The structure was solved by direct methods using SHELX-76.[16] Hydrogen atoms were included at calculated sites (C–H, 0.97 Å). Full-matrix least-squares refinement of an overall scale factor, positional and thermal (anisotropic non-hydrogen, isotropic hydrogen) parameters converged (all shifts $< 0.02\sigma$ with R^* 0.033, R_w 0.039 and $w = 1.11/(\sigma^2(F_o) + 0.00037F_o^2)$. Maximum excursions in a final difference map were +0.20 e Å^{-3} and −0.20 e Å^{-3}. Scattering factors and anomalous dispersion terms used were those supplied in SHELX-76.[16] All calculations were carried out by using SHELX-76, and plots were drawn using ORTEP.[17]

Registry No. 1, 114563-22-3; 2, 114550-77-5; 3, 824-79-3; 4, 114550-78-6; 5, 114550-79-7; 6a, 114550-80-0; 6b, 114550-81-1; 7, 114550-82-2; 8, 114550-83-3; 9a, 114550-84-4; 9b, 114550-85-5; 10, 114550-86-6; 11, 114550-87-7; 14, 114550-88-8; 15, 114550-89-9; *p*-toluenesulfinyl chloride, 10439-23-3; acetic formic anhydride, 2258-42-6.

Supplementary Material Available: X-ray crystallographic data for compound **9a** including positional parameters, anisotropic thermal parameters, and complete listings of bond distances and angles (5 pages). Ordering information is given on any current masthead page.

(16) Sheldrick, G. M. "SHELX-76, A Program for X-ray Crystal Structure Determination", University of Cambridge, 1976.
(17) Johnson, C. K. "ORTEP, A Thermal Ellipsoid Plotting Program", Oak Ridge National Laboratories, Oak Ridge, 1965.

Reagents for the Stepwise Functionalization of Spermine

R. J. Bergeron* and J. S. McManis

Department of Medicinal Chemistry, J. Hillis Miller Health Center, University of Florida, Gainesville, Florida 32610

Received December 15, 1987

Introduction

In recent years, there has been growing interest in the polyamines putrescine, spermidine, and spermine. These amines are widespread in nature and are implicated in the control of proliferative processes.[1-3] This latter role is largely responsible for the recent surge in the synthesis of polyamine derived compounds. We have, in recent years, synthesized a number of polyamine analogues which have demonstrated potent antineoplastic activity[4] and have proven useful in studies both of the polyamine cellular uptake apparatus[5] and polyamine metabolism.[6] Although not as widely distributed in nature as putrescine and spermidine, the tetraamine spermine forms the backbone of many alkaloids.[7] Further, there is much interest currently in the biological activity of synthetic analogues[8] of spermine, as spermine analogues have proven to be the most potent antineoplastics of all the polyamine derivatives.[4]

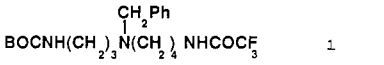
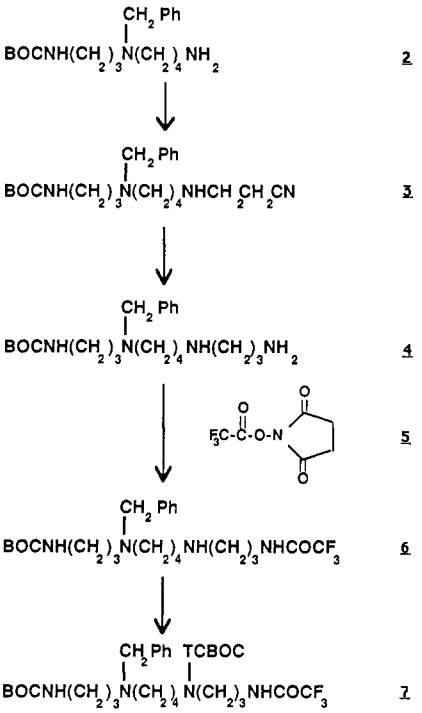


Figure 1.

Scheme I. Synthesis of Tetraprotected Spermine[a]



[a] BOC = $CO_2C(CH_3)_3$; TCBOC = $CO_2C(CH_3)_2CCl_3$.

Although several partially functionalized spermidine reagents have been developed,[9,10] only two such spermine reagents have been prepared.[11,12] Specifically, spermine has been selectively modified as the bis(hexahydropyrimidine) using formaldehyde[11] and as its N^1,N^{12}-bis(phthalimide) derivative.[12] However, these reagents do not allow differentiation between the two primary or two secondary nitrogens.

