The Reaction of 4-Substituted Aryl Isocyanates with $NaBH_4$/Trifluoroacetic Acid (TFA)

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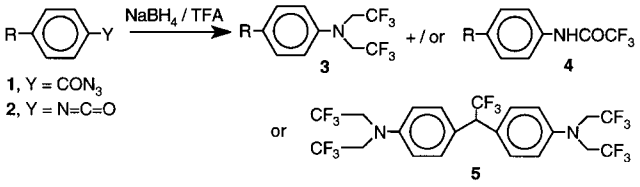
Abstract: Treatment of 4-substituted aryl isocyanates (*cf*. **2a–f**) with $NaBH_4$/TFA leads to the corresponding 4-substituted *N*,*N*-bis(2,2,2-trifluoroethyl)aniline derivatives (**3a–d**) in excellent yield except where an electron-withdrawing group is present (*cf*. **2e**) or the *para*-position is open (*cf*. **2f**).

Key words: isocyanates, rearrangement, reductive alkylation, trifluoroethylanilines, sodium borohydride

Acyloxyborohydrides, prepared by reaction of alkali borohydrides with carboxylic acids, have been of considerable utility in organic synthesis.[1] The combination of sodium borohydride and TFA in particular, inter alia, has been effective for the reduction of nitriles,[2] amides,[3–5] di- and triaryl methanols,[6] diaryl ketones[7] and activated monoaryl ketones.[8] Additionally, valuable *N*-trifluoroethylations of amines[5] and novel formation of 1,1,1-trifluoro-2,2-diarylethanes from the corresponding arenes[9] have been reported with this reagent. In line with the latter two findings, recently, we found that 4-substituted aroyl azides **1** react with $NaBH_4$ in TFA to form the corresponding 4-substituted *N*,*N*-bis(2,2,2-trifluoroethyl)aniline derivatives **3** or other products **4** or **5** depending on the nature of the substituent in the *para*-position.[10] While the mechanisms of these novel transformations are unclear, it seems likely that the initial step in all cases is an acid-induced Curtius rearrangement to an isocyanate.[11] Accordingly, to test the likelihood of an isocyanate intermediate, and to provide another potentially useful synthetic procedure, we subjected a series of aryl isocyanates (*viz*. **2a–f**) to reduction with $NaBH_4$ in TFA at room temperature (Scheme). The results mirrored those with the corresponding aroyl azides, lending support to the premise that isocyanates are intermediates therein, except that in most cases a 10–15% yield of the appropriate trifluoroacetylaniline derivative **4** also was isolated.[12] Thus, where the *para* substituent was electron donating (*viz*. **2c–d**) or weakly electron withdrawing (*viz*. **2a–b**) efficient transformation (71–82%) to the corresponding *N*,*N*-bis(2,2,2-trifluoroethyl)aniline derivatives **3a–d** was observed (Table). With a resonance withdrawing group on the aryl ring (*viz*. **2e**, R = NO_2) the major product (78%) was 4-nitro-*N*-trifluoroacetylaniline (**4**, R = NO_2). This result differed from that with 4-nitrobenzoyl azide (**1**, R = NO_2) where 4-nitroaniline was the major product (in addition to **4**) and, additionally, the reaction time (4 days) was considerably shorter than that for the aroyl azide (14 days). It is possible that, for the latter, the initial rearrangement to the isocyanate is very slow and, thus, over 14 days there is sufficient time for hydrolysis to 4-nitroaniline to occur both from the isocyanate and the trifluoroacetylaniline derivative **4**. Hydrolysis of the latter also would be slow and might occur to only a minor extent in the 4 day timescale of the present reaction. Like the corresponding aroyl azide, further reductive acylation occurred when the *para* position of the aryl isocyanate was open and phenyl isocyanate (**2f**) gave 2,2-bis({4-[*N*,*N*-bis(2,2,2-trifluoroethyl)anilino]})-1,1,1-trifluoroethane (**5**) in 73% yield.



Scheme

The identities of the products **3a–d**, **4**, **5** were ascertained from their satisfactory spectral (IR, ^1H and ^{13}C NMR) and microanalytical data and by comparison with an authentic sample (for **4**). The main feature of their IR spectra was the C–F stretch at *ca*. 1150 cm^{-1} and the presence of CF_3 groups was also apparent in their ^1H NMR spectra from the splitting of the adjacent methylene (in **3a–d**, **5**) or methine protons (in **5**) into quartets (J = 8–10 Hz). Further evidence for CF_3 incorporation was garnered from the ^{13}C NMR spectra wherein the methylene or methine carbon atoms adjacent to the CF_3 appeared as quartets (J = 33 and 27 Hz, respectively), as did the corresponding CF_3 carbons (J = 281 and 278 Hz, respectively).

From the results of this study it is very likely that, in the reaction of aroyl azides with $NaBH_4$/TFA, initial rearrangement to the isocyanate does take place and, overall, with the limitations described, we have developed a useful

Table Reactions of 4-Substituted Aryl Isocyanates **2** with $NaBH_4$/TFA

2	R	Product	Yield (%)[a]	mp (°C)	lit. mp (°C)
a	Br	**3a**	82	84–5	83.5–4.5[10]
b	Cl	**3b**	78	73–4	73–4[10]
c	Me	**3c**	71	72–3	72–3[10]
d	MeO	**3d**	80	oil	oil[10]
e	NO_2	**4**	78	149–50	147–9[14]
f	H	**5**	73	82–3	82–3[10]

[a] Yield of isolated pure product.

preparation of *N*,*N*-bis(trifluoroethyl)anilines **3** and related species. It should be noted that the current approach is favoured over that from aroyl azides in that the isocyanates are commercially available (the aroyl azides are not) and are safer to work with.[13]

Reactions of 4-Substituted Aryl Isocyanates 2 with $NaBH_4$ / TFA; General Procedure

To TFA (25 mL) was added $NaBH_4$ (3 pellets, each ~0.4g) with stirring. After complete dissolution, the aryl isocyanate (0.001 mol) was introduced and, after 24 h, an additional pellet (broken into 4 pieces) was added and the mixture was stirred for a further 72 h. After cooling to 0 °C the mixture was made basic (to pH 8–9) with aq NaOH (15%, w/v) and extracted with CH_2Cl_2 (4 × 100 mL). The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to yield a slightly impure product which was purified by column chromatography (silica gel, hexane/CH_2Cl_2(usually 80:20) as eluant).

