$Cu(OAc)_2$/malononitrile/water: a simple reaction system for synthesis of aromatic nitriles from aldoximes

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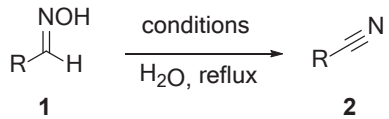
A simple method for the preparation of nitriles in moderate to good yield has been achieved by treatment of aromatic and heterocyclic aldoximes with malononitrile in water at reflux in the presence of copper acetate as catalyst. Arylaldoximes with an electron-donating group showed the highest reactivity, their conversion being achievable at room temperature.

Keywords: nitrile, aldoxime, copper salt, malononitrile

Nitriles are important intermediates in organic synthesis and numerous methods for their synthesis have been reported. Among these methods, the conversion of an aldoxime into a nitrile is considered to be one of the most efficient and convenient methods. Usually, this conversion is achieved either *via* the dehydration of aldoximes using various dehydration reagents such as acid anhydrides,[1] thionyl chloride and its derivatives,[2] acids,[3] phosphorus-containing compounds,[4] or by treating aldoximes with a variety of metal catalysts, our interest being in copper salts.[5–11] Recently we reported the preparation of aromatic and heterocyclic nitriles by treating the corresponding aldehydes with hydroxylamine and CuO in refluxing MeCN.[12] We now report an improved method in which the oximes are not formed *in situ* but are used as starting materials and malononitrile replaces acetonitrile, $Cu(OAc)_2$ replaces CuO and water is the solvent.

Results and discussion

For our optimisation studies, we selected benzaldoxime (**1**; R = Ph) as a model substrate to investigate the influence of ratio of reactants and various metal salts on the yields of benzonitrile (**2**; R = Ph) (Scheme 1). The results are listed in Table 1. As shown in the table, use of copper(II) acetate alone resulted in no product and the yield of benzonitrile is very low when malononitrile was used alone (Table 1, entries 1 and 2). When both $Cu(OAc)_2 \cdot H_2O$ and malononitrile were used, the reaction was completed within 2 h and benzonitrile was obtained



1 **2**

Scheme 1

Table 1 Optimisation of the reaction conditions (catalyst, duration of reaction) for the conversion of benzaldoxime (**1a**; R = Ph) to benzonitrile (**2a**; R = Ph) (Scheme 1)[a]

Entry	Malononitrile (equiv.)	Catalyst (0.05 equiv.)	Time (h)	Yield (%)[b]
1	–	$Cu(OAc)_2 \cdot H_2O$	2	0
2	0.5	–	6	5
3	0.5	$Cu(OAc)_2 \cdot H_2O$	1.5	71
4	1.0	$Cu(OAc)_2 \cdot H_2O$	1.5	84
5	1.0	$Cu(NO_3)_2 \cdot 3H_2O$	1.5	75
6	1.0	$CuSO_4 \cdot 5H_2O$	1.5	73
7	1.0	$CuCl_2 \cdot 2H_2O$	1.5	55
8	1.0	CuO	1.5	30
9	1.0	$NiCl_2 \cdot 6H_2O$	1.5	39

[a]Reaction conditions: a stirred mixture of benzaldoxime (**1a**; R = Ph), malononitrile and a catalyst in water (8 mL) was reacted for various times.
[b]Isolated yield.

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in 71% yield (Table 1, entry 3). Increasing the amounts of malononitrile (from 0.5 to 1.0 equiv.) inhibited the formation of by-products (benzaldehyde and benzamide) leading to an increased yield of benzonitrile of 84% (Table 1, entry 4). As well as $Cu(OAc)_2 \cdot H_2O$, the catalytic activities of other copper salts and $NiCl_2 \cdot 6H_2O$ were also examined (Table 1, entries 5–9). These metal salts showed some level of catalytic activity, but the catalytic activities were inferior to that of $Cu(OAc)_2 \cdot H_2O$. In the case of $CuCl_2 \cdot 2H_2O$, benzaldoxime disappeared in 1.5 h, but the selectivity for nitrile formation was relatively lower (Table 1, entry 7). CuO and $NiCl_2 \cdot 6H_2O$ exhibited poor catalytic activities, benzonitrile being obtained in low yield and most of the benzaldoxime remained unreacted (Table 1, entries 8 and 9).

