Substitution Reactions of Hindered Cyclic Sulfamidates

Jeffrey J. Posakony,[a] Timothy J. Tewson*[b]

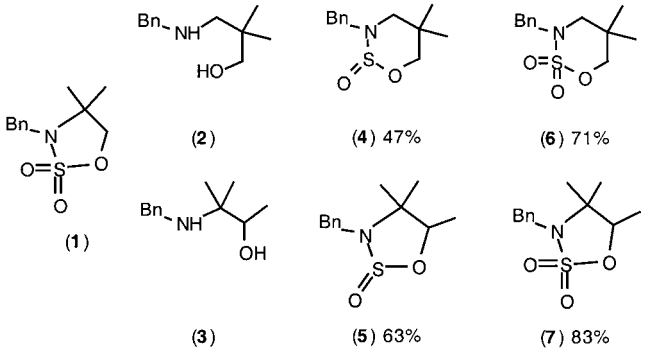
[a] University of Washington, Department of Radiology Imaging Research Laboratory, Rm NW041, Box 356004, 1959 NE Pacific St., Seattle, WA 98195, USA

[b] University of Iowa PET, Imaging Center, Department of Radiology, 0911Z JPP, 200 Hawkins Drive, Iowa City, Iowa, 52242-1007, USA
Fax +1(319)3536512; E-mail: timothy-tewson@uiowa.edu

Received 18 March 2001; revised 6 March 2002

Abstract: Five- and six-membered cyclic sulfamidates, [1,2,3]-oxathiazolidine- and [1,2,3]-oxathiazinane-2,2-dioxides, with the leaving group oxygen at sterically hindered centers were synthesized and treated with selected nucleophiles (azide, cyanide, fluoride, butylamine, *sec*-butylamine, *tert*-amylamine, and imidazole) in substitution reactions to demonstrate the general utility and limitations of these substrates. Substitutions adjacent to quaternary carbon centers were accomplished with relative ease. In contrast to the 4,4-dimethyl substituted 5-membered sulfamidate **1**, which reacted with the entire set of nucleophiles, the more hindered 5-membered and 6-membered sulfamidates (**7** and **6**, respectively) reacted only with the first few of this set.

Key words: nucleophilic additions, steric hindrance, amines, substituent effects, cyclic sulfamidates



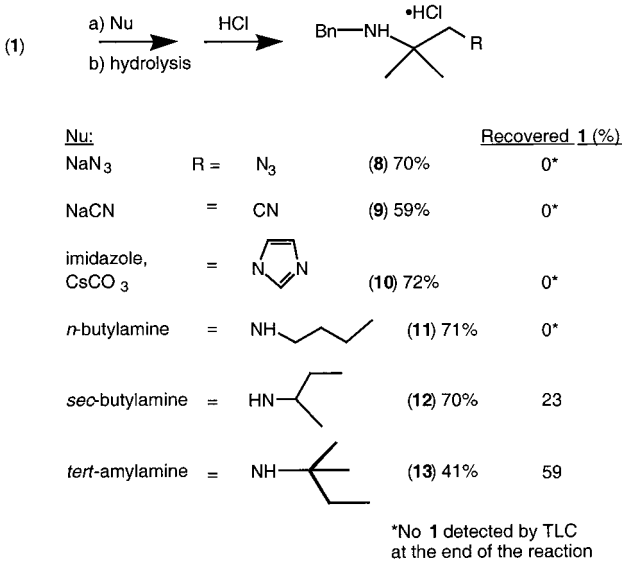
Figure

Cyclic sulfamidates are reactive electrophiles and have been useful in the conversion of amino alcohols to uniquely substituted amines.[1–6] Recently, the hindered cyclic sulfamidate **1** was described in the synthesis of fluoro-*tert*-butylamine.[7–9] Compound **1** was highly reactive toward fluoride, giving the expected substitution product at a carbon center adjacent to a quaternary carbon, a substitution analogous to a neopentyl substitution, which is known to be difficult. We then became interested in probing the limitations of substitution reactions of **1** and even more hindered sulfamidates (Figure) such as **6** and **7**. Sulfamidate **6** incorporates a quarternary carbon center in a 6-membered ring, and sulfamidate **7** incorporates tertiary and quaternary carbon centers in a 5-membered ring. We report here the results of our experiments with progressively more hindered sulfamidates, **1**, **6** and **7** in displacement reactions with a set of useful nucleophiles and a varied degree of steric bulk (e.g. azide, cyanide, fluoride, imidazole, butyl-, *sec*-butyl, and *tert*-amyl amines). These results will have implications for the usefulness of hindered cyclic sulfamidates in the production of sterically hindered amines.

The synthesis of **1** was described previously.[7–9] The remaining sulfamidates were synthesized using similar conditions by treating the corresponding *N*-benzyl amino alcohols (**2** and **3**) with thionyl chloride to produce the sulfamidites (**4** and **5**) which were then oxidized with ruthenium tetroxide to afford **6** and **7** in 33 and 52% overall yield, respectively.

