Reactions of 1-Aza-3-ethylbicyclo[1.1.0]butane with Electrophiles. A Facile Entry into New, *N*-Substituted 3-Ethylideneazetidines and 2-Azetines

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Reaction of 1-aza-3-ethylbicyclo[1.1.0]butane (**3**) with N_2O_4 under a variety of experimental conditions afforded several products, **4**–**7**, all of which resulted via addition across the strained central C(3)–N σ-bond in **3**. The corresponding reactions of $ClCO_2Et$, Tf_2O, and Ms_2O with **3** also have been studied. These reactions provide useful methods for synthesizing *N*-substituted 3-ethylideneazetidines and 2-azetines.

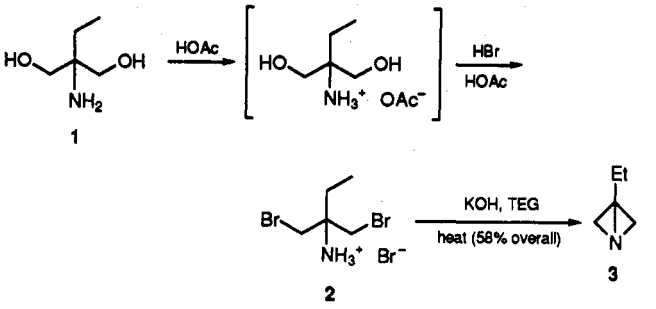
Introduction

Nitrogen-containing small-ring heterocyclic compounds that contain several NO_2 groups are of intense current interest to the energetic materials community, since compounds of this type are members of an important class of explosives and propellants. An example in this regard is 1,3,3-trinitroazetidine (TNAZ), whose synthesis was first reported in 1990.[1a] Substituted azetidines (i.e., azacyclobutanes) have attracted attention in recent years; this attention has focused upon their synthesis[2] and investigation of the biological activity of some substituted azetidines.[3] Moreover, functionalized azetidines occur in nature; recently, there has been a surge in activity in the total synthesis of natural products which contain this unusual heterocyclic ring system.[4,5]

As part of a continuing program which is concerned with the synthesis and chemistry of polynitropolycyclic compounds,[6] we have undertaken a study of the reaction of 1-aza-3-ethylbicyclo[1.1.0]butane[7] (**3**) with N_2O_4. In so doing, we hoped to be able to add the elements of N_2O_4 across the strained central C(3)–N σ-bond in **3**, with the expectation that the resulting adduct(s) might serve as useful intermediates from which new polynitro-substituted azetidines might be prepared. Precedents in this regard are supplied by the results of previously reported studies of addition of N_2O_4 across the strained central C(1)–C(3) σ-bond in bicyclo[1.1.0]butanes,[1b] bicyclo[1.1.1]pentanes,[8] and [1.1.1]propellanes.[9] Although the synthesis of **3** has been reported previously,[7] no study of its reaction with N_2O_4 has hitherto been reported.

In the course of this work, reactions of **3** with several different electrophiles (i.e., $ClCO_2Et$, Tf_2O, and Ms_2O) have been studied. In many cases, these reactions have provided useful new intermediates for synthesizing new N-substituted 3-ethylideneazetidines and 2-azetines.

Scheme 1



Results and Discussion

Compound **3** was prepared in 58% overall yield in two steps from 2-amino-2-ethyl-1,3-propanediol. A modification of Funke's[7] procedure was used for this purpose (Scheme 1).

The reaction of **3** with N_2O_4 was studied under a variety of experimental conditions; the results of these studies are summarized in Table 1. The structures of products **4** and **5** were established unequivocally by application of X-ray crystallographic methods. The structures of **6** and **7** were arrived at via analysis of their respective IR spectra and ^1H and ^{13}C NMR spectra. In a separate experiment, **6** was synthesized via direct oxidation of **5** by using 98% HNO_3–$(CF_3CO)_2O$.

Although N_2O_4 adds smoothly across the highly strained C(3)–N σ-bond in **3**, the data shown in Table 1 confirm the fact that this does not result in the introduction of both a new *N*-NO_2 and a new *C*-NO_2 group into the resulting azetidine. Thus, the behavior of **3** toward N_2O_4 differs markedly from that of the corresponding strained carbocyclic systems, cited above.[1,8,9]

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(3) (a) Takeuchi, T.; Prokop, D. J. *Biochem. Biophys. Acta* **1969**, *175*, 142. (b) Prokop, D. J. *Biochem. Biophys. Acta* **1969**, *175*, 156.

(4) E.g., mugineic acid: (a) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron* **1993**, *49*, 8211. (b) Matsuura, F.; Hamada, Y.; Shioiri, T. *Tetrahedron Asymmetry* **1992**, *3*, 1069.

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(8) Wiberg, K. B.; Ross, B. S.; Isbell, J. J.; McMurdie, M. *J. Org. Chem.* **1993**, *58*, 1372.

