Efficient Methods for the Synthesis of Arylacetonitriles

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Abstract: Various approaches to [2-fluoro-4-(trifluoromethyl)phenyl]acetonitrile were investigated. Two of these methods were selected and applied to a variety of electron-deficient substrates, thereby expanding the scopes of the procedures.

Key words: nitriles, nucleophilic aromatic substitutions, decarboxylations, Wittig reactions, reductions

Arylacetonitrile derivatives are synthetically interesting and useful compounds. The active methylene moiety provides an entry to the synthesis of heterocyclic compounds, whereas the cyano group can be involved in a number of transformation, e.g. dipolar cycloadditions reactions.[1] Among the methods for the synthesis of this class of compound are the classical reaction of benzyl halides[3] or sulfonates[3,4] with the cyanide ion; the dehydration of arylacetaldoximes[2,3,5,6] or primary amides,[2–4] and the more-recent synthesis based on β-(*N*,*N*-dimethylamino)styrenes containing electron-withdrawing substituent on the benzene ring.[7] During a phase of process development, we found it necessary to synthesize [2-fluoro-4-(trifluoromethyl)phenyl]acetonitrile on a multi-gram scale. We identified an efficient process for the synthesis of this compound and we utilized the results in optimizing a general method for the synthesis of electron-deficient arylacetonitriles that can be applied to a variety of substrates. A retrosynthetic analysis, involving two disconnections (**a** and **b**) based on the commercial availability of starting materials, is shown in Figure 1.

The first approach (disconnection **a**; Figure 1) involves the reduction of aldehyde **3** followed by activation of the primary alcohol and cyanide substitution, or aldehyde homologation through formation of an oxime and subsequent dehydration. In the second approach (disconnection **b**; Figure 1), the cyanomethyl group is introduced onto the benzene ring by a palladium-catalyzed coupling reaction of bromide **4a** or through nucleophilic substitution of fluoride **4b**, followed by decarboxylation.

In our first attempt (Scheme 1), we reduced aldehyde **3** with sodium borohydride to give the corresponding benzyl alcohol **2a** quantitatively.[8] This was converted into the benzyl chloride derivative by treatment with thionyl chloride at 80 °C over three days.[9] Unfortunately, the substitution with cyanide by treatment with potassium cyanide in dimethyl sulfoxide[8] gave undesired products resulting from the homocoupling of the starting chloride. As a result of the discouraging results of this preliminary reaction and the toxicity of potassium cyanide, we decided to investigate an alternative approach.

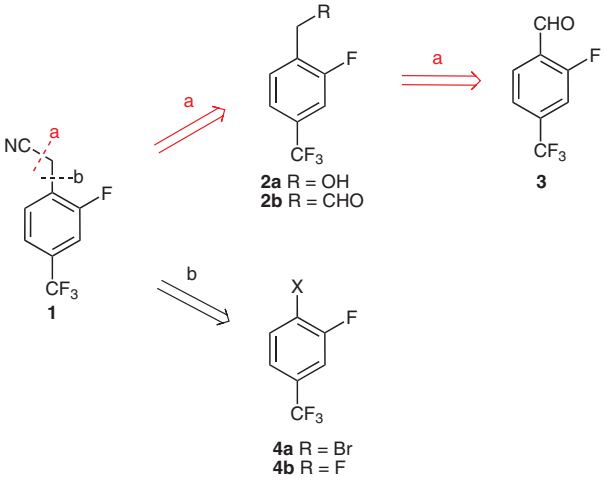
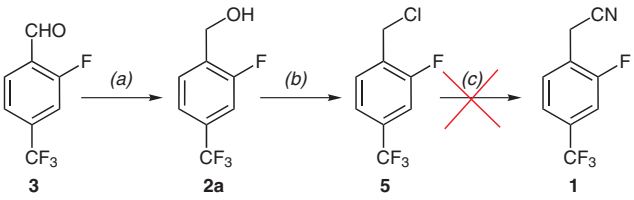


Figure 1 Retrosynthetic approach to the synthesis of [2-fluoro-(4-trifluoromethyl)phenyl]acetonitrile (**1**)



Scheme 1 *Reagents and conditions*: (a) $NaBH_4$, EtOH, 0 °C to 20 °C, 1 h (quant.); (b) $SOCl_2$, 80 °C, 3 days (91%); (c) KCN, KI, DMSO, 20 °C, 3 h.

Treatment of aldehyde **3** with (methoxymethyl)(triphenyl)phosphonium chloride and a 0.5 M solution of potassium hexamethyldisilazide in toluene at room temperature gave the corresponding vinyl ether, which was hydrolyzed with a 2 M solution of hydrogen chloride in refluxing acetone to give the homologated aldehyde **2b**.[10] The compound **2b** was then converted into the corresponding oxime derivative **6** as a mixture of *cis*- and *trans*-isomers (Scheme 2, method A).[11]

Oxime **6** was submitted to various dehydration conditions[12] (Table 1) in attempts to obtain the desired arylacetonitrile **1**. The best results were achieved by slow addition of a solution of thionyl chloride in tetrahydrofu-

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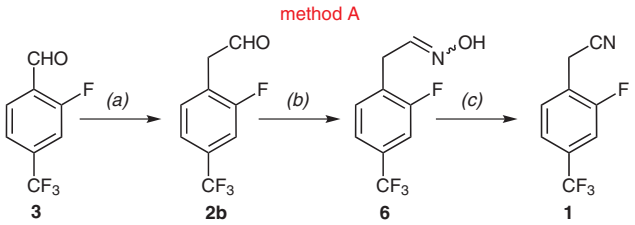


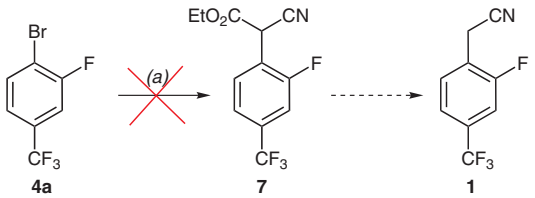
Scheme 2 *Reagents and conditions*: (a) $Ph_3P(CH_2OMe)Cl$, KHMDS, toluene, 20 °C, 3 h, then 2 M HCl, acetone, reflux, 12 h; (b) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, reflux, 2 h; (c) see Table 1 for conditions.

