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Oligomer Formation via Reactions of 3-Ethyl-1-azabicyclo[1.1.0]butane with Arenesulfonyl Azides

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Abstract. Electrophilic additions of arenesulfonyl azides (i.e., TsN_3 and NsN_3) to 3-ethyl-1-azabicyclo-[1.1.0]butane (**1**) in $CDCl_3$ at 80 °C has been observed to result in the formation of oligomeric products. The mechanism of these reactions probably involves the formation of a carbocationic intermediate, i.e., *N*-arenesulfonyl-3-ethyl-3-azetidinyl carbocation, which subsequently can be trapped *in situ* either by $:N_3^-$ or by **1** to afford the observed reaction products.

Introduction. 3-Substituted 1-azabicyclo[1.1.0]butanes were first synthesized in the late 1960s.[1,2] Despite their unusual and highly strained bicyclic structures, little interest was shown initially in pursuing the chemistry of compounds of this type. However, the current decade has witnessed a renaissance of interest in 1-azabicyclo[1.1.0]butane chemistry.[3] Thus, reactions of carbenes[4] and a variety of other electrophiles[5,6] with 3-substituted 1-azabicyclo[1.1.0]butanes have been reported recently. In addition, their use as intermediates in the synthesis of energetic materials, e. g., 1,3,3-trinitroazetidine ("TNAZ") in particular, has been reported.[7]

In the present study, we observed that reactions of arenesulfonyl azides with 3-ethyl-1-azabicyclo-[1.1.0]butane (**1**) result in electrophilic addition of the elements of $ArSO_2$-N_3 across the highly strained N-C(3) σ-bond to afford a simple 1,3-adduct. Interestingly, this reaction is accompanied by the formation of several oligomeric products. We now report the results of our studies of reactions of *p*-toluenesulfonyl azide ("tosyl azide", TsN_3) and *p*-nitrobenzenesulfonyl azide ("nosyl azide", NsN_3) and our attempts to account for these results mechanistically.

Results and Discussion. The reaction of TsN_3 with **1** was performed in a sealed NMR tube ($CDCl_3$ solvent) that was placed in a thermostatted bath at 80 °C for 7 days. The course of the reaction could be monitored conveniently by ^1H NMR spectroscopic analysis. Under these conditions, TsN_3 reacts only very slowly with **1**; *ca.* half of this substrate was recovered unchanged at the conclusion of the reaction. The remaining material consisted of a gross mixture of several products that could be separated conveniently via column chromatography. Along with the product that resulted via simple electrophilic addition of the elements of TsN_3 across the N-C(3) σ-bond in **1**, (i.e, **2**, which was isolated in 28% yield), several oligomeric products (**3-7**, Scheme 1) also were isolated and subsequently were fully characterized (see the Experimental Section).

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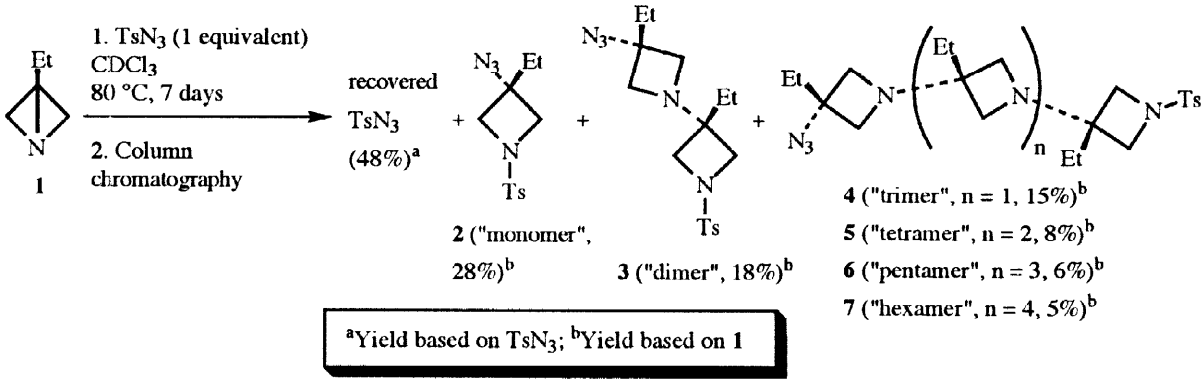
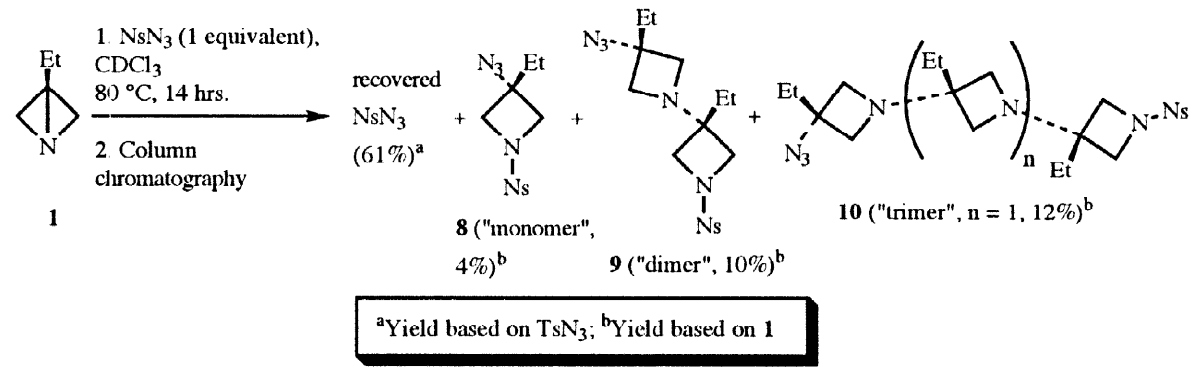
Scheme 1



The corresponding reaction of NsN_3 with **1** also was studied. This reaction proved to be considerably more facile than that of TsN_3 with **1** when the two reactions were performed under comparable environmental conditions. After the former reaction had proceeded at 80 °C for 14 h, the sealed NMR tube was opened, and the reaction products were isolated via column chromatography (see the Experimental Section). Recovered (unreacted) NsN_3 (61%) was thereby obtained along with "monomeric" adduct (**8**, 4%) and oligomeric products [i.e., **9** (10%) and **10** (12%), Scheme 2].

