A Convenient Method for the Synthesis of Activated *N*-Methylcarbamates[+]

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An investigation of methods to efficiently prepare activated *N*-methylcarbamates is reported. *N*-(Methylcarbamoyloxy)succinimide (**3a**), aryl *N*-methylcarbamates **3b–d** and 2,2,2-trifluoro-1-(trifluoromethyl)ethyl *N*-methylcarbamate (**3e**) have been prepared in 70–80% yields from the corresponding chloroformates **5a–e**, which were prepared as crystalline solids by the condensation of trichloromethyl chloroformate (**1**) or bis(trichloromethyl) carbonate (**2**) with hydroxy compounds **4a–e** in high yields.

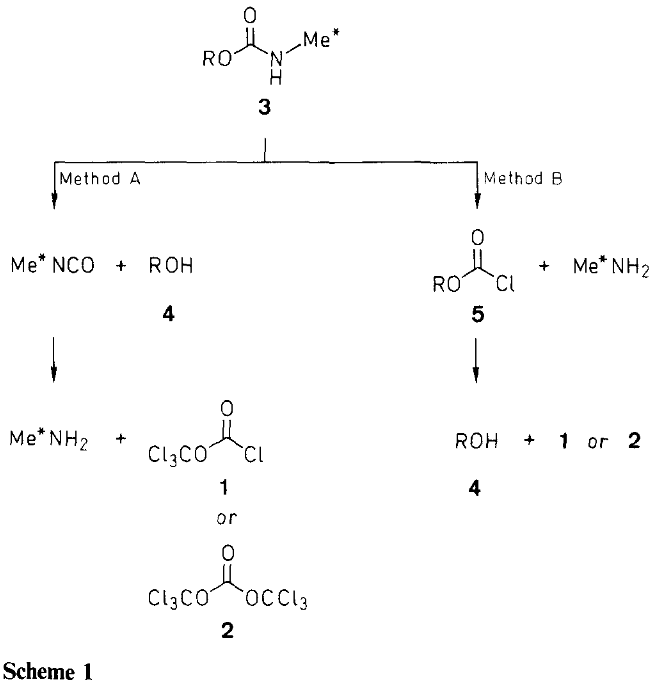
In recent years, trichloromethyl chloroformate (**1**) or bis(trichloromethyl) carbonate (**2**) has been frequently used in organic synthesis as phosgene sources.[1–4] These liquid or crystalline phosgene equivalents have the advantage of being much easier to handle than the highly toxic gaseous phosgene. Generally, **1** or **2** is used for the chloroformylation[3] or carbonation[1,3,5] of hydroxy or amino groups, for the chlorination of carboxylic acids,[3] and for the preparation of α-chloro chloroformates from aldehydes.[4] These reactions produce many important intermediate compounds including some that are employed in the synthesis of peptides,[2,5,6] and in the activation of poly-*N*-[2-hydroxy-1,1-bis(hydroxymethyl)ethyl]acrylamide gels for affinity chromatography.[7]

In the course of our investigation on the design of anticancer compounds we synthesized an alkylnitrosourea linked to a DNA-intercalating methidium structure by coupling the corresponding aminoalkylmethidium and an activated ester, succinimidyl *N*-methyl-*N*-nitrosocarbamate. The nitrosocarbamate reagent was prepared by nitrosation of the activated carbamate which was prepared by the addition of *N*-hydroxysuccinimide with methyl isocyanate.[8] In continuation of this work, we now report a simple and more convenient method that is also amenable to the preparation of ^{3}H-labeled *N*-methylcarbamates from ^{3}H-labeled methylamine hydrochloride and **1** or **2**. In this paper, unlabeled methylamine hydrochloride was employed instead of the ^{3}H-labeled one.