Table 1 Conditions for Dehydration of Oxime **6**

Conditions	Results
Ph_3P, I_2, CH_2Cl_2, r.t.	complete conversion, but difficulties in removal of (O)PPh_3
$RuCl_2$(*p*-cymene)$_2$, 4-Å MS, MeCN, 80 °C	incomplete conversion
PvCl, pyridine, reflux	complex mixture
wet AcOH, reflux	no reaction
KF, Al_2O_3	no reaction
Burgess reagent, THF, reflux	complex mixture
$SOCl_2$, THF, <20 °C	complete conversion

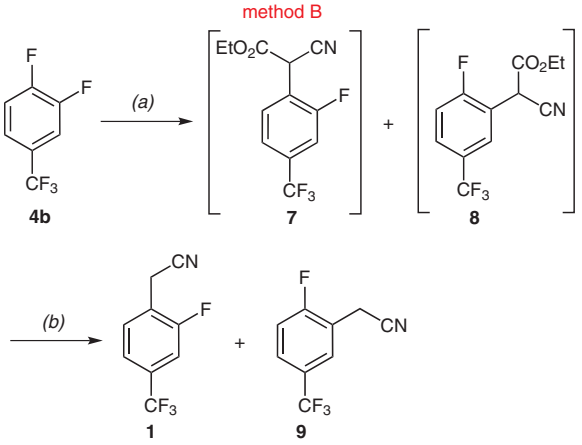
ran while the internal temperature was kept below 20 °C. After distillation under reduced pressure, **1** was isolated as a colorless liquid in a 33% overall yield.

Initially, we envisaged a synthesis of intermediate **7** by palladium-catalyzed coupling[13] of halide **4a** with ethyl cyanoacetate (Scheme 3). Various sources of palladium [tris(dibenzylideneacetone)dipalladium or dichlorobis(triphenylphosphine)palladium] and ligands [tributylphosphine, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (BINAP), or (2-biphenyl)di-*tert*-butylphosphine] were tested without success.

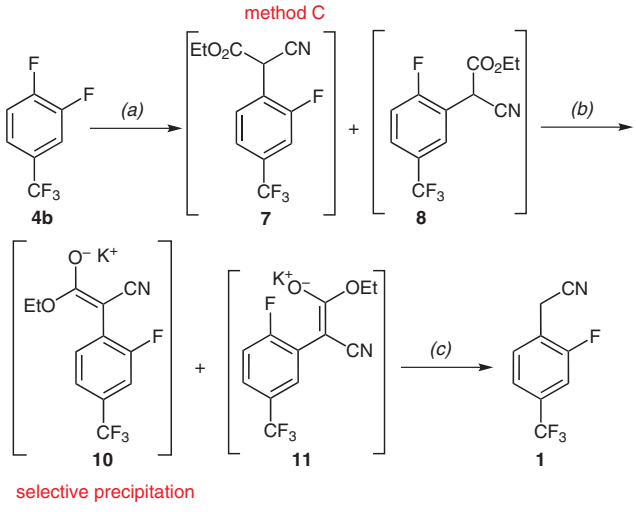


Scheme 3 *Reagents and conditions*: (a) Pd source, ligand, EtO_2CCH_2CN, K_3PO_4, toluene, 90 °C, 12 h.

To overcome this problem, we attempted the nucleophilic aromatic substitution[14] of fluoride **4b** with ethyl cyanoacetate and potassium carbonate in the presence of a catalytic amount of benzyltriethylammonium chloride in dimethyl sulfoxide at 90 °C (Scheme 4, method B); this gave intermediate **7** with complete conversion. We first attempted to perform the decarboxylation step by treatment with 4 M hydrochloric acid in ethanol at 80 °C for 48 h, but the results were unsatisfactory. We then attempted a Krapcho decarboxylation,[15] which gave a cleaner compound within 18 h. The crude mixture was purified as previously described to give a pale yellow liquid in 82% overall yield. However, the final compound **1** was contaminated with 5% of its regioisomer **9**, formed during the aromatic nucleophilic substitution. Purification of compound **1** from its regioisomer **9** proved to be extremely challenging. We therefore shifted our attention to the purification of the precursor compound **7** of its regioisomer **8**; intermediates **7** and **8** were treated with potassium *tert*-butoxide to give the corresponding potassium salts **10** and **11**, respectively. At this point, **10** could be selectively precipitated and purged of impurities. After acidification and Krapcho decarboxylation, product **1** was obtained in 70% overall yield (Scheme 5) and in better than 98% purity. For the sake of clarity, this modification of method B is referred to as method C.



Scheme 4 *Reagents and conditions*: (a) EtO_2CCH_2CN, K_2CO_3, $BnN^+Et_3Cl^-$, DMSO, 90 °C, 19 h; (b) NaCl, DMSO, 110 °C, 18 h (82% overall).

