A Facile Synthesis of Azidoformate *via* Chloroformate

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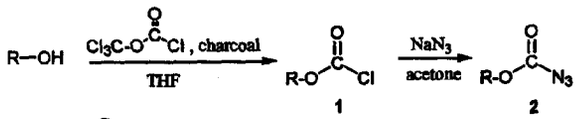
This work synthesized chloroformates by slowly adding alcohols into a suspension of trichloromethyl chloroformate, instead of phosgene, along with activated charcoal in tetrahydrofuran. This chloroformylation yielded chloroformates in near quantitative yield. The subsequent reaction between chloroformates and sodium azide in dry acetone produced azidoformates in a high yield.

INTRODUCTION

The decomposition of azide by photolysis or thermolysis produced nitrene intermediate which is involved in the intervention of C-H bond to form amines, in the dehydrogenation to produce alkenes, or in the formation of aziridines by adding alkenes. As a precursor of nitrenes, reactions involving alkyl azides (R-N_3), aryl azides (Ar-N_3), and acyl azides (RCON_3) are well documented.[1] However, the reaction of the azidoformates (RO-CO-N_3) has been limited to commercial azides, such as ethyl azidoformate, or other synthetic azidoformates which were formed by reacting with chloroformates.[2] The chloroformates are generally synthesized by the reaction of the corresponding alcohols with phosgene (carbonyl dichloride, bp 8.2 °C)[3] or a solution of phosgene in toluene or benzene.[4] Owing to its volatility and toxicity, phosgene is difficult to obtain commercially. Therefore, trichloromethyl chloroformate (TCF, bp 128 °C), a phosgene dimer, has been recently used as a substitute for phosgene. A related investigation has demonstrated that the chloroformylation of α-amino acid is involved in the rapid decomposition of TCF with activated charcoal and the simultaneous reaction of resulting phosgene with amino acid.[5] This work presents, for the first time, an alternative method for preparing chloroformates using TCF.

RESULTS AND DISCUSSION

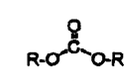
Chloroformates **1** is normally prepared with TCF in the presence of a base.[6] In this work, a large amount of dialkyl carbonates **3** was formed by further reacting the chloroformate product with alcohol.[7] After several attempts, an excess amount of TCF was used to prevent the formation of dialkyl carbonates **3**, although a half-mole amount of TCF would theoretically be required for a complete reaction with a mole of alcohol. Slowly adding alcohol into TCF could even avoid the side product formation because chloroformate is less reactive towards alcohol than phosgene. Therefore, a yield of **1** was markedly improved by slowly adding an equivalent of alcohol to the suspension of 0.75 equivalent of TCF and a catalytic amount of charcoal in dry tetrahydrofuran (THF) at room temperature. A near quantitative yield of chloroformates **1** was obtained as a clear oil. No evidence suggested the formation of appreciable quantities of dialkyl carbonate **3**. The absence of a hydroxyl band in the IR spectrum implied the completeness of the reaction as well as the absence of trichloromethyl signal (δ ca. 110)[8] in the ^{13}C NMR spectrum, further indicating the formation of chloroformates **1** instead of trichloromethyl carbonates **4**. The chloroformates could be used in the following reaction without further purification.



1 **2**

R

a: $CH_2CH_2CH_2CH_2CH_2CH_3$
b: $CH_2CH(CH_3)CH_2CH_2CH_3$
c: $CH(CH_3)CH_2CH_2CH_2CH_3$
d: $CH_2CH_2CH_2CH_2CH{=}CH_2$
e: CH_2Ph
f: $CH_2CH_2CH_2Ph$
g: $CH_2CH(CH_3)Ph$
h: $CH(CH_3)Ph$
i: Ph
j: p-$MeOC_6H_4$
k: $CH_2CH{=}CHPh$
l: $C(CH_3)_2CH_2CH_2CH_3$



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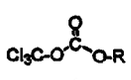

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By using the above method, TCF was treated with phenol. Even at reflux THF solution, phenyl chloroformate (**1i**) was not found to be a reaction product. The starting material was recovered quantitatively. However, phenyl chloroformate (**1i**) was successfully prepared by slowly adding one equiva-

Dedicated to the memory of the late Professor Ta-shue Chou

lent of triethylamine to the mixture of phenol, TCF and charcoal in a sealed tube heated at 120 °C. The same result was observed with *p*-methoxyphenol to form *p*-methoxyphenyl chloroformate (**1j**). Interestingly, charcoal, triethylamine and heat were deemed necessary to promote the chloroformylation of phenols.

