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ON THE REACTION OF INDOLE WITH SODIUM BOROHYDRIDE IN TRIFLUOROACETIC ACID[1]

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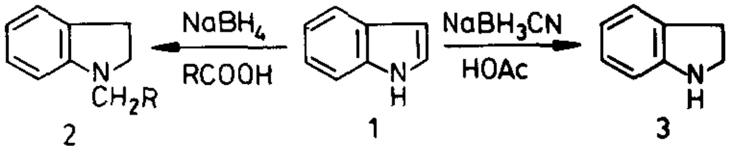
Abstract - The reaction of indole (1) with sodium borohydride in trifluoroacetic acid gives, successively, indoline (3), N-(2,2,2-trifluoroethyl)indoline (4), and 1,1,1-trifluoro-2,2-bis[5-(N-(2,2,2-trifluoroethyl)indolinyl)]ethane (5), whose structure is established by chemical and spectral means. Similar reactions are observed with N-methylaniline (8) and anisole, but not with dibenzazepines 13 and 15, which give only N-trifluoroethylation.

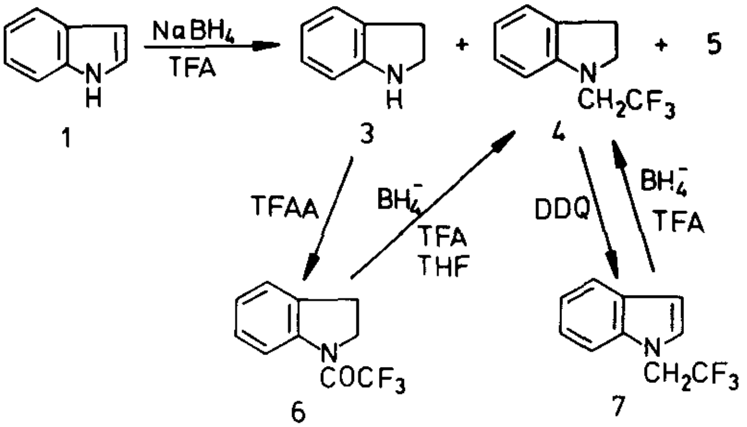
Several years ago we reported[2] that sodium borohydride ($NaBH_4$) in carboxylic acid media effects the reduction and alkylation of indoles to give N-alkylindolines, 1→2, but that sodium cyanoborohydride ($NaBH_3CN$) in acetic acid at room temperature brings about reduction of the indole double bond without N-alkylation, 1→3.[3,4]



In contrast to the other carboxylic acids that we studied,[2,5] the stronger acids formic and trifluoroacetic (TFA) gave somewhat erratic results with indole and lower yields of 2 and 3. In an earlier paper we described[6] the structure of the major product that forms in the reaction of 1 with $NaBH_4/HCO_2H$. We now report our studies on the reaction of 1 (and 3) with $NaBH_4$/TFA.

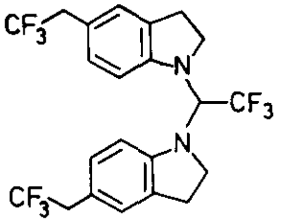
Treatment of a mixture of $NaBH_4$ pellets (Ventron) and TFA at 25°C with 1 followed by refluxing and the addition of more $NaBH_4$ gives, after 6 h and then workup, a crude product which can be separated into a basic and neutral fraction. Distillation of each fraction or flash chromatography (hexane: Et_2O) of the crude product *in toto* affords indoline (3) (bp 54°C/0.6 torr) (40% yield), identified by comparison with a commercial sample (ir, uv, tlc), and two neutral compounds 4 (5% yield) and 5 (13% yield) (Scheme I).

Scheme I

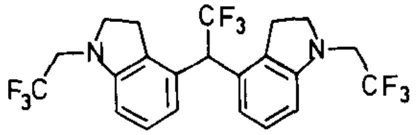


The reaction of indoline (3) with $NaBH_4$/TFA/60°C gives recovered 3 (51%), 4 (7%), and 5 (34%). The minor neutral product 4 is N-(2,2,2-trifluoroethyl)indoline[7] (bp 55°C /0.7 torr) as evidenced from its spectral and analytical data,[12] and further characterized by independent synthesis. Thus, treatment of 3 with trifluoroacetic anhydride (TFAA) (PhH, 0-5°C) gives N-trifluoroacetylindoline (6)[13] (96% yield). Reduction of 6 using Umino's procedure[14] for reducing amides affords 4 (58% yield) identical with that obtained from 1 (tlc, ir, ^1H nmr, ^{19}F nmr). Furthermore, 4 can be oxidized to N-(2,2,2-trifluoroethyl)indole (7)[15] with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (PhH, 25°C, 1 h) in 89% yield, and 7 can be reduced back to 4 with $NaBH_4$/TFA/25°C in 40% yield but not with $NaBH_4$/HOAc/reflux (3% yield) in accord with our observations[3] on weakly basic indoles under these conditions. Attempts to alkylate 3 with 2,2,2-trifluoroethyl iodide or p-toluenesulfonate under several conditions were unsuccessful.