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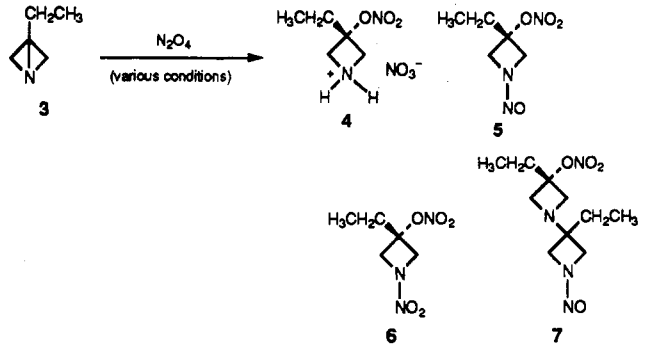
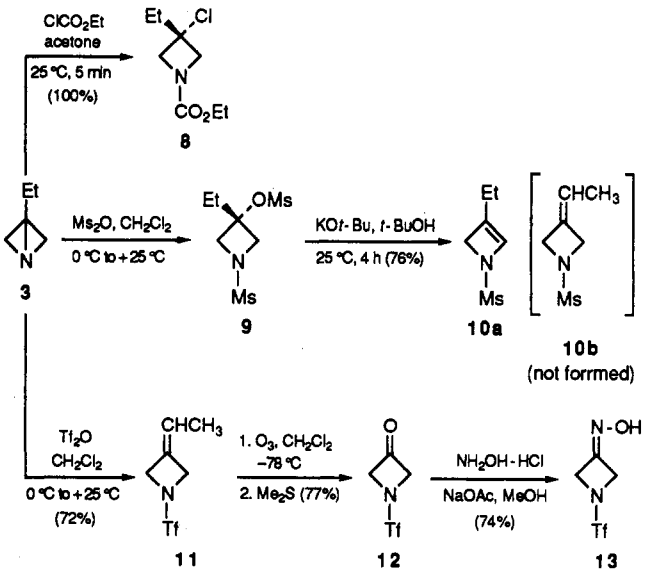
Table 1. Reactions of 3 with N_2O_4



meth-od	conditions	products (% yield) 4	5	6	7
A	Et_2O–THF–pentane (1:1:1), 1.1 mmol of N_2O_4, −40 °C (15 min), warm to rt (45 min), argon, nonaqueous workup	30	23		
B	CH_2Cl_2, excess N_2O_4, 0 °C (15 min), argon		70		
C	Et_2O, excess N_2O_4, 0 °C (25 min), argon		72		
D	CH_2Cl_2, excess N_2O_4, 0 °C (1 h), atmospheric O_2		36		4
E	Et_2O, excess N_2O_4, 0 °C (10 min), O_2 bubbler		68		
F	Et_2O, excess N_2O_4, 0 °C (10 min), hν (450-W medium pressure Hg lamp)		20	21	

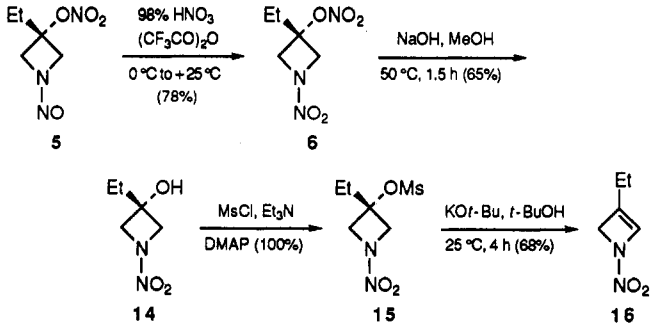
Scheme 2



Reactions of **3** with some additional electrophiles were studied. Thus, $ClCO_2Et$ was found to add smoothly across the C(3)–N σ-bond in **3**, thereby affording *N*-carbethoxy-3-chloro-3-ethylazetidine (**8**) in essentially quantitative yield. Similarly, methanesulfonyl anhydride (Ms_2O) and triflic anhydride (Tf_2O) add across this same σ-bond in **3**. In the case of Ms_2O, simple 1,2-addition occurs with concomitant formation of *N*-(methanesulfonyl)-3-ethyl-3-[(methanesulfonyl)oxy]azetidine (**9**) (74%). Base-promoted elimination of MsOH from **9** afforded *N*-(methanesulfonyl)-2-ethyl-2-azetine (**10a**, 76%, Scheme 2).

However, the corresponding reaction of **3** with Tf_2O is more complex. In this case, a simple addition product is not isolated; instead, the reaction proceeds to afford an alkene, *N*-[(trifluoromethane)sulfonyl]-3-ethylideneazetidine (**11**, 68%). Unequivocal characterization of **11** was accomplished via ozonolysis (to afford the corresponding ketone **12**) followed by oxime formation (to afford **13**); the structure of **13** was established via application of X-ray crystallographic methods. The foregoing results are summarized in Scheme 2.

Scheme 3



It seems reasonable to suggest that Tf_2O, like Ms_2O, simply adds across the C(3)–N σ-bond in **3** to form an intermediate, i.e., *N*-[(trifluoromethane)sulfonyl]-3-ethyl-3-(triflyloxy)azetidine, which is not stable to the reaction conditions employed for its formation. Thus, this putative intermediate spontaneously eliminates TfOH to afford the observed product **11**. In this event, it is interesting to note that this spontaneous elimination step proceeds to form an alkene which contains an *exocyclic* carbon–carbon double bond. By way of contrast, base-promoted elimination of MsOH from **9** affords an alkene, **10a**, which contains an *endocyclic* carbon–carbon double bond. The results of MOPAC calculations[10] (AM1 Hamiltonian)[11] reveal that **10a** is favored thermodynamically *vis-à-vis* **10b** by *ca.* 12 kcal/mol. Thus, we conclude that base-promoted elimination of MsOH from **9** affords **10a** via a kinetically controlled process. A detailed study of the mechanism of this elimination reaction is underway in our laboratory.

