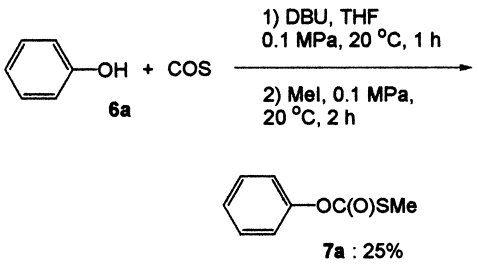
Finally, the synthesis of phenyl chloroformates (**5a**) using carbon monoxide or carbonyl sulfide as a carbonyl source was examined.

Phenol (**6a**) smoothly 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 similar conditions. *S*-Methyl *O*-phenyl carbonothioate (**7a**) was given in moderate yield (Eq. (6)). To the best of our knowledge, this is the first example of sulfur-assisted carbonylation of phenols with carbon monoxide.



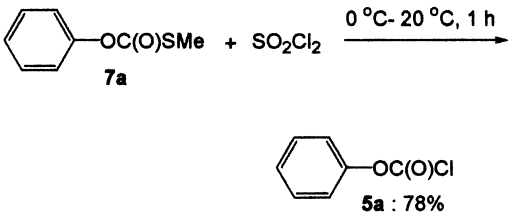
(6)

The carbonylation of phenol (**6a**) with carbonyl sulfide was also examined in the same manners. However, because of low basicity of phenol (**6a**), *S*-methyl *O*-phenyl carbonothioate (**7a**) was afforded in low yield (Eq. (7)).



(7)

Then, the chlorination of *S*-methyl *O*-phenyl carbonothioate (**7a**) by sulfuryl chloride successfully occurred under mild conditions. Purification by vacuum distillation afforded phenyl chloroformates (**5a**) in 78% yield (Eq. 8).



(8)

Fig. 1 shows a plausible pathway for the formation of CbzCl (**1a**) from benzyl alcohol (**2a**) by the sulfur-assisted carbonylation and the chlorination by sulfuryl chloride.

At first, carbonyl sulfide is formed in situ from carbon monoxide and sulfur in the presence of DBU. The carbonylation of **2a** with carbonyl sulfide generates a DBU salt of carbonothioate (**8a**) in the presence of DBU. Then, esterification with methyl iodide of **8a** gives *S*-methyl *O*-benzyl carbonothioate (**3a**). Finally, chlorination of *S*-methyl *O*-benzyl carbonothioate (**3a**) with sulfuryl chloride affords CbzCl (**1a**) as a final product.

3. Conclusion

A useful and efficient synthetic method which is a non-phosgene route to CbzCl (**1a**) was developed, in which CbzCl (**1a**) was synthesized by the carbonylation of benzyl alcohol (**2a**) with carbon monoxide and elemental sulfur

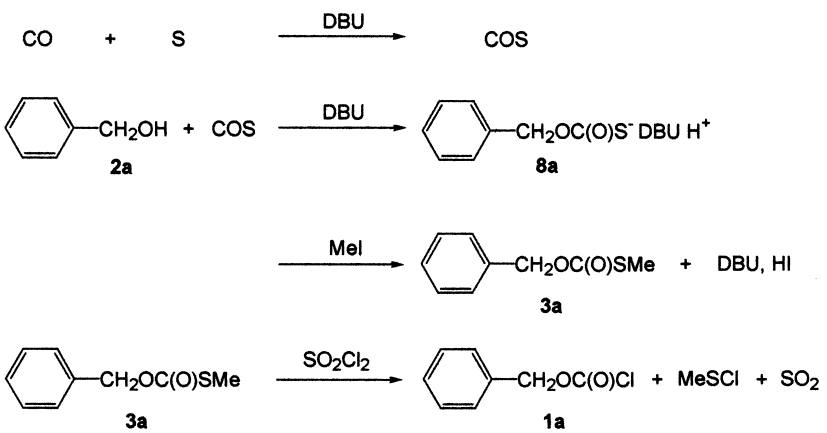


Figure. 1. A plausible reaction pathway.

(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 CbzCl (**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.

4. Experimental

4.1. General

FT-IR spectra were recorded on a Nicolet Magna-IR 550 instrument. ^{1}H and ^{13}C NMR spectra were obtained on a JEOL JNM-AL300 (300 MHz, 75 MHz) instrument. Chemical shifts were reported in ppm relative to tetramethylsilane (δ-units). Mass and exact mass spectra were recorded on a JEOL JMS-600 spectrometer. Benzyl alcohols (**2a**–**d**), phenol (**5a**), methyl iodide, ethyl iodide, THF, DBU, bases, sulfur (99.5%), carbon monoxide (99.9%), carbonyl sulfide (96%), and sulfuryl chloride were used as purchased.

4.1.1. Typical procedure for the synthesis of *S*-methyl *O*-benzyl carbonothioate (3a) from carbon monoxide and sulfur. 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 argon atmosphere. The reaction mixture was stirred for 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, 50 mL×3). 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 89% yield (1.62 g). *S*-Methyl *O*-benzyl carbonothioate (**3a**):[25] IR (neat) 1710, 1135 cm^{-1}; ^{1}H 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, 128.4, 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.