In a previous paper, we reported the synthesis of a triprotected spermidine reagent **1** (Figure 1), containing three independently removable, or orthogonal,[13] *N*-protecting groups.[10] This same reagent was utilized in the production of a spermine reagent with four independent amine-protecting groups. These protecting groups include benzyl, *tert*-butoxycarbonyl (BOC), trifluoroacetyl, and the

(1) For recent reviews, see: (a) Tabor, C. W.; Tabor, H. *Annu. Rev. Biochem.* **1976**, *45*, 285–306. (b) Janne, J.; Poso, H.; Raina, A. *Biochem. Biophys. Acta* **1978**, *473*, 241–293. (c) Pegg, A. E.; McCann, P. P. *Am. J. Physiol.* **1982**, *243*, C212–C221. (d) Bachrach, U.; Kaye, A.; Chayen, R., Eds. *Advances in Polyamine Research*; Raven: New York, 1983; Vol. 4.
(2) Heby, O. *Differentiation (Berlin)* **1981**, *19*, 1–20.
(3) Pohjanpelto, P.; Virtanen, I.; Holtta, E. *Nature (London)* **1981**, *293*, 475–477.
(4) Bergeron, R. J.; Neims, A. J.; McManis, J. S.; Hawthorne, T. R.; Vinson, J. R. T.; Bortell, R.; Ingeno, M. J. *J. Med. Chem.*, in press.
(5) Porter, C. W.; Bergeron, R. J.; Stolowich, N. J. *Cancer Res.* **1982**, *42*, 4072–4078.
(6) Porter, C. W.; Miller, J.; Bergeron, R. J. *Cancer Res.* **1984**, *44*, 126–128.
(7) (a) Seifert, K.; Johne, S.; Hesse, M. *Helv. Chim. Acta* **1982**, *65*, 2540–2547. (b) Guggisberg, A.; Preno, R.; Hesse, M. *Helv. Chim. Acta* **1986**, *69*, 1012–1016. (c) Pais, M.; Sarfati, R.; Jarreau, F.-X., Goutarel, R. *Tetrahedron*, **1973**, *29*, 1001–1010.
(8) (a) Yanagawa, H.; Ogawa, Y.; Egami, F. *Z. Allg. Mikrobiol.* **1976**, *16*, 627–632. (b) Binnig, F.; Hoerhammer, W. Ger. Offen. 2557657, 1977; *Chem. Abstr.* **1977**, *87*, 133866e. (c) Tsushima, S.; Otsu, K. Jpn. Kokai Tokkyo Koho JP 61 17542 [86 17542], 1986; *Chem. Abstr.* **1986**, *105*, 60482e.
(9) (a) Humora, M.; Quick, J. *J. Org. Chem.* **1979**, *44*, 1166–1168. (b) Eugster, C. H.; Walchli-Schaer, E. *Helv. Chim. Acta.* **1978**, *61*, 928–935. (c) Ganem, B.; McManis, J. S. *J. Org. Chem.* **1980**, *45*, 2041–2042. (d) Bergeron, R. J.; Burton, P. S.; McGovern, K. A.; Kline, S. J. *Synthesis* **1981**, 732–733.
(10) Bergeron, R. J.; Garlich, J. R.; Stolowich, N. J. *J. Org. Chem.* **1984**, *49*, 2997–3001.
(11) Chantrapromma, K.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 23–24.
(12) Sosnovsky, G.; Lukszo, J. *Z. Naturforsch., B: Anorg. Chem., Org. Chem.* **1986**, *41B*, 122–129.
(13) Barany, G.; Merrifield, R. B. *J. Am. Chem. Soc.* **1977**, *99*, 7363–7365.

0022-3263/88/1953-3108$01.50/0

new group 2,2,2-trichloro-*tert*-butoxycarbonyl (TCBOC). Our flexible spermine reagent is accessible in four facile steps from N^1-(*tert*-butoxycarbonyl)-N^4-benzylspermidine (**2**), a precursor to a triprotected polyamine **1**, which is easily accessible from commercially available starting materials such as acrylonitrile and benzylamine.

Results and Discussion

We determined that removal of the benzyl, *tert*-butoxycarbonyl, and trifluoroacetyl protecting groups of the spermidine reagent **1**, the precursor to the spermine reagent, required mild hydrogenolysis, brief exposure to trifluoroacetic acid, and treatment with potassium carbonate in refluxing methanol, respectively.[10] These conditions eliminated a large number of amine-protecting groups as candidates for the fourth independent group of spermine.

Fortunately, the 2,2,2-trichloro-*tert*-butoxycarbonyl group (TCBOC) group[14] provides a satisfactory solution to this dilemma. It is cleaved by mild metal reduction employing zinc dust in dilute acid, producing free amine, 1,1-dichloro-2-methylpropene, and carbon dioxide. This protecting group is reported to be stable to acid and base.