Scheme 2

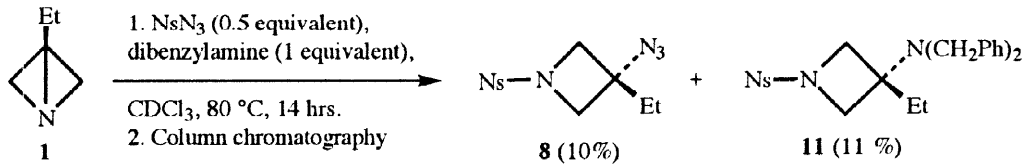


When the reaction of NsN_3 with **1** was performed in the presence of added dibenzylamine, two "monomeric" adducts were obtained in low yield: *N*-nosyl-3-azido-3-ethyl-azetidine (**8**, 10%) and *N*-nosyl-3-(dibenzylamino)-3-ethylazetidine (**11**, 12%). Formation of **11** in this reaction most likely resulted via intermolecular nucleophilic trapping of a carbocationic intermediate, i.e., *N*-nosyl-3-ethyl-3-azetidinyl carbocation.

Two control experiments were performed in an effort to gain additional information regarding the mechanism of formation of **11**. In the first experiment, **1** was allowed to react with dibenzylamine in the absence of added NsN_3. The reaction mixture was heated at 80 °C for several days, and the progress of the reaction was monitored periodically *via* analysis of its ^1H NMR spectrum. No change was observed in the appearance of the ^1H NMR spectrum of the reaction mixture after the reaction had been allowed to proceed at 80 °C for 5 days. This result establishes the fact the **11** could not have been formed via direct reaction of **1** with dibenzylamine.

In the second experiment, *N*-nosyl-3-azido-3-ethylazetidine (**8**) was allowed to react with dibenzylamine (Scheme 3). The reaction mixture was heated at 80 °C, and the progress of the reaction was monitored periodically *via* analysis of its ^{1}H NMR spectrum. No change was observed in the appearance of the ^{1}H NMR spectrum of the reaction mixture after the reaction had been carried out at 80 °C for 28 h. This result indicates that **11** was not formed in the reaction of **1** with NsN_3 and dibenzylamine simply via secondary reaction of **8** with dibenzyl-amine. Accordingly, we conclude that **11** must be a primary reaction product, i.e., that which results via successful competition of dibenzylamine vs. azide ion in nucleophilic trapping of the critical reaction intermediate, *N*-nosyl-3-ethyl-3-azetidinyl carbocation.

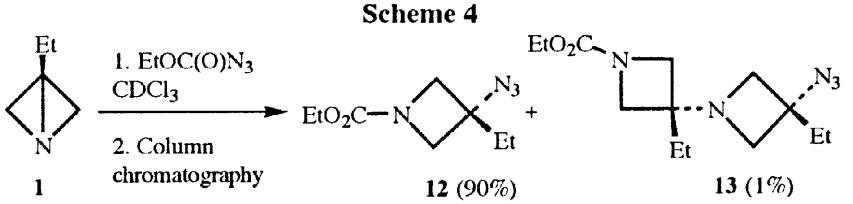
Scheme 3



We also attempted to trap the intermediate carbocation by intorducing KI/(18-crown-6) into the reaction of both TsN_3 and of NsN_3 with **1**. Interstingly, iodide ion proved to be ineffective as a nucleophilic trap in these experiments. The reasons for the failure of iodide ion to function effectively in this capacity are not clear.

For purposes of comparison, the corresponding reaction of **1** with ethyl azidoformate (EtO_2C-N_3) was studied. This reaction proved to be considerably more facile than either the corresponding reactions of TsN_3 or of NsN_3 with **1**. Thus, reaction of EtO_2C-N_3 with **1** in $CDCl_3$ was complete within 24 h at ambient temperature. Column chromatographic purification of the mixture of reaction products thereby obtained afforded *N*-ethoxycarbonyl-3-azido-3-ethylazetidine (**12**, 90%) and *N*-(*N'*-ethoxycarbonyl-3'-ethyl-3'-azetidinyl)-3-azido-3-ethylazetidine (**13**, 1%, Scheme 4).

Scheme 4



Conclusions. A mechanism that is capable of accounting for the formation of oligomers in the reaction of TsN_3 with **1** and that is consistent with the results of the foregoing control experiments is suggested in Scheme 5.

