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Stereocontrolled Synthesis of Angularly Substituted 1-Azabicyclic Rings by Cationic 2-Aza-Cope Rearrangements

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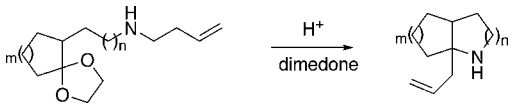
ABSTRACT



A new synthesis of 1-azabicyclic molecules having angular substitution is reported. This method can be employed to prepare a range of 1-azabicylic rings, including ones containing vicinal quaternary carbon centers and three contiguous stereocenters.

The cationic 2-aza-Cope rearrangement (2-azonia-[3,3]-sigmatropic rearrangement), which generally takes place at (or slightly above) room temperature, is a notably mild method for forming carbon−carbon bonds (Figure 1).[1,2] As

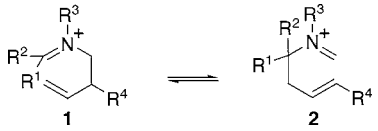


Figure 1. Cationic 2-aza-Cope rearrangement.

the 3-alkenyliminium cations equilibrated in this way are often of similar energy,[3] several methods have been developed to drive this sigmatropic rearrangement to provide a single product. These methods range from trapping one sigmatropic isomer by a Mannich[4] or ene[5] cyclization to selectively cleaving the iminium ion functional group of one sigmatropic isomer.[6] This paper describes the first directed cationic 2-aza-Cope rearrangement in which the starting iminium ion isomer **1** is derived from a ketone ($R^1 = R^2 =$ alkyl), thereby introducing a fully substituted carbon adjacent to nitrogen in the product **2**.

As a prelude to total synthesis endeavors in the alkaloid area, we became interested in the possibility of constructing angularly substituted 1-azabicyclic ring systems such as **6**

(1) First described by Geissman; see: Horowitz, R. M.; Geissman, T. A. *J. Am. Chem. Soc.* **1950**, *72*, 1518−1522.

(2) For reviews, see: (a) Heimgartner, H.; Hansen, H. J.; Schmid, H. In *Iminium Salts in Organic Chemistry*; Böhme, H., Viehe, H. G., Eds.; Wiley: New York, 1979; pp 655−732. (b) Przheval'skii, N. M.; Grandberg, I. I. *Russ. Chem. Rev.* **1987**, *5*, 477. (c) Blechert, S. *Synthesis* **1989**, 71−82.

(3) For representative examples where the "product" sigmatropic isomer predominates by virtue of it being stabilized by delocalization, see: (a) Knabe, J.; Ruppenthal, V. *Arch Pharm.* **1966**, *299*, 159−165. (b) Winterfeldt, E.; Franzischka, W. *Chem. Ber.* **1967**, *100*, 3801−3807. (c) Deloisy, S.; Kunz, H. *Tetrahedron Lett.* **1998**, *39*, 791−794.

(4) For representative examples, see: (a) Overman, L. E.; Kakimoto, M. *J. Am. Chem. Soc.* **1979**, *101*, 1310−1312. (b) Agami, C.; Couty, F.; Lin, J.; Mikaeloff, A.; Poursoulis, M. *Tetrahedron* **1993**, *49*, 7239−7250. For brief reviews, see: (c) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352−359. (d) Overman, L. E. *Aldrichem. Acta* **1995**, *28*, 107−120. (e) Royer, J.; Bonin, M.; Micouin, L. *Chem. Rev.* **2004**, *104*, 2311−2352.

(5) For representative examples, see: (a) Rischke, H.; Wilcock, J.; Winterfeldt, E. *Chem. Ber.* **1973**, *106*, 3106−3118. (b) Mooiweer, H. H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 3451−3462. (c) Gelas-Mailhe, Y.; Gramain, J. C.; Louvet, A.; Remuson, R. *Tetrahedron Lett.* **1992**, *33*, 73−76. (d) ref 4b.

(6) For representative examples, see: (a) Overman, L. E.; Yokomatsu, T. *J. Org. Chem.* **1980**, *45*, 5229−5230. (b) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 1877−1879. (c) Hart, D. J.; Yang, T.-K. *J. Org. Chem.* **1985**, *50*, 235−242. (d) Agami, C.; Couty, F.; Poursoulis, M. *Synlett* **1992**, 847−848. (e) Bennett, D. J.; Hamilton, N. M. *Tetrahedron Lett.* **2000**, *41*, 7961−7964. (f) ref 4b.

