153.5 (s), 170.2 (s), 172.3 (s); EIMS m/z (rel intensity) 172 (M^+, 5), 130 (46), 129 (43), 102 (39), 87 (29), 86 (69), 59 (18), 43 (100); HRMS m/z calcd for $C_6H_8N_2O_4$ 172.0484, found m/z 172.0478. Anal. Calcd for $C_6H_8N_2O_4$: C, 41.86; H, 4.68; N, 16.27. Found: C, 41.52; H, 4.73; N, 15.94.

1-Acetyl-5-hydroxyhydantoin (2h): mp 139–143 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 2.62 (3 H, s), 5.61 (1 H, d, J = 8 Hz), 7.53 (1 H, d, J = 8 Hz, exchanges with D_2O), 11.65 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 24.7 (q), 77.5 (d), 153.4 (s), 168.7 (s), 170.7 (s); EIMS m/z (rel intensity) 158 (M^+, 6), 130 (9), 116 (36), 115 (45), 88 (15), 87 (23), 72 (34), 43 (100); HRMS m/z calcd for $C_5H_6N_2O_4$ 158.0328, found 158.0293. Anal. Calcd for $C_5H_6N_2O_4$: C, 37.98; H, 3.83; N, 17.72. Found: C, 37.75; H, 3.96; N, 17.51.

1-(Chloroacetyl)-5-hydroxyhydantoin (2i): mp 138–143 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 4.75 (1 H, d, J = 16 Hz), 4.86 (1 H, d, J = 16 Hz), 5.55 (1 H, d, J = 8 Hz), 7.64 (1 H, d, J = 8 Hz, exchanges with D_2O), 11.72 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 44.8 (t), 78.0 (d), 153.2 (s), 165.0 (s), 170.5 (s); EIMS m/z (rel intensity) 174 ($M^+ - H_2O$, 10), 143 (27), 115 (62), 72 (99), 44 (100); CIMS (C_4H_{10}) m/z (rel intensity) 193 (MH^+, 100). Anal. Calcd for $C_5H_5N_2O_4Cl$: C, 31.19; H, 2.62; N, 14.55. Found: C, 31.16; H, 2.45; N, 15.12.

1-(Methoxyacetyl)-5-hydroxyhydantoin (2j): mp 171–172 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 3.34 (3 H, s), 4.40 (1 H, d), 4.49 (1 H, d), 5.52 (1 H, s), 11.62 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 58.6 (q), 72.0 (t), 77.6 (d), 153.3 (s), 169.1 (s), 171.0 (s); EIMS m/z (rel intensity) 72 (26), 45 (100); CIMS (C_4H_{10}) m/z (rel intensity) 189 (MH^+, 100). Anal. Calcd for $C_6H_8N_2O_5$: C, 38.30; H, 4.28; N, 14.89. Found: C, 37.72; H, 4.05; N, 14.30.

1-Benzoyl-5-hydroxyhydantoin (2l): mp 102–104 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 5.80 (1 H, s), 7.5–7.7 (5 H, m), 11.52 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 78.3 (d), 128.2 (d), 129.0 (d), 132.5 (d), 134.6 (s), 152.5 (s), 168.2 (s), 171.0 (s); EIMS m/z (rel intensity) 220 (M^+, 6), 105 (100), 77 (11); HRMS m/z calcd for $C_{10}H_8N_2O_4$ 220.0484, found m/z 220.0491. Anal. Calcd for $C_{10}H_8N_2O_4$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.73; H, 3.81; N, 12.51.

1-Anisoyl-5-hydroxyhydantoin (2m): mp 158–161 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 3.39 (3 H, s), 5.83 (1 H, d, J = 8 Hz), 7.00 (2 H, d, J = 9 Hz), 7.49 (1 H, d, J = 8 Hz, exchanges with D_2O), 7.68 (2 H, d, J = 9 Hz), 11.46 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 55.5 (q), 78.1 (d), 113.2 (d), 126.2 (s), 131.6 (d), 152.5 (s), 162.7 (s), 167.0 (s), 171.0 (s); EIMS m/z (rel intensity) 250 (M^+, 11), 177 (4), 152 (4), 151 (5), 136 (12), 135 (100), 107 (4); HRMS m/z calcd for $C_{11}H_{10}N_2O_5$ 250.0589, found 250.0586. Anal. Calcd for $C_{11}H_{10}N_2O_5$: C, 52.80; H, 4.03; N, 11.20. Found: C, 52.56; H, 4.24; N, 11.48.