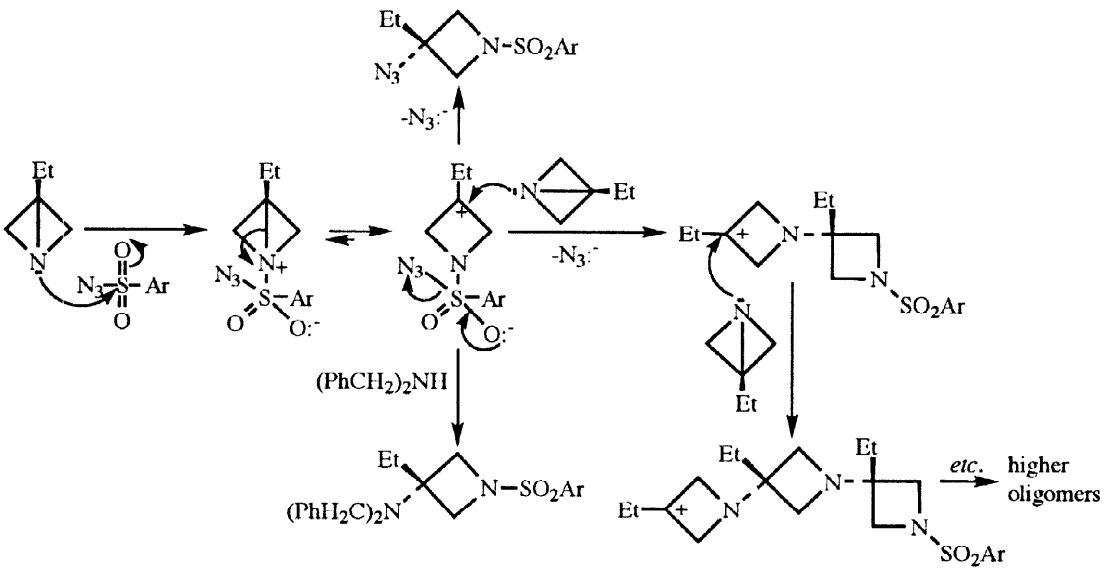
Experimental Section

Melting points are uncorrected. Elemental microanalyses were performed by personnel at M-H-W Laboratories, Phoenix, AZ.

Reaction of 3-Ethyl-1-azabicyclo[1.1.0]butane (1) with *p*-Toluenesulfonyl azide. Method A. To a solution of **1** (176 mg, 2.1 mmol) in $CDCl_3$ (0.5 mL) was added freshly prepared *p*-toluenesulfonyl azide[8] (TsN_3, 417 mg, 2.1 mmol). The resulting mixture was placed in a 5 mm NMR sample tube. The tube was sealed and then was heated in an external oil bath at 80 °C for several days. The progress of the reaction was monitored periodically *via* analysis of its ^{1}H NMR spectrum. After seven days, resonances that correspond to **1**

could no longer be detected in the ^{1}H NMR spectrum of the reaction mixture. The NMR tube was opened, and the crude reaction mixture contained therein was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 10-100% EtOAc-hexane gradient elution scheme.

Scheme 5



The first chromatography fraction contained recovered TsN_3 (197 mg, 48%). Continued elution of the chromatography column afforded a second fraction that contained *N*-*p*-toluenesulfonyl-3-azido-3-ethylazetidine[6c] (**2**). When this fraction was concentrated *in vacuo*, pure **2** (163 mg, 28%) was obtained as a colorless microcrystalline solid: mp 81-82 °C (lit.[6c] mp 81-82 °C). The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **2**.[6c]

Continued elution of the chromatography column afforded the third fraction, which, when concentrated *in vacuo*, afforded pure *N*-(*N'*-*p*-toluenesulfonyl-3'-ethyl-3'-azetidinyl)-3-azido-3-ethylazetidine (**3**, 70 mg, 18%) as a colorless, viscous oil: IR (neat) 2976 (vs), 2876 (s), 2104 (vs), 1595 (m), 1456 (s), 1384 (vs), 1255 (s), 1149 (vs), 1084 (s), 912 (m), 812 (m), 729 (s), 678 cm^{-1} (vs); ^{1}H NMR ($CDCl_3$) δ 0.74 (t, J = 7.3 Hz, 3 H), 0.84 (t, J = 7.3 Hz, 3 H), 1.44 (q, J = 7.3 Hz, 2 H), 1.64 (q, J = 7.3 Hz, 2 H), 2.44 (s, 3 H), 2.87 (s, 4 H), 3.40 (*AB*, J_{AB} = 8.7 Hz, 2 H), 3.62 (*AB*, J_{AB} = 8.7 Hz, 2 H), 7.38 (*AB*, J_{AB} = 8.3 Hz, 2 H), 7.74 (*AB*, J_{AB} = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.6 (q), 8.0 (q), 21.6 (q), 28.5 (t), 29.8 (t), 54.5 (t), 56.1 (t), 57.7 (s), 59.5 (s), 128.4 (d), 129.8 (d), 131.3 (s), 144.2 (s). Anal. Calcd for $C_{17}H_{25}N_5O_2S$: C, 56.18; H, 6.93. Found: C, 55.99; H, 7.07.

The fourth chromatography fraction, when concentrated *in vacuo*, afforded pure **4** (46 mg, 15%), as a colorless, viscous oil; IR (neat) 3267 (w), 2974 (s), 2874 (m), 2102 (s), 1602 (m), 1458 (m), 1340 (s), 1170 (s), 1101 (s), 821 (m), 673 cm^{-1} (s); ^{1}H NMR ($CDCl_3$) δ 0.71 (t, J = 7.3 Hz, 3 H), 0.72 (t, J = 7.3 Hz, 3 H), 0.92 (t, J = 7.3 Hz, 3 H), 1.34 (q, J = 7.3 Hz, 2 H), 1.40 (q, J = 7.3 Hz, 2 H), 1.76 (q, J = 7.3 Hz, 2 H), 2.43 (s, 3 H), 2.47 (*AB*, J_{AB} = 7.7 Hz, 2 H), 2.88 (*AB*, J_{AB} = 7.7 Hz, 2 H), 3.14 (*AB*, J_{AB} = 7.9 Hz, 2 H), 3.22 (*AB*, J_{AB} = 7.9 Hz, 2 H), 3.33 (*AB*, J_{AB} = 8.5 Hz, 2 H), 3.61 (*AB*, J_{AB} = 8.5 Hz, 2 H), 7.37 (*AB*, J_{AB} = 8.1 Hz, 2 H), 7.73 (*AB*, J_{AB} = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.6 (q), 7.9 (q), 8.2 (q), 21.6 (q), 28.6 (t), 28.8 (t), 30.0 (t), 51.3 (t), 54.9 (t), 56.5 (t), 57.5 (s), 57.6 (s), 59.9 (s), 128.3 (d), 129.8 (d), 131.4 (s), 144.1 (s). Anal. Calcd for $C_{22}H_{34}N_6O_2S$: C, 59.17; H, 7.67. Found: C, 58.96; H, 7.63.

