A Simple Synthetic Method for Tetraaza[3.3.3.3]meta- and paracyclopanes by Alkylation of *N*-Substituted Trifluoroacetamide[1]

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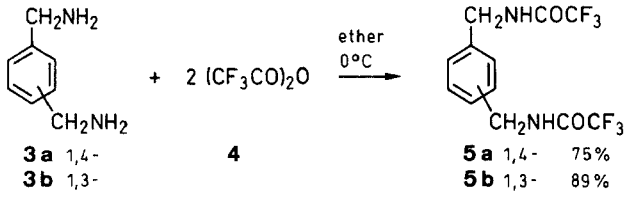
A simple and practical synthesis of the title compounds **1b** and **2b** is described. Alkylation of *N*-substituted trifluoroacetamides (**5a** and **b**) with appropriate dibromides (**6** and **9**) in the presence of sodium hydride in *N,N*-dimethylformamide at 100 °C, or powdered potassium hydroxide in refluxing acetone, followed by removal of the trifluoroacetyl group and *N*-methylation of the resultant amines provides the desired **1b** and **2b** in 21 and 19% overall yields, respectively, along with their lower and higher homologs.

In a continuing study aimed at developing simple methods for the synthesis of tetraaza[3.3.3.3]paracyclophanes[2-4] as artificial host molecules,[5] we found that the alkylation of *N*-substituted trifluoroacetamides (**5a** and **b**) with the corresponding bis(bromomethyl)benzenes (**6** and **9**), followed by removal of the trifluoroacetyl group and *N*-methylation of the resultant amines afforded tetraaza[3.3.3.3]para- and metacyclophanes (**1b** and **2b**) in reasonable yields.

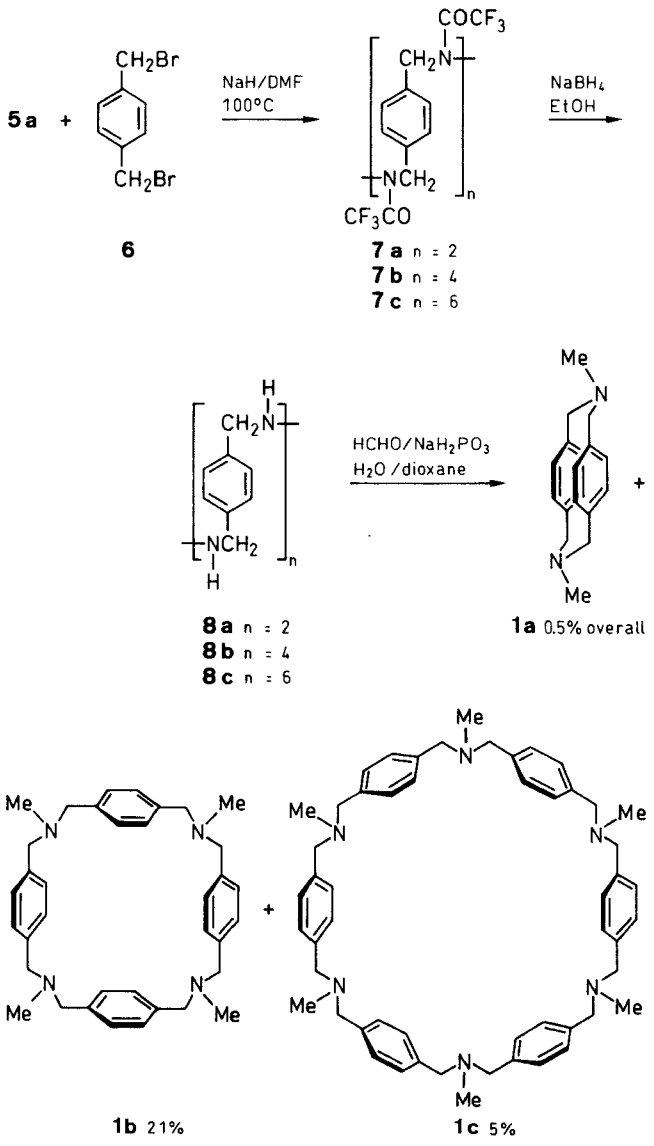
In our laboratory, two syntheses of tetraaza[3.3.3.3]paracyclophanes have been developed; the first method employed an amide formation reaction between an acid chloride and an amine in the critical coupling reaction, followed by reduction of the resultant cyclic amide.[2,3] The second approach utilized an *N*-alkylation reaction of *p*-toluenesulfonamide and subsequent removal of the tosyl groups.[4,6] There have been several reports on the synthesis of secondary amines by alkylation of *N*-trifluoroacetamides and subsequent removal of the trifluoroacetyl groups.[7-9] Usui et al. have reported the successful application of the method to the synthesis of 2,11-diaza[3.3]anthracenophanes.[10]