The preparation of the spermine reagent **7** begins with spermidine reagent precursor **2**, in which N^8 is free (Scheme I). Acrylonitrile (0.84 equiv) is added to **2** in methanol and stirred for 1 day to afford mononitrile **3** in quantitative yield. The cyano group in **3** is selectively reduced to the primary amine by employing conditions developed in this group (hydrogen, Raney nickel, ethanolic sodium hydroxide)[15] to give N^1-(*tert*-butoxycarbonyl)-N^4-benzylspermine (**4**) in 75% yield. The primary amine is next trifluoroacetylated in the presence of the secondary amino group of **4**. The most widely used reagent, trifluoroacetic anhydride (TFAA), is quite reactive and does not discriminate between primary and secondary amino groups.[16] Thus we turned our attention to the active ester *N*-(trifluoroacetoxy)succinimide (**5**), in hopes of acylating the less hindered primary amine. Acylating agent **5**, easily prepared from *N*-hydroxysuccinimide and trifluoroacetic anhydride, has been used to prepare *N*-hydroxysuccinimide esters of α-N-protected amino acids.[17] However, no instance of direct N-acylation with compound **5** has been reported. Thus, when a benzene solution of reagent **5** (0.93 equiv) was slowly added to diamine **4** in methylene chloride at 0 °C and stirred at room temperature, triprotected spermine **6**, cleanly trifluoroacetylated at the primary site, was obtained in 82% yield. Trifunctionalized spermine **6**, a versatile protected polyamine in its own right, was generated in three steps from diprotected spermidine **2**.

We next determined whether the selective monoacylation of diamine **4** with active agent **5** was a general reaction. Competition experiments in which a limited amount of reagent **5** was added to pairs of amines showed that it was in fact a highly sterically selective acylating agent. Addition of a solution of **5** to an equimolar mixture of benzylamine and *N*-benzylmethylamine led to greater than 95% primary acylation to give *N*-benzyltrifluoroacetamide in 70% yield (with <5% secondary acylated product) after purification. However, employing trifluoroacetic anhydride in the same competition is reported to generate a 3:2 mixture of primary to secondary trifluoroacetylated amines.[16]

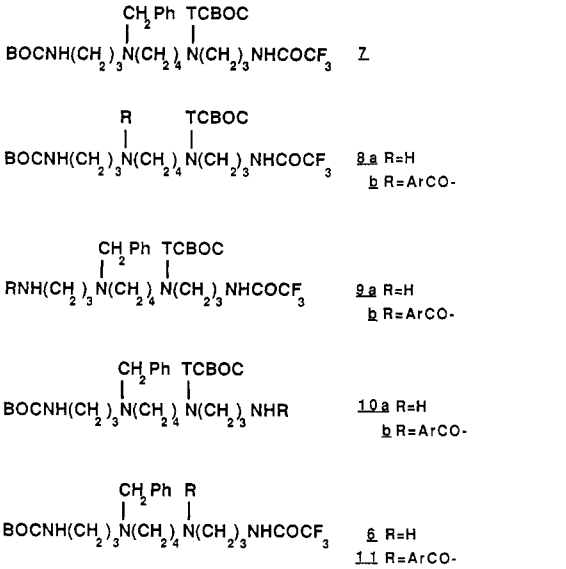
Similar results were obtained when a pair of aromatic amines was reacted with agent **5**. That is, exclusive primary amine acylation resulted upon treatment of aniline and *N*-methylaniline with reagent **5** (0.9 equiv) to give *N*-phenyltrifluoroacetamide in 85% yield upon purification. When this pair was reacted with trifluoroacetic anhydride (0.8 equiv) and triethylamine in methylene chloride, a 3:1 mixture of primary to secondary acylated amine resulted. Thus, an easily generated reagent **5** for the selective trifluoroacetylation of primary amines is available. Even the addition of a methyl group to a primary amine essentially blocked its acylation with active ester **5** in the presence of the primary amine, which reacted efficiently. This selectivity is noteworthy in view of the strongly electrophilic nature of the trifluoroacetyl group. Our method thus complements the reported conditions[16] by which a secondary amine is trifluoroacetylated in the presence of a primary amine.

Finally, triprotected spermine **6** was acylated with 2,2,2-trichloro-1,1-dimethylethyl chloroformate under biphasic conditions[14] to produce tetrafunctionalized spermine **7** in 86% chromatographed yield.

We next deprotected and refunctionalized each nitrogen of spermine to demonstrate the independence of the protecting groups and thus the versatility of the new reagent. It is apparent that a number of spermine-based natural products and other biologically active spermine compounds could be assembled with reagent **7**.