Continued elution of the chromatography fraction afforded a fifth fraction which, when concentrated *in vacuo*, afforded pure **5** (23 mg, 8%) as a colorless, viscous oil: IR (neat) 2964 (s), 2864 (m), 2096 (vs), 1591

(m), 1456 (m), 1352 (vs), 1165 (vs), 1076 (s), 900 (m), 815 (m), 732 (s), 673 cm^{-1} (vs); ^1H NMR ($CDCl_3$) δ 0.71 (t, J = 7.3 Hz, 3 H), 0.73 (t, J = 7.3 Hz, 3 H), 0.89 (t, J = 7.3 Hz, 3 H), 0.94 (t, J = 7.3 Hz, 3 H), 1.32-1.55 (m, 6 H), 1.79 (q, J = 7.3 Hz, 2 H), 2.43 (s, 3 H), 2.50 (*AB*, J_{AB} = 7.5 Hz, 2 H), 2.84 (*AB*, J_{AB} = 7.3 Hz, 2 H), 2.91 (*AB*, J_{AB} = 7.3 Hz, 2 H), 3.18 (*AB*, J_{AB} = 7.5 Hz, 2 H), 3.23 (*AB*, J_{AB} = 7.5 Hz, 2 H), 3.34 (*AB*, J_{AB} = 7.5 Hz, 2 H), 3.38 (*AB*, J_{AB} = 8.4 Hz, 2 H), 3.65 (*AB*, J_{AB} = 8.4 Hz, 2 H), 7.36 (*AB*, J_{AB} = 8.2 Hz, 2 H), 7.75 (*AB*, J_{AB} = 8.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.7 (q), 8.0 (q), 8.1 (q), 8.3 (q), 21.6 (q), 28.7 (t), 28.9 (t), 29.0 (t), 30.1 (t), 51.5 (t, 2C), 55.0 (t), 56.4 (t), 57.4 (s), 57.7 (s), 57.9 (s), 60.0 (s), 128.3 (d), 129.7 (d), 131.6 (s), 144.0 (s). Anal. Calcd for $C_{27}H_{43}N_7O_2S$: C, 61.22; H, 8.18. Found: C, 60.98; H, 7.98.

Subsequently, a sixth chromatography fraction was collected. When concentrated *in vacuo*, this fraction afforded pure **6** (15 mg, 6%) as a colorless, viscous oil; IR (neat) 3281 (w), 2937 (s), 2885 (m), 2108 (s), 1608 (s), 1460 (m), 1342 (s), 1161 (vs), 1093 (s), 910 (s), 812 (m), 736 (vs), 671 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 0.69-0.89 (m, 12 H), 0.94 (t, J = 7.3 Hz, 3 H), 1.32-1.42 (m, 4 H), 1.48-1.61 (m, 4 H), 1.79 (q, J = 7.3 Hz, 2 H), 2.43 (s, 3 H), 2.52 (*AB*, J_{AB} = 7.1 Hz, 2 H), 2.82 (*AB*, J_{AB} = 7.0 Hz, 2 H), 2.95 (2 overlapping *AB*, J_{AB}= 7.0 Hz, 4 H), 3.18-3.27 (m, 6 H), 3.37 (*AB*, J_{AB} = 7.7 Hz, 2 H), 3.38 (*AB*, J_{AB} = 8.4 Hz, 2 H), 3.66 (*AB*, J_{AB} = 8.4 Hz, 2 H), 7.36 (*AB*, J_{AB} = 8.1 Hz, 2 H), 7.73 (*AB*, J_{AB} = 8.1 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.7 (q), 8.0 (q), 8.2 (q), 8.3 (q), 21.6 (q), 28.7 (t), 28.9 (t), 29.1 (t), 30.1 (t), 51.4 (t), 51.6 (t), 51.7 (t), 55.0 (t), 56.4 (t), 57.5 (s), 57.6 (s), 57.8 (s), 57.9 (s), 60.0 (s), 128.3 (d), 129.7 (d), 131.6 (s), 144.0 (s). Anal. Calcd for $C_{32}H_{52}N_8O_2S$: C, 62.71; H, 8.55. Found: C, 62.63; H, 8.42.

Finally, a seventh chromatography fraction was collected which, when concentrated *in vacuo*, afforded pure **7** (12 mg, 5%), as a colorless, viscous oil: IR (neat) 3348 (w), 2924 (vs), 2858 (m), 2106 (s), 1608 (w), 1460 (m), 1348 (s), 1167 (s), 1085 (s), 916 (m), 817 (m), 742 (s), 683 cm^{-1} (s); ^1H NMR ($CDCl_3$) δ 0.72, (2 overlapping t, J = 7.3 Hz, 6 H), 0.80-0.89 (m, 9 H), 0.93 (t, J = 7.3 Hz, 3 H), 1.32-1.42 (m, 4 H), 1.46-1.61 (m, 6 H), 1.79 (q, J = 7.3 Hz, 2 H), 2.43 (s, 3 H), 2.51 (*AB*, J_{AB} = 7.4 Hz, 2 H), 2.82 (*AB*, J_{AB} = 7.0 Hz, 2 H), 2.89-2.97 (m, 6 H), 3.19-3.30 (m, 8 H), 3.36 (*AB*, J_{AB} = 7.3 Hz, 2 H), 3.38 (*AB*, J_{AB}= 8.4 Hz, 2 H), 3.66 (*AB*, J_{AB} = 8.4 Hz, 2 H), 7.35 (*AB*, J_{AB} = 8.3 Hz, 2 H), 7.73 (*AB*, J_{AB} = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.7 (q), 8.0 (q), 8.2 (q), 8.2 (q), 21.6 (q), 28.7 (t), 28.9 (t), 28.9 (t), 29.0 (t), 30.1 (t), 51.5 (t), 51.6 (t), 51.7 (t), 55.0 (t), 56.4 (t), 57.5 (s), 57.7 (s), 57.7 (s), 57.9 (s), 60.0 (s), 128.3 (d), 129.7 (d), 131.7 (s), 144.0 (s). Anal. Calcd for $C_{37}H_{61}N_9O_2S$: C, 63.85; H, 8.83. Found: C, 63.90; H, 8.86.

