A Novel Synthesis of 2-Azabicyclo[2.1.1]hexane from Pyridine

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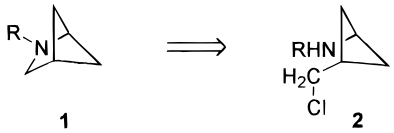
The reported synthesis of the parent 2-azabicyclo[2.1.1]-hexane ring system **1**, unsubstituted on the ring carbons, is based upon the final ring closure of 1-(*N*-alkylamino)-3-(chloromethyl)cyclobutanes **2** and requires 10 overall synthetic steps.[1] We desired a more convenient route, which might offer further synthetic opportunities, to prepare this small strained heterocyclic ring system. Although other approaches to substituted 2-azabicyclo-[2.1.1]hexane ring systems have been described, they are not readily amenable to synthesis of the parent ring.[2,3] Here, we report a new approach, which is convenient for the preparation of useful quantities of the 2-azabicyclo-[2.1.1]hexane ring system **1**. The new method is based upon previous observations that *N*-(alkoxycarbonyl)-2-azabicyclo[2.2.*n*]alk-5-enes **3** ($n = 1, 2$) undergo rearrangement to dibromides **4** upon addition of bromine to the double bond.[4,5]

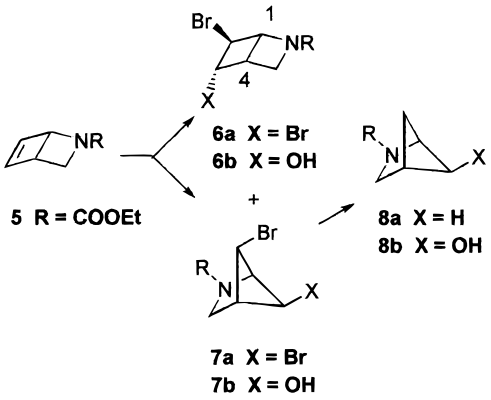


1 **2**

3a n = 1 **3b** n = 2 **4a** n = 1 **4b** n = 2

The key synthetic intermediate, *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene (**5**), has been synthesized readily in multigram quantities in two steps from pyridine.[6] As shown in Scheme 1, bromination of alkene **5** at −5 °C in dichloromethane afforded dibromide mixtures in 61−78% isolated yield. The isomer ratio of unrearranged dibromide **6a** and rearranged dibromide **7a** obtained on gram-scale runs was 55:45 as determined by comparison of the integrated ^{1}H NMR resonance for H_4 at δ 3.38 of dibromide **6a** with that for H_4 of dibromide **7a** at δ 3.17. The ratio of isomers is kinetically determined, since the purified dibromides were stable at 25 °C in $CDCl_3$.

Scheme 1



The structure of the unrearranged dibromide **6a** was assigned on the basis of coupling patterns in the ^{1}H NMR spectrum. The absence of coupling between H-1 at δ 4.65 and H-6 at δ 4.55 is consistent with an endo orientation for H-6 based upon the near 90° dihedral angle relationship for H-1 and H-6. The couplings of H-5 at δ 4.91 with H-6 ($J = 5.1$ Hz) and with H-4 at δ 3.38 ($J = 7.8$ Hz) are consistent with a trans relationship for H-5 and H-6 and a cis relationship for H-5 and H-4. The structure of the rearranged dibromide **7a** was also assigned by ^{1}H NMR. Protons H-1 at δ 4.56 and H-4 at δ 3.17 show four-bond coupling ($J = 6.9$ Hz). The equivalent H-3 protons appear as a singlet at δ 3.56, and the equivalent H-5 and H-6 protons appear as a singlet at δ 4.05; the absence of vicinal coupling between H-1/H-4 and their adjacent protons H-5/H-6 suggests dihedral angles close to 90°, which is consistent with an arrangement for the two bromine atoms in **7a** anti to the nitrogen bridge. The ^{13}C NMR spectrum of rearranged dibromide **7a** showed four lines for the five-ring carbon atoms and is consistent with the molecular symmetry in which C-5 and C-6 are equivalent. The desired 2-azabicyclo[2.1.1]hexane **8a** was synthesized uneventfully in 89% yield from rearranged dibromide **7a** by tributyltin hydride removal of the bromine atoms.

