Homolytic Alkylations of Highly Electron-deficient Aromatic Compounds Involving Electron and Proton Transfers†

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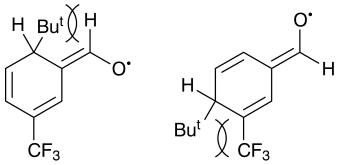
Regioselective homolytic alkylations leading to substitution for highly electron-deficient aromatics such as fluoro- or trifluoromethyl-substituted benzaldehydes and benzonitriles are observed *via* electron transfer chain processes in the presence of 1,4-diazabicyclo[2.2.2]octane.

Alkylmercury halides have proved to be a convenient source of alkyl radicals[1] for the reductive alkylations of various compounds, *i.e.* α,β-unsaturated ketones, esters, lactones, iminium ions and amides.[2] Amines such as 1,4-diazabicyclo-[2.2.2]octane (DABCO) can promote the oxidative homolytic reactions of alkylmercury halides with unsaturated compounds when the adduct radicals possess acidic hydrogen atoms.[3,4]

Based on our previous work,[4] we have extended the oxidative alkylation reaction to a wider range of electron-deficient aromatic compounds. As far as we know, no examples of alkylations of fluoro- or trifluoromethyl-substituted acylbenzenes and benzonitriles are reported in the literature.

Attempted photolysis of Bu^tHgCl with 2-fluorobenzaldehyde in Me_2SO is not very successful with only 4% reaction (Table 1, entry 1). However, when DABCO is added to the reaction mixture, 2-fluoro-4-(1,1-dimethylethyl)-benzaldehyde is obtained readily in 53% yield (91% conversion; Table 1, entry 2). Surprisingly enough, the reaction is quite clean and highly regioselective. Photochemical reactions of Bu^tHgCl–DABCO with 3-fluorobenzaldehyde also give rise to 3-fluoro-4-(1,1-dimethylethyl)benzaldehyde as an exclusive product in 66% yield (Table 1, entry 3).

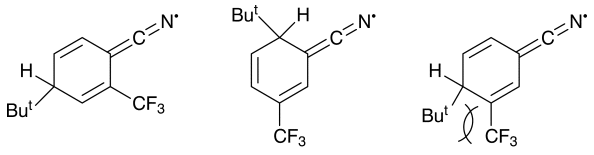


1 **2** **3**

In contrast to fluorobenzaldehydes, the yield of the photolysis reaction of 3-(trifluoromethyl)benzaldehyde with Bu^tHgCl–DABCO (Table 1, entry 4) is drastically reduced suggesting the unfavourable contribution of the sterically hindered radical adduct intermediates of **1** and **2**. Photolysis of 2-(trifluoromethyl)benzaldehyde (Table 1, entry 5) also gives low yield, probably because of the unfavorable steric effect in **3**.

Fluoro- or trifluoromethyl-substituted benzonitriles were examined to extend the synthetic utility and to confirm the aldehyde steric inhibition of resonance in the adduct radicals such as **1** or **3**, since the linear resonance form of cyanobenzenes can avoid steric hindrance between the cyano group and the *ortho* substituent.

In general, photolysis of benzonitrile derivatives produced better yield of *tert*-butylated product than benzaldehyde derivatives (Table 1, entries 7–11). Moreover, in photolysis of trifluoromethyl-substituted benzonitriles, the yield of *tert*-butylation was improved drastically (86–94%) over that for the aldehyde derivative case, independent of the position of the CF_3 group (Table 1, entries 9–11). Apparently, the adduct radical is almost free from steric strain because of a linear resonance structure such as **4** and **5**.