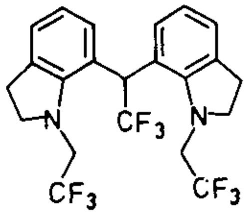
The molecular formula of the major neutral product 5 (mp 104.5-105.5°C) is $C_{22}H_{19}N_2F_9$ from mass spectrometry and combustion analysis.[16] The ir and uv spectra of 5 are very similar to those of 4. The ^{19}F nmr spectrum clearly indicates that 5 contains two equivalent $-CH_2CF_3$ groups (71.5 ppm, t, $^3J_{HF}$ = 9.8 Hz) and one $>CHCF_3$ group (66.8 ppm, d, $^3J_{HF}$ = 9.8 Hz). By comparison the N-CH_2CF_3 group in 4 resonates at 71.4 ppm (t, $^3J_{HF}$ = 9.8 Hz). These data suggest that 5 is comprised of two N-(2,2,2-trifluoroethyl)indolinyl groups bridged with a $>CHCF_3$ group. The symmetry of 5 is further revealed by the ^{13}C nmr spectrum which shows signals for only 12 carbons.[16] Since the ^1H nmr spectrum displays the ratio 6:1:12 for aryl: methine:methylene protons, 5 must be one of A-E.



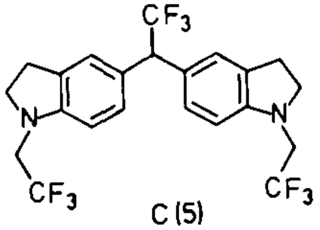
A



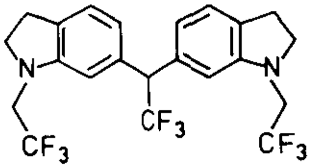
B



E

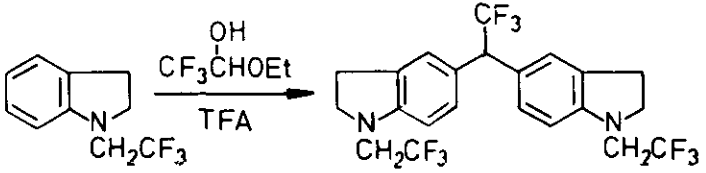


C (5)



D

The ^1H nmr spectrum (60 or 300 MHz) of 5 also reveals two high-field aromatic protons at 6.35 ppm as a sharp doublet (J = 8.4 Hz). Since the ortho and para protons in aromatic amines are invariably shielded[17] relative to benzene (7.3 ppm), structures B and D can be excluded from consideration because they would each have four such protons and, in fact, would exhibit more complex spliting due to meta coupling. The lack of additional ortho coupling involving these two protons eliminates structure E. Structure A is unlikely on a mechanistic basis (presumed to be an unstable aminal) and, in any event, can be rejected by our observation that 4 is converted to 5 upon treatment with $NaBH_4$/TFA/reflux (52% yield). Hence 5 must have structure C. This is reasonable mechanistically since para substitution in the Friedel-Crafts alkylation of arenes with aldehydes to give para, para'-diarylmethanes is well known (e.g., the synthesis of DDT from chlorobenzene, CCl_3CHO, and H_2SO_4).[18] Moreover, we believe[5] that trifluoroacetaldehyde or its synthetic equivalent is generated in the reaction between $NaBH_4$ and TFA. Indeed, 4 is transformed into 5 by treatment with commercially available trifluoroacetaldehyde ethyl hemiacetal in refluxing TFA (57% yield).



