ORGANIC LETTERS

2002
Vol. 4, No. 8
1259−1262

The Rearrangement Route to 3-CH_2X-2-azabicyclo[2.1.1]hexanes. Substituent Control of Neighboring Group Participation

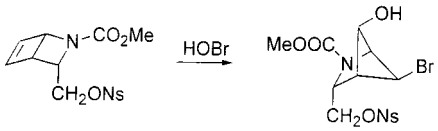
Grant R. Krow,* Jing Yuan, Guoliang Lin, and Philip E. Sonnet

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

grantkrow@aol.com

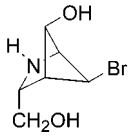
Received January 7, 2002

ABSTRACT



The stereocontrolled synthesis of a functionalized 3-hydroxymethyl-2-azabicyclo[2.1.1]hexane synthon for a variety of methano-bridged pyrrolidines has been effected. The key step in an electrophilic addition–rearrangement route uses a 3-nosyloxymethyl group in the 2-azabicyclo[2.2.0]-hex-5-ene precursor in order to suppress unwanted competitive oxygen neighboring group participation.

The 3-hydroxymethyl-2-azabicyclo[2.1.1]hexane **1** is a multifunctional synthon with a range of potentially useful applications. As a methanobridged pyrrolidine, we required **1** as the key component for projects designed to prepare conformationally constrained analogues of the biologically significant amino acids proline and hydroxyproline,[1] diamines for preparation of new fluoroquinolone antibiotics,[2] and aryloxyamines with potential nicotinic receptor agonist activity.[3] Additionally, the stereochemically defined substituent array gives structure **1** potential utility for the development of molecular libraries.[4]



1

Of several synthetic routes to 2-azabicyclo[2.1.1]hexanes,[5,6] only the rearrangement approach[7] has been reported for the formation of 3-substituted structures.[7b,c] The success of the rearrangement route for 3-methyl and 3-phenyl derivatives has relied upon the steric effect associated with these groups. However, with the 3-*endo*-hydroxymethyl precursor **2**, the steric effect cannot be relied upon. The proximal hydroxyl group in bromonium ion **3** is poised for intramolecular

(1) (a) Piela, L.; Nemethy, G.; Scheraga, H. A. *J. Am. Chem. Soc.* **1987**, *109*, 4477. (b) Montelione, G. T.; Hughes, P.; Clardy, J.; Scheraga, H. A. *J. Am. Chem. Soc.* **1986**, *108*, 6765. (c) Han, W.; Pelletier, J. C.; Mersinger, L.; Ketner, C. A.; Hodge, C. N. *Org. Lett.* **1999**, *1*, 1875.

(2) Park, T. H.; Ha, Y. H.; Jeong, D. Y. Patent Application WO 98-KR246 19989898; *Chem. Abstr.* **1999**, *130*, 182388.

(3) (a) Lynch, J. K.; Holladay, M. W.; Ryther, K. B.; Bai, H.; Hsiao, C.-N.; Morton, H. E.; Dickman, D. A.; Arnold, W.; King, S. A. *Tetrahedron: Asymmetry* **1998**, *9*, 2791. (b) Bannon, A. W.; Decker, M. W.; Holladay, M. W.; Curzon, P.; Donnelly-Roberts, D.; Puttfarcken, P. S.; Bitner, R. S.; Diaz, A.; Dickerson, A. H.; Porsolt, R. D.; Williams, M.; Arneric, S. P. *Science* **1998**, *279*, 77.

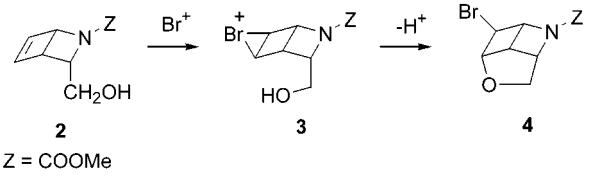
(4) For a library based upon 4-hydroxyproline, see: Goldberg, M.; Smith, L., II; Tamayo, N.; Kiselyov, A. S. *Tetrahedron* **1999**, *55*, 13887. For a library based upon amide diols, see: Lee, C. E.; Kick, E. K.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 9735.

