Monosubstituted Malononitriles: Efficient One-Pot Reductive Alkylations of Malononitrile with Aromatic Aldehydes

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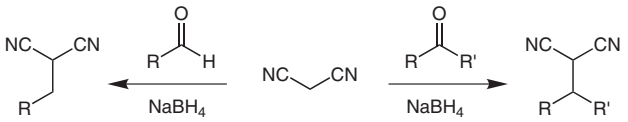
Abstract: A powerful new one-pot method has been developed for the reductive alkylation of malononitrile with aromatic aldehydes. This new procedure has vastly improved the yield and efficiency of the process, and increased the scope of the aromatic aldehydes. Incorporating water as the catalyst in ethanol for the condensation step allows stoichiometric amounts of malononitrile and aldehyde to be employed. The reduction step takes place quickly and efficiently with sodium borohydride to give monosubstituted malononitriles via filtration or extraction. The product from 2-quinolinecarboxaldehyde quickly rearranges to a novel indolizine, while alkylation of the monosubstituted derivative provides an unsymmetrically disubstituted malononitrile that does not rearrange.

Key words: malononitrile, aldehydes, condensation, reduction, heterocycles

Carbon–carbon bond forming reactions are extremely important and often a difficult task in organic synthesis for the production of complex targets from simpler building blocks.[1] Synthesis of monosubstituted malononitriles via C–C bond formation has been a challenging problem for organic chemists.[2] The most direct route to monosubstituted malononitriles is the alkylation of malononitrile, but this method generally produces various amounts of disubstituted malononitriles from overalkylation. Moreover, unreacted malononitrile is mostly present in the product mixture. More selective methods for the synthesis of monosubstituted malononitriles have generally followed a two reaction sequence. The first step is a Knoevenagel condensation between malononitrile and an aldehyde or ketone. The intermediate dicyanoalkene is reduced in a second step to afford the desired monosubstituted malononitrile. Recently, there has been a good deal of research on the Knoevenagel condensation[3] as well as the reduction of the electron-deficient olefins.[4] Work from this laboratory has found that sodium borohydride in isopropyl alcohol can produce monosubstituted malononitriles in good to excellent yields in a single reductive alkylation step (Scheme 1).[5]

The Hantzsch (1,4-dihydropyridine) ester has recently been utilized in the one-pot reductive benzylation of malononitrile under solvent-free mechanical milling conditions to give excellent yields on a small scale for



Scheme 1

benzaldehyde and substituted benzaldehydes with electron-withdrawing groups.[6] Two independent reports have recently shown that the Knoevenagel condensation step between malononitrile and aromatic aldehydes can simply occur in ethanol[3c] or water[3d] with no added catalysts. Indeed, water can be an excellent reaction accelerant for a variety of organic reactions[7] and the green chemistry implications of utilizing aqueous media for C–C bond formations has been fruitful.[8] Our continued work, reported here, utilized this discovery to vastly improve the yield, efficiency, and scope of aromatic aldehydes for the reductive alkylation.

Our research began with exploring the use of water or ethanol for the condensation of malononitriles with benzaldehyde. In water at room temperature the reaction oiled out and it was anticipated that this problem would become even worse with our intended scope of hydrophobic aldehydes. In absolute ethanol the condensation reaction was extremely sluggish. We found that the reaction was most efficient with a mixture of water and ethanol. In most cases we used 95% ethanol with a concentration of 1.0 M for aldehyde and malononitrile. Table 1 shows the variety of aldehydes employed and the times required for the condensation to be completed. The condensation reactions could be stirred several days without any complication. Dilution of the resultant mixture with additional ethanol and cooling the reaction in an ice-water bath preceded sodium borohydride reduction. We have also adopted a simple aqueous filtration workup for many of the derivatives (see experimental). This has allowed us to scale reactions – vanillin (Table 1, entry 13) was performed on a 100 mmol scale. Another advantage of the one-pot synthesis – particularly on larger scales – is avoiding transfers and handling of hazardous intermediates.[9]

Although product **16** contained a heterocyclic system, we next moved our research to test the reductive alkylation reaction with heterocyclic carboxaldehdyes (Table 2). First, furan and thiophene were selected as examples of five-membered heterocycles. 2-Thiophenecarboxaldehyde and furfural both performed very well with the latter

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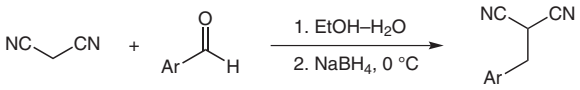
Table 1 Reductive Alkylation of Malononitrile with Aromatic Aldehydes