Method B. To a solution of **1** (328 mg, 3.9 mmol) in $CDCl_3$ (0.5 mL) was added freshly prepared TsN_3[8] (155 mg, 0.78 mmol). The resulting mixture was placed in a 5 mm NMR sample tube, and the tube was sealed and then was placed in an external oil bath maintained at 80 °C. The reaction mixture was heated at 80 °C for several days, and the progress of the reaction was monitored periodically *via* analysis of its ^1H NMR spectrum. After seven days, resonances that correspond to **1** could no longer be detected in the ^1H NMR spectrum of the reaction mixture. The NMR tube was opened, and the crude reaction mixture contained therein was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 15-100% EtOAc-hexane gradient elution scheme.

The first chromatography fraction thereby obtained, when concentrated *in vacuo*, afforded pure **2** (91 mg, 8%) as a colorless microcrystalline solid: mp 81-82 °C (lit.[6c] mp 81-82 °C). The IR, ^1H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **2**.[6c]

Continued elution of the chromatography column afforded a second fraction. When concentrated *in vacuo*, pure **3** (20 mg, 3%) was obtained as a colorless, viscous oil. The IR, ^1H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **3**.

Continued elution of the chromatography column afforded a third fraction, which, when concentrated *in vacuo*, afforded pure **4** (31 mg, 5%), as a colorless, waxy solid. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **4**.

The fourth chromatography fraction, when concentrated *in vacuo*, afforded pure **5** (38 mg, 7%) as a viscous oil. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **5**.

Continued elution of the chromatography column afforded a fifth fraction which, when concentrated *in vacuo*, yielded pure **6** (19 mg, 4%), as a colorless, viscous oil. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **6**.

Subsequently, a sixth chromatography fraction was collected. When concentrated *in vacuo*, this fraction afforded pure **7** (25 mg, 6%), as a colorless, viscous oil. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **7**. Additional chromatography fractions were collected, but the contents of these fractions were not identified or further characterized.

Method C. To a solution of **1** (105 mg, 1.26 mmol) in $CDCl_3$ (0.5 mL) was added freshly prepared *p*-toluenesulfonyl azide[8] (TsN_3, 124 mg, 0.63 mmol). The resulting mixture was placed in a 5 mm NMR sample tube, and $F_3B{\cdot}OEt_2$ (1 drop, catalytic amount) was added. The tube was sealed and then agitated to thoroughly mix the contents. The reaction mixture was allowed to stand at ambient temperature for several hours, during which the progress of the reaction was monitored periodically *via* analysis of its ^{1}H NMR spectrum. After 4 h, resonances that correspond to **1** could no longer be detected in the ^{1}H NMR spectrum of the reaction mixture. After 48 h, the NMR tube was opened, and the crude reaction mixture was concentrated *in vacuo*. The residue was purified via preparative thick layer chromatography on silica gel by eluting with 20% EtOAc-hexane.

Workup of the first chromatography fraction thereby obtained afforded unreacted TsN_3 (90 mg, 73%). Workup of a second chromatography fraction afforded **2** (8 mg, 2%), as a colorless microcrystalline solid: mp 81-82 °C (lit.[6c] mp 81-82 °C). The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **2**.[6c]

Continued elution of the chromatography plate gave pure **3** (19 mg, 8%) as a colorless, viscous oil. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **3**.

Workup of the fourth chromatography fraction gave pure **4** (10 mg, 5%) as a colorless, viscous oil. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **4**.

Method D. To a solution of **1** (48 mg, 0.57 mmol) in $CDCl_3$ (0.5 mL) was added freshly prepared TsN_3[8] (113 mg, 0.57 mmol) and KI-(18-crown-6)[9] (271 mg, 0.63 mmol) at ambient temperature. The resulting mixture was placed in a 5 mm NMR sample tube. The tube was sealed and then was agitated vigourously to assure thorough mixing of the reactants. The reaction mixture was allowed to stand at ambient temperature, and the progress of the reaction was monitored periodically *via* analysis of its ^{1}H NMR spectrum. After 30 h, ^{1}H NMR resonance signals that correspond to **1** could no longer be detected. The NMR tube was opened, and the reaction mixture contained therein was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 10-20% EtOAc-hexane gradient elution scheme.

The first chromatography fraction contained recovered TsN_3 (5 mg, 4%). Continued elution of the chromatography column afforded a second fraction that contained **2** (126 mg, 79%), which was isolated as a

colorless microcrystalline solid: mp 81-82 °C (lit.[6c] mp 81-82 °C). The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **2**.[6c]

Continued elution of the chromatography column afforded a third fraction that contained pure **3** (9 mg, 9%) as a colorless, viscous oil. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **3**.