After removal of each protecting group, the resulting trifunctionalized tetraamine was acylated with *p*-toluoyl chloride (triethylamine, CH_2Cl_2) as depicted in Scheme II. Debenzylation of spermine reagent **7** was effected catalytically by mild conditions ($PdCl_2$, HOAc) to afford amine **8a** in 60% yield. Exposure of reagent **7** to neat trifluoroacetic acid for 20 min removed the BOC group and afforded primary amine **9a** in 90% yield after a basic workup. It is noteworthy that the TCBOC group was not cleaved by these acidic conditions. Hydrolysis of the trifluoroacetyl group of **7** with excess potassium carbonate in refluxing aqueous methanol for 2 h gave primary amine **10a** in 95% yield. Finally, reductive cleavage of the TCBOC group in **7** was accomplished with freshly acti-

Scheme II. Deprotection and Refunctionalization of the Spermine Reagent[a]



[a] Ar = *p*-$CH_3C_6H_4$.

(14) Eckert, H.; Listl, M.; Ugi, I. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 361–362.
(15) Bergeron, R. J.; Garlich, J. R. *Synthesis* **1984**, 782–784.
(16) Barrett, A. G. M.; Lana, J. C. A. *J. Chem. Soc., Chem. Commun.* **1978**, 471–472.
(17) Sakakibara, S.; Inukai, N. *Bull. Chem. Soc. Jpn.* **1965**, *38*, 1979–1984.

vated zinc dust in THF buffered at pH 4 with potassium dihydrogen phosphate[18] to give triprotected spermine reagent **6** in 77% yield.

This stepwise deprotection–refunctionalization is expected to work equally well for analogues of spermine (3-4-3 methylene chains) such as the tetraamines thermine (3-3-3 carbon chains), isolated from the bacterium *Thermus thermophilus*,[19] and canavalmine (4-3-4 carbon chains) from the sword bean plant *Canavalia gladiata*.[20]

The spermine reagent is stable and may be stored long term.

Experimental Section

All reagents were purchased from Aldrich Chemical Company and were used without further purification. Sodium sulfate was employed as a drying agent, and solvents were routinely distilled. Silica gel 60 for column chromatography was purchased from EM Science, Darmstadt, West Germany. Preparative-layer chromatography was carried out on silica gel GF plates (2 mm thick) purchased from Analtech, Newark, DE. Proton NMR spectra were recorded on a Varian EM-390 instrument and, unless otherwise noted, were run in $CDCl_3$ with chemical shifts given in parts per million downfield from an internal tetramethylsilane standard (coupling constants are in hertz). Elemental analyses were performed by Atlantic Microlabs, Atlanta, GA.

1-[*N*-(*tert*-Butoxycarbonyl)amino]-4-benzyl-4,9-diazadodecanenitrile (3). A solution of acrylonitrile (1.38 g, 26.0 mmol) in CH_3OH (5 mL) was added slowly by syringe to N^1-(*tert*-butoxycarbonyl)-N^4-benzylspermidine (**2**)[10] (10.37 g, 30.9 mmol) in CH_3OH (5 mL) at 0 °C. After 1 day at room temperature, the solution was concentrated and chromatographed (62 g SiO_2, 50% EtOH/$CHCl_3$); a portion of the product (2.5 g) was rechromatographed (210 g SiO_2, 40% EtOH/$CHCl_3$) to give a total of 10.27 g of **3** (quantitative yield): NMR δ 1.4–1.8 (m, 16 H), 2.3–3.3 (m, 12 H), 3.53 (s, 2 H), 5.3–5.4 (br s, 1 H), 7.35 (m, 5 H). Anal. Calcd for $C_{22}H_{36}N_4O_2$: C, 68.00; H, 9.34; N, 14.42. Found: C, 67.75; H, 9.27; N, 14.32.

N^1-(*tert*-Butoxycarbonyl)-N^4-benzylspermine (4). Nitrile **3** (10.25 g, 26.4 mmol) in absolute EtOH (25 mL) was added to a Parr bottle (500-mL capacity), followed by addition of 1 N NaOH in 95% EtOH (245 mL) and W-2 Raney nickel slurry (2.19 g). The mixture was shaken under a hydrogen atmosphere (40 psi) for 15 h. The catalyst was filtered and rinsed with 95% EtOH (3 × 25 mL). After removal of most of the solvent, 10% NaOH was added until oil appeared and pH ≥13. After extraction of the aqueous phase with ether (4 × 100 mL), the organic layer was washed with brine (2 × 50 mL), dried, and concentrated to give 9.42 g of oil. Purification by column chromatography (180 g of SiO_2, 10% concentrated NH_4OH/CH_3OH) provided 7.78 g of **4** (75% yield): NMR δ 1.35–1.8 (m, 20 H), 2.32–2.89 (m, 10 H), 3.16 (q, 2 H, J = 7), 3.53 (s, 2 H), 5.4 (br s, 1 H), 7.33 (m, 5 H). Anal. Calcd for $C_{22}H_{40}N_4O_2$: C, 67.31; H, 10.27; N, 14.27. Found: C, 67.14; H, 10.33; N, 14.18.