On the basis of the above results, we could conclude that the optimal conditions for the conversion of benzaldoxime to benzonitrile is by treatment with $Cu(OAc)_2 \cdot H_2O$ and malononitrile in water at reflux for 1–2 h. This optimum method was then applied to other aryl and heteroaryl aldoximes (**1**; R = various) and the yields of the corresponding nitriles (**2**; R = various) are shown in Table 2. Substrates bearing strong electron-donating groups showed relatively high reactivity and the reaction could be completed within 60 min (Table 2, entries 2–4). In contrast, the conversion of aldoximes with an electron-withdrawing group required a longer time (Table 2, entries 7 and 8). In the case of 4-(dimethylamino)benzaldoxime, use of ethanol in place of water could reduce the generation of by-products and improve the product yield (Table 2, entry 3). An

Table 2 Yields of a series of nitriles (**2**; R = various) prepared by reaction of an aldoxime (**1**; R = various) with malononitrile in the presence of $Cu(OAc)_2$ in water (Scheme 1)[a]

Entry	Nitrile	R	Time (h)	Yield (%)[b]
1	**2a**	C_6H_5	1.5	84
2	**2b**	4-MeO–C_6H_4	1	86
3	**2c**	4-N$(CH_3)_2$–C_6H_4	1	75[c]
4	**2d**	4-OH–C_6H_4	1	83
5	**2e**	4-Me–C_6H_4	1.5	78
6	**2f**	3-MeO–4-MeO–C_6H_3	1.5	85
7	**2g**	4-NO_2–C_6H_4	2	80
8	**2h**	2-Cl–C_6H_4	2	91[d]
9	**2i**	(*E*)-C_6H_5–CH=CH	1.5	88
10	**2j**	9-Anthryl	1.5	87
11	**2k**	4-Pyridyl	2	81
12	**2l**	2-Thienyl	1	63

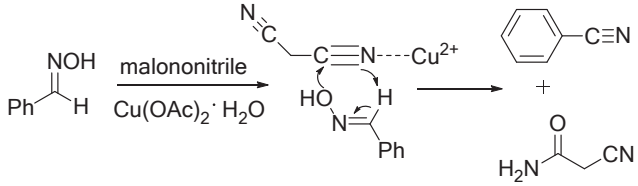
[a]Reaction conditions: a stirred mixture of an oxime (2 mmol), malononitrile (2 mmol) and $Cu(OAc)_2$ (0.1 mmol) in water (8 mL) was refluxed for various times.
[b]Isolated yield.
[c]Ethanol was used in place of H_2O.
[d]4 mmol malononitrile was used.

Table 3 Yields of a series of nitriles containing electron-attracting groups (**2**; R = various) prepared by reaction of the corresponding aldoxime (**1**; R = various) with malononitrile and $Cu(OAc)_2$ (Scheme 1)[a]

Entry	Nitrile	R	Yield (%)[b]
1	**2b**	4-MeO–C_6H_4	81
2	**2c**	4-$N(CH_3)_2$–C_6H_4	70
3	**2d**	4-OH–C_6H_4	80
4	**2f**	3-MeO–4-MeO–C_6H_3	77
5	**2l**	2-Thienyl	56

[a]Reaction conditions: a stirred mixture of an aldoxime (2 mmol), malononitrile (4 mmol) and $Cu(OAc)_2$ (0.10 mmol) in EtOH/water (1:1) (8 mL) was allowed to react at 25 °C for 24 h.

[b]Isolated yield.