(5) For photochemical routes, see: (a) Schell, F. M.; Cook, P. M.; Hawkinson, S. W.; Cassady, R. E.; Thiessen, W. E. *J. Org. Chem.* **1979**, *44*, 1380. (b) Pirrung, M. C. *Tetrahedron Lett.* **1980**, *21*, 4577. (c) Hughes, P.; Martin, M.; Clardy, J. *Tetrahedron Lett.* **1980**, *21*, 4579. (d) Hughes, P.; Clardy, J. *J. Org. Chem.* **1988**, *53*, 4793. (e) Tamura, Y.; Ishibashi, H.; Hirai, M.; Kita, Y.; Ikeda, M. *J. Org. Chem.* **1975**, *40*, 2702. (f) Ikeda, M.; Uchno, T.; Takahashi, M.; Ishibashi, H.; Tamura, Y.; Kido, M. *Chem. Pharm. Bull.* **1985**, *33*, 3279. (g) Swindel, C. S.; Patel, B. P.; deSolms, S. J.; Springer, J. P. *J. Org. Chem.* **1987**, *52*, 2346. (h) Esslinger, C. S.; Koch, H. P.; Kavanaugh, M. P.; Philips, D. P.; Chamberlain, A. R.; Thompson, C. M.; Bridges. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 3101. (i) Piotrowski, D. W. *Synlett.* **1999**, 1091.

(6) For nucleophilic substitution ring closure routes, see ref 2 and (a) Gaoni, Y. *Org. Prep. Proced. Int.* **1995**, *27*, 185. (b) Stevens, C.; De Kimpe, N. *J. Org. Chem.* **1996**, *61*, 2174. (c) Lescop, C.; Mevellec, L.; Huet, F. *J. Org. Chem.* **2001**, *66*, 4187.

10.1021/ol020007g CCC: $22.00
Published on Web 03/22/2002

nucleophilic attack to give tricyclic structure **4**. The problem is then: How might carbamate nitrogen be enabled to compete successfully as an intramolecular nucleophile with a proximal oxygen atom poised to form a five-membered ring oxonium ion? Herein we describe a successful solution to the competitive neighboring group problem and also some novel results during the preparation of 3-hydroxymethyl-2-azabicyclo[2.1.1]hexane derivatives having additional useful halide and hydroxyl functionality in the C_5 and C_6 one carbon bridges.



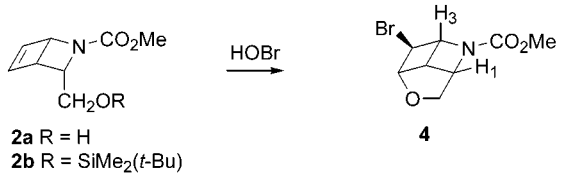
The synthesis of the desired 3-*endo*-hydroxymethyl precursor **2a** from pyridine has been described.[8] According to a published protocol (Table 1),[7b,9] addition of NBS to a solution of the alcohol in 2:1 DMSO/water (entry 1) resulted in isolation of the azatricycle **4** in 54% yield; no other product was isolated. The 4-*exo*-bromo stereochemistry was assigned on the basis of $J_{3,4} = 0$ Hz, indicative of a *trans* relationship of H_3 and H_4. To decrease the likelihood of oxygen participation, the oxygen was protected as **2b** with a bulky and relatively acid stable TBDMS group (entry 2). It was hoped that a steric effect would fix the oxygen into a conformation not conducive to neighboring group participation. Structure **2b** took a longer time to react because of solubility problems, but again only tricycle **4** was isolated in 50% yield.

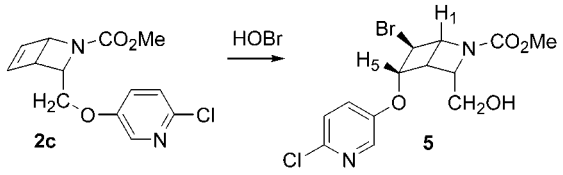
Table 1. Aqueous NBS Reactions with 3-*endo*-Substituted-2-azabicyclo[2.2.0]hex-5-enes **2**

no.	reactant	R	method[a]	time (h)	tricycle **4** (yield, %)	bicycle **6** (yield, %)
1	**2a**	H	A	19	54	
2	**2b**	$Si(CH_3)_2(t\text{-Bu})$	A	69	50[b]	
3	**2c**	2-Cl-5-pyridyl	A[c]	19		*d*
4	**2d**	SO_2Ph-*p*-NO_2	A	42	9[e]	16
5	**2d**	SO_2Ph-*p*-NO_2	B	2.5	19	69