Scheme 1

N-Trifluoroacetylated amines **5a,b** were readily prepared from the commercially available bis(aminomethyl)benzenes **3a,b** by treatment with trifluoroacetic anhydride in diethyl ether (Scheme 1).[10a,11] 1,4-Bis(bromomethyl)-benzene **6** and 1,4-bis(trifluoroacetaminomethyl)benzene **5a** were coupled in the presence of sodium hydride in *N,N*-dimethylformamide at 100 °C to afford a mixture of cyclic amides **7a–c**. The trifluoroacetyl groups were readily removed with sodium borohydride in refluxing ethanol[12] to give a mixture of cyclic amines **8a–c**, which were *N*-methylated by a modified Leuckart–Wallach reaction[13] using a salt of phosphonic acid as a reducing agent[14] to afford a mixture of cyclic *N*-methylamines **1a–c**. Separation of the mixture was accomplished by gel filtration chromatography on Sephadex LH-20 with chloroform–methanol (3:1–2:1) to provide **1b** in 21% overall yield along with **1c** (5%) and **1a** (0.5%) as shown in Scheme 2.

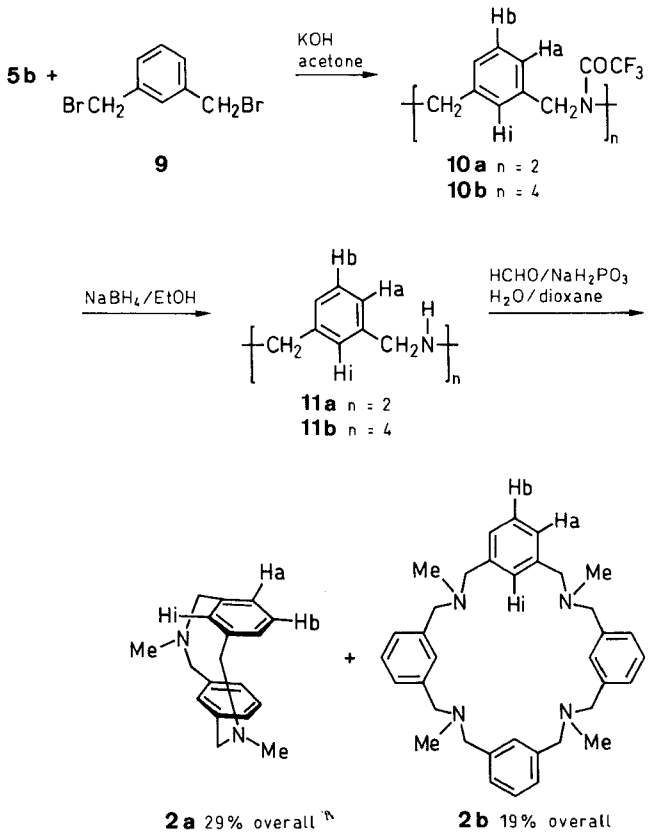
This method has been successfully applied to the synthesis of azametacyclophane **2b**. In the coupling reaction, the use of potassium hydroxide–acetone[15] in place of sodium hydride–N,N-dimethylformamide resulted in better yields of the cyclic product **10a,b**. 1,3-Bis(bromomethyl)benzene **9** was coupled with the amide **5b** in the presence of powdered potassium hydroxide in refluxing acetone to afford a mixture of cyclic amides **10a,b**.



