Reactions of Sodium Borohydride in Acidic Media; XVI.[1] *N*-Methylation of Amines with Paraformaldehyde/Trifluoroacetic Acid

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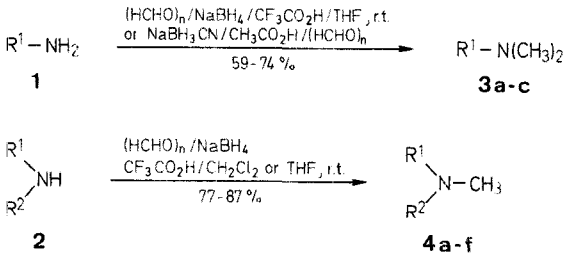
Primary and secondary amines are *N*-methylated to afford tertiary amines with the combination of paraformaldehyde, sodium borohydride, and trifluoroacetic acid.

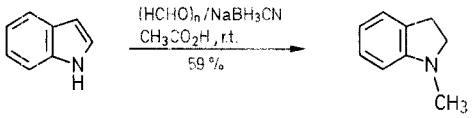
Several years ago we reported[2] the *N*-alkylation of amines using sodium borohydride in anhydrous carboxylic acid media. This novel reaction was extended by others[3] to the use of solid carboxylic acids, and the resulting amine alkylation methodology has since found wide application in synthesis.[4] However, the *N*-methylation of amines proved to be capricious and difficult to perform due to the exceptional vigor of the reaction of sodium borohydride with neat formic acid.[2,4] Moreover, the instability of anhydrous formic acid[5] has curtailed its utility in this *N*-methylation reaction.

We now report a new amine *N*-methylation procedure which obviates the need for formic acid, but which retains the overall convenience[2,3,4] and efficiency of this general alkylation method. Thus, treatment of a primary or secondary aliphatic or aromatic amine **(1, 2)** with paraformaldehyde, sodium borohydride, and trifluoroacetic acid, neat or in tetrahydrofuran, affords the corresponding *N*-methylated tertiary amine **(3, 4)** in good yield (Table). The rationale for using trifluoroacetic acid stems from our earlier observations[4] that *N*-trifluoroethylation is minimal under the usual alkylation conditions.



As summarized in the Table, several modes of addition of the reagents may be employed (Methods A,B,C), but the best way is to add trifluoroacetic acid slowly to a mixture of amine, sodium borohydride, and paraformaldehyde in tetrahydrofuran (Method A). Since the reductive amination of formaldehyde with secondary amines is invariably faster than the same reaction with primary amines,[6] it has not been possible to *N*-monomethylate primary amines under our conditions. Thus, methylation of benzylamine **(1a)** gives *N,N*-dimethylbenzylamine **(3a)** in 72% yield.

With primary aromatic amines **(1b, 1c)** we find that the use of paraformaldehyde/sodium cyanoborohydride/acetic acid (Method D) is more efficient than the other methods, which use sodium borohydride/trifluoroacetic acid. This may be due to a competing Baeyer condensation of the activated arene with trifluoroacetaldehyde.[1] We have shown earlier[7] that the combination sodium cyanoborohydride/acetic acid does not lead to *N*-ethylation at room temperature. These latter conditions with paraformaldehyde (Method D) also serve to convert indole **(5)** into 1-methyl-2,3-dihydroindole **(6)**. In this regard, we observed earlier[8] that **5** with sodium borohydride in formic acid gave **6** in only 16% yield, the major product being derived from "indole dimer".



5 **6**

In summary, we have described a simple method for the *N*-methylation of amines, via reductive amination, that features the use of solid paraformaldehyde as a convenient source of formaldehyde and avoids using the expensive and toxic sodium cyanoborohydride, which has been frequently used in reduction aminations.[9] Moreover, our methodology would appear to be an attractive alternative to other recent *N*-methylation procedures.[10]

N-Methyldibenzylamine (4c) (Method A):
To a stirred mixture of dibenzylamine (**2c**; 1.01 g, 5.13 mmol), paraformaldehyde (1.51 g, 50.3 mmol), and $NaBH_4$ (0.99 g, 26 mmol) in THF (50 mL) at 25°C under nitrogen is added dropwise over 1 h trifluoroacetic acid (25 mL). The resulting mixture is stirred at 25°C for 24 h, then poured into a mixture of 25% aqueous NaOH (75 mL) and ice chips to make strongly alkaline (pH 11), diluted with saturated NaCl solution (75 mL), and extracted with CH_2Cl_2 (3 × 75 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a pale yellow liquid (1.28 g). Vacuum distillation gives product **4c** as a colorless liquid; yield: 0.86 g (80%); b.p. 125°C/0.7 Torr (Lit.[18] b.p. 143°C/1 Torr).