Sulfamidates **1**, **6** and **7** were treated with selected nucleophiles (from the set of azide, cyanide, fluoride, butylamine, *sec*-butylamine, *tert*-amylamine, and imidazole) under a variety of conditions. After hydrolysis of the N–SO_3^- intermediates, the products were purified by chromatography or by recrystallization of their hydrochloride salts.

Sulfamidate **1** reacted readily with azide and cyanide to yield **8** (70%) and **9** (59%), respectively (Scheme 1). The



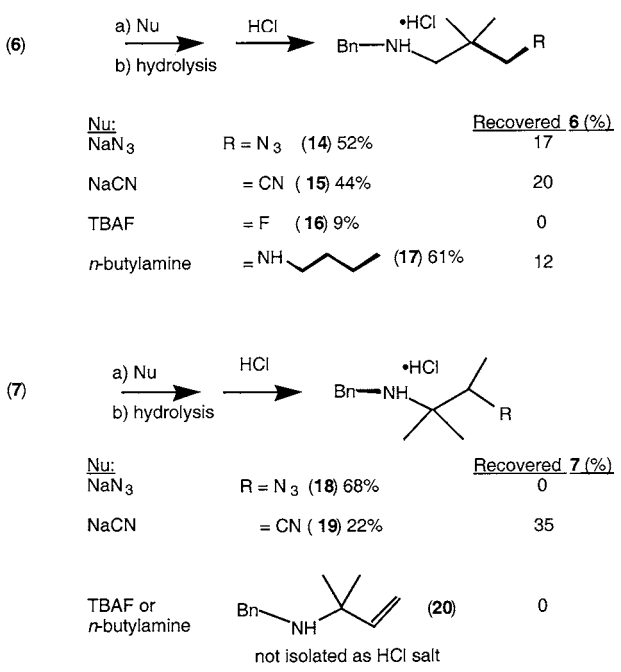
Scheme 1

Synthesis 2002, No. 7, 21 05 2002. Article Identifier:
1437-210X,E;2002,0,07,0859,0864,ftx,en;M00901SS.pdf.

ISSN 0039-7881

previously described reaction of **1** with fluoride yielded *N*-benzyl fluoro-*tert*-butylamine in 78% yield.[8,9] Imidazole, in the presence of cesium carbonate, reacted with **1** to yield **10** after hydrolysis (72%); in contrast, triethylamine did not promote this reaction. *N*-butyl-, *sec*-butyl-, and even *tert*-amylamine reacted with **1** to yield the diaminopropanes **11**–**13**, in 71, 70, and 41% yields, respectively. However, the syntheses of **12** and **13** required refluxing **1** in neat *sec*-butylamine and *tert*-amylamine for 3 days and 7 days, respectively. There was no indication of other products in the synthesis of **12** and **13** and significant amounts of unreacted **1** were recovered.

The 6-membered **6** and 5-membered, hindered **7** underwent substitution only with the less bulky nucleophiles of the series (Scheme 2). Compound **6** reacted with sodium azide and sodium cyanide in DMF at 100 °C to yield **14** and **15** in 52 and 44% yields, respectively. The reaction of **6** with TBAF yielded a small amount of **16** (9%), while the reaction with neat butylamine to produce **17** (61%) required 8 days at reflux. No reaction was observed when a solution of **6** was refluxed for ~2 days with *sec*-butylamine. Compound **7** reacted with sodium azide and sodium cyanide in DMF at ~100 °C to yield **18** and **19** in 68% and 22% yields, respectively. However, only the elimination product **20** was isolated when **7** was treated with butylamine or TBAF.



Scheme 2

It is interesting that the fluoride ion (as TBAF), a small nucleophile, afforded low yields with **6** and only the elimination product with **7**. Other factors, in addition to steric restrictions limiting the substitution reaction are likely to be involved. TBAF is known to be basic and induce eliminations with some substrates, including cyclic sulfamidates.[10] Better results might be obtained using a less basic source of fluoride, such as (triphenylsilyl)difluorosilicate;[11] and the results of such experiments will be reported elsewhere. HPLC analyses of the fluorination reaction of **6** (data not shown) indicated that several products are formed with during the initial fluorination step. It is conceivable that **6** also undergoes S_N2 attack at the carbon adjacent to nitrogen. Such a substitution would require the sulfonamide as the leaving group, similar to the substitution reactions of *N*-sulfonyl aziridines.[12] In addition, the product of this substitution could itself be susceptible to S_N2 attack at the carbon adjacent to oxygen. Additional displacement reactions and the fact that substitutions at neopentyl centers are frequently accompanied by rearrangements could help explain the additional products observed by HPLC.

