Sodium Borohydride as the Only Reagent for the Efficient Reductive Alkylation of Malononitrile with Ketones and Aldehydes

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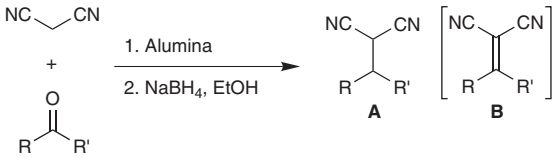
Abstract: An efficient and convenient method for the synthesis of primary and secondary monosubstituted malononitriles has been developed. In this method, sodium borohydride in isopropanol has a catalytic effect on the initial condensation between malononitrile and aldehydes or ketones at 0 °C. The sodium borohydride also simultaneously acts as a reagent and reduces the unsaturated intermediate formed in situ by the condensation. This simple reductive alkylation method effectively consumes all malononitrile and selectively produces only monosubstituted malononitriles. Unsymmetrically disubstituted malononitriles are prepared via alkylation of these monosubstituted derivatives.

Key words: malononitrile, ketones, aldehydes, condensations, reductions

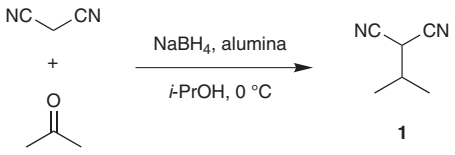
Control over the synthesis of monosubstituted malononitriles has been a challenging problem in organic chemistry. The most general and direct route to monosubstituted malononitriles is the alkylation of malononitrile, but this method generally produces various amounts of disubstituted malononitriles from over-alkylation when malononitrile is the limiting agent. Indeed, symmetrically disubstituted malononitriles can be efficiently prepared in this manner.[1] Keeping the alkylating agent to a minimum causes the product to be contaminated with significant amounts of unreacted malononitrile, which must be separated from the desired monosubstituted malononitrile.[2] Secondary alkyl substituents are relatively difficult to obtain via alkylation with longer reaction times required and lower yields obtained.[2c]

More selective methods for the synthesis of monosubstituted malononitriles followed a two-reaction sequence. The first step is a Knoevenagel condensation between malononitrile and a ketone or aldehyde.[3] The intermediate dicyanoalkene is reduced in a second step to afford the desired monosubstituted malononitrile.[4] The Knoevenagel condensations with malononitrile were carried out with alumina,[3a] $AlPO_4/Al_2O_3$,[3b] or amino acids.[3c] Various reducing agents included the Hantzsch 1,4-dihydropyridine ester,[4a] a polymer-supported NAD(P)H model,[4b] indium,[4c] or indium(III) chloride/sodium borohydride reagent system.[4d] Current work from this laboratory found a one-pot-two-step synthesis that produced secondary monosubstituted malononitriles in good to excellent yields (Scheme 1).[5] In this synthesis, alumina is used for the condensation, sodium borohydride in ethanol for the reduction. The Hantzsch 1,4-dihydropyridine ester was very recently utilized in the one-pot reductive benzylations of malononitrile under solvent-free mechanical milling conditions to give excellent yields for deactivated benzaldehydes.[6]



Scheme 1

The present investigation began with the hypothesis that lower yields from some of the one-pot syntheses could be attributed to the high concentration of intermediate dicyanoalkene (**B**) on the alumina in the presence of excess ketone before the ethanol and sodium borohydride were added. If the borohydride could be added while the condensation was taking place, intermediate **B** would remain at a low concentration and be reduced to **A** as it formed. The biggest concern was how competitive direct reduction of the ketone would be to the desired condensation reaction. Brown reported that ketones are only slowly reduced with sodium borohydride in isopropanol, so subsequently isopropanol was selected to replace ethanol as the solvent.[7] The reaction was carried out with malononitrile and excess acetone in isopropanol at 0 °C, and then the solid mixture of alumina and sodium borohydride was added in one portion (Scheme 2). Unfortunately, the yield did not improve, but unexpectedly we found that this reaction (combined condensation and reduction steps) was considerably faster than the previously reported condensation step.[8]



Scheme 2

The reaction was efficient in producing the desired product and the competing reduction reaction between sodium borohydride and acetone was not competitive enough to

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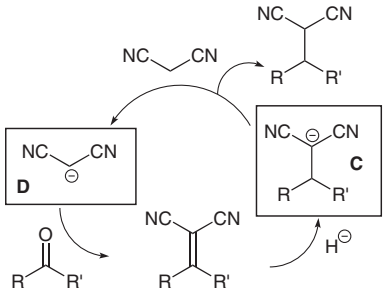
consume the borohydride before the condensation reaction was complete and all the unsaturated intermediate was successfully reduced. There is no literature to support the catalysis with sodium borohydride but further investigation was warranted. It was reported that aliphatic carboxylic acids and aromatic aldehydes were condensed in the presence of sodium borohydride, but in this condensation the borohydride and carboxylic acid were completely reacted and excess acid was distilled off before the aldehyde was added and the reaction carried out in *N*-methyl-2-pyrrolidinone (NMP) at 202 °C.[9]

