A General Procedure to Access Methylene Ether Isonitrile Derivatives

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Abstract: Isonitriles are essential building blocks for multicomponent reactions. A convenient and simple two-step synthesis of the little known methylene ether isonitrile derivatives is presented.

Key words: formamide, dehydration, isonitrile/isocyanide, multicomponent reactions

Multicomponent reactions such as the Ugi and Passerini reactions can rapidly provide large arrays of molecular diversity.[1] Accessing molecular diversity is of paramount importance in the search for new biologically active candidates, and multicomponent reactions provide an additional tool in this endeavour. The success of these reactions in delivering such diversity is, however, reliant upon the size of the building block arsenal. Considering that isonitriles play a major role in multicomponent reactions, attempts to explore the synthesis of new isonitrile derivatives are warranted. In the course of our own work we required methylene ether isonitriles **1**. Surprisingly, these compounds are not well known, which is in stark contrast to the sulfur analogues **2**,[2] and substituted derivatives **3** (Figure 1).[3]

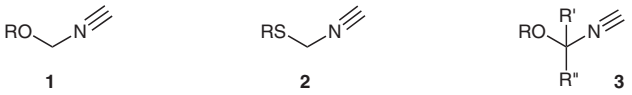
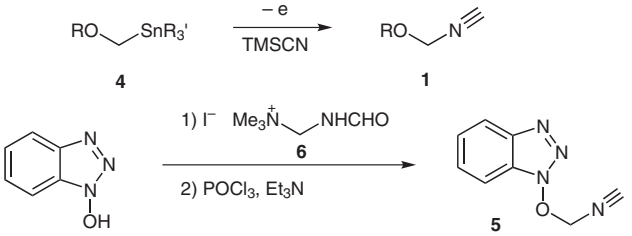


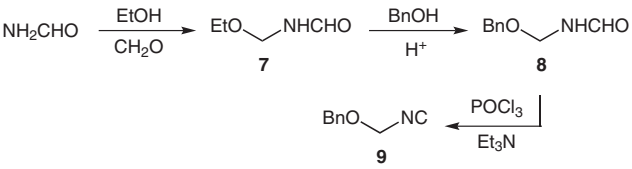
Figure 1 Isonitriles **1–3**



Scheme 1

The first of only two reports on methylene ether isonitriles **1** describes the electrochemical conversion of organotin methylene ethers **4** into **1** by Yoshida,[4] while Sasaki[5] synthesised 1-(isocyanomethyloxy)benzotriazole (**5**) from formamide **6** (Scheme 1).

Initially, we were attracted to the Sasaki procedure, but a report by Threadgill[6] detailing a two-step synthesis of formamide **7**, as opposed to a three-step protocol for formamide **6**, then caught our attention. Synthesis of formamide **7** was straightforward, but the key to the development of a new method for the construction of methylene ether isonitrile derivatives **1** was functionalisation of **7**. After some optimisation, it was discovered that treatment of **7** with benzyl alcohol in the presence of sulfuric acid gave the benzyl derivative **8** (61%). It should be noted that attempts to use the Threadgill[6] procedure to directly access **8** failed. A number of protocols[7] for conversion of **8** into methylene ether isonitrile **9** were investigated, with the most common procedure, $POCl_3/Et_3N$, giving the best results (Scheme 2).



Scheme 2

In view of this success, we now report a convenient two-step procedure for the synthesis of methylene ether isonitrile derivatives **1** (Table 1) in yields ranging from 0–58%. The yield of the product was somewhat dependent on stereoelectronic effects. For example, in the benzyl series electron-withdrawing substituents (entries 1 and 2) afforded products in modest yields (58 and 55%, respectively), whereas electron-donating substituents decreased the yield by more than half as seen in entries 4 and 5. This trend is most likely due to the stabilisation of an incipient carbocation formed in competition when the benzyl alcohol is in contact with the acidic media required to form the intermediate formamide **8**. Interestingly, the phenoxy (entry 6) derivative failed to deliver the product. Primary aliphatics (entries 7–10) worked satisfactorily, however, hindered secondary (entry 12) and acid labile side chains (entry 13) did not perform particularly well.

