Bis(dealkoxycarbonylation) of Nitroarylmalonates: A Facile Entry to Alkylated Nitroaromatics

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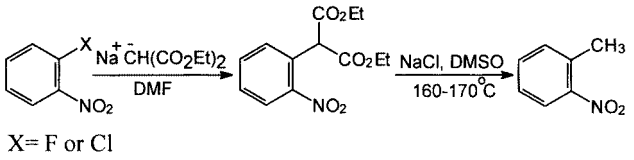
Abstract: A simple approach to alkylated nitroaromatics from substituted nitroaryl malonic esters by double decarboxylation is detailed.

Key words: nucleophilic aromatic substitutions, Krapcho's decarboxylation, alkylations, nitrotoluene, arenes

Introduction of alkyl groups in aromatic rings is an important step in organic synthesis. The conventional Friedel–Crafts alkylation,[1] alkyation of metallated arenes, particularly in the presence of directed metallating groups (ortho effect),[2] nucleophilic addition to arene-transition metal carbonyl complexes,[3] transition metal catalysed nucleophilic substitution of aryl halides,[4] aromatic substitution via nucelophilic addition to electron deficient arenes (including *vicarious* and *ipso*)[5] and olefin insertion via C-H activation[6] are some of the elegant methods to realise the phenomenon. Hoz et al.[7] have recently demonstrated the application of trialkyboranes in base-promoted alkylation of nitroaromatics.

Decarboxylation of aryl substituted malonic esters under Krapcho's conditions are known to provide aryl acetic esters in good yield.[8] However, to the best of our knowledge, bis(decarboxylation) of arylmalonic esters has not been reported. In continuation of our ongoing program to synthesise medicinally important oxindole derivatives, we observed by serendipity the complete decarboxylation of nitroaryl malonates under Krapcho's procedure. This observation has been exploited to synthesise alkyl nitroaromatics which otherwise need number of steps.

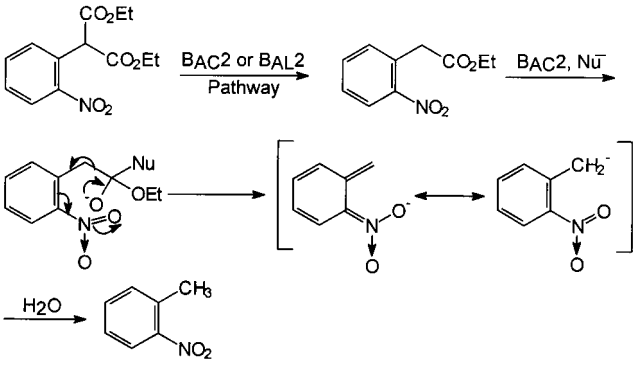
For example, *o*-chloro/*o*-fluoronitrobenzene was converted to nitrophenyl malonic ester which on exposure to NaCl in wet DMSO at 160–170 °C for 24 hours gave *o*-nitrotoluene in 55% yield (Scheme 1). Encouraged with this, various nitroaryl malonic esters were prepared from the corresponding halonitrobenzenes by a modified procedure.[9] Nitrohaloaromatic compounds were treated with sodium salt of diethyl malonate in DMF at ambient temperature to provide the corresponding diethyl (nitrophenyl)malonates in good yields (Table). These compounds were subjected to Krapcho's reaction (NaCl, DMSO, H_2O, 160–170 °C) to afford the nitrotoluenes (Table, Entries 1–4 and 6) and nitroxylenes (Table, Entries 5 and 7). Overall improved yields with shorter reaction timings were observed when modified Krapcho's condition i.e. dibasic salt $MgCl_2.6H_2O$ in dimethyl acetamide at 140–150 °C was employed.[10]



Scheme 1

To elaborate the scope of this investigation, different disubstituted malonic esters (Table, Entries 8–11) were prepared from halonitrobenzenes and monoalkyl malonic esters. Exposure of these compounds to the similar conditions described above, enabled to access various alkyl nitrobenzenes (Table, Entries 8–11).