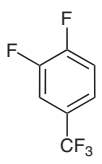
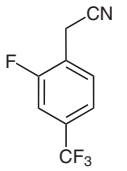
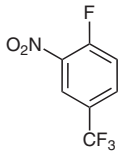
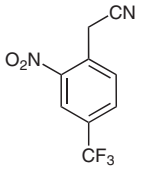
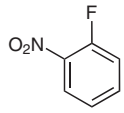
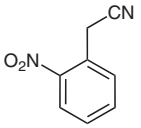
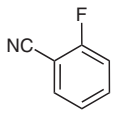
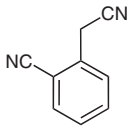
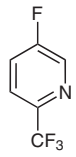
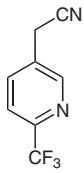


Scheme 5 *Reagents and conditions*: (a) EtO_2CCH_2CN, K_2CO_3, $BnN^+Et_3Cl^-$, DMSO, 90 °C, 19 h; (b) *t*-BuOK, CH_2Cl_2; (c) i. 1 M HCl, CH_2Cl_2; ii. NaCl, DMSO, 110 °C, 18 h (70% overall).

When method C was performed on a multi-gram scale, arylacetonitrile **1** was obtained in a high yield and high purity, thereby proving the efficiency of the methodology.

Because of the good results obtained with methods B and C, we decided to expand the scope of these procedures. Four electron-deficient aryl fluorides were converted into the corresponding arylacetonitriles in good-to-excellent yields (Table 2). Both methods could be easily applied, but method C could be advantageous when there are problems of purification, as in entry 1, or when the scale is so small that the use of distillation to purify the final product could be technically challenging.

Table 2 Formation of Arylacetonitriles from Aryl Fluorides

Entry	ArF	$ArCH_2CN$	Yield	
			Method B	Method C
1			82%[a]	70%
2			79%	quant
3			58%	54%
4			37%	56%
5			50%	–

[a] Contaminated with 5% of regioisomer **9**

To summarize, two slightly different approaches for the synthesis of arylacetonitriles from aryl fluorides were developed and demonstrated on a multi-gram scale. Furthermore, these methods were demonstrated on various electron-deficient substrates, and gave yields ranging from 38 to 99%, and produced products with a purity of more than 98%.

All materials were purchased from commercial suppliers and were used without purification. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C on a Varian INOVA 400 MHz or a 600 MHz NMR spectrometer operating at 399.7 MHz or 599.7 MHz, respectively, for protons and at 100.52 MHz or 150.8 MHz, respectively, for carbon-13. MS were recorded on an Agilent 1100 series instrument. HRMS measurements within ±5 ppm were performed on a Waters UPLC coupled with a Waters LCT Premiere XE mass spectrometer equipped with an electrospray ion source operating in negative-ion mode.

Method A

[2-Fluoro-4-(trifluoromethyl)phenyl]acetaldehyde (2b)

A 0.5 M soln of KHMDS in toluene (23.7 mL, 11.9 mmol, 1.2 equiv) was added dropwise over 10 min to a suspension of $MeOCH_2P^+Ph_3Cl^-$ (3.9 g, 11.4 mmol, 1.15 equiv) in toluene (40 mL) at 0 °C under N_2. The soln was stirred for 30 min at 25 °C then cooled to 0 °C. A soln of 2-fluoro-4-(trifluoromethyl)benzaldehyde (1.9 g, 9.89 mmol, 1 equiv) was added dropwise, and the resulting mixture was stirred for 3 h at 25 °C. H_2O (50 mL) was added, and the phases were separated. The organic layer was washed successively with H_2O (50 mL), 20 wt% NH_4Cl (50 mL), and brine (50 mL) then dried (Na_2SO_4). The suspension was filtered through a plug of silica gel that was then washed with cyclohexane (350 mL). The filtrate was concentrated under reduced pressure to give an oil (1.26 g) that was dissolved in acetone (20 mL) and treated with 4 M aq HCl (10 mL). The mixture was stirred overnight at reflux, and then the solvent was partially removed, the residue was diluted with MTBE (20 mL), and the phases were allowed to separate. The aqueous layer was extracted with MTBE (20 mL). The combined organic phases were washed with H_2O (16 mL) and brine (16 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an oil; yield: 1.04 g. This was used in the next step without further purification.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 9.79 (m, 1 H), 7.43 (d, *J* = 7.7 Hz, 1 H), 7.38 (d, *J* = 9.2 Hz, 1 H), 7.35 (t, *J* = 7.7 Hz, 1 H), 3.84 (s, 2 H).

^{13}C NMR (151 MHz, $CDCl_3$): δ = 196.59 (s), 160.73 (d, *J* = 248.5 Hz), 132.37 (d, *J* = 4.6 Hz), 131.85 (qd, *J* = 33.4, 8.1 Hz), 123.79 (d, *J* = 17.3 Hz), 121.27 (q, *J* = 3.5 Hz), 123.15 (qd, *J* = 272.6, 2.3 Hz), 112.96 (dq, *J* = 25.3, 3.5 Hz), 43.65 (s).

HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_9H_6F_4O$: 205.0277; found: 205.0282.

