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A Novel Route to the Synthesis of 3-Pyridine Carboxaldehydes by Vilsmeier Reagent

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A NOVEL ROUTE TO THE SYNTHESIS OF 3-PYRIDINE CARBOXALDEHYDES BY VILSMEIER REAGENT

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Abstract: 2-Chloro-5-aryl-3-pyridine carboxaldehydes are obtained by Vilsmeier reaction of 4-aryl-3-buten-2-one oxime. The suspected intermediate *N*-(2-arylethenyl)acetamides also give the same 2-chloro-5-aryl-3-pyridine carboxaldehydes under identical reaction condition.

3-Pyridine carboxaldehyde derivatives are valuable intermediates for the synthesis of a wide variety of biologically active compounds which act as muscarinic agonists[1a], anticonvulsant[1b], antimicrobial and antitumor[1c], bypoglycemic[1d], and antiulcer[1c] agents.

Halomethyleniminium salt is a reactive intermediate involved in the Vilsmeier-Haack-Arnold reaction[2]. The Vilsmeier reagent is utilised for formylation of various activated aromatic and heteroaromatic compounds[3]. Recently from our laboratory we have reported the synthesis of *N*-formyl lactams by the treatment of Vilsmeier reagent on various cyclic ketoxime[4]. Apart from this various functional groups which are

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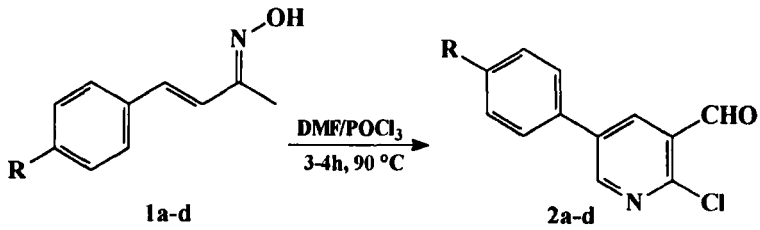
strategically located have been effected to cyclization[5]. Earlier reports from our laboratory describe a new mild method for the synthesis of various nitrogen and oxygen based heterocyclic compounds using the Vilsmeier reagent[6].

As part of our studies on this versatile reagent, we have developed a simple and facile route towards the synthesis of 2-chloro-5-phenyl-3-pyridine carboxaldehyde from 4-phenyl-3-buten-2-one oxime. Accordingly, 4-phenyl-3-buten-2-one oxime **1a** on treatment with 8 equivalents of Vilsmeier reagent in DMF as solvent at 90 °C for 3-4 h, cyclizes to give 2-chloro-5-phenyl-3-pyridine carboxaldehyde **2a** in 19 % yield. Similarly other substituted oximes underwent cyclization smoothly (Scheme 1).

Scheme 1



1a-d **2a-d**

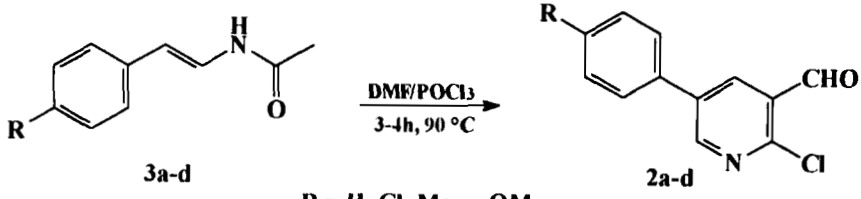
R = H, Cl, Me or OMe

Initially, the reaction of 4-phenyl-3-buten-2-one oxime **1a** with Vilsmeier reagent might have undergone the Beckmann rearrangement to give *N*-(2-phenylethenyl) acetamide **3a** and *N*-methyl cinnamamide. This *N*-(2-

phenylethenyl)acetamide undergoes further reaction with Vilsmeier reagent to give 3-pyridine carboxaldehyde. Literature survey reveals that there is not much report regarding the reaction of enaminoketone with Vilsmeier reagent.

