An Efficient One-Pot Synthesis of Azidoformates from Alcohols Using Triphosgene: Synthesis of *N*-Carbobenzyloxy Azetidin-2-ones

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Abstract: An efficient use of triphosgene for the preparation of various azidoformates from alcohols and sodium azide is described. The method is applied to various chiral alcohols including glucose diacetonide to get the corresponding azidoformates. One of these azidoformates has been successfully utilized for the synthesis of *N*-carbobenzyloxy-β-lactams.

Key words: azidoformate, alcohol, sodium azide, triphosgene, azetidin-2-one

Over the last few years triphosgene [bis(trichloromethyl)carbonate] has emerged as a versatile synthetic auxiliary for the synthesis of some important classes of organic compounds.[1] This white crystalline compound has proved to be safe and advantageous in comparison with its gaseous congener, phosgene. In our recent publication[2] we have reported an efficient use of triphosgene as an acid activator in the construction of β-lactam rings by keteneimine cycloaddition reactions. We have also used triphosgene for the preparation of acylazides from acids and sodium azide.[3] In this communication we wish to report the application of triphosgene as a reagent for one pot preparation of various azidoformates from alcohols and sodium azide under very mild reaction conditions. The utility of azidoformates for the synthesis of *N*-carbobenzyloxy-β-lactams is also described in this communication.

Interest in the synthesis of azidoformates stems from their increasing use as protecting agents for amino groups in peptide synthesis.[4] They are valuable synthetic intermediates for many heterocyclic compounds.[5]

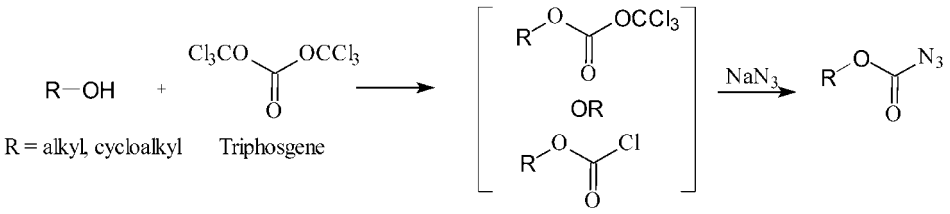
Azidoformates are generally prepared by reacting corresponding chloroformates with alkali metal azides.[6] The other method for azidoformates involves nitrosation of carbazates using sodium nitrite and acetic acid. The carbazates are prepared from alcohols, acid chloride and hydrazine.[7] The azidoformates are also prepared by reacting alcohol with hazardous phosgene[8] to generate corresponding chloroformate which is further reacted with alkali metal azide or hydrazoic acid.

Triphosgene has been employed for the one-pot preparation of azidoformates.[9] Various alcohols were reacted with triphosgene in the presence of sodium azide and triethylamine at 0 °C followed by stirring at room temperature for 24 h afforded azidoformates in very good yields (Table 1). The in situ generated chloroformate or carbonate reacts directly with sodium azide to get azidoformate (Scheme 1).

The reaction conditions are very mild and can be employed for the synthesis of various chiral azidoformates starting from chiral alcohols (see entries 4–10, Table 1). The diacetonide, readily available from D-glucose,[10] was also efficiently transformed to its azidoformate in very good yield (see entry 5, Table 1).

Methoxy alcohol was prepared from (+)-3-carene, naturally occurring monoterpene, by our reported procedure.[2b] This alcohol also gave azidoformate in excellent yield when reacted with triphosgene and sodium azide (see entry 8, Table 1).