As shown in Scheme 2, addition of bromine to cycloadduct **5** should be favored on the open exo face to afford bromonium ion **9**. The bridged ion **9** can be trapped by regioselective attack of bromide ion from the C-5 endo face remote from the *N*-ethoxycarbonyl substituent to give unrearranged dibromide **6a**. Competitively, participation by nitrogen can lead to the formation of aziridinium ion **10**.[7] Regioselective attack of bromide ion on intermediate **10,** at the C-1 position farthest from the bromine at C-5, gives the rearranged dibromide **7a**. No other stereoisomeric dibromides, which might have been formed by the alternative attack of bromide ion at C-6 of

(1) Stevens, C.; De Kimpe, N. *J. Org. Chem.* **1996**, *61*, 2174−2178.
(2) For syntheses of 1-substituted 2-azabicyclo[2.1.1]hexanes from substituted cyclobutylamines, see: (a) Gaoni, Y. *Org. Prop. Proced. Int.* **1995**, *27*, 185. For photochemical ring closure of *N*-vinyl-*N*-allylamines to give 1-substituted and 1,5-bridged 2-azabicyclo[2.1.1]hexanes, see: (b) Hughes, P.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 4793. (c) Hughes, P.; Martin, M.; Clardy, J. *Tetrahedron Lett.* **1980**, *21*, 4579. (d) Pirrung, M. C. *Tetrahedron Lett.* **1980**, *21*, 4577. (e) Tamura, Y.; Ishibashi, H.; Hirai, M.; Kita, Y.; Ikeda, M. *J. Org. Chem.* **1975**, *40*, 2702.
(3) For synthesis of 1,4-dimethyl-2-aza-3-oxobicyclo[2.1.1]hexane, see: Paquette, L. A.; Allen, G. R., Jr.; Broadhurst. M. J. *J. Am. Chem. Soc.* **1971**, *93*, 4503.
(4) Raasch, M. S. *J. Org. Chem.* **1975**, *40*, 161.
(5) Krow, G. R.; Shaw, D. A.; Jovais, C. S.; Ramjit, H. G. *Synth. Commun.* **1983**, 575. (b) Krow, G. R.; Lee, Y. B.; Raghavachari, R.; Szczepanski, S. W.; Alston, P. V. *Tetrahedron* **1991**, *47*, 8499. (c) Krow, G. R.; Raghavachari, R.; Shaw, D. A.; Zacharias, D. E. *Trends Heterocycl. Chem.* **1990**, *1*, 1.
(6) (a) Fowler, F. W. *J. Org. Chem.* **1972**, *37*, 1321. (b) Beecken, P.; Bonfiglio, J. N.; Hasan, I.; Piwinski, J. J.; Weinstein, B.; Zollo, K. A.; Fowler, F. W. *J. Am. Chem. Soc.* **1979**, *101*, 6677.

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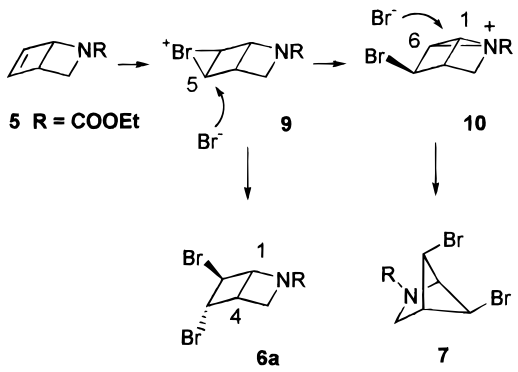
Scheme 2



bromonium ion intermediate **9** or C-6 of aziridinium ion **10**, were observed.