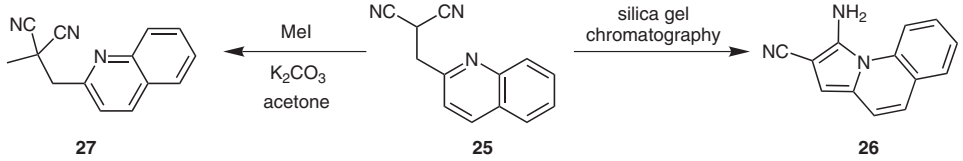
Entry	Ar	Product	Time (h)[a]	Yield (%)[b]	Yield (%)[c]
1	Ph	**1**	1	98	85
2	4-$MeOC_6H_4$	**2**	1	94	88
3	4-MeC_6H_4	**3**	3.5	92	76
4	4-BrC_6H_4	**4**	2	94	94
5	4-ClC_6H_4	**5**	2	96	91
6	3-ClC_6H_4	**6**	4	88	–[d]
7	2-ClC_6H_4	**7**	24	94	–[d]
8	4-$NO_2C_6H_4$	**8**	2	96	90
9	3-$NO_2C_6H_4$	**9**	1.5	97	88
10	2-$NO_2C_6H_4$	**10**	0.5	97	84
11	4-HOC_6H_4	**11**	18	80	85
12	3-HOC_6H_4	**12**	18	76	–[d]
13	4-HO-3-$MeOC_6H_3$	**13**	24	84	74
14	2-(4-ClBnO)C_6H_4	**14**	3	75	–[d]
15	4-$Me_2NC_6H_4$	**15**	2.5	98	90
16	4-(2-pyridyl)C_6H_4	**16**	24	98	–[e]
17	2,6-$Cl_2C_6H_3$	**17**	4	92	86
18	2,4,6-$Cl_3C_6H_2$	**18**	24	97	–[e]
19	2-fluorenyl	**19**	3	62	–[e]
20	(*E*)-PhCH=CH	**20**	16	81	53

[a] Time refers to the condensation step.
[b] Isolated yield of purified compound using extraction method workup.
[c] Isolated yield of purified compound using filtration method workup.
[d] No precipitate formed and extraction method workup must be used.
[e] Filtration method workup was not attempted.

example requiring 50% aqueous ethanol in order for the precipitate to form in the condensation step. Both 3- and 4-pyridinecarboxaldehydes, afforded the alkylated products **23** and **24** in good yields (Table 2). 2-Pyridinecarboxaldehyde (Table 2, entry 5) did not produce any desired product nor could any intermediate olefin be detected before the reduction step.

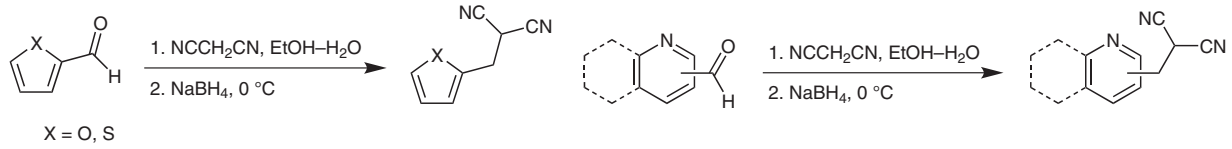
When this new and improved reductive alkylation procedure was attempted with 2-quinolinecarboxaldehyde (Table 2, entry 6), the crude product **25** was observed but it 'decomposed' upon attempted purification via recrystallization or column chromatography. Fortunately when the reaction and entire workup was carried out at 0 °C, essentially pure **25** was obtained. Later, it was found that **25** rearranged on TLC and created a single fluorescent spot with an R_f value greater than expected for the quinoline substituted malononitrile. Nucleophilic attack of the quinoline nitrogen on the carbon of the nitrile followed by a proton transfer and a tautomerization explain how indolizine **26** is created (Scheme 2). Single crystal X-ray analysis was applied to confirm the structure of this novel rearranged product.[10] The importance of these aromatic heterocycles can be appreciated by the new methods that have been developed for the synthesis of indolizine derivatives.[11] A recent report from another group shows a similar reaction as one possible outcome from a 2-formyl-1,4-dihydropyridine reaction.[12] Monosubstituted malononitrile **25** could be carefully alkylated with iodomethane prior to purification.[2a,5] Only C-alkylation – formation of another C–C bond – was observed and disubstituted malononitrile **27** was obtained in good yield and the structure confirmed by single crystal X-ray analysis.[10] The importance of efficient syntheses of unsymmetrically disubstituted malononitriles can be realized by the latest patents declaring their applications for controlling various pests.[13]

Attempts were made to further broaden the scope of our optimized reaction to other aldehydes and ketones. Aliphatic aldehydes (propanal and 2,2-dimethylpropanal) did not successfully condense in ethanol or water, and when the reduction step took place little product was obtained.[14] Although reaction with *trans*-cinnamaldehyde was successful (**20**), *trans*-crotonaldehyde would not undergo noticeable condensation in aqueous ethanol. Acetophenone, an aryl ketone, also afforded the product, but it was contaminated with ~20% of 1-phenylethanol from direct reduction of the ketone and was determined to be less satisfying than our previously reported method.[5] Lastly, we examined other activated methylene moieties. Ethyl cyanoacetate and ethyl nitroacetate were both allowed to react with 4-nitrobenzaldehyde (the most reactive aldehyde toward malononitrile) and we found that the product was obtained in good yield from the cyano ester, but no product was detected from the nitro ester (Scheme 3). Ethyl cyanoacetate was allowed to react with 4-chlorobenzaldehyde but no precipitate was detected for the