N-(Methylcarbamoyloxy)succinimide (**3a**) can be prepared from methylamine hydrochloride by the two methods shown in the retrosynthesis diagram (Scheme 1). Using method A, compound **3** can be obtained in good yield (> 80%)[9] by the reaction of *N*-hydroxysuccinimide **4a** with methyl isocyanate. In order to maximize the yield of methyl isocyanate from methylamine,[10] the direct carbonylation of methylamine was attempted with **1** in dioxane, but the yield of methyl isocyanate was also low (44%) (see Experimental).

On the other hand, method B has clear advantages over method A because the expensive and hazardous ^{3}H-labeled methylamine is used in the last step of the reaction sequence (Scheme 1). The strategy for the synthesis of **3** by method B is outlined in Scheme 2.

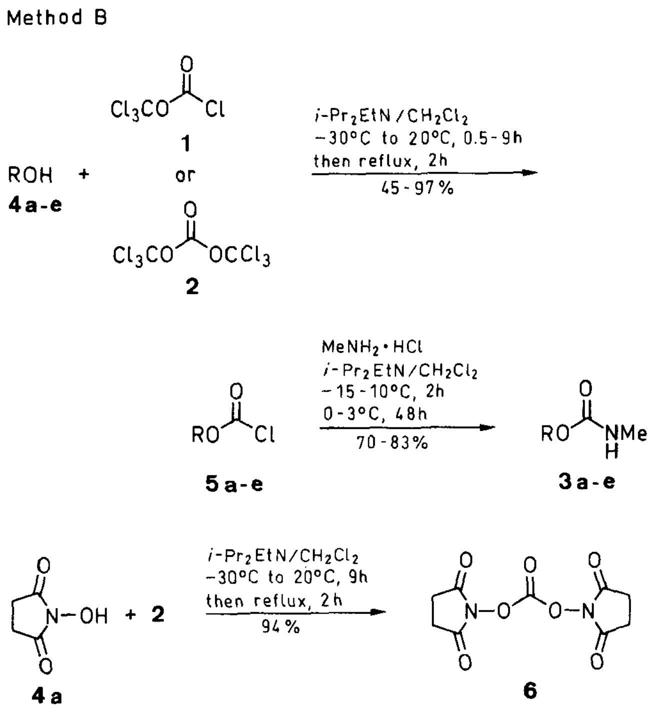
The yield of the carbamate **3a** was low (24%) when the reaction of **4a** with **1** was carried out in a one-pot procedure without first isolating the intermediate succinimidyl chloroformate (**5a**). Improved yields of carbamate **3** were obtained when the intermediate chloroformate **5** was isolated.

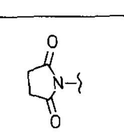


Scheme 1

In order to determine the optimum conditions for the synthesis of **5a**, **4a** was allowed to react with **1** under varying conditions. The results are summarized in Table 1. Initially, compound **4a** was treated with 1.4 equivalents of **1** in the presence of a large excess of triethylamine in dichloromethane at 0 °C for 30 minutes followed by refluxing for 2 hours. However, the reaction mixture did not afford any **5a**. This failure to detect **5a** could result from its decomposition by the excess nucleophilic triethylamine. Indeed, an equimolar amount of the less-nucleophilic ethyldiisopropylamine gave crystalline **5a** in excellent yield (81%) under the same conditions. It should be noted that chloroformate **5a** is also very sensitive to ethyldiisopropylamine as evidenced by the lower yield of **5a** when even a small excess of the amine is used.

Under the optimized reaction conditions, 4-nitrophenol (**4b**) and 2,4,5-trichlorophenol (**4c**) also gave the corresponding chloroformates **5b** and **5c** in high yields (~ 90 and 80%, respectively). This same procedure provided only a 45% yield for the conversion of pentafluorophenol (**4d**) to ester **5d**. The chloroformates **5c** and **5d**, however, were obtained in excellent yields (~ 95 and 80%, respectively) when the reaction mixture was first slowly warmed up to 20 °C before refluxing.