Pure intermediate formamides were isolated in several cases (e.g., entries 3, 8, 10, and 12, Procedure A, see also experimental). In all other instances, a mixture consisting predominantly of formamide and unreacted alcohol was subjected to dehydration (Procedure B). (Dodecyloxy)methyl isonitrile (**18**) was generated from both pure and impure *N*-[(dodecyloxy)methyl]formamide and the

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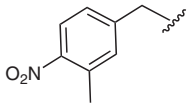
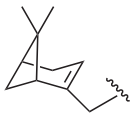
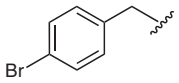
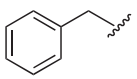
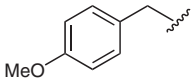
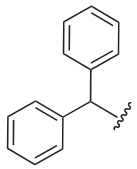
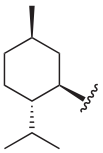
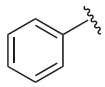
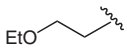
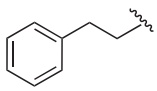
Table 1 Methylene Ether Isonitrile Derivatives Prepared

Entry	R		Yield (%)[a]	Entry	R		Yield (%)[a]
1[b]		**10**	58	8[c]		**16**	40
2[b]		**11**	55	9		**17**	64[d,e] 12[d,f]
3[c]		**9**	41	10[c]		**18**	41
4[b]		**12**	20	11		**19**	78[d,g] 19[d,f]
5[b]		**13**	19	12[c]		**20**	23
6		**14**	0	13[b]		**21**	14
7[b]		**15**	42				

[a] Isolated two step overall yield from *N*-[(ethoxy)methyl]formamide unless otherwise indicated.
[b] Procedure B.
[c] Procedure A.
[d] Estimated yield from crude ^{1}H NMR spectrum due to compound sensitivity.
[e] One-step yield from *N*-[(ethoxy)methyl]formamide.
[f] Two-step overall yield from formamide.
[g] One-step yield from *N*-[(isopropyloxy)methyl]formamide.

two-step yields were comparable, indicating that the presence of unreacted alcohol has no adverse effect on isonitrile yield.

The ^{13}C NMR spectra of all the isonitriles synthesised featured two 1:1:1 triplets that could be attributed to the carbons attached to the isonitrile nitrogen. $^1J(^{14}N,^{13}C)$ values were in good agreement with those reported previously for other isonitriles.[8]

In conclusion, a convenient and simple two-step synthesis of the little known methylene ether isonitrile derivatives is presented. Yields are moderate to low, but considering the only alternative is electrochemical oxidation of toxic stannanes, our methodology is a substantial improvement, offering many new building blocks for important reactions, such as the Ugi type.

^{1}H and ^{13}C NMR spectra were recorded with Bruker AV300 (300.13 MHz; 75.47 MHz), AV400 (400.13 MHz; 100.62 MHz and DRX500 (500.13 MHz; 125.77 MHz) spectrometers in $CDCl_3$. Coupling constants are given in Hz and chemical shifts are expressed as values in ppm. GC-MS data were recorded on a Shimadzu GC-17A Ver.3 mass spectrometer: MS QP5050A, ionisation at 70 eV. Low resolution EI-MS measurements were recorded in positive ionisation mode on a Bruker Esquire HCT (High Capacity 3D ion trap) instrument with a Bruker ESI source. High resolution EI-MS data were obtained on a Finnigan MAT900. High resolution EI accurate mass measurements were recorded in positive mode on a Bruker MicrOTOF-Q (quadrupole - Time of Flight) instrument with a Bruker ESI source. Accurate mass measurements were carried out with external calibration using sodium formate as reference calibrant. Column chromatography was undertaken on silica gel (Flash Silica gel 230–400 mesh) with distilled solvents. Petroleum ether (PE) refers to the fraction boiling at 40–60 °C.