The rearrangement method has been extended to allow the formation of the first 5-hydroxy-2-azabicyclo[2.1.1]-hexane **8b** (Scheme 1). The photocycloadduct **5** was reacted with HOBr to afford in 70−80% yield a 7:3 mixture of unrearranged bromohydrin **6b** and rearranged bromohydrin **7b**. The integrated intensity for H-5 of the unrearranged bromohydrin **6b** and the combined integration for the carbamate methyl groups were used to calculate the isomer ratio. Tributyltin hydride removal of the bromine atom from bromohydrin **7b** afforded *N*-(ethoxycarbonyl)-5-*anti*-hydroxy-2-azabicyclo-[2.1.1]hexane (**8b**) in 63% yield. The herein described rearrangement−reduction protocol using *N*-(alkoxycarbonyl)-1,2-dihydropyridine photocycloadduct **5** is short and amenable to scale-up, and has the potential to provide numerous functionalized derivatives of the novel 2-azabicyclo[2.1.1]hexane ring system.[8]

Experimental Section

N-(Ethoxycarbonyl)-2-azabicyclo[2.2.0]oct-5-ene (**5**) was prepared according to the literature procedure for the *N*-(methoxycarbonyl) analogue.[6a] ^{1}H NMR spectra were recorded at 300 MHz, and ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ solvent. High-resolution mass spectra were recorded at an ionizing voltage of 70 eV. Flash column chromatography of photoproduct **5** and dibromide **7a** was performed using Acros activated basic Al_2O_3 (50−200 μm) using 1:1 hexane/ether as eluent. Other flash column chromatography was performed using Fisher Davisil Grade 633 silica gel Type 60A (200−425 mesh); TLC was performed on silica gel GF 500 or 1000 μm (Analtech, Inc.).

Preparation of *N*-(Ethoxycarbonyl)-5-*endo*-6-*exo*-dibromo-2-azabicyclo[2.2.0]hexane (6a) and *N*-(Ethoxycarbonyl)-5-*anti*-6-*anti*-dibromo-2-azabicyclo[2.1.1]hexane (7a). A solution of bromine (113 mg, 0.71 mmol) in CH_2Cl_2 (3 mL) was added dropwise to a cold (−5 °C) solution of *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene (**5**)[6] (108 mg, 0.71 mmol) in CH_2Cl_2 (10 mL) under argon, and the resulting solution was stirred for 2 h. The temperature was then raised to room temperature and stirred for an additional 16 h. The solution was diluted with ether (25 mL), washed with 10% aqueous sodium bisulfite (10 mL) and water (10 mL), dried over $MgSO_4$, and filtered, and solvent was removed in vacuo to provide an oil, which upon column chromatography (4:1 hexane/ether) gave 96 mg (49%) of unrearranged dibromide **6a** (R_f = 0.30, 3:1 hexane/ether): ^{1}H NMR δ 1.26 (3H, t, J = 7.2 Hz), 3.38 (1H, dddd, J = 7.8, 7.2, 4.2, 2.7 Hz), 4.16 (2H, q, J = 7.2 Hz), 4.28 (1H, dd, J = 9.3, 7.2 Hz), 4.47 (1H, dd, J = 9.3, 2.7 Hz), 4.55 (1H, d, J = 5.1 Hz), 4.65 (1H, d, 4.2 Hz), 4.91 (1H, dd, J = 7.8, 5.1 Hz); ^{13}C NMR δ 14.5, 35.8, 51.3, 51.8, 52.1, 61.6, 67.6, 154.9; HRMS *m*/*z* 311.9234, 313.9202, 315.9197, calcd for C_8H_{12}79/79, 79/81, 81/81Br_2NO_2, 311.9235, 313.9214, 315.9194. Dibromide **6a** remained unchanged after 18 h at 70 °C. There also was obtained 76 mg (39%) of rearranged dibromide **7a** (R_f = 0.23, 3:1 hexane/ether): ^{1}H NMR δ 1.26 (3H, t, J = 7.2 Hz), 3.17 (1H, d, J = 6.9 Hz), 3.56 (2H, s), 4.05 (2H, s), 4.15 (2H, q, J = 7.2 Hz), 4.56 (1H, d, J = 6.9 Hz); ^{13}C NMR δ 14.6, 50.1, 50.7, 51.0, 61.9, 66.1, 154.9; HRMS *m*/*z* 311.9233, 313.9199, 315.9166, calcd for C_8H_{12}79/79, 79/81, 81/81Br_2NO_2, 311.9234, 313.9214, 315.9193. The roughly 5:4 ratio of dibromides **6a**:**7a** was found to vary from 1:2 to 5:4, although all scale-up attempts have been near 55:45. To facilitate scale-up, an alternative workup procedure, which involves elimination of HBr from unrearranged dibromide **6a** and the possibility of thermal decomposition of the elimination product formed,[5] was developed for the isolation of dibromide **7a**. A solution of bromine (2.09 g, 13 mmol) in CH_2Cl_2 (25 mL) was added dropwise over 40 min to a cold (−5 °C) solution of *N*-(ethoxycarbonyl)-2-azabicyclo[2.2.0]hex-5-ene (**5**)[6] (2.0 g, 13 mmol) in CH_2Cl_2 (80 mL) under argon. Reaction and workup as above provided 3.56 g of an oil that was dissolved in diazabicycloundecane (DBU) (8 mL) and stirred at 65−70 °C for 4 h under argon. Water (25 mL) was added, and the solution was extracted with ether (4 × 25 mL); the extract was dried over sodium sulfate and filtered, and solvent was removed in vacuo to provide after column chromatography 1.05 g (26%) of rearranged dibromide **7a**. After 30 d in $CDCl_3$ at 25 °C, dibromide **7a** remained unchanged.