5-Hydroxy-5-(trifluoromethyl)hydantoin (3): mp 181–182 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 8.33 (1 H, s, exchanges with D_2O), 9.34 (1 H, s, exchanges with D_2O), 11.34 (1 H, br, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 82.8 (q, J = 33 Hz), 121.7 (q, J = 285 Hz), 155.7 (s), 169.1 (q, J = 3 Hz); EIMS m/z (rel intensity) 115 ($M^+ - CF_3$, 24), 87 (3), 44 (100); CIMS (C_4H_{10}) m/z (rel intensity) 185 (MH^+, 100). Anal. Calcd for $C_4H_3N_2O_3F_3$: C, 26.10; H, 1.64; N, 15.22. Found: C, 26.40; H, 1.72; N, 15.49.

5-Hydroxyhydantoin (4): mp 153–156 °C (lit.[14] mp 157–158 °C; ^1H NMR (270 MHz, DMSO-d_6) δ 5.09 (1 H, d, J = 8 Hz), 6.68 (1 H, d, J = 8 Hz, exchanges with D_2O), 8.28 (1 H, s, exchanges with D_2O), 10.59 (1 H, br s, exchanges with D_2O); ^{13}C NMR (70 MHz, DMSO-d_6) δ 77.3 (d), 157.3 (s), 174.9 (s); EIMS m/z (rel intensity) 116 (M^+, 3), 88 (100), 60 (23), 59 (55), 45 (62).

Parabanic acid (5): mp 236–240 °C dec lit.[1] mp 238–244 °C (dec); ^1H NMR (270 MHz, DMSO-d_6) δ 11.75 (2 H, br); EIMS m/z (rel intensity) 114 (M^+, 72), 86 (64), 43 (100).

1-Methylparabanic acid: mp 145–148 °C (lit.[15] mp 155–157 °C); ^1H NMR (270 MHz, DMSO-d_6) δ 2.92 (3 H, s), 12.00 (1 H, br); EIMS m/z (rel intensity) 128 (M^+, 13), 101 (7), 43 (100).

1,3-Dimethylparabanic acid: mp 150 °C (lit.[2] mp 153 °C); ^1H NMR (270 MHz, DMSO-d_6) δ 2.97 (6 H, s); EIMS m/z (rel intensity) 142 (M^+, 100), 114 (10), 70 (19).

(14) Henson, E. B.; Gallop, P. M.; Hauschka, P. V. *Tetrahedron* **1981**, *37*, 2561.

(15) Maly, R.; Hintergger, F. *Monatsh. Chem.* **1881**, *2*, 87.

Benzoylurea: mp 215 °C (lit.[16] mp 211–213 °C); ^1H NMR (270 MHz, CD_3OD) δ 5.30 (1 H, br), 7.48–7.87 (5 H, m), 8.38 (2 H, br); EIMS m/z (rel intensity) 164 (M^+, 46), 147 (5), 136 (16), 121 (7), 120 (5), 105 (100), 77 (17).

***N*-Formylbenzamide**: mp 84 °C; ^1H NMR (270 MHz, CD_3OD) δ 7.5–8.0 (5 H, m), 9.31 (1 H, s); EIMS m/z (rel intensity) 149 (M^+, 16), 122 (5), 121 (61), 105 (100), 77 (10).

Chloroacetic acid in the ozonolysis of (**1i**) was identified by comparing the mass spectrum with that of authentic sample and determined by gas chromatography. The conditions were as follows: column, 2% FFAP on Gas Chrom Q (80–100 mesh), 4 mm × 1 m, glass; column temperature, 80–210 °C, programmed at 10 °C min^{-1}; injection temperature, 220 °C; detector temperature, 240 °C; detector, FID.