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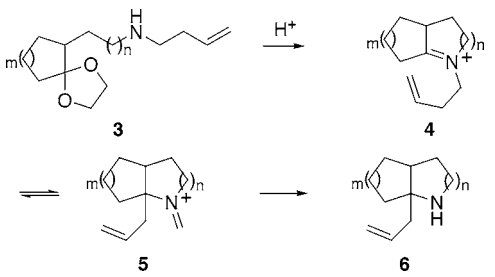
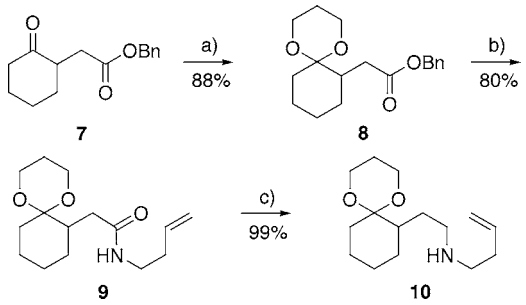
Scheme 1. Preparation of Angularly Substituted 1-Azabicyclic Ring Systems



by the sequence outlined in Scheme 1. The substantial challenge would be rendering the sigmatropic reorganization irreversible, as the fully substituted iminium cation **4** is considerably more stable than formaldiminium ion sigmatropic isomer **5**.[7,8] For the sequence posited in Scheme 1 to succeed, an efficient method for scavenging the methylene unit of the less stable formaldiminium ion isomer **5** would be required.

The high-yielding sequence we developed for preparing the monocyclic aminoketal starting materials is outlined in Scheme 2. This representative synthesis begins with (2-oxocyclohexyl)acetic acid benzyl ester (**7**),[9] which is ketalized in the presence of scandium triflate to provide 1,3-dioxolane **8**. Cleavage of the benzyl ester of this product, followed by coupling of the resulting acid with 3-butenylamine, gave amide **9** in excellent yield. Lithium aluminum hydride reduction of this intermediate then delivered cyclohexyl aminoketal **10** in 70% overall yield for the four steps.[10]

Scheme 2. Representative Synthesis of Monocyclic Aminoketal Starting Materials[a]



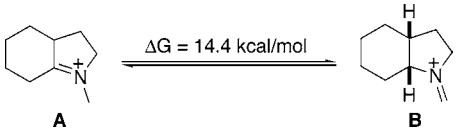
[a] Conditions: (a) 1,3-Propanediol, 5 mol % $Sc(OTf)_3$, methyl orthoformate, MeCN. (b) (i) H_2, $Pd(OH)_2/C$; (ii) 3-butenylamine hydrochloride, EDCI, *i*-Pr_2NEt, CH_2Cl_2. (c) $LiAlH_4$, Et_2O.

Initial survey experiments showed that **10** was quickly transformed to the corresponding iminium ion **4** ($m = 2$, $n = 1$) when heated in methanol at 60 °C in the presence of just less than 1 equiv of trifluoroacetic acid (TFA). However, the transformation of this iminium ion to the desired angularly substituted bicyclic amine **6** ($m = 2$, $n = 1$) could not be realized by selective hydrolysis of formaldiminium ion **5** ($m = 2$, $n = 1$). For example, including up to 3 equiv of water and heating the reaction at temperatures as high as 110 °C left **4** ($m = 2$, $n = 1$) unchanged. However, the addition of 2.5 equiv of dimedone[11] resulted at 80 °C in slow but clean formation of octahydroindole **6** ($m = 2$, $n = 1$). This reaction takes place at a convenient rate at 120 °C, either in the absence of solvent or in toluene at high concentration (Table 1, entry 1).