4-Bromo-*N*,*N*-bis(2,2,2-trifluoroethyl)aniline (3a)

Colorless solid, yield; 0.276g (82%), mp 84–85 °C (CH_2Cl_2/hexane).

IR (KBr): ν = 2973, 2925 (alkyl CH), 1595, 1390, 1244, 1167, 1015, 805 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.99 (q, 4H, *J* = 8.5 Hz, CH_2CF_3), 6.78 (d, 2H, *J* = 9.0 Hz, H_{arom}), 7.36 (d, 2H, *J* = 9.0 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 52.09 (q, *J* = 33 Hz, CH_2CF_3), 112.86, 116.29, 125.01 (q, *J* = 281 Hz, CH_2CF_3), 132.20, 145.61.

$C_{10}H_8BrF_6N$: Calc. C 35.74, H 2.40, N 4.17; Found: C 35.74, H 2.49, N 3.91.

4-Chloro-*N*,*N*-bis(2,2,2-trifluoroethyl)aniline (3b)

Colorless solid, yield; 0.228g (78%), mp 73–74 °C (CH_2Cl_2/hexane).

IR (KBr): ν = 2925 (alkyl CH), 1601, 1387, 1264, 1167, 1109, 1015, 812 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.99 (q, 4H, *J* = 8.5 Hz, CH_2CF_3), 6.83 (d, 2H, *J* = 9.0 Hz, H_{arom}), 7.23 (d, 2H, *J* = 9.0 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 52.23 (q, *J* = 33 Hz, CH_2CF_3), 116.04, 124.98 (q, *J* = 281 Hz, CH_2CF_3), 125.72, 129.30, 145.21.

$C_{10}H_8ClF_6N$: Calc. C 41.19, H 2.77, N 4.80; Found: C 41.50, H 2.63, N 4.79.

4-Methyl-*N*,*N*-bis(2,2,2-trifluoroethyl)aniline (3c)

Colorless solid, yield; 0.193g (71%), mp 72–73 °C (CH_2Cl_2/hexane).

IR (KBr): ν = 2926 (alkyl CH), 1621, 1523, 1266, 1156, 1111, 1018, 808 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 2.70 (s, 3H, CH_3), 3.97 (q, 4H, *J* = 8.6 Hz, CH_2CF_3), 6.85 (d, 2H, *J* = 8.5 Hz, H_{arom}), 7.09 (d, 2H, *J* = 8.5 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 20.20, 52.45 (q, *J* = 33 Hz, CH_2CF_3), 115.32, 125.28 (q, *J* = 281 Hz, CH_2CF_3), 129.92, 130.16, 144.51.

$C_{11}H_{11}F_6N$: Calc. C 48.72, H 4.01, N 5.17; Found: C 48.67, H 4.09, N 5.23.

4-Methoxy-*N*,*N*-bis(2,2,2-trifluoroethyl)aniline (3d)

colorless oil, yield; 0.23g (80%).

IR (NaCl): ν = 2959, 2841 (alkyl CH), 1516, 1466, 1392, 1262, 1151, 1039, 822 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.76 (s, 3H, CH_3), 3.91 (q, 4H, *J* = 8.7 Hz, CH_2CF_3), 6.83 (d, 2H, *J* = 9.3 Hz, H_{arom}), 6.93 (d, 2H, *J* = 9.3 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 53.76 (q, *J* = 32 Hz, CH_2CF_3), 55.52, 114.72, 119.07, 125.25 (q, *J* = 281 Hz, CH_2CF_3), 141.16, 154.80.

$C_{11}H_{11}F_6NO$: Calc. C 46.00, H 3.86, N 4.88; Found: C 46.13, H 4.02, N 4.93.

2,2-(Bis(4-[*N*,*N*-bis(2,2,2-trifluoroethyl)anilino])-1,1,1-trifluoroethane (5)

Colorless solid, yield; 0.23g (73%), mp 82–83 °C (CH_2Cl_2/hexane).

IR (KBr): ν = 2968 (alkyl CH), 1617, 1524, 1399, 1265, 1152, 1116, 1020, 820 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.01 (q, 8H, *J* = 8.0 Hz, CH_2CF_3), 4.54 (q, 1H, *J* = 10.0 Hz, $CHCF_3$), 6.86 (d, 4H, *J* = 8.0 Hz, H_{arom}), 7.26 (d, 4H, *J* = 8.0 Hz, H_{arom}).

^{13}C NMR ($CDCl_3$): δ = 51.86 (q, *J* = 33 Hz, CH_2CF_3), 53.69 (q, *J* = 27 Hz, $CHCF_3$) 114.22, 125.17 (q, *J* = 281 Hz, CH_2CF_3), 126.33 (q, *J* = 278 Hz, $CHCF_3$), 127.24, 130.04, 146.11.

$C_{22}H_{17}F_{15}N_2$: Calc. C 44.46, H 2.88, N 4.71; Found: C 44.43, H 2.82, N 4.68.

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