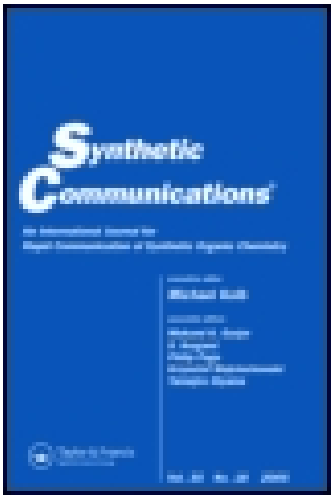

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New Method of Synthesizing *N*-Alkoxycarbonyl-*N*-arylamide with Triphosgene

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Abstract: *N*-Chloroformyl-*N*-arylcarbamate, the key intermediate for the synthesis of some excellent pesticides, was synthesized through a new method with triphosgene instead of toxic phosgene. It cannot be obtained through the traditional method using triethylamine as a nucleophile. When triethylamine was replaced by a stronger base, sodium hydride, the product was obtained in good yield.

Keywords: Chlorocarbonylation, *N*-chloroformyl-*N*-arylcarbamate, triphosgene

INTRODUCTION

Indoxacard (DPX-JW062, JW062) is a new oxadiazine insecticide introduced by the E. I. DuPont Company that has shown outstanding field activity, environmental compatibility, and safety to nontarget organisms.[1] Besides Indoxacard, many compounds with condensed bicyclic or tricyclic structure were studied, and many of them showed good insecticidal activity to lepidopteran larvae.[2]

Most of the analogous insecticides have an *N*-alkoxycarbonyl-*N*-arylamide side chain, which can be introduced by *N*-chloroformly-*N*-arylcarbamate. The preparation of *N*-chloroformyl-*N*-arylcarbamate is very important in the synthesis of such insecticides. *N*-Chloroformyl-*N*-

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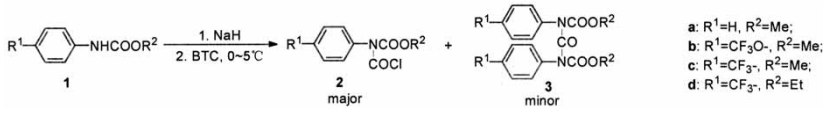
arylcarbamate was obtained through the chlorocarbonylation of *N*-arylcarbamate with phosgene.[3] However, phosgene is a toxic gas and easy to diffuse, which makes the syntheses potentially hazardous.

Over the past few years triphosgene [bis(trichloromethyl)-carbonate, BTC] has emerged as a versatile synthetic reagent for the synthesis of a large variety of organic compounds.[4] Compared with phosgene, BTC is not only safer to use and more conveniently handled, transported, and stored, but in addition, being a solid, it can be weighed exactly. Reactions using this reagent are normally carried out under mild conditions and afford and afford good to excellent yields. This white crystalline compound has now replaced its gaseous congener phosgene.

RESULTS AND DISCUSSION

In most cases using triphosgene, a nucleophile, usually a tertiay amine (triethylamine, pyridine, etc.), is demanded for the generation of phosgene in situ.[5] To our surprise, no product was found when we followed the traditional method using triethylamine as the nucleophile. However, the products were obtained in good yield when the reactants were treated with a stronger base sodium hydride to form anions, which acted as nucleophilic attacker (Scheme 1).

In the chlorocarbonylation reaction, the by-product was *N*,*N*′-dialkoxycarbonyl-*N*,*N*′-diarylcarbamide (**3**), which can be detected by gas chromatography/mass selective detector system (GC/MS). Besides, there were usually a little of unchanged substrate *N*-arylcarbamate (**1**). The percentage of the by-product and unchanged reactant were controlled by the reaction condition, especially the amount of sodium hydride and triphosgene (Table 1). When the theoretic amount of sodium hydride and triphosgene was used, the results were unsatisfactory and the conversion of **1** was low (Entry 1). It suggests to us that the amount of triphosgene was insufficient. However, by increasing the amount of triphosgene, the by-product was reduced a little, but the conversion was as low as before (Entry 2.) By increasing the amount of sodium hydride, a higher conversion was achieved, but the by-product increased much more than the product (**2**) (Entries 3 and 4). It reveals that the excessive amount of sodium hydride is important for the completion of the reaction; because the anion formed by **1** and sodium hydride cannot be dissolved in the solution, it prevents the interior sodium hydride from reacting with **1**. The formation of the by-product **3** is due to reaction of the substrate (**1**) with the product (**2**) in the presence of a strong



Scheme 1.