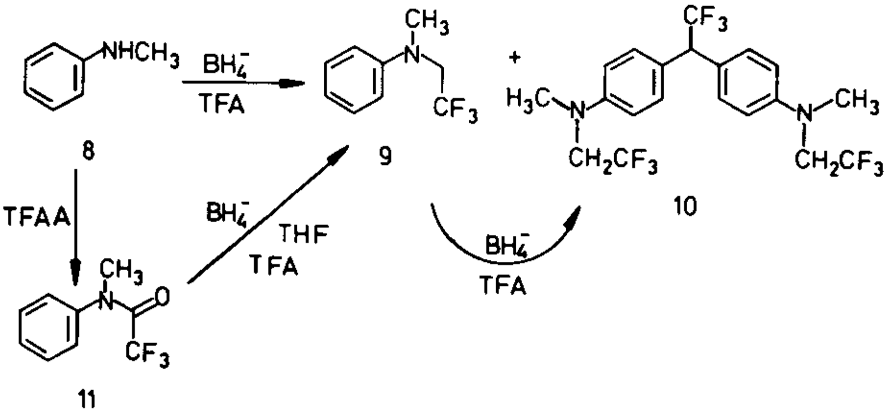
4

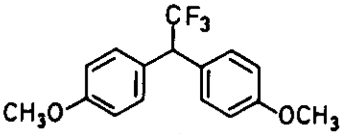
5 (C)

Since we find that 3 is converted first to 4 and then to 5 with NaBH$_4$/TFA, it seems clear that the reaction sequence is: 1→3→4→5. It is interesting to note that we observe no products resulting from the formation and subsequent reactions of "indole dimer"[19] and "trimer"[20] which form in acid including TFA.[21] This is presumably because 1 is reduced to 2 faster than dimerization of 1 can occur.

We next examined the reaction of several other substrates with NaBH$_4$/TFA. The reaction of N-methylaniline (8) with NaBH$_4$/TFA parallels that of 3, as shown in Scheme II, to give N-(2,2,2-trifluoroethyl)-N-methylaniline (9)[22] (2% yield) and 1,1,1-trifluoro-2,2-bis[4-(N-(2,2,2-trifluoroethyl)-N-methylanilino)]ethane (10)[23] (22% yield). The para substitution pattern in 10 is clearly evident from the ^{1}H and ^{13}C nmr spectra. Treatment of 9 with NaBH$_4$/TFA/reflux gives 10 (46% yield), and 9 can by synthesized from amide 11[24] (89% from 8) by reduction using Umino's procedure[14] (32% yield).

Scheme II



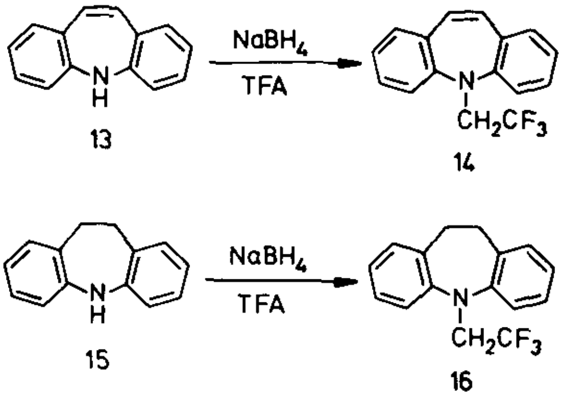


12

Anisole reacts with NaBH$_4$/TFA to give 1,1,1-trifluoro-2,2-bis(4-methoxyphenyl)ethane (12)[25] (47% yield), a known compound[26] with DDT-like insecticidal properties.[27]

An attempt to reduce the double bond in 5H-dibenz[b,f]azepine (13) using NaBH$_4$/TFA led only to N-(2,2,2-trifluoroethyl)-5H-dibenz-[b,f]azepine (14)[28] (61% yield) and not to N-(2,2,2-trifluoroethyl)-10,11-dihydro-5H-dibenz[b,f]azepine

(16)[29] which was prepared independently from 15 (44% yield). In both cases the yields are for recrystallized and analytically pure material.



ACKNOWLEDGMENTS

This investigation was supported in part by Merck Sharp and Dohme Research Laboratories, the Research Committee of Dartmouth College, and the Petroleum Research Fund, administered by the American Chemical Society. We also thank Dr. Catherine E. Costello (Massachusetts Institute of Technology) for the high resolution mass spectra (National Institutes of Health Research Grant FR00317 from the Division of Research Facilities and Resources) and Mr. Robert C. Wade of Ventron Corporation (Danvers, Mass.) for a supply of sodium borohydride.

