

Convenient synthesis of 3,5,7-trimethyl-1-azonia-adamantanes

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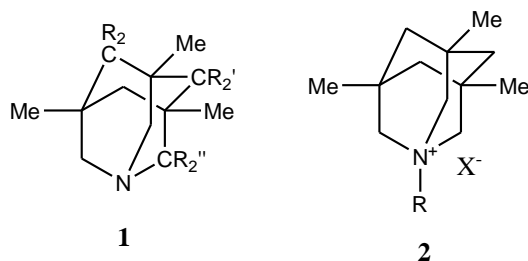
Abstract

A convenient synthesis of 3,5,7-trimethyl-1-azonia-adamantanes (2) is described. The esterification of *cis,cis*-1,3,5-tris(hydroxymethyl)-1,3,5-trimethylcyclohexane (3) with trifluoromethanesulfonic anhydride, followed by the reaction with primary amines, yields azonia-adamantanes 2. On the other hand, the esterification of triol 3 with TFAA also affords *cis,cis*-1,3,5-tris[(trifluoroacetoxy)methyl]-1,3,5-trimethylcyclohexane (5). However, the reaction of triester 5 with 2-(2-aminoethyl)pyridine does not give the corresponding azonia-adamantane, but 2,2,2-trifluoro-*N*-[2-(pyridin-2-yl)ethyl]-acetamide (6). The β -methylene protons in azonia-adamantane 2a [R = 2-(pyridin-2-yl)ethyl] are very active. Both acids and bases react with 2a to yield 2-vinylpyridine. The elimination reaction of 2a with lithium methoxide is available for the synthesis of 3,5,7-trimethyl-1-aza-adamantane (1).

Keywords: Azonia-adamantanes, lithium methoxide, vinylpyridine

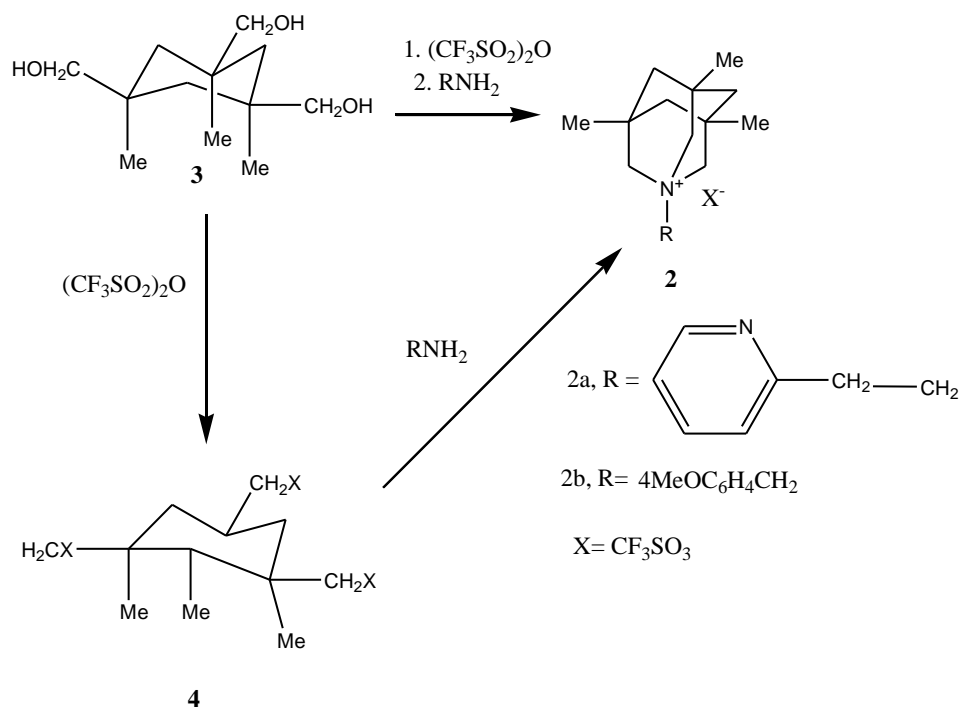
Introduction

3,5,7-Trimethyl-1-aza-adamantane structures (1) have been applied as highly twisted amides,¹ self-organization systems,² and rigid models.³ These structures have been also attracting considerable interest because of their pharmacological activity.⁴ In contrast, there have been few studies on 3,5,7-trimethyl-1-azonia-adamantanes 2, and many synthetic steps have been needed.⁵ In this paper, we report a convenient synthetic method for 3,5,7-trimethyl-1-azonia-adamantanes 2. We also present an elimination reaction of 2a [R = 2-(pyridin-2-yl)ethyl] to give azonia-adamantane 2c (R = H) and 2-vinylpyridine.