^{1}H-NMR ($CDCl_3$): δ = 7.35 (s, 10 H); 3.55 (s, 4 H); 2.15 (s, 3 H).

Methiodide of **4c**; m.p. 189–191°C (Lit.[18] m.p. 193°C).

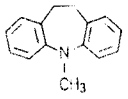
N-Methyldiphenylamine (4e) (Method B):
To trifluoroacetic acid (50 mL), stirred at 0–5°C under nitrogen, is added over 5 min $NaBH_4$ (10 pellets, 3 g, 80 mmol). The resulting mixture is allowed to warm to 25°C, charged with paraformaldehyde (1.8 g, 61 mmol), and then a solution of diphenylamine (**2e**; 1.04 g, 6.15 mmol) in CH_2Cl_2 (25 mL) is added dropwise over 5 min. The resulting mixture is stirred at 25°C for 30 min, then carefully poured into 25% aqueous NaOH (75 mL) and ice chips to make strongly alkaline (pH 11), diluted with saturated NaCl solution (75 mL), and extracted with CH_2Cl_2 (3 × 75 mL). The combined extracts are dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a red liquid (0.99 g). Vacuum distillation affords product **4e** as a colorless liquid; yield: 0.87 g (77%); b.p. 125–130°C/1.5 Torr (Lit.[21] b.p. 148–149°C/12 Torr).

^{1}H-NMR ($CDCl_3$): δ = 7.4–6.9 (m, 10 H); 3.4 (s, 3 H).

4-Methoxy-N,N-dimethylaniline (3c) (Method D):
To a stirred mixture of 4-methoxyaniline (**1c**; 1.02 g, 8.29 mmol) and paraformaldehyde (2.50 g, 83.3 mmol) in AcOH (50 mL) at 25°C under nitrogen, is added in one portion sodium cyanoborohydride (2.51 g, 40.2 mmol). The resulting mixture is stirred at 25°C for 18 h, then carefully poured into 25% aqueous NaOH (100 mL) and ice chips to make strongly alkaline (pH 11) and extracted with CH_2Cl_2 (3 × 75 mL). The combined extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to afford a dark purple solid (1.00 g). Flash chromatography (1:1 hexane/ether) gives product **3c** as a colorless solid; yield: 0.94 g (74%); m.p. 37–38°C (Lit.[15] m.p. 37–38.5°C).

^{1}H-NMR ($CDCl_3$): δ = 6.75 (s, 4 H); 3.7 (s, 3 H); 2.85 (s, 6 H).

Table. *N*-Methylated Tertiary Amines **(3, 4, 6)** from Amines **(1, 2, 5)**, Paraformaldehyde, Sodium Borohydride, and Trifluoroacetic Acid

Product[a]	R^1	R^2	Method[b]	Yield[c] (%)	m.p. (°C) or b.p. (°C)/Torr		m.p. (°C) of Methiodide[d]	
					found	reported	found	reported
3a	$CH_2C_6H_5$	–	A	72	185–190/760	178/766[11]	176–177	179[12]
3b	C_6H_5	–	D	59	200–205/760	194/760[13]	221–223	224[14]
3c	4-$CH_3OC_6H_4$	–	D	74	37–38	37–38.5[15]		–
4a	CH_3	C_6H_5	A	83	200–205/760	194/760[13]	221–223	224[14]
4b	CH_3	$-(CH_2)_2C_6H_5$	A	87	210–215/760	203–205/760[16]	225–227	227[17]
4c	$CH_2C_6H_5$	$CH_2C_6H_5$	A	80	125/0.7	143/1[18]	189–191	193[18]
4d	$CH_2C_6H_5$	C_6H_5	A	78	125–130/1.5	108–112/1–2[19]	152–153	156[20]
4e	C_6H_5	C_6H_5	B	77	125–130/1.5	148–149/12[21]	–	–
			C	53				
4f			D	82	105–106	107–108[22]	–	–
6			D	59	68–73/1	35–36/0.35[7]	191–193	195–196[23]

[a] All products exhibited ^{1}H-NMR spectra consistent with their assigned structures.
[b] Method A: Trifluoroacetic acid is added to a mixture of the amine, paraformaldehyde, and sodium borohydride in tetrahydrofuran.
Method B: Paraformaldehyde and then the amine are added to a mixture of sodium borohydride pellets in trifluoroacetic acid.
Method C: Sodium borohydride pellets are added to a mixture of the amine and paraformaldehyde in trifluoroacetic acid.
Method D: Sodium cyanoborohydride is added to a mixture of the amine and paraformaldehyde in acetic acid.
[c] Refers to purified material (distillation or flash chromatography).
[d] Prepared by allowing the amine to react with excess methyl iodide neat in a vial at room temperature or with brief heating. The solid methiodides were collected and recrystallized from methanol.

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