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Registry No. **1a**, 66-22-8; **1b**, 608-34-4; **1c**, 65-71-4; **1d**, 4212-49-1; **1e**, 15761-83-8; **1f**, 54-20-6; **1g**, 26305-13-5; **1h**, 626-48-2; **1i**, 18592-13-7; **1j**, 124461-06-9; **1k**, 672-45-7; **1l**, 13345-09-0; **1m**, 33166-97-1; **1n**, 615-77-0; **1o**, 874-14-6; **1p**, 51-20-7; **1q**, 51-21-8; **2a**, 43152-24-5; **2b**, 124443-47-6; **2c**, 77719-76-7; **2d**, 124443-48-7; **2g**, 124443-49-8; **2h**, 124443-50-1; **2i**, 124443-51-2; **2j**, 124443-52-3; **2l**, 124443-53-4; **2m**, 124443-54-5; **3**, 105480-41-9; **4**, 29410-13-7; 1-methylparabanic acid, 3659-97-0; 1,3-dimethylparabanic acid, 5176-82-9; parabanic acid, 120-89-8; *N*-benzoylurea, 614-22-2; 6-(*p*-methoxyphenyl)-2-thiouracil, 33166-87-9.

(16) Kurzer, F.; Taylor, S. A. *J. Chem. Soc.* **1960**, 3234.

A Highly Convergent Synthesis of Benzimidazolylpiperidines

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The lithiation of suitably protected imidazoles and benzimidazoles has recently attracted considerable synthetic attention.[1] Of the various groups used to protect the imidazole nitrogen, the benzyl group is generally considered to be unsuitable due to problems of competing benzylic metalation.[2] We have maintained a long-standing interest in the chemistry and pharmacology of 4-aroylpiperidines. In this regard, we wished to prepare some 4-(2-benzimidazolyl)piperidines related to Astemizole (1), a recently marketed nonsedating antihistamine.[3] We now report a convenient synthesis of benzimidazolylpiperidine **2**, which relies on the acylation of 1-(4-fluorobenzyl)-benzimidazole. The 4-fluorobenzyl group in this instance not only serves as a protecting group allowing C_2-deprotonation but also as a part of the desired pharmacophore.

The benzimidazole portion of **2** was synthesized via the alkylation of benzimidazole (**3**) with 4-fluorobenzyl chloride

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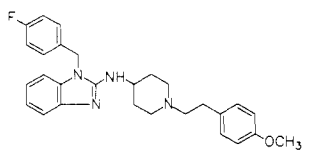
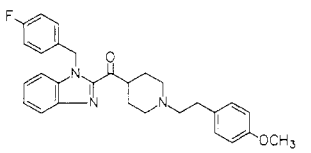


1



2

(NaH, DMF) giving protected benzimidazole **4** in 57% yield.[4] Metalation of **4** with *n*-butyllithium (THF, −78 °C) gave a red solution, which was quenched after 20 min with D_2O. Examination of the 300-MHz ^1H NMR spectrum of the product of this reaction revealed that metalation had occurred exclusively at the 2-position, no deuterium incorporation in the benzylic position being observed. The synthesis of the piperidine portion of **2** was accomplished via the alkylation of isonipecotic acid methyl ester[5] with 4-methoxyphenethyl bromide[6] (K_2CO_3, DMF), affording **5** in 63% yield. The synthesis of **2** was then completed by reacting the aforementioned anion of **4** with piperidine **5**, yielding the desired benzimidazolylpiperidine **2** in 38% yield[7] (Scheme I).

As part of this study, we also wished to prepare derivatives of **2** in which the phenethyl moiety was replaced by substituents containing carbanion-sensitive functional groups. To this end, isonipecotic acid methyl ester was protected with di-*tert*-butyl dicarbonate (aqueous NaOH, *tert*-butyl alcohol), giving **6** in 92% yield. Reaction of **6** with the anion of **4** gave a 34% yield[7] of *t*-Boc-benzimidazolylpiperidine, **7**, which was deprotected (TFA), yielding piperidine salt **8** in 84% yield. A variety of side chains could then be introduced. For example, alkylation of **8** with 4-methoxyphenethyl bromide completed a second synthesis of **2** in 57% yield while reaction with chlorobutyrophenone[8] **9** afforded a 57% yield of diketone **10**.