S_N2 displacements at neopentyl centers are typically very slow and are often impractical as synthetic routes. The high reactivity of these hindered substrates (**1**, **6** and **7**) must be due, in part, to the increased access to the reactive carbon afforded by the ring structure of the cyclic sulfamidate in comparison to acyclic substrates (e.g. with leaving groups like iodide, tosylate, mesylate, triflate, etc.). In contrast to **1**, which reacted with some very hindered nucleophiles, definite limits were encountered with the reactivity of **6** and **7**. The necessary kinetic data have not yet been obtained that would clearly demonstrate whether these substrates react via direct substitution (S_N2) or nucleophilic capture (S_N1) of a transient carbocation derived from the cyclic sulfamidate. However, the fact that many of these reactions proceed cleanly to a single product in good yields suggests that a direct substitution is involved.

In summary, the three hindered cyclic sulfamidates **1**, **6** and **7** were synthesized using standard methodologies. An investigation of these sulfamidates was performed by treating these substrates with a set of useful nucleophiles with varied degrees of steric bulk (azide, cyanide, imidazole (for **1** only), butylamine, *sec*-butylamine, and *tert*-amylamine). Sulfamidate **1** reacted with all these nucleophiles in moderate to excellent yields at the carbon adjacent to the tertiary carbon. The more hindered **6** and **7** were more limited in their reactivity. Sulfamidate **6** underwent substitution reactions with azide, cyanide, TBAF and butylamine. Although **7** reacted with azide, and cyanide, it underwent elimination to produce **20** with treated with TBAF and butylamine. These cyclic sulfamidates are adequate substrates for preparing a variety of sterically hindered amines.

Melting points were determined using an Electrothermal® melting point apparatus and are uncorrected. Low resolution mass spectrometry was performed on a Micromass Quattro II Tandem Quadrupole Mass Spectrometer (electrospray ionization). High resolution mass spectrometry was performed using a Micromass 70SEQ Tandem Hybrid Mass Spectrometer (FAB) or a PE BiosysteMS: Mariner electrospray (TOF) instrument. ^{1}H- and ^{19}F NMR spectra were obtained with a GE Omega 300 MHz spectrometer. ^{1}H-chemical shifts are reported in ppm (δ) and ^{19}F-chemical shifts are referenced to $CFCl_3$. Coupling constants are rounded to the nearest 0.5 Hz. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Prior to elemental analysis, samples

were dried under vacuum at 40−50 °C. Flash column chromatography was performed using silica gel (Merck, grade 9385, 230−400 mesh). Analytical TLC and R_f values were determined using Analtech GF silica gel plates (0.25 mm); preparative TLC was performed using Analtech GF silica gel plates (1 mm). Unless otherwise noted, reagents were purchased from Aldrich Chemical Co. Solvents were ACS reagent grade or better. Unless otherwise noted, anhyd solvents (Aldrich) were used as received except for CH_2Cl_2 which was dried by storing over activated, crushed 4Å molecular sieves. Stable HCl salts were obtained by dissolving the product in Et_2O or Et_2O–MeOH and bubbling $HCl_{(g)}$ through the solution; the resulting precipitate was then collected and washed thoroughly with Et_2O.

3-(Benzylamino)-2,2-dimethyl-propan-1-ol (2)
A mixture of 3-amino-2,2-dimethyl-propan-1-ol (Lancaster Synthesis, 3 g, 29 mmol) and benzaldehyde (3.1 mL, 30.5 mmol) in benzene (50 mL) was refluxed for 4 h during which time H_2O was removed using a Dean−Stark apparatus. The solvent was then removed and the residual oil was dissolved in MeOH (40 mL). The soln was then cooled to 0 °C and $NaBH_4$ (1.67 g, 44 mmol) was added in 3 equal portions over several minutes. The mixture was stirred for 2 h and then 6 N NaOH (7 mL) was added and the solvent evaporated. The residue was dissolved in H_2O (30 mL) and extracted with Et_2O (4 × 15 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed. The product was crystallized by adding heptane to the residual oil and stored at 10 °C to yield 4.6 g (82%) of **2**; mp 33.5−35.5 °C.

The ^{1}H NMR data are similar to those reported in the literature.[13]

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.24. Found: C, 74.56; H, 10.18; N, 7.52.

3-(Benzylamino)-3-methyl-butan-2-ol (3)
Compound **3** was synthesized from benzaldehyde and 3-amino-3-methyl-butan-2-ol[14] in 40% yield by the method used for the synthesis of **2**. The product was crystallized from heptane; mp 60.5−62.5 °C.

^{1}H NMR ($CDCl_3$): δ = 1.04 and 1.17 [s, 2 × 3 H, $C(CH_3)_2$], 1.15 (d, 3 H, J = 6.3 Hz, $CHCH_3$), 1.3−1.6 (br s 2 H, NH, OH), 3.60 (q, 1 H, J = 6.3 Hz, $CHCH_3$), 3.71 (s, 2 H, benzyl H), 7.25−7.40 (m, 5 H, phenyl H).

MS: m/z = 194 (100, M + H).

Anal. Calcd for $C_{12}H_{19}NO$: C, 74.57; H, 9.91; N, 7.24. Found: C, 74.59; H, 10.11; N, 7.06.