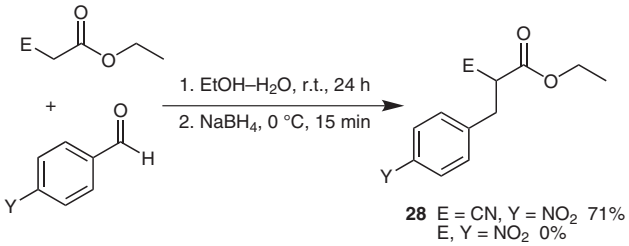
Scheme 2

Table 2 Reductive Alkylation of Malononitrile with Heteroaromatic Aldehydes



Entry	Heteroaryl	Product	Time (h)[a]	Yield (%)[b]
1	2-thienyl	**21**	3	93
2	2-furyl	**22**	24	95
3	4-pyridyl	**23**	3	71
4	3-pyridyl	**24**	3	79
5	2-pyridyl	–	2	0
6	2-quinolinyl	**25**	4	91

[a] Time refers to the condensation step.
[b] Isolated yield of purified compound using extraction method workup.



Scheme 3

Knoevenagel condensation and after treatment with sodium borohydride, only a minor amount of C–C bond formation was detected.

In summary, a wide range of aromatic and heteroaromatic aldehydes can be coupled together efficiently with malononitrile in a C–C bond forming reductive alkylation. In this one-pot synthesis, aqueous ethanol is the only requirement for complete condensation prior to addition of sodium borohydride for the selective reduction. For reaction workup, it is recommended that one should attempt to follow the filtration method and only if a precipitate fails to form would extraction with organic solvent be required. We also have found that 2-quinolinecarboxaldehyde does not produce an exceptionally stable product with malononitrile and the product rearranges to efficiently yield a substituted indolizine. Monosubstituted malononitriles can be further utilized as reactants in alkylation reactions to form unsymmetrically disubstituted malononitriles as we have illustrated by the isolation of a stable 2-quinoline derivative. Finally, it has been determined that ethyl cyanoacetate works with only very reactive aromatic aldehydes and that methylene acidity is not limiting reactivity since ethyl nitroacetate does give the desired product.

Analytical TLC was performed using Baker-Flex silica gel IB-F plates and visualized using a UV lamp and/or stained with basic $KMnO_4$ [2.3 g $KMnO_4$, 15 g K_2CO_3, 1.9 mL 2.5 M NaOH in 300 mL distilled (DI) H_2O]. Flash chromatography was performed using silica gel (35–70 μm, ~6 nm pore) from Acros or pre-packed silica column (32–63 μm, 60 Å pore) from Analogix. ^1H NMR spectra and ^{13}C NMR with ^1H decoupled spectra were recorded on a JEOL Eclipse spectrometer at 400 MHz or 300 MHz and 100 MHz or 75 MHz, respectively. ^1H chemical shifts are reported in ppm downfield from internal tetramethylsilane and ^{13}C chemical shifts are reported in ppm relative to $CDCl_3$ (77.00 ppm) or acetone-d_6 (29.84 ppm). All chemicals were used as received without further purification. Elemental analyses were determined at MidWest Microlab, Indianapolis, IN.

One-Pot Reductive Alkylation of Malononitrile with Aromatic Aldehydes; General Procedure

Malononitrile (661 mg, 10 mmol) was dissolved in 95% EtOH (10 mL) and to this solution was added the appropriate aromatic aldehyde (10 mmol). The solution was stirred at r.t. until precipitation was complete or overnight.[9] Additional EtOH (20 mL) was added and the mixture cooled to 0 °C in an ice bath. $NaBH_4$ (169 mg, 5 mmol) was introduced to the vigorously stirred mixture and the reduction was complete in about 10 min.

Extraction method workup: To the reaction mixture was added DI H_2O (50 mL) and CH_2Cl_2 (25 mL), followed by aq 1.0 M HCl until all hydride was quenched.[15] The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered, concentrated via rotoevaporation and then under high vacuum, and purified via recrystallization or column chromatography.

Filtration method workup: The reaction mixture was poured into a large beaker containing DI H_2O (40 mL) and aq 1.0 M HCl was added until all hydride was quenched. The reaction flask was washed with DI H_2O (20 mL), combined with the quenched mixture in the beaker and the solution/mixture was then cooled in an ice bath. Additional cold H_2O was added until precipitation was complete. If crystallization/precipitation did not occur, then the mixture was extracted (see Extraction Method Workup above). The cold precipi-

tate was collected by vacuum filtration and washed with cold DI H_2O (20 mL).