Transetherification of *N*-(Ethoxymethyl)formamide (7); *N*-[(Dodecyloxy)methyl]formamide; Typical Procedure A

A stirred mixture of dodecan-1-ol (2.9 g, 16 mmol), *N*-(ethoxymethyl)formamide (**7**; 0.80 g, 7.8 mmol) and concd H_2SO_4 (2 drops) was heated at ca. 110 °C (oil bath temp.) for 1 h at atmospheric pressure and then for 2 h at ca. 300 Torr. The mixture was loaded directly onto a flash chromatography column [PE–EtOAc–Et_3N (75:25:0.5) → EtOAc–Et_3N (100:0.5)] and the title compound was collected as a colourless oil (0.93 g, 52%).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22 (d, *J* = 1.4 Hz, 1 H), 8.12 (d, *J* = 11.6 Hz, 1 H), 7.03 (br s, 1 H), 6.75 (br s, 1 H), 4.69 (d, *J* = 6.8 Hz, 2 H), 4.57 (d, *J* = 7.1 Hz, 2 H), 3.43 (t, *J* = 6.7 Hz, 2 H), 3.36 (t, *J* = 6.6 Hz, 2 H), 1.51–1.45 (m, 4 H), 1.19 (m, 36 H), 0.81 (t, *J* = 6.7 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 161.8, 73.3, 68.8, 68.4, 67.7, 31.8, 29.53, 29.51, 29.47, 29.32, 29.29, 29.2, 26.0, 22.6, 14.0.

ESI-MS: *m*/*z* = 266 [M + Na^+].

HRMS (ESI): *m*/*z* calcd for $C_{14}H_{29}NO_2$ + Na: 266.2091; found: 266.2094.

_N_-{[(1_R_)-(7,7-Dimethylbicyclo[2.2.1]hept-2-en-2-yl)methyloxy]methyl}formamide

Colourless oil; yield: 51%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.24 (d, *J* = 1.4 Hz, 1 H), 8.12 (d, *J* = 11.6 Hz, 1 H), 6.67 (br s, 1 H), 6.46 (br s, 1 H), 5.50–5.48 (m, 2 H), 4.72 (dd, *J* = 6.8, 0.9 Hz, 2 H), 4.58 (d, *J* = 7.3 Hz, 2 H), 3.86–3.85 (m, 2 H), 3.83–3.82 (m, 2 H), 2.41–2.32 (m, 2 H), 2.26–2.22 (m, 4 H), 2.10 (td, *J* = 5.4, 1.2 Hz, 2 H), 2.16–2.06 (m, 2 H), 1.25 (s, 3 H), 1.24 (s, 3 H), 1.12 (d, *J* = 8.6 Hz, 1 H), 1.10 (d, *J* = 8.7 Hz, 1 H), 0.78 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.3, 161.6, 144.5, 144.2, 121.4, 120.5, 71.9, 71.6, 70.1, 67.8, 43.4, 43.2, 40.72, 40.68, 37.9, 31.5, 31.4, 31.22, 31.19, 26.1, 26.0, 21.0.

ESI-MS: *m*/*z* = 232 [M + Na^+].

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{19}NO_2$ + Na: 232.1308; found: 232.1299.

_N_-[(1_R_,2_S_,5_R_)-(2-Isopropyl-5-methylcyclohexyloxy)methyl]formamide

Colourless oil; yield: 30%.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (d, *J* = 1.6 Hz, 1 H), 8.09 (d, *J* = 11.6 Hz, 1 H), 7.20 (br s, 1 H), 6.95 (br s, 1 H), 4.83–4.76 (m, 1 H), 4.64–4.52 (m, 1 H), 3.19 (td, *J* = 10.5, 4.3 Hz, 1 H), 3.09 (td, *J* = 10.5, 4.2 Hz, 1 H), 2.07–1.90 (m, 4 H), 1.58–1.49 (m, 4 H), 1.31–1.26 (m, 2 H), 1.16–1.02 (m, 2 H), 0.95–0.72 (m, 18 H), 0.67 (d, *J* = 6.9 Hz, 3 H), 0.65 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.5, 161.6, 77.3, 76.1, 71.0, 66.5, 48.0, 47.9, 40.8, 40.5, 34.2, 34.1, 31.3, 25.24, 25.16, 22.95, 22.93, 22.08, 22.04, 20.87, 20.80, 15.88, 15.80.

ESI-MS: *m*/*z* = 236 [M + Na^+].

HRMS (ESI): *m*/*z* calcd for $C_{12}H_{23}NO_2$ + Na: 236.1621; found: 232.1621.