Method E. To a solution of **1** (60 mg, 0.72 mmol) in $CDCl_3$ (0.5 mL) was added freshly prepared TsN_3[8] (142 mg, 0.72 mmol) and KI-(18-crown-6)[9] (31 mg, 0.072 mmol, 0.1 equivalent) at ambient temperature. The resulting mixture was placed in a 5 mm NMR sample tube. The tube was sealed and then was agitated vigorously to assure thorough mixing of the reactants. The reaction mixture was allowed to stand at ambient temperature, and the progress of the reaction was monitored periodically *via* analysis of its ^{1}H NMR spectrum. After 7 days, ^{1}H NMR resonance signals that correspond to **1** could no longer be detected. The NMR tube was opened, and the reaction mixture contained therein was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 10-20% EtOAc-hexane gradient elution scheme.

The first chromatography fraction contained recovered TsN_3 (16 mg, 11%). Continued elution of the chromatography column afforded a second fraction that contained **2** (172 mg, 85%), which was isolated as a colorless microcrystalline solid: mp 81-82 °C (lit.[6c] mp 81-82 °C). The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **2**.[6c]

Continued elution of the chromatography column afforded a second fraction that contained pure **3** (10 mg, 8%) as a colorless, viscous oil. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **3**.

Control Experiment: Reaction of 3-Ethyl-1-azabicyclo[1.1.0]butane (1) with *N*-*p*-toluenesulfonyl-3-azido-3-ethylazetidine (2). To a solution of **1** (93 mg, 1.1 mmol) in $CDCl_3$ (0.5 mL) was added *N*-*p*-toluenesulfonyl-3-azido-3-ethylazetidine (**2**, 244 mg, 0.87 mmol). The resulting mixture was placed in a 5 mm NMR sample tube. The tube was sealed and then was placed in an external oil bath maintained at 80 °C. The reaction mixture was heated at 80 °C for several days, and the progress of the reaction was monitored periodically *via* analysis of its ^{1}H NMR spectrum. No change was observed in the appearance of the ^{1}H NMR spectrum of the reaction mixture after the reaction had been carried out at 80 °C for 7 days. The NMR tube was allowed to cool to ambient temperature. The tube then was opened, and F_3B-OEt_2 (3 drops) was added to the reaction mixture. After 1 h, the crude reaction mixture contained therein was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by eluting with 10% EtOAc-hexane. Pure *N*-*p*-toluenesulfonyl-3-azido-3-ethylazetidine[6c] (**2**, 231 mg, 95%) was recovered as a colorless microcrystalline solid: mp 81-82 °C (lit.[6c] mp 81-82 °C). The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **2**.[6c]

Reaction of 3-Ethyl-1-azabicyclo[1.1.0]butane (1) with *p*-Nitrobenzenesulfonyl Azide (NsN_3). Method A. To a solution of **1** (61 mg, 0.73 mmol) in $CDCl_3$ (0.6 mL) was added NsN_3[10] (167 mg, 0.73 mmol). The resulting mixture was placed in a 5 mm NMR sample tube. The tube was sealed and then was placed in an external oil bath maintained at 80 °C. The reaction mixture was heated at 80 °C, and the progress of the reaction was monitored periodically *via* analysis of its ^{1}H NMR spectrum. After 14 h, ^{1}H NMR resonance signals that correspond to **1** could no longer be detected. The NMR tube was opened, and the reaction mixture contained therein was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 10-30% EtOAc-hexane gradient elution scheme.

The first chromatography fraction contained recovered NsN_3 (102 mg, 61%). Continued elution of the chromatography column afforded a second fraction that contained *N*-*p*-nitrobenzenesulfonyl-3-azido-3-ethylazetidine (**8**, 8.0 mg, 4%), which was obtained as a colorless microcrystalline solid. Recrystallization of this

material from EtOAc-hexane afforded analytically pure **8** as a colorless microcrystalline solid: mp 122-123 °C; IR (KBr) 2107 (m), 1526 (vs), 1354 (vs), 1167 (s), 745 (m), 648 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 3 H), 1.75 (q, J = 7.2 Hz, 2 H), 3.73 (*AB*, J_{AB} = 9.1 Hz, 2 H), 3.84 (A*B*, J_{AB} = 9.1 Hz, 2 H), 8.02 (*AB*, J_{AB} = 9.0 Hz, 2 H), 8.42 (A*B*, J_{AB} = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.7 (q), 29.5 (t), 59.1 (s), 59.6 (t), 124.5 (d), 129.2 (d), 140.8 (s), 150.6 (s). Anal. Calcd for $C_{11}H_{13}N_5O_4S$: C, 42.44; H, 4.21. Found: C, 42.61; H, 4.50.

Continued elution of the chromatography column afforded a third fraction, which, when concentrated *in vacuo*, afforded pure *N*-(*N'*-*p*-nitrobenzenesulfonyl-3'-ethyl-3'-azetidinyl)-3-azido-3-ethylazetidine (**9**, 15 mg, 10%) as a colorless microcrystalline solid. Recrystallization of this material from EtOAc-hexane afforded analytically pure **9** as a colorless microcrystalline solid: mp 98-99 °C; IR (KBr) 2092 (m), 1533 (vs), 1353 (s), 1160 (s), 863 (m), 738 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.75 (t, J = 7.2 Hz, 3 H), 0.88 (t, J = 7.2 Hz, 3 H), 1.41 (q, J = 7.2 Hz, 2 H), 1.71 (q, J = 7.2 Hz, 2 H), 3.05 (s, 4 H), 3.46 (*AB*, J_{AB} = 8.7 Hz, 2 H), 3.79 (A*B*, J_{AB} = 8.7 Hz, 2 H), 8.03 (*AB*, J_{AB} = 8.9 Hz, 2 H), 8.42 (A*B*, J_{AB} = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.6 (q), 8.1 (q), 28.5 (t), 29.9 (t), 55.0 (t), 56.3 (t), 58.1 (s), 59.6 (s), 124.4 (d), 129.2 (d), 141.5 (s), 150.5 (s). Anal. Calcd for $C_{16}H_{22}N_6O_4S$: C, 48.72; H, 5.62. Found: C, 48.59; H, 5.78.