(*E*/*Z*)-[2-Fluoro-4-(trifluoromethyl)phenyl]acetaldehyde Oxime (6)

The aldehyde **2b** was dissolved in EtOH (5.4 mL) and treated successively with NH_2OH HCl (0.7 g, 10.07 mmol) and Et_3N (1.56 mL, 11.19 mmol). The mixture was then stirred at reflux for 1 h. The solvent was removed, and the mixture was diluted with H_2O (10 mL) and MTBE (15 mL). The biphasic system was separated, and the aqueous phase was further extracted with MTBE (15 mL). The combined organic layers were washed with 3 M HCl (15 mL), H_2O (15 mL), and brine (15 mL) then dried (Na_2SO_4), filtered, and concentrated under reduced pressure; yield: 0.96 g. The product was used in the next step without further purification.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 11.23 (s, 1 H), 10.74 (s, 1 H), 7.58 (m, 6 H), 7.47 (t, *J* = 5.3 Hz, 1 H), 6.83 (t, *J* = 5.3 Hz, 1 H), 3.71 (d, *J* = 5.3 Hz, 2 H), 3.59 (d, *J* = 5.3 Hz, 2 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 160.2 (d, *J* = 247.1 Hz, 1 C), 161.0 (d, *J* = 247.1 Hz, 1 C), 146.3 (s, 1 C), 145.9 (s, 1 C), 132.4 (d, *J* = 5.1 Hz, 1 C), 132.3 (d, *J* = 5.1 Hz, 1 C), 129.4 (d, *J* = 15.1 Hz, 2 C), 129.3 (m, 2 C), 121.3 (m, 2 C), 123.4 (qd, *J* = 272.4, 3.0 Hz, 2 C), 112.6 (m, 2 C), 28.9 (d, *J* = 2.0 Hz, 1 C), 24.8 (d, *J* = 2.0 Hz, 1 C).

^{19}F NMR (376 MHz, acetone-d_6): δ = –116.66 (s, 1 F), –63.10 (s, 3 F).

MS (ESI): *m/z* $[M + H]^+$ = 222.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_9H_7F_4NO$: 220.0386; found: 220.0380.

[2-Fluoro-4-(trifluoromethyl)phenyl]acetonitrile (1)

The oxime **6** was dissolved in THF (19.2 mL), and $SOCl_2$ (1.48 mL, 17.08 mmol) was slowly added while the temperature was kept below 20 °C. The soln was stirred at r.t. for 1 h and then concentrated under reduced pressure. The residue was dissolved in MTBE and the soln was filtered through a silica plug, which was washed with additional MTBE. The filtrate was concentrated under reduced pressure to give the required product; yield: 0.8 g (40%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.22 (s, 2 H), 7.66–7.71 (m, 1 H), 7.74 (t, *J* = 7.71 Hz, 1 H), 7.80 (m, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 159.7 (d, *J* = 249.0 Hz), 131.6 (d, *J* = 3.7 Hz), 130.6 (qd, *J* = 33.0, 8.6 Hz), 123.7 (d, *J* = 16.5 Hz), 123.1 (qd, *J* = 272.2, 2.4 Hz), 121.9 (quin, *J* = 3.7 Hz), 117.5 (s), 113.1 (dq, *J* = 24.4, 3.7 Hz), 17.1 (d, *J* = 3.7 Hz).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –113.96, –61.20.

MS (ESI): *m/z* [M + H]$^+$ = 202.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_9H_5F_4N$: 202.0280; found: 202.0285.

Method B

Ethyl Cyano[2-fluoro-4-(trifluoromethyl)phenyl]acetate (7)

A suspension of 3,4-$F_2C_6H_3CF_3$ (100 g, 549 mmol, 1.1 equiv), EtO_2CCH_2CN (53.2 mL, 500 mmol, 1 equiv), $BnN^+Et_3Cl^-$ (11.4 g, 50 mmol, 0.1 equiv) and K_2CO_3 (325 mesh; 207 g, 1.5 mol, 3 equiv) in DMSO (300 mL) was stirred at 90 °C under N_2 for 20 h. The mixture was then cooled to 20 °C, diluted with EtOAc (500 mL), and further cooled to 5 °C. 6 M aq HCl (500 mL) was added dropwise, leading to precipitation of a white solid. The resulting suspension was stirred for 30 min until the solid completely dissolved. The biphasic system was separated, and the organic layer was washed with H_2O (2 × 300 mL) and brine (300 mL). The organic layer was mixed with DMSO (200 mL) and then concentrated under reduced pressure to give a brown soln of **7** in DMSO that was used without further treatment.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.21 (t, *J* = 7.12 Hz, 3 H), 4.26 (q, *J* = 7.12 Hz, 2 H), 6.11 (s, 1 H), 7.72–7.83 (m, 2 H), 7.90 (dd, *J* = 10.25, 1.27 Hz, 1 H).

^{13}C NMR (100.52 MHz, DMSO-d_6): δ = 13.72, 37.45, 63.23, 113.73, 115.16, 122.26, 122.98, 123.29, 131.90, 132.33, 159.73, 163.87.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –112.65 (m, 1 F), –61.41 (s, 3 F).

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_{12}H_9F_4NO_2$: 274.0491; found: 274.0499.

[2-Fluoro-4-(trifluoromethyl)phenyl]acetonitrile (1)

Brine (100 mL) was added to the previously obtained brown soln of **7**, and the resulting mixture was stirred at 107 °C under N_2 for 18 h. The mixture was allowed to cool down to 20 °C then diluted with EtOAc (500 mL) and H_2O (200 mL). The mixture was then stirred at 20 °C for 30 min and then the biphasic system was separated. The organic layer was washed successively with H_2O (100 mL) and brine (100 mL) then concentrated under reduced pressure (50 mbar, 35 °C) to give a brown oily residue that was purified by distillation under reduced pressure (bp 84–92 °C, 6 mbar) to give [2-fluoro-(4-trifluoromethyl)-phenyl]acetonitrile (**1**) as a pale yellow liquid; yield: 91.4 g (82%; purity ~ 95% by NMR). The product was contaminated with ~5% of the isomeric nitrile **9**.