Scheme 2

A similar deprotection and *N*-methylation provided a mixture of *N*-methylamines **2a,b**. The crude product was triturated with acetone and the resultant crystals were isolated by filtration to afford essentially pure **2b** in 19% overall yield. Separation of the filtrate by gel filtration chromatography on Sephadex LH-20 with chloroform–methanol (4:1) afforded **2a** in 29% yield (Scheme 3). In general, the major product of the present coupling reaction is [3⁴]cyclophane in paracyclophane, whereas it is [3²]homolog in metacyclophane.

Separation of a mixture of the *N*-trifluoroacetylated amines (**7a–c** or **10a,b**), precursors of free amines (**8a–c** or **11a,b**), can be carried out by silica gel column chromatography with dichloromethane. Compound **7a** and **10a** are readily separated from their higher oligomers. However, for the isolation of **7b** and **10b**, a combination of silica gel chromatography and recrystallization is essential. Separation of a mixture of the free amines (**8a–c** or **11a,b**) is effected by gel filtration chromatography with chloroform–methanol or silica gel chromatography with chloroform–methanol–28% aqueous ammonia (100:10:1).[16] However, deprotection of the isolated *N*-trifluoroacetylated amines is preferred as a preparation method of the free amines.



Scheme 3

In conclusion, the present method offers a facile and practical synthesis of tetraaza[3⁴]meta- and paracyclophanes, **1b** and **2b** in gram quantities in a single experiment, considerably reduces the reaction time as compared with conventional methods,[2–4] and also has the great advantage that the trifluoroacetyl groups are readily removed after the coupling reaction.

Further application of this method to the synthesis of functionalized tetraaza[3⁴]cyclophanes and other novel azamacrocycles, as well as conformational analysis of diaza[3²]- and tetraaza[3⁴]cyclophanes are now in progress.

Melting points were measured on a Yanako MP-S3 melting point apparatus and are uncorrected. ^{1}H NMR spectra were measured on JEOL JNM-EX 270 and JNM-GSX 400 spectrometers with TMS as an internal standard. DMF was dried over molecular sieves 4A. Acetone was dried over $CaSO_4$ and decanted before use. R_f values were determined with Merck 60 F-254 precoated silica gel on alumina sheets using CH_2Cl_2/MeOH/NH_4OH (100:10:1) solvent system except where noted.[16] Compounds **2b**, **5a,b**, **7a,b**, **10a,b** and **11b** gave satisfactory microanalyses: C,H,N ± 0.3%.

1,4-Bis(trifluoroacetaminomethyl)benzene **5a** and its 1,3-isomer **5b** were prepared by treatment of 1,4- or 1,3-bis(bromomethyl)benzene **3a** and **b** with $(CF_3CO)_2O$ in dry Et_2O in 75 and 89% yields, respectively.[10a,11]

5a: colorless needles from $CHCl_3$–acetone, mp 190–192°C (Lit.[10a] 205–206°C).

MS (70 eV): m/z = 328 (M^+).

IR (KBr): ν = 3282 (N–H), 1698 (C=O), 1183 (C–F) cm^{-1}.

^{1}H NMR ($CDCl_3$/DMSO-d_6): δ = 4.37 (d, 4H, J = 5.4 Hz, benzylic), 7.24 (s, 4H, aromatic), 9.93 (t, 2H, J = 5.4 Hz, –CONH–).

5b: colorless needles from acetone–toluene, mp 165.5–167°C.

MS (70 eV): m/z = 328 (M^+).

IR (KBr): ν = 3294 (N–H), 1702 (C=O), 1176 (C–F) cm^{-1}.