The alumina catalyst was removed to determine if sodium borohydride had a catalytic effect and promoted the initial condensation step,[10] or might simply activate the alumina. The reaction of malononitrile with acetone was carried out under conditions comparable to those depicted in Scheme 2, with the exception of alumina. In this case, the secondary monosubstituted malononitrile product was still prepared quickly and efficiently with borohydride as the only catalyst and reagent. This indicates without a doubt that sodium borohydride affected the condensation step of this reductive alkylation. Although no direct evidence of sodium borohydride interacting with malononitrile to catalyze the condensation step was found, the borohydride reduction of the condensation product in the second step generates substituted malononitrile anion **C** (Scheme 3). This base is converted into the product and generates more of the less basic malononitrile anion **D**, which can then continue this condensation–reduction cycle. It is unclear, whether this alone can account for the rate enhancement observed, or if other catalytic activity exists.

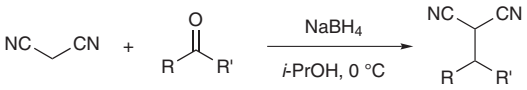


Scheme 3

The scope of this novel reaction with various ketones was investigated and the results of this study are shown in Table 1. When less volatile ketones were employed, it was observed that ketone reduction does take place and the corresponding alcohol is present in the crude product. This competitive reaction does not prevent all the malononitrile from being consumed. The reaction is successful with ketones containing secondary alkyl groups (Table 1, entry 3). When the reaction was extended to very hindered ketones such as pinacolone (3,3-dimethyl-2-butanone, a tertiary alkyl ketone), the relative rate of direct ketone reduction was much faster than the desired condensation–reduction and the product was not isolated.

This novel reaction with sodium borohydride (but no alumina) was also examined for the synthesis of primary monosubstituted malononitriles by utilizing aldehydes in place of the ketones. The results of this study are shown in Table 2. In these cases, the aldehyde reduction was quite competitive with the desired reaction. This was only problematic for the high-boiling aldehydes where the corre-

Table 1 Sodium Borohydride in the Reductive Alkylation of Malononitrile with Ketones



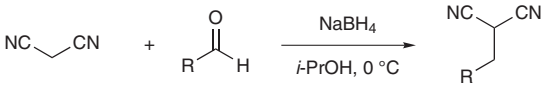
Entry	R	R′	Product	Time (min)	Yield (%)[a]
1	Me	Me	**1**	2	77
2	Me	Et	**2**	5	83
3	Me	*i*-Pr	**3**	300	73
4	Me	$CH_2CH(Me)_2$	**4**	20	67
5	Me	*n*-Pentyl	**5**	60	77
6	Me	CH_2CO_2Et	**6**	50	68
7	Et	Et	**7**	240	81
8	-$(CH_2)_4$-		**8**	5	86
9	-$(CH_2)_5$-		**9**	5	83
10	-$(CH_2)_7$-		**10**	45	72
11	Me	Ph	**11**	480	64

[a] Isolated yield after purification by column chromatography, vacuum distillation, or steam distillation.

sponding alcohols formed from the direct reduction were not easily evaporated. In these cases, vacuum distillation was used to remove most of the impurities before the desired compound was isolated by column chromatography or recrystallization. Carrying out the Knoevenagel condensation as a separate step prior to reduction now becomes a practical alternative.[3,5,10]

When malononitrile was replaced in this novel reaction with diethyl malonate, there was no evidence for the reductive alkylation using sodium borohydride. Meldrum's acid was reported to undergo Knoevenagel condensation with aromatic aldehydes, using potassium phosphate in ethanol followed directly by sodium borohydride for the conjugated reduction.[11] This was quite similar to the earlier one-pot synthesis for malononitriles reported from this lab.[5] When Meldrum's acid was reacted with an aldehyde or ketone at 0 °C in isopropanol, only direct reduction of the aldehyde or ketone was detected. This establishes that acidity is not the determining factor because Meldrum's acid is considerably more acidic than malononitrile.[12] Current research examines the importance of the cyano groups of malononitrile and explores other potential electron-withdrawing groups.