3-5	R	3-5	R
a		d	2,3,4,5,6-F_5C_6
b	4-$O_2NC_6H_4$	e	$(CF_3)_2CH$
c	2,4,5-$Cl_3C_6H_2$		

Scheme 2

Using bis(trichloromethyl) carbonate (**2**), chloroformate **5c** was obtained in 90% yield, while the yield of **5e** was only 47%. Contrary to our expectation, the reaction of **4a** with **2** did not afford the corresponding chloroformate **5a**, but gave *N,N'*-discuccinimidyl carbonate (**6**) in 94% yield.[11]

The chloroformate **5a** has been previously prepared from potassium[12] or dicyclohexylamine[13] salts of **4a** and phosgene in 75 to 80% yield, but as an oil. In addition, Stevenson and Young succeeded in isolating crystalline **5a**, but not in a high yield (54%).[6] In comparison with previous methods, the present method has the advantage of higher yield of the crystalline **5a** and the easier handling of the liquid or crystalline phosgene equivalents **1** or **2**.

The synthesized chloroformates **5a–e** (1.8 equivalents) were treated with methylamine hydrochloride in the presence of two equivalents (stoichiometric amounts) of ethyldiisopropylamine at low temperature (−15 to −10 °C) for 2 hours, and the mixture was then stirred in an ice-bath for 2 days to give crystalline *N*-methylcarbamates **3a–e** in 70–83% yield, respectively (Table 2). The overall yield of **3a** from **1** was higher using method B (65%) as compared to method A (35%), and to the methyliminotriphenylphosphorane method[10] (46%). The strategy employed in the synthesis of **3** by method B would also minimize the loss of the expensive and hazardous ^{3}H-labeled material because it is introduced in the final step of the synthesis. For example, the loss of the ^{3}H-alkylamine would be approximately 20% in the synthesis of ^{3}H-labeled **3a**.

Chloroformates **5** are very unstable at room temperature and are readily decomposed by amines, acids, protic solvents, and atmospheric moisture. Consequently, **5a–d** must be stored at low temperature (< −15 °C) under an argon atmosphere. 2,2,2-Trifluoro-1-(trifluoromethyl)ethyl ester **5e** is so labile that even under these protective conditions it cannot be preserved for long. Accordingly, it is better to prepare **5e** immediately before use.

The structures of **3** and **5** were determined by their spectroscopic properties and by elemental analyses (Tables 3 and 4) or by comparison of physical and spectroscopic properties reported in the literature.

Table 1. Preparation of Chloroformates **5a–e** from **4a–e** and **1** or **2** in the Presence of Ethyldiisopropylamine[a]

Run	Product	Phosgene Source	Time (h)				Yield[b] (%)	mp (°C)[c] (solvent)	Molecular Formula or Lit. mp (°C)
			0°C	0–20°C	33–34°C	reflux			
1[d]	**5a**	**1**	0.5	–	–	2	0	–	–
2	**5a**	**1**	0.5	–	–	2	81	35.4–35.6 (THF)	36–37[6]
3[e]	**5a**	**1**	0.5	–	–	2	55	35.4–35.6 (THF)	–
4	**5b**	**1**	0.5	–	–	2	88–90	77.0–78.5 (THF)	81–82[14]
5	**5c**	**1**	0.5	–	–	2	83	56.2–58.2 (THF)	58–62[6]
6	**5d**	**1**	0.5	–	–	2	45	5.5–6.5[f] (THF)	$C_7ClF_5O_2$ (246.5)
7	**5c**	**1**	3	6	–	2	97	56.5–58.3 (THF)	–
8	**5d**	**1**	3	4	1.5	2	79	4.3–6.0[f] (THF)	–
9	**5c**	**2**	3	6	–	2	90	58.3–60.9 (THF)	–
10	**5e**	**2**	3	6	–	2	47[g]	liquid	$C_4HClF_6O_2$ (230.0)

[a] Molar ratio **4**/**1**/*i*-Pr_2EtN = 1.0 : 1.4 : 1.0 unless otherwise designated.
[b] Yield of pure isolated product **5** based on **4**.
[c] Uncorrected.
[d] In this run, Et_3N (6 equiv) was used instead of *i*-Pr_2EtN.
[e] In this run, a small excess amount of *i*-Pr_2EtN (1.7 equiv) was used.
[f] Freezing point.
[g] Yield of **5e** was determined by ^{19}F NMR.