Table 1. Effect of the reaction conditions

Entry	Substrate	3*n*(BTC)/*n*(**1**)	*n*(NaH)/*n*(**1**)	Composition of crude product (%)[a]			Yield (%)	Purity[b]
				1	**2**	**3**		
1	**1a**	1	1	61	31	8	—	—
2	**1a**	3	1	60	35	5	—	—
3	**1a**	3	2	22	49	29	—	—
4	**1a**	2	3	5	79	16	60	86
5	**1a**	3	3	0	95	5	90	96
6	**1a**	6	3	0	96	4	91	97
7	**1b**	3	3	6	76	18	45	87
8	**1b**	4	4	4	86	10	81	89
9	**1b**	6	6	2	85	13	79	88
10	**1c**	3	3	2	91	7	85	95
11	**1d**	3	3	3	95	2	90	98

[a]GC assays of the reaction mixture treated by ice water.
[b]GC purity of isolated product.

base, sodium hydride, so the excessive triphosgene should be used to inhibit the side reaction. When the amount of sodium hydride and triphosgene both increased, the percentage of the product observably increased and the by-product and unchanged reactant increased a little (Entries 5, 6, 9–11). Further increase of triphosgene shows little contribution to the result (Entries 5 and 6).

EXPERIMENTAL

^{1}H NMR spectra were measured on a Varian VA 400-MHz spectrometer with TMS as an internal standard. Melting points were determined using a Yanaco MP-500 apparatus and are uncorrected. HRMS were performed on Micromass EI-TOF-MS instrument. GC were run on HP6890 gas chromatography. GC/MS were performed on HP6890GC/5973MSD gas chromatography/mass selective detector system.

General Method for the Synthesis of *N*-Chloroformyl-*N*-arylcarbamate

In a first reaction flask, 0.013 mol of *N*-arylcarbamate (**1**) was dissolved in 20 mL of toluene. Then 52% sodium hydride in mineral oil was added followed by 8 mL of glyme (ethylene glycol dimethyl ether) within 15 min. The reaction mixture was stirred overnight (ca. 16 h) without external

heating. In a second reaction flask, triphosgene was dissolved in 10 mL of toluene, which was cooled to 0–5 °C. The reaction mixture from the first flask, a thick slurry, was slowly added to the second flask containing the triphosgene solution at 0–5 °C. After addition was complete, the mixture was stirred for additional 0.5 h at the same temperature. Then the reaction mixture is cooled to about °C, and 20 mL of ice water was added to the reaction mixture with vigorous stirring. The toluene layer is separated from the aqueous layer, washed twice with 20 mL of ice water, and dried with $MgSO_4$. The dried toluene solution was then distilled in vacuum to take off the toluene. When the toluene was removed, 2 mL of hexane was added. The hexane solution is then cooled to 0–5 °C, whereupon the product was precipitated, recovered by filtration, washed with additional cold hexane, and dried to obtained a white crystal as product.

Data

Methyl *N*-chloroformyl-*N*-phenylcarbamate (**2a**), mp 127–128 °C (lit.[6] 128 °C); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.4–7.5(m, 3H), 7.2–7.3 (m, 2H), 3.81 (s, 3H); HRMS, m/z: 213.0194 (M^+, calcd. 213.0193), 178.0543 ([M-Cl]$^+$), 134.0608 ([M-Cl-CO_2]$^+$), 119.0353 (base, [M-ClCOOCH3]$^+$).