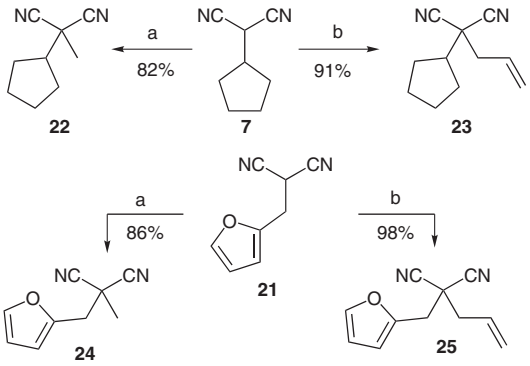
Table 2 Sodium Borohydride in the Reductive Alkylation of Malononitrile with Aldehydes



Entry	R	Product	Time (min)	Yield (%)[a]
1	Me	**12**	4[b]	87[b]
2	Et	**13**	10	77
3	Pr	**14**	30	80
4	$(Me)_2CHCH_2$	**15**	30	78
5	*i*-Pr	**16**	25	75
6	*t*-Bu	**17**	150	69
7	Ph	**18**	20	83
8	$4\text{-}CH_3C_6H_4$	**19**	20	61
9	$4\text{-}CH_3OC_6H_4$	**20**	20	63
10[c]	$4\text{-}NO_2C_6H_4$	**21**	30[d]	60
11	2-Furanyl	**22**	30	86

[a] Isolated yield after purification by column chromatography, vacuum distillation, or recrystallization.
[b] 50 min and 52% using $NaBH_3CN$.
[c] Solvent was THF–*i*-PrOH (1:1).
[d] Slow concomitant addition of aldehyde and borohydride.

Unsymmetrically disubstituted malononitriles can be prepared via alkylation without difficulties, once the monosubstituted derivative is obtained.[2] Applying iodomethane or allyl bromide as alkylating agent with anhydrous potassium carbonate in acetone, secondary (**8**) and primary (**22**) monosubstituted malononitriles both react with equal proficiency (Scheme 4). Unsymmetrically disubstituted malononitriles were reported in the patent literature to be potent insecticides.[13] The nitriles can be reduced to prepare unique diamines, which can be further derivatized to create, for example, new cyclic ureas.[1a] One of the two nitrile groups (which are prochiral) could be selectively converted into some other functional groups, such as those employed for enantiotopic group selective hydrolysis with *Rhodococcus* amidase.[2a,14]



Scheme 4 *Reagents and conditions*: a) MeI, K_2CO_3, acetone; b) Allyl bromide, K_2CO_3, acetone.

In conclusion, this one-step method involving sodium borohydride for the synthesis of monosubstituted malononitriles is simple and expedient for numerous aldehydes and ketones. There is a limitation if the ketone or aldehyde is precious because the aldehyde or ketone is introduced in excess to ensure complete consumption of malononitrile and to compensate for competitive reduction. This limitation can be partly overcome by applying high-dilution conditions (slow addition of the sodium borohydride and the aldehyde or ketone concurrently) or by performing the condensation as a separate step.[3,5,10] The primary and secondary monosubstituted malononitriles, selectively synthesized, can then be utilized for further reaction such as alkylation shown here. Many other manipulations can also be applied (such as nitrile hydrolysis or reduction) now that the monosubstituted malononitriles can be prepared quickly and efficiently.

Analytical thin-layer chromatography (TLC) was performed using Baker-Flex silica gel IB-F plates and visualized using a UV lamp and basic $KMnO_4$ soln [$KMnO_4$ (2.3 g), K_2CO_3 (15 g), 2.5 M NaOH soln (1.9 mL) in 300 mL deionized H_2O]. Flash chromatography was performed using silica gel (35–70 μm, ca. 60 Å pore) from Acros or prepacked silica column (32–63 μm, 60 Å pore) from Analogix. Melting points are uncorrected. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL Eclipse spectrometer at 400 MHz and 100 MHz, respectively. ^1H chemical shifts are reported in ppm downfield from internal tetramethylsilane and ^{13}C chemical shifts are reported in ppm relative to $CDCl_3$ (77.0). Elemental Analyses were performed at Midwest Microlab, Indianapolis, IN. Propanal, butanal, benzaldehyde, and furfural were freshly distilled before use.

Reductive Alkylation of Malononitrile with Ketones and Aldehydes; General Procedure

A solution of malononitrile (1 equiv, 9.8–40 mmol) and ketone or aldehyde (1.9–9.6 equiv) in isopropanol (2 mL/mmol of malononitrile) was cooled to 0 °C. Sodium borohydride (ca. 1 equiv) was added and the reaction stirred until complete according to TLC. On several occasions, if any intermediate olefin was present or remaining ketone or aldehyde required reducing, more borohydride (up to 0.6 equiv) was added. The reaction was carefully quenched with H_2O and 1M HCl soln, extracted with CH_2Cl_2, filtered, and concentrated. The crude product could be purified by column chromatography, recrystallization, vacuum or steam distillation.

Isopropylmalononitrile (1)[5]

Malononitrile (1.32 g, 20.0 mmol), acetone (2.32 g, 40.0 mmol), and sodium borohydride (0.757 g, 20.0 mmol) yielded an oil (1.66 g, 77%).