All melting points were measured on a Mitamura micro melting apparatus and are uncorrected. GLC analyses were performed on a Hewlett-Packard 5730 A gas chromatograph, 2 m glass column, 20 mL/min carrier gas, 10% OV-17 on chromosorb (8/100 mesh) at 60°C. IR spectra were taken on a Hitachi Model 260-50, JEOL Model IR-5300 (FT-IR) or Mattson Alpha Centauri (FT-IR) spectrophotometer. ^{1}H NMR spectra were determined on a JEOL PMX-60SI or JNM FX-90Q spectrometer, and ^{13}C and ^{19}F NMR spectra were obtained using a JNM FX-90Q spectrometer. Mass spectra were recorded with a Hitachi M-80 double focussing mass spectrometer. Elemental analyses were performed at the Micro Analysis Laboratory of Chiba University.

Trichloromethyl chloroformate (**1**) was purchased from Aldrich Chemical Co., Inc. or kindly donated from Hodogaya Chemical Co., Ltd. Bis(trichloromethyl) carbonate (**2**) was prepared by photo-chlorination of dimethyl carbonate in CCl_4.[3] 1,1,1,3,3,3-Hexafluoro-2-propanol (**4e**) was kindly donated from Central Glass Co., Ltd. All other reagents were of commercial quality.

Table 2. Preparation of *N*-Methylcarbamates **3a–e** from **5a–e** and Methylamine Hydrochloride in the Presence of Ethyldiisopropylamine[a]

Product	Yield[b] (%)	mp (°C) (Solvent)	Molecular Formula[c] or Lit. mp (°C)
3a	80	147.5–151.2 ($EtOAc/Et_2O$)	148–152[9]
3b	72	154.1–154.9 ($CHCl_3$)	$C_8H_8N_2O_4$ (196.2)
3c	79	157.8–158.4 ($CHCl_3$)	157–158[9]
3d	83	123.0–124.4 ($CHCl_3$)	$C_8H_4F_6NO_2$ (241.1)
3e	70	73.2–74.0 (CCl_4)	$C_5H_5F_6NO_2$ (225.0)

[a] Molar ratio $5/MeNH_2 \cdot HCl/i\text{-}Pr_2EtN = 1.8:1.0:2.0$ unless otherwise designated.
[b] Yield of isolated product **3** based on $MeNH_2 \cdot HCl$.
[c] Satisfactory microanalyses obtained: C ±0.20, H ±0.04, N ±0.17.

Preparation of Methyl Isocyanate from Methylamine Hydrochloride by Method A:

To a stirred suspension of $MeNH_2 \cdot HCl$ (1.37 g, 20 mmol) in anhydr. dioxane (10 mL) was added trichloromethyl chloroformate (**1**; 6.6 g, 33 mmol, 1.7 equiv) and the stirred mixture was heated at 60–65°C for 4.5 h and then at 100°C for 1 h. The mixture was then distilled and the distillate analyzed with GLC in order to determine the quantity of methyl isocyanate in the solution; yield: 44%.