In conclusion, the highly convergent nature of the described methodology readily permits the preparation of multigram quantities of benzimidazolylpiperidines such as **2** and **10**.[9] Further studies addressing the biological activities of these compounds are currently in progress and will be reported at a later date.

Experimental Section[10]

Melting points were determined in open capillaries on a Thomas-Hoover apparatus and are uncorrected. IR spectra were obtained on a Perkin-Elmer 1800 spectrophotometer. ^1H NMR spectra were obtained on Varian XL300 and Gemini 300 spectrometers. Flash chromatography[11] was performed on silica gel (Merck 60, 230–400 mesh).

1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazole (4). To a stirred, room temperature solution of benzimidazole (11.8 g, 0.100 mol) and dry DMF (10 mL) was added portionwise NaH (4.4 g, 0.11 mol, 60% oil dispersion). After 30 min, 4-fluorobenzyl chloride (14.6 g, 0.101 mol) was added dropwise. After 17 h the reaction was quenched into H_2O. The aqueous mixture was extracted with a 2:1 mixture of EtOAc/toluene. The organic layer was washed twice with H_2O and once with saturated aqueous NaCl before being dried over anhydrous Na_2SO_4. The drying agent was removed by filtration, and the filtrate was evaporated at reduced pressure, affording an oil which was purified by flash chromatography (20% acetone/EtOAc). Kugelrohr distillation (230–245 °C (0.2 mm)) afforded an oil which solidified to a colorless solid: 1.08 g (57%); mp 60–62 °C; ^1H NMR ($CDCl_3$) δ 5.32 (s, 2 H), 6.97–7.07 (m, 2 H), 7.10–7.20 (m, 2 H), 7.22–7.32 (m, 3 H), 7.80–7.86 (m, 1 H), 7.93 (s, 1 H). Anal. Calcd for $C_{14}H_{11}FN_2$: C, 74.32; H, 4.90; N, 12.38. Found: C, 74.25; H, 4.94; N, 12.23.

1-[2-(4-Methoxyphenyl)ethyl]-4-piperidinecarboxylic Acid Methyl Ester (5). To a stirred, room temperature mixture of isonipecotic acid methyl ester, hydrochloride (15.0 g, 83.5 mmol), K_2CO_3 (23.1 g, 0.167 mol), and DMF (300 mL) was added 1-(2-bromoethyl)-4-methoxybenzene (17.97 g, 83.5 mmol). The reaction was then heated at 90 °C for 17 h. The reaction was poured into H_2O, and the aqueous mixture was extracted with a 2:1 mixture of EtOAc/toluene. The organic layer was washed twice with H_2O and once with saturated aqueous NaCl before being dried over anhydrous Na_2SO_4. The drying agent was removed by filtration, and the filtrate was evaporated at reduced pressure leaving an oil. Purification of this oil by flash chromatography (EtOAc) and crystallization from cyclohexane gave a colorless solid: 14.59 g (63%); mp 66–68 °C; IR (KBr) 1730, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71–1.98 (m, 4 H), 2.07 (dt, J = 11.5, 2.5 Hz, 2 H), 2.31 (tt, J = 11.0, 4.1 Hz, 1 H), 2.49–2.58 (m, 2 H), 2.70–2.78 (m, 2 H), 2.95 (dt, J = 11.5, 3.4 Hz, 2 H), 3.68 (s, 3 H), 3.78 (s, 3 H), 6.82 (d, J = 8.6 Hz, 2 H), 7.11 (d, J = 8.6 Hz, 2 H). Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.50; H, 8.40; N, 4.94.

1-(1,1-Dimethylethyl)-1,4-piperidinedicarboxylic Acid 4-(Methyl ester) (6). To a stirred suspension of isonipecotic acid methyl ester, hydrochloride (5.00 g, 27.8 mmol), and *tert*-butyl alcohol (56 mL) was added 1 M aqueous NaOH (29 mL, 29 mmol). After all of the starting ester had dissolved, di-*tert*-butyl dicarbonate (6.68 g, 30.6 mmol) was added. After 48 h, the excess *tert*-butyl alcohol was evaporated at reduced pressure. The concentrate was diluted with H_2O, and the aqueous mixture was extracted three times with EtOAc. The EtOAc extracts were combined, washed with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration, and the filtrate was evaporated at reduced pressure leaving an oil. Kugelrohr distillation (160–170 °C (0.3 mm)) afforded a clear colorless oil: 6.21 g (92%); IR (film) 1730, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H), 1.54–1.70 (m, 2 H), 1.80–1.93 (m, 2 H), 2.46 (tt, J = 11.1, 3.8 Hz, 1 H), 2.83 (br t, J = 12.3 Hz, 2 H), 3.69 (s, 3 H), 3.93–4.09 (m, 2 H). Anal. Calcd for $C_{12}H_{21}NO_4$: C, 59.24; H, 8.70; N, 5.76. Found: C, 58.92; H, 8.76; N, 5.45.