^{1}H NMR ($CDCl_3$/acetone-d_6): δ = 4.51 (s, 4H, benzylic), 7.26 (m, 4H, aromatic), 8.7–9.3 (m, 2H, –CONH–).

***N,N',N'',N'''*-Tetramethyl-2,11,20.29-tetraaza[3.3.3.3]paracyclophane (1b):**

To a stirred mixture of amide **5a** (6.57 g, 20.0 mmol) and DMF (200 mL) was added a 60% dispersion of NaH in mineral oil (1.61 g, 40 mmol) at room temperature under N_2. The mixture was stirred for 30 min at r.t. and then heated at 100°C for 30 min. To the mixture was added dropwise a DMF solution (250 mL) of the bromide **6** (5.31 g, 20.0 mmol) over a period of 1 h, then the mixture was stirred overnight at 100°C under N_2. After removal of the solvent in vacuo, the residue was diluted with water (250 mL) and extracted with CH_2Cl_2 (450 mL). The combined CH_2Cl_2 extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated.

To residue **7** (9.75 g) were added $NaBH_4$ (10.5 g, 266 mmol) and EtOH (200 mL), and the mixture was refluxed for 3 h. After being cooled, the solvent was removed. The residue was diluted with water, acidified to pH 1 with concentrated HCl, and the acidic solution was washed with CH_2Cl_2 (250 mL). The aqueous layer was made alkaline (pH 11) with dil. aq NaOH and extracted with CH_2Cl_2 (150 mL, × 3). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated.

The resultant pale yellow oil **8** (5.60 g), 37% formalin (20 mL), 1 M aq NaH_2PO_3 (200 mL), and dioxane (200 mL) were stirred at 60°C overnight. After being cooled, the precipitate **(A)** was collected by filtration and the filtrate was washed with CH_2Cl_2 (100 mL × 2). The aqueous layer was made alkaline (pH 11) with dil. aq NaOH to give a suspension. The precipitate **(A)** was dissolved in dilute HCl solution, filtered, and the filtrate was made alkaline (pH 11) with dil. aq NaOH to afford a white suspension. The combined suspensions were extracted with CH_2Cl_2 (150 mL × 3) and the combined CH_2Cl_2 extracts were dried over $MgSO_4$, filtered, and evaporated. The resultant pale yellow oil **1** (4.93 g) was triturated with MeCN (160 mL) and sonicated. The precipitate was collected by filtration (**B**, 3.39 g, mainly **1b** and **c**). Concentration of the filtrate afforded a pale yellow oil (**C**, 760 mg). Separation of **B** by gel filtration chromatography on Sephadex LH-20 with $CHCl_3$/MeOH, 3:1–2:1) provided **1b** (1.11 g, 21%) and **1c** (282 mg, 5%),[17] while **C** was separated by preparative TLC (silica gel, CH_2Cl_2/MeOH/NH_4OH, 100:10:1) to give **1a** (25 mg, 0.5%).

7a: colorless plates from CH_2Cl_2–hexane, mp 211–213 °C. R_f (silica gel; CH_2Cl_2/AcOEt, 40:1) = 0.78.

FAB-MS (mNBA): m/z = 430 (M^+).

IR (KBr): ν = 1682 (C=O), 1181 (C–F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.68 (br s, 4 H benzylic), 4.77 (br s, 4 H, benzylic), 6.78 (s, aromatic), 6.78 (d, J = 8.1 Hz, aromatic), 6.83 (s, aromatic), 6.83 (d, J = 8.1 Hz, aromatic).[18]

7b: colorless needles from CH_2Cl_2–hexane, mp 238–239 °C. R_f (silica gel, CH_2Cl_2/AcOEt, 40:1) = 0.65.

FAB-MS (mNBA): m/z = 861 (M^+ + 1).

IR (KBr): ν = 1683 (C=O), 1198 (C–F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.1–4.6 (m, 16 H, benzylic), 6.8–7.1 (m, 16 H, aromatic).