Benzylmalononitrile (1)[5]

The general procedure, followed to scale using malononitrile (0.667 g, 10.09 mmol), benzaldehyde (1.071 g, 10.09 mmol), and $NaBH_4$ (0.196 g, 5.18 mmol), afforded a solid; yield: 1.538 g (98%); mp 88–89 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.30 (m, 5 H), 3.90 (t, *J* = 7.0 Hz, 1 H), 3.29 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.9, 129.2, 129.1, 128.7, 112.2, 36.5, 24.8.

4-Methoxybenzylmalononitrile (2)[5]

The general procedure, followed to scale using malononitrile (0.682 g, 10.3 mmol), 4-methoxybenzaldehyde (1.388 g, 10.2 mmol), and $NaBH_4$ (0.193 g, 5.10 mmol), afforded a solid; yield: 1.799 g (94%); mp 89.5–91 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (d, *J* = 8.8 Hz, 2 H), 6.93 (d, *J* = 8.8 Hz, 2 H), 3.86 (t, *J* = 7.0 Hz, 1 H), 3.82 (s, 3 H), 3.24 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.9, 130.3, 124.9, 114.7, 112.2, 55.3, 36.1, 25.3.

4-Methylbenzylmalononitrile (3)[5]

The general procedure, followed to scale using malononitrile (0.672 g, 10.2 mmol), 4-methylbenzaldehyde (1.22 g, 10.2 mmol), and $NaBH_4$ (0.192 g, 5.09 mmol), afforded a solid; yield: 1.601 g (92%); mp 78.5–80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (s, 4 H), 3.87 (t, *J* = 7.0 Hz, 1 H), 3.26 (d, *J* = 7.0 Hz, 2 H), 2.36 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 129.9, 129.8, 128.9, 112.3, 36.1, 24.9, 21.0.

4-Bromobenzylmalononitrile (4)[6]

The general procedure, followed to scale using malononitrile (1.321 g, 20 mmol), 4-bromobenzaldehyde (3.700 g, 20 mmol), and $NaBH_4$ (0.3785 g, 10 mmol), afforded a solid; yield: 4.432 g (94%); mp 94–94.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, *J* = 8.4 Hz, 2 H), 7.20 (d, *J* = 8.4 Hz, 2 H), 3.94 (t, *J* = 6.6 Hz, 1 H), 3.23 (d, *J* = 6.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 132.4, 131.8, 130.8, 123.0, 112.0, 35.8, 24.6.

4-Chlorobenzylmalononitrile (5)[6]

The general procedure, followed to scale using malononitrile (0.660 g, 10 mmol), 4-chlorobenzaldehyde (1.411 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol), afforded a solid; yield: 1.831 g (96%); mp 90–90.5 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.40 (d, *J* = 8.1 Hz, 2 H), 7.25 (d, *J* = 8.1 Hz, 2 H), 3.92 (t, *J* = 6.7 Hz, 1 H), 3.27 (d, *J* = 6.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.0, 131.2, 130.5, 129.5, 111.9, 35.9, 24.6.

3-Chlorobenzylmalononitrile (6)[4e]

The general procedure followed to scale using malononitrile (1.321 g, 20 mmol), 3-chlorobenzaldehyde (2.814 g, 20 mmol), and $NaBH_4$ (0.377 g, 10 mmol) afforded an oil; yield: 3.322 g (87%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.18 (m, 4 H), 3.95 (t, *J* = 7.6 Hz, 1 H), 3.23 (d, *J* = 7.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 134.9, 134.7, 130.5, 129.2, 129.0, 127.3, 112.0, 35.9, 24.6.

2-Chlorobenzylmalononitrile (7)[13d]

The general procedure, followed to scale using malononitrile (0.660 g, 10 mmol), 2-chlorobenzaldehyde (1.405 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol), afforded an oil; yield: 1.792 g (94%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.32 (m, 4 H), 4.11 (t, *J* = 8.0 Hz, 1 H), 3.46 (d, *J* = 8.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.8, 131.7, 130.6, 130.3, 130.0, 127.6, 112.0, 34.6, 22.5.

4-Nitrobenzylmalononitrile (8)[6]

The general procedure, followed to scale using malononitrile (0.660 g, 10 mmol), 4-nitrobenzaldehyde (1.51 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol), afforded a solid; yield: 1.94 g (96%); mp 151–152 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 8.8 Hz, 2 H), 7.56 (d, *J* = 8.8 Hz, 2 H), 4.05 (t, *J* = 6.8 Hz, 1 H), 3.43 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.3, 139.7, 130.4, 124.4, 111.5, 36.0, 24.4.

