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A facile method for the synthesis of nicotinonitriles from ketones via a one-pot chloromethyleneiminium salt mediated three-component reaction

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We dedicate this Letter to our beloved teacher and research guide Dr. C. V. Asokan who passed away on February 3, 2007 due to leukaemia

Abstract—Simple enolizable ketones such as acetophenones and benzalacetones were treated with malononitrile under Vilsmeier–Haack reaction conditions to afford 2-chloronicotinonitriles. The reaction proceeds via a one-pot chloromethyleneiminium salt mediated three-component reaction followed by sequential cyclization and aromatization under Vilsmeier–Haack reaction conditions.
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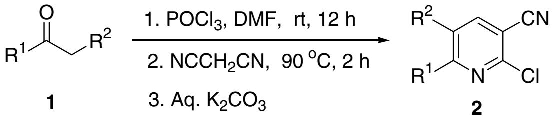
The Vilsmeier–Haack reaction has emerged as a popular tool for the formylation and acylation of a large number of aromatic and heteroaromatic compounds.[1–4] Appropriately substituted alkenes, alcohols, acetals, ketals, dithioketals and ketene dithioacetals undergo a variety of transformations on treatment with the Vilsmeier–Haack reagent.[5–12] Typically the reactions of active methylene compounds with reagents of the Vilsmeier type afford β-chloromethyleneiminium salts or β-chlorovinyl aldehydes,[13] which have been recognized as useful intermediates in heterocyclic synthesis.[1] We have made attempts to explore the synthetic utility of these functionalized chloromethyleneiminium salt intermediates for the synthesis of heterocyclic compounds, in particular substituted pyridines[14–18] and pyrroles.[19,20] Recently, we have shown that the Vilsmeier–Haack reagent can act as a Knoevenagel base/buffer for the synthesis of 5-aroyl-2-chloro-6-(methylsulfanyl)nicotinonitriles from α-oxoketene dithioacetals.[18] We envisioned that this new strategy would be applicable to simple enolizable ketones for the synthesis of a variety of pyridine derivatives. Our results, which are communicated in this Letter, demonstrate an example of the Vilsmeier–Haack reaction as a three-component reaction for the synthesis of nicotinonitriles from acetophenones and benzal acetones. This approach is novel in heterocyclic synthesis and should have wide applications in chloromethyleneiminium salt mediated annulation reactions.

On treatment with the Vilsmeier–Haack reagent, enolizable carbonyl compounds undergo iminoalkylation to afford chloro-substituted vinamidinium salts. The synthetic potential of these iminium salts has been exploited for the synthesis of substituted pyrroles[21–23] and pyridines[24] employing multistep reaction strategies. During the course of our attempts to synthesize functionalized chloropyridines from α-oxoketenedithioacetals,[18] we observed that functionalized methyleneiminium salts undergo in situ addition reactions with malononitrile to afford simple Knoevenagel type adducts, which are cyclized and aromatized under the same conditions to give substituted 2-chloropyridines. In an attempt to prepare 6-aryl-2-chloropyridines, which are usually synthesized via a three-step reaction from acetophenones,[25] simple



Scheme 1.

Keywords: Vilsmeier–Haack reaction; Three-component synthesis; Nicotinonitrile; Knoevenagel reaction.

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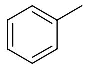
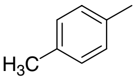
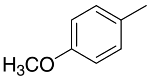
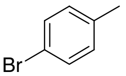
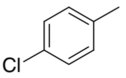
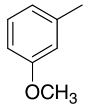
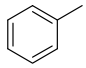
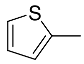
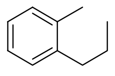
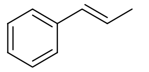
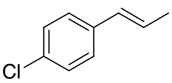
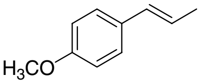
Table 1. Synthesis of 4,5-disubstituted 2-chloronicotinonitriles **2**

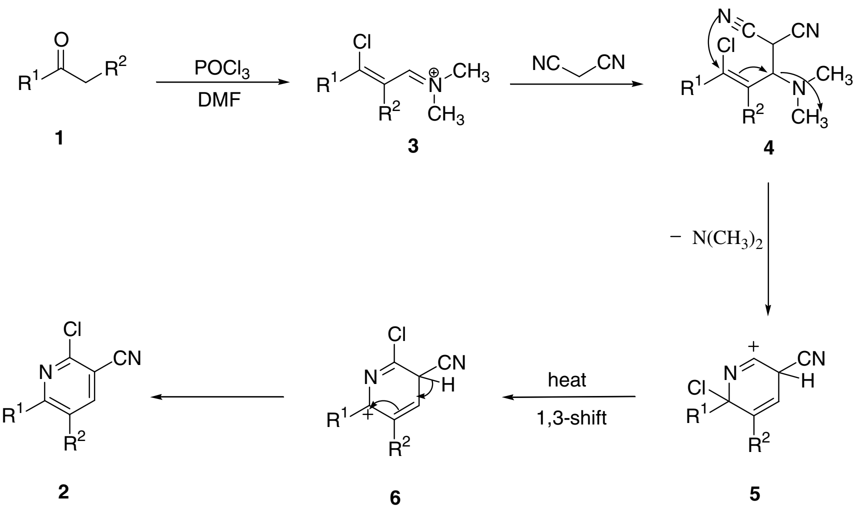
1, 2	R^1	R^2	Yield (%)
a		H	52
b		H	64
c		H	44
d		H	37
e		H	52
f		H	49
g		CH_3	79
h		H	5
i			87
j		H	24
k		H	58
l		H	2