Finally, the major product **5**, formed via addition of N_2O_4 across the C(3)–N σ-bond in **3**, was converted into *N*-nitro-3-ethyl-2-azetine (**16**) via the sequence of reactions shown in Scheme 3. Thus, oxidation of the *N*-NO group in **5** to *N*-NO_2 afforded **6** (78% yield). Base-promoted hydrolysis of the *O*-nitrate ester group in **6** then gave **14** (65% yield). Esterification of the resulting alcohol with MsCl produced an essentially quantitative yield of **15**; subsequent base-promoted elimination of the elements of MsOH from **15** afforded the corresponding 2-azetine **16** (68% yield).

Relatively few substituted 2-azetines have been reported in the literature. Examples in this regard generally fall into one (or both) of two categories: (i) they contain electron-withdrawing substituents on the ring nitrogen atoms (e.g., *N*-Ts or *N*-CO_2Me),[12a] and/or (ii) they possess a conjugating electron-donating substituent on the 2-position (e.g., Ph or OR) and/or a conjugating electron-withdrawing substituent on the 3-position (e.g., CN).[13] Relatively little is known about the chemistry of these unusual compounds, which nominally might be regarded as being highly strained enamines.[12b]

(10) Stewart, J. J. P. MOPAC, version 6.0; QCPE 504.
(11) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(12) (a) Warrener, R. N.; Kretschmer, G.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1977**, 896. (b) However, it has been reported[12a] that *N*-(*p*-toluenesulfonyl)-2-azetine fails to undergo typical enamine cycloaddition reactions with, e.g., tetracyanoethylene or with 1,3-diphenylisobenzofuran.
(13) For examples, see: Moore, J. A.; Ayers, R. S. *Small Ring Heterocycles-Part 2*; Hassner, A., Ed.; Wiley: Interscience, New York, 1983; pp 1–217.

It should be noted that *N*-nitro enamines (i.e., *N*-nitro vinylamines) also are relatively rare. Acyclic examples have been reported by Russian investigators;[14] however, to our knowledge, **16** is the first example of a cyclic *N*-nitro enamine.

In the past, 3-azetidinols generally have been synthesized via reactions of epichlorohydrin with various amines.[1] However, this method does not lend itself to the preparation of 3-alkyl-3-X-azetidines. The synthetic routes described herein and presented in Schemes 1–3 provide powerful new synthetic methodology for this purpose.

Experimental Section

Melting points are uncorrected. 2-Amino-2-ethylpropane-1,3-diol was used as obtained from Aldrich Chemical Co. High-resolution mass spectra were obtained at the Midwest Center for Mass Spectrometry, Department of Chemistry, University of Nebraska, Lincoln, NE 68588-0362.

2-Amino-1,3-dibromo-2-ethylpropane Hydrobromide (2). A modification of the procedure described by Funke[7a] was used to synthesize **2**. Thus, a solution of 2-amino-2-ethylpropane-1,3-diol (60.0 g, 0.5 mol) in $CHCl_3$ (500 mL) was cooled to 5 °C in an ice–water bath. To this cooled solution was added portionwise with stirring glacial HOAc (45 g, 0.75 mol). The external cold bath then was removed, and the resulting mixture was allowed to warm gradually to rt during 45 min. Diethyl ether (300 mL) was added, and the resulting mixture was filtered. The residue was washed with Et_2O (3 × 50 mL) and then dried *in vacuo*. 2-Ammonio-2-ethylpropane-1,3-diol acetate (89.0 g, 99%) was obtained as a colorless microcrystalline solid: mp 133–135 °C. This material was used as obtained in the next step.

The ammonium acetate salt (5.0 g, 28 mmol) was dissolved in a solution of 30% HBr in acetic acid (20 mL), and the resulting solution was cooled to 5 °C in an ice bath. Dry HBr gas was passed into this cooled solution until the reaction mixture was saturated with HBr, and the resulting thick syrup was heated in a sealed tube at 170 °C for 12 h. The reaction mixture then was cooled to rt and was diluted with water (100 mL). The resulting aqueous mixture was concentrated *in vacuo*. The residue was dissolved in hot EtOH (100 mL). The resulting solution was clarified with Norite and then was filtered. The filtrate was concentrated *in vacuo* to afford **2** (6.7 g, 73%) as a colorless microcrystalline solid: mp 234–235 °C (lit.[7a] mp 230 °C).