Cyclic Sulfamidite and Sulfamidate; General Procedure
Sulfamidites **4** and **5** were synthesized by the same methodology used to produce the *N*-benzyl sulfamidite precursor to **1**, 3-benzyl-4,4-dimethyl-[1,2,3]-oxathiazolidine-2-oxide, as described previously.[8] Similarly, the previously described RuO_4-oxidation conditions were used to convert **4** and **5** to **6** and **7**, respectively. Sulfamidites **4** and **5** are mixtures of diasteromers and give complex ^{1}H NMR spectra; their ^{13}C NMR spectra were not obtained.

3-Benzyl-5,5-dimethyl-[1,2,3]-oxathiazinane-2-oxide (4)
Compound **2** (2 g, 10.3 mmol) was used to produce **4**. Purification by repeated column chromatography (3 times; silica/CH_2Cl_2−acetone, 50:1) yielded 1.18 g (47%) of **4** as a colorless oil; R_f 0.68.

^{1}H NMR ($CDCl_3$): δ = 0.81 and 1.16 [2 × s, 2 × 3 H, $C(CH_3)_2$], [2.21 (dd, 1 H, J_1 = 12 Hz, J_2 = 2 Hz), 3.18 (d, 1 H, J = 12 Hz), 3.36 (dd, 1 H, J_1 = 11.3 Hz, J_2 = 2.4 Hz), and 4.49 (dd, 1 H, J_1 = 11.0 Hz, J_2 = 0.5 Hz), ring CH_2] 3.54 and 4.25 (2 × d, 2 × 1 H, J = 14.1 Hz, benzyl H), 7.28−7.34 (m, phenyl H).

MS: m/z = 262 (65, M + Na), 240 (25, M + H), 176 (100).

Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.33; H, 7.42; N, 5.85.

3-Benzyl-4,4,5-trimethyl-oxathiazolidine-2-oxide (5)
Compound **3** (0.3 g, 1.6 mmol) was used to produce crude **5,** which was purified by filtration through a pad of silica using CH_2Cl_2−acetone, 20:1 to yield 0.25 g (63%) of an oil.

^{1}H NMR ($CDCl_3$): δ = [1.02 (s), 1.17 (s), 1.23 (s), and 1.34 (s); 6 H, $C(CH_3)_2$], 1.35 and 1.44 (2 × d, 3 H, J = 6.6 Hz, $CH(CH_3)$, 4.08 and 4.30 (2 × d, 2 × 1 H, AB system, J = 14.4 Hz, benzyl H), 4.26 and 4.90 (2 × q, 1 H, J = 6.6 Hz, $CH(CH_3)$ 7.26−7.42 (m, 5 H, phenyl H).

MS: m/z = 240 (55, M + H), 176 (100).

Anal. Calcd for $C_{12}H_{17}NO_2S$: C, 60.22; H, 7.16; N, 5.85. Found: C, 60.44; H, 7.43; N, 5.77.

3-Benzyl-5,5-dimethyl-[1,2,3]-oxathiazinane-2,2-dioxide (6)
Compound **4** (0.5 g) was used to produce **6,** which was purified by filtration through silica gel using CH_2Cl_2 and subsequent recrystallization from CH_2Cl_2−heptane to afford 0.38 g (71%); mp 61−62 °C; R_f 0.6 (CH_2Cl_2).

^{1}H NMR (CD_3CN): δ = 1.02 [s, 6 H, $C(CH_3)_2$], 2.97 (s, 2 H, ring CH_2), 4.28 and 4.30 (2 × s, 2 × 2 H, benzyl and ring CH_2), 7.28−7.32 (m, 5 H, phenyl H).

^{13}C NMR ($CDCl_3$): δ = 22.48, 31.65, 52.59, 58.71, 81.87, 128.11, 128.61, 128.66, 134.77.

MS: m/z = 278 (100, M + Na), 256 (5, M + H).

Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.44; H, 6.71; N, 5.48. Found: C, 56.44; H, 6.89; N, 5.35.

3-Benzyl-4,4,5-trimethyl-oxathiazolidine-2,2-dioxide (7)
Compound **5** (0.15 g, 0.63 mmol) was used to produce **7,** which was purified by filtration through a pad of silica gel using Et_2O and subsequent recrystallization from CH_2Cl_2−heptane to afford 0.134 g (83%); mp 64−65 °C.

^{1}H NMR ($CDCl_3$): δ = 1.15 and 1.22 [s, 2 × 3 H, $C(CH_3)_2$], 1.41 (d, 3 H, J = 6.3 Hz, $CHCH_3$), 4.16 and 4.36 (2 × d, 2 × 1 H, AB system, J = 15.9 Hz, benzyl H), 4.64 (q, 1 H, J = 6.3 Hz, $CHCH_3$), 7.30−7.45 (m, 5 H, phenyl H).

^{13}C NMR ($CDCl_3$): δ = 13.67, 17.58, 23.73, 45.34, 65.35, 85.49, 127.93, 128.21, 128.59, 136.20.