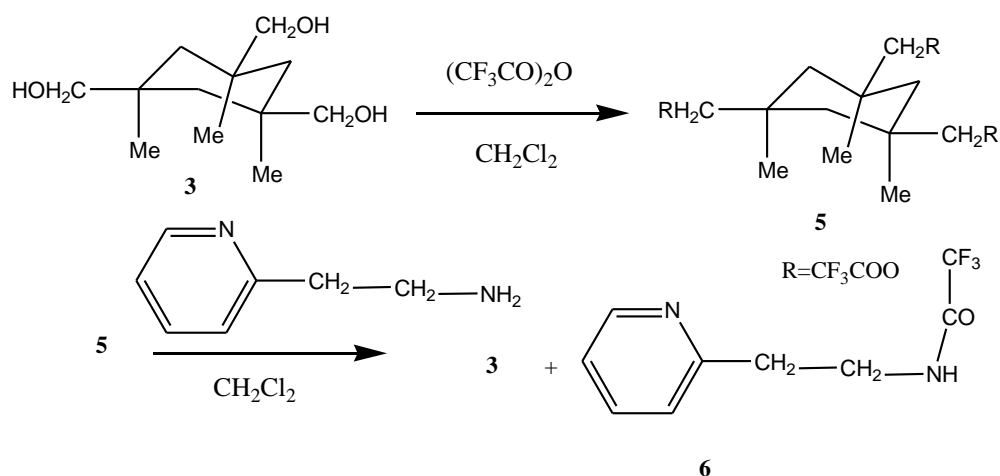


Results and Discussion

As shown in Scheme 1, the esterification of *cis,cis*-1,3,5-tris(hydroxymethyl)-1,3,5-trimethylcyclohexane (**3**)⁶ with trifluoromethanesulfonic anhydride (4 equiv),⁷ followed by reactions with primary amines (4 equiv), gave 3,5,7-trimethyl-1-azonia-adamantanes **2** [**2a**, R = 2-(pyridin-2-yl)ethyl, 23%; **2b**, R = 4-methoxybenzyl, 31%]. The ¹H NMR, ¹³C NMR (DEPT), ¹H-¹³C COSY spectra supported the structure of **2**. Mayer and co-workers indicated that triester **4** (X = trifluoromethylsulfonyloxy) is easily obtained by the reaction of triol **3** with trifluoromethanesulfonic anhydride and is available for the trisubstituted tripodal ligand.⁷ In this case, however, the corresponding triamines could not be obtained. We have already shown that the steric repulsion of the *ipso* methyl groups in the cyclohexane ring causes the unexpected reactions⁸ and stabilizes the molecular structures.⁹ This finding suggests that the proximity effect works efficiently in the synthesis of azonia-adamantanes **2**.



