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Tetrahedron 62 (2006) 8398–8403
Tetrahedron

Facile and selective synthesis of chloronicotinaldehydes by the Vilsmeier reaction

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Received 16 January 2006; revised 30 May 2006; accepted 8 June 2006
Available online 7 July 2006

Abstract—Eleven enamides were prepared by adopting different procedures. The various enamides prepared were subjected to Vilsmeier reaction using (i) $POCl_3$/DMF; (ii) diphosgene/DMF; (iii) triphosgene/DMF leading to the formation of various multisubstituted chloronicotinaldehydes. Studies carried out indicate that Vilsmeier reagent concentration and the replacement of $POCl_3$ by diphosgene or triphosgene, provides excellent selectivity and higher yields. Under modified reaction conditions one can get only chloronicotinaldehydes and not the chloropyridines as products. The various advantages in using diphosgene and triphosgene are illustrated. The mechanism of formation of chloronicotinaldehyde was discussed.

1. Introduction

Among heterocyclic compounds, pyridine and its derivatives are important compounds and are present in many biological systems.[1,2] Among the various applications of these pyridine derivatives, the pharmaceutical and agrochemical[3] applications are more important. Extensive studies have been carried out on the synthesis of pyridine compounds owing to their wide importance as drugs, biologically active natural products, and for other various applications. Introducing a formyl group into the aromatic ring system of pyridine is particularly significant, considering the lack of reactivity of pyridines toward electrophilic substitution reactions compared to benzenoids. The formyl group present on the pyridine ring opens up the possibility of carrying out a diverse range of functional group transformations. Furthermore, chloronicotinaldehydes are very good precursors for annulation of a wide variety of heterocyclic ring systems.

Vilsmeier reaction was initially used for the formylation of activated aromatic substrates and carbonyl compounds;[4] it is now used as a powerful synthetic tool for the construction of many heterocyclic compounds[5–10] such as quinolines, indoles, quinozolines, and pyridines. The synthesis of various substituted chloronicotinaldehydes using Vilsmeier reaction have been much less reported in the literature.[11,12] Meth-Cohn and Westwood reported the synthesis of 2-chloropyridines, pyridones, and quinolines using enamides under Vilsmeier reaction conditions.[12] This led us to conduct a systematic investigation on the feasibility of cyclization of enamides under Vilsmeier conditions to synthesize chloronicotinaldehydes. These chloronicotinaldehydes are very good precursors for the synthesis of arachidonic acid metabolite heterocyclic analogues 8-HETE.[13,14] Our continuing interest in the synthesis of heterocycles for biological activity[15] led us to report a facile and an efficient method for the synthesis of various substituted chloronicotinaldehydes (pyridine-3-carboxaldehyde) from enamides. Studies carried out on the formation of chloronicotinaldehydes in Vilsmeier reactions dramatically improved the selectivity and yield by using diphosgene/triphosgene compared to classical method of using $POCl_3$ in the formation of Vilsmeier reagent.

2. Results and discussion

Various enamides (**1**–**11**; Scheme 1) were prepared for the purpose of synthesizing various chloronicotinaldehydes (**12**–**22**; Scheme 1). Enamides **1**–**5** were synthesized by condensing appropriate aldehyde with benzylamine[16] to form initially a Schiff base and followed by acetylation[17] using acetic anhydride and triethylamine. Aldol condensation of benzaldehyde/*p*-methoxybenzaldehyde with acetone provided an α,β-unsaturated ketones, which were converted into the corresponding oximes and subsequent treatment using PCl_5[11] afforded enamides **6** and **7**. Enamide **8** was prepared by treating propiophenone oxime with Fe powder in the presence of acetic anhydride and acetic acid.[18] β-Keto ester was first converted into an enamine derivative,

Keywords: Enamides; Vilsmeier reaction; Diphosgene/triphosgene; Chloronicotinaldehydes; Selectivity; Mechanism.
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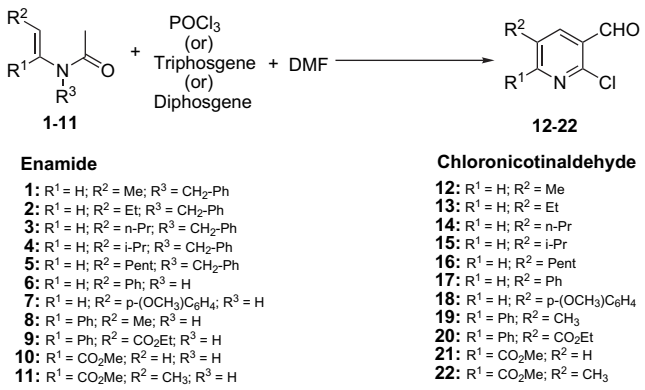
0040–4020/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.06.026

which was acetylated to give enamide[19] **9**. Serine and threonine methyl ester hydrochlorides[20] were prepared and then converted into the corresponding enamides[21,22] **10** and **11**.