8a: colorless crystals from benzene–hexane, mp 219–221 °C (decomp. Lit.[4] 227.2–234 °C).

MS (70 eV, %): m/z = 237 (M^+ – 1, 17%), 238 (M^+, 79%), 239 (M^+ + 1, 15%).

IR (KBr): ν = 3277 (N–H) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.77 (s, 2 H, NH), 3.90 (br s, 8 H, benzylic), 6.80 (s, 8 H, aromatic).

8b: colorless needles from C_6H_6–hexane, mp 143–146 °C.

MS (70 eV, %): m/z = 476 (M^+, 12%), 477 (M^+ + 1, 9%), 478 (M^+ + 2, 15%), 479 (M^+ + 3, 5%).

IR (KBr): ν = 3231 (N–H) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.63 (s, 4 H, Nh), 3.70 (s, 16 H, benzylic), 7.07 (s, 16 H, aromatic). [Lit.[4] 1.63 (NH), 3.70 (benzylic), 7.07 (aromatic)].

1a: colorless plates from MeOH, mp 144–146 °C (Lit.[4] mp 140–143 °C).

R_f = 0.51.

MS (70 eV, %): m/z = 265 (M^+ – 1, 28%), 266 (M^+, 100%), 267 (M^+ + 1, 40%), 268 (M^+ + 2, 6%).

^1H NMR ($CDCl_3$): ν = 2.61 (s, 6 H, –Me), 3.55 (br s, 8 H, benzylic), 6.83 (br s, 8 H, aromatic).

1b: colorless needles from EtOH, mp 195–196.5 °C (Lit.[4] mp 195.5–197 °C).

R_f = 0.43.

MS (70 eV, %): m/z = 532 (M^+, 2%), 533 (M^+ + 1, 22%), 534 (M^+ + 2, 13%).

^{1}NMR (CD_2Cl_2): δ = 2.29 (s, 12 H, –Me), 3.29 (s, 16 H, benzylic), 7.25 (s, 16 H, aromatic).

1c: colorless needles from MeOH, mp 194–196 °C. R_f = 0.35.

FAB-MS (mNBA): m/z = 798 (M^+).

^1H NMR ($CDCl_3$): δ = 2.17 (s, 18 H, –Me), 3.45 (s, 24 H, benzylic), 7.30 (s, 24 H, aromatic). [Lit.[5a] 2.17 (–Me), 3.47 (benzylic), 7.27 (aromatic)].

N,N′,N″,N‴-Tetramethyl-2,11,20,29-tetraaza[3.3.3.3]metacyclophane (2b):

To a refluxing mixture of bromide **9** (5.28 g, 20.0 mmol), amide **5b** (6.57 g, 20.0 mmol), and acetone (450 mL) was added powdered KOH in four portions (1 g × 4) at 15 min intervals. Then the mixture was stirred for an additional 2 h at reflux. The acetone was removed and the residue was extracted with CH_2Cl_2 (700 mL). The combined CH_2Cl_2 solution was washed with brine and evaporated. To residue **10** were added $NaBH_4$ (10 g) and EtOH (350 mL), and the mixture was refluxed for 2 h with stirring. The solvent was evaporated and the residue was diluted with water, acidified (pH 1) with conc. HCl and washed with CH_2Cl_2 (100 mL × 2) to remove condensation products derived from acetone. The aqueous layer was made alkaline (pH 11) and extracted with CH_2Cl_2 (150 mL × 3). The combined extracts were washed with brine and concentrated to dryness. The resultant yellow oil **11**, 1 molar aq NaH_2PO_3 (600 mL), 37% formalin (20 mL), and dioxane (280 mL) were stirred at 60 °C overnight. The mixture was made alkaline (pH 11) and extracted with CH_2Cl_2 (total 1 L). The combined extracts were washed with brine, dried over $MgSO_4$, filtered, and evaporated to afford a colorless viscous oil, which was triturated with acetone (25 mL) and the precipitate was collected by filtration, washed with a small amount of acetone, and air-dried to give **2b** (1.03 g, 19%). Concentration of the filtrate and the separation of the residue by gel filtration chromatography on Sephadex LH-20 with $CHCl_3$/MeOH (4:1) afforded Me_2N_2[3²]MCP **2a** (1.54 g, 29%).