Preparation of *N*-(Ethoxycarbonyl)-2-azabicyclo[2.1.1]-hexane (8a). The dibromide **7a** (176 mg, 0.56 mmol) and 2,2′-azobis(2-methylpropionitrile) (AIBN) were dissolved in benzene (10 mL), tributyltin hydride (454 μL, 491 mg, 1.69 mmol) was added, and the resulting solution was heated to 80 °C for 2 h. The reaction mixture was cooled to room temperature, and the benzene was removed in vacuo to give a residue that upon chromatography (10:1 hexane/ether) gave 77 mg (89%) of compound **8a** (R_f = 0.6, 1:1 hexane/ether): ^{1}H NMR δ 1.23 (3H, t, J = 7.2 Hz), 1.34 (2H, dd, J = 4.8, 1.8 Hz), 1.87, 2H, m), 2.80 (1H, m), 3.30 (2H, s), 4.11 (2H, q, J = 7.2 Hz), 4.36 (1H, br); ^{13}C NMR δ 15.5, 39.2, 41.2, 49.7, 61.4, 157.0; HRMS *m*/*z* 155.0938, calcd for $C_8H_{13}NO_2$ 155.0938.

Preparation of *N*-(Ethoxycarbonyl)-6-*exo*-bromo-5-*endo*-hydroxy-2-azabicyclo[2.2.0]hexane (6b) and *N*-(Ethoxycarbonyl)-5-*anti*-bromo-6-*anti*-hydroxy-2-azabicyclo[2.1.1]-hexane (7b). To the photoproduct **5** (2 g, 13 mmol) in DMSO (60 mL) and H_2O (30 mL) at −5 °C was added *N*-bromosuccinimide (6.97 g, 39 mmol) in small portions so that the temperature never exceeded 0 °C.[9] Upon completion of the addition, the solution was stirred for 14 h, diluted with water (50 mL), and extracted with ether (5 × 50 mL). The combined extracts were washed with H_2O (2 × 25 mL) and dried over $MgSO_4$, solvent was removed in vacuo, and flash silica gel chromatography of the residue (2:1 ether/hexane) gave 1.72 g (53%) of unrearranged bromohydrin **6b** (R_f = 0.57, 5:1 ether/hexane): ^{1}H NMR δ 1.24 (3H, t, J = 7.2 Hz), 3.29 (1H, dddd, J = 7.8, 7.5, 4.8, 3.0 Hz), 3.49 (1H, b), 4.08 (1H, dd, J = 9.3, 7.5 Hz), 4.12 (2H, q, J = 7.2 Hz), 4.31 (1H, d, J = 4.2 Hz), 4.35 (1H, d, J = 4.8 Hz), 4.45 (1H, dd, J = 9.3, 3.0 Hz), 4.66 (1H, dd, J = 7.8, 4.2 Hz); ^{13}C NMR δ 14.6, 35.2, 47.2, 52.2, 61.5, 63.8, 75.2, 155.6; HRMS *m*/*z* 170.0818, calcd for $C_8H_{12}NO_3$ − Br 170.0817. Also obtained was 0.57 g (17%) of rearranged bromohydrin **7b** (R_f = 0.43, 5:1 ether/hexane): ^{1}H NMR δ 1.25 (3H, t, J = 7.2 