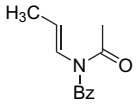
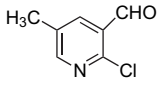
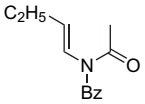
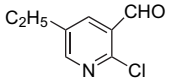
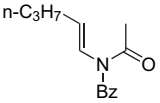
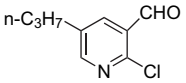
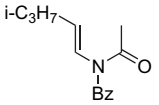
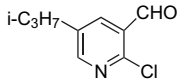
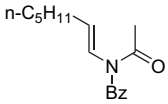
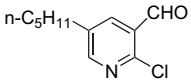
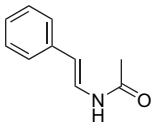
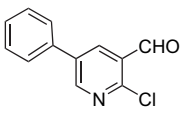
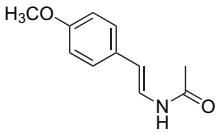
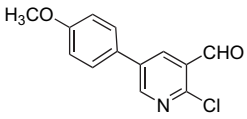
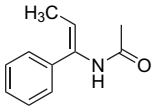
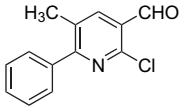
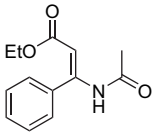
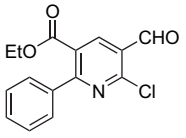
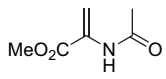
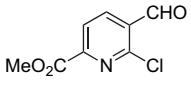
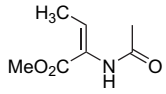
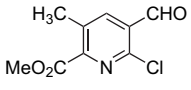
Scheme 1.

Scheme 1 illustrates the synthesis of various chloronicotinaldehydes (Table 1). A DMF solution of enamide was added to the excess Vilsmeier reagent (7 equiv) initially prepared from DMF and $POCl_3$/diphosgene/triphosgene. The reaction mixture was held at room temperature and then refluxed at ~75 °C. The crude product was extracted and purified by column chromatography (Table 1). Various chloronicotinaldehydes **12**–**22** were synthesized with very good yields by using enamides **1**–**11** that are listed in Table 1.

The results arranged in Table 2 show that the selectivity toward the formation of chloronicotinaldehyde improved upon increasing Vilsmeier reagent concentration. Enamide **1** was used for the studies as a representative example to understand selectivity and yield improvements. Upon using 2.5 equiv of Vilsmeier reagent (entry 1; Table 2) the yield of chloronicotinaldehyde **12** was less and 2-chloro-5-methylpyridine **23** was the major product (Scheme 2). Using excess of Vilsmeier reagent (7 equiv entry 5; Table 2), chloronicotinaldehyde **12** was obtained as the major product with a trace amount of 2-chloro-5-methylpyridine **23** (Scheme 2). Replacing $POCl_3$ by triphosgene (entries 9 and 10; Table 2) provided the same selectivity in the formation of chloronicotinaldehyde but with higher yields (Scheme 2). The diphosgene (liquid) or triphosgene (solid) are employed because they are safe substitutes for the toxic phosgene gas, offer mild reaction conditions, provide excellent yields, and avoid the formation of inorganic phosphorus salts. The same procedure was extended to other enamides **2**–**11** and the corresponding chloronicotinaldehydes **13**–**22** were synthesized in higher yields (Table 1).

A mechanism is proposed to explain the formation of chloronicotinaldehydes with selectivity (Scheme 3). The enamide initially reacts with Vilsmeier reagent to form bis-enamine having a chloro group (Scheme 3). The net result is the formation of a more nucleophilic bis-enamine. The bis-enamine undergoes formylation to produce two possible mono-formylated bis-enamines. The mono-formylated bis-enamine can undergo cyclization to give 2-chloro-5-methyl pyridine[23] (**23**) or the mono-formylated bis-enamine can undergo second formylation before undergoing cyclization. The second formylation process is quite possible at higher concentrations

Table 1. Synthesis of substituted chloronicotinaldehydes

S.No.	Enamides (**1**–**11**)	Chloronicotinaldehydes (**12**–**22**)	Yields[a] (%)
1			94
2			92
3			92
4			91
5			90
6			92
7			92
8			90
9			88
10			90
11			90

[a] Isolated yields using diphosgene/triphosgene.

of Vilsmeier reagent and the same was observed (Table 2; Scheme 2). The di-formylated bis-enamine undergoes cyclization to give the substituted chloronicotinaldehyde (pyridine-3-carboxaldehyde), which is the main product. The products isolated were substituted chloronicotinaldehyde and benzyl chloride (in the case of enamides **1**–**5**). The dimethylamine remains in aqueous phase as amine hydrochloride after work up. These observations clearly indicate that under modified Vilsmeier reaction conditions (i.e., at higher Vilsmeier reagent concentrations) the enamide undergoes