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Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry

Publication details, including instructions for authors and subscription information: <u>http://www.tandfonline.com/loi/lsyc20</u>

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To cite this article: Radhakrishnan Sridhar & Paramasivan T. Perumal (2003): Synthesis of Acyl Azides Using the Vilsmeier Complex, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 33:4, 607-611

To link to this article: http://dx.doi.org/10.1081/SCC-120015815

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SYNTHETIC COMMUNICATIONS[®] Vol. 33, No. 4, pp. 607–611, 2003

Synthesis of Acyl Azides Using the Vilsmeier Complex

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ABSTRACT

A facile synthesis of substituted cinnamoyl and benzoyl azides starting from their respective acids using DMF and $POCl_3$ in the presence of sodium azide is reported.

Key Words: Chloromethyleniminium ion; Acyl azide; Nitrene; Nitrogen heterocycle.

The electrophilic substitution of chloromethyleniminium ion, termed as the Vilsmeier reaction is feasible on compounds with electron rich substituents.^[1] Currently, we are engaged in the synthesis of nitrogen heterocycles through the versatility of the DMF–POCl₃ Vilsmeier complex.^[2]

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DOI: 10.1081/SCC-120015815 Copyright © 2003 by Marcel Dekker, Inc. 0039-7911 (Print); 1532-2432 (Online) www.dekker.com

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Acyl azides continue to contribute much towards heterocyclic synthesis.^[3] Formation of nitrene by acyl azides pave the way to addition reactions, radical induced decompositions and rearrangements thereby leading to excellent synthetic routes.^[3–5]

A number of methods are available for the synthesis of acyl azides by reacting acid chlorides,^[6] acid anhydrides,^[13] aldehydes^[7] or esters^[8] with reagents like sodium azide,^[9] tetraalkylammonium,^[10a] guanidium,^[10b] tributylstannyl,^[11] trimethylsilyl^[12] and diethylaluminium azides^[8] or with pyridinium hydrazoic acid salt.^[14] Synthesis of acyl azides using polymer supported reagent^[15] has been reported. However, among these, only a very few are reproducible but rather expensive.

Phosgene,^[6] employed alongwith DMF in the earlier method for the synthesis of acyl azide, is highly toxic. We have chosen DMF and POCl₃, which are milder, for the preparation of acyl azide. Addition of POCl₃ facilitates the reaction to be one-pot since it forms the Vilsmeier adduct with DMF at first, which then complexes with the carboxylic acid and reacts with sodium azide to form the acyl azide in excellent yield. When the reaction was carried out with triethylammonium salt of carboxylic acid in the presence of sodium azide, the same product was obtained but in lesser yield (70%) due to the equilibrium existing between the carboxylic acid adduct and the DMF–POCl₃ complex (Sch. 1).

Reactions carried out at elevated temperatures resulted in the rearrangement of acyl azide and hydrolysis of the azide occurs in the presence of moisture. Higher yields were obtained by stirring the reaction mixture at temperatures slightly above $10-15^{\circ}$ C for about 3 h, under moisture free conditions. This method for the preparation of acyl azides is very simple without requiring any drastic experimental conditions. The yield, melting point and reaction time are summarized in the Table 1.

The excellence of this method lies in the in situ complex generation by $DMF-POCl_3$ and the carboxylic acid, which then reacts with sodium azide resulting in the formation of carboxylic acid azide. Thus this method provides an easy route to acyl azides directly from carboxylic acids.

EXPERIMENTAL PROCEDURE

All the solvents were distilled prior to use from an appropriate drying agent. Melting points reported are uncorrected. Infrared spectra were recorded as KBr pellets on a Perkin Elmer FT-IR instrument. Nuclear Magnetic Resonance spectra were recorded on a Brucker spectrometer, at 300 MHz (PMR) and at 75 MHz (¹³C NMR). Mass spectra were obtained on a Perkin Elmer Mass Spectrometer.

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Experimental Procedure for Compounds 2a-2e and 4a-4c

To a stirred solution of carboxylic acid (0.005 mol) and triturated sodium azide (0.0055 mol) mixture in 5 mL of freshly dried DMF at icecold condition, 0.015 mol of freshly distilled POCl₃ was added very slowly. The reaction mixture was stirred at $10-15^{\circ}$ C for 2-3 h. Then it was poured into crushed ice, followed by neutralization with 10% sodium hydroxide solution to neutral pH. The crude products obtained were purified by recrystallization from an ethyl acetate and petroleum ether mixture.

Spectral data for compound 2a: ¹H NMR (300 MHz, CDCl₃) δ : 7.772–7.717 (d, J = 16.5 Hz, 1H), 7.515–7.281 (m, 5H), 6.443–6.388 (d, J = 16.5 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ : 172.003, 146.676, 133.735, 131.049, 128.943, 128.494, 118.983; IR (KBr) cm⁻¹: 2148,

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Product ^a	Substituent		Viald	m n ^b	Penction
	R_1	R_2	(%)	(°C)	time (h)
2a	Н	Н	90	86 (86) ^[16]	2
2b	Me	Н	92	110 ^c	2
2c	Н	Cl	95	140 ^c	3
2d	NO_2	Н	88	120 ^c	2
2e	OMe	OMe	97	160 ^c	3
4a	Н	Н	80	$-(31-32)^{[17]}$	2
4b	Н	Cl	85	46 (46) ^[17]	3
4c	NO_2	Н	90	67 (67–69) ^[17]	3

Table 1. Acyl azides synthesized using the Vilsmeier complex.

^aProducts were characterized by ¹H NMR, ¹³C NMR, IR, and mass spectra. ^bMelting points recorded were uncorrected.

^cGave satisfactory elemental analysis data.

2103, 1683, 1202, 980, 941; MS (*m*/*z*): 145 (M-28). Analysis: C₉H₇N₃O requires: C, 62.43; H, 4.05; N, 24.28. Found: C, 62.54; H, 4.15; N, 24.19.

ACKNOWLEDGMENT

One of the authors (R. S.) is thankful to Council of Scientific and Industrial Research, New Delhi for financial support.

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Received in the UK December 3, 2001



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