IR (thin film, NaCl): 2973, 2917, 2880, 2256, 1466, 1396, 1378, 1235, 1176, 1134, 883 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.63 (d, *J* = 5.5 Hz, 1 H), 2.39–2.34 (m, 1 H), 1.25 (d, *J* = 7.0 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.9, 31.2, 30.3, 19.5.

***Sec*-Butylmalononitrile (2)[5]**

Malononitrile (0.681 g, 10.3 mmol), 2-butanone (7.10 g, 98.5 mmol), and $NaBH_4$ (0.381 g, 10.1 mmol) yielded an oil (0.984 g, 83%).

IR (thin film, NaCl): 2971, 2937, 2882, 2255, 1459 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.72 (d, *J* = 5.1 Hz, 1 H), 2.16–2.05 (m, 1 H), 1.74–1.63 (m, 1 H), 1.57–1.45 (m, 1 H), 1.15 (d, *J* = 7.0 Hz, 3 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.3, 111.8, 36.6, 28.5, 26.3, 16.0, 10.7.

(1,2-Dimethylpropyl)malononitrile (3)[5]

Malononitrile (0.739 g, 11.2 mmol), 3-methyl-2-butanone (3.04 g, 35.3 mmol), and $NaBH_4$ (0.385 g, 10.2 mmol) yielded an oil (1.12 g, 73%).

IR (thin film, NaCl): 2969, 2933, 2906, 2880, 2254, 1465, 1396, 1388, 1373 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (d, *J* = 6.0 Hz, 1 H), 2.01–1.81 (m, 2 H), 1.24 (d, *J* = 7.0 Hz, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.6 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.8, 111.9, 41.3, 30.3, 27.4, 20.5, 17.9, 13.4.

(1,3-Dimethylbutyl)malononitrile (4)[5]

Malononitrile, 4-methyl-2-pentanone (5.02 g, 50.1 mmol), and $NaBH_4$ (0.382 g, 10.1 mmol) yielded an oil (1.07 g, 67%).

IR (thin film, NaCl): 2961, 2915, 2874, 2254, 1469, 1390, 1370 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.63 (d, *J* = 5.1 Hz, 1 H), 2.30–2.17 (m, 1 H), 1.72–1.58 (m, 1 H), 1.44–1.31 (m, 2 H), 1.24–1.16 (m, 3 H), 0.98–0.84 (m, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.3, 111.7, 42.7, 33.5, 29.4, 25.0, 23.0, 21.5, 16.8.

(1-Methylhexyl)malononitrile (5)

Malononitrile (0.670 g, 10.1 mmol), 2-heptanone (4.58 g, 40.0 mmol), and $NaBH_4$ (0.390 g, 10.3 mmol) yielded an oil (1.07 g, 77%).

IR (thin film, NaCl): 2960, 2933, 2861, 2254, 1463 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.66 (d, *J* = 5.1 Hz, 1 H), 2.21–2.10 (m, 1 H), 1.64–1.54 (m, 1 H), 1.50–1.25 (m, 7 H), 1.23 (d, *J* = 6.6 Hz, 3 H), 0.89 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.3, 111.8, 35.3, 33.4, 31.2, 29.0, 26.0, 22.2, 16.6, 13.7.

Anal. Calcd for $C_{10}H_{16}N_2$: C, 73.13; H, 9.82; N, 17.06. Found: C, 72.81; H, 9.84; N, 16.80.

Ethyl 4,4-Dicyano-3-methylbutanoate (6)[5]

Malononitrile (0.337 g, 5.10 mmol), ethyl acetoacetate (0.989 g, 7.60 mmol), and $NaBH_4$ (0.190 g, 5.02 mmol) yielded an oil (0.621 g, 68%).

IR (thin film, NaCl): 2983, 2917, 2256, 1731, 1387, 1189 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 4.33 (d, *J* = 4.8 Hz, 1 H), 4.18 (q, *J* = 7.2 Hz, 2 H), 2.71–2.60 (m, 1 H), 2.57–2.54 (m, 2 H), 1.33 (d, *J* = 6.9 Hz, 3 H), 1.29 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.2, 112.0, 111.3, 60.7, 36.8, 31.8, 27.6, 16.5, 13.6.

(1-Ethylpropyl)malononitrile (7)[5]

Malononitrile (0.663 g, 10.0 mmol), 3-pentanone (3.60 g, 41.8 mmol), and $NaBH_4$ (0.392 g, 10.4 mmol; 0.191 g, 5.05 mmol)[15] yielded an oil (1.11 g, 81%).

IR (thin film, NaCl): 2970, 2933, 2882, 2254, 1460, 1388, 1220 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.78 (d, 1 H, *J* = 5.1 Hz), 1.92–1.85 (m, 1 H), 1.74–1.62 (m, 4 H), 1.02 (t, *J* = 7.5 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.2, 43.0, 26.4, 23.7, 10.7.