MS: m/z = 256 (100, M + H).

Anal. Calcd for $C_{12}H_{17}NO_3S$: C, 56.44; H, 6.71; N, 5.48. Found: C, 56.46; H, 6.83; N, 5.39.

Substitution Reactions
The nucleophilic displacement reactions were carried out under a variety of conditions. After solvent removal, the formed N−SO_3 intermediates were then hydrolyzed by treating with 20% $H_2SO_{4(aq)}$−Et_2O (1:1, 20 mL/g of sulfamidate). The mixture was stirred for 2 h at r.t. and then the organic phase, which contained unreacted starting material, was separated from the aq phase. The aq phase was then adjusted to pH = 10−12 using solid Na_2CO_3, the product was extracted into Et_2O and subsequently purified by column chromatography or by recrystallization of its HCl salt. ^{13}C NMR spectra from the three nitriles are provided as representatives of the three series of products.

1-Azido-2-benzylamino-2-methylpropane (8)
Compound **1** (0.1 g, 0.4 mmol) and NaN_3 (39 mg, 0.6 mmol) were added to anhyd DMF (1 mL); the mixture was stirred overnight at r.t. and then refluxed for 1 h to complete the reaction (TLC). The

solvent was evaporated and the residual product was hydrolyzed to yield 72 mg (88%) of crude **8**.

^{1}H NMR (CD_3CN): δ = 1.14 [s, 6 H, $C(CH_3)_2$], 3.29 (s, 2 H, CH_2N_3), 3.72 (s, 2 H, benzyl H), 7.22−7.41 (m, 5 H, phenyl H).

MS: *m*/*z* = 205.2 (100, M + H).

8·HCl

The product was converted to its HCl salt and then purified by recrystallization from MeOH−EtOAc to afford 59 mg (70%); mp 179−183 °C (dec.).

Anal. Calcd for $C_{11}H_{17}ClN_4$: C, 54.88; H, 7.12; N, 23.26. Found: C, 54.89; H, 7.18; N, 23.12.

3-Benzylamino-3-methyl-butyronitrile (9)
Compound **1** (0.1 g, 0.4 mmol) and NaCN (29 mg, 0.6 mmol) were dissolved in anhyd DMF (1 mL) and the mixture was stirred for 24 h at r.t. After solvent evaporation and subsequent hydrolysis, 69 mg of crude **9** was isolated as an oil.

^{1}H NMR (CD_3CN): δ = 1.26 [s, 6 H, $C(CH_3)_2$], 1.45 (br s 1 H, NH), 2.58 (s, 2 H, CH_2CN), 3.73 (s, 2 H, benzyl H), 7.25−7.41 (m, 5 H, phenyl H).

^{13}C NMR (DMSO-d_6): δ = 24.36, 27.61, 32.45, 54.24, 118.19, 129.76, 130.20, 130.95, 131.27.

MS: *m*/*z* = 211.2 (15, M + Na), 189.2 (100, M + H).

9·HCl

A sample (42 mg) was converted to its HCl salt to yield 32 mg (59%); mp 255−256 °C (dec.).

Anal. Calcd for $C_{12}H_{17}ClN_2$: C, 64.13; H, 7.63; N, 12.46. Found: C, 63.90; H, 7.77; N, 12.28.

1-(2-Benzylamino-2-methyl-propyl)-imidazole (10)
A mixture of **1** (0.2 g, 0.83 mmol), imidazole (0.565 g, 8.3 mmol) and Cs_2CO_3 (1.3 g, 4 mmol) in anhyd DMF (5 mL) was heated to 100 °C with stirring for 30 min. The solvent was removed and the mixture was hydrolyzed. Purification of crude **10** by column chromatography (silica/CH_2Cl_2−MeOH, 20:1; R_f 0.41) and conversion to its HCl salt in MeOH−Et_2O afforded 0.202 g (72%) of a white powder. Attempts to recrystallize **10**·2HCl from MeOH−EtOAc or MeOH−Et_2O were unsuccessful.

10·2HCl

^{1}H NMR (DMSO-d_6): δ = 1.47 [s, 6 H, $C(CH_3)_2$], 4.24 (s, 2 H, benzyl H), 4.77 [s, 2 H, CH_2N(imidazole)], 7.4 (m, 3 H, phenyl H), 7.7 [m, 3 H, phenyl and 4 (or 5)-imidazolyl H], 7.85 (t, 1 H, 5 (or 4)-imidazolyl H], 9.31 (s, 1 H, 2-imidazolyl H), 9.80−10.0 (br s, 1.5 H, NH).

^{13}C NMR (DMSO-d_6): δ = 20.94, 44.64, 53.21, 58.77, 119.70, 123.60, 128.44, 128.71, 128.81, 130.32, 132.16.

MS: *m*/*z* = 230.0 (35, M + H), 162 (100, M + H –$C_3H_4N_2$).