Ethyl Cyano[2-nitro-4-(trifluoromethyl)phenyl]acetate

K_2CO_3 (325 mesh; 3.3 g, 23.88 mmol) and $BnN^+Et_3Cl^-$ (21.6 mg, 0.10 mmol) were added to a soln of 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (1.8 g, 8.61 mmol) and EtO_2CCH_2CN (853 μL, 8.02 mmol) in DMSO (4.5 mL) at r.t. under N_2, and the mixture was heated to 90 °C and stirred for 12 h. The mixture was then cooled to r.t., diluted with EtOAc (10 mL), and poured into a cooled 6 M HCl (20 mL). The biphasic system was separated, and the aqueous phase was extracted with EtOAc (15 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to give ethyl cyano[2-nitro-4-(trifluoromethyl)phenyl]acetate as an oil; yield: 2.7 g (>99%; uncorrected).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.22 (t, *J* = 7.03 Hz, 3 H), 4.25 (q, *J* = 7.03 Hz, 2 H), 6.41 (s, 1 H), 8.04 (m, 1 H), 8.34 (d, *J* = 7.03 Hz, 1 H), 8.58 (m, 1 H).

^{13}C NMR (100.52 MHz, DMSO-d_6): δ = 13.76, 40.94, 63.25, 114.76, 123.26, 129.61, 131.63, 134.53, 147.28, 163.48.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –61.68 (s, 3 F).

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_{12}H_9F_3N_2O_4$: 301.0436; found: 301.0437.

[2-Nitro-4-(trifluoromethyl)phenyl]acetonitrile

A soln of ethyl cyano[2-nitro-4-(trifluoromethyl)phenyl]acetate (2.7 g, 8.93 mmol) in a mixture of DMSO (4 mL) and brine (1 mL) was heated at 120 °C until the reaction was complete (7 h), then cooled to r.t. The resulting mixture was diluted with EtOAc (20 mL) and H_2O (5 mL), and the biphasic system was separated. The organic layer was washed successively with H_2O (5 mL) and brine (5 mL), then dried (Na_2SO_4) and concentrated under reduced pressure. The resulting brown oil was purified by column chromatography [cyclohexane–EtOAc (85:15)] to give an orange oil; yield: 1.6 g (79%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.47 (s, 2 H), 7.98 (d, *J* = 8.10 Hz, 1 H), 8.23 (dd, *J* = 8.10, 1.17 Hz, 1 H), 8.46 (d, *J* = 1.17 Hz, 1 H).

^{13}C NMR (100.52 MHz, DMSO-d_6): δ = 21.62, 117.32, 122.56, 122.79, 129.81, 130.87, 130.99, 132.99, 148.06.

^{19}F NMR (376 MHz, DMSO-d_6): δ = –61.48 (s, 3 F).

MS (ESI): *m/z* [M + H]$^+$ = 231.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_9H_5F_3N_2O_2$: 229.0225; found: 229.0028.

Ethyl Cyano(2-nitrophenyl)acetate

K_2CO_3 (325 mesh; 3.3 g, 23.88 mmol) and $BnN^+Et_3Cl^-$ (21.6 mg, 0.10 mmol) were added to a soln of 1-fluoro-2-nitrobenzene (1.2 g, 8.50 mmol) and EtO_2CCH_2CN (853 μL, 8.02 mmol) in DMSO (4.5 mL) at r.t. under N_2. The resulting mixture was heated to 90 °C and stirred for 12 h, then cooled to r.t.. The soln was then diluted with EtOAc (10 mL) and poured into cooled 6 M HCl (20 mL). The biphasic system was separated, and the aqueous phase was extracted with EtOAc (15 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to give an oil; yield: 2.08 g (>99%; uncorrected).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.19 (t, *J* = 7.12 Hz, 3 H), 4.22 (qd, *J* = 7.12, 1.10 Hz, 2 H), 6.25 (s, 1 H), 7.78 (m, 2 H), 7.92 (dt, 1 H), 8.29 (dd, *J* = 8.10, 1.27 Hz, 1 H).

^{13}C NMR (100.52 MHz, DMSO-d_6): δ = 13.77, 41.23, 62.89, 115.37, 125.67, 126.02, 131.17, 133.18, 135.27, 146.72, 164.02.

HRMS (ESI): *m/z* [M – H]$^-$ calcd for $C_{11}H_{10}N_2O_4$: 233.0562; found: 233.0561.

(2-Nitrophenyl)acetonitrile

A soln of ethyl cyano(2-nitrophenyl)acetate (1.87 g, 7.99 mmol) in a mixture of DMSO (4 mL) and brine (1 mL) was heated at 120 °C until the reaction was complete (7 h), then cooled to r.t. The resulting mixture was diluted with EtOAc (20 mL) and H_2O (5 mL), and the biphasic system was separated. The organic layer was washed successively with H_2O (5 mL) and brine (5 mL) then dried (Na_2SO_4) and concentrated under reduced pressure. A brown solid was obtained that was purified by precipitation in EtOAc (6 mL) and cyclohexane (10 mL) to give a yellow solid; yield: 0.75 g (58%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.35 (s, 2 H), 7.66 (ddd, 1 H), 7.71–7.76 (m, 1 H), 7.83 (dt, 1 H), 8.16 (dd, 1 H).

^{13}C NMR (100.52 MHz, DMSO-d_6): δ = 21.54, 117.85, 125.41, 126.36, 129.68, 131.70, 134.60, 147.63.

MS (ESI): *m/z* $[M + H]^+$ = 163.

HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_8H_6N_2O_2$: 161.0351; found: 161.0350.