Scheme 2

ortho substituent appears to have an effect on the yield of the reaction; two equiv. of malononitrile were used to avoid the formation of aldehyde by-product when 2-chlorobenzaldoxime was converted to the corresponding nitrile (Table 2, entry 8). Thiophene-2-carbaldehyde oxime showed high reactivity and the reaction was completed after a relatively short reaction time of 1 h. However, in this case, the corresponding nitriles were obtained in relatively low yields and the yield of the corresponding amide was appreciable (Table 2, entry 12). In addition, it should be noted that aliphatic aldoximes could not effectively be converted to the corresponding nitriles in this reaction system; various by-products were formed and separation was difficult.

In the course of the study on conversion of aldoximes with electron-donating groups to the corresponding nitriles, we found that the conversion of these aldoximes could be achieved at room temperature. As shown in Table 3, treatment of such aldoximes with $Cu(OAc)_2 \cdot H_2O$ and malononitrile (2.0 equiv.) in a mixed solvent of ethanol and water at room temperature for a relatively long time (24 h) gave nitriles in moderate to good yield.

Regarding the mechanism of the reaction, we thought that the reaction mechanism is likely to be similar to that reported previously.[5,6,12–15] A proposed mechanism is shown in Scheme 2. The coordination of malononitrile to copper ion results in an enhanced electrophilicity of the nitrile carbon facilitating the nucleophilic addition of benzaldoxime, the resulting complex disproportionating to give benzonitrile and 2-cyanoacetamide. It is noteworthy that the two nitrile groups are equivalent in malononitrile and the nitrile group in 2-cyanoacetamide may also react with aldoxime.

Conclusions

In conclusion, we describe a simple method for the conversion of aldoximes to nitriles in an environmentally friendly aqueous media by the combined use of a copper salt as catalyst and malononitrile. Using this method aldoximes, including aromatic aldoximes and heterocyclic aldoximes, were converted into the corresponding nitriles in moderate to good yield. Some as aldoximes having electron-donating groups could be converted into the corresponding nitriles at room temperature.

Experimental

Reagent grade chemicals were purchased from Aladdin Reagent (Shanghai, P.R. China) and were used without further purification. Melting points were determined on a Thomas Hoover capillary apparatus and were uncorrected. NMR spectra were obtained on a Bruker DPX-500 or a DPX-400 spectrometer (^{1}H NMR at 500 or 400 Hz, ^{13}C NMR at 125 or 100 Hz) in $CDCl_3$ or DMSO-d_6 using TMS as internal standard. Chemical shifts (δ) are given in ppm and coupling constants (*J*) are given in hertz (Hz). Thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Yields refer to the isolated yields of the products after purification by silica-gel column chromatography (300 mesh). Aldoximes were synthesised according to a literature method.[16] All the nitriles are known compounds and they were characterised by melting points or NMR spectra.

Synthesis of nitriles; general procedure

Aldoxime (2 mmol), $Cu(OAc)_2 \cdot H_2O$ (0.1 mmol), malononitrile (2 mmol) and H_2O (8 mL) were added to a 25 mL round-bottom flask equipped with a magnetic stirrer. The mixture was heated to reflux for 1–2 h. After cooling to room temperature, ethyl acetate (30 mL) was added to the reaction mixture. The separated organic layer was washed with saturated aqueous sodium bicarbonate (1 × 15 mL) and water (1 × 15 mL) and then dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane) to give the corresponding nitriles.

Benzonitrile (**2a**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:15) to give benzonitrile as a colourless liquid (173 mg, 84%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.48 (t, *J* = 8.0 Hz, 2H), 7.61 (m, 1H), 7.66 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 112.5, 118.8, 129.1, 132.1, 132.7. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

4-Methoxybenzonitrile (**2b**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:4) to give 4-methoxybenzonitrile as a white solid (229 mg, 86%); m.p. 57–58 °C (lit.[2] m.p. 58 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.87 (t, *J* = 5.0 Hz, 3H), 6.96 (m, 2H), 7.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 55.5, 104.0, 114.8, 119.2, 133.9, 162.9. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[18]