Anal. Calcd for $C_{14}H_{19}N_3$·2(HCl)·2.25(H_2O): C, 49.06; H, 7.50; N, 12.25. Found: C, 49.10; H, 7.63; N, 12.42.

***N*^{1}-Butyl-*N*^{2}-benzyl-2-methylpropane-1,2-diamine (11)**
A soln of **1** (0.1 g, 0.4 mmol) and butylamine (0.4 mL, 4mmol) in anhyd CH_3CN (1 mL) was refluxed and stirred for 6.5 h. Some starting material remained, thus additional butylamine (0.4 mL) and CH_3CN (0.5 mL) were added and refluxing was continued for 18 h. The mixture was cooled to r.t., an unidentified precipitate was filtered off, then the solvent was evaporated and the mixture hydrolyzed to yield 77 mg (82%) of crude **11** as an oil.

^{1}H NMR (CD_3CN): δ = 0.92 (t, 3 H, *J* = 7.2 Hz, butyl CH_3), 1.09 [s, 6 H, $C(CH_3)_2$], 1.3−1.45 [m, 5 H, butyl $CH_3(CH_2)_2$ and NH], 2.48 [s, 2 H, $C(CH_3)_2CH_2$], 2.56 (t, 2 H, *J* = 7.0 Hz, butyl CH_2NH), 3.66 (s, 2 H, benzyl H), 7.20−7.40 (m, 5 H, phenyl H).

MS: *m*/*z* = 235.2 (100, M + H), 162.1 (30, M + H – $C_4H_{11}N$), 128.1 (35).

A sample (64 mg) was converted to its HCl salt and purified recrystallization from MeOH−EtOAc to yield 64 mg (71%).

11·2HCl

Mp 216−219.5 °C.

Anal. Calcd for $C_{15}H_{28}Cl_2N_2$: C, 58.62; H, 9.18; N, 9.11. Found: C, 58.51; H, 9.35; N, 9.03.

***N*^{1}-(*sec*-Butyl)-*N*^{2}-benzyl-2-methylpropane-1,2-diamine (12)**
A soln of **1** (0.20 g, 0.83 mmol) in *sec*-butylamine (10 mL) was stirred and refluxed for 3 d. TLC showed that some material remained. After solvent removal the residue was hydrolyzed; 47 mg (23%) of **1** was recovered and 0.175 g of crude **12** was isolated.

MS: *m*/*z* = 235.1 (80, M + H), 162 (100, M + H – $C_4H_{11}N$).

^{1}H NMR (CD_3CN): δ = 0.88 (t, *J* = 7.5 Hz, 3 H, butyl CH_2CH_3), 0.99 (d, *J* = 6.3 Hz, 3 H, butyl $CHCH_3$), 1.08 [s, 6 H, $C(CH_3)_2$], 1.25−1.5 (m, 2 H, butyl CH_2), 2.0 (br s NH), overlapping signals [2.45 (m, butyl CH), 2.44 and 2.54 (2 × d, AB system, *J* = 11.4 Hz, benzyl H); 3 H], 3.65 [s, 2 H, $C(CH_3)_2CH_2N$], 7.2−7.35 (m, 5 H, phenyl H).

The product was converted to its HCl salt; yield was 0.173 g (70%) of **12**·2HCl. Recrystallization attempts using MeOH−Et_2O, CH_2Cl_2 or EtOAc were unsuccessful. **12**·2HCl

Anal. Calcd for $C_{15}H_{28}Cl_2N_2$: C, 58.62; H, 9.18; N, 9.11. Found: C, 58.24; H, 9.45; N, 8.92.

***N*^{1}-(*tert*-Amyl)-*N*^{2}-benzyl-2-methylpropane-1,2-diamine (13)**
Compound **1** (0.20 g, 0.83 mmol) was added to *tert*-amylamine (10 mL,) and the mixture was stirred and refluxed for 7 d. TLC showed some remaining starting material. After solvent removal and hydrolysis, 0.118 g (59%) of unreacted **1** was recovered.

Crude **13**

^{1}H NMR ($CDCl_3$): δ = 0.83 (t, *J* = 7.5 Hz, 3 H, amyl CH_2CH_3), 1.00 (s, 6 H, amyl CH_3), 1.11 [s, 6 H, $HNC(CH_3)_2$], 1.1 (br s 2 H, NH) 1.38 (q, *J* = 7.5 Hz, 2 H, amyl CH_2CH_3), 2.44 [s, 2 H, $C(CH_3)_2CH_2$], 3.66 (s, 2 H, benzyl H), 7.25−7.41 (m, 5 H, phenyl H).

MS: *m*/*z* = 249.1 (75, M + H), 162 (100, M + H – $C_5H_{13}N$).

The product was converted to its HCl salt (0.103 g, 41%), which could not be recrystallized.

13·2HCl

Mp 216−218.5 °C.

Anal. Calcd for $C_{16}H_{30}Cl_2N_2$: C, 59.80; H, 9.41; N, 8.71. Found: C, 59.14; H, 9.67; N, 8.50.