Ethyl Cyano(2-cyanophenyl)acetate

K_2CO_3 (325 mesh; 3.3 g, 23.88 mmol) and $BnN^+Et_3Cl^-$ (21.6 mg, 0.10 mmol) were added to a soln of 2-fluorobenzonitrile (1.1 g, 9.08 mmol) and EtO_2CCH_2CN (853 μL, 8.02 mmol) in DMSO (4.5 mL) at r.t. under N_2, and the resulting mixture was heated to 90 °C and stirred for 12 h. The mixture then was cooled to r.t., diluted with EtOAc (10 mL), and poured into cooled 6 M HCl (20 mL). The biphasic system was separated, and the aqueous phase was extracted with EtOAc (15 mL). The combined organic layers were washed with H_2O then dried (Na_2SO_4) and concentrated under reduced pressure to give an oil; yield: 1.6 g (82%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.23 (t, *J* = 7.12 Hz, 3 H), 4.26 (q, *J* = 7.16 Hz, 2 H), 6.07 (s, 1 H), 7.65–7.72 (m, 2 H), 7.81–7.87 (m, 1 H), 8.00–8.03 (m, 1 H).

^{13}C NMR (100.52 MHz, DMSO-d_6): δ = 13.74, 41.63, 63.25, 111.84, 115.36, 116.35, 130.05, 130.25, 133.82, 134.16, 134.23, 163.97.

HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{12}H_{10}N_2O_2$: 213.0664; found: 213.0662.

2-(Cyanomethyl)benzonitrile

A soln of ethyl cyano(2-cyanophenyl)acetate (1.6 g, 7.47 mmol) in DMSO (4 mL) and brine (1 mL) was heated at 120 °C until the reaction was complete (7 h), then cooled to r.t. The resulting mixture was diluted with EtOAc (20 mL) and H_2O (5 mL), and the biphasic system was separated. The organic layer was washed successively with H_2O (5 mL) and brine (5 mL) then dried (Na_2SO_4) and concentrated under reduced pressure. A brown solid was obtained that was purified by precipitation in EtOAc (6 mL) and cyclohexane (10 mL) to give a yellow solid; yield: 0.392 g (37%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.35 (s, 2 H), 7.66 (ddd, 1 H), 7.71–7.76 (m, 1 H), 7.83 (dt, 1 H), 8.16 (dd, 1 H).

^{13}C NMR (100.52 MHz, DMSO-d_6): δ = 21.54, 117.85, 125.41, 126.36, 129.68, 131.70, 134.60, 147.63.

MS (ESI): *m/z* $[M + H]^+$ = 143.

HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_9H_6N_2$: 141.0453; found: 141.0450.

Ethyl Cyano[6-(trifluoromethyl)pyridin-3-yl]acetate

K_2CO_3 (11.3 g, 81.76 mmol) and $BnN^+Et_3Cl^-$ (0.68 g, 2.98 mmol) were added to a soln of 5-fluoro-2-(trifluoromethyl)pyridine (5 g, 30.29 mmol) and EtO_2CCH_2CN (3.5 mL, 32.91 mmol) in DMSO (50 mL). The resulting mixture was heated to 90 °C for 3 h then cooled to r.t. The slurry was then diluted with EtOAc (50 mL) and slowly treated with 6 M HCl (50 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resulting material was dried under a high vacuum for several hours to give a reddish oil; yield: 9.5 g (>99%; uncorrected).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.33 (t, *J* = 7.2 Hz, 3 H), 4.31 (q, *J* = 7.2 Hz, 2 H), 4.88 (s, 1 H), 7.80 (d, *J* = 8.1 Hz, 1 H), 8.07 (dd, *J* = 8.1, 1.5 Hz, 1 H), 8.82 (d, 1.5 Hz, 1 H).

^{13}C NMR (100.52 MHz, $CDCl_3$): δ = 13.81, 41.02, 64.22, 114.03, 120.87, 121.06, 129.27, 137.10, 148.90, 149.34, 163.40.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –68.12 (s, 3 F).

MS (ESI): *m/z* $[M + H]^+$ = 259.

HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_{11}H_9F_3N_2O_2$: 257.0538; found: 257.0544.

[6-(Trifluoromethyl)pyridin-3-yl]acetonitrile

A soln of ethyl cyano[6-(trifluoromethyl)pyridin-3-yl]acetate (9.5 g, 36.79 mmol) in DMSO (100 mL) was treated with brine (50 mL). The resulting orange soln was heated to 110–120 °C. After 2 h, the mixture was cooled to 25 °C, diluted with EtOAc (100 mL), and washed successively with H_2O (100 mL) and brine (100 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated under reduced pressure to give an oil that was purified on silica gel (EtOAc–cyclohexane, 1:1); yield: 3.42 g (50%).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 3.89 (s, 2 H), 7.75 (d, *J* = 8.1 Hz, 1 H), 7.94 (dd, *J* = 8.1, 1.7 Hz, 1 H), 8.70 (d, 1.7 Hz, 1 H).

^{13}C NMR (150.81 MHz, $CDCl_3$): δ = 21.15, 115.93, 120.76 (q, *J* = 2.6 Hz), 120.77 (q, *J* = 274.0 Hz), 129.31, 136.92, 148.17 (q, *J* = 34.8 Hz), 149.27.

MS (ESI): *m/z* $[M + H]^+$ = 187.

HRMS (ESI): *m/z* $[M - H]^-$ calcd for $C_8H_5F_3N_2$: 185.0327; found: 185.0325.