4 **5** **6**

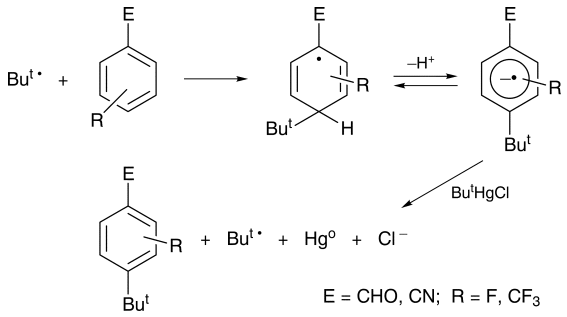
In the case of benzaldehyde derivatives, we do not observe any *ortho tert*-butylated product because the radical adduct intermediates such as **1** are sterically hindered. It is interesting to note that *tert*-butylation of 3-(trifluoromethyl)benzonitrile has occurred exclusively *ortho* to the cyano group instead of *para* (Table 1, entry 10). The severe steric strain between the *tert*-butyl group and trifluoromethyl group may explain the lack of *para* substitution in **6**, while **5** resulting from *ortho* attack has much less steric strain.

A plausible mechanism for the oxidative *para tert*-butylation is presented in Scheme 1.

Dialkylations are observed with a radical having a lower steric requirement than $Bu^{t\bullet}$. Thus, photolysis (360 nm) of 4 equiv. each of cyclohexylmercury chloride and DABCO with 4-(trifluoromethyl)benzonitrile in Me_2SO for 15 h produced 2-cyclohexyl-4-(trifluoromethyl)benzonitrile in 40% yield accompanied by 29% of 2,6-dicyclohexylated product.

Experimental

^1H NMR spectra were recorded on a 300 MHz Jeol or 500 MHz Bruker instrument and ^{13}C NMR spectra were recorded on 75 or 125 MHz Bruker instruments. Chemical shifts are reported in ppm from tetramethylsilane (TMS). High resolution mass spectra were



Scheme 1

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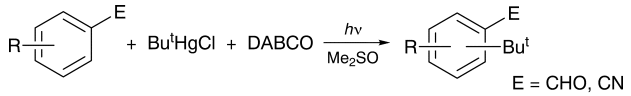
†This is a **Short Paper** as defined in the Instructions for Authors, Section 5.0 [see *J. Chem. Research (S)*, 1998, Issue 1]; there is therefore no corresponding material in *J. Chem. Research (M)*.

Table 1 Photolysis of Bu^tHgCl with benzaldehydes or benzonitriles for 48 h in Me_2SO in the presence of DABCO at 30–35 °C[a]



Entry	Substrate	DABCO (equiv.)	Product	Yield (%)[b]
1	2-FC_6H_4CHO	—	2-Fluoro-4-(1,1-dimethylethyl)benzaldehyde	4[c]
2	2-FC_6H_4CHO	4	2-Fluoro-4-(1,1-dimethylethyl)benzaldehyde	53[c]
3	3-FC_6H_4CHO	4	3-Fluoro-4-(1,1-dimethylethyl)benzaldehyde	66[c]
4	3-$CF_3C_6H_4CHO$	4	3-(Trifluoromethyl)-4-(1,1-dimethylethyl)benzaldehyde[d]	tr[c]
5	2-$CF_3C_6H_4CHO$	4	2-(Trifluoromethyl)-4-(1,1-dimethylethyl)benzaldehyde	27[c]
6	2-$CF_3C_6H_4CN$	—	2-(Trifluoromethyl)-4-(1,1-dimethylethyl)benzonitrile	4[c]
7	2-FC_6H_4CN	4	2-Fluoro-4-(1,1-dimethylethyl)benzonitrile	78[e]
8	3-FC_6H_4CN	4	3-Fluoro-4-(1,1-dimethylethyl)benzonitrile	84[e]
9	2-$CF_3C_6H_4CN$	4	2-(Trifluoromethyl)-4-(1,1-dimethylethyl)benzonitrile	86[c,f]
10	3-$CF_3C_6H_4CN$	4	5-(Trifluoromethyl)-2-(1,1-dimethylethyl)benzonitrile	91[e]
11	4-$CF_3C_6H_4CN$	4	4-(Trifluoromethyl)-2-(1,1-dimethylethyl)benzonitrile	94[e]

[a]0.1 M substrate and 0.4 M Bu^tHgCl. [b]By GC with octane as an internal standard. Unreacted benzaldehydes or benzonitriles remained in all experiments. [c]Photolysis at 254 nm with a Pyrex filter in a Rayonet photoreactor. [d]Identified by GC–MS only and regioselectivity was not determined. [e]Photolysis at 360 nm in a Rayonet photoreactor. [f]~3% of *o-tert*-butylated isomer was observed.

recorded on a Jeol-DX 303 mass spectrometer. Infrared spectra (IR) were recorded on a Nicolet 205 FT-IR.