4-[[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]carbonyl]-1-piperidinecarboxylic Acid 1,1-Dimethylethyl Ester (7). To a stirred, −78 °C, solution of **4** (9.80 g, 46.2 mmol) and dry THF (80 mL) under argon was added via syringe a 2.5 M solution of *n*-butyllithium in hexane (20.0 mL, 50.0 mmol). After 15 min, a solution of **6** (11.24 g, 46.2 mmol) and dry THF (30 mL) was added via a dropping funnel. After 15 min the reaction was quenched by the addition of CH_3OH (10 mL). The cooling bath was removed, and when the reaction mixture reached room temperature it was poured into saturated aqueous NH_4Cl. The aqueous mixture was extracted three times with Et_2O. The Et_2O extracts were combined, washed with saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the filtrate was evaporated at reduced pressure leaving an oil. Purification of this oil by flash chromatography (20% EtOAc/hexane) and crystallization from cyclohexane afforded a colorless solid: 6.8 g (34%); mp 114–115 °C; IR (KBr) 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.47 (s, 9 H), 1.54–1.71 (m, 2 H), 1.93 (br d, J = 12.6 Hz, 2 H), 2.93 (br t, J = 12.6 Hz, 2 H), 4.06 (tt, J = 11.6, 3.6 Hz, 1 H), 4.12–4.26 (m, 2 H), 5.80 (s, 2 H), 6.91–7.01 (m, 2 H), 7.06–7.16 (m, 2 H), 7.35–7.47 (m, 3 H), 7.90–7.94 (m, 1 H). Anal. Calcd for $C_{25}H_{28}FN_3O_3$: C, 68.63; H, 6.45; N, 9.60. Found: C, 68.81; H, 6.51; N, 9.56.

[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]-4-piperidinylmethanone Mono(trifluoroacetate) (8). A solution of **7** (1.65 g, 3.77 mmol) and TFA (10 mL) was stirred at room temperature for 30 min. The reaction was diluted with Et_2O (150 mL), and the mixture was then cooled in an ice bath. The precipitate was collected by filtration, washed with Et_2O, and dried

(4) The yields presented in this manuscript were calculated following purification to analytical purity (C, H, N, ±0.32% of theoretical).

(5) Hanousek, V.; Prelog, V. *Collect. Czech. Chem. Commun.* **1932**, *4*, 259.

(6) Shoesmith, J. B.; Connor, R. J. *J. Chem. Soc.* **1927**, 2230.

(7) The relatively low yields of **2** and **4** which we report are largely due to mechanical losses incurred in crystallization. We have observed the formation of small quantities of 2-*n*-butyl-1-(4-fluorobenzyl)benzimidazole as well as some other minor, as yet unidentified, byproducts.

