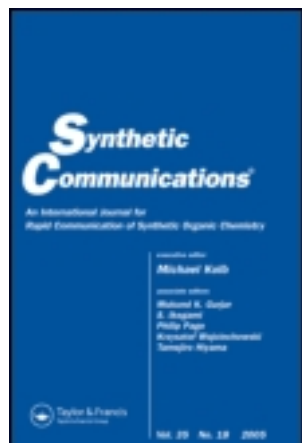


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### Mild and Efficient Method for the Synthesis of Nitriles

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## Mild and Efficient Method for the Synthesis of Nitriles

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### ABSTRACT

The treatment of aldoximes with a mixture of DMAD and triethylamine serve as an efficient and mild method for the synthesis of aromatic and  $\alpha,\beta$ -unsaturated nitriles in high yields at room temperature.

*Key Words:* Nitriles; Hydrazine; DMAD; Oximes.

### RESULTS AND DISCUSSION

The carbon–nitrogen triple bond formation may be achieved by aldoxime dehydration, *O*-acyloxime pyrolysis, base catalyzed decomposition of aldoxime *O*-2,4-dinitrophenyl ethers, elimination of amines from aldehyde hydrazones or hydrazone salts, etc.<sup>[1]</sup> The use of dimethyldioxirane, for the conversion of aldehyde *N,N*-dimethylhydrazones into the corresponding

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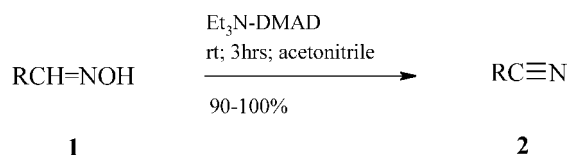
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nitriles under mild conditions was reported.<sup>[2]</sup> In all of these methods the starting material is an isolated oxime, *O*-substituted oxime, or aldehyde hydrazone derivative. Nitrile syntheses at the other extreme involve the in situ formation and dehydration of the oxime.<sup>[1,3]</sup> The aryl and alkyl aldehydes were converted to the corresponding nitriles in refluxing acetonitrile using hydroxylamine and phthalic anhydride as reagents in one pot.<sup>[4]</sup> A conversion of aldehydes to nitriles using a solid-supported hydrazine was also reported.<sup>[5]</sup>

Recently, we have reported the synthesis of nitriles<sup>[6]</sup> involving dehydrocarbamoylation of *O*-phenylcarbamoylated oximes, easily available by our method.<sup>[7]</sup> We herein report an easily applicable mild and efficient method for the conversion of aldoximes to the corresponding nitriles treating them with 2 equiv. of commercially available DMAD and triethylamine in acetonitrile at room temperature (see Sch. 1).

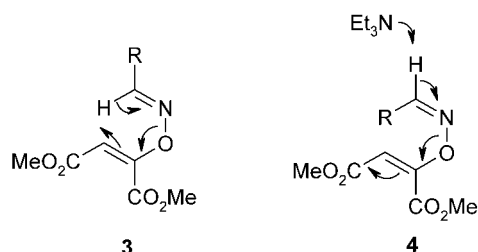
Aldoximes **1** were treated with DMAD in order to prepare corresponding adducts **3** (see Fig. 1). We needed them as starting materials in hetero Diels–Alder reactions. The treatment of the aldoximes with DMAD in the absence of triethylamine did not lead to any reaction after stirring for 24 hr at room temperature. However, the same reaction led to the formation of nitriles when the reaction was performed in the presence of triethylamine. The best ratio of the oxime, amine, and DMAD for the quantitative (see Table 1 for the yields) conversion of the oxime was found to be 1 : 1 : 2 in the cases of **1b–h** and 1 : 2 : 2 in the cases of **1a, i, and j**. The aimed products could be detected easily by HPLC, two peaks with higher retention times than the nitrile and starting oxime appear at the start of the reaction and gradually disappear within 3 hr. We assume that the amine activates the oxime in the nucleophilic addition to DMAD leading to the formation of but-2-endioic acid esters (see Fig. 1) which could undergo synchronous elimination via **3** or via the E<sub>2</sub> like transition state **4** to give the final product **2** and dimethyloxaloacetate. Probably the aromatic ring in the aldoximes favor the elimination process. Attempts to convert propionaldoxime and phenylacetaldoxime to the corresponding nitriles at room temperature failed.