Method C

Potassium (*E,Z*)-2-cyano-1-ethoxy-2-[2-fluoro-4-(trifluoromethyl)phenyl]ethylenolate (10):

A suspension of 3,4-$F_2C_6H_3CF_3$ (100 g, 549 mmol, 1.1 equiv) and EtO_2CCH_2CN (53.2 mL, 500 mmol, 1 equiv), BnN^+Et_3 Cl^- (11.4 g, 50 mmol, 0.1 equiv), and K_2CO_3 (325 mesh; 207 g, 1.5 mol, 3 equiv) in DMSO (300 mL) was stirred at 90 °C under N_2 for 19 h. The mixture was allowed to cool to 20 °C, diluted with EtOAc (500 mL), and then further cooled to 5 °C. 6 M HCl (500 mL) was added dropwise, leading to precipitation of a white solid. The resulting suspension was stirred for 30 min until the precipitate completely dissolved. The biphasic system was separated, and the organic layer was washed with H_2O (2 × 300 mL) and brine (300 mL). The organic layer was dried (Na_2SO_4), filtered, and evaporated to dryness. MTBE (300 mL) was added followed by *t*-BuOK (47 g, 418 mmol, 0.8 equiv) in small portions while the temperature was kept below 30 °C. The mixture was then concentrated under vacuum to give a thick slurry. MeCN (500 mL) was added and the mixture was concentrated to 250 mL. The slurry was cooled at 5–8 °C and stirred for 10–12 h. The solid was filtered off, washed with MeCN (50 mL), and dried under vacuum at 40 °C to give a pale yellow solid; yield: 143.4 g (96%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 7.12 Hz, 3 H), 3.95 (q, *J* = 7.12 Hz, 2 H), 7.07–7.18 (m, 2 H), 8.25 (m, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 168.1 (s), 154.7 (d, *J* = 243.6 Hz), 134.7 (d, *J* = 9.7 Hz), 125.9 (s), 125.4 (br. s), 124.5 (qd, *J* = 269.7, 2.9 Hz), 119.8 (m), 118.2 (qd, *J* = 32.9, 7.7 Hz), 111.2 (dq, *J* = 26.1, 3.9 Hz), 56.6 (s), 50.3 (s), 15.1 (s).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –113.19 (m, 1 F) –59.41 (s, 3 F).

MS (ESI): *m/z* $[M + H]^+ = 314$

HRMS (ESI): *m/z* $[M - K]^-$ calcd for $C_{12}H_8F_4KNO_2$: 274.0491; found: 274.0490

[2-Fluoro-4-(trifluoromethyl)phenyl]acetonitrile

The solid obtained above (143.4 g, 527 mmol) was dissolved in H_2O (215 mL) and the pH was adjusted to 7 with concd HCl (44 mL) while the temperature was kept below 30 °C. DMSO (300 mL) was added followed by NaCl (40 g, 684 mmol, 1.4 equiv), and the mixture was heated at 110 °C for 12–15 h until conversion was complete. The mixture was then cooled at 25 °C, and CH_2Cl_2 (450 mL) was added, followed by H_2O (330 mL). The phases were separated. The aqueous phase was back-extracted with CH_2Cl_2 (300 mL). The combined organic phases were washed with H_2O (3 × 500 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. The product was purified by distillation under reduced pressure to give a colorless liquid; yield: 74.9 g [70%; purity: ~99% (NMR)].

Potassium (*E,Z*)-2-Cyano-1-ethoxy-2-[2-nitro-4-(trifluoromethyl)phenyl]ethylenolate

K_2CO_3 (325 mesh, 3.3 g, 23.88 mmol) and $BnN^+Et_3Cl^-$ (21.6 mg, 0.10 mmol) were added to a soln of 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (1.8 g, 8.61 mmol) and EtO_2CCH_2CN (853 μL, 8.02 mmol) in DMSO (4.5 mL) at r.t. under N_2. The resulting mixture was heated to 90 °C, stirred for 12 h, cooled to r.t., diluted with EtOAc (10 mL), and poured into a cooled 6 M HCl (20 mL). The biphasic system was separated, and the aqueous phase was extracted with EtOAc (15 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to give an oil. This residue (1.9 g, 6.29 mmol) was dissolved in MTBE (5.6 mL), and *t*-BuOK (760 mg, 6.77 mmol) was added portionwise. The resulting mixture was stirred overnight at r.t., and then evaporated to give a purple oil (yield: 1.23 g, 42%) that was used in the next step without further purification.

^{1}H NMR (600 MHz, DMSO-d_6): δ = 7.74 (s, 1 H), 7.67 (d, *J* = 8.6 Hz, 1 H), 7.50 (dd, *J* = 8.6, 1.6 Hz, 1 H), 3.92 (q, *J* = 7.2 Hz, 2 H), 1.12 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 166.9 (s), 142.1 (s), 140.3 (s), 127.1 (s), 126.5 (m), 124.5 (s), 122.3 (q, *J* = 4.6 Hz), 124.2 (q, *J* = 270.4 Hz), 117.2 (q, *J* = 33.4 Hz), 57.7 (s), 57.3 (s), 15.0 (s).

^{19}F NMR (376 MHz, DMSO-d_6): δ = –60.01 (s, 3 F).

HRMS (ESI): *m/z* $[M - K]^-$ calcd for $C_{12}H_8F_3KN_2O_4$: 301.0436; found: 301.0438.

[2-Nitro-4-(trifluoromethyl)phenyl]acetonitrile

A suspension of the potassium salt obtained above (1.22 g, 3.58 mmol) in CH_2Cl_2 (28 mL) was treated with 1 M HCl (14 mL), and the resulting biphasic system was stirred until complete dissolution occurred and then allowed to separate. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL), and the combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give an oil. The oil was dissolved in DMSO (4 mL) and treated with brine. The mixture was stirred at 115 °C for 12 h then cooled to r.t. The resulting mixture was diluted with EtOAc (30 mL) and H_2O (15 mL). The biphasic system was separated, and the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to give [2-nitro-4-(trifluoromethyl)phenyl]acetonitrile; yield: 0.823 g (quantitative).