3-Nitrobenzylmalononitrile (9)[6]

The general procedure, followed to scale using malononitrile (1.321 g, 20 mmol), 3-nitrobenzaldehyde (2.302 g, 15 mmol), and $NaBH_4$ (0.378 g, 10 mmol), afforded a solid; yield: 2.69 g (88%); mp 137.5–138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.64 (d, *J* = 4.8 Hz, 1 H), 8.60 (s, 1 H), 7.72 (d, *J* = 7.9 Hz, 1 H), 7.37 (dd, *J* = 7.9, 4.8 Hz, 1 H), 4.14 (t, *J* = 7.0 Hz, 1 H), 3.32 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 135.4, 134.6, 130.5, 124.2, 124.0, 111.5, 36.0, 24.5.

2-Nitrobenzylmalononitrile (10)[6]

The general procedure, followed to scale using malononitrile (1.982 g, 30 mmol), 2-nitrobenzaldehyde (4.534 g, 30 mmol), and $NaBH_4$ (0.568 g, 15 mmol), afforded a solid; 5.10 g (84%); mp 82–83 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, *J* = 8.1 Hz, 1 H), 7.75 (dd, *J* = 7.7, 7.3 Hz, 1 H), 7.62 (dd, *J* = 8.1, 7.3 Hz, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 4.45 (t, *J* = 7.7 Hz, 1 H), 3.60 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.6, 134.5, 133.4, 130.4, 128.2, 126.0, 111.9, 35.1, 23.6.

4-Hydroxybenzylmalononitrile (11)[13d]

The general procedure, followed to scale using malononitrile (1.982 g, 30 mmol), 4-hydroxybenzaldehyde (3.668 g, 30 mmol), and $NaBH_4$ (0.566 g, 15 mmol), afforded a solid; yield: 4.40 g (85%); mp 173–175 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (d, *J* = 8.8 Hz, 2 H), 6.86 (d, *J* = 8.8 Hz, 2 H), 4.92 (br s, 1 H), 3.86 (t, *J* = 7.0 Hz, 1 H), 3.23 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.0, 130.6, 125.1, 116.1, 112.2, 36.1, 25.3.

3-Hydroxybenzylmalononitrile (12)[16]

The general procedure, followed to scale using malononitrile (1.978 g, 30 mmol), 3-hydroxybenzaldehyde (3.667 g, 30 mmol), and $NaBH_4$ (0.567 g, 15 mmol), afforded a solid; yield: 3.94 g (76%); mp 49–51 °C.

^{1}H NMR (400 MHz, acetone-d_6): δ = 7.22 (t, *J* = 7.7 Hz, 1 H), 6.94–6.88 (m, 2 H), 6.86–6.82 (m, 1 H), 4.73 (t, *J* = 7.0 Hz, 1 H), 3.34 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, acetone-d_6): δ = 158.5, 136.8, 130.7, 121.2, 117.1, 116.0, 114.3, 36.4, 25.2.

4-Hydroxy-3-methoxybenzylmalononitrile (13)[4f]

The general procedure, followed to scale using malononitrile (6.615 g, 100 mmol), vanillin (15.21 g, 100 mmol), and $NaBH_4$ (1.893 g, 50 mmol), afforded a solid; yield: 14.88 g, 74%); mp 86–88 °C.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 6.93 (d, *J* = 8.4 Hz, 1 H), 6.85–6.79 (m, 2 H), 5.68 (br s, 1 H), 3.91 (s, 3 H), 3.87 (t, *J* = 7.0 Hz, 1 H), 3.23 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 146.8, 146.1, 124.7, 122.2, 115.0, 112.3, 111.5, 56.0, 36.6, 25.3.

2-(4-Chlorobenzyloxy)benzylmalononitrile (14)

2-(4-Chlorobenzyloxy)benzaldehyde

2-(4-Chlorobenzyloxy)benzaldehyde[17] was prepared following modified literature conditions for alkylation of salicylaldehyde.[18] Salicylaldehyde (0.61 g, 5 mmol) and 4-chlorobenzyl chloride (0.64 g, 4 mmol) were stirred in DMF (10 mL). Na_2CO_3 (1.06 g, 10 mmol) and a catalytic amount of NaI were added, and the mixture was heated to 100 °C. The heating mantel was removed after 8 h and the mixture was allowed to cool to r.t. before the addition of Et_2O (50 mL) and H_2O (50 mL). The layers were separated, and the aqueous portion was extracted with Et_2O (40 mL). The combined organics were then washed with H_2O (4 × 30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4), filtered, and rotoevaporated to give 0.55 g (56%), after recrystallization from EtOH.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.50 (s, 1 H), 7.82 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.53–7.46 (m, 1 H), 7.34 (s, 4 H), 7.03–6.97 (m, 2 H), 5.11 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 189.4, 160.6, 135.8, 134.5, 133.9, 128.8, 128.50, 128.46, 125.0, 121.1, 112.8, 69.5.

Compound 14

The general procedure, followed to scale using malononitrile (0.143 g, 2.17 mmol), 2-(4-chlorobenzyloxy)benzaldehyde (0.530 g, 2.17 mmol), and $NaBH_4$ (0.041 g, 1.08 mmol), afforded an oil; yield: 0.483 g (75%); mp 67–68 °C.