_N_-[(Benzyloxy)methyl]formamide

Flash chromatographic purification [CH_2Cl_2–Et_3N (100:0.5) → CH_2Cl_2–MeOH–Et_3N (90:10:0.5)] followed by removal of traces of benzyl alcohol via Kugelrohr distillation provided the benzyl ether as a pale yellow oil in 61% yield.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29 (d, *J* = 1.5 Hz, 1 H), 8.16 (d, *J* = 11.7 Hz, 1 H), 7.37–7.26 (m, 10 H), 6.52 (br s, 1 H), 6.34 (br s, 1 H), 4.84 (d, *J* = 7.0 Hz, 2 H), 4.67 (d, *J* = 7.3 Hz, 2 H), 4.57 (s, 2 H), 4.51 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 165.6, 162.0, 137.4, 136.6, 128.41, 128.38, 128.2, 127.63, 127.62, 72.3, 70.3, 69.0, 67.9.

ESI-MS: *m*/*z* = 188 [M + Na^+].

HRMS (ESI): *m*/*z* calcd for $C_9H_{11}NO_2$ + Na: 188.0682; found: 188.0686.

_N_-[(Isopropyloxy)methyl]formamide

The title compound was obtained as a colourless oil in 19% yield via the procedure developed by Threadgill[6] for *N*-(ethoxymethyl)formamide.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23 (s, 1 H), 8.15 (d, *J* = 11.8 Hz, 1 H), 6.67 (br s, 1 H), 6.39 (br s, 1 H), 4.75 (d, *J* = 6.8 Hz, 2 H), 4.62 (d, *J* = 7.1 Hz, 2 H), 3.77 (sept, *J* = 6.1 Hz, 1 H), 3.69 (sept, *J* = 6.1 Hz, 1 H), 1.14 (d, *J* = 6.1 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.6, 161.9, 70.8, 69.3, 68.4, 66.1, 22.0, 21.9.

EI-MS: *m*/*z* (%) = 102 (16, [M^+ – CH_3]), 74 (46), 58 (100), 43 (80).

Isonitriles by Dehydration of Formamides; (Dodecyloxy)methyl Isonitrile (18); Typical Procedure A

Under argon, anhyd Et_3N (2.3 mL, 17 mmol) followed by a solution of anhyd $POCl_3$ (0.35 mL, 3.8 mmol) in anhyd THF (2.7 mL) were added to a stirred solution of *N*-[(dodecyloxy)methyl]formamide (0.82 g, 3.4 mmol) in THF (6.0 mL) at 0 °C. The mixture was stirred at 10 °C for 20 min and then poured onto crushed ice. The product was extracted into Et_2O (3 × 10 mL) and the combined organic phases were washed with aq 10% Na_2CO_3 (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (PE–EtOAc–Et_3N, 75:25:0.5) furnished **18** (0.60 g, 79%) as a pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.72 (s, 2 H), 3.59 (t, *J* = 6.5 Hz, 2 H), 1.59 (quint, *J* = 6.7 Hz, 2 H), 1.24 (m, 18 H), 0.85 (t, *J* = 6.5 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.6 (1:1:1 t, *J* = 4.0 Hz), 72.6 (1:1:1 t, *J* = 5.2 Hz), 70.3, 31.8, 29.6, 29.55, 29.5, 29.4, 29.3, 29.2, 28.9, 25.8, 22.6, 14.0.

MS (EI): *m*/*z* (%) = 210 (2, [M^+ – CH_3]), 196 (1), 182 (1), 168 (3), 154 (2), 140 (5), 126 (3), 112 (6), 97 (35), 83 (53), 69 (52), 55 (67), 41 (100).

(Benzyloxy)methyl Isonitrile (9)

Colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.33 (m, 5 H), 4.76 (s, 2 H), 4.70 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 161.1 (1:1:1 t, *J* = 4.1 Hz), 135.1, 128.5, 128.4, 128.2, 71.0 (1:1:1 t, *J* = 5.5 Hz), 71.0.

MS (EI): *m*/*z* (%) = 147 (7, [M^+]), 117 (100), 105 (22), 91 (89), 77 (56), 65 (51), 51 (51), 41 (42).