Cyclopentylmalononitrile (8)[5]

Malononitrile (0.664 g, 10.1 mmol), cyclopentanone (2.55 g, 30.3 mmol), and $NaBH_4$ (0.382 g, 10.1 mmol) yielded an oil (1.16 g, 86%).

IR (thin film, NaCl): 2963, 2912, 2873, 2256, 1453 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.67 (d, *J* = 6.6 Hz, 1 H), 2.51 (m, 1 H), 2.10–2.01 (m, 2 H), 1.83–1.72 (m, 2 H), 1.72–1.61 (m, 2 H), 1.60–1.43 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.5, 40.5, 30.1, 27.1, 24.8.

Cyclohexylmalononitrile (9)[5]

Malononitrile (0.662 g, 10.0 mmol), cyclohexanone (2.95 g, 30.1 mmol), and $NaBH_4$ (0.378 g, 9.99 mmol) yielded an oil (1.24 g, 83%).

IR (thin film, NaCl): 2934, 2858, 2254, 1452 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.57 (d, *J* = 5.5 Hz, 1 H), 2.04–1.94 (m, 3 H), 1.91–1.83 (m, 2 H), 1.77–1.69 (m, 1 H), 1.39–1.13 (m, 5 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.0, 39.1, 29.7, 29.2, 25.1, 24.9.

Cyclooctylmalononitrile (10)

Malononitrile (0.727 g, 11.0 mmol), cyclooctanone (5.02 g, 39.8 mmol), and $NaBH_4$ (0.424 g, 11.2 mmol) yielded an oil (1.40 g, 72%).

IR (thin film, NaCl): 2924, 2855, 2252, 1474, 1448 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.55 (d, *J* = 5.8 Hz, 1 H), 2.30–2.20 (m, 1 H), 1.90–1.72 (m, 4 H), 1.70–1.42 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.5, 39.6, 30.5(2), 26.1, 26.0, 24.9.

Anal. Calcd for $C_{11}H_{16}N_2$: C, 74.96; H, 9.15; N, 15.89. Found: C, 75.05; H, 9.17; N, 15.72.

(1-Phenylethyl)malononitrile (11)[5]
Malononitrile (0.672 g, 10.2 mmol), acetophenone (3.63 g, 30.2 mmol), and $NaBH_4$ (0.389 g, 10.3 mmol) yielded an oil (1.11 g, 64%).

IR (thin film, NaCl): 3090, 3066, 3033, 2977, 2906, 2255, 1497, 1455, 1387 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.30 (m, 5 H), 3.85 (d, *J* = 6.2 Hz, 1 H), 3.49–3.42 (m, 1 H), 1.65 (d, *J* = 7.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.1, 129.0, 128.6, 127.1, 112.0, 111.8, 40.9, 30.9, 17.6.

Ethylmalononitrile (12)[2c]
Malononitrile (0.715 g, 10.8 mmol), acetaldehyde (2.37 g, 53.8 mmol), and $NaBH_4$ (0.413 g, 10.9 mmol) yielded an oil (0.847 g, 87%).

IR (thin film, NaCl): 2984, 2917, 2884, 2259, 1462 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.75 (t, *J* = 6.6 Hz, 1 H), 2.13–2.06 (m, 2 H), 1.25 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.6, 24.6, 23.9, 10.8.

Propylmalononitrile (13)[16]
Malononitrile (1.33 g, 20.1 mmol), propanal (4.71 g, 81.1 mmol), and $NaBH_4$ (0.763 g, 20.2 mmol) yielded an oil (1.68 g, 77%).

IR (thin film, NaCl): 2969, 2925, 2879, 2256, 1723 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.72 (t, *J* = 7.0 Hz, 1 H), 2.03–1.98 (m, 2 H), 1.71–1.60 (m, 2 H), 1.03 (t, *J* = 7.4 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.7, 32.3, 21.2, 19.7, 12.6.

Butylmalononitrile (14)[2c]
Malononitrile (2.65 g, 40.1 mmol), butanal (8.62 g, 120 mmol), and $NaBH_4$ (1.54 g, 40.7 mmol) yielded an oil (3.91 g, 80%).

IR (thin film, NaCl): 2962, 2933, 2877, 2257, 1468 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.71 (t, *J* = 7.0 Hz, 1 H), 2.07–1.99 (m, 2 H), 1.65–1.56 (m, 2 H), 1.47–1.36 (m, 2 H), 0.96 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.8, 35.2, 28.7, 27.2, 22.7, 22.0.

(3-Methylbutyl)malononitrile (15)[17]
Malononitrile (1.37 g, 20.7 mmol), 3-methylbutanal (6.87 g, 79.8 mmol), and $NaBH_4$ (0.787 g, 20.8 mmol) yielded an oil (2.22 g, 78%).