One-Pot Synthesis of *N*-(Methylcarbamoyloxy)succinimide (3a) by Method B:

To a stirred suspension of *N*-hydroxysuccinimide (**4a**; 1.2 g, 10.4 mmol) in dry CH_2Cl_2 (50 mL) under an Ar atmosphere was slowly added trichloromethyl chloroformate (**1**; 2.7 g, 13.7 mmol, 1.3 equiv) at −30°C. *i*-Pr_2EtN (2.3 g, 17.7 mmol, 1.7 equiv) was then added dropwise, and after stirring at 0°C for 30 min, the mixture was refluxed for 2 h and then cooled to −15°C. To this cold mixture was slowly added $MeNH_2 \cdot HCl$ (1.12 g, 17 mmol, 1.6 equiv) and *i*-Pr_2EtN (2.8 g, 21 mmol, 2 equiv) in the order specified. The mixture was stirred at −10 to −15°C for 50 h and then diluted with dry CH_2Cl_2 (30 mL). The solution was successively washed

Table 3. Spectroscopic Data of Chloroformates **5a–e** Prepared

Product	IR (KBr) ν (cm^{-1})	^{1}H NMR (CCl_4/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	^{19}F NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
5a	1850, 1780, 1200, 750	2.60 (s, 4H)	25.7, 169.4, 173.1		
5b	1785, 1520, 1340, 1200, 745	7.20 (d, 2H, J = 8), 8.00 (d, 2H, J = 8)	119.8, 123.8, 147.0, 153.4, 161.7		201 (M$^+$, 6), 63 (100), 200.9821[a]
5c	1780, 1280, 1130, 1100, 1080, 740	7.20 (s, 1H), 7.40 (s, 1H)	118.0, 119.6, 124.7, 130.0, 131.4, 145.3, 151.8		
5d	1810, 1225		124.3–147.5, 148.6	−161.5 (t, 2F, J = 19.5), −156.3 (t, 1F, J = 19.5), −153.3 (d, 2F, J = 19.5)	
5e	1800, 1180, 740	–[b]	–[b]	−75.7 (s, 6F)	

[a] HRMS (for $C_7H_4ClO_4N$).
[b] ^{1}H and ^{13}C NMR spectra were not determined because it was very unstable. The structure of **5e** was identified by the derivation to **3e** in addition to IR and ^{19}F NMR spectra.

Table 4. Spectroscopic Data of *N*-Methylcarbamates **3a–e** Prepared

Product	IR (KBr) ν (cm^{-1})	^{1}H NMR (CCl_4/TMS) δ, J (Hz)	^{13}C NMR ($CDCl_3$/TMS) δ	^{19}F NMR ($CDCl_3$/TMS) δ, J (Hz)	MS (70 eV) m/z (%)
3a	3340, 1775, 1740	2.65 (d, 3H), 2.70 (t, 4H), 3.10 (s, 1H)	25.3, 27.6, 152.2, 170.3		
3b	3350, 1730	2.80 (d, 3H, J = 5), 4.90 (s, 1H), 7.00 (d, 2H, J = 5), 7.90 (d, 2H, J = 9)	26.2, 121.0, 123.9, 143.1, 152.6, 155.4		196 (M$^+$, 3), 139 (92)
3c	3350, 1760	2.80 (d, 3H, J = 5), 4.95 (s, 1H), 7.15 (s, 1H), 7.3 (s, 1H)	27.9, 125.7, 126.4, 129.9, 131.3, 146.0, 153.3		
3d	3340, 1740	2.85 (d, 3H, J = 5), 5.1 (s, 1H)	28.2, 128.8–143.1, 152.2	−163.3 (t, 2F, J = 19.5), −159.2 (t, 1F, J = 19.5), −153.8 (d, 2F, J = 19.5)	241 (M$^+$, 2), 184 (88)
3e	3350, 1740	2.8 (d, 3H, J = 5), 4.9 (s, 1H, J = 5)	28.0, 67.8, 127.0, 153.2	−74.3 (s, 6F)	225 (M$^+$, 60), 74 (100)

with cold 1 M HCl (50 mL) and sat. aq $NaHCO_3$ (30 mL), and then concentrated under reduced pressure to give the crude product, which was recrystallized from THF or a mixture of Et_2O and EtOAc; yield: 0.44 g (24%); mp 147.0–151.0 °C (Lit.[9] 148–152 °C). Spectral data are shown in Table 2.