1-Ethyl-3-azabicyclo[1.1.0]butane (3).[7b] A mixture of **2** (6.0 g, 18 mmol) and KOH (11.2 g, 144 mmol) in tetraethylene glycol (TEG, 20 mL) was heated at 180 °C for 45 min, during which time product distilled from the reaction mixture, giving pure **3** (1.2 g, 79%) as a colorless oil: bp 86 °C (1 atm) [lit.[7b] bp 87 °C (1 atm)]; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, J = 7.4 Hz, 3 H), 0.95 (s, 2 H), 1.82 (q, J = 7.4 Hz, 2 H), 2.05 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 9.7 (q), 20.3 (t), 31.2 (s), 52.9 (t).

Reaction of 1-Aza-3-ethylbicyclo[1.1.0]butane (3) with N_2O_4. Method A. A solution of N_2O_4 (20% v/v in ether, 0.50 mL, 1.1 mmol) was added to a 1:1:1 mixture of dry THF, ether, and pentane (6 mL), and the resulting solution was cooled externally to −40 °C. To this cold solution was added with stirring a solution of **3** (100 mg, 1.2 mmol) in a 1:1:1 mixture of dry THF, ether, and pentane (6 mL). The resulting mixture was stirred at −40 °C for 15 min, at which time the cold bath was removed, and the reaction mixture was allowed to warm gradually to rt during 45 min. The reaction mixture contained a free-flowing colorless precipitate and a yellow sticky mass. The colorless solid was collected by suction filtration, leaving the yellow mass behind in the reaction flask. The residue was washed with pentane (10 mL) and then dried *in vacuo*. The resulting crude solid was recrystallized from CH_2Cl_2–EtOAc–MeOH mixed solvent to afford pure **4** (53 mg, 30%) as a colorless microcrystalline solid: mp 102–103 °C; IR (KBr) 3061 (br, m), 2973 (br, m), 1633 (s), 1357 (s), 844 cm^{-1} (s); ^{1}H NMR (CD_3OD) δ 1.05 (t, J = 7.5 Hz, 3 H), 2.25 (q, J = 7.7 Hz, 2 H), 4.31 (AB, J_{AB} = 12.4 Hz, 2 H), 4.42 (AB, J_{AB} = 12.4 Hz, 2 H); ^{13}C NMR (CD_3OD) δ 7.0 (q), 27.2 (t), 55.3 (t), 85.9 (s). Anal. Calcd for $C_5H_{11}N_3O_6$: C, 28.71; H, 5.30; N, 20.09. Found: C, 29.00; H, 5.47; N, 20.00. The structure of **4** has been established unequivocally via X-ray crystallographic methods.

Diethyl ether (25 mL) was added to the filtrate, and the resulting mixture was washed sequentially with water (10 mL) and brine (20 mL). The organic layer was dried (Na_2SO_4), and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on a silica gel column (1.5 cm × 10 cm, 10% EtOAc–hexane eluent). Compound **5** (48 mg, 23%) was obtained as a pale yellow oil, which solidified upon trituration with CH_2Cl_2. The resulting solid was purified by recrystallization from CH_2Cl_2–hexane to afford pure **5** as a colorless microcrystalline solid: mp 41–42 °C; IR (film) 2972 (br, w), 1641 (s), 1548 (s), 1299 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 1.02 (t, J = 8.0 Hz, 3 H), 2.15 (dq, J = 6.0, 2.0 Hz, 2 H), 4.21 (br s, 2 H), 4.95 (br s, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.3 (q), 27.1 (t), 60.6 (t), 63.0 (t), 82.8 (s). Anal. Calcd for $C_5H_9N_3O_4$: C, 34.29; H, 5.18; N, 23.99. Found: C, 34.36; H, 5.17; N, 23.88. The structure of **5** has been established unequivocally via X-ray crystallographic methods.

Method B. A solution of **3** (83 mg, 1.0 mmol) in CH_2Cl_2 (5 mL) was cooled to 0 °C. To this cooled solution was added with stirring neat N_2O_4 (1 mL, excess) dropwise via syringe under argon at 0 °C. After the addition of N_2O_4 had been completed, the resulting homogeneous reaction mixture was stirred at 0 °C for 15 min. Ethyl alcohol (5 mL) then was added, and the reaction mixture was concentrated *in vacuo*. The residual pale yellow oil was purified by column chromatography on silica gel (10% EtOAc–hexane eluent). Pure **5** (120 mg, 70%), a pale yellow oil, was obtained as the only reaction product. This material was identical in all respects with **5** produced via method A (*vide supra*).

Method C. A solution of **3** (100 mg, 1.20 mmol) in dry Et_2O (10 mL) was cooled to 0 °C. Dinitrogen tetraoxide gas (excess) was bubbled slowly through the cooled reaction mixture during 10 min, during which time the reaction mixture was stirred vigorously. The resulting mixture was stirred at 0 °C for an additional 15 min and then poured rapidly into saturated aqueous NaCl (50 mL). The organic layer was separated, and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed sequentially with water (25 mL) and brine (25 mL) and dried (Na_2SO_4), and the filtrate was concentrated *in vacuo*. The residue was purified via column chromatography on a short silica gel column by eluting with 30% EtOAc–hexane. Pure **5** (151 mg, 72%) was obtained as a pale yellow oil which was identical in all respects with **5** produced via method A (*vide supra*).