The fourth chromatography fraction, when concentrated *in vacuo*, afforded pure **10** (14 mg, 12%), as a colorless microcrystalline solid. Recrystallization of this material from EtOAc-hexane afforded analytically pure **10** as a colorless microcrystalline solid: mp 105-106 °C; IR (KBr) 2099 (s), 1526 (vs), 1354 (vs), 1180 (w), 738 (m), 655 cm^{-1} (m); ^1H NMR ($CDCl_3$) δ 0.74 (t, J = 7.3 Hz, 3 H), 0.75 (t, J = 7.3 Hz, 3 H), 0.93 (t, J = 7.3 Hz, 3 H), 1.40 (q, J = 7.3 Hz, 2 H), 1.41 (q, J = 7.3 Hz, 2 H), 1.78 (q, J = 7.3 Hz, 2 H), 2.65 (*AB*, J_{AB} = 7.7 Hz, 2 H), 3.02 (A*B*, J_{AB} = 7.7 Hz, 2 H), 3.17 (*AB*, J_{AB} = 7.9 Hz, 2 H), 3.25 (A*B*, J_{AB} = 7.9 Hz, 2 H), 3.45 (*AB*, J_{AB} = 8.5 Hz, 2 H), 3.77 (A*B*, J_{AB} = 8.5 Hz, 2 H), 8.03 (*AB*, J_{AB} = 9.0 Hz, 2 H), 8.42 (A*B*, J_{AB} = 9.0 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 7.7 (q), 8.0 (q), 8.2 (q), 28.7 (t), 28.9 (t), 29.9 (t), 51.5 (t), 55.4 (t), 56.5 (t), 57.7 (s), 57.9 (s), 59.8 (s), 124.3 (d), 129.2 (d), 141.6 (s), 150.4 (s). Anal. Calcd for $C_{21}H_{31}N_7O_4S$: C, 52.81; H, 6.54. Found: C, 52.93; H, 6.37.

Method B. To a solution of **1** (42 mg, 0.51 mmol) in $CDCl_3$ (0.6 mL) was added NsN_3[10] (116 mg, 0.51 mmol) and KI-(18-crown-6)[9] (219 mg, 0.51 mmol). The resulting mixture was placed in a 5 mm NMR sample tube at ambient temperature. The tube was sealed and then was agitated vigorously to assure thorough mixing of the reactants. The reaction mixture was allowed to stand at ambient temperature, and the progress of the reaction was monitored periodically *via* analysis of its ^1H NMR spectrum. After 1.5 h, ^1H NMR resonance signals that correspond to **1** could no longer be detected. The NMR tube was opened, and the reaction mixture contained therein was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 10-20% EtOAc-hexane gradient elution scheme.

The first chromatography fraction contained recovered NsN_3 (9.0 mg, 8%). Continued elution of the chromatography column afforded a second fraction that contained *N*-*p*-nitrobenzenesulfonyl-3-azido-3-ethylazetidine (**8**, 114 mg, 72%), which was obtained as a colorless microcrystalline solid: mp 122-123 °C. The IR, ^1H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **8**.

Continued elution of the chromatography column afforded the third fraction, which, when concentrated *in vacuo*, afforded pure *N*-(*N'*-*p*-nitrobenzenesulfonyl-3'-ethyl-3'-azetidinyl)-3-azido-3-ethylazetidine (**9**, 7.0 mg, 7%) as a colorless microcrystalline solid: mp 98-99 °C. The IR, ^1H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **9**.

Method C. To a solution of **1** (70 mg, 0.84 mmol) in $CDCl_3$ (0.6 mL) was added NsN_3[10] (106 mg, 0.46 mmol) and dibenzylamine (173 mg, 0.87 mmol). The resulting mixture was placed in a 5 mm NMR sample tube. The tube was sealed and then was placed in an external oil bath maintained at 80 °C. The reaction mixture was heated at 80 °C, and the progress of the reaction was monitored periodically *via* analysis of its ^1H NMR

spectrum. After 14 h, ^{1}H NMR resonance signals that correspond to **1** could no longer be detected. The NMR tube was opened, and the reaction mixture contained therein was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using 10% EtOAc-hexane as eluent.

The first chromatography fraction contained *N*-*p*-nitrobenzenesulfonyl-3-dibenzylamino-3-ethylazetidine (**11**, 42 mg, 11%) as a pale yellow microcrystalline solid. Recrystallization of this material from CH_2Cl_2-hexane afforded analytically pure **11** as a colorless microcrystalline solid: mp 148-149 °C; IR (KBr) 1533 (m), 1354 (m), 1167 (vs), 739 (m), 607 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 1.15 (t, J = 7.4 Hz, 3 H), 1.92 (q, J = 7.4 Hz, 2 H), 3.21 (*AB*, J_{AB} = 8.2 Hz, 2 H), 3.38 (s, 4 H), 3.47 (A*B*, J_{AB} =8.2 Hz, 2 H), 6.83-6.88 (m, 4 H), 7.11-7.18 (m, 6 H), 7.88 (*AB*, J_{AB} = 8.9 Hz, 2 H), 8.47 (A*B*, J_{AB} = 8.9 Hz, 2 H); ^{13}C NMR ($CDCl_3$) δ 8.8 (q), 24.2 (t), 53.5 (t), 59.1 (s), 59.6 (t), 124.2 (d), 127.4 (d), 128.2 (d), 128.3 (d), 129.8 (d), 139.1 (s), 139.8 (s), 150.3 (s). Anal. Calcd for $C_{25}H_{27}N_3O_4S$: C, 64.50; H, 5.85. Found: C, 64.41; H, 5.76.

Continued elution of the chromatography column afforded a third fraction, which, when concentrated *in vacuo*, afforded pure *N*-*p*-nitrobenzenesulfonyl-3-azido-3-ethylazetidine (**8**, 25 mg, 10%) as a colorless microcrystalline solid: mp 122-123 °C. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **8**.