***N*-(Trifluoroacetoxy)succinimide (5).** Compound **5** was prepared from *N*-hydroxysuccinimide and trifluoroacetic anhydride according to the literature[17] and stored in benzene in the freezer.

N^1-(*tert*-Butoxycarbonyl)-N^4-benzyl-N^{12}-(trifluoroacetyl)spermine (6). A solution of **5** (15.5 mL, 0.34 M in benzene, 5.27 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise over a period of 2 h to a solution of **4** (2.21 g, 5.63 mmol) in CH_2Cl_2 (240 mL) at 0 °C with stirring. The solution was stirred in the cold bath for 2 h more and then washed with 5% $NaHCO_3$ (140 mL). The aqueous layer was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic extracts were washed with water (100 mL), dried, and concentrated to give 2.63 g of crude product. Column chromatography (70 g SiO_2, 0.5% concentrated NH_4OH/CH_3OH) generated 2.11 g of **6** (82% yield): NMR δ 1.35–1.8 (m, 18 H), 2.3–2.6 (m, 6 H), 2.7–2.9 (m, 2 H), 3.13 (q, 2 H, J = 7), 3.34–3.56 (m, 4 H), 5.2 (br s, 1 H), 7.31 (m, 5 H). Anal. Calcd for $C_{24}H_{39}F_3N_4O_3$: C, 59.00; H, 8.05; N, 11.47. Found: C, 58.80; H, 8.12; N, 11.34.

N^1-(*tert*-Butoxycarbonyl)-N^4-benzyl-N^9-(2,2,2-trichloro-*tert*-butoxycarbonyl)-N^{12}-(trifluoroacetyl)spermine (7). 2,2,2-Trichloro-1,1-dimethylethyl chloroformate (0.52 g, 2.17 mmol) in anhydrous ether (25 mL) was added to **6** (0.97 g, 1.99 mmol) in ether (30 mL) and ice-cold 0.2 N NaOH (30 mL). The mixture was shaken in a separatory funnel for 10 min, and the layers were separated. The aqueous phase was extracted with Et_2O (2 × 35 mL) and the combined extracts were washed with brine (50 mL), dried, and evaporated to give 1.40 g oil. Column chromatography (360 g SiO_2, 3% EtOH/$CHCl_3$) afforded 1.181 g (86%) of spermine reagent **7**: NMR δ 1.4–2.0 (2 s + m, 23 H), 2.3–2.6 (m, 4 H), 3.02–3.57 (m, 10 H), 5.2 (br s, 1 H), 7.3 (m, 5 H), 8.0 (br s, 1 H). Anal. Calcd for $C_{29}H_{44}Cl_3F_3N_4O_5$: C, 50.34; H, 6.41; N, 8.10. Found: C, 50.58; H, 6.39; N, 7.98.

Debenzylation of 7 (8a). Palladium chloride (12.4 mg, 0.0699 mmol) was added to a solution of **7** (0.126 g, 0.182 mmol) in acetic acid (3.3 mL). The mixture was stirred under hydrogen at one atmosphere for 19.5 h. The catalyst was filtered and washed with methanol (50 mL), and then the filtrate was cooled in dry ice/acetone and evaporated under high vacuum to a white solid. Chloroform (15 mL) and then cold 2% NaOH (10 mL) were added and the layers separated. The aqueous phase was extracted further with $CHCl_3$ (3 × 15 mL), and the combined extracts were washed with water (10 mL), dried, and concentrated to give 0.15 g of crude product. Purification by column chromatography (8.7 g SiO_2, 0.5% concentrated NH_4OH/CH_3OH) led to a band that was concentrated with ethanol, dissolved in $CHCl_3$, dried, filtered through diatomaceous earth, and concentrated to give 66 mg of **8a** for a 60% yield: NMR δ 1.3–2.0 (m, 24 H), 2.5–2.8 (m, 4 H), 3.08–3.5 (m, 8 H), 5.1 (br s, 1 H), 8.0–8.1 (br s, 1 H). Anal. Calcd for $C_{22}H_{38}Cl_3F_3N_4O_5$: C, 43.90; H, 6.36; N, 9.31. Found: C, 44.08; H, 6.37; N, 9.29.

