Synthesis of 2-Azaadamantan-6-one: A Missing Isomer

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Supporting Information

ABSTRACT: 2-Azaadamantan-6-one and its Boc and ethylene ketal derivatives were synthesized from 9-oxo endo-bicyclo[3.3.1]non-6-ene-3-carboxylic acid. Similarly, the Cbz, Boc, and ethylene ketal derivatives of 2-azaadamantan-4-one were synthesized from endo-bicyclo[3.3.1]non-6-ene-3-carboxylic acid. Key steps were Curtius rearrangements to form benzyl carbamates, followed by spontaneous intramolecular attack of the carbamate nitrogen on transient bromonium ion or epoxide intermediates to effect ring closure to azaadamantane intermediates. The reaction sequence leading to 2-azaadamantan-6-one is consistent with the formation of a transient tetracyclic keto aziridine intermediate.

INTRODUCTION

Aza and polyazaadamantanes continue to play important roles in organic and medicinal chemistry.1−13 Among the most useful members of the azaadamantane family are the azaadamantanones 1−4 (Figure 1). 1-Azaadamantan-2-one (1) was obtained by the pyrolysis of N-Boc amino acid 6.19 Compound 7, the benzamide derivative of 2-azaadamantan-4-one (3), the third isomer of this family, was synthesized from unsaturated bicyclic carboxylic acid 8 in seven steps in 31% overall yield.20 Key steps in this synthesis were a Curtius rearrangement, leading to 9, followed by epoxidation and spontaneous intramolecular attack of the amide nitrogen on the transient epoxide intermediate to form the alcohol precursor of 7. As described in a 2018 patent,21 compound 10, the N-benzyl derivative of 2-azaadamantan-6-one (4) and fourth isomer of this family, was synthesized from bicyclo[3.3.1]nonane-3,7,9-trione mono ethylene ketal (11)22 in four steps in 15% overall yield. The key step in this synthesis was a reductive amination to form azaadamantane 12. In this work,21 compounds were characterized only by low-resolution mass spectrometry data.

We envisioned that a similar reaction sequence to that executed by Staas and Spurlock20 in the synthesis of 7 (Scheme 1) with 9-oxo endo-bicyclo[3.3.1]non-6-ene-3-carboxylic acid (13) (vide infra) rather than 8 could provide an avenue to obtain 4. Such an approach was recently exemplified by Kozawa and Endo23 and Shibuya et al.24 who converted 8 to carbamate 14 via a Curtius rearrangement, followed by bromine-mediated cyclization to 15 (Scheme 2). Hydrogenolysis of 15 yielded the desired 2-azaadamantane 16. Although the presumed β-bromo azaadamantane reaction intermediate 17 was not isolated, the authors were able to characterize its tetracyclic aziridine cyclization product 18 which underwent hydrogenolysis to 16.23 More directly, Shibuya et al.24 converted 14 to 16 in one step by intramolecular hydrogenation with four equivalents of triffic acid.

Figure 1. 1-Azaadamantan-2-one (1), 1-azaadamantan-4-one (2), 2-azaadamantan-4-one (3), and 2-azaadamantan-6-one (4).
RESULTS AND DISCUSSION

Accordingly, we prepared starting material 13 in three steps from bicyclo[3.3.1]nonane-2,6-dione in 55% overall yield according to a modified method of Stetter and Dorsch. Conversion of 13 to carbamate 19 (83% yield) was readily achieved by a Curtius rearrangement, followed by reaction with benzyl alcohol using the reaction protocol described by Shibuya et al. (Scheme 3). Several attempts using hydrofluoroacetic acid (TFA) as the tripeptide and K2CO3 as the base failed to afford the desired carbamate 19. However, exposure of 19 to either bromine at 0 °C or N-bromosuccinimide (NBS) at room temperature (rt) afforded cyclization to bromo azadamantane carbamate 20 in 97–99% yield. Treatment of 20 with H2, Pd/C, and K2CO3 in MeOH (or EtOH) afforded a one-pot Cbz deprotection and debromination to afford the desired 4, which due to its high water solubility was converted to Boc derivative 21 in an overall yield of 77%. Deprotection of 21 with ethereal hydrogen chloride afforded 4 as the hydrochloride salt in 94% yield (Scheme 4). In addition, 23, the ethylene ketal derivative of 4, was obtained from 21 in a two-step sequence with an overall yield of 77%

Next, in an attempt to convert 20 to key intermediate 21 in a one-pot reaction, we exposed 20 to H2, Pd/C, Boc2O, and Et3N in dioxane (Scheme 5). Unexpectedly, this reaction formed 24, the transcarbamylation product, not the desired 21. Product 24 was also formed when using tetrahydrofuran (THF) as the solvent or the K2CO3 as the base. As we had not observed 26 in the conversion of 20 to 4 via 21, we recognized that 24 afforded another opportunity to synthesize 26. Thus, deprotection of 24 with trifluoroacetic acid (TFA) afforded 25 as the trifluoroacetate salt in 92% yield. Treatment of 25 with K2CO3 in MeOH effected cyclization to 26. Hydrogenation of the crude reaction product afforded 4. However, the instability of 26 precluded its isolation, and we could only characterize it by extraction with CDCl3 followed by NMR and high-resolution mass spectrometry (HRMS) analysis.