Methyl *N*-chloroformyl-*N*-(4-trifluoromethoxy)phenylcarbamate (**2b**), mp 96–98 °C (lit.[3] 97–99 °C); ^{1}H NMR (400 MHz, $CDCl_3$), δ: 7.30 (s, 4H), 3.80 (s, 3H); HRMS, m/z: 297.0017 (M^+, calcd. 297.0015), 253.0118 ([M-CO_2]$^+$), 218.0430 ([M-Cl-CO_2]$^+$), 203.0195 (base, [M-Cl$COOCH_3$]$^+$).

Methyl *N*-chloroformyl-*N*-(4-trifluoromethyl)phenylcarbamate (**2c**), mp 109–111 °C; ^{1}H NMR (400 MHz,$CDCl_3$), δ: 7.74 (d, 2H, $J = 8.0$ Hz), 7.41 (d, 2H, $J = 8.0$ Hz), 3.84 (s, 3H); HRMS, m/z: 281.0066 (M^+, calcd. 281.0066), 246.0381 ([M-Cl]$^+$), 237.0170 ([M-CO_2]$^+$), 202.0481 ([M-Cl-CO_2]$^+$), 187.0236 (base, [M-Cl$COOCH_3$]$^+$).

Ethyl *N*-chloroformyl-*N*-(4-trifluoromethyl)phenylcarbamate (**2d**), mp 94–95 °C; ^{1}H NMR (400 MHz,$CDCl_3$), δ: 7.73 (d, 2H, $J = 8.0$ Hz), 7.40 (d, 2H, $J = 8.0$ Hz), 4.30 (q, 2H, $J = 7.2$ Hz); 1.26 (t, 3H, $J = 7.2$ Hz); HRMS, m/z: 295.0225 (M^+, calcd. 295.0223), 223.0013 ([M-HCOOCHCH_2]$^+$), 188.0325 ([M-HCOOCHCH_2-Cl]$^+$), 187.0237 (base, [M-HCOOCHCH_2-HCl]$^+$).

EIMS Data of 3a–3d

N,*N*′-Dimethoxycarbonyl-*N*,*N*′-diphenylcarbamide (**3a**), m/z: 328 (M^+), 209 ([M-PhNCO]$^+$), 178 ([M-PhNCO-OCH_3]$^+$), 150 ([M-PhNCO-OCH_3-CO]$^+$), 134 ([M-PhNCO-OCH_3-CO_2]$^+$), 119 (base, [PhNCO]$^+$).

N,*N*′-Dimethoxycarbonyl-*N*,*N*′-di(4-trifluoromethoxy)phenylcarbamide (**3b**), *m*/*z*: 293 ([M-$CF_3OPhNCO$]$^+$), 262 ([M-$CF_3OPhNCO$-OCH_3]$^+$), 234 ([M-$CF_3OPhNCO$-OCH_3-CO]$^+$), 218 ([M-$CF_3OPhNCO$-OCH_3-CO_2]$^+$), 203 (base, [$CF_3OPhNCO$]$^+$).

N,*N*′-Dimethoxycarbonyl-*N*,*N*′-di(4-trifluoromethoxyl)phenylcarbamide (**3c**), *m*/*z*: 277 ([M-CF_3PhNCO]$^+$), 246 ([M-CF_3PhNCO-OCH_3]$^+$), 218 ([M-CF_3PhNCO-OCH_3-CO]$^+$), 202 (base, [M-CF_3PhNCO-OCH_3-CO_2]$^+$), 187 ([CF_3PhNCO]$^+$).

N,*N*′-Dimethoxycarbonyl-*N*,*N*′-di(4-trifluoromethoxy)phenylcarbamide (**3d**), *m*/*z*: 305 ([M-CF_3PhNCO]$^+$), 260 ([M-CF_3PhNCO-OC_2H_5]$^+$), 232 ([M-CF_3PhNCO-OC_2H_5-CO]$^+$), 216 (base, [M-CF_3PhNCO-OC_2H_5-CO_2]$^+$), 187 ([CF_3PhNCO]$^+$).

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