enolizable ketones such as acetophenones were treated with malononitrile under the Vilsmeier–Haack reaction conditions. According to the reported procedure, the Vilsmeier–Haack reagent was prepared and ketone **1a** was added. The reaction mixture was stirred at room temperature for 12 h, followed by addition of 1.5 equiv of malononitrile and heating at 90 °C for 2 h. Work-up using aqueous saturated potassium carbonate solution and purification of the crude product by column chromatography using hexane/ethyl acetate gave 6-aryl-2-chloronicotinonitrile **2a** in good yield.[26] It is interesting to note that functionalized ketones such as benzalacetones **1b–l** also react under these conditions to give the corresponding chloropyridines **2b–l** (Scheme 1, Table 1).

A literature survey showed that 2-chloro-6-phenylnicotinonitrile is an important substrate for the synthesis of natural products such as vitamins.[25] In 1998, Cyranski et al. reported crystallographic studies on this substance and showed that the molecule was not planar.[27] The angle between the phenyl group and the pyridinyl group is 3° and hence the symmetry of the molecule is lost. This was also evident from the ^{13}C NMR data herein reported.[25]

The mechanism for the formation of pyridines **2a–l** can be explained by the well known Vilsmeier–Haack reaction of acetophenones[1] for the formation of functionalized chloromethyleneiminium salt intermediates **3** followed by addition of malononitrile to the intermediates, which results in the formation of adducts **4**. The adducts, on intramolecular cyclization with elimination of dimethylamine and 1,3-shift of the chlorine atom followed by aromatization affords 2-chloropyridines **2** (Scheme 2).

In conclusion, simple enolizable ketones undergo one-pot iminoalkylation followed by sequential condensation with malononitrile, cyclization and aromatization under Vilsmeier–Haack reaction conditions to afford 2-chloronicotinonitriles. This methodology opens a



Scheme 2.

new route to a one-pot multicomponent reaction under Vilsmeier–Haack reaction conditions.

Acknowledgements

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.06.032.

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26. *Representative experimental procedure*: The Vilsmeier–Haack reagent was prepared by the slow addition of $POCl_3$ (2.4 mL, 25 mmol) to DMF (21 mL, 250 mmol) at 0 °C followed by stirring at room temperature for 15 min. Appropriate acetophenone (5 mmol) was added to this reagent. The reaction mixture was stirred at room temperature for 12 h, followed by the one-pot addition of malononitrile (1 g, 15 mmol) and heating at 90 °C for 2 h. The reaction mixture was poured into aqueous saturated potassium carbonate solution (100 mL), and extracted with ethyl acetate (3×50 mL). The combined organic layer was evaporated to give a crude product which was purified by column chromatography using hexane/ethyl acetate (95:5) to afford 4,5-disubstituted 2-chloronicotinonitriles **2a**–**l**. 2-Chloro-6-phenylnicotinonitrile **2a** was prepared by the reaction of acetophenone **1a** (600 mg, 5 mmol) with malononitrile in the presence of Vilsmeier–Haack reagent and the crude reaction mixture was column chromatographed over silica gel (60–120 mesh) using hexane/ethyl acetate as the eluent. The yellow coloured solid was characterized on the basis of spectral data; mp 112–114 °C; yield 560 mg (52%); [$C_{12}H_7ClN_2$ requires C, 67.15; H, 3.29; N, 13.05; Cl, 16.52. Found: C, 67.37; H, 3.31; N, 13.09; Cl, 16.61.]; ν_{max} (KBr) 3040, 2220 (CN), 1580 (CO), 1447, 1342, 1196 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29 (1H, d, $J = 11.4$ Hz, Py 5-H), 7.46–7.54 (3H, m, Ph), 7.79 (2H, d, $J = 8$ Hz, Ph), 8.06 (1H, d, $J = 11.4$ Hz, Py 4-H); ^{13}C NMR (75.47 MHz, $CDCl_3$) δ 111.4, 113.2, 119.3, 127.7, 129.0, 129.3, 131.8, 132.4, 134.9, 151.0, 154.9; EI-MS m/z: 216 (M^+ [^{37}Cl], 11%), 214 (M^+ [^{35}Cl], 27), 180 (18), 179 (100), 154 (12), 152 (59), 127 (5), 125 (23), 105 (4), 99 (11), 77 (22).
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