In the case of cinnamyl alcohol, comparing ^{1}H and ^{13}C NMR spectral data with those of commercial cinnamyl chloride, revealed that the product after chloroformylation with TCF in the presence of a catalytic amount of charcoal was cinnamyl chloride. The stability of cinnamyl cation caused easy cleavage of the bond between cinnamyl and oxygen followed by the capture of a chloride ion. Notably, a low temperature was chosen to diminish the cinnamyl chloride formation. After several trials, the suitable temperature to synthesize cinnamyl chloroformate (**1k**) in a quantitative yield was -40 °C. Owing to the instability of **1k** at room temperature, the work-up procedure was implemented under 0 °C.

While extending our investigation to the more difficult synthesis of *t*-hexyl chloroformate (**1l**), reacting the sterically crowded *t*-hexyl alcohol reacted with TCF yielded no detectable compound after the reaction mixture was concentrated under a reduced pressure at room temperature. We believe the formed *t*-hexyl chloroformate (**1l**) decomposed into alkenes under room temperature. This observation correlated with the fact that the *t*-butyl chloroformate decomposes appreciably at 10 °C and is very easily hydrolyzed.[9] The technique employed to synthesize **1k** was also applied to preparing *t*-hexyl chloroformate (**1l**). The generation of **1l** was proven by isolating *t*-hexyl N,N-diethylcarbamate [$CH_3CH_2CH_2C(CH_3)_2$-$OCON(C_2H_5)_2$][10] which was obtained from the reaction of this chloroformate with diethylamine at -40 °C . Consequently, this method was also satisfactory for use with 3° alcohols.

Several routes to azidoformates consist of methods from alcohol treated with 1,1-carbonyldiimidzole followed by sodium azide (NaN_3),[11] or from the carbazate, formed by the reaction of chloroformate with hydrazine, reacted with sodium nitrite in acetic acid.[12] However, the conventional method for preparing azidoformates was the reaction between chloroformate and NaN_3.[3,4,13] Owing to the insolubility of NaN_3 in organic solvent, water together with acetone or phase transfer catalyst was used. In the presence of water, a side product in this step was dialkyl carbonate again. This side product was formed by reacting chloroformates **1** with alcohol which was generated from the hydrolysis of some amount of chloroformate. To effectively suppress the formation of dialkyl carbonate, our results demonstrated that chloroformates **1** would be converted into azidoformates **2** with NaN_3 in dry acetone. In order to confirm the structure of azidoformate, the infrared spectrum showed characteristic absorptions at 2100-2200 cm^{-1} for N_3 group and 1728-1740 cm^{-1} for C=O group.[14] Table 1 summarizes the physical and spectroscopic data of azidoformates **2**. The lower yield of cinnamyl azidoformate (**2k**) was attributed to the partial formation of cinnamyl chloride from the decomposition of cinnamyl chloroformate (**1k**) under a reaction at room temperature. On the other hand, the same method could not produce any *t*-hexyl azidoformate (**2l**). Notably, alkene formation competed with azidoformate formation for *t*-hexyl chloroformate (**1l**) at room temperature. To keep **1l** intact, in this work, the reaction was proceeded at 0 °C. Moreover, no product was found with recovered starting material which was perhaps attributed to the low reactivity of a two-phase reaction between **1l** and NaN_3.

In summary, this work has successfully synthesized chloroformates **1** in a near quantitative yield using TCF to replace phosgene in the reaction with alcohol and using charcoal as catalyst. Because TCF is a liquid which can be handled easily and safely, the method proposed herein can rapidly synthesize chloroformates. Moreover, the subsequent reaction of chloroformates with NaN_3 in dry acetone produces azidoformates **2** in a high yield.