4-(Dimethylamino)benzonitrile (**2c**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:10) to give 4-(dimethylamino)benzonitrile as a white solid (219 mg, 75%); m.p. 71–73 °C (lit.[5] m.p. 70–72 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.05 (t, *J* = 5.0 Hz, 6H), 6.64 (m, 2H), 7.47 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 39.9, 97.5, 111.5, 120.6, 133.3, 152.5. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

4-Hydroxybenzonitrile (**2d**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:3) to give 4-hydroxybenzonitrile as a white solid (198 mg, 83%); m.p. 110–112 °C (lit.[19] m.p. 110 °C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 6.91 (m 2H), 7.65 (m, 2H), 10.61 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 102.9, 116.5, 119.3, 134.3, 160.4. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

4-Methylbenzonitrile (**2e**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:10) to give 4-methylbenzonitrile as an oil (183 mg, 78%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.43 (d, *J* = 3.0 Hz, 3H), 7.28 (m, 2H), 7.55 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 21.8, 109.4, 119.1, 129.8, 132.0, 143.7. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

3,4-Dimethoxybenzonitrile (**2f**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:6) to give 3,4-dimethoxybenzonitrile as a white solid (277 mg, 85%); m.p. 66–67 °C (lit.[20] m.p. 65–66 °C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.91 (d, *J* = 3.0 Hz, 3H), 3.94 (d, *J* = 2.5 Hz, 3H), 6.91 (dd, J_1 = 8.0 Hz, J_2 = 3.0 Hz, 1H), 7.08 (m, 1H), 7.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 56.07, 56.13, 103.9, 111.3, 114.0, 119.2, 126.4, 149.2, 152.9. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

4-Nitrobenzonitrile (**2g**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:5) to give 4-nitrobenzonitrile as a white solid (236 mg, 80%); m.p. 146–147 °C (lit.[21] m.p. 148 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.89 (d, *J* = 8.4 Hz, 2H), 8.36 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 116.8, 118.3, 124.3, 133.5, 150.1. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

2-Chlorobenzonitrile (**2h**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:15) to give 2-chlorobenzonitrile as a white solid (250 mg, 91%); m.p. 43–44 °C (lit.[18] m.p. 42.1–43.8 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (m, 1H), 7.54 (m, 2H), 7.68 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 113.5, 115.9, 127.1, 130.0, 133.8, 134.0, 136.9. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

*(*E*)-Cinnamonitrile* (**2i**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:10) to give (*E*)-cinnamonitrile as an oil (227 mg, 88%); ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.89 (d, *J* = 16.8 Hz, 1H), 7.39–7.46 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 96.4, 118.1, 127.3, 129.1, 131.2, 133.6, 150.5. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

Anthracene-9-carbonitrile (**2j**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:10) to give anthracene-9-carbonitrile as an orange solid (353 mg, 87%); m.p. 174–175 °C (lit.[22] m.p. 175–176 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (m, 2H), 7.70 (m, 2H), 8.05 (d, *J* = 8.4 Hz, 2H), 8.40 (d, *J* = 8.8 Hz, 2H), 8.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 105.4, 117.2, 125.2, 126.3, 128.87, 128.91, 130.6, 132.6, 133.2. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

Isonicotinonitrile (**2k**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:1) to give isonicotinonitrile as a white solid (169 mg, 81%); m.p. 76–77 °C (lit.[23] m.p. 77–78°C); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (m, 2H), 8.84 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 116.3, 120.4, 125.2, 150.8. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

Thiophene-2-carbonitrile (**2l**): The residue was purified by column chromatography on silica gel (ethyl acetate/*n*-hexane = 1:15) to give thiophene-2-carbonitrile as a colourless liquid (137 mg, 63%); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14 (m, 1H), 7.63 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 110.0, 114.2, 127.6, 132.5, 137.4. The ^{1}H and ^{13}C NMR data of this compound are in good agreement with the reported data.[17]

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