Method D. A solution of **3** (900 mg, 10.8 mmol) in CH_2Cl_2 (10 mL) was cooled to 0 °C. To this cooled solution was added with stirring neat N_2O_4 (4 mL, excess) dropwise via syringe. During this period, the reaction mixture was continually exposed to atmospheric oxygen. After the addition of N_2O_4 had been completed, the resulting mixture was stirred for 1 h and then was poured over crushed ice (10 g). The resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic extracts were washed sequentially with 10% aqueous $NaHCO_3$ (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried (Na_2SO_4), and the filtrate was concentrated *in vacuo*. The yellow residue was purified via column chromatography on silica gel (3% EtOAc–hexane eluent). Workup of the initial chromatography fractions afforded **5** (680 mg, 36%). Continued elution of the chromatography column with 5% EtOAc–hexane afforded **7** (100 mg, 4%) as a yellow microcrystalline solid: mp 65–66 °C; IR (film) 2970 (s), 2866 (m), 1639 (vs), 1631 (vs), 1454 (m), 1407 (s), 1353 (s), 1303 (vs), 1277 (s), 1248 (s), 852 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3 H), 0.97 (t, J = 7.4 Hz, 3 H), 1.62 (q, J = 7.3 Hz, 2 H), 2.12 (q, J = 7.4 Hz, 2 H), 3.28 (dd, J = 4.7, 8.0 Hz, 2 H), 3.44 (t, J = 8.2 Hz, 2 H), 3.76 [d(*AB*), J = 13.1, 2.1 Hz, 1 H], 3.99 [d(*AB*), J = 15.0, 2.0 Hz, 1 H], 4.45 [d(*AB*), J = 11.2, 2.1 Hz, 1 H], 4.73 (d(*AB*), J = 11.2, 1.9 Hz, 1 H]; ^{13}C NMR ($CDCl_3$) δ 7.3 (q), 7.8 (q), 26.6 (t), 28.5 (t), 55.7 (t), 56.0 (t), 56.2 (t), 58.1 (t), 59.6 (s), 82.2 (s). Anal. Calcd for $C_{10}H_{18}N_4O_4$: C, 46.50; H, 7.02; N, 21.69. Found: C, 46.60; H, 7.11; N, 21.41.

(14) (a) Vereshchagin, L. I.; Kirillova, L. P.; Luzgina, G. M.; Gareev, G. A. *J. Org. Chem. U.S.S.R.* **1985**, *21*, 806 and references cited therein. (b) Gafarov, A. N.; Zakirova, G. T.; Novikov, S. S.; Ermolaeva, V. A.; Vorob'eva, V. V. *J. Org. Chem. U.S.S.R.* **1973**, *9*, 44.

Method E. A solution of **3** (100 mg, 1.20 mmol) in dry Et_2O (50 mL) was cooled to 0 °C. Oxygen gas (excess) and N_2O_4 gas (excess) were bubbled slowly through the cooled reaction mixture during 10 min, during which time the reaction mixture was stirred vigorously. The reaction was quenched via addition of water (50 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (25 mL) and dried (Na_2SO_4), and the filtrate was concentrated *in vacuo*. Compound **5** (143 mg, 68%) was obtained as a pale yellow oil which was identical in all respects with **5** produced via method A (*vide supra*).

Method F. A solution of **3** (83 mg, 1.0 mmol) in anhydrous Et_2O (100 mL) was placed in the immersion well of a photochemical apparatus which was cooled to 0 °C in an external cold bath. Dinitrogen tetraoxide was bubbled through this cooled solution during 10 min while the reaction mixture was being irradiated with a 450-W Hanovia medium-pressure Hg immersion lamp. At the conclusion of this irradiation period, the immersion lamp was turned off, and excess N_2O_4 was purged from the system by bubbling argon through the reaction mixture. The resulting mixture was carefully concentrated *in vacuo*, and the residue was purified via column chromatography on silica gel (2% EtOAc–hexane eluent). Workup of the initial chromatography fractions furnished **6** (40 mg, 21%) as a pale yellow oil which solidified up on long standing at rt. Recrystallization of the resulting solid from hexane afforded pure **6**: mp 35–36 °C; IR (KBr) 2979 (m), 1639 (s), 1539 (s), 1462 (m), 1341 (s), 1307 (s), 1265 (s), 1178 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3 H), 2.15 (q, J = 7.4 Hz, 2 H), 4.48 (*AB*, J_{AB} = 10.6 Hz, 2 H), 4.52 (*AB*, J_{AB} = 10.6 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.2 (q), 27.0 (t), 64.6 (t), 79.4 (s). Anal. Calcd for $C_5H_9N_3O_5$: C, 31.41; H, 4.74; N, 21.98. Found: C, 31.65; H, 4.85; N, 21.96. Continued elution of the column with 5% EtOAc–hexane afforded pure **5** (35 mg, 20%).