EXPERIMENT SECTION

General

IR spectra were recorded on a Nicolet Magna FT-IR spectrometer as thin films. NMR spectra were recorded on Bruker AC-200 FT-NMR spectrometers; all chemical shifts are reported in ppm from tetramethylsilane as an internal standard. MS and HRMS spectra were recorded on a VG 70-250S spectrometer. Elemental analyses were performed on a Heraeus CHN-RAPID elemental analyzer. Column chromatography was carried out using silica gel. All reactions were carried out under an atmosphere of dry nitrogen.

The General Procedure for the Preparation of Chloroformates 1a-h

A suspension of TCF (0.59 g, 3 mmol) in THF (25 mL) along with activated charcoal (5 mg, 0.4 mmol) was stirred at room temperature for 10 min. A solution of alcohol (4 mmol) in THF (10 mL) was added dropwise for more than 6 hr. The reaction mixture was stirred for an additional 1 hr at rt. The resulting mixture was filtered and concentrated to produce chloroformates **1a-h** as a colorless liquid. The chloroformate could be used in the following reaction without further purification. The representative ^{1}H and ^{13}C NMR spectral data for hexyl chloroformate (**1a**) were as follows. ^{1}H NMR ($CDCl_3$)δ 0.90 (t, 3H, CH_3, J = 6.6 Hz), 1.2-1.4 (m, 6H, 3 × CH_2), 1.73

Table 1. Selected Physical and Spectroscopic Data of Azidoformates **2**

Product	Yield[a] %	Molecular formula[b]	IR cm^{-1}	^1H NMR ($CDCl_3$) δ, ppm	^{13}C NMR ($CDCl_3$) δ, ppm
2a	94	$C_7H_{13}N_3O_2$	2176, 2134 1731	0.88 (t, 3H, CH_3, J = 6.8 Hz), 1.2-1.8 (m, 8H, 4 x CH_2), 4.19 (t, 2H, OCH_2, J = 6.8 Hz)	13.9, 22.4, 25.2, 28.3, 31.3, 68.8, 157.5
2b	96	$C_7H_{13}N_3O_2$	2186, 2153 1731	0.91 (t, 3H, CH_3, J = 7.0 Hz), 0.92 (d, 3H, CH_3, J = 6.7 Hz), 1.1-2.0 (m, 5H, CH and 2 x CH_2), 4.0-4.2 (m, 2H, OCH_2)	14.1, 16.5, 19.8, 32.2, 35.2, 73.5, 157.6
2c	94	$C_7H_{13}N_3O_2$	2187, 2136 1728	0.88 (t, 3H, CH_3, J = 6.6 Hz), 1.27 (d, 3H, CH, J = 6.3 Hz), 1.2-1.7 (m, 6H, 3 x CH_2), 4.86 (sextet, 1H, OCH, J = 6.3 Hz)	13.8, 19.6, 22.3, 27.6, 35.3, 76.5, 157.0
2d	92	$C_7H_{13}N_3O_2$	2158, 2110 1728	1.4-2.1 (m, 6H, 3 x CH_2), 4.22 (t, 2H, OCH_2, J = 6.6 Hz), 4.9-5.1 (m, 2H, CH_2=C), 5.79 (ddt, 1H, C=CH, J = 17.0, 10.2, 6.6 Hz)	24.8, 27.8, 33.1, 68.5, 115.0, 137.9, 157.5
2e	95	$C_8H_7N_3O_2$	2167, 2141 1729	5.20 (s, 2H, OCH_2), 7.36 (s, 5H, C_6H_5)	67.0, 128.5, 128.6, 128.8, 134.3, 157.4
2f	91	$C_{10}H_{11}N_3O_2$	2187, 2139 1737	2.04 (tt, 2H, CH_2, J = 7.2, 6.4 Hz), 2.73 (t, 2H, $PhCH_2$, J = 7.2 Hz), 4.25 (t, 2H, OCH_2, J = 6.4 Hz), 7.3-7.4 (m, 5H, C_6H_5)	29.9, 31.7, 67.7, 126.1, 128.3, 128.4, 140.5, 157.4
2g	95	$C_{10}H_{11}N_3O_2$	2170, 2143 1731	1.33 (d, 3H, CH_3, J = 7.1 Hz), 3.15 (sextet, 1H, CH, J = 7.1 Hz), 4.2-4.4 (m, 2H, OCH_2), 7.2-7.4 (m, 5H, C_6H_5)	17.7, 38.8, 73.2, 127.0, 127.2, 128.6, 142.1, 157.4
2h	92	$C_9H_9N_3O_2$	2188, 2134 1731	1.60 (d, 3H, CH_3, J = 6.7 Hz), 5.83 (q, 1H, OCH, J = 6.7 Hz), 7.3-7.4 (m, 5H, C_6H_5)	21.9, 77.2, 126.0, 128.4, 128.6, 140.0, 156.8
2i	94	$C_7H_5N_3O_2$	2201, 2160 1740	7.1-7.5 (m, 5H, C_6H_5)	120.8, 126.5, 129.5, 150.5, 156.2
2j	96	$C_8H_7N_3O_2$	2194, 2156 1743	3.78 (s, 3H, OCH_3), 6.88 and 7.08 (d, each 2H, C_6H_4, J = 9.2 Hz)	55.5, 114.5, 121.6, 144.1, 156.6, 157.7
2k	75	$C_{10}H_9N_3O_2$	2180, 2134 1728	4.86 (dd, 2H, OCH_2, J = 6.7, 1.2 Hz), 6.28 (dt, 1H, PhC=CH, J = 15.9, 6.5 Hz), 6.71 (d, 1H, PhCH=C, J = 15.9 Hz), 7.2-7.4 (m, 5H, C_6H_5)	68.9, 121.3, 126.7, 128.4, 128.7, 135.7, 135.9, 157.4