To our knowledge these are the first dehydrations of aldoximes with triethylamine–DMAD mixture reported. The extremely high yields and



Scheme 1.

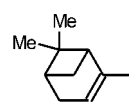
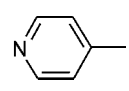
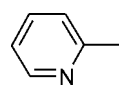




**Figure 1.** Suggested transition states for the fragmentation of *N*-benzilidenaminoxy-but-2-endioic acid esters.

the mild conditions and the formation of easily separable mixture are the advantages of the method developed. The isolation of the product involves only an extraction where the by-products remain in the water phase. The evaporation of the solvent gave nearly pure nitrile, which is further purified by recrystallization or flash column chromatography or simply by filtering

**Table 1.** Synthesis of nitriles<sup>a</sup> **2a–j**.

R	Yield (%)	Mp (°C)	R	Yield (%)	Mp (°C)
<b>2a</b> Ph	92 <sup>b</sup>	Oil	<b>2f</b> 3-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	98	116 <sup>c</sup>
<b>2b</b> 4-MeOC <sub>6</sub> H <sub>4</sub>	100	60 <sup>d</sup>	<b>2g</b> 4-ClC <sub>6</sub> H <sub>4</sub>	99	93–94 <sup>d</sup>
<b>2c</b> 2,3-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	96	47 <sup>d</sup>	<b>2h</b> 	90	Oil
<b>2d</b> 3,4-(MeO) <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	95	68 <sup>d</sup>	<b>2i</b> 	98 <sup>e</sup>	80 <sup>d</sup>
<b>2e</b> 2-NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	98	111 <sup>c</sup>	<b>2j</b> 	97	Oil

<sup>a</sup>All prepared nitriles are known in literature and were identified by comparing their physical and spectral data with those of authentic samples.

<sup>b</sup>The yields were also determined by HPLC and were nearly quantitative for all of the cases.

<sup>c</sup>Recrystallized from water.

<sup>d</sup>Recrystallized from acetonitrile-water.

<sup>e</sup>In the cases of benzaldoxime and pyridine aldoximes the ratio of the oxime, amine and DMAD is 1 : 2 : 2.



through short silica packed column. The prepared nitriles **2a–j** were identified by comparison of their physical constants and spectral characteristics with those of commercially available or prepared by our previous method.<sup>[6]</sup>

## EXPERIMENTAL

Melting points were determined on an Electrothermal Digital melting point apparatus. IR spectra were recorded on a Mattson 1000 FTIR. <sup>1</sup>H NMR spectra were recorded on a Varian 200 MHz spectrometer. Commercially available oximes or prepared from the corresponding aldehydes were used as starting materials. The reactions were monitored by HPLC using C<sub>18</sub> column and UV detector. Water–acetonitrile (60:40) was used as a mobile phase.

### General Procedure

To a solution of aldoxime **2** (3 mmol) in acetonitrile (15 mL) triethylamine (0.303 g, 3 mmol) and DMAD (0.852 g, 6 mmol) were added and the mixture stirred at room temperature for 3 hr. The solvent was evaporated under vacuum and water (50 mL) was added<sup>a</sup> to the residue and then extracted with chloroform (3 × 15 mL). The combined extracts were washed with water (2 × 15 mL) and dried (anh. Na<sub>2</sub>SO<sub>4</sub>), filtered, and the solvent evaporated. The crude products were purified by crystallization or flash column chromatography or filtering through short silica gel packed column using ethyl acetate hexane mixture as eluent.

**Benzonitrile (2a).** See Table 1 for the yields and melting points. IR (neat)  $\nu_{\text{CN}}$  2229 cm<sup>-1</sup>.