The structure of 26 was strongly suggested by 10 signals in the 13C{1H} NMR spectrum including a downfield signal at 212.8 ppm, three methylene carbons in the APT spectrum, and a molecular formula of C9H11NO determined by HRMS. This structural assignment was consistent with key COSY correlations, which identified H-9 as the only methine hydrogen with vicinal coupling to its hydrogen partners on the adjacent methine carbons C-3 and C-7. Further, a 15N–1H heteronuclear multiple bond correlation experiment showed that 2-N is a tertiary amine by the chemical shift and absence of a directly bonded hydrogen; these data also revealed two-bond correlations between 2-N and the hydrogen atoms on methine carbons C-1 and C-9 and three-bond correlations, which identified H-9 as the only methine hydrogen with vicinal coupling to its hydrogen partners on the adjacent methine carbons C-3 and C-7. The instability of 26 precluded its isolation, and we could only characterize it by extraction with CDCl3 followed by NMR and high-resolution mass spectrometry (HRMS) analysis.

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The deprotonization of both 16 and 20 in MeOH and EtOH solvents during hydrogenolysis presumably occurs via S_N2 cyclization to form an aziridinium bromide intermediate, which after formation of the free base undergoes further hydrogenolysis opening the aziridine ring. Because loss of bromide was not observed in aprotic dioxane and THF solvents, we modeled the intramolecular S_N2 reaction to better understand the effects of solvent and the carbonyl substituent. Figure 2 shows the potential energy diagram for the intramolecular conversion of 17 and 25 to their respective aziridinium salts 18H and 26H. Using the M06-2x functional of Zhao and Truhlar,29 transition-state structures were located and used as inputs for intrinsic reaction coordinate calculations. The following results are of interest: (1) both the free energy of activation and the free energy of the reaction are lower for 17 versus 25; (2) the less than ideal angle of S_N2 attack of 152.8°
is the same for both nonketone and ketone azaadamantane transition states; (3) base neutralization of 26H⁺ is more exergonic compared to that of 18H⁺ (modeled with sodium carbonate base); and (4) changing to a less polar THF solvent increases both the free energy of activation and endergonic value of the reaction.

From these data, we surmise that decrease in stability of the aziridinium product by the presence of an electron-withdrawing ketone or a decrease in solvent polarity makes aziridinium ion formation less favorable. These results also imply that the initial basicity of the azaadamantane is the key factor in the formation of the aziridine intermediate; the more basic the azaadamantane, the more favorable the S_N2 cyclization. Isodesmic modeling of proton affinity differences between 17 and 25 indicates that 17 is approximately four pKₐ units more basic than 25 (Supporting Information). The substantial decrease in basicity afforded by a carbonyl group three bonds from the aza group is consistent with the withdrawal of electron density by both inductive and field effects. Encouraged by the successful conversion of 13 to 4, we then sought to use a similar approach to convert 8 to 3 (Scheme 6).

The starting material bicyclic carbamate 14 was obtained from 8 according to the method of Shibuya et al. Treatment of 14 with meta-chloroperoxybenzoic acid (m-CPBA) effected cyclization to hydroxy azaadamantane carbamate 27 in 81% yield; 27 was presumably formed as the anti epimer assuming back-side attack of the epoxide by the carbamate. Oxidation of 27 furnished 28, the Cbz derivative of 3 in 93% yield. Transcarbamylation of 28 afforded the corresponding Boc derivative 29 in 98% yield. However, all attempts to synthesize 3 by hydrogenolysis of 28 or acid-promoted deprotection of 29 failed. Nevertheless, we were able to convert 28 to 31, the ethylene ketal derivative of 3, in a three-step two-pot sequence with an overall yield of 96%. Thus, 3, unlike 4, is stable only when one of its two functional groups is in a protected form.

In summary, we synthesized 2-azaadamantan-6-one (4) and its Boc (21) and ethylene ketal (26) derivatives. We also describe syntheses of the Cbz (28), Boc (29), and ethylene ketal (31) derivatives of 2-azaadamantan-4-one (3). We anticipate that these azaadamantanes will be useful starting points for further exploration because of the rich chemistry available for their ketone and secondary aliphatic amine functional groups.