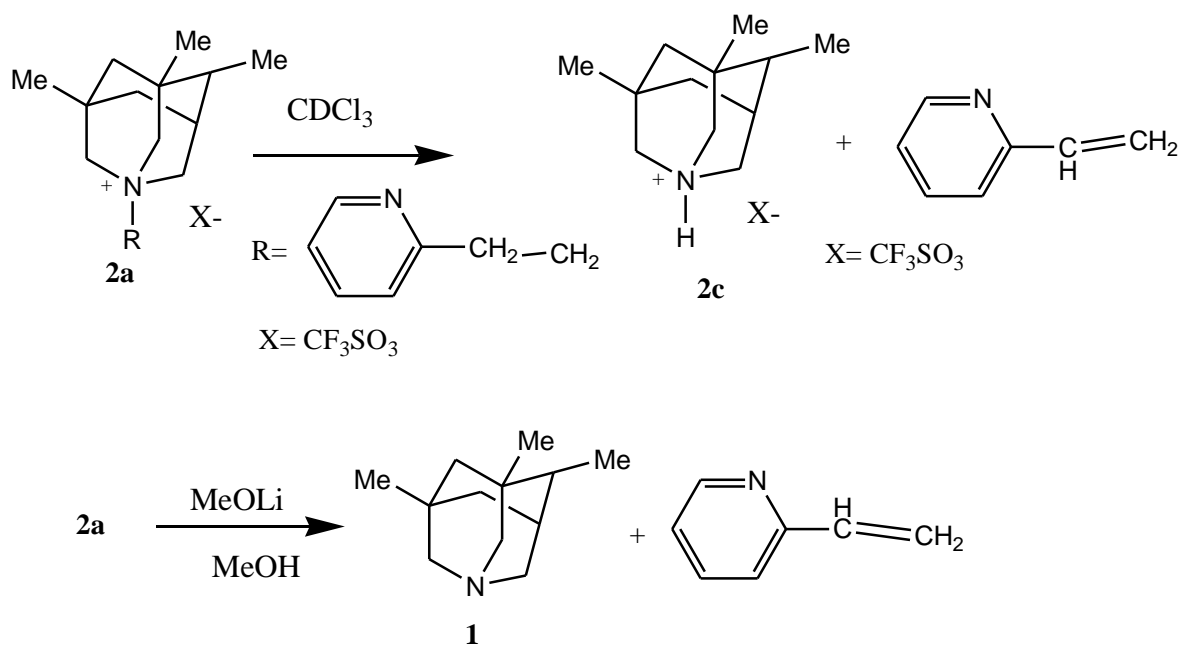
Scheme 1



Scheme 2

On the other hand, the esterification of triol 3 with TFAA (4 equiv) also afforded triester 5 (Scheme 2). However, the reaction of triester 5 with 2-(2-aminoethyl)pyridine (3 equiv) did not give the corresponding azonia-adamantane, but trifluoro-acetamide 6 (Scheme 2). It is well-known that reactions of carboxylic acid esters with amines yield acid amides.¹⁰ The low solubility of triol 3 in CH₂Cl₂ promotes this reaction. It is suggested that trifluoroacetate lacks the function as the counter anion. The reaction of triol 3 with methanesulfonic anhydride (3 equiv) did not give the corresponding triester. The ¹H NMR spectrum of the reaction mixture indicated the signals of unreacted triol 3 and methanesulfonic anhydride.

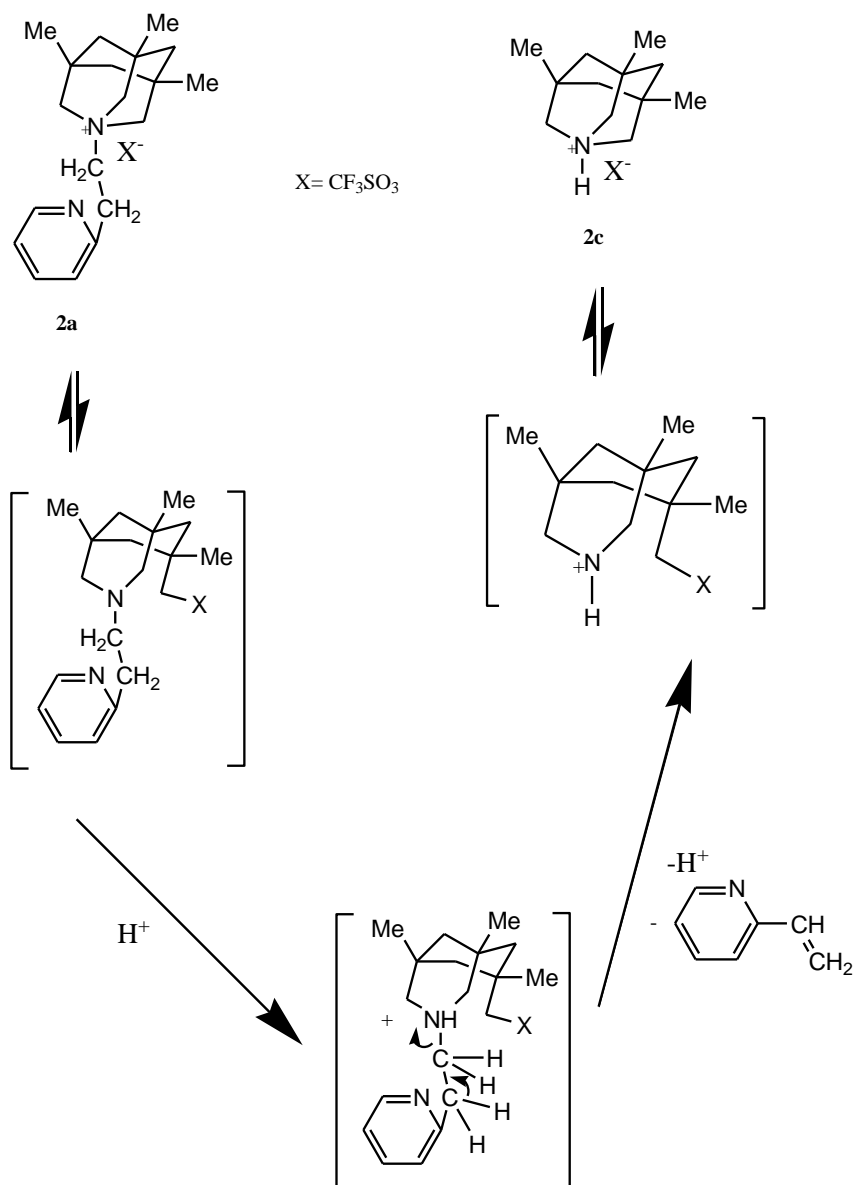
Azonias-adamantane 2a was not stable in CDCl₃. Allowing the CDCl₃ solution of 2a to stand at room temperature for 5 days gave azonias-adamantane 2c (R = H) and 2-vinylpyridine (Scheme 3). However, 2a did not yield 2c either in DMSO-*d*₆ or in acetone-*d*₆ at room temperature for 2 weeks. We have already described that acid catalysis works in chloroform.^{6,8} Scheme 4 shows a plausible mechanism for the reaction of 2a to 2c. It has been clarified that 3,5,7-trimethyl-1-azabicyclo[3.3.1]nonane structures easily undergo the interconversion to the corresponding 3-azabicyclo[3.3.1]nonane structures.^{1,2} It is suggested that azonias-adamantane 2a is in equilibrium with the C-N bond cleavage form, and adhesion of a proton to the nitrogen atom in this form yields 2c and 2-vinylpyridine. This reaction resembles acid-catalyzed alkene formation reactions of alcohols. Azonias-adamantane 2a reacts not only with acids but also with bases. The reaction of 2a with lithium methoxide in methanol afforded aza-adamantane 1⁵ and 2-vinylpyridine (Scheme 3). This reaction is also available for the convenient synthesis of aza-adamantane 1. Triethylamine did not react with 2a at all. The acidity of β-methylene protons in azonias-adamantane 2a has a large influence on these reactions.