Potassium (*E,Z*)-2-Cyano-1-ethoxy-2-(2-nitrophenyl)ethylenolate

K_2CO_3 (325 mesh, 3.3 g, 23.88 mmol) and $BnN^+Et_3Cl^-$ (21.6 mg, 0.10 mmol) were added to a soln of 1-fluoro-2-nitrobenzene (1.2 g, 8.50 mmol) and EtO_2CCH_2CN (853 μL, 8.02 mmol) in DMSO (4.5 mL) at r.t. under N_2. The resulting mixture was heated to 90 °C, stirred for 12–18 h, and then cooled to r.t., diluted with EtOAc (10 mL), and poured into cooled 6 M HCl (20 mL). The biphasic system was separated, and the aqueous phase was extracted with EtOAc (15 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to give an oil; yield 2.1 g. This residue was dissolved in MTBE (5.6 mL), and *t*-BuOK (760 mg, 6.77 mmol) was added portionwise. The resulting mixture was stirred for 2 h at r.t., treated with CH_2Cl_2 (2 mL), and then stirred for 30 min at r.t. The solvent was removed to give a purple solid that was used in the next step without further purification; yield: 1.5 g (65%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.10 (t, *J* = 7.03 Hz, 3 H), 3.87 (q, *J* = 7.03 Hz, 2 H), 6.75 (ddd, *J* = 8.25, 6.98, 1.37 Hz, 1 H), 7.26 (ddd, *J* = 8.30, 6.93, 1.56 Hz, 1 H), 7.41–7.52 (m, 2 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 167.3, 144.3, 136.1, 130.6, 127.3, 126.3, 124.7, 118.6, 56.7, 54.3, 15.2.

MS (ESI): *m/z* $[M + H]^+ = 273$.

HRMS (ESI): *m/z* $[M - K]^-$ calcd for $C_{11}H_9KN_2O_4$: 233.0562; found: 233.0562

(2-Nitrophenyl)acetonitrile

The suspension of the potassium salt obtained above (1.5 g, 5.51 mmol) in CH_2Cl_2 (28 mL) was treated with a 1 M HCl soln (14 mL). The biphasic system was stirred until complete dissolution and allowed separating. The aqueous layer was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4) and concentrated under reduced pressure to oil. The oil was dissolved in DMSO (4 mL) and treated with a brine soln. The mixture was stirred at 115 °C for 12 h. After cooling to r.t., the resulting mixture was diluted with EtOAc (30 mL) and H_2O (15 mL). The biphasic system was separated and the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were washed with H_2O dried (Na_2SO_4) and concentrated under reduced pressure affording (2-nitrophenyl)acetonitrile; yield: 0.892 g (54%).

Potassium (*E,Z*)-2-Cyano-2-(2-cyanophenyl)-1-(ethoxy)ethylenolate

K_2CO_3 (325 mesh, 3.3 g, 23.88 mmol) and $BnN^+Et_3Cl^-$ (21.6 mg, 0.10 mmol) were added to a soln of 2-fluorobenzonitrile (1.1 g, 9.08 mmol) and EtO_2CCH_2CN (853 μL, 8.02 mmol) in DMSO (4.5 mL) at r.t. under N_2. The resulting mixture was heated to 90 °C, stirred for 12–18 h, was cooled to r.t., diluted with EtOAc (10 mL), and poured into cooled 6 M HCl (20 mL). The biphasic system was separated, and the aqueous phase was back-extracted with EtOAc (15 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure to give an oil. The residue (1.5 g) was dissolved in MTBE (5.6 mL) and *t*-BuOK (760 mg, 6.77 mmol) was added portionwise. The resulting mixture was stirred for 2 h at r.t. to give a suspension that was treated with CH_2Cl_2 (2 mL) and stirred for 30 min at r.t. The slurry was filtered to give a solid that was washed with CH_2Cl_2 (3 × 5 mL) and dried in an oven at 40 °C under reduced pressure; yield: 1.41 g (62%).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.15 (t, *J* = 7.12 Hz, 3 H), 3.94 (q, *J* = 7.12 Hz, 2 H), 6.78 (td, *J* = 7.47, 1.27 Hz, 1 H), 7.21–7.30 (m, 1 H), 7.34–7.39 (m, 1 H), 7.60–7.73 (m, 1 H).

^{13}C NMR (151 MHz, DMSO-d_6): δ = 167.7, 145.4, 133.2, 131.0, 126.9, 126.1, 119.7, 119.6, 105.6, 56.6, 54.8, 15.2.

MS (ESI): *m/z* $[M + H]^+ = 253$.

HRMS (ESI): *m/z* $[M - K]^-$ calcd for $C_{12}H_9KN_2O_2$: 213.0664; found: 213.0664.

2-(Cyanomethyl)benzonitrile

A suspension of the potassium salt obtained above (1.41 g, 5.59 mmol) in CH_2Cl_2 (28 mL) was treated with 1 M HCl (14 mL). The biphasic system was stirred until complete dissolution occurred and then separated. The aqueous layer was extracted with CH_2Cl_2 (2×30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure to give an oil. This residue was dissolved in DMSO (4 mL) and treated with brine. The mixture was stirred at 115 °C for 12 h then cooled to r.t. The resulting mixture was diluted with EtOAc (30 mL) and H_2O (15 mL). The biphasic system was separated and the aqueous layer was extracted with EtOAc (15 mL). The combined organic layers were washed with H_2O, dried (Na_2SO_4), and concentrated under reduced pressure; yield: 0.445 g (56%).

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