The scope of this method for preparing 1-azabicyclic molecules containing angular allyl substituents is outlined in Table 1. As the transformation is slowed dramatically if more than 1 equiv of TFA is present, we found it most convenient to carry out the reaction in the presence of 1 equiv of this acid and 0.1 equiv of morpholine. To simplify isolation and purification of the bicyclic amine products, the crude reaction product was directly converted to the corresponding benzyloxycarbonyl derivative prior to isolation. Using this two-step procedure, a variety of angularly functionalized hexahydrocyclopenta[*b*]pyrrole, octahydro[1]-pyridine, octahydroindole, decahydroquinoline, octahydrocyclohepta[*b*]pyrrole, and decahydrocyclohepta[*b*]pyridine carbamates were prepared in good yield.

Several trends are apparent in the data summarized in Table 1. For example, reaction rate varies substantially with ring size. For substrates having no additional substituents, iminium ions generated from five- (entries 2−4) and six-membered (entries 1 and 8) aminoketals rearrange faster than those generated from seven-membered precursors (entries 9 and 10).[12,13] Incorporation of additional substitution on either side of the acetal carbon resulted in slower reaction rates; nonetheless, yields in these cases were high (entries 5 and 7).[14] However, aminoketal **18** containing an (*E*)-3-pentenyl fragment reacted extremely slowly even at 130 °C to provide hydroindole **19** in low yield (entry 6). The hexahydrocyclopenta[*b*]pyrrole, octahydro[1]pyrindine, and octahydroindole products are formed with high cis stereoselectivity; observation of a ^1H NOE between the angular hydrogen and the allylic hydrogens of the angular allyl group confirmed the

(7) For example, the model rearrangement **A** to **B** is calculated to be endothermic by 14.4 kcal/mol (ab initio calculations using DFT/B3LYP/6-21G* as implemented in the Spartan 2002 software package).[8]



(8) Wavefunction, Inc.: Irvine, CA; 2002.

(9) Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2049−2052.

(10) Cyclic aminoketals **12**, **14**, **18**, **23**, **26**, and **29** were generated in a manner analogous to that of **10**, whereas **16** and **20** were accessed by related routes; details are provided in Supporting Information.

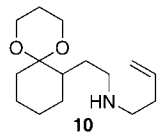
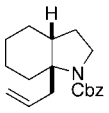
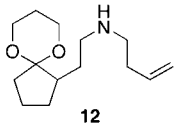
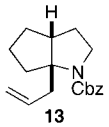
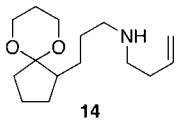
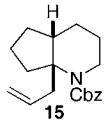
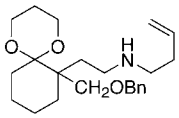
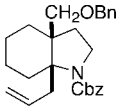
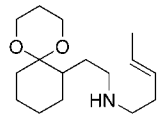
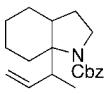
(11) These results contrast with the reaction of related aldehyde-derived iminium ions described in ref 6a, wherein the hydrolysis-directed reaction could be realized in the absence of dimedone.

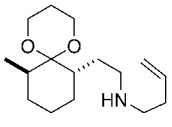
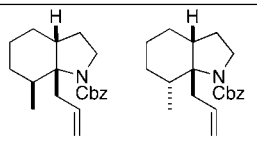
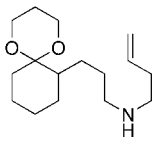
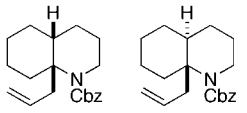
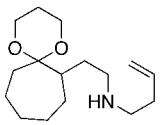
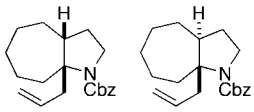
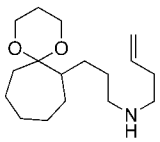
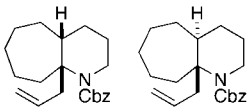
(12) This trend parallels the endothermicity of the cationic 2-aza-Cope rearrangement as analyzed computationally with model compounds analogous to those shown in ref 7.[13]

(13) Aron, Z. D. Ph.D. Dissertation, University of California−Irvine, Irvine, CA, 2004; these details will be discussed in a future full account of this work.

(14) At elevated reaction temperatures, dimedone decomposition was observed as a competitive process and sequential addition of this reagent over time was required to achieve useful yields in these cases.