4.1.2. *S*-Methyl *O*-*o*-chlorobenzyl carbonothioate (3b). IR (neat) 1715, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 5.36 (s, 2H), 7.26–7.30 (m, 2H), 7.37–7.43 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 66.0, 126.9, 129.5, 129.7, 129.8, 133.0, 133.6, 171.4; MS (*m*/*z*, %) 218 (5), 216 (M$^+$, 13), 127 (36), 125 (100). Exact MS calcd for $C_9H_9O_2ClS$: 216.0012. Found: 216.0002.

4.1.3. *S*-Methyl *O*-*o*-bromobenzyl carbonothioate (3c). IR (neat) 1715, 1140 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.37 (s, 3H), 5.34 (s, 2H), 7.17–7.42 (m, 3H), 7.56–7.59 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ13.5, 68.2, 123.3, 127.5, 129.9, 129.9, 132.8, 134.7, 171.4; MS (*m*/*z*, %) 262 (1), 260 (M$^+$, 1), 181 (61), 171 (97), 169 (100), 90 (14), 89 (9). Exact MS calcd for $C_9H_9O_2BrS$: 259.9507. Found: 259.9515.

4.1.4. *S*-Methyl *O*-*p*-methoxybenzyl carbonothioate (3d). IR (neat) 1710, 1135 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.81 (s, 3H), 5.18 (s, 2H), 6.89 (d, *J*=9 Hz, 2H), 7.30 (d, *J*=9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 55.3, 68.9, 114.0, 127.4, 130.3, 159.9, 171.6; MS (*m*/*z*, %) 212 (M$^+$, 28), 168 (6), 122 (9), 121 (100), 77 (5). Exact MS calcd for $C_{10}H_{12}O_3S$: 212.0507. Found: 212.0469.

4.1.5. *S*-Methyl *O*-phenyl carbonothioate (7a). IR (neat) 1730, 1110 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (s, 3H), 7.15 (d, *J*=8 Hz, 2H), 7.24 (t, *J*=8 Hz, 1H), 7.38 (t, *J*=8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.6, 121.2, 126.1, 129.4, 151.2, 170.7; MS (*m*/*z*, %) 168 (M$^+$, 27), 140 (100), 75 (92). Exact MS calcd for $C_8H_8O_2S$: 168.0245. Found: 168.0210.

4.2. Typical procedure for the synthesis of *S*-methyl *O*-benzyl carbonothioate (3a) by the carbonylation with carbonyl sulfide

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 argon atmosphere. The reaction mixture was stirred for additional 2 h at 20°C. The resulting mixture was then poured into 1N HCl (100 mL), and extracted with *t*-butyl methyl ether (100 mL×3). After evaporation of solvents and purification by vacuum distillation, *S*-methyl *O*-benzyl carbonothioate (**3a**) was obtained in 87% yield (15.76 g).

4.2.1. *S*-Ethyl *O*-benzyl carbonothioate (3e). IR (neat) 1710, 1135 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.32 (t, *J*=7 Hz, 3H), 2.88 (q, *J*=7 Hz, 2H), 5.24 (s, 2H), 7.35 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.9, 25.4, 68.7, 128.3, 128.4, 128.6, 135.3, 171.1; MS (*m*/*z*, %) 196 (M$^+$, 23), 92 (17), 91 (100), 77 (7), 65 (9). Exact MS calcd for $C_{10}H_{12}O_2S$: 196.0558. Found: 196.0548.

4.2.2. General procedure for the synthesis of CbzCl (1a) by the chlorination of 3a with sulfuryl chloride. 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 argon atmosphere. The reaction mixture was stirred for additional 1 h at 20°C. After evaporation of volatile compounds (SO_2Cl_2 and MeSCl), CbzCl (**1a**) was given in 100% yield (3.41 g) in an almost pure form. After further purification by vacuum distillation accompanied with a partial decomposition, **1a** was obtained in 72% yield (2.47 g). CbzCl (**1a**): IR (neat) 1780, 1145 cm^{-1}; ^{1}H 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).[26]

4.2.3. *o*-Chlorobenzyl chloroformate (1b). IR (neat) 1775, 1145 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.43 (s, 2H), 7.28–7.38 (m, 2H), 7.42–7.46 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 70.4, 127.1, 129.8, 130.7, 131.1, 134.2, 150.6; MS (*m/z*, %) 206 (17), 204 (M^+, 29), 127 (32), 125 (100), 89 (26). Exact MS calcd for $C_8H_6O_2Cl_2$: 203.9745. Found: 203.9774.

4.2.4. *o*-Bromobenzyl chloroformate (1c). IR (neat) 1775, 1135 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.41 (s, 2H), 7.25 (t, J=8 Hz, 1H), 7.35 (t, J=8 Hz, 1H), 7.44 (d, J=8 Hz, 1H), 7.61 (d, J=8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 72.6, 123.9, 127.8, 130.6, 130.8, 132.8, 133.1, 150.5; MS (*m/z*, %) 250 (31), 248 (M^+, 24), 171 (78), 169 (100), 125 (65), 89 (26). Exact MS calcd for $C_8H_6O_2BrCl$: 247.9240. Found: 247.9236.

4.2.5. Phenyl chloroformate (5a). IR (neat) 1785, 1120 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.22 (d, J=8 Hz, 2H), 7.31 (t, J=8 Hz, 1H), 7.42 (t, J=8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 120.3, 127.2, 129.8, 149.4, 151.6; MS (*m/z*, %) 158 (32), 156 (M^+, 100), 93 (37), 77 (90), 65 (40). Exact MS calcd for $C_7H_5O_2Cl$: 155.9978. Found: 155.9975.

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