Acylation of 8a (8b). *p*-Toluoyl chloride (16.0 mg, 0.104 mmol) in CH_2Cl_2 (2 mL) was added to **8a** (54 mg, 0.090 mmol) and triethylamine (13.0 mg, 0.128 mmol) in CH_2Cl_2 (2 mL) and the solution stirred for 21 h and then diluted with CH_2Cl_2 (15 mL). The reaction was washed with 5% $NaHCO_3$ (15 mL), and the layers were separated. After two more extractions with CH_2Cl_2 (15 mL), the organic extracts were washed with water (15 mL), dried, and evaporated to give 76 mg of the product. Purification by preparative-layer chromatography (5% EtOH/$CHCl_3$) afforded 56 mg of **8b** (87% yield): NMR δ 1.3–2.0 (m, 23 H), 2.40 (s, 3 H), 2.9–3.6 (m, 12 H), 5.2 (br s, 1 H), 7.28 (s, 4 H), 8.0 (br s, 1 H). Anal. Calcd for $C_{30}H_{44}Cl_3F_3N_4O_6$: C, 50.04; H, 6.16; N, 7.78. Found: C, 49.78; H, 6.13; N, 7.61.

Removal of BOC from 7 (9a). Spermine reagent **7** (0.184 g, 0.266 mmol) was dissolved in trifluoroacetic acid (TFA, 4 mL) and stirred at room temperature for 20 min (Drierite tube). Excess TFA was evaporated under a stream of nitrogen, and the residue was dissolved in $CHCl_3$ (25 mL), which was washed with ice-cold 0.56 N NaOH (25 mL). After further extraction with $CHCl_3$ (2 × 25 mL), the organic phase was washed with water (25 mL), dried, and evaporated to give 0.141 g of **9a** (90% yield): NMR δ 1.3–2.05 (m, 14 H) 2.25–2.9 (m, 8 H), 3.05–3.65 (m, 8 H), 7.32 (m, 5 H). Anal. Calcd for $C_{24}H_{36}Cl_3F_3N_4O_3$: C, 48.70; H, 6.13; N, 9.47. Found: C, 48.50; H, 6.17; N, 9.38.

Acylation of 9a (9b). *p*-Toluoyl chloride (37.3 mg, 0.241 mmol) in CH_2Cl_2 (8.5 mL) was added to **9a** (0.125 g, 0.211 mmol) and triethylamine (24.2 mg, 0.239 mmol) and the solution stirred for 1 day and then diluted with CH_2Cl_2 (25 mL). The reaction was washed with 5% $NaHCO_3$ (25 mL), and the layers were separated. After two more extractions with CH_2Cl_2 (25 mL), the organic phase was washed with water (40 mL), dried, and evaporated to give 0.21 g of product. Purification by preparative-layer chromatography (4% EtOH/$CHCl_3$) led to 0.129 g of **9b** (86% yield): NMR δ 1.3–1.95 (m, 14 H), 2.3–2.65 (m, 7 H), 2.95–3.6 (m, 10 H), 6.8 (br s, 1 H), 7.1–7.8 (m, 10 H), 8.2 (br s, 1 H). Anal. Calcd for $C_{32}H_{42}Cl_3F_3N_4O_4 \cdot H_2O$: C, 52.79; H, 6.09; N, 7.69. Found: C, 53.18; H, 5.84; N, 7.77.

Trifluoroacetamide Cleavage of 7 (10a). Potassium carbonate (0.19 g, 1.37 mmol) was added to **7** (0.182 g, 0.263 mmol) in CH_3OH (10 mL) and H_2O (0.6 mL), and the reaction was heated

(18) Just, G.; Grozinger, K. *Synthesis* **1976**, 457–458.
(19) Oshima, T. *Biochem. Biophys. Res. Commun.* **1975**, *63*, 1093–1098.
(20) Fujihara, S.; Nakashima, T.; Kurogochi, Y. *Biochem. Biophys. Res. Commun.* **1982**, *107*, 403–410.

at reflux for 2 h. Solvent was evaporated, and water (30 mL) was added to the residue, which was extracted with $CHCl_3$ (3 × 25 mL). The organic phase was washed with water (15 mL), dried, and concentrated to yield 66 mg of product. The aqueous layers were further basified with ice-cold 5% NaOH (10 mL) and extracted with $CHCl_3$ (4 × 40 mL). After a water wash (25 mL), solvent was removed to give 0.149 g (combined) **10a** for a 95% yield: NMR δ 1.35–1.95 (m, 25 H), 2.25–2.85 (m, 6 H), 2.95–3.38 (m, 6 H), 3.50 (s, 2 H), 5.32 (br s, 1 H), 7.33 (m, 5 H). Anal. Calcd for $C_{27}H_{45}Cl_3N_4O_4$: C, 54.41; H, 7.61; N, 9.40. Found: C, 54.28; H, 7.64; N, 9.31.