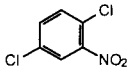
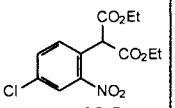
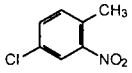
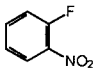
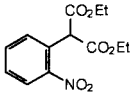
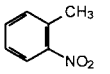
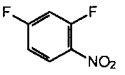
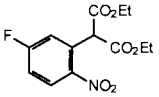
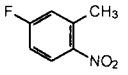
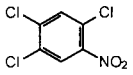
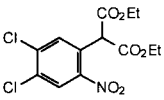
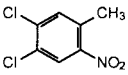
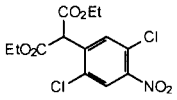
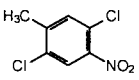
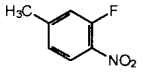
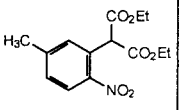
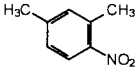
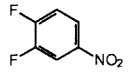
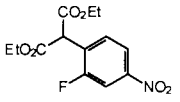
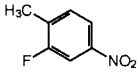
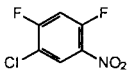
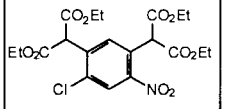
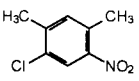
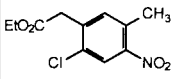
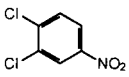
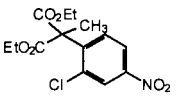
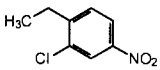
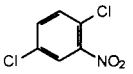
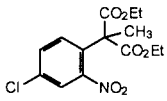
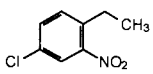
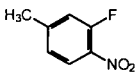
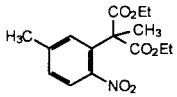
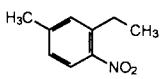
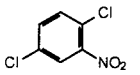
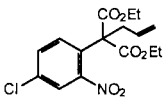
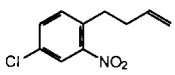
The proposed mechanism involves two stages: initial decarboxylation of malonate via competitive $B_{AC}2$ or $B_{AL}2$ pahtway[8] to give *o*-nitrophenyl acetate which then undergoes further decarboxylation to give *o*-nitrotoluene. Since simple aryl malonic esters (without electron-withdrawing NO_2 group) stops at first decarboxylation itself, a rationale can be suggested that the second decarboxylation in the case of nitroaryl-malonic esters becomes viable because of mesomeric stabilisation of benzylic anion by nitro group at *o*/*p* position (Scheme 2).



Scheme 2

In conclusion, we have developed a mild and efficient procedure for alkylated aromatics which otherwise are difficult to prepare, starting from halonitrobenzenes. Needless to mention that the nitro group present in these products can be a surrogate for introducing a variety of functionalities in the aromatic ring.

Table Synthesis of Alkylnitrobenzenes[a,b]

Entry	Halonitro benzenes	Aryl malonates	Reaction conditions	Alkyl nitrobenzenes	Yields
1			A, 24 h		55%[a]
2			A, 24 h B, 24 h		35%[a] 77%
3			A, 48 h B, 20 h		50%[a] 73%
4			A, 12 h		60%[b]
					20%[b]
5			B, 12 h		80%[a]
6			B, 24 h		65%[a]
7			B, 7 h		60%[c]
					20%
8			B, 15 h		72%
9			B, 15 h		75%
10			B, 20 h		69%
11			B, 24 h		45%

[a] Conditions: A: NaCl/DMSO/H_2O, 160−170 °C; B: $MgCl_2$•$6H_2O$/DMA, reflux.

[b] All the known compounds were identified by comparison with authentic samples. The products shown under Entries 1-3, 5 and 6 are commercially available from Sigma-Aldrich Corporation/Lancaster Synthesis L, while those under Entries 4 are reported in Dictionary of Organic Compounds, **1996**, *3*, 2073. 5-Chloro-2,4-dimethylnitrobenzene (Entry 7) is reported in Dictionary of Organic Compounds, **1996**, *2*, 1335 (see also Experimental).

Starting materials and reagents were purchased from Aldrich, Fluka or Lancaster and used as received. TLC was performed on pre-coated silica gel plates (E-Merck, 60 F_{254}) and visualized by UV irradiation or spraying with anisaldehyde or phosphomolybdic acid stains followed by heating. NMR spectra were recorded on Bruker spectrophotometers (AC 200, MSL 300) with TMS as an internal standard. IR spectra were obtained from Perkin-Elmer 16 PC- FTIR spectrophotometer. EI Mass spectra were recorded on Finnigan MAT-1020. Combustion data were recorded on Elmentar-Vario-EL (Heraeus company Ltd. Germany).