Scheme 3

Conclusions

We have described the convenient synthesis of 3,5,7-trimethyl-1-azonia-adamantanes 2. In this synthesis, trifluoromethanesulfonate works as the key counter anion. The similar reaction of triester 5 with 2-(2-aminoethyl) pyridine does not give the corresponding azonia-adamantane, but trifluoro-acetamide 6. We have also shown that the elimination reaction of azonia-adamantane 2 containing β -methylene protons is available for the synthesis of aza-adamantane 1.



Scheme 4

Experimental Section

General Procedures. All reactions were performed in oven-dried glassware equipped with a magnetic stirring bar under an argon atmosphere, using standard syringe techniques. CH_2Cl_2 was distilled from CaH_2 and stored over molecular sieves. All other solvents were of anhydrous grade. *cis,cis*-1,3,5-Tris(hydroxymethyl)-1,3,5-trimethylcyclohexane (**3**)⁶ and *cis,cis*-1,3,5-trimethyl-1,3,5-tris[(trifluoromethylsulfonyl)methyl]cyclohexane (**4**)⁷ were prepared by the similar procedures previously reported. All other reagents were of commercial grade. ^1H (500 MHz) and ^{13}C (125.7 MHz) NMR spectra were recorded in CDCl_3 , $\text{DMSO}-d_6$, or acetone- d_6 .

3,5,7-Trimethyl-1-[2-(pyridin-2-yl)ethyl]-1-azonia-adamantane trifluoromethanesulfonate (2a).