### EXPERIMENTAL SECTION

#### General

Melting points are uncorrected. 1D 1H and 13C NMR spectra were generated with a 500 MHz spectrometer using CDCl₃ and DMSO-d₆ as solvents. Chemical shifts are reported in parts per million (ppm) and are relative to internal (CH₃)₄Si (0 ppm) for 1H and CDCl₃ (77.0 ppm) or DMSO-d₆ (39.7 ppm) for 13C NMR. Electron ionization gas chromatography–MS (EI GC–MS) data were obtained using a quadrupole mass spectrometer with 30 m DB-5 type columns.
and a He flow rate of 1 mL/min. We used a silica gel (silica) particle size of 40–63 μm for all flash column chromatography. Reported reaction temperatures are those of the oil bath.

2-Azaadamantan-6-one Hydrochloride (4). A mixture of 21 (200 mg, 0.80 mmol) and 1 M HCl solution in diethyl ether (5 mL) was stirred at rt for 12 h. The resulting solid was filtered and washed with diethyl ether to afford 4 (141 mg, 94%) as a white solid. mp > 350 °C (dec.). 1H NMR (DMSO-d6): δ 2.03–2.14 (m, 4H), 2.38–2.47 (m, 4H), 2.55 (d, J = 3.9 Hz, 2H), 3.69 (s, 2H), 9.69 (s, 2H); 13C NMR (DMSO-d6): δ 34.3, 43.2, 46.0, 212.6. Anal. Calcld for C9H13NO: C, 57.02; H, 7.83; N, 6.04. Found: C, 57.42; H, 7.66; N, 5.96.

Benzyl(9-oxobicyclo[3.3.1]non-6-yl)carbamate (19). To a mixture of 9-oxobicyclo[3.3.1]non-6-ene-3-carboxylic acid (13) (8.00 g, 44.4 mmol) and K2CO3 (2.29 g, 16.6 mmol), toluene (75 mL), and THF (15 mL) was heated under reflux for 2 h before addition of BnOH (12.83 g, 46.6 mmol) were added at rt. The resulting mixture was stirred at rt for 3 h before addition of H2O (5 mL). The organic layer was washed with 1 N NaOH (30 mL) and brine (30 mL), dried over anhydrous MgSO4, and concentrated to afford 19 (141 mg, 88%) as a white solid. mp 76–78 °C. 1H NMR (DMSO-d6): δ 1.45 (d, J = 12.8 Hz, 3H), 2.14 (m, 4H), 2.24 (m, 4H), 2.72 (d, J = 11.6 Hz, 2H), 2.71 (s, 1H), 4.35 (s, 0.5H), 4.48 (s, 0.5H), 4.57 (s, 0.5H), 5.14–5.26 (m, 2H), 7.27–7.41 (m, 5H); 13C NMR (DMSO-d6): δ 31.7, 31.9, 37.5, 37.7, 39.8, 40.2, 44.1, 44.8, 45.5, 50.5, 50.5, 51.2, 53.2, 53.7, 54.1, 67.7, 128.1, 128.4, 128.7, 136.2, 154.4, 154.3, 210.8. HRMS (ESI-TOF) m/z: [M]+ calcld for C17H18BrNO2 363.0470; found, 363.0483.

Benzyl 4-Bromo-6-oxo-2-azaadamantane-2-carboxylate (20). Method 1. To a mixture of 19 (5.71 g, 20.0 mmol) and K2CO3 (5.53 g, 40.0 mmol) in CH2CN (20 mL) at 0 °C was added dropwise a solution of bromine (4.79 g, 30.0 mmol) in CH3CN (6 mL). The resulting mixture was stirred for 30 min at 0 °C and then partitioned between EtOAc (100 mL) and H2O (50 mL). The organic layer was washed with brine (100 mL), dried over anhydrous MgSO4, and concentrated to afford 20 (7.21 g, 99%) as a white solid. mp 92–93 °C. 1H NMR (DMSO-d6): δ 1.45 (d, J = 2.8 Hz, 3H), 1.71–1.82 (m, 4H), 1.92 (d, J = 10.9 Hz, 6H), 3.96 (s, 4H), 4.10 (s, 1H), 4.23 (s, 1H); 13C NMR (DMSO-d6): δ 28.5, 33.3, 33.6, 35.1, 44.8, 63.4, 64.31, 79.1, 110.1, 154.3. Step 2. A mixture of 20 (120 mg, 0.34 mmol) and 1 M ethereal HCl (3 mL) was stirred at rt for 12 h. The resulting solid was filtered and washed with diethyl ether to afford 23 (56 mg, 77%) as a white solid. mp 337–338 °C. 1H NMR (DMSO-d6): δ 1.92 (d, J = 11.6 Hz, 6H), 2.02–2.15 (m, 4H), 3.47 (s, 2H), 3.92 (s, 4H), 9.28 (s, 2H); 13C NMR (DMSO-d6): δ 30.8, 33.5, 45.8, 64.7, 108.4. Anal. Calcld for C8H16BrN2O3: HCl: C, 57.02; H, 7.83; N, 6.04. Found: C, 57.42; H, 7.66; N, 6.04.