***N*-Nitro-3-ethyl-3-(nitrooxy)azetidine (6).** A solution of trifluoroacetic anhydride (5.0 g, 24 mmol) and 98% HNO_3 (5.0 g, 79 mmol) was cooled to 0 °C. To this cooled solution was added dropwise with stirring **5** (500 mg, 2.8 mmol). After the addition had been completed, the cold bath was removed, and the reaction mixture was allowed to warm gradually to rt during 1 h. The reaction mixture was poured onto crushed ice (50 g), and the resulting aqueous suspension was extracted with EtOAc (3 × 35 mL). The combined extracts were washed sequentially with water (50 mL), 10% aqueous $NaHCO_3$ (50 mL), and brine (25 mL). The organic layer was dried (Na_2SO_4), and the filtrate was concentrated *in vacuo*. The residual pale yellow oil was purified via bulb-to-bulb distillation in a Kügelrohr apparatus. Pure **6** (400 mg, 78%) was obtained as a colorless oil: bp 175 °C (0.1 mmHg) which gradually solidified upon long standing at rt to afford a colorless microcrystalline solid: mp 35–36 °C. The IR, ^1H NMR, and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained for **6** which was prepared via reaction of **3** with N_2O_4 (method C, *vide supra*).

***N*-Carbethoxy-3-chloro-3-ethylazetidine (8).** To a solution of **3** (83 mg, 1.0 mmol) in acetone (2 mL) at rt was added with stirring ethyl chloroformate (200 mg, excess), and the resulting mixture was stirred at rt for 5 min. The reaction mixture was concentrated *in vacuo*, and the residue was dried thoroughly under high vacuum. Compound **8** (190 mg, 100%) was obtained as a colorless oil: IR (film) 2971 (s), 2881 (m), 1708 (s), 1412 (s), 1375 (s), 1169 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.00 (t, J = 7.5 Hz, 3 H), 1.21 (t, J = 7.5 Hz, 3 H), 1.96 (q, J = 7.8 Hz, 2 H), 4.01–4.20 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 8.6 (q), 14.6 (q), 34.3 (t), 61.2 (t), 63.5 (s), 63.7 (t), 156.5 (s); HRMS m/z 191.0715 (M^+), calcd for $C_8H_{14}ClNO_2$ 191.0713.

***N*-(Methanesulfonyl)-3-ethyl-3-[(methanesulfonyl)oxy]azetidine (9).** A solution of **3** (166 mg, 2.0 mmol) in CH_2Cl_2 (5 mL) under argon was cooled to 0 °C. To this cooled solution was added with stirring in one portion methanesulfonic anhydride (417 mg, 2.4 mmol). The cold bath was removed, and the resulting mixture was allowed to warm gradually to rt. The reaction mixture was stirred at rt for 2 h. Water (10 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed sequentially with water (15 mL) and brine (25 mL). The organic layer was dried (Na_2SO_4), and the filtrate was concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2 to afford pure **9** (380 mg, 74%) as a colorless microcrystalline solid: mp 79–80 °C; IR (KBr) 3018 (m), 2934 (m), 1454 (m), 1365 (s), 1317 (s), 1153 (s), 1069 (m), 968 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.07 (t, J = 8.0 Hz, 3 H), 2.19 (q, J = 8.0 Hz, 2 H), 2.91 (s, 3 H), 3.10 (s, 3 H), 3.91 (*AB*, J_{AB} = 10.0 Hz, 2 H), 4.30 (*AB*, J_{AB} = 10 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.4 (q), 29.9 (t), 37.1 (q), 40.5 (q), 59.7 (t), 81.7 (s). Anal. Calcd for $C_7H_{15}NO_5S$: C, 32.67; H, 5.87; N, 5.44. Found: C, 32.66; H, 5.94; N, 5.39.

***N*-(Methanesulfonyl)-2-azetine (10a).** A mixture of **9** (80 mg, 0.3 mmol) and freshly sublimed KO*t*-Bu (100 mg, excess) in dry *t*-BuOH (2 mL) under argon was stirred at rt for 4 h. A slow stream of argon then was passed through the reaction mixture to promote evaporation of the solvent. The residue was triturated with dry hexane (5 mL). Hexane was decanted from the precipitate, and the solvent was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using 10% EtOAc–hexane as eluent. Pure **10a** (38 mg, 76%) was obtained as a colorless microcrystalline solid: mp 38–39 °C; IR (film) 2934 (s), 1634 (w), 1444 (m), 1317 (vs), 1220 (s), 1157 (vs), 1042 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.07 (t, J = 8.0 Hz, 3 H), 2.18 (q, J = 8.0 Hz, 2 H), 2.90 (s, 3 H), 4.25 (s, 2 H), 6.25 (t, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.3 (q), 20.1 (t), 33.8 (q), 60.5 (t), 132.8 (d), 137.5 (s). Anal. Calcd for $C_6H_{11}NO_2S$: C, 44.69; H, 6.88; N, 8.69. Found: C, 44.63; H, 7.03; N, 8.69.