Most products were isolated by flash column chromatography on silica gel (230–400 mesh ATSM, purchased from Merck) with eluents of mixed solvents (hexane and ethyl acetate). GC yields were determined by using an internal standard (octane) and were corrected with predetermined response factors.

General procedure.—The aromatic substrates (1 mmol) and reagents were dissolved in 10 ml of Me_2SO in a flame-dried Pyrex test tube under a nitrogen atmosphere and irradiated with a UV lamp in a Rayonet photoreactor. Workup involved treatment with 50 ml of aqueous $Na_2S_2O_3$ followed by diethyl ether extraction and washing of the diethyl ether extract with brine. After drying over $MgSO_4$ and evaporation of the solvent, the GC yield was determined with an internal standard (octane) and if necessary, the products were isolated by flash column chromatography using ethyl acetate–hexane as the eluent.

2-*Fluoro*-4-(1,1-*dimethylethyl*)*benzaldehyde*: obtained as a colorless liquid, 53%. ^1H NMR (300 MHz, $CDCl_3$) δ_H 10.32 (1 H, s), 7.80 (1 H, t, *J* 8.0 Hz), 7.29 (1 H, m), 7.17 (1 H, dd, *J* 1.6 and 12.6 Hz), 1.34 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 187.04, 186.97, 166.44, 163.10, 161.64, 161.54, 128.34, 128.31, 121.85, 121.81, 121.68, 121.57, 113.53, 113.25, 35.56, 30.82; ν_{max}/cm^{-1} 3094, 3043, 2982, 2875, 2773, 1698, 1622 (Found: *m*/*z* 180.0941. $C_{11}H_{13}OF$ requires M_r, 180.0950).

3-*Fluoro*-4-(1,1-*dimethylethyl*)*benzaldehyde*: obtained as a colorless liquid, 66%. ^1H NMR (300 MHz, $CDCl_3$) δ_H 9.93 (1 H, d, *J* 1.8 Hz), 7.56–7.58 (1 H, m), 7.46–7.50 (2 H, m), 1.39 (9 H, d, *J* 1.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 190.79, 163.23, 161.23, 144.47, 144.38, 136.28, 136.22, 127.98, 127.93, 125.84, 125.82, 116.22, 116.01, 34.94, 34.92, 29.61, 29.58; ν_{max}/cm^{-1} 3073, 3027, 2971, 2869, 2849, 2732, 1698, 1617 (Found: *m*/*z*, 180.0959. $C_{11}H_{13}OF$ requires M_r, 180.0950).

2-(*Trifluoromethyl*)-4-(1,1-*dimethylethyl*)*benzaldehyde*: obtained as a colorless liquid, 27%. ^1H NMR (300 MHz, $CDCl_3$) δ_H 10.33 [1 H, br s (q)], 8.05 (1 H, d, *J* 8.2 Hz), 7.75 (1 H, br s), 7.69 (1 H, d, *J* 8.2 Hz), 1.35 (9 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 188.82, 157.96, 131.20, 130.91, 129.16, 125.01, 123.12, 123.07, 123.03, 122.98, 122.83, 35.51, 30.88; ν_{max}/cm^{-1} 3053, 2977, 2875, 2849, 2798, 1693, 1617 (Found: *m*/*z*, 230.0898. $C_{12}H_{13}OF_3$ requires M_r, 230.0919).