1-Azido-3-benzylamino-2,2-dimethylpropane (14)
A stirred mixture of **6** (0.3 g, 1.2 mmol) and NaN_3 (0.115 g, 1.8 mmol) in anhyd DMF (3 mL) was heated for 3 h at 100 °C. The solvent was evaporated under reduced pressure, the residual product was hydrolyzed and crude **14** (0.18 g) was isolated as an oil.

^{1}H NMR ($CDCl_3$): δ = 0.91 [s, 6 H, $C(CH_3)_2$], 1.3 (br s 1 H, NH), 2.43 (s, 2 H, propyl $HNCH_2$), 3.21 (s, 2 H, CH_2N_3), 3.78 (s, 2 H, benzyl H), 7.25−7.40 (br m, 5 H, phenyl H).

MS: *m*/*z* = 219.2 (M + H, 100).

The crude product was converted to its HCl salt and recrystallized from MeOH−EtOAc to yield 0.156 g (52%) of **14**·HCl.

Mp 174.5−179 °C.

Anal. Calcd for $C_{12}H_{19}ClN_4$: C, 56.57; H, 7.52; N, 21.98. Found: C, 56.29; H, 7.68; N, 21.66.

A small amount of **6** (50 mg) was recovered from the reaction.

4-Benzylamino-3,3-dimethylbutyronitrile (15)

A stirred mixture of **6** (0.3 g, 1.2 mmol) and NaCN (92 mg, 1.9 mmol) in anhyd DMF (3 mL) was heated at 100 °C for 3 h. The solvent was evaporated under reduced pressure and the residual product was hydrolyzed; 0.125 g of crude **15** was isolated as an oil.

^{1}H NMR ($CDCl_3$): δ = 1.04 [s, 6 H, $C(CH_3)_2$], 1.4 (br s 1 H, NH), 2.38 (s, 2 H, propyl $HNCH_2$), 2.49 (s, 2 H, CH_2CN), 3.80 (s, 2 H, benzyl H), 7.25−7.40 (m, 5 H, phenyl H).

MS: *m*/*z* = 203.2 (M + H, 100).

The product was converted to its HCl salt and recrystallized from MeOH−EtOAc to yield 0.123 g (44%).

15·HCl

Mp 151−153.5 °C.

^{13}C NMR (DMSO-d_6): δ = 24.40, 27.65, 32.47, 50.72, 54.18, 118.20, 128.54, 128.91, 130.41, 131.27.

Anal. Calcd for $C_{13}H_{19}ClN_2$: C, 65.39; H, 8.02; N, 11.73. Found: C, 65.18; H, 8.14; N, 11.59.

A small amount of **6** (25 mg) was recovered from the reaction.

3-Benzylamino-1-fluoro-2,2-dimethylpropane (16)

A stirred mixture of **6** (0.10 g, 0.39 mmol) and TBAF (0.8 mmol) in CH_3CN (5 mL) was refluxed for 3 h; no starting material remained (TLC). After hydrolysis, **16** was isolated as an oil.

^{1}H NMR ($CDCl_3$): δ = 0.93 [d, 6 H, J_{HF} = 1.8 Hz, $C(CH_3)_2$], 2.48 (d, 2 H, J_{HF} = 1.8 Hz, propyl $HNCH_2$), 3.79 (s, 2 H, benzyl H), 4.20 (d, 2 H, *J* = 48 Hz, CH_2F), 7.25−7.35 (m, 5 H, phenyl H).

^{19}F NMR ($CDCl_3$): δ = −225.83 (tm, *J* = 48 Hz).

MS: *m*/*z* = 196 (100, M + H).

The product was converted to its HCl salt (16 mg, 18%). Recrystallization from MeOH−EtOAc afforded 8 mg (~9%).

16·HCl

Mp 222−225 °C dec.

Anal. Calcd for $C_{12}H_{19}ClFN$: C, 62.19; H, 8.26; N, 6.04. Found: C, 62.19; H, 8.40; N, 5.98.

***N*^{1}-Butyl-*N*^{3}-benzyl-2,2-dimethylpropane-1,3-diamine (17)**

A soln of **6** (0.3 g) in butylamine (10 mL) and the mixture was refluxed for 8 d. After solvent removal and hydrolysis, crude **17** (0.19 g) was isolated as an oil. A small amount of **6** (35 mg) was recovered from the reaction.

^{1}H NMR ($CDCl_3$): δ = 0.93 (overlapping s and t, 9 H, *J* = 6.6 Hz, $C(CH_3)_2$ and butyl CH_3), [1.36 (m) and 1.45 (m,) over a broad hump (6 H), butyl CH_2 and NH], 2.45 and 2.46 [2 × s, 4 H, $CH_2C(CH_3)_2CH_2$], 2.58 (t, 2 H, *J* = 7.5 Hz, butyl CH_2NH), 3.80 (s, 2 H, benzyl H), 7.25−7.34 (m, 5 H, phenyl H).

MS: *m*/*z* = 249.2 (100).