***N*-[(Trifluoromethane)sulfonyl]-3-ethylideneazetidine (11).** A solution of **3** (500 mg, 6.02 mmol) in CH_2Cl_2 (5 mL) under argon was cooled to 0 °C. To this cooled solution was added dropwise with stirring trifluoromethanesulfonic anhydride (2.0 g, 7.22 mmol). After the addition of Tf_2O had been completed, the resulting mixture was allowed to warm gradually to rt. The reaction mixture was stirred at rt for 2 h and then was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel (10% EtOAc–hexane eluent). Pure **11** (932 mg, 72%) was obtained as a colorless oil: IR (film) 2951 (s), 2878 (m), 1385 (s), 1223 (s), 1197 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.57 (dt, J = 8.0, 2.0 Hz, 3 H), 4.76 (d, J = 2.0 Hz, 4 H), 5.48 (centrosymmetric multiplet, 1 H); ^{13}C NMR ($CDCl_3$) δ 13.6 (q), 60.1 (t), 60.9 (t), 110.4 (s), 116.8 (s), 120.0 (d), 123.2 (s), 123.3 (s), 129.6 (s); HRMS m/z 215.0238 (M^+), calcd for $C_6H_8F_3NO_2S$ 215.0251.

***N*-[(Trifluoromethane)sulfonyl]azetidin-3-one (12).** A solution of **11** (260 mg, 1.20 mmol) in dry CH_2Cl_2 (10 mL) was cooled externally to −78 °C in an external dry ice–acetone bath. Into this stirred, cold solution was bubbled ozone gas. The progress of the reaction was monitored periodically via TLC. The reaction was stopped when TLC analysis indicated the absence of starting material. Excess ozone was purged from the reaction by bubbling argon through the cold reaction mixture for *ca.* 5 min. The reaction then was quenched via addition of Me_2S (4 mL, excess). The cold bath was removed, and the reaction mixture was allowed to warm gradually to rt. The reaction mixture then was concentrated *in vacuo*, and the residue was purified via column chromatography (10% EtOAc–hexane eluent). Pure **12** (190 mg, 77%) was obtained as a colorless oil: IR (film) 2950 (m), 1831 (s), 1383 (s), 1220 (s), 1091 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 5.02 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 74.1 (t), 109.9 (s), 116.3 (s), 122.6 (s), 129.0 (s), 189.7 (s); HRMS m/z 133.99118 [$(M - CF_3)^+$], calcd for $C_4H_4F_3NO_3S$ 133.99119.

***N*-[(Trifluoromethane)sulfonyl]azetidin-3-one Oxime (13).**[15] A mixture of ketone **12** (300 mg, 1.47 mmol) and NaOAc (500 mg, 6.0 mmol) in MeOH (25 mL) was cooled to 0 °C. To this cooled mixture was added NH_2OH·HCl (150 mg, 2.17 mmol) in one portion. The external cold bath then was removed, and the reaction mixture was refluxed for 24 h. The reaction mixture was concentrated *in vacuo*. Water (10 mL) was added to the residue, and the resulting aqueous suspension was extracted with ether (3 × 20 mL). The combined organic extracts were washed sequentially with water (25 mL) and brine (25 mL). The organic layer was dried (Na_2SO_4), and the filtrate was concentrated *in vacuo*. The residue was recrystallized from CH_2Cl_2–hexane to afford pure **13** (240 mg, 74%) as a colorless microcrystalline solid: mp 117–118 °C; IR (KBr) 3298 (s), 2928 (m), 1465 (s), 1391 (s), 1206 (vs), 1090 (s), 1032 cm^{-1} (w); ^1H NMR ($CDCl_3$) δ 4.96

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(m, 4 H); ^{13}C NMR ($CDCl_3$) δ 61.1 (t), 110.0 (s), 116.4 (s), 122.8 (s), 128.9 (s), 143.8 (s). Anal. Calcd for $C_4H_5F_3N_2O_3S$: C, 22.02 H, 2.31; N, 12.84. Found: C, 22.28; H, 2.30; N, 12.75.

***N*-Nitro-3-ethylazetidin-3-ol (14).** To a solution of **6** (50 mg, 0.26 mmol) in MeOH (5 mL) was added crushed NaOH pellets (150 mg, 3.75 mmol), and the resulting mixture was heated at 50 °C for *ca.* 90 min. The reaction mixture was cooled to rt and then was concentrated *in vacuo*. Water (10 mL) was added to the colorless solid residue, and the resulting mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed sequentially with water (10 mL) and brine (10 mL). The organic layer was dried (Na_2SO_4), and the filtrate was concentrated *in vacuo*. The residue, a pale yellow oil, was purified via column chromatography on silica gel (10% EtOAc–hexane eluent). Pure **14** (24 mg, 65%) was obtained as a pale yellow oil: IR (film) 3480 (s), 2971 (m), 1514 (vs), 1451 (m), 1332 (vs), 1266 (s), 1184 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.98 (t, J = 7.4 Hz, 3 H), 1.79 (q, J = 7.4 Hz, 2H), 2.82 (bs, 1 H), 4.27 (s, 4 H); ^{13}C NMR ($CDCl_3$) δ 7.5 (q), 31.5 (t), 68.3 (s), 68.9 (t); HRMS *m/z* 147.0768, 147.0764 [$(M + H)^+$], calcd for $C_5H_{10}N_2O_3$ 147.0770.