IR (thin film, NaCl): 2960, 2918, 2873, 2256, 1469 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.70 (t, *J* = 6.8 Hz, 1 H), 2.06–1.97 (m, 2 H), 1.71–1.59 (m, 1 H), 1.54–1.44 (m, 2 H), 0.94 (d, *J* = 5.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.8, 35.2, 28.7, 27.2, 22.7, 22.0.

(2-Methylpropyl)malononitrile (16)[18]
Malononitrile (0.680 g, 10.3 mmol), 2-methylpropanal (2.81 g, 39.0 mmol), and $NaBH_4$ (0.419 g, 11.1 mmol) yielded an oil (0.943 g, 75%).

IR (thin film, NaCl): 2964, 2921, 2876, 2256, 1471, 1392, 1373 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.71 (t, *J* = 7.5 Hz, 1 H), 1.95–1.91 (m, 3 H), 1.02 (d, *J* = 6.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 112.8, 38.6, 25.8, 21.2, 20.6.

(2,2-Dimethylpropyl)malononitrile (17)[12]
Malononitrile (0.649 g, 9.82 mmol), trimethylacetaldehyde (3.10 g, 36.0 mmol; 1.73 g, 20.1 mmol),[19] and $NaBH_4$ (0.763 g, 20.2 mmol) yielded an oil (0.889 g, 69%).

IR (thin film, NaCl): 2965, 2918, 2869, 2255, 1477 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 3.74 (t, *J* = 6.8 Hz, 1 H), 2.01 (d, *J* = 7.0 Hz, 2 H), 1.05 (s, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 113.7, 43.8, 30.8, 28.5, 18.3.

Benzylmalononitrile (18)[4c]
Malononitrile (1.28 g, 19.4 mmol), benzaldehyde (6.38 g, 60.1 mmol), and $NaBH_4$ (0.767 g, 20.3 mmol; 0.381 g, 10.1 mmol) yielded a solid (2.51 g, 83%); mp 86–87 °C.

IR (pellet, KBr): 3030, 2915, 2258, 1496, 1454, 1446, 1075, 749, 701 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.25 (m, 5 H), 3.90 (t, *J* = 7.0 Hz, 1 H), 3.28 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.9, 129.3, 129.1, 128.8, 112.2, 36.7, 24.9.

(4-Methylbenzyl)malononitrile (19)[20]
Malononitrile (0.669 g, 10.1 mmol), 4-methylbenzaldehyde (4.18 g, 34.8 mmol), and $NaBH_4$ (0.381 g, 10.1 mmol; 0.188 g, 4.97 mmol)[21] yielded a solid (1.05 g, 61%); mp 79–80 °C.

IR (pellet, KBr): 2933, 2258, 1516, 1348, 1030, 790 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.05 (s, 4 H), 3.87 (t, *J* = 7.0 Hz, 1 H), 3.25 (d, *J* = 7.0 Hz, 2 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 129.9, 129.8, 128.9, 112.3, 36.2, 25.0, 21.0.

(4-Methoxybenzyl)malononitrile (20)[4c]
Malononitrile (0.654 g, 9.90 mmol), 4-methoxybenzaldehyde (3.33 g, 24.5 mmol), and $NaBH_4$ (0.420 g, 11.1 mmol) yielded a solid (1.04 g, 63%); mp 89–90.5 °C.

IR (thin film, NaCl): 2934, 2919, 2836, 2257, 1610, 1508, 1249, 1175, 1029 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, 2 H, *J* = 8.8), 6.91 (d, *J* = 8.8 Hz, 2 H), 3.85 (t, *J* = 6.9 Hz, 1 H), 3.81 (s, 3 H), 3.23 (d, *J* = 6.9 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.8, 130.2, 124.7, 114.5, 112.1, 55.2, 35.9, 25.1.

(4-Nitrobenzyl)malononitrile (21)[6]
Malononitrile (0.689 g, 10.4 mmol), 4-nitrobenzaldehyde (2.99 g, 19.8 mmol), and $NaBH_4$ (0.202 g, 5.34 mmol; 0.194 g, 5.13 mmol)[21] yielded a solid (1.26 g, 60%); mp 151–152.5 °C.

IR (pellet, KBr): 2930, 2258, 1604, 1520, 1347, 1292, 1106, 858, 790, 712 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.6 Hz, 2 H), 7.55 (d, *J* = 8.6 Hz, 2 H), 4.04 (t, *J* = 6.5 Hz, 1 H), 3.42 (d, *J* = 6.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 139.7, 130.4, 124.5, 111.5, 36.0, 24.4.

Furfurylmalononitrile (22)[4c]
Malononitrile (1.35 g, 20.4 mmol), furfural (6.02 g, 62.6 mmol), and $NaBH_4$ (0.812 g, 21.5 mmol; 0.420 g, 11.1 mmol)[21] yielded an oil (2.55 g, 86%).