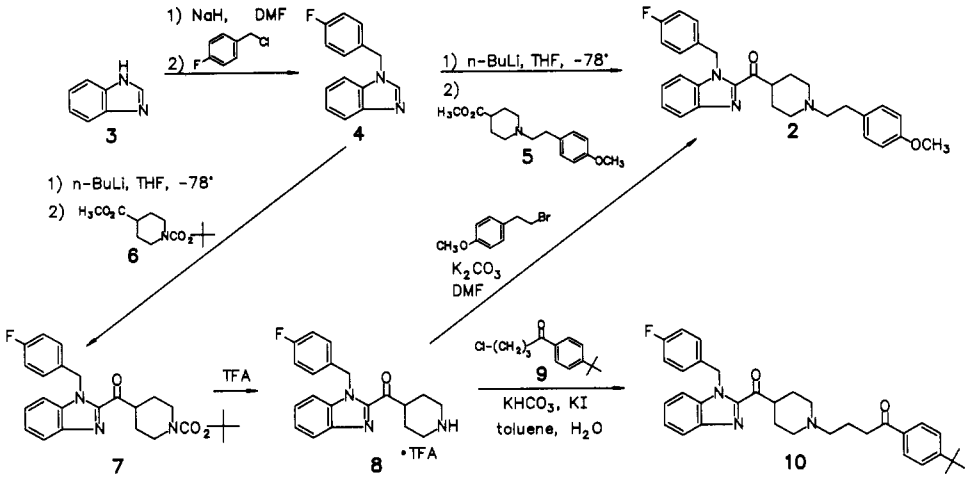
(8) Van de Westeringh, C.; Hermans, B., Raeymaekers, F.; Van der Eycken, C. *Ind. Chim. Belg.* **1960**, *25*, 1073.

(9) Preliminary pharmacological evaluation of **2** indicates that it is a potent antihistamine.

(10) The product names in this section were provided by Chemical Abstracts Service, Columbus, OH.

(11) Still, W. G.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Scheme I



by suction. Crystallization from EtOH/Et_2O afforded colorless needles: 1.43 g (84%); mp 213–215 °C dec; IR (KBr) 1690, 1680 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.68–1.84 (m, 2 H), 2.05–2.18 (m, 2 H), 3.11 (dt, J = 12.6, 2.6 Hz, 2 H), 3.30–3.45 (m, 2 H), 4.13 (tt, J = 11.4, 3.5 Hz, 1 H), 5.86 (s, 2 H), 7.09–7.23 (m, 4 H), 7.37–7.51 (m, 2 H), 7.77 (d, J = 7.8 Hz, 1 H), 7.89 (d, J = 8.1 Hz, 1 H), 8.62 (br s, 1 H). Anal. Calcd for $C_{20}H_{20}FN_3O \cdot CF_3CO_2H$: C, 58.54; H, 4.69; N, 9.31. Found: C, 58.55; H, 4.77; N, 9.29.

[1-[(4-Fluorophenyl)methyl]-1*H*-benzimidazol-2-yl][1-[2-(4-methoxyphenyl)ethyl]-4-piperidinyl]methanone (2). To a stirred, −78 °C, solution of **4** (1.13 g, 5.00 mmol) and dry THF (12 mL) under argon was added via syringe a 2.5 M solution of *n*-butyllithium in hexane (2.1 mL, 5.2 mmol). After 15 min a solution of **5** (1.39 g, 5.01 mmol) and dry THF (6 mL) was added dropwise via syringe. After 5–10 min, the cooling bath was removed, and after 30 min the reaction was quenched by the addition of saturated aqueous NH_4Cl. The aqueous mixture was extracted twice with EtOAc. The EtOAc extracts were combined, washed with saturated aqueous NaCl, and dried over anhydrous Na_2SO_4. The drying agent was removed by filtration, and the filtrate was evaporated at reduced pressure leaving an oil. Purification of this oil by flash chromatography (EtOAc) and crystallization from cyclohexane afforded off-white, matted needles: 0.90 g (38%); mp 109–111 °C; IR (KBr) 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71–1.88 (m, 2 H), 1.98 (br d, J = 11.9 Hz, 2 H), 2.24 (dt, J = 11.6, 2.5 Hz, 2 H), 2.54–2.62 (m, 2 H), 2.72–2.80 (m, 2 H), 3.05 (dt, J = 11.6, 3.2 Hz, 2 H), 3.78 (s, 3 H), 3.88 (tt, J = 11.5, 3.8 Hz, 1 H), 5.79 (s, 2 H), 6.79–6.86 (m, 2 H), 6.90–7.00 (m, 2 H), 7.06–7.17 (m, 4 H), 7.33–7.46 (m, 3 H), 7.87–7.96 (m, 1 H). Anal. Calcd for $C_{29}H_{30}FN_3O_2$: C, 73.86; H, 6.41; N, 8.91. Found: C, 73.98; H, 6.48; N, 8.90.