A solution of trifluoromethanesulfonic anhydride (2.2 mL, 13 mmol) in dry CH_2Cl_2 (15 mL) was added to a suspension of triol 3 (723 mg, 3.34 mmol) and pyridine (1.2 mL) in dry CH_2Cl_2 (15 mL) at 0 °C. After the mixture was stirred for 2 h at 0 °C, the precipitates were filtered, and the solution was passed through a silica gel column. Removal of the solvent under reduced pressure gave crude triester 4. Unpurified triester 4 was dissolved in dry CH_2Cl_2 (10 mL), and 2-(2-aminoethyl) pyridine (1.85 g, 15.1 mmol) was added to the solution. The solution was stirred for 3 days at room temperature, and dilute aqueous NaOH was added. The CH_2Cl_2 layer was separated, and the aqueous phase was extracted with CH_2Cl_2 . The combined CH_2Cl_2 solutions were dried with MgSO_4 , followed by filtration, the filtrate was concentrated to remove volatiles. Azonia-adamantane 2a (338 mg, 23%) was purified by recrystallization from CH_2Cl_2 /diethyl ether. 2a: colorless crystals; ^1H NMR (CDCl_3 , 500 MHz) δ 0.99 (9H, s, CH_3), 1.33 (3H, d, $^2J_{\text{HH}} = 13.0$ Hz, CHaHe), 1.50 (3H, d, $^2J_{\text{HH}} = 13.0$ Hz, CHaHe), 3.24 (6H, s, CH_2N), 3.53–3.57 (2H, m, $\text{CH}_2\text{CH}_2\text{pyr}$), 3.90–3.94 (2H, m, $\text{CH}_2\text{CH}_2\text{N}$), 7.40–7.43 (1H, m, pyrH), 7.85–7.87 (1H, m, pyrH), 7.94–7.97 (1H, m, pyrH), 8.49–8.50 (1H, m, pyrH); ^{13}C NMR (CDCl_3 , 125.7 MHz) δ 25.53 (CH_3), 28.31 ($\text{CH}_2\text{CH}_2\text{pyr}$), 31.56 [$(\text{CH}_2)_2\text{CCH}_3$], 46.07 (CCH_2C), 64.81 ($\text{CH}_2\text{CH}_2\text{N}$), 67.27 (CH_2N), 123.75 (pyridine carbon), 126.72 (pyridine carbon), 141.04 (pyridine carbon), 145.92 (pyridine carbon), 153.88 (pyridine carbon); IR (KBr) ν/cm^{-1} 1259, 1167, 1026, 637; Anal. Calcd for $\text{C}_{20}\text{H}_{29}\text{F}_3\text{N}_2\text{O}_3\text{S}$: C, 55.28; H, 6.73; N, 6.45. Found: C, 55.22; H, 6.83; N, 6.51.

1-(4-Methoxybenzyl)-3,5,7-trimethyl-1-azonia-adamantane trifluoromethanesulfonate (2b).

The similar manner that was employed in the preparation of 2a was used with triol 3 (746 mg, 3.45 mmol), trifluoromethanesulfonic anhydride (2.0 mL, 12 mmol), and 4-methoxybenzylamine (1.91 g, 13.9 mmol). Azonia-adamantane 2b (479 mg, 1.06 mmol) was obtained in 31% yield. 2b: colorless solids; ^1H NMR (CDCl_3 , 500 MHz) δ 0.91 (9H, s, CH_3), 1.22 (3H, d, $^2J_{\text{HH}} = 12.8$ Hz, CHaHe), 1.38 (3H, d, $^2J_{\text{HH}} = 12.8$ Hz, CHaHe), 3.06 (6H, s, CH_2N), 3.79 (3H, s, OCH_3), 4.49 (2H, s, NCH_2Ar), 6.87 (2H, d, $^3J_{\text{HH}} = 8.7$ Hz, ArH), 7.39 (2H, d, $^3J_{\text{HH}} = 8.7$ Hz, ArH); ^{13}C NMR (CDCl_3 , 125.7 MHz) δ 25.57 (CH_3), 31.36 [$(\text{CH}_2)_2\text{CCH}_3$], 45.98 (CCH_2C), 55.33 (OCH_3), 65.67 (CH_2N), 69.10 (NCH_2Ar), 114.45 (aromatic carbon), 117.80 (aromatic carbon), 120.75 (q, $^1J_{\text{CF}} = 320$ Hz, CF_3), 134.67 (aromatic carbon), 161.20 (aromatic carbon); IR (KBr) ν/cm^{-1} 1265, 1150, 1030, 637; Anal. Calcd for $\text{C}_{21}\text{H}_{30}\text{F}_3\text{N}_2\text{O}_4\text{S}$: C, 56.11; H, 6.73; N, 3.12. Found: C, 56.03; H, 6.88; N, 3.19.