Acylation of 10a (10b). *p*-Toluoyl chloride (36.9 mg, 0.239 mmol) in CH_2Cl_2 (6 mL) was added to **10a** (0.130 g, 0.218 mmol) and triethylamine (27.6 mg, 0.273 mmol) and the solution stirred for 1 day. The reaction was worked up by the method of **9b** to give 0.17 g of the crude product. Preparative-layer chromatography (3% EtOH/$CHCl_3$) furnished 0.137 g of **10b** for an 88% yield: NMR δ 1.37–2.05 (m, 23 H), 2.3–2.62 (m, 7 H), 3.02–3.6 (m, 10 H), 5.3 (br s, 1 H), 7.15–7.92 (m, 10 H). Anal. Calcd for $C_{35}H_{51}Cl_3N_4O_5 \cdot H_2O$: C, 57.41; H, 7.30; N, 7.65. Found: C, 57.70; H, 7.01; N, 7.67.

Removal of TCBOC from 7 (6). Freshly activated[21] zinc dust (0.98 g, 15.0 mmol) was added to **7** (0.181 g, 0.262 mmol) in distilled THF (5 mL) with stirring. Potassium dihydrogen phosphate (1.0 M, 1.0 mL) was added and the mixture stirred for 21 h. The solids were filtered and washed with THF and the filtrate concentrated. Ice-cold 5% NaOH (20 mL) was added to the residue, followed by extraction with $CHCl_3$ (3 × 25 mL). The organic phase was washed with water (20 mL), dried, and concentrated to give 0.135 g of the crude product. Column chromatography (8.0 g SiO_2, CH_3OH) produced 98 mg of **6** (77% yield): NMR δ 1.35–1.85 (m, 18 H), 2.3–2.67 (m, 6 H), 2.7–2.9 (m, 2 H), 3.17 (q, 2 H, J = 7), 3.36–3.6 (m, 4 H), 5.3–5.4 (br s, 1 H), 7.3–7.4 (m, 5 H).

Acylation of 6 (11). *p*-Toluoyl chloride (46.3 mg, 0.300 mmol) in CH_2Cl_2 (5 mL) was added to **6** (from **7**, 0.135 g, 0.276 mmol) and triethylamine (29.5 mg, 0.292 mmol) in CH_2Cl_2 (5 mL), and the solution was stirred for 1 day. The reaction was diluted with CH_2Cl_2 (20 mL) and washed with 5% $NaHCO_3$ (20 mL). After further extraction with CH_2Cl_2 (2 × 20 mL), the organic phase was washed with H_2O (20 mL), dried, and evaporated to give 0.18 g of oil. Purification by preparative-layer chromatography (4% EtOH/$CHCl_3$) gave 0.149 g of **11** for an 89% yield: NMR δ 1.2–2.0 (m, 17 H), 2.2–2.55 (m, 7 H), 2.95–3.65 (m, 10 H), 5.15 (br s, 1 H), 7.2–7.4 (m, 9 H), 8.5 (br s, 1 H). Anal. Calcd for $C_{32}H_{45}F_3N_4O_4$: C, 63.35; H, 7.48; N, 9.23. Found: C, 63.19; H, 7.55; N, 9.15.

Benzylamine and *N*-Benzylmethylamine with 5. Reagent **5** in benzene (0.34 M, 6.0 mL, 2.04 mmol) was added by syringe over 4 min to a rapidly stirred solution of benzylamine (0.23 g, 2.15 mmol) and *N*-benzylmethylamine (0.26 g, 2.15 mmol) in dry CH_2Cl_2 (50 mL) at 0 °C under N_2. The reaction was stirred for 21 h (0 °C to room temperature). After solvent removal, 1 N HCl (20 mL) was added and the mixture extracted with ether (3 × 20 mL). The combined organic phase was washed with brine (20 mL), dried, and concentrated to give 0.336 g of the product. Column chromatography (10 g SiO_2, 30% *n*-hexane/$CHCl_3$) combining all eluant beginning with column loading through the UV-active band gave 0.285 g of *N*-benzyltrifluoroacetamide (70% yield). Note: *N*-benzyl-*N*-methyltrifluoroacetamide elutes faster than *N*-benzyltrifluoroacetamide. NMR δ 4.53 (d, 2 H, J = 6), 6.6–7.53 (m, 6 H). A multiplet at δ 3.0 indicated less than 5% *N*-benzyl-*N*-methyltrifluoroacetamide.