Alternate Preparation of 2. To a stirred, room temperature mixture of **8** (1.82 g, 4.03 mmol), K_2CO_3 (1.39 g, 10.0 mmol), and DMF (15 mL) was added 1-(2-bromoethyl)-4-methoxybenzene (0.87 g, 4.0 mmol). The reaction was then heated at 90 °C for 22 h. The reaction was poured into H_2O, and the aqueous mixture was extracted with a 2:1 mixture of EtOAc/toluene. The organic layer was washed twice with H_2O and once with saturated aqueous NaCl before being dried over anhydrous Na_2SO_4. The drying agent was removed by filtration, and the filtrate was evaporated at reduced pressure leaving an oil. Purification of this oil by flash chromatography (EtOAc) and crystallization from cyclohexane afforded off-white, matted needles: 1.08 g (57%). This material was spectroscopically identical with the previous sample of **2**. Anal. Calcd for $C_{29}H_{30}FN_3O_2$: C, 73.86; H, 6.41; N, 8.91. Found: C, 73.73; H, 6.50; N, 8.90.

1-[4-(1,1-Dimethylethyl)phenyl]-4-[4-[[1-[(4-fluorophenyl)methyl]-1*H*-benzimidazol-2-yl]carbonyl]-1-piperidinyl]-1-butanone (10). A stirred mixture of **8** (5.00 g, 11.1 mmol), **9** (6.20 g, 26.0 mmol), $KHCO_3$ (2.5 g, 25 mmol), KI (0.19 g, 1.1 mmol), toluene (50 mL), and H_2O (5 mL) was refluxed 72 h. The reaction was poured into H_2O, and the aqueous mixture was extracted with EtOAc. The EtOAc layer was washed with H_2O and saturated aqueous NaCl before being dried over anhydrous $MgSO_4$. The drying agent was removed by filtration, and the filtrate was evaporated at reduced pressure leaving an oil. Purification of this oil by flash chromatography (EtOAc) and crystallization from cyclohexane/hexane afforded colorless matted needles: 3.4 g (57%); mp 105–106 °C; IR (KBr) 1690, 1670 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H), 1.63–1.80 (m, 2 H), 1.87–2.01 (m, 4 H), 2.16 (dt, J = 11.8, 2.4 Hz, 2 H), 2.43 (t, J = 7.3 Hz, 2 H), 2.92–3.03 (m, 4 H), 3.85 (tt, J = 11.6, 3.8 Hz, 1 H), 5.79 (s, 2 H), 6.90–7.00 (m, 2 H), 7.07–7.15 (m, 2 H), 7.34–7.50 (m, 5 H), 7.89–7.94 (m, 3 H). Anal. Calcd for $C_{34}H_{38}FN_3O_2$: C, 75.67; H, 7.10; N, 7.79. Found: C, 75.65; H, 7.16; N, 7.78.

Registry No. **2**, 124461-07-0; **3**, 51-17-2; **4**, 124443-67-0; **5**, 124461-08-1; **6**, 124443-68-1; **7**, 124443-69-2; **8**, 124443-71-6; **9**, 43076-61-5; **10**, 124443-72-7; methyl 4-piperidinecarboxylate hydrochloride, 7462-86-4; 4-fluorobenzyl chloride, 352-11-4; 1-(2-bromoethyl)-4-methoxybenzene, 14425-64-0.

Direct Polynitroaliphatic Alcohol Addition to Alkenes. 1. Synthesis of New 2-Fluoro-2,2-dinitroethyl Acetals and Ethers[1]

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Acetal- and ether-compounds containing the 2-fluoro-2,2-dinitroethoxy structure represent an important class of energetic compounds for potential use in formulated propellant and explosive materials, but, their synthesis routes are severely limited. This limitation results from the inherent instability of the *gem*-2,2-dinitroaliphatic alcohol structure in alkaline or acidic solution[4] and from the very weak nucleophilic properties exhibited by this class of alcohol reactants.[5-7] Therefore, the usual alkaline or acidic conditions for converting alcohols into acetals or ethers cannot be used with *gem*-2,2-dinitroaliphatic alcohols like 2-fluoro-2,2-dinitroethanol (FDNEOH) because deformylation occurs, producing formaldehyde and either

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