In order to confirm that the reaction proceeds through the Beckmann rearrangement, we independently carried out the following reaction. The Beckmann rearrangement of 4-phenyl-3-buten-2-one-α-oxime with PCl_5 to give *N*-(2-phenylethenyl)acetamide **3a**[7]. Reaction of **3a** with Vilsmeier reagent under identical condition of **1a** affords the same 2-chloro-5-phenyl-3-pyridine carboxaldehyde in moderate yield (Scheme 2). All the products were characterised by ^1H NMR, ^{13}C NMR, Mass. The overall yields of the products are summarised in Table 1.

Scheme 2



3a-d **2a-d**

R = H, Cl, Me or OMe

The two-step process improved the yield of 3-pyridine carboxaldehydes. The decrease in the yield of 3-pyridine carboxaldehydes in one-pot Beckmann rearrangement of oximes **1a-d** under Vilsmeier condition may be attributed to formation of other product along with *N*-(2-arylethenyl)acetamide in the initial step.

Table 1. Reaction products of 4-aryl-3-buten-2-one oximes and *N*-(2-arylethenyl)acetamides with Vilsmeier reagent

Sl. No	Starting material	R	Product[a]	% Yield[b]	m.pt. °C
1	**1a**	H	**2a**	19	83
	3a	H	**2a**	40	83
2	**1b**	Cl	**2b**	30	157
	3b	Cl	**2b**	45	157
3	**1c**	CH_3	**2c**	21	126
	3c	CH_3	**2c**	39	126
4	**1d**	OCH_3	**2d**	18	–[c]
	3d	OCH_3	**2d**	23	–[c]

a: All the products were duly characterised by ^{1}H NMR, ^{13}C NMR, Mass, IR, elemental analysis.
b: Isolated yield. c: Dense liquid

The synthesis of pyridine derivatives has been previously reported by novel dimerisation of *N,N*-dialkylcyanoacetamide with hot $POCl_3$[8]. Thus it is a first report on the synthesis of 2-chloro-5-phenyl-3-pyridine carboxaldehyde from both 4-phenyl-3-buten-2-one oxime and *N*-(2-phenylethenyl)acetamide using Vilsmeier reagent. The formation of 2-chloro-5-phenyl-3-pyridinecarboxaldehyde is probably due to Beckmann rearrangement, double formylation at activated methyl group followed by 6π electrocyclic ring closure and then hydrolysis.

Typical Experimental Procedure

Preparation of 2-chloro-5-phenyl-3-pyridine carboxaldehyde(2a)

N-(2-phenylethenyl)acetamide (**3a**, 0.805 g, 5 mmol) was dissolved in DMF (9.66 mL, 60 mmol) and cooled to 0 °C. $POCl_3$ (3.73 mL, 40 mmol) was added

dropwise with stirring over a period of 20-30 min. The reaction mixture was stirred for 1 h at room temperature and then stirred at 90 °C for 4 h. After the completion of reaction the reaction mixture was cooled and poured into ice water, neutralised with sodium acetate. The crude solid was filtered, the mother liquid was extracted with chloroform (3 × 50 mL), dried over sodium sulphate and evaporated to dryness. The resulting crude product was purified by column chromatography (90 : 10 petroleum ether : ethyl acetate) to afford pure **2a** as grey solid in 40 % yield. m.p 83 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 10.45 (s, 1H), 8.77 (d, 1H, J = 2.7 Hz), 8.36 (d, 1H, J = 2.7 Hz), 7.57-7.42 (m, 5H); C^{13} NMR (75 MHz, $CDCl_3$): δ 189.28, 152.19, 135.91, 135.16, 134.87, 129.60, 129.43, 129.12, 128.43, 127.05; IR (KBr) 1696 cm^{-1}; MS m/z 217(M^+). Anal. Calcd. for $C_{12}H_8ClNO$: C, 66.22; H, 3.70; N, 6.44; Found: C, 65.98; H, 4.02; N, 6.47.

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