[(1_R_)-(7,7-Dimethylbicyclo[2.2.1]hept-2-en-2-yl)methyloxy]methyl Isonitrile (16)

Bright yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 5.60–5.58 (m, 1 H), 4.71 (d, *J* = 12.1 Hz, 1 H), 4.66 (d, *J* = 12.1 Hz, 1 H), 4.05–3.95 (m, 2 H), 2.41–2.35 (m, 1 H), 2.28–2.24 (m, 2 H), 2.13 (td, *J* = 5.7, 1.4 Hz, 1 H), 2.12–2.07 (m, 1 H), 1.26 (s, 3 H), 1.11 (d, *J* = 8.7 Hz, 1 H), 0.79 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5 (1:1:1 t, *J* = 4.1 Hz), 142.8, 123.2, 72.0, 70.8 (1:1:1 t, *J* = 5.4 Hz), 43.2, 40.5, 37.9, 31.4, 31.2, 25.9, 20.9.

MS (EI): *m*/*z* (%) = 191 (1, [M^+]), 176 (1), 161 (3), 146 (7), 134 (9), 119 (55), 105 (40), 91 (100), 79 (54), 65 (18), 41 (77).

(1_R_,2_S_,5_R_)-(2-Isopropyl-5-methylcyclohexyloxy)methyl Isonitrile (20)

Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.80 (d, *J* = 12.5 Hz, 1 H), 4.73 (d, *J* = 12.5 Hz, 1 H), 3.40 (td, *J* = 10.6, 4.3 Hz, 1 H), 2.15–2.02 (m, 2 H), 1.68–1.59 (m, 2 H), 1.42–1.31 (m, 1 H), 1.26–1.17 (m, 1 H),

1.06–0.82 (m, 3 H), 0.90 (d, *J* = 6.5 Hz, 3 H), 0.88 (d, *J* = 7.1 Hz, 3 H), 0.79 (d, *J* = 6.9 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.0 (1:1:1 t, *J* = 4.2 Hz), 78.5, 69.9 (1:1:1 t, *J* = 5.3 Hz), 47.8, 39.5, 34.1, 31.3, 25.2, 23.0, 22.1, 20.9, 16.0.

MS (EI): *m*/*z* (%) = 180 (5, [$M^+ - CH_3$]), 138 (59), 125 (65), 110 (73), 95 (100), 81 (98), 67 (85), 55 (90), 41 (100).

(Isopropyloxy)methyl Isonitrile (19)
Orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.75 (s, 2 H), 3.94 (sept, *J* = 6.2 Hz, 1 H), 1.21 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.0 (1:1:1 t, *J* = 4.3 Hz), 71.4, 70.0 (1:1:1 t, *J* = 5.4 Hz), 21.5.

(Ethoxy)methyl Isonitrile (17)
Orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.74 (s, 2 H), 3.67 (q, *J* = 7.0 Hz, 2 H), 1.23 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5 (1:1:1 t, *J* = 4.1 Hz), 72.3 (1:1:1 t, *J* = 5.4 Hz), 65.5, 14.3.

One-Pot Preparation of Isonitiles via Pure Transetherified Formamides; [(4-Bromobenzyl)oxy]methyl Isonitrile (11); Typical Procedure B
A stirred mixture of 4-bromobenzyl alcohol (2.1 g, 11 mmol), *N*-(ethoxymethyl)formamide (**7**; 0.61 g, 5.9 mmol) and concd H_2SO_4 (2 drops) was heated at ca. 110 °C (oil bath temp) for 1 h at atmospheric pressure and then for 2 h at ca. 300 Torr. Flash chromatography [CH_2Cl_2–Et_3N (100:0.5) → CH_2Cl_2–MeOH–Et_3N (90:10:0.5)] provided a mixture of *N*-[(4-bromobenzyloxy)methyl]formamide and unreacted 4-bromobenzyl alcohol. The mixture was taken up in anhyd THF (16 mL), chilled to 0 °C and treated with anhyd Et_3N (6.7 mL, 48 mmol) followed by a solution of anhyd $POCl_3$ (0.93 mL, 10 mmol) in THF (7 mL). The mixture was stirred at 10 °C for 20 min and then poured onto crushed ice. The product was extracted into Et_2O (3 × 10 mL) and the combined organic phase was washed with aq 10% Na_2CO_3 (20 mL), dried ($MgSO_4$), and concentrated in vacuo. Flash chromatography (PE–EtOAc–Et_3N, 75:25:0.5) afforded **11** (0.74 g, 55%) as an orange oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 4.75 (s, 2 H), 4.62 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.5 (1:1:1 t, *J* = 4.0 Hz), 134.2, 131.6, 129.7, 122.4, 71.2 (1:1:1 t, *J* = 5.6 Hz), 70.3.