IR (ATR): 3061, 3035, 3014, 2914, 2876, 2256, 1603, 1590, 1496, 1454, 1246, 807, 759 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ= 7.39 (d, *J* = 8.4 Hz, 2 H), 7.38–7.30 (m, 3 H) 7.27 (dd, *J* = 7.3, 1.5 Hz, 1 H), 7.01 (td, *J* = 7.5, 0.9 Hz, 1 H), 6.95 (d, *J* = 8.0 Hz, 1 H), 5.08 (s, 2 H), 4.10 (t, *J* = 7.7 Hz, 1 H), 3.33 (d, *J* = 7.7 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.2, 134.6, 134.3, 131.5, 130.3, 129.1, 128.8, 121.6, 121.5, 112.5, 111.9, 69.5, 32.6, 22.6.

Anal. Calcd for $C_{17}H_{13}ClN_2O$: C, 68.81; H, 4.42; N, 9.44. Found: C, 68.81; H, 4.82; N, 9.54.

4-Dimethylaminobenzylmalononitrile (15)[16]

The general procedure, followed to scale using malononitrile (0.660 g, 10 mmol), 4-dimethylaminobenzaldehyde (1.491 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol), afforded a solid; yield: 1.958 g (98%); mp 59.5–61 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18 (d, *J* = 8.6 Hz, 2 H), 6.71 (d, *J* = 8.6 Hz, 2 H), 3.81 (t, *J* = 7.0 Hz, 1 H), 3.21 (d, *J* = 7.0 Hz, 2 H), 2.96 (s, 6 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 150.5, 129.9, 120.1, 112.6, 112.5, 40.3, 36.1, 25.4.

4-(2-Pyridyl)benzylmalononitrile (16)

The general procedure, followed to scale using malononitrile (0.132 g, 2 mmol), 4-(2-pyridyl)benzaldehyde (0.366 g, 2 mmol), and $NaBH_4$ (0.037 g, 1 mmol), afforded a solid; yield: 0.460 g (98%); mp 128–129 °C.

IR (ATR): 3090, 3060, 3015, 2922, 2256, 1587, 1565, 1467, 1434, 1019, 853, 767, 737 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.69 (d, *J* = 4.8 Hz, 1 H), 8.03 (d, *J* = 8.0 Hz, 2 H), 7.78–7.71 (m, 2 H), 7.43 (d, *J* = 8.0 Hz, 2 H), 7.28–7.24 (m, 1 H), 3.95 (t, *J* = 7.0 Hz, 1 H), 3.34 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3, 149.7, 139.8, 136.8, 133.5, 129.5, 127.6, 122.4, 120.1, 36.3, 24.7.

Anal. Calcd for $C_{15}H_{11}N_3$: C, 77.23; H, 4.75; N, 18.01. Found: C, 76.88; H, 4.95; N, 17.87.

2,6-Dichlorobenzylmalononitrile (17)[13d]

The general procedure, followed to scale using malononitrile (0.667 g, 10 mmol), 2,6-dichlorobenzaldehyde (1.76 g, 10 mmol), and $NaBH_4$ (0.190 g, 5.0 mmol), afforded a solid; yield: 2.08 g (92%); mp 82–84 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41 (d, *J* = 8.4 Hz, 2 H), 7.28 (t, *J* = 8.4 Hz, 1 H), 4.24 (t, *J* = 8.4 Hz, 1 H), 3.74 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 135.9, 130.6, 129.2, 128.8, 111.6, 31.8, 20.9.

2,4,6-Trichlorobenzylmalononitrile (18)

2,4,6-Trichlorobenzaldehyde

2,4,6-Trichlorobenzaldehyde[19] was prepared following a modified directed ortho-metalation procedure.[20] 1,3,5-Trichlorobenzene (1.84 g, 10.1 mmol) was dissolved in THF (40 mL) under argon. The solution was cooled to –78 °C via a dry ice and acetone bath. After the stirred solution was cooled completely (~30 min), *n*-BuLi (4 mL, 10.00 mmol) was added dropwise via a syringe over 20 min. The solution was kept at –78 °C and stirred for 30 min before DMF (1.2 mL, 17.4 mmol) was added via a syringe. After the addition was complete, the solution was stirred at –78 °C for 1.5 h. The reaction was then quenched with aq 3 N HCl (40 mL) and then allowed to warm to r.t. The mixture was extracted with EtOAc (60 mL). The organic layer was then washed with aq $NaHCO_3$ (40 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated via rotary evaporation to afford 1.93 g (92%) of product.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.44 (s, 1 H), 7.42 (s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 187.6, 139.3, 137.6, 129.8, 128.8.

Compound 18

The general procedure, followed to scale using malononitrile (0.473 g, 7.16 mmol), 2,4,6-trichlorobenzaldehyde (1.50 g, 7.16 mmol), and $NaBH_4$ (0.135 g, 3.58 mmol), afforded a solid; yield: 1.80 g (97%); mp 91.5–92.5 °C.