***N*-Nitro-3-ethyl-2-azetine (16).** A mixture of **14** (100 mg, 0.68 mmol), triethylamine (340 mg, 3.4 mmol), and DMAP (15 mg, catalytic amount) in CH_2Cl_2 (5 mL) was cooled to 0 °C. To this cooled mixture was added dropwise with stirring MsCl (116 mg, 1.02 mmol). After the addition of MsCl had been completed, the cold bath was removed, and the reaction mixture was allowed to warm gradually to rt and then stirred at ambient temperature for 2 h. The reaction mixture was diluted with ice-cold water (25 mL), and the resulting aqueous suspension was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed sequentially with water (10 mL), cold 10% aqueous HCl (10 mL), water (10 mL), and brine (25 mL). The organic layer was dried (Na_2SO_4), and the filtrate was concentrated *in vacuo*. Compound **15** (150 mg, 100%) was obtained as a viscous red oil: IR (film) 2976 (m), 1637 (m), 1532 (vs), 1338 (vs), 1304 (s), 1236 (m), 1160 (s), 969 (s), 894 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 1.08 (t, J = 7.3 Hz, 3 H), 2.17 (q, J = 7.3 Hz, 2H), 3.11 (s, 3 H), 4.40 (*AB*, J_{AB} = 10.5 Hz, 2 H), 4.69 (*AB*, J_{AB} = 10.5 Hz, 2 H). This material was used as obtained, without additional purification or characterization.

A mixture of methanesulfonate **15** (90 mg, 0.4 mmol) and freshly sublimed KO*t*-Bu (72 mg, 0.65 mmol) in dry t-BuOH (2 mL) was stirred at rt under argon for 4 h. A slow stream of argon then was passed through the reaction mixture to promote evaporation of the solvent. The residue thereby obtained was triturated with dry hexane (5 mL), whereupon a viscous pale yellow oil precipitated. Hexane was decanted from this oil, and the residue was concentrated *in vacuo*. Compound **16** (35 mg, 68%) was obtained as a pale yellow oil; IR (film) 3114 (w), 2967 (m), 1534 (s), 1450 (m), 1431 (w), 1307 (s), 1257 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 1.08 (t, J = 7.4 Hz, 3 H), 2.18 (q, J = 7.4 Hz, 2 H), 4.74 (s, 2 H), 6.61 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 11.0 (q), 19.5 (t), 66.4 (t), 135.1 (d), 136.1 (s); HRMS *m/z* 128.0592 (M^+), calcd for $C_5H_8N_2O_2$ 128.0586.

X-ray Structure Determination of 4, 5, and 13.[16a] All data were collected on an Enraf-Nonius CAD-4 diffractometer by using the ω (**4**) or ω–2θ (**5** and **13**) scan technique, Mo Kα radiation (λ = 0.71073 Å), and a graphite monochromator. Standard procedures developed in our laboratory for this purpose have been described previously.[16b] X-ray data obtained for **4** and **5** are presented in Table 2. Data were corrected for Lorentz and polarization effects but not for absorption. The structures were solved by direct methods [SIR[17] (**4**) and MULTAN[18] (**5**)]. In each case, the model was refined by using full-matrix least-squares techniques. The treatment of thermal parameters was based upon a number of observed data. In **4**, only the oxygen and ethyl carbon atoms were treated in this fashion, whereas in **5**, sufficient data were available to permit all non-hydrogen atoms to be so treated. Hydrogen atoms were located on difference maps and then included in the model in idealized positions [$U(H) = 1.3B_{eq}$-(C)]. All computations other than those specified were performed by using MolEN.[19] Scattering factors were taken from the usual sources.[20]

Table 2. X-ray Structure Data for 4, 5, and 13

compound	4	5	13
formula	$C_5H_{11}N_3O_6$	$C_5H_9N_3O_4$	$C_4H_4F_3N_2O_3S$
size (mm)	0.05 × 0.12 × 0.48	0.20 × 0.25 × 0.42	0.35 × 0.38 × 0.40
space group	$P2_1/c$	$P2_1/c$	$P1$
a (Å)	13.195(3)	7.3784(5)	5.6161(4)
b (Å)	6.8524(6)	7.7726(6)	6.9505(4)
c (Å)	21.957(4)	14.2170(8)	11.530(1)
α (deg)	90	90	104.037(6)
β (deg)	100.996(13)	98.024(5)	96.821(6)
γ (deg)	90	90	107.889(5)
V (Å^3)	1948.8(5)	807.4(1)	406.3(1)
Z	8	4	2
D_c (g/cm^{-3})	1.426	1.441	1.784
μ (cm^{-1})	1.22	1.17	4.11
$2\theta_{max}$	44	56	50
total refl	2741	2216	1433
unique refl	2626	2079	1433
R_{int}	0.036	0.023	–
$I \geq 3\sigma(I)$	1221	1130	993
parameters	193	109	127
R, R_w	0.0549, 0.0848	0.0509, 0.0471	0.0778, 0.0788
$(\Delta/\sigma)_{max}$	<0.01	<0.01	<0.3
$r_{min}; r_{max}$	0.23, –0.26	0.20, –0.17	0.45, –0.48

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Supplementary Material Available: Copies of the ^1H and ^{13}C NMR spectra of **12**, **14**, and **16** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(16) (a) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK. (b) Mason, M. R.; Smith, J. M.; Bott, S. G.; Barron, A. R. *J. Am. Chem. Soc.* **1993**, *115*, 4971.

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