Control Experiments: A. Reaction of 3-Ethyl-1-azabicyclo[1.1.0]butane (1) with Dibenzylamine. To a solution of **1** (106 mg, 1.27 mmol) in $CDCl_3$ (0.5 mL) was added dibenzylamine (251 mg, 1.27 mmol). The resulting mixture was placed in a 5 mm NMR sample tube, and the tube was sealed and then was placed in an external oil bath maintained at 80 °C. The reaction mixture was heated at 80 °C for several days, and the progress of the reaction was monitored periodically *via* analysis of its ^{1}H NMR spectrum. No change was observed in the appearance of the ^{1}H NMR spectrum of the reaction mixture after the reaction had been carried out at 80 °C for 5 days.

B. Reaction of *N*-*p*-Nitrobenzenesulfonyl-3-azido-3-ethylazetidine (8) with Dibenzylamine. To a solution of **8** (65 mg, 0.21 mmol) in $CDCl_3$ (0.5 mL) was added dibenzylamine (41 mg, 0.21 mmol). The resulting mixture was placed in a 5 mm NMR sample tube, and the tube was sealed and then was placed in an external oil bath maintained at 80 °C. The reaction mixture was heated at 80 °C and the progress of the reaction was monitored periodically *via* analysis of its ^{1}H NMR spectrum. No change was observed in the appearance of the ^{1}H NMR spectrum of the reaction mixture after the reaction had been carried out at 80 °C for 28 h.

Reaction of 3-Ethyl-1-azabicyclo[1.1.0]butane (1) with Ethyl Azidoformate. Method A. To a solution of **1** (110 mg, 1.32 mmol) in $CDCl_3$ (1 mL) at ambient temperature was added with stirring a solution of ethyl azidoformate[11] (152 mg, 1.32 mmol) in $CDCl_3$ (1 mL) in three portions during 1 h. The resulting mixture was stirred at ambient temperature for 24 h and then was concentrated *in vacuo*. The residue was purified via column chromatography on silica gel by using a 10-20% EtOAc-hexane gradient elution scheme.

The first chromatography fraction contained *N*-ethoxycarbonyl-3-azido-3-ethylazetidine[6b] (**12**, 235 mg, 90%) as a colorless oil. The IR, ^{1}H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **12**.[6b]

Continued elution of the chromatography column afforded a second fraction that contained *N*-(*N*'-ethoxycarbonyl-3'-ethyl-3'-azetidinyl)-3-azido-3-ethylazetidine (**13**) (6 mg, 1%), which was isolated as a colorless oil; IR (neat) 2968 (s), 2108 (vs), 1707 (vs), 1423 (s), 1375 (s), 1344 (m), 1259 (m), 1124 cm^{-1} (m); ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 7.3 Hz, 3 H), 0.95 (t, J = 7.3 Hz, 3 H), 1.24 (t, J = 7.0 Hz, 3 H), 1.56 (q, J = 7.3 Hz, 2 H), 1.80 (q, J = 7.3 Hz, 2 H), 3.23 (*AB*, J_{AB} = 7.6 Hz, 2 H), 3.30 (A*B*, J_{AB} = 7.6 Hz, 2 H), 3.59 (*AB*, J_{AB} = 9.4 Hz, 2 H), 3.89 (A*B*, J_{AB} = 9.4 Hz, 2 H), 4.10 (q, J = 7.0 Hz, 4 H); ^{13}C NMR ($CDCl_3$) δ 7.8 (q), 8.2 (q), 14.7 (q), 28.7 (t), 30.0 (t), 53.2 (t), 56.6 (t), 59.1 (s), 59.9 (s), 61.1 (t), 156.8 (s). Anal. Calcd for $C_{13}H_{23}N_5O_2$: C, 55.50; H, 8.24; Found: C, 55.42; H, 8.38.

Method B. To a solution of **1** (186 mg, 2.24 mmol) in $CDCl_3$ (1.5 mL) at ambient temperature, was added ethyl azidoformate[11] (86 mg, 0.74 mmol), and the resulting mixture was stirred at ambient temperature for 6 days. An additional quantity of ethyl azidoformate (189 mg, 1.64 mmol) then was added to the reaction mixture, and the resulting mixture was stirred at ambient temperature for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified via column chromatography on silica gel by using a 10-20% EtOAc-hexane gradient elution scheme.

The first chromatography fraction contained **12**[6b] (417 mg, 94%), which was thereby obtained as a colorless oil. The IR, ^1H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra reported previously for authentic **12**.[6b]

Continued elution of the chromatography column afforded a second fraction that contained **13** (4.0 mg, 1%), which was isolated as a colorless oil. The IR, ^1H NMR and ^{13}C NMR spectra of this material are identical in all respects with the corresponding spectra obtained previously for authentic **13**.

Method C. To a solution of **1** (84 mg, 1.01 mmol) in $CDCl_3$ (1.5 mL) at ambient temperature was added ethyl azidoformate[11] (46 mg, 0.40 mmol). The resulting mixture was refluxed for 24 h. At the conclusion of the reaction, the reaction mixture was allowed to cool gradually to ambient temperature, whereupon an additional quantity of ethyl azidoformate (102 mg, 0.89 mmol) was added, and the resulting mixture was stirred at ambient temperature for an additional 24 h. Analysis of the ^1H and ^{13}C NMR spectra of the crude reaction mixture indicated the presence of resonance signals that correspond to unreacted ethyl azidoformate, *N*-ethoxycarbonyl-3-azido-3-ethylazetidine[6b] (**12**) and only a trace of *N*-(*N'*-ethoxycarbonyl-3'-ethyl-3'-azetidin-yl)-3-azido-3-ethylazetidine (**13**).

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