Chloroformates 5a–e; General Procedure:
In a dry 200 mL flask equipped with an Ar inlet adaptor, a rubber septum and a magnetic stirring bar, was placed **4a–e** (14.4 mmol) in dry CH_2Cl_2 (50 mL). The mixture was cooled to −30 °C and trichloromethyl chloroformate (**1**; 3.92 g, 19.8 mmol, 1.4 equiv.) and *i*-Pr_2EtN (1.86 g, 14.4 mmol, 1 equiv) were each slowly added in the order specified. The resultant solution was stirred at 0 °C for 3 h, at 20 °C for 6 h, and at reflux temperature for an additional 2 h. The solvent was then evaporated in vacuo to give a crystalline solid which was suspended in THF (20 mL). The mixture was decanted to remove the crystalline *i*-$Pr_2EtN \cdot HCl$ and the supernatant was evaporated to dryness under reduced pressure. The crude product obtained was crystallized from THF. Results are shown in Table 1 with mp, and spectroscopic properties (IR; ^1H, ^{13}C and ^{19}F NMR; MS) are summarized in Table 3.

***N,N'*-Disuccinimidyl Carbonate (6):**
In a dry 200 mL flask equipped with an Ar inlet adaptor, a rubber septum and a magnetic stirring bar are placed *N*-hydroxysuccinimide (**4a**; 2.00 g, 17.4 mmol) and bis(trichloromethyl) carbonate (**2**; 7.24 g, 24.4 mmol, 1.4 equiv) in dry CH_2Cl_2 (50 mL), and the mixture was cooled to −30 °C. To the mixture was added dropwise *i*-Pr_2EtN (2.24 g, 17.4 mmol, 1 equiv). The resultant mixture was subsequently stirred at 0 °C for 3 h, allowed to warm to 20 °C over 6 h, and then refluxed for additional 2 h. The mixture was condensed under reduced pressure to give crystalline solid, which was suspended in THF (20 mL). The precipitate was isolated by filtration and washed well with THF (2 × 20 mL), and then crystallized from MeCN. Yield: 94%; mp 209.3–211.5 °C (MeCN) (Lit.[11] 211–215 °C).

IR (KBr) ν = 1840, 1780, 1745 cm^{-1} (Lit.[11] 1840, 1780, 1750).

^{13}C NMR ($CDCl_3$/DMSO/TMS in an NNE pulse mode): δ = 25.17 (4C), 168.46 (1C), 172.26 (4C).

***N*-Methylcarbamates 3a–e; General Procedure:**
In a dry 200 mL flask equipped with an Ar inlet adaptor, a rubber septum and a magnetic stirring bar were placed $MeNH_2 \cdot HCl$ (0.10 g, 1.5 mmol) and **5a–e** (2.7 mmol, 1.8 equiv) in dry CH_2Cl_2 (50 mL). The mixture was then cooled to −15 °C and *i*-Pr_2EtN (0.39 g, 3.0 mmol, 2 equiv) was added dropwise. After stirring at ~0 °C for 48 h, the mixture was concentrated in vacuo to give the crude product **3a–e**, which was purified by silica gel chromatography (Merck silica gel 60, 230–400 mesh) with $CHCl_3$ as eluent. Yields and mp are shown in Table 2 and spectroscopic properties are summarized in Table 4.

We are indebted to Hodogaya Chemical Co., Ltd. for giving trichloromethyl chloroformate **(1)** *and to Central Glass Co., Ltd. for giving 1,1,1,3,3,3-hexafluoro-2-propanol* **4e**, *and grateful to Mr. Kazuhiko Yoshimura for his assistance in the experimental work.*

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