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12. **4**: ^{1}H nmr ($CDCl_3$) δ 2.8 (m, 2H), 3.3 (m, 4H), 6.3-7.1 (m, 4H); ^{13}C nmr ($CDCl_3$) δ 28.6, 51.9 (q, $^2J_{CF}$ = 33.4 Hz), 54.6, 106.4, 118.6, 124.6, 125.2 (q, $^1J_{CF}$ = 279.9 Hz), 127.3, 128.9, 150.8; ^{19}F nmr ($CDCl_3$, rel to $CFCl_3$) δ 71.4 (t, $^3J_{HF}$ = 9.8 Hz); ir (neat) ν 2930, 2850, 1610, 1495, 1315, 1260, 1140, 1025 cm^{-1}; uv (EtOH) λ max 247, 257, 298 nm; mass spectrum, m/e (rel int) 201 (M^+, 33), 132 (100), 117 (29), 103 (6.5), 91 (14), 77 (16), 65 (30). Anal. calcd for $C_{10}H_{10}NF_3$: C, 59.70; H, 5.01; N, 6.96. Found: C, 59.92; H, 5.08; N, 6.87.

13. **6**: mp 65-66°C; ^{1}H nmr ($CDCl_3$) δ 3.2 (m, 2H), 4.3 (m, 2H), 7.2 (m, 3H), 8.2 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 28.3, 47.7, 116.0 (q, $^1J_{CF}$ = 287.5 Hz), 117.8, 124.7, 125.7, 127.7, 131.5, 141.5; ^{19}F nmr ($CDCl_3$, rel to $CFCl_3$) δ 73.1 (s); ir ($CHCl_3$) ν 2920, 1700, 1490, 1255, 1150 cm^{-1}; uv (EtOH) λ max 257, 268 sh, 282, 288 nm; mass spectrum, m/e (rel int) 215 (M^+, 89), 146 (52), 128 (66), 118 (88), 91 (100), 77 (17), 69 (23), 65 (34). Anal. calcd for $C_{10}H_8NOF_3$: C, 55.82; H, 3.75; N, 6.51. Found: C, 55.94; H, 3.76; N, 6.50.

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15. **7**: mp 46.5-47°C; ^{1}H nmr ($CDCl_3$) δ 4.5 (q, 2H, $^3J_{HF}$ = 9 Hz), 6.45 (d, 1H, J = 4 Hz), 6.9-7.2 (m, 4H), 7.55 (m, 1H); ^{13}C nmr ($CDCl_3$) δ 47.3 (q, $^2J_{CF}$ = 35.2 Hz), 103.6, 108.9, 120.3, 121.1, 122.4, 123.7 (q, $^1J_{CF}$ = 280.8 Hz), 128.1, 128.5, 136.5; ^{19}F nmr ($CDCl_3$, rel to $CFCl_3$) δ 71.9 (t, $^3J_{HF}$ = 9.8 Hz); ir ($CHCl_3$) ν 3060, 3000, 2950, 1465, 1270, 1230, 1210, 1165, 1140 cm^{-1}; uv (EtOH) λ max 263, 277, 281 sh, 289 nm; mass spectrum, m/e (rel int) 199 (M^+, 16), 130 (42), 103 (6), 85 (7), 77 (14), 40 (100). Anal. calcd for $C_{10}H_8NF_3$: C, 60.31, H, 4.05; N, 7.03. Found: C, 60.42; H, 4.13; N, 6.93.

16. **5**: ^{1}H nmr ($CDCl_3$) δ 2.9 (m, 4H), 3.4 (m, 8H), 4.4 (q, 1H, J = 10.2 Hz), 6.35 (d, 2H, J = 8.4 Hz), 7.0 (m, 4H); ^{13}C nmr ($CDCl_3$) δ 28.5, 51.7 (q, $^2J_{CF}$ = 33.5 Hz), 54.2 (q, $^2J_{CF}$ = 27.2 Hz), 54.7, 106.1, 125.1 (q, $^1J_{CF}$ = 280.0 Hz), 125.2, 126.2, 126.5 (q, $^1J_{CF}$ = 280.5 Hz), 128.2, 129.5, 150.4; ^{19}F nmr ($CDCl_3$, rel to $CFCl_3$) δ 66.8 (d, 3F, $^3J_{HF}$ = 9.8 Hz), 71.5 (t, 6F, $^3J_{HF}$ = 9.8 Hz);

ir ($CHCl_3$) ν 2940, 2860, 1625, 1510, 1275, 1160 cm^{-1}; uv (EtOH) λ max 262, 298 nm; mass spectrum, m/e (rel int) 482 (M^+, 11), 413 (48), 282 (7), 213 (4), 207 (11), 172 (100), 130 (40). Anal. calcd for $C_{22}H_{19}N_2F_9$: C, 54.78; H, 3.97; N, 5.81. Found: C, 54.72; H, 3.99; N, 5.81.