MS (EI): *m*/*z* (%) = 227 (9, [M^+, ^{81}Br]), 225 (8, [M^+, ^{79}Br]), 197 (16), 195 (16), 185 (29), 183 (22), 171 (37), 169 (54), 157 (16), 155 (11), 146 (13), 116 (100), 105 (22), 89 (77), 77 (52), 63 (19), 41 (40).

HRMS (EI): *m*/*z* calcd for $C_9H_8{}^{81}BrN$: 226.9764; found: 226.9769; *m*/*z* calcd for $C_9H_8{}^{79}BrNO$: 224.9784; found: 224.9788.

[(3-Methyl-4-nitrobenzyl)oxy]methyl Isonitrile (10)
Pale yellow solid.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.91 (d, *J* = 8.3 Hz, 1 H), 7.28 (s, 1 H), 7.28 (d, *J* = 7.9 Hz, 1 H), 4.82 (s, 2 H), 4.70 (s, 2 H), 2.55 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.8 (1:1:1 t, *J* = 4.0 Hz), 148.5, 140.9, 133.8, 131.6, 125.7, 124.8, 71.7 (1:1:1 t, *J* = 5.7 Hz), 69.9, 20.2.

MS (EI): *m*/*z* (%) = 206 (3, [M^+]), 189 (29), 159 (5), 132 (100), 119 (9), 104 (18), 91 (16), 77 (24), 65 (16), 51 (13).

HRMS (EI): *m*/*z* calcd for $C_{10}H_{10}N_2O_3$: 206.0686; found: 206.0694.

[(2-Phenylethyl)oxy]methyl Isonitrile (15)
Pale yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39–7.33 (m, 2 H), 7.30–7.25 (m, 3 H), 4.69 (s, 2 H), 3.87 (t, *J* = 6.9 Hz, 2 H), 2.97 (t, *J* = 6.9 Hz, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.8 (1:1:1 t, *J* = 4.1 Hz), 137.6, 128.6, 128.2, 126.3, 72.4 (1:1:1 t, *J* = 5.7 Hz), 70.5, 35.2.

MS (EI): *m*/*z* (%) = 161 (17, [M^+]), 131 (42), 116 (70), 103 (83), 91 (100), 77 (34), 65 (41), 51 (42), 41 (32).

[(Diphenylmethyl)oxy]methyl Isonitrile (13)
Yellow oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43–7.35 (m, 10 H), 5.85 (s, 1 H), 4.76 (s, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 161.3 (1:1:1 t, *J* = 3.8 Hz), 139.3, 128.5, 128.1, 127.2, 81.1, 69.5 (1:1:1 t, *J* = 5.4 Hz).

MS (EI): *m*/*z* (%) = 223 (27, [M^+]), 183 (20), 167 (83), 152 (16), 146 (18), 105 (100), 83 (34), 77 (37), 51 (17).

HRMS (EI): *m*/*z* calcd for $C_{15}H_{13}NO$: 223.0992; found: 223.0993.

[(4-Methoxybenzyl)oxy]methyl Isonitrile (12)
Colourless oil.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27 (d, *J* = 8.8 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 4.70 (s, 2 H), 4.61 (s, 2 H), 3.79 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.9 (1:1:1 t, *J* = 4.0 Hz), 159.7, 129.9, 127.0, 113.8, 70.6 (1:1:1 t, *J* = 5.4 Hz), 70.5, 55.0.

MS (EI): *m*/*z* (%) = 177 (20, [M^+]), 147 (24), 135 (15), 121 (100), 107 (15), 91 (16), 77 (29), 40 (11).

[(2-Ethoxyethyl)oxy]methyl Isonitrile (21)
Colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.76 (s, 2 H), 3.73–3.71 (m, 2 H), 3.58–3.56 (m, 2 H), 3.46 (q, *J* = 7.0 Hz, 2 H), 1.14 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.8 (1:1:1 t, *J* = 4.1 Hz), 72.7 (1:1:1 t, *J* = 5.5 Hz), 69.0, 68.9, 66.5, 14.9.

MS (EI): *m*/*z* (%) = 84 (17, [$M^+ - OEt^-$]), 73 (6), 59 (46), 44 (100), 40 (37).

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