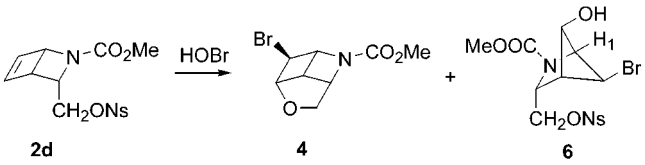
[a] A. NBS (3 equiv), DMSO:H_2O (2:1), 0 °C to rt. B. NBS (2.5 equiv), THF:H_2O (2:1), 0 °C to rt. [b] Recovered **2b** (4.6%). [c] DMSO:H_2O:CH_2Cl_2 (2:1:1). [d] Isolated rearranged **5** (67%). [e] Recovered unreacted **2d** (64%).

In the belief that the oxygen attached to an electron-withdrawing chloropyridyl group would be less amenable to neighboring group participation, and that an aryl group would not be subject to nucleophilic displacement to give azatricycle **4**, we next investigated compound **2c** (entry 3).[8] The product using the general procedure was identified as azabicycle **5** in which, as shown by NOE effects between H_{5x} and the pyridyl ring protons, the chloropyridoxy group had migrated from C_7 to C_5. Again, the desired participation by carbamate nitrogen was not observed.





The hydroxyl group was next protected with an electron-withdrawing *p*-nitrobenzenesulfonyl (nosyl) group as **2d** (entry 4). We were unable to find precedent for neighboring group nucleophilic participation by the carbon-bonded oxygen atom of a tosylate group,[10] and it was expected that the oxonium ion intermediate **7** would be inductively destabilized. Reaction of nosylate **2d** according to the general procedure (entry 4) was sluggish but did result in a low conversion (16%) to the desired rearranged bicycle **6**, which had the characteristic $J_{1,4} = 7.5$ Hz of this ring system.[7] To overcome the slow reactivity problem, the solvent was changed to 2:1 THF:water (entry 5). Improved solubility led to an enhanced reaction rate and to isolation of the desired rearrangement product **6** in 69% yield accompanied by a smaller amount of the tricycle **4**. There was a 7:2 preference for participation by carbamate nitrogen over nosylate oxygen, a surprising neighboring group.



A mechanistic proposal for the formation of the observed products is shown in Scheme 1. An initially formed bromonium ion, **3**, might be attacked by the oxygen atom on the methylene group to give a five-membered ring oxonium ion, **7**. If the group R on the oxonium ion **7** is attacked by water (path a), the tricycle **4** is formed (entries 1−2, 4−5).[11] If the R group on oxonium ion **7** is not labile, preferential attack of water at the methylene (path b) results in migration of the OR group from methylene to C_5, as observed in the

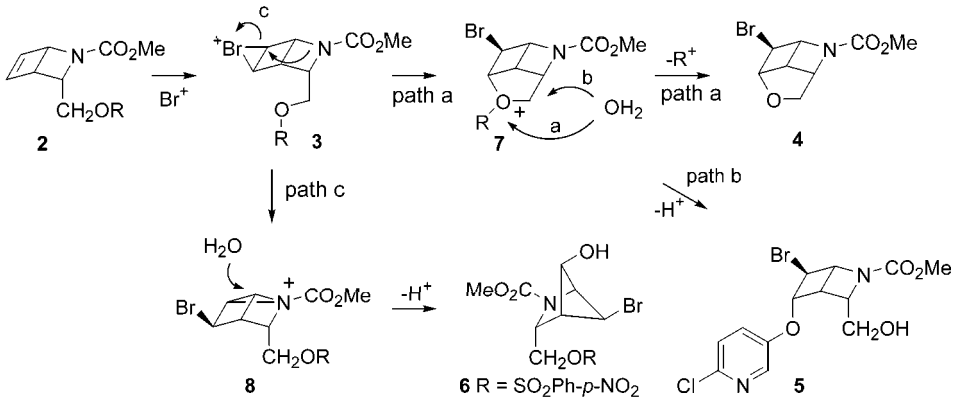
(7) (a) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63*, 8558. (b) Krow, G. R.; Lester, W. S.; Liu, N.; Yuan, J.; Hiller, A.; Duo, J.; Herzon, S. B.; Nguyen, Y.; Cannon, K. *J. Org