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22. 9: bp 54-55°C/0.4 torr; ^1H nmr ($CDCl_3$) δ 2.95 (s, 3H), 3.8 (q, 2H, J = 9 Hz), 6.35 (m, 3H), 7.25 (m, 2H); ^{13}C nmr ($CDCl_3$) δ 39.0, 54.2 (q, $^2J_{CF}$ = 32.6 Hz), 112.6, 118.1, 125.5 (q, $^1J_{CF}$ = 283.0 Hz), 129.1, 148.5; ^{19}F nmr ($CDCl_3$, rel to $CFCl_3$) δ 70.8 (t, $^3J_{HF}$ = 9.8 Hz); ir (neat) ν 2920, 1610, 1515, 1375, 1270, 1160, 1000 cm^{-1}; uv (EtOH) λ max 245, 290 nm; mass spectrum, m/e 189.0776 (M^+, calcd for $C_9H_{10}NF_3$ 189.0765), 138, 120 (100%), 105, 104, 77.
23. 10: mp 74.5-75.5°C; ^1H nmr ($CDCl_3$) δ 3.0 (s, 6H), 3.8 (q, 4H, J = 9 Hz), 4.5 (q, 1H, J = 9 Hz), 6.7 (m, 4H), 7.2 (m, 4H); ^{13}C nmr ($CDCl_3$) δ 39.0, 53.6 (q, $^2J_{CF}$ = 27.3 Hz), 54.1 (q, $^2J_{CF}$ = 32.7 Hz), 112.5, 125.2, 125.4 (q, $^1J_{CF}$ = 282.8 Hz), 126.4 (q, $^1J_{CF}$ = 280.3 Hz), 129.7, 147.9; ^{19}F nmr ($CDCl_3$, rel to $CFCl_3$) δ 66.9 (d, 3F, $^3J_{HF}$ = 9.8 Hz), 71.0 (t, 6H, $^3J_{HF}$ = 9.8 Hz); ir ($CHCl_3$) ν 2910, 1615, 1520, 1375, 1265, 1150 cm^{-1}; uv (EtOH) λ max 257, 292 nm; mass spectrum, m/e (rel int) 458 (M^+, 19), 389 (69), 305 (22), 277 (3), 270 (8), 221 (10), 194 (18), 160 (100), 118 (67). Anal. calcd for $C_{20}H_{19}N_2F_9$: C, 52.41; H, 4.18; N, 6.11. Found: C, 52.37; H, 4.22; N, 6.06.
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25. 12: ^1H nmr ($CDCl_3$) δ 3.65 (s, 6H), 4.5 (q, 1H, J = 10 Hz), 6.8 (m, 4H), 7.3 (m, 4H); ^{13}C nmr ($CDCl_3$) δ 53.8 (q, $^2J_{CF}$ = 27.4 Hz), 55.0, 113.9, 126.3 (q, $^1J_{CF}$ = 280.1 Hz), 127.6, 129.9, 159.0; ^{19}F nmr ($CDCl_3$, rel to $CFCl_3$) δ 66.9 (d, $^3J_{HF}$ = 9.8 Hz); ir (neat) ν 2950, 2850, 1620, 1520, 1270, 1255,

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28. 14: mp 69-70°C; ^{1}H nmr (CCl_4) δ 3.8 (q, 2H, J = 9 Hz), 6.8 (s, 2H), 7.2 (m, 8H); ^{19}F nmr (CCl_4, rel to $CFCl_3$) δ 71.6 (t, $^3J_{HF}$ = 8.6 Hz); ir (neat) ν 3060, 1600, 1570, 1475, 1270, 1140 cm^{-1}; uv (95% EtOH) λ max (ε) 253.5 (21,500), 286 nm (6,700). Anal. calcd for $C_{16}H_{12}NF_3$: C, 69.81; H, 4.39; N, 5.09. Found: C, 69.87; H, 4.58; N, 5.29.

29. 16: mp 60.5-62°C; ^{1}H nmr (CCl_4) δ 3.15 (s, 4H), 4.3 (q, 2H, J = 9 Hz), 7.0 (s, 8H); ^{19}F nmr (CCl_4, rel to $CFCl_3$) δ 70.4 (t, $^3J_{HF}$ = 8.6 Hz); ir (neat) 3060, 2950, 1590, 1490, 1445, 1280, 1240 cm^{-1}; uv (EtOH) λ max (ε) 248 nm (6,300). Anal. calcd for $C_{16}H_{14}NF_3$: C, 69.31; H, 5.09; N, 5.05. Found: C, 69.21; H, 4.97; N, 5.04.

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