2-*Fluoro*-4-(1,1-*dimethylethyl*)*benzonitrile*: obtained as a colorless liquid, 78%. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.54 (1 H, dd, *J* 6.9 and 8.2 Hz), 7.27 (1 H, dd, *J* 1.7 and 8.2 Hz), 7.21 (1 H, dd, *J* 1.7 and 11.1 Hz), 1.33 (9 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 164.23, 162.18, 160.31, 160.26, 132.95, 121.98, 121.96, 114.22, 113.65, 113.49, 98.32, 98.20, 35.55, 30.77; ν_{max}/cm^{-1} 3043, 2971, 2910, 2870, 2238, 1622 (Found: *m*/*z* 177.0952. $C_{11}H_{12}NF$ requires M_r, 177.0954).

3-*Fluoro*-4-(1,1-*dimethylethyl*)*benzonitrile*: obtained as a colorless liquid, 84%. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.29–7.37 (2 H, m), 7.19–7.24 (1 H, m), 1.32 (9 H, d, *J* 1.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 163.02, 159.68, 143.37, 143.21, 128.42, 128.33, 127.97, 127.92, 119.93, 119.56, 117.73, 111.21, 111.07, 34.91, 34.88, 29.49, 29.45; ν_{max}/cm^{-1} 3094, 2966, 2921, 2885, 2243, 1566 (Found: *m*/*z*, 177.0960. $C_{11}H_{12}NF$ requires M_r, 177.0954).

2-(*Trifluoromethyl*)-4-(1,1-*dimethylethyl*)*benzonitrile*: obtained as a colorless liquid, 86%. ^1H NMR (500 MHz, $CDCl_3$) δ_H 7.76–7.80 (2 H, m), 7.70 (1 H, dd, *J* 1.7 and 8.2 Hz), 1.38 (9 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 157.38, 134.56, 132.86, 132.61, 132.35, 132.10, 129.18, 123.82, 123.79, 123.75, 123.71, 123.69, 121.51, 119.33, 115.70, 107.02, 35.52, 30.70; ν_{max}/cm^{-1} 3043, 2971, 2905, 2880, 2243, 1617 (Found: *m*/*z*, 227.0921. $C_{12}H_{12}NF_3$ requires M_r 227.0922).

5-(*Trifluoromethyl*)-2-(1,1-*dimethylethyl*)*benzonitrile*: obtained as a colorless liquid, 91%. ^1H NMR (300 MHz, $CDCl_3$) δ_H 7.89 (1 H, dd, *J* 1.4 and 0.5 Hz), 7.71–7.75 (1 H, m), 7.62 (1 H, d, *J* 8.5 Hz), 1.52 (9 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ_C 157.63, 132.31, 132.26, 132.20, 132.15, 129.65, 129.31, 129.27, 129.22, 129.18, 128.75, 128.42, 128.30, 127.18, 124.81, 121.20, 118.84, 117.60, 111.67, 35.96, 29.86; ν_{max}/cm^{-1} 3040, 2974, 2882, 2238, 1620 (Found: *m*/*z*, 227.0909. $C_{12}H_{12}NF_3$ requires M_r, 227.0922).

4-(*Trifluoromethyl*)-2-(1,1-*dimethylethyl*)*benzonitrile*: obtained as a colorless liquid, 94%. ^1H NMR (300 MHz, $CDCl_3$) δ_H (1 H, d, *J* 8.0 Hz), 7.70 (1 H, s), 7.54 (1 H, m), 1.52 (9 H, s); ^{13}C NMR (125 MHz, $CDCl_3$) δ_C 154.97, 135.98, 134.75, 134.31, 133.88, 133.44, 128.68, 125.06, 123.34, 123.29, 123.24, 123.19, 123.12, 123.07, 123.02, 122.97, 121.44, 118.92, 117.83, 114.34, 35.89, 29.88; ν_{max}/cm^{-1} 3084, 2977, 2926, 2880, 2238, 1485 (Found: *m*/*z*, 227.0924. $C_{12}H_{12}NF_3$ requires M_r, 227.0922).

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