IR (thin film, NaCl): 3153, 3126, 2919, 2259, 1599, 1505, 1433, 1147, 1076, 1016, 746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (s, 1 H), 6.41–6.36 (m, 2 H), 4.05 (t, *J* = 7.0 Hz, 1 H), 3.37 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.4, 143.2, 112.0, 110.6, 109.6, 29.1, 22.4.

Alkylation of Monosubstituted Malononitriles; General Procedure

The purified monosubstituted malononitrile (**8** or **22**) was dissolved in acetone (5 mL/mmol) and alkyl halide (ca. 2 equiv) and anhyd K_2CO_3 (ca. 2.5 equiv) were added. The mixture was stirred at r.t. overnight or until complete by TLC. The reaction mixture was washed with Et_2O and filtered through a pad of celite. The crude product was concentrated via rotary evaporation and could be purified via flash chromatography.

2-Cyclopentyl-2-methylmalononitrile (23)

Cyclopentylmalononitrile (**8**, 0.670 g, 4.99 mmol), MeI (1.44 g, 10.1 mmol) and anhyd K_2CO_3 (1.73 g, 12.5 mmol) yielded an oil (0.549 g, 82%).

IR (thin film, NaCl): 3056, 2960, 2871, 2249, 1735, 1457, 1383, 1378, 1266, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (quin, *J* = 8.5 Hz, 1 H), 2.05–1.95 (m, 2 H), 1.86–1.75 (m, 2 H), 1.75 (s, 3 H), 1.68–1.50 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.7, 47.0, 35.6, 28.7, 24.9, 23.4.

Anal. Calcd for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.72; H, 8.25; N, 18.80.

2-Allyl-2-cyclopentylmalononitrile (24)

Cyclopentylmalononitrile (**8**, 0.476 g, 3.54 mmol), allyl bromide (1.23 g, 10.2 mmol), and anhyd K_2CO_3 (1.74 g, 12.5 mmol) yielded an oil (0.561 g, 91%).

IR (thin film, NaCl): 2963, 2872, 2246, 1644, 1448 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.95–5.85 (m, 1 H), 5.40–5.38 (m, 2 H), 2.63 (d, *J* = 7.0 Hz, 2 H), 2.38–2.29 (m, 1 H), 2.30–1.95 (m, 2 H), 1.84–1.75 (m, 2 H), 1.68–1.53 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 129.8, 122.4, 114.9, 45.4, 42.0, 40.6, 28.9, 25.0.

Anal. Calcd for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.70; H, 8.10; N, 15.74.

2-Furfuryl-2-methylmalononitrile (25)

Furfurylmalononitrile (**22**, 0.569 g, 3.89 mmol), MeI (1.44 g, 10.2 mmol) and anhyd K_2CO_3 (1.73 g, 12.5 mmol) yielded an oil (0.536 g, 86%).

IR (thin film, NaCl): 2254, 1502, 1150, 1014, 909 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.44 (d, *J* = 1.1 Hz, 1 H), 6.46–6.37 (m, 2 H), 3.33 (s, 2 H), 1.80 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 143.3, 115.5, 110.7, 110.5, 36.7, 31.6, 23.7.

Anal. Calcd for $C_9H_8N_2O$: C, 67.49; H, 5.03; N, 17.49. Found: C, 67.43; H, 5.11; N, 17.19.

2-Allyl-2-furfurylmalononitrile (26)[12b]

Furfurylmalononitrile (**22**, 0.713 g, 4.88 mmol), allyl bromide (1.23 g, 10.2 mmol), and anhyd K_2CO_3 (1.74 g, 12.6 mmol) yielded an oil (0.889 g, 98%).

IR (thin film, NaCl): 3150, 3124, 3087, 2986, 2927, 2250, 1502, 1440, 1149, 1013, 938, 743 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43 (s, 1 H), 6.46–6.36 (m, 2 H), 5.96–5.84 (m, 1 H), 5.48–5.37 (m, 2 H), 3.30 (s, 2 H), 2.67 (d, 2 H, *J* = 7.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.1, 143.4, 128.3, 123.5, 114.6, 110.8, 110.7, 40.6, 37.4, 35.1.

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References

(1) (a) Qian, F.; McCusker, J. E.; Zhang, Y.; Main, A. D.; Chlebowski, M.; Kokka, M.; McElwee-White, L. *J. Org. Chem.* **2002**, *67*, 4086. (b) Bloomfield, J. J. *J. Org. Chem.* **1961**, *26*, 4112.

(2) (a) Wu, Z.-L.; Li, Z.-Y. *J. Org. Chem.* **2003**, *68*, 2479. (b) Meguro, M.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 694. (c) Díez-Barra, E.; de la Hoz, A.; Moreno, A.; Sánchez-Verdú, P. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2589.

(3) (a) Texier-Boullet, F.; Foucaud, A. *Tetrahedron Lett.* **1982**, *23*, 4927. (b) Cabello, J. A.; Campelo, J. M.; Garcia, A.; Luna, D.; Marinas, J. M. *J. Org. Chem.* **1984**, *49*, 5195. (c) Prout, F. S. *J. Org. Chem.* **1953**, *18*, 928.