Bis(decarboxylation) of Nitroarylmalonates; General Procedure

Condition A: A mixture of diethyl (halonitrophenyl)malonate (5 mmol), NaCl (1.17 g, 20 mmol), and H_2O (10 mmol) in DMSO (20 mL) was heated at 160−170 °C (monitored by TLC). The mixture was partitioned between Et_2O (50 mL) and H_2O (50 mL), the Et_2O was dried (Na_2SO_4) and concentrated to afford the residue which was chromatographically purified on silica gel to afford the pure product (Table).

Condition B: A mixture of diethyl (halonitrophenyl)malonate (5 mmol) and $MgCl_2.6H_2O$ (3.11 g, 10 mmol) in dimethyl acetamide (10 mL) was heated at 140−150 °C (monitored by TLC). The mixture was worked up as described above to provide the pure product (Table).

5-Chloro-2,4-dimethylnitrobenzene

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3 H), 2.60 (s, 3 H), 7.20 (s,1 H), 8.05 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.5, 19.7, 124.67, 131.8, 134.5, 141.8, 146.6.

IR ($CHCl_3$): ν = 764, 1364,1568 cm^{-1}.

Anal. calcd for $C_8H_8ClNO_2$: C, 51.75; H, 4.31; N, 7.54. Found: C, 52.0; H, 4.39; N, 7.58.

Ethyl (2-Chloro-5-methyl-4-nitro)phenylacetate

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.27 (t, 3 H, J = 7.4 Hz), 2.45 (s, 3 H), 3.93 (s, 2 H), 4.15 (q, 2 H, *J* = 7.4 Hz), 7.20 (s, 1 H), 8.10 (s, 1 H).

IR ($CHCl_3$): ν = 760, 1344, 1522, 1768 cm^{-1}.

3-Chloro-4-ethylnitrobenzene

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, *J* = 10.4 Hz), 2.86 (q, 2 H, *J* = 10.4 Hz), 7.41 (d, 1 H, *J* = 10.3 Hz), 8.05 (dd, 1 H, *J* = 3.4, 10.3 Hz), 8.20 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.3, 26.9, 121.7, 124.3, 129.7, 134.5, 146.4, 149.0.

IR ($CHCl_3$): ν = 890, 1124, 1348, 1520, 2974 cm^{-1}.

EI-MS: *m*/*z*: 185 (M^+).

Anal. calcd for $C_8H_8ClNO_2$: C, 51.75; H, 4.31; N, 7.54. Found: C, 52.1; H, 4.37; N, 7.80.

5-Chloro-2-ethylnitrobenzene

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, *J* = 8.5 Hz), 2.88 (q, 2 H, *J* = 8.5 Hz), 7.32 (d, 1 H, *J* = 10.1 Hz), 7.48 (dd, 1 H, *J* = 2.3, 10.5 Hz), 7.85 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.8, 25.8, 124.6, 132.3, 132.9, 138.0.

IR ($CHCl_3$): ν = 760, 764, 1120, 1354, 1530 cm^{-1}.

EI-MS: *m*/*z*: 185 (M^+).

Anal. calcd for $C_8H_8ClNO_2$: C, 51.75; H, 4.31. Found: C, 51.85; H, 4.43.

2-Ethyl-4-methylnitrobenzene

^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.28 (t, 3 H, *J* = 8.3 Hz), 2.41 (s, 3 H), 2.91 (q, 2 H, *J* = 8.3 Hz), 7.15 (m, 2 H), 7.82 (d, 1 H, *J* = 8.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.9, 21.3, 26.3, 124.9, 127.3, 131.1, 139.1, 143.3.

IR ($CHCl_3$): ν = 836, 1344, 1520, 1588, 2928 cm^{-1}.

Anal. calcd for $C_9H_{11}NO_2$: C, 65.44; H, 6.66; N, 8.48. Found: C, 65.20; H, 6.92; N, 8.40.

2-(But-3-enyl)-5-chloronitrobenzene

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.38 (q, 2 H, *J* = 8.2 Hz), 2.96 (t, 2 H, *J* = 8.2 Hz), 5.05 (m, 2 H), 5.79 (m, 1 H), 7.29 (d, 1 H, *J* = 9.6 Hz), 7.45 (d, 1 H, *J* = 9.6 Hz), 7.90 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.9, 34.3 116.1, 124.6, 132.7, 133.0, 136.5, 149.6.

IR ($CHCl_3$): ν = 1278, 1350, 1530, 3080 cm^{-1}.

Anal. calcd for $C_{10}H_{10}ClNO_2$: C, 56.75; H, 4.76; N, 6.62, found: C, 56.62; H, 4.47; N, 6.82.

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