

## An efficient and convenient $\text{KF}/\text{Al}_2\text{O}_3$ mediated synthesis of nitriles from aldehydes

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**Abstract**— $\text{KF}/\text{Al}_2\text{O}_3$  brings about a facile one-pot and economical conversion of various aryl and alkyl aldehydes into the corresponding nitriles in high yields by reaction with hydroxylamine hydrochloride.

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Nitriles are useful precursors for the synthesis of amines, amides, ketones, carboxylic acids and esters. Nitriles are used for the preparation of 1,2-diarylimidazoles as potent anti-inflammatory agents,<sup>1</sup> thiazole analogues as inhibitors of superoxide,<sup>2</sup> benzamides possessing activity of fibrinogen antagonists,<sup>3</sup> tetrazole derivatives as anticoronavirus drugs,<sup>4</sup> triazolo[1,5-*c*]pyrimidines with potential antiasthma activity,<sup>5</sup> and the commercially important angiotensin 1 receptor ligands, losartan and valsartan.<sup>6</sup> Several methods are known for the transformation of aldehydes into nitriles, including: (a) dehydration of aldoximes;<sup>7</sup> (b) 1,2-elimination reactions of *O*-substituted aldoximes;<sup>8</sup> (c) 1,2-elimination reactions of aldehyde trimethylhydrazonium iodides<sup>9</sup> and aldehyde *N*-tosylimines<sup>10</sup> using base. Nitriles can also be prepared directly from aldehydes via the corresponding aldoximes.<sup>11</sup> Unfortunately, most of the reported methods suffer from serious drawbacks such as difficultly available reagents, low yields, drastic reaction conditions and tedious work-up procedures.<sup>11c,12</sup> This report describes a useful method for the preparation of nitriles from a variety of aldehydes using  $\text{KF}/\text{Al}_2\text{O}_3$ .

In recent years, many heterogeneous organic reactions have been performed with reagents immobilized on porous solid supports, with advantages over conventional solution phase reactions because of good dispersion of active reagent sites, better selectivity and easier work-

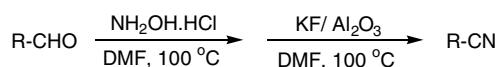
up. The recycling of some of these solid-supported reagents renders these processes truly eco-friendly green protocols. The application of  $\text{KF}/\text{Al}_2\text{O}_3$  to organic synthesis has provided new methods for a wide array of organic reactions, many of which are staples of synthetic organic chemistry.<sup>13</sup> Its benefits have been achieved by taking advantage of the strongly basic nature of  $\text{KF}/\text{Al}_2\text{O}_3$ , which has allowed it to replace organic bases in a number of reactions.<sup>7a,14</sup> The high efficacy and ease of product isolation prompted us to investigate its use for a one-pot conversion of aldehydes into nitriles. To our knowledge, no studies are known in the literature exploiting the above system for achieving this conversion.

We report here a simple and economical procedure for the direct transformation of aldehydes into nitriles by treatment with hydroxylamine hydrochloride catalyzed by  $\text{KF}$  (40% by weight)/ $\text{Al}_2\text{O}_3$  in dry *N,N*-dimethylformamide (DMF) at 100 °C (Scheme 1).

Several aldehydes (alkyl and aryl) were readily converted into the corresponding nitriles in good to high yields (Table 1). The structures of all the products were established from their analytical and spectral (IR, <sup>1</sup>H and <sup>13</sup>C NMR) properties. Potassium fluoride and alumina are both inexpensive and commercially available.

**Keywords:** Aldehydes; Nitriles;  $\text{KF}/\text{Al}_2\text{O}_3$ ; Heterogeneous reaction; Hydroxylamine hydrochloride.

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Scheme 1.

**Table 1.** Conversion of aldehydes into nitriles catalyzed by KF/Al<sub>2</sub>O<sub>3</sub>

Entry	Aldehydes	Time (h)	Nitriles	Yields (%) <sup>a</sup>
1	3-Nitrobenzaldehyde	4.5	3-Nitrobenzoxitrile	89
2	4-Methoxybenzaldehyde	7	4-Methoxybenzoxitrile	91
3	4-Methylbenzaldehyde	7.5	4-Methylbenzoxitrile	83
4	2-Methoxybenzaldehyde	9	2-Methoxybenzoxitrile	87
5	Benzaldehyde	5	Benzoxitrile	77
6	1-Naphthaldehyde	6	1-Cyanonaphthalene	73
7	3-Methylbenzaldehyde	8	3-Methylbenzoxitrile	79
8	3-Bromobenzaldehyde	7	3-Bromobenzoxitrile	90
9	Phenylacetaldehyde	10.5	Benzylcyanide	82
10	Crotonaldehyde	9	<i>trans</i> -Crotonoxitrile	78
11	3-Butenal <sup>b</sup>	10	Allyl cyanide	79
12	Valeraldehyde	8	Valeronitrile	76
13	Hexanal	7.5	Hexanenitrile	74
14	Decanal	8.5	Decanonitrile	78

<sup>a</sup> Yields of isolated pure products.

<sup>b</sup> This compound was prepared by controlled hydrolysis of its dimethyl acetal, itself obtained by reaction of allylmagnesium chloride with trimethylorthoformate; <sup>17</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  9.65 (1H, t,  $J = 1$  Hz), 6.05–5.80 (1H, m), 5.36–5.18 (2H, m), 3.22–3.17 (2H, m).

The reaction between an aldehyde and hydroxylamine hydrochloride produces first the corresponding aldoxime, which is then converted into the nitrile by dehydration. This heterogeneous system offers an easy work-up that includes evaporation of DMF, addition of a suitable solvent to the residue, filtration to remove the solid material, washing with water and evaporation of the solvent.

In summary, a new reliable, economical and practical method for the synthesis of nitriles from the corresponding aldehydes has been developed that features a simple reaction procedure, easy work-up, ready availability of the reagent and high yields of the products.

*Conversion of aldehydes into nitriles; general procedure:* A solution of hydroxylamine hydrochloride (1.1 mmol) and aldehyde (1 mmol) in anhydrous DMF (10 mL) was heated at 100 °C. To this mixture was added with stirring, over a period of 15 min, KF/Al<sub>2</sub>O<sub>3</sub> (7.25 g, 40% by weight)<sup>7a</sup> and heating was continued for the appropriate time (Table 1). After completion of the reaction, DMF was removed in vacuo, dichloromethane (20 mL) was added and the mixture filtered; the filtrate was washed with water (2 × 10 mL) and dried over anhydrous sodium sulfate. The solvent was evaporated to give the crude nitrile, which was purified by preparative thin layer chromatography (silica gel, eluent *n*-hexane/EtOAc = 7:3).

*Allyl cyanide:* Bp 115–117 °C (lit.<sup>15</sup> bp 116–121 °C); IR (neat):  $\nu$  2220, 1636, 1408, 983, 924 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  5.82–5.69 (1H, m), 5.50–5.43 (1H, m), 5.35–5.30 (1H, m), 3.14 (2H, dt,  $J = 6.7, 1.7$  Hz); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  125.94, 119.48, 117.15, 21.37.

*4-Methoxybenzoxitrile:* Mp 59 °C (lit.<sup>16</sup> mp 57–59 °C); IR (KBr):  $\nu$  2150, 1596, 1498, 1255, 1177, 823 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  7.61 (2H, d,  $J = 8.5$  Hz), 6.96 (2H, d,  $J = 8.5$  Hz), 3.88 (3H, s); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>):  $\delta$  162.85, 133.94, 119.27, 114.76, 103.78, 55.56.

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