This was converted to its HCl salt and recrystallized from MeOH−EtOAc to yield 0.213 g (61%).

17·HCl

Mp 240−242.5 °C.

Anal. Calcd for $C_{16}H_{30}Cl_2N_2$: C, 59.80; H, 9.41; N, 8.71. Found: C, 59.69; H, 9.65; N, 8.73.

2-Azido-3-benzylamino-3-methylbutane (18)

A soln of **7** (0.1 g, 0.4 mmol) and NaN_3 (40 mg, 0.62 mmol) in anhyd DMF was heated to 110 °C for 15 min. After solvent evaporation and hydrolysis of the residual product, crude **18** (70 mg) was isolated as an oil.

^{1}H NMR ($CDCl_3$): δ = 1.14 and 1.16 [2 × s, 6 H, $C(CH_3)_2$], 1.34 (d, 3 H, *J* = 6.6 Hz, $CHCH_3$), 1.45 (br s 1 H, NH), 3.61 (q, 1 H, *J* = 6.6 Hz,CHN_3), 3.71 and 3.77 (2 × d, 2 × 1 H, AB system, *J* = 12 Hz, benzyl H), 7.25−7.40 (m, 5 H, phenyl H).

MS: *m*/*z* = 219 (100, M + H), 148 (50).

After conversion to its HCl salt, the product was recrystallized from MeOH−EtOAc to yield 68 mg (68%).

18·HCl

Mp 154−156.5 °C.

Anal. Calcd for $C_{12}H_{19}ClN_4$·0.25 H_2O: C, 55.59; H, 7.58; N, 21.60. Found: C, 55.76; H, 7.70; N, 21.53.

3-Benzylamino-2,3-dimethylbutyronitrile (19)

A soln of **7** (0.1 g, 0.4 mmol) and NaCN in anhyd DMF (1.5 mL) was heated to 100 °C for 3 h. After evaporating the solvent under reduced pressure and applying the standard hydrolysis procedure, crude **19** (26 mg) was isolated as an oil. A small amount of **7** (35 mg) was recovered from the reaction. **19**:

^{1}H NMR ($CDCl_3$): δ = 1.24 and 1.30 [2 × s, 6 H, $C(CH_3)_2$], 1.32 (d, 3 H, *J* = 7.2 Hz, $CHCH_3$), 2.80 (q, 1 H, *J* = 7.2 Hz, CHCN), 3.64 and 3.76 (2 × d, 2 × 1 H, AB system, *J* = 12.3 Hz, benzyl H), 7.25−7.40 (m, 5 H, phenyl H).

MS: *m*/*z* = 203.2 (M + H, 100), 176.1 (M+, 10).

A sample was converted to its HCl salt and recrystallized from MeOH−EtOAc to yield 32 mg (22%).

19·HCl

Mp 192.5–195 °C.

^{13}C NMR (DMSO-d_6): δ =12.89, 20.23, 22.06, 32.23, 44.78, 59.56, 120.41, 128.42, 138.84, 130.66, 131.82.

Anal. Calcd for $C_{13}H_{19}ClN_2$·0.33 H_2O: C, 63.79; H, 8.03; N, 11.44. Found: C, 63.70; H, 8.32; N, 11.06.

Benzyl-(1,1-dimethyl-allyl)-amine (20)

A soln of **7** (0.05 g, 0.20 mmol) in butylamine (5 mL) was refluxed for 3 d. The standard hydrolysis procedure was applied and unreacted **7** (5 mg) and crude **20** were recovered. Crude **20** was purified by preparative TLC (silica/CH_2Cl_2−acetone, 1:1; R_f 0.38) to yield 0.015 g (44%) of an oil. Compound **20** was unstable at r.t. over a period of 2–3 weeks, yielding a mixture of products (TLC).

MS: *m*/*z* = 176 (30, M + H), 108 (100).

The reaction of **7** (20 mg) with TBAF (1.5 equiv) in CD_3CN (1 mL) was monitored by ^{1}H NMR. After 1 h at 80 °C, approximately 50% of **7** was consumed and the sole product was an elimination product by integration. Workup of a sample of this reaction using the standard hydrolyis conditions afforded **20** (yield not determined).

^{1}H NMR ($CDCl_3$): δ = 1.25 [s, 6 H, $C(CH_3)_2$], 3.46 (s, 2 H, benzyl H), 5.10 and 5.11 (overlapping d, 2 H, J_1 = 10.5 Hz, J_2 = 17.4 Hz, vinyl CH_2), 5.85 (dd, 1 H, J_1 = 10.2 Hz, J_2 = 17.7 Hz, vinyl CH), 7.22–7.35 (m, 5 H, phenyl H).

HRMS: *m*/*z* calcd for $C_{12}H_{18}N$ (M + 1), 176.14392; found, 176.14367.

Acknowledgement

We would like to thank Dr. John Grierson for many useful discussions and the National Institutes of Health for funding: Grants HL60221 and HL36728.

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