Table 1. Synthesis of Angularly Substituted 1-Azabicyclic Rings by Methylene Transfer-Driven Cationic 2-Aza-Cope Rearrangements[a]

entry	aminoketal	product	temp, h	yield
1[c]	 **10**	 **11**	120, 2.3	79%
2	 **12**	 **13**	80, 3	96%
3			120, 0.7	86%
4	 **14**	 **15**	120, 1.7	85%
5[d]	 **16**	 **17**	130, 7.5	80%
6[d]	 **18**	 **19**	130, 48	<15%

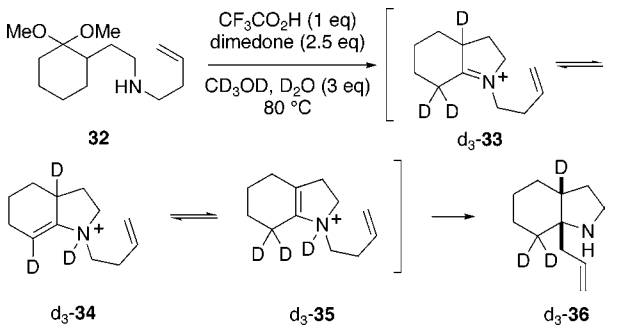
entry	aminoketal	product[b]	temp, h	yield
7[d]	 **20**	 **21** (11:1) **22**	130, 14	82%
8	 **23**	 **24** (1.2:1) **25**	120, 1.7	81%
9[d]	 **26**	 **27** (9:1) **28**	130, 14	64%
10[d]	 **29**	 **30** (3.5:1) **31**	130, 14	71%

[a] Typical reaction conditions: TFA (1.0 equiv), morpholine (0.1 equiv), dimedone (2.5 equiv), followed by reaction of the crude product in chloroform with benzyl chloroformate (2.5 equiv) and Na_2CO_3. [b] Product ratios were determined from yields of pure products; these ratios were confirmed by analysis of ^{1}H NMR spectra of the crude reaction product. [c] As demonstrated by ^{1}H NMR analysis using an internal standard, a 78% yield was obtained when the reaction was conducted at 2 M in toluene in a sealed reaction vessel at 120 °C for 2.7 h. [d] Performed with portionwise addition of 4.0 equiv of dimedone over 4 h.

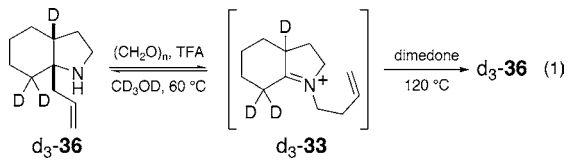
cis ring fusion for these products and for the other cis isomers shown in Table 1. In general, the diastereoselectivities observed are consistent with the formation of thermodynamic product mixtures.[13]

Several additional experiments provide insight into the mechanism of this synthesis of angularly substituted 1-azabicyclic rings. First, three carbon-bound deuterium atoms are introduced when the synthesis of hydroindole **36** is carried out in deuterated methanol (Scheme 3). The location of deuterium atoms in d_3-**36** shows that the initially formed tetrasubstituted iminium ion equilibrates with its two possible enamonium tautomers faster than it converts to the hydroindole product. Such equilibration also rationalizes the result reported in Table 1, entry 7, in which methyl epimers **21** and **22** of the *cis*-octahydroindole product were formed from isomerically pure aminoketal precursor **20**.

Scheme 3. Equilibrium between the Initially Formed Iminium Ion and Its Enamine Tautomers

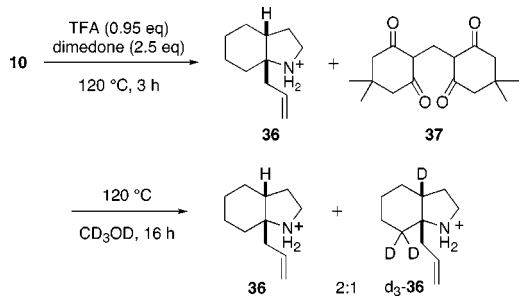


To examine the reversibility of this synthesis of angularly substituted 1-azabicyclics, homoallylamine d_3-**36** was heated at 60 °C in the presence of 1 equiv of TFA and an excess of paraformaldehyde in deuterated methanol (eq 1). Within 20 h, complete conversion to iminium ion d_3-**33** was observed by ^{1}H NMR. Addition of a large excess of dimedone to this solution and heating at 120 °C for 20 h returned the starting azabicyclic amine d_3-**36**, thereby confirming the expected reversibility of the cationic 2-aza-Cope rearrangement.