After developing an efficient method for azidoformate we were interested in the application of these azidoformates for their synthetic utility. We have successfully used benzylazidoformate for the synthesis of *N*-carbobenzyloxy-β-lactams (Scheme 2). This application was a part of our on going research program on the synthesis β-lactams.[11]



Scheme 1

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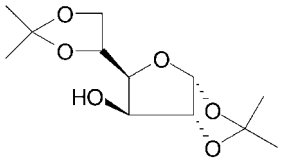
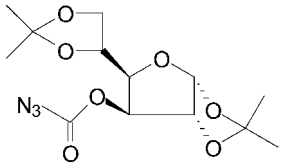
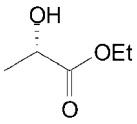
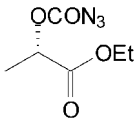
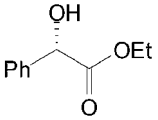
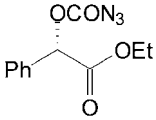
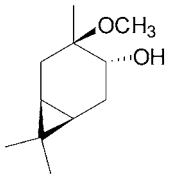
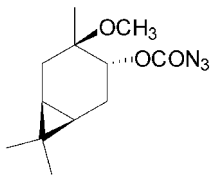
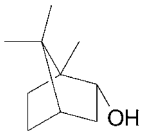
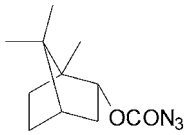
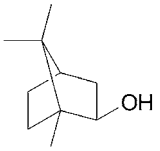
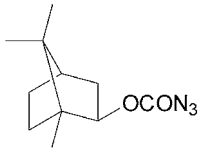
Table 1 Preparation of Various Azidoformates from Alcohols and Sodium Azide Using Triphosgene

Entry No.	Alcohol	Azidoformate	Yield (%)
1	Benzyl alcohol	Benzyl azidoformate	77
2	Cyclohexyl alcohol	Cyclohexyl azidoformate	90
3	$CH_3(CH_2)_6CH_2OH$	$CH_3(CH_2)_6CH_2OCON_3$	81
4	L-Menthol	Menthyl azidoformate	64
5			65
6			69
7			66
8			86
9			86
10			78

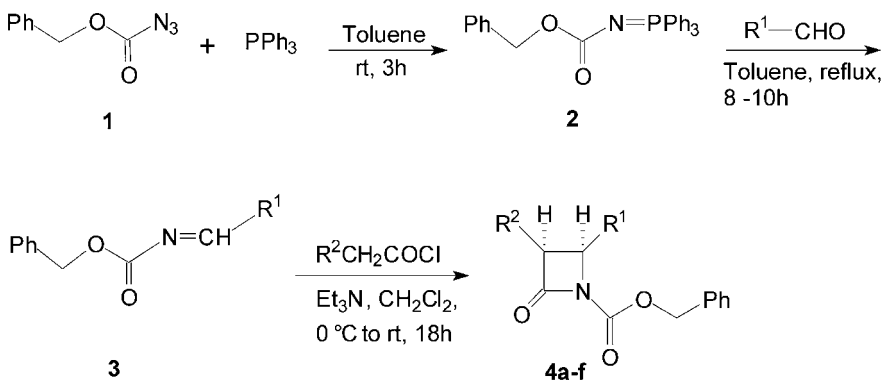
The iminophosphorane, which is readily generated from benzyl azidoformate and triphenyl phosphine, was treated with benzaldehyde to get aza-Wittig reaction product in very good yield. This product was used further for the cycloaddition reaction with ketene, generated from acid chloride, using Staudinger reaction conditions to get *N*-carbobenzyloxy-β-lactams (**4a**–**f**)[12] in good yields (Table 2).

In summary, we have demonstrated a general one-pot method for the preparation of azidoformates from alcohols and sodium azide using triphosgene. We have also shown the utility of azidoformate for the synthesis of *N*-carbobenzyloxy-β-lactams. The work on further application of azidoformates as well as chiral azidoformates for asymmetric synthesis is in progress.

Table 2 Synthesis of *N*-Carbobenzyloxy azetidin-2-ones (**4a**–**f**)

Entry No.	Compound	R^1	R^2	Yield (%)[a,b]	Mp (°C)
1	**4a**	-Ph	-OPh	78	128
2	**4b**	-PMP	-OPh	80	106
3	**4c**	-PMP	-OBz	73	95
4	**4d**	-Styryl	-OPh	56	Thick oil
5	**4e**	-Styryl	-OBz	65	Thick oil
6	**4f**	-Furfuryl	-OPh	84	109

[a] Isolated yields.
[b] All the compounds gave satisfactory elemental analyses and spectral data.