Aniline and *N*-Methylaniline with 5. Reagent **5** in benzene (0.34 M, 6.0 mL, 2.04 mmol) was added by syringe over 3 min to a rapidly stirred solution of aniline (0.21 g, 2.25 mmol) and *N*-methylaniline (0.23 g, 2.15 mmol) in dry CH_2Cl_2 (25 mL) at 0 °C under N_2. The reaction was stirred for 15 h (0 °C to room temperature). After solvent removal, 1 N HCl (25 mL) was added and the mixture extracted with ether (3 × 25 mL). The organic phase was washed with brine (25 mL), dried, and concentrated to give 0.37 g of solid. Column chromatography (30.6 g SiO_2, 30% *n*-hexane/$CHCl_3$) combining all eluant beginning with column loading through the UV-active band furnished 0.328 g of *N*-phenyltrifluoroacetamide (85% yield). Note: *N*-methyl-*N*-phenyltrifluoroacetamide elutes faster than *N*-phenyltrifluoroacetamide. NMR δ 7.1–8.2 (m).

Aniline and *N*-Methylaniline with Trifluoroacetic Anhydride. Trifluoroacetic anhydride (0.40 g, 1.90 mmol) in dry CH_2Cl_2 (15 mL) was added dropwise over 15 min to a stirred solution of aniline (0.21 g, 2.25 mmol), *N*-methylaniline (0.23 g, 2.15 mmol), and triethylamine (0.3 mL, 2.15 mmol) in CH_2Cl_2 (15 mL). After being stirred for 12 h, the reaction was worked up following the prior procedure to give 0.22 g of product. Column chromatography (10.6 g SiO_2, 30% *n*-hexane/$CHCl_3$) gave 0.155 g of product, which contained a 3:1 mixture of *N*-phenyltrifluoroacetamide and *N*-methyl-*N*-phenyltrifluoroacetamide. NMR δ 3.37 (s, *N*-methyl).

Acknowledgment. Financial support was provided by the National Institutes of Health, Grant CA-37606.

Registry No. **2**, 90914-14-0; **3**, 114491-93-9; **4**, 114491-94-0; **5**, 5672-89-9; **6**, 114491-95-1; **7**, 114491-96-2; **8a**, 114491-97-3; **8b**, 114504-97-1; **9a**, 114491-98-4; **9b**, 114504-98-2; **10a**, 114491-99-5; **10b**, 114492-00-1; **11**, 114492-01-2; spermine, 71-44-3; acrylonitrile, 107-13-1; benzylamine, 100-46-9; *N*-benzylmethylamine, 103-67-3; *N*-benzyltrifluoroacetamide, 7387-69-1; *N*-benzyl-*N*-methyltrifluoroacetamide, 68464-36-8; aniline, 62-53-3; *N*-methylaniline, 100-61-8; *N*-phenyltrifluoroacetamide, 404-24-0; *N*-methyl-*N*-phenyltrifluoroacetamide, 345-81-3.

(21) *Organic Syntheses*; Wiley: New York, 1955; Collect. Vol. III, pp 410–412.

Direct Conversion of Silyl Ethers into Alkyl Bromides with Boron Tribromide

Sunggak Kim* and Jung Ho Park

Department of Chemistry, Korea Advanced Institute of Science and Technology, Seoul 130-012, Korea

Received October 9, 1987

Direct conversion of silyl ethers such as *tert*-butyldimethylsilyl (TBDMS)[1] and *tert*-butyldiphenylsilyl (TBDPS)[2] ethers into synthetically useful functional groups without deprotection seems to be very important for further manipulation in the synthesis of complex molecules. It has been reported that silyl ethers have been directly converted into the corresponding acetates with acetic anhydride/ferric chloride[3] and an acid chloride/zinc chloride.[4] Furthermore, direct conversion of silyl ethers into alkyl bromides with triphenylphosphine dibromide[5] and triphenylphosphine/carbon tetrachloride[6] has been recently reported during our studies on the same subject.

We have found that boron tribromide in methylene chloride is very effective for the conversion of TBDMS and TBDPS ethers into the corresponding bromides in high yields (eq 1). It has been known that TBDMS ethers are

$$ROR' + BBr_3 \xrightarrow[CH_2Cl_2]{\text{room temperature}} RBr \qquad (1)$$

R′ = TBDMS, TBDPS

deprotected to the alcohols with boron trifluoride etherate[7] and dimethylboron bromide.[8] Furthermore, it has been

(1) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(2) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975.
(3) Ganem, B.; Small, V. R. *J. Org. Chem.* **1974**, *39*, 3728.
(4) Kim, S.; Lee, W. *J. Synth. Commun.* **1986**, *16*, 659.
(5) Aizpurua, J. M.; Cossio, F. P.; Palomo, C. *J. Org. Chem.* **1986**, *51*, 4941.
(6) Mattes, H.; Benezra, C. *Tetrahedron Lett.* **1987**, *28*, 1697.
(7) Kelly, D. R.; Roberts, S. M.; Newton, R. F. *Synth. Commun.* **1979**, *9*, 295.

0022-3263/88/1953-3111$01.50/0