The reversibility of the overall synthesis of angularly substituted 1-azabicyclics was established by the experiment

Scheme 4. Reversibility of the Rearrangement and Methylene Transfer Steps



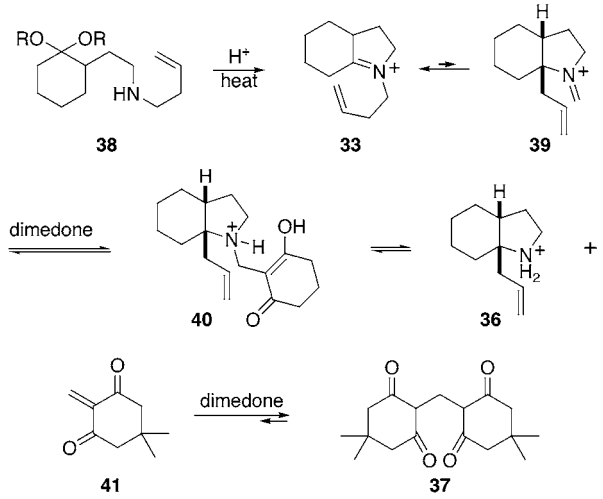
summarized in Scheme 4. As the formaldiminium ion derived from **36** rapidly rearranges to form iminium ion **33**, which is in tautomeric equilibrium with enamonium ions **34** and **35**, exposing ammonium ion **36** to the dimedone-formaldehyde adduct **37** in deuterated methanol would reveal the reversibility of both the cationic 2-aza-Cope rearrangement and the methylene transfer step. Accordingly, the crude mixture of ammonium ion **36** and dimedone-formaldehyde adduct **37** formed from aminoketal **10** was heated at 120 °C in deuterated methanol in a sealed tube for 16 h (Scheme 4). The formation of a 2:1 mixture of ammonium ion **36** and its d_3 congener after aqueous workup establishes the reversibility of the overall reaction.[15]

The mechanism outlined in Scheme 5 is consistent with observations made to date. Exposure of an aminoketal such as **38** to acid at high-temperature results in the formation of an equilibrium mixture consisting of iminium ion **33**, its enammonium tautomers (not shown), and the rearranged formaldiminium ion **39**. Reaction of the latter with dimedone gives the 1-azabicyclic product **36** and the formaldehyde-dimedone adduct **37**, likely via the intermediacy of adduct **40** and methylenedione **41**. The highly favorable equilibrium for forming dimedone adduct **37** from the reaction of dimedone with methylenedione **41** is undoubtedly responsible for the success of this synthesis.

In summary, a new synthesis of 1-azabicyclic molecules containing angular allyl substitution is reported. This reaction

(15) Dimedone decomposes at elevated temperatures in the presence of ammonium salts, which is likely responsible for the incomplete deuterium incorporation observed in this experiment.

Scheme 5. Proposed Mechanism



has been used to prepare a range of 1-azabicylic rings, including ones containing vicinal quaternary carbon centers or three contiguous stereocenters. This disclosure constitutes the first report that the highly endothermic cationic 2-aza-Cope rearrangement of ketone-derived iminium ions can be directed by subsequent methylene transfer, thereby forming amine products containing a fully substituted carbon adjacent to nitrogen. The development of asymmetric variants of this synthesis of nitrogen heterocycles and applications of this chemistry in target directed synthesis are under current investigation.

Acknowledgment. This research was supported by the U.S. National Institute of Neurological Disorders and Stroke (Grant NS-12389) and by a Lilly Graduate Fellowship to Z.D.A. NMR and mass spectra were determined at UC Irvine with instruments purchased with the assistance of the NSF and NIH shared instrumentation programs.

Supporting Information Available: Schemes showing synthetic routes, reagents, and yields for the synthesis of compounds **16** and **20**; experimental procedures, characterization data, and copies of ^{1}H and ^{13}C NMR spectra for key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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