**4-Methoxybenzonitrile (2b).** IR (KBr)  $\nu_{\text{CN}}$  2238 cm<sup>-1</sup>; <sup>1</sup>H NMR CDCl<sub>3</sub>  $\delta$  ppm 3.91 (3H, s), 6.95–7.83 (4H, m); Anal. Calcd for C<sub>8</sub>H<sub>7</sub>NO (133,15): C, 72.17; H, 5.30; N, 10.52; Found: C, 72.20; H, 5.25; N, 10.45.

**2,3-Dimethoxybenzonitrile (2c).** IR (KBr)  $\nu_{\text{CN}}$  2238 cm<sup>-1</sup>; <sup>1</sup>H NMR CDCl<sub>3</sub>  $\delta$  ppm 3.91 (6H, s), 7.02–7.60 (3H, m); Anal. Calcd for C<sub>9</sub>H<sub>9</sub>NO<sub>2</sub> (163,18): C, 66.25; H, 5.56; N, 8.58; Found: C, 66.30; H, 5.50; N, 8.63.

<sup>a</sup>The 4-chlorobenzonitrile crystallises as white needles after adding of water directly to the acetonitrile solution and could be separated by filtration.



**3,4-Dimethoxybenzotrile (2d).** IR (KBr)  $\nu_{\text{CN}}$  2238  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\text{CDCl}_3$   $\delta$  ppm 3.90 (6H, s), 7.05–7.60 (3H, m); Anal. Calcd for  $\text{C}_9\text{H}_9\text{NO}_2$  (163,18): C, 66.25; H, 5.56; N, 8.58; Found: C, 66.32; H, 5.53; N, 8.61.

**2-Nitrobenzotrile (2e).** IR (KBr)  $\nu_{\text{CN}}$  2238  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\text{CDCl}_3$   $\delta$  ppm 7.05–8.30 (4H, m); Anal. Calcd for  $\text{C}_7\text{H}_4\text{N}_2\text{O}_2$  (148,12): C, 56.76; H, 2.72; N, 18.91; Found: C, 56.70; H, 2.80; N, 18.95.

**3-Nitrobenzotrile (2f).** IR (KBr)  $\nu_{\text{CN}}$  2238  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\text{CDCl}_3$   $\delta$  ppm 7.05–8.30 (4H, m); Anal. Calcd for  $\text{C}_7\text{H}_4\text{N}_2\text{O}_2$  (148,12): C, 56.76; H, 2.72; N, 18.91; Found: C, 56.75; H, 2.82; N, 18.90.

**4-Chlorobenzotrile (2g).** IR (KBr)  $\nu_{\text{CN}}$  2238  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\text{CDCl}_3$   $\delta$  ppm 7.06–8.0 (4H, m); Anal. Calcd for  $\text{C}_7\text{H}_4\text{ClN}$  (137, 57): C, 61.12; H, 2.93; N, 10.18; Found: C, 61.15; H, 3.00; N, 10.15.

**(R)-6,6-Dimethylbicyclo[3.1.1]hept-2-ene-2-carbonitrile (2h).** IR (neat)  $\nu_{\text{CN}}$  2238  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR  $\text{CDCl}_3$   $\delta$  ppm 0.83 (3H, s), 1.18 (1H, d,  $J = 10$  Hz) 1.41 (3H, s), 2.18 (1H, s), 2.50 (3H, m), 2.87 (1H, m), 6.23 (1H, s); Anal. Calcd for  $\text{C}_{10}\text{H}_{13}\text{N}$  (147,22): C, 81.59; H, 8.90; N, 9.51; Found: C, 81.65; H, 8.75; N, 9.60.

**Isonicotinonitrile (2i).** IR (KBr)  $\nu_{\text{CN}}$  2236  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_6\text{H}_4\text{N}_2$  (104,11): C, 69.22; H, 3.87; N, 26.91; Found: C, 69.20; H, 3.88; N, 26.90.

**Pyridine-2-carbonitrile (2j).** IR (neat)  $\nu_{\text{CN}}$  2238  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_6\text{H}_4\text{N}_2$  (104,11): C, 69.22; H, 3.87; N, 26.91; Found: C, 69.25; H, 3.90; N, 26.92.

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