cis,cis-1,3,5-Tris[(trifluoroacetoxy)methyl]-1,3,5-trimethylcyclohexane (5). A solution of trifluoroacetic anhydride (2.0 mL, 14 mmol) in dry CH_2Cl_2 (15 mL) was added to a suspension of triol 3 (725 mg, 3.35 mmol) and pyridine (1.2 mL) in dry CH_2Cl_2 (15 mL) at 0 °C. After the mixture was stirred for 2.5 h at 0 °C, the solution was passed through a silica gel column. Removal of the solvent under reduced pressure gave triester 5 (1.59 g, 94%). 5: colorless solids; ^1H NMR (CDCl_3 , 500 MHz) δ 1.25 (9H, s, CH_3), 1.32 (3H, d, AB, $^2J_{\text{HH}} = 14.2$ Hz, CHaHe), 1.34 (3H, d, AB, $^2J_{\text{HH}} = 14.2$ Hz, CHaHe), 3.94 (6H, s, CH_2O); ^{13}C NMR (CDCl_3 , 125.7 MHz) δ 25.43 (CH_3), 34.27 [$(\text{CH}_2)_2\text{CCH}_3$], 38.85 (CCH_2C), 77.40 (CH_2O), 114.48 (q, $^1J_{\text{CF}}$

= 285 Hz, CF₃), 157.38 (q, ²JCF = 43 Hz, COO); Anal. Calcd for C₁₈H₂₁F₉O₆: C, 42.87; H, 4.20. Found: C, 43.54; H, 4.14.

2,2,2-Trifluoro-N-[2-(pyridin-2-yl)ethyl]-acetamide (6). 2-(2-aminoethyl)pyridine (1.28 g, 10.4 mmol) was added to a CH₂Cl₂ solution (10 mL) of triester 5 (1.59 g, 3.16 mmol). While the solution was stirred for 3 h at room temperature, precipitates were formed. The precipitates were filtered and washed with diethyl ether. Triol 3 (658 mg, 3.04 mmol) was obtained in 96% yield. After the filtrate was concentrated to remove volatiles, the residue was extracted with CH₂Cl₂. Removal of the solvent under reduced pressure gave acetamide 6 (1.99 g, 96%). Further purification was carried out by recrystallization from diethyl ether/hexane. 6: pale yellow crystals; ¹H NMR (CDCl₃, 500 MHz) δ 3.00–3.02 (2H, m, CH₂), 3.72–3.75 (2H, m, CH₂), 7.13–7.16 (2H, m, pyrH), 7.59–7.63 (1H, m, pyrH), 8.40 (1H, br. s, NH), 8.47–8.48 (1H, m, pyrH); ¹³C NMR (CDCl₃, 125.7 MHz) δ 35.13 (CH₂), 38.66 (CH₂), 115.97 (q, ¹JCF = 287 Hz, CF₃), 121.90 (pyridine carbon), 123.43 (pyridine carbon), 136.91 (pyridine carbon), 149.02 (pyridine carbon), 156.97 (q, ²JCF = 37 Hz, CO), 158.94 (pyridine carbon); IR (KBr)/v/ cm⁻¹ 3202, 1724; Anal. Calcd for C₉H₉F₃N₂O: C, 49.55; H, 4.16; N, 12.84. Found: C, 49.62; H, 4.19; N, 12.81.

3,5,7-Trimethyl-1-aza-adamantane (1).⁵ A solution of azonia-adamantane 2a (76.3 mg, 0.18 mmol) in methanol (20 mL) was added to a 12% lithium methoxide methanol solution (2 mL) at 0 °C. After the mixture was stirred for 18 h at room temperature, water (1 mL) was added to the solution. Volatiles were removed under reduced pressure, and the residue was extracted with CH₂Cl₂. Removal of the solvent under reduced pressure gave aza-adamantane 1⁵ (24.9 mg, 79%).

NMR Monitoring experiment. Azonia-adamantane 2a (2.1 mg, 0.005 mmol) was added to CDCl₃ (0.8 mL) in an NMR tube. Allowing the solution to stand at room temperature for 5 days gave azonia-adamantane 2c (R = H) and 2-vinylpyridine. 2c: ¹H NMR (CDCl₃, 500 MHz) δ 0.96 (9H, s, CH₃), 1.37 (3H, d, ²JHH = 12.7 Hz, CHaHe), 1.44 (3H, d, ²JHH = 12.7 Hz, CHaHe), 3.00 (6H, s, CH₂N), 10.70 (1H, br. s, NH); ¹³C NMR (CDCl₃, 125.7 MHz) δ 25.89 (CH₃), 30.05 [(CH₂)₂CCH₃], 47.22 (CCH₂C), 59.53 (CH₂N).

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