10a: colorless crystals from CH_2Cl_2–hexane; mp 116–118 °C. R_f (silica gel, CH_2Cl_2) = 0.48.

MS (70 eV): m/z = 430 (M^+).

IR (KBr): ν = 1690 (C=O), 1201 (C–F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.62, 4.65 (s, 8 H, benzylic), 6.13, 6.50, 6.59 (s, 2 H, aromatic Hi), 6.9–7.2 (m, 6 H, aromatic Ha and Hb).

10b: colorless crystals from CH_2Cl_2–hexane; mp 245–246 °C. R_f (silica gel, CH_2Cl_2) = 0.20.

MS (70 eV): m/z = 860 (M^+).

IR (KBr): ν = 1673, 1693 (C=O), 1200 (C–F) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 4.35–4.55 (m, 16 H, benzylic), 6.74, 6.77, 6.84, 6.90 (s, 4 H, aromatic Hi), 7.10–7.50 (m, 12 H, aromatic Ha and Hb).

11a: colorless granules from C_6H_6–hexane; mp 120–121.5 °C (Lit.[4] 117.5–118.5 °C).

MS (70 eV, %): m/z = 238 (M^+, 64%), 239 (M^+ + 1, 37%), 240 (M^+ + 2, 6%).

IR (KBr): ν = 3263 (N–H) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.99 (s, 2 H, NH), 3.91 (s, 8 H, benzylic), 6.68 (d, 4 H, J = 7.6 Hz, aromatic Ha), 6.82 (t, 2 H, J = 7.6 Hz, aromatic Hb), 7.37 (s, 2 H, aromatic Hi).

11b: colorless plates from C_6H_6; mp 151–153 °C.

MS (70 eV, %): m/z = 476 (M^+, 11%), 477 (M^+ + 1, 34%), 478 (M^+ + 2, 12%).

IR (KBr): ν = 3261 (N–H) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 1.64 (s, 4 H, –NH), 3.81 (s, 16 H, benzylic), 7.06–7.24 (m, 16 H, aromatic).

2a: colorless crystals from CH_2Cl_2–hexane; mp 98–100 °C (Lit.[4] 98.5–99.5 °C).

MS (70 eV, %): m/z = 265 (M^+ – 1, 13%), 266 (M^+, 72%), 267 (M^+ + 1, 16%).

^1H NMR ($CDCl_3$): δ = 2.66 (s, 6 H, Me), 3.61 (s, 8 H, benzylic), 6.64 (d, 4 H, J = 6.9 Hz, aromatic Ha), 6.72 (t, 2 H, J = 6.3 Hz, aromatic Hb), 7.42 (br s, 2 H, aromatic Hi).

2b: colorless plates from CH_2Cl_2; mp 200–202 °C.

MS (70 eV, %): m/z = 531 (M^+ – 1, 7%), 532 (M^+, 9%), 533 (M^+ + 1, 24%).

^1H NMR ($CDCl_3$): δ = 2.21 (s, 12 H, –Me), 3.48 (s, 16 H, benzylic), 7.15–7.23 (m, 12 H, aromatic Ha and Hb), 7.40 (s, 4 H, aromatic Hi).

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(17) The separation was repeated three times; about 1 g of the sample per 200 g of dry Sephadex LH-20 was charged.
(18) *N*-Trifluoroacetylated cyclophanes **7a,b** and **10a,b** show very complex ^{1}H NMR spectra due to the restricted rotation of the amide bonds. Conformational analysis of these compounds will be reported elsewhere.