[a] Yield in two steps from alcohol

[b] All compounds were analyzed for C, H and N, and results agreed to ± 0.4% of the theoretical values or analyzed by high resolution mass spectral measurement with satisfactory values.

(quintet, 2H, CH_2, J = 6.6 Hz), 4.32 (t, 2H, OCH_2, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$) δ 13.8, 22.4, 25.1, 28.2, 31.2, 72.3, 150.5. The chloroformates could be used in the following reaction without further purification.

The General Procedure for the Preparation of Chloroformates 1i-j

In a sealed tube, TCF (0.30 g, 1.5 mmol), alcohol (2 mmol) in THF (6 mL) and activated charcoal (2.4 mg, 0.2 mmol) was added. A solution of triethylamine (0.2 g, 2 mmol) in THF (4 mL) was added dropwise over 10 min. Efficient stirring was necessary to obtain a homogeneous solution. The reaction mixture was stirred for 3 hr at 120 °C. The resulting solution was filtered and concentrated to afford chloroformates **1i-j** as a colorless liquid. The chloroformates could be used in the following reaction without further purification.

The General Procedure for the Preparation of Chloroformates 1k-l

A suspension of TCF (0.79 g, 4 mmol) in THF (25 mL) along with activated charcoal (5 mg, 0.4 mmol) was stirred at -40 °C for 30 min. A solution of alcohol (4 mmol) in THF (10 mL) was added dropwise for more than 12 hr. The reaction mixture was stirred for an additional 3 hr at -40 °C. The resulting mixture was filtered and concentrated at 0 °C to afford chloroformates **1k-l** as a colorless liquid. The representative ^1H and ^{13}C NMR spectral data for **1k**: ^1H NMR ($CDCl_3$) δ 4.85 (d, 2H, OCH_2, J = 6.7 Hz), 6.22 (dt, 1H, C=CH, J = 15.8, 6.7 Hz), 6.68 (d, 1H, PhCH=C, J = 15.8 Hz), 7.2-7.4 (m, 5H, C_6H_5); ^{13}C NMR ($CDCl_3$) δ 72.2, 120.1, 126.7, 128.4, 128.5, 135.2, 137.0, 150.3. The chloroformates could be used in the following reaction at low temperature without further purification.

The General Procedure for the Preparation of Azidoformates 2a-k

To a suspension of NaN3 (0.52 g, 8 mmol) in dry acetone (20 mL) was added chloroformate 1a-k (4 mmol) and stirred for 3 hr at room temperature. The reaction mixture was filtered, concentrated under reduced pressure, and chromatographed over silica gel eluting with hexane-EtOAc (30:1) to yield azidoformate 2a-k as colorless liquid. Table 1 summarizes the physical and spectroscopic data.

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Key Words

Chloroformate; Azidoformate; Trichloromethyl chloroformate.

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