Hz), 2.98 (1H, d, J = 7.2 Hz), 3.45 (1H, d, J = 9.0 Hz), 3.52 (1H, d, J = 9.0 Hz), 3.55 (1H, br), 4.06 (1H, d, J = 7.5 Hz), 4.13 (2H, q, J = 7.2 Hz), 4.24 (1H, d, J = 7.5 Hz), 4.38 (1H, d, J = 7.2 Hz); ^{13}C NMR δ 14.6, 49.2, 49.9, 52.0, 61.7, 65.8, 84.9, 155.4; HRMS *m*/*z* 170.0803, calcd for $C_8H_{12}NO_3$ − Br 170.0817.

(7) (a) Begley, W. J.; Lowe, G.; Cheetham, A. K.; Newsam, J. M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2620. Addition of HOBr to an *N*-alkyl-2-aza-3-oxobicyclo[2.2.0]hex-5-ene afforded *only unrearranged* 6-*exo*-bromo-5-*endo*-hydroxy addition product. (b) Krow, G. R.; Fan, D. M. *J. Org. Chem*. **1974**, *39*, 2674.

(8) We note also that 2-azabicyclo[2.1.1]hexanes have been converted to their corresponding 3-oxo derivatives (lactams). See ref 2b.

(9) Krow, G. R.; Shaw, D. A.; Szczepanski, S.; Ramjit, H. G. *Synth. Commun*. **1984**, 429.

Preparation of *N*-(Ethoxycarbonyl)-5-*anti*-hydroxy-2-azabicyclo[2.1.1]hexane (8b). According to the procedure described for the preparation of compound **8a**, the bromohydrin **7b** (73 mg, 0.29 mmol) was debrominated using tributyltin hydride (118 μL, 127 mg, 0.44 mmol). Workup and column chromatography (2:1 ether/hexane) gave 31 mg (63%) of the alcohol **8b** (R_f = 0.36, 3:1 ether/hexane): ^{1}H NMR δ 1.24 (3H, t, J = 7.2 Hz), 1.61 (1H, dd, J = 7.5, 7.2 Hz), 2.65 (1H, d, J = 7.2 Hz), 2.89 (1H, d, J = 7.5 Hz), 3.35 (2H, s), 3.75 (1H, br), 4.07 (1H, d, J = 7.2 Hz), 4.12 (2H, q, J = 7.2 Hz), 4.15 (1H, dd, J = 7.2, 1.8 Hz); ^{13}C NMR δ 14.6, 36.8, 43.9, 48.2, 61.1, 63.2, 81.1, 156.1; HRMS FAB m/z 172.0971, calcd for $C_8H_{14}NO_3$ (MH^+) 172.0974.

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Supporting Information Available: Alternate procedures for reductive debromination of rearranged dibromides **7a** and **7b** using tris(trimethylsilyl)silane (TTMSS), 300 MHz ^{1}H NMR spectra and 75 MHz ^{13}C NMR spectra for compounds **6a**,**b**, **7a**,**b**, and **8a**,**b** (12 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.

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