(4) (a) Garden, S. J.; Guimarães, C. R. W.; Corréa, M. B.; de Oliveira, C. A. F.; da Cunha Pinto, A.; de Alencastro, R. B. *J. Org. Chem.* **2003**, *68*, 8815. (b) Zhang, B.; Zhu, X.-Q.; Lu, J.-Y.; He, J.; Wang, P. G.; Cheng, J.-P. *J. Org. Chem.* **2003**, *68*, 3295. (c) Ranu, B. C.; Dutta, J.; Guchhait, S. K. *Org. Lett.* **2001**, *3*, 2603. (d) Ranu, B. C.; Samanta, S. *Tetrahedron* **2003**, *59*, 7901.

(5) Sammelson, R. E.; Allen, M. J. *Synthesis* **2005**, 543.

(6) Zhang, Z.; Gao, J.; Xia, J.-J.; Wang, G.-W. *Org. Biomol. Chem.* **2005**, *3*, 1617.

(7) Brown, H. C.; Wheeler, O. H.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 214.

(8) Isolated yield for the previous one-pot method (ref. 5) was 83% and the reaction time was 10 min for the condensation step. The current yield was 78% in ≤6 min for both steps.

(9) Chiriac, C. I.; Tanasa, F.; Onciu, M. *Tetrahedron Lett.* **2003**, *44*, 3579.

(10) Condensation of malononitrile with acetone-d_6 was observed in this lab using NMR and TLC but complete condensation without any catalyst takes more than 24 h at r.t. A solution of malononitrile and acetone in *i*-PrOH (0.5 M and 1.0 M, respectively; similar to our reaction conditions, but without $NaBH_4$) only produces small amounts (ca. 20%) of condensation product after 24 h at r.t. when analyzed by TLC. For a recent report on the Knoevenagel condensation of malononitrile with aromatic aldehydes in EtOH without catalyst, see: Wang, X.-S.; Zeng, Z.-S.; Li, Y.-L.; Shi, D.-Q.; Tu, S.-J.; Wei, X.-Y.; Zong, Z.-M. *Synth. Commun.* **2005**, *35*, 1915.

(11) Desai, U. V.; Pore, D. M.; Mane, R. B.; Solabannavar, S. B.; Wadgaonkar, P. P. *Synth. Commun.* **2004**, *34*, 25.

(12) (a) For information about Meldrum's acid pK_a = 7.3 in DMSO, see: Arnett, E. M.; Maroldo, S. G.; Schilling, S. L.; Harrelson, J. A. *J. Am. Chem. Soc.* **1984**, *106*, 6759. (b) For information about malononitrile pK_a = 11.1 in DMSO, see: Matthews, W. S.; Bares, J. E.; Bartmess, J. E.; Bordwell, F. G.; Cornforth, F. J.; Drucker, G. E.; Margolin, Z.; McCallum, R. J.; McCollum, G. J.; Vanier, N. R. *J. Am. Chem. Soc.* **1975**, *97*, 7006.

(13) (a) Okada, S.; Oohira, D.; Otaka, K. PCT Int. Appl. WO 2004020399, **2004**; *Chem. Abstr.* **2004**, *140*, 235428.
(b) Otaka, T.; Ohira, D. Jpn. Kokai Tokkyo Koho JP 2004099597, **2004**; *Chem. Abstr.* **2004**, *140*, 303517.
(c) Otaka, K.; Oohira, D.; Suzuki, M. PCT Int. Appl. WO 2002090321, **2002**; *Chem. Abstr.* **2002**, *137*, 352788.
(d) Otaka, K.; Suzuki, M.; Oohira, D. PCT Int. Appl. WO 2002089579, **2002**; *Chem. Abstr.* **2002**, *137*, 369842.
(14) Yokoyama, M.; Kashiwagi, M.; Iwasaki, M.; Fuhshuku, K.; Ohta, H.; Sugai, T. *Tetrahedron: Asymmetry* **2004**, *15*, 2817.
(15) The second portion of $NaBH_4$ was added after 90 min.
(16) Wada, M.; Mitsunobu, O. *Tetrahedron Lett.* **1972**, *13*, 1279.
(17) Echevarria, A.; Martin, M.; Perez, C.; Rozas, I. *Arch. Pharm. (Weinheim, Ger.)* **1994**, *327*, 303.
(18) Chikashita, H.; Nishida, S.; Miyazaki, M.; Morita, Y.; Itoh, K. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 737.
(19) Additional trimethylacetaldehyde was added after 60 min.
(20) Bauer, T.; Thomann, R.; Mülhaupt, R. *Macromolecules* **1998**, *31*, 7651.
(21) The second portion of $NaBH_4$ was added after 20 min.