IR (ATR): 3086, 2906, 2259, 1724, 1580, 1547, 1436, 1376, 1214, 1138, 1075, 1016, 877, 861, 817, 672 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 2 H), 4.60 (t, *J* = 8.4 Hz, 1 H), 4.10 (d, *J* = 8.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.4, 135.7, 128.9, 127.9, 111.4, 31.4, 20.9.

Anal. Calcd for $C_{10}H_5Cl_3N_2$: C, 46.28; H, 1.94; N, 10.79. Found: C, 46.57; H, 2.08; N, 10.52.

2-Fluorenylmethylmalononitrile (19)

The general procedure, followed to scale using malononitrile (0.138 g, 2.08 mmol), 2-fluorenecarboxaldehyde (0.405 g, 2.07 mmol), and $NaBH_4$ (0.037 g, 1 mmol), afforded a solid; yield: 0.3133 g (62%); mp 163.5–164 °C.

IR (ATR): 3044, 2922, 2259, 1450, 1428, 1402, 1032, 1005, 954, 887, 848, 837, 800, 762, 725 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (t, *J* = 4.8 Hz, 2 H), 7.56 (d, *J* = 7.7 Hz, 1 H), 7.50 (s, 1 H), 7.41–7.37 (m, 1 H), 7.35–7.31 (m, 2 H), 3.94 (t, *J* = 7.0 Hz, 1 H), 3.92 (s, 2 H), 3.36 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 144.2, 143.3, 142.3, 140.7, 131.2, 127.7, 127.2, 126.9, 125.7, 125.1, 120.4, 120.1, 112.3, 36.82, 36.77, 25.1.

Anal. Calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.47. Found: C, 83.36; H, 4.91; N, 11.40.

trans-Cinnamylmalononitrile (20)[4c]

The general procedure, followed to scale using malononitrile (0.661 g, 10 mmol), *trans*-cinnamaldehyde (1.33 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol), afforded a solid; yield: 0.959 g (53%); mp 65–66.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.46–7.25 (m, 5 H), 6.70 (d, *J* = 15.8 Hz, 1 H), 6.17 (dt, *J* = 15.8, 7.7 Hz, 1 H), 3.82 (t, *J* = 6.6 Hz, 1 H), 2.91 (dd, *J* = 7.7, 6.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 137.0, 135.5, 128.6, 128.4, 126.6, 119.7, 112.2, 34.0, 23.2.

2-Thienylmethylmalononitrile (21)[13c]

The general procedure, followed to scale using malononitrile (0.681 g, 10.3 mmol), 2-thiophenecarboxaldehyde (1.142 g, 10.18 mmol), and $NaBH_4$ (0.194 g, 5.1 mmol), afforded a solid; yield: 1.0593 g (96%); mp 46.5–47 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, *J* = 5.1 Hz, 1 H), 7.12 (d, *J* = 3.3 Hz, 1 H), 7.03 (dd, *J* = 5.1, 3.3 Hz, 1 H), 3.94 (t, *J* = 6.6 Hz, 1 H), 3.54 (d, *J* = 6.6 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 133.9, 128.4, 127.7, 126.5, 111.9, 31.1, 25.5.

2-Furfurylmalononitrile (22)[5]

The general procedure, followed to scale using malononitrile (0.681 g, 10.3 mmol), furfural (1.142 g, 10.18 mmol), and $NaBH_4$ (0.194 g, 5.1 mmol) in 50% aq EtOH, afforded an oil; yield: 1.0593 g (96%).

^{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.

4-Pyridinemethylmalononitrile (23)

The general procedure, followed to scale using malononitrile (0.330 g, 5 mmol), 4-pyridinecarboxaldehyde (0.535 g, 5 mmol), and $NaBH_4$ (0.094 g, 2.5 mmol), afforded a solid; yield: 0.56 g (72%); mp 92.5–93 °C.

IR (ATR): 3045, 2921, 2261, 1959, 1604, 1563, 1445, 1421, 1350, 1223, 1194, 1184, 994, 883, 825, 753 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.67 (d, *J* = 4.8 Hz, 2 H), 7.28 (d, *J* = 4.8 Hz, 2 H), 4.14 (t, *J* = 7.0 Hz, 1 H), 3.29 (d, *J* = 7.0 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.6, 141.4, 124.0, 111.7, 35.4, 23.8.

Anal. Calcd for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.74. Found: C, 68.62; H, 4.55; N, 26.56.

3-Pyridinemethylmalononitrile (24)

The general procedure, followed to scale using malononitrile (0.330 g, 5 mmol), 3-pyridinecarboxaldehyde (0.535 g, 5 mmol), and $NaBH_4$ (0.094 g, 2.5 mmol), afforded a solid; yield: 0.62 g (79%); mp 70–71 °C.