Scheme 2

Acknowledgement

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(9) *General Experimental Procedure for the Preparation of Azidoformates:* To a stirred solution of alcohol (1 mmol) and sodium azide (2 mmol) in acetone (10 mL) was added triethylamine (1.5 mmol) at 0 °C. The reaction mixture was stirred at this temperature for 15 min and a solution of triphosgene (0.5 mmol) in acetone (5 mL) was added dropwise at 0 °C over about 15 min. The reaction mixture was stirred at this temperature for 1 h and slowly allowed to warm up to room temperature. It was stirred for 24 h at room temperature. The reaction mixture was filtered to remove insoluble salts and the filtrate was diluted with an equal volume of water. It was extracted with EtOAc (3 × 20 mL) and the organic extract was washed with water (10 mL) and brine (10 mL) and dried (Na_2SO_4). The solvent was removed and the residue was purified by column chromatography to get pure azidoformate in good yield (Table 1). [**CAUTION**: We did not observe any untoward incidence while working with azidoformates. However, the use of hood and safety shield is recommended as *tert*-butyl azidoformate is known to decompose above 80 °C with apparent detonation.[13]]. Spectral data for benzyl azidoformate ^{1}H NMR ($CDCl_3$, 200MHz): δ 5.25 (s, 2 H), 7.45 (s, 5 H); IR (KBr, $CHCl_3$) 2166, 2140, 1736, 1498, 1456, 1377, 1236 cm^{-1}; Anal. Calcd for $C_8H_7N_3O_2$: C, 54.23; H, 3.98; N, 23.71. Found: C, 54.47; H, 3.95; N, 23.67.

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(12) *General Experimental Procedure for the Synthesis of N-Carbobenzyloxy-β-lactams* (**4a**–**f**): To a solution of benzyl azidoformate (1 mmol) in toluene (10 mL) was added triphenyl phosphine (1 mmol) and the reaction mixture was stirred at room temperature for 3 h. Aldehyde (1 mmol) was added to the reaction and refluxed for 8–10 h. Solvent was removed under reduced pressure and dry diethyl ether (15 mL) was added to the residue. The solid triphenyl phosphineoxide separated was removed by filtration and the solvent was removed to get imine **3**. These imines were found to be unstable and used further without purification. A solution of above imine (1 mmol) in dichloromethane (15 mL) and triethylamine (4 mmol) was cooled to 0 °C and

a solution of acid chloride in CH_2Cl_2 (10 mL), was added slowly with stirring in about 20 min. The reaction mixture was allowed to warm up to room temperature and stirred for 18 h. It was washed with water (15 mL), saturated sodium bicarbonate solution (10 mL), brine (10 mL) and dried over sodium sulfate. Solvent was removed under reduced pressure and the crude product was purified by column chromatography to get β-lactams **4a**–**f** in good yield. Spectral data for β-lactam (**4a**): ^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.87 (d, *J* = 14.7 Hz, 1 H), 4.75 (d, *J* = 4.4 Hz, 1 H), 4.91 (d, *J* = 14.7 Hz, 1 H), 5.40 (d, *J* = 4.4 Hz, 1 H), 6.70 (d, *J* = 7.8 Hz, 2 H), 6.85 (t, *J* = 7.8 Hz, 1 H), 7.10–7.33 (m, 12 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 44.10, 61.34, 82.04, 115.45, 121.84, 127.84, 128.13, 128.53, 128.76, 129.05, 132.61, 134.67, 156.80, 159.56, 165.48; IR (KBr, $CHCl_3$) 1758, 1596, 1494, 1236 cm^{-1}; Anal. Calcd for $C_{23}H_{19}NO_4$: C, 73.98; H, 5.12; N, 3.75. Found: C, 73.79; H, 4.98; N, 3.77.

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