tert-Butyl 4-Bromo-6-oxo-2-azaadamantane-2-carboxylate (24). A mixture of 20 (365 mg, 1.00 mmol), di-tert-butyl dicarbonate (262 mg, 1.20 mmol), and triethylamine (202 mg, 2 mmol) in dioxane (10 mL) was stirred under H2 at rt for 12 h and then filtered. The filtrate was concentrated and redissolved in EtOAc (50 mL), washed with 1 N HCl (10 mL), saturated NaHCO3 (10 mL), and brine (10 mL), dried over anhydrous MgSO4, and concentrated. The crude reaction product was purified by column chromatography (silica, hexane/EtOAc, 5:1) to afford 24 (290 mg, 88%) as a white solid. mp 76–77 °C. 1H NMR (CDCl3): δ 1.49 (s, 9H), 2.00 (t, J = 10.5 Hz, 1H), 2.10 (t, J = 12.8 Hz, 1H), 2.14–2.24 (m, 1H), 2.33 (dt, J = 15.7, 8.1 Hz, 1H), 2.70 (s, 1H), 2.76 (t, J = 11.9 Hz, 1H), 2.98 (s, 1H), 4.35 (s, 0.5H), 4.41 (s, 0.5H), 4.48 (s, 0.5H), 4.57 (s, 0.5H), 4.58 (s, 1H); 13C NMR (CDCl3): δ...
A mixture of 24 (220 mg, 0.67 mmol), TFA (1 mL), and CH₂Cl₂ (5 mL) was stirred at rt for 24 h and then concentrated in vacuo at rt. The residue was mixed with diethyl ether (10 mL) and stirred for 30 min. The precipitate was collected by filtration and washed with diethyl ether (2 mL) to afford 25 (212 mg, 92%) as a white solid. mp 138–139 °C.

1H NMR (CDCl₃): δ 8.2 (s, 1H), 7.9 (d, J = 14.1 Hz, 1H), 2.69 (d, J = 14.3 Hz, 1H), 2.58 (d, J = 14.6 Hz, 1H), 2.57 (d, J = 14.6 Hz, 1H), 2.09 (d, J = 14.6 Hz, 1H), 2.07 (s, 1H), 3.73 (s, 1H), 3.92 (s, 1H), 4.00 (s, 1H), 4.90 (s, 1H), 5.00 (s, 1H), 10.9 (s, 1H), 10.50 (d, J = 14.6 Hz, 1H). 13C NMR (CDCl₃): δ 30.7, 31.0, 31.3, 32.8, 33.1, 34.8, 35.3, 35.5, 45.9, 60.4, 60.7, 74.4, 75.2, 107.9, 108.5, 135.8, 136.6, 149.7, 150.5. HRMS (ESI-TOF) m/z: [M⁺] calcd for C₁₃H₁₃NO₃, 252.0944; found, 252.0946.

4-Bromo-6-oxo-2-Azaadamantane Trifluoroacetate (25). A mixture of 24 (220 mg, 0.67 mmol), TFA (1 mL), and CH₂Cl₂ (5 mL) was stirred at rt for 24 h and then concentrated in vacuo at rt. The residue was mixed with diethyl ether (10 mL) and stirred for 30 min. The precipitate was collected by filtration and washed with diethyl ether (2 mL) to afford 25 (212 mg, 92%) as a white solid. mp 138–139 °C.

1H NMR (CDCl₃): δ 8.2 (s, 1H), 7.9 (d, J = 14.1 Hz, 1H), 2.69 (d, J = 14.3 Hz, 1H), 2.58 (d, J = 14.6 Hz, 1H), 2.57 (d, J = 14.6 Hz, 1H), 2.09 (d, J = 14.6 Hz, 1H), 2.07 (s, 1H), 3.73 (s, 1H), 3.92 (s, 1H), 4.00 (s, 1H), 4.90 (s, 1H), 5.00 (s, 1H), 10.9 (s, 1H), 10.50 (d, J = 14.6 Hz, 1H). 13C NMR (CDCl₃): δ 30.7, 31.0, 31.3, 32.8, 33.1, 34.8, 35.3, 35.5, 45.9, 60.4, 60.7, 74.4, 75.2, 107.9, 108.5, 135.8, 136.6, 149.7, 150.5. HRMS (ESI-TOF) m/z: [M⁺] calcd for C₁₃H₁₃NO₃, 252.0944; found, 252.0946.
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