IR (ATR): 3038, 2997, 2881, 2618, 2552, 2248, 1595, 1575, 1479, 1446, 1424, 1024, 789 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.71–8.62 (m, 2 H), 7.72 (d, *J* = 7.0 Hz, 1 H), 7.38 (dd, *J* = 7.0, 4.8 Hz, 1 H), 3.98 (t, *J* = 6.8 Hz, 1 H), 3.33 (d, *J* = 6.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.1, 150.0, 136.8, 128.7, 123.8, 111.9, 33.6, 24.5.

Anal. Calcd for $C_9H_7N_3$: C, 68.78; H, 4.49; N, 26.74. Found: C, 68.58; H, 4.45; N, 26.56.

2-Quinolinemethylmalononitrile (25)

The general procedure, followed to scale using malononitrile (0.336 g, 5.1 mmol), 2-quinolinecarboxaldehyde (0.80 g, 5.1 mmol), and $NaBH_4$ (0.094 g, 2.5 mmol), afforded a crude solid; yield: 0.949 g (91%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.4 Hz, 1 H), 8.06 (d, *J* = 8.8 Hz, 1 H), 7.84 (d, *J* = 8.4 Hz, 1 H), 7.78–7.73 (m, 1 H), 7.60–7.55 (m, 1 H), 7.34 (d, *J* = 8.4 Hz, 1 H), 4.95 (t, *J* = 7.4 Hz, 1 H), 3.71 (d, *J* = 7.4 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.3, 147.5, 137.3, 130.1, 129.0, 127.6, 127.3, 127.0, 120.6, 113.1, 38.1, 20.5.

1-Aminopyrrolo[1,2-*a*]quinoline-2-carbonitrile (26)

The general procedure, followed to scale using malononitrile (0.330 g, 5 mmol), 2-quinolinecarboxaldehyde (0.786 g, 5 mmol), and $NaBH_4$ (0.094 g, 2.5 mmol), afforded a solid after column chromatography on silica gel; yield: 0.865 g (83%); mp 148–148.5 °C.

IR (ATR): 3352, 3308, 3235, 3135, 3051, 2212, 1625, 1643, 1559, 1524, 1474, 1430, 1402 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (d, *J* = 8.4 Hz, 1 H), 7.57 (d, *J* = 7.7 Hz, 1 H), 7.48–7.43 (m, 1 H), 7.38–7.34 (m, 1 H), 7.07 (d, *J* = 9.5 Hz, 1 H), 6.87 (d, *J* = 9.5 Hz, 1 H), 6.50 (s, 1 H), 4.30 (br s, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 141.1, 134.1, 128.4, 127.1, 126.9, 125.8, 124.9, 119.6, 118.9, 116.6, 116.3, 101.5, 83.9.

Anal. Calcd for $C_{13}H_9N_3$: C, 75.35; H, 4.38; N, 20.28. Found: C, 75.37; H, 4.53; N, 20.01.

2-Methyl-2-(2-quinolinemethyl)malononitrile (27)

The crude monosubstituted malononitrile **25** was alkylated with MeI (0.724 g, 5.1 mmol) in the presence of K_2CO_3 (0.705 g, 5.1 mmol) in acetone (10 mL) to afford a solid after column chromatography on silica gel; yield: 0.949 g (86%); mp 148–148.5 °C.

IR (ATR): 3069, 3004, 2953, 2248, 1618, 1599, 1570, 1506, 1425, 1275, 1199, 1137, 816, 783, 751 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.19 (d, *J* = 8.4 Hz, 1 H), 8.13 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.1 Hz, 1 H), 7.77–7.72 (m, 1 H), 7.59–7.55 (m, 1 H), 7.40 (d, *J* = 8.4 Hz, 1 H), 3.59 (s, 2 H), 1.97 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.5, 147.7, 137.2, 130.0, 129.4, 127.5, 127.3, 127.0, 121.2, 116.2, 45.7, 30.9, 24.9.

Anal. Calcd for $C_{14}H_{11}N_3$: C, 76.00; H, 5.01; N, 18.99. Found: C, 75.88; H, 5.16; N, 18.98.

Ethyl 2-Cyano-3-(4-nitrophenyl)propanoate (28)[4g]

The general procedure for the one-pot reductive alkylation of malononitrile, followed to scale using ethyl cyanoacetate (1.131 g, 10 mmol), 4-nitrobenzaldehyde (1.51 g, 10 mmol), and $NaBH_4$ (0.189 g, 5 mmol), afforded a solid; yield: 1.76 g (71%); mp 56–58 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J* = 8.4 Hz, 2 H), 7.48 (d, *J* = 8.4 Hz, 2 H), 4.27 (q, *J* = 7.1 Hz, 2 H), 3.79 (dd, *J* = 8.0, 5.8 Hz, 1 H), 3.39 (dd, *J* = 14, 5.8 Hz, 1 H), 3.33 (dd, *J* = 14, 8.0 Hz, 1 H), 1.30 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8, 147.6, 142.5, 130.2, 124.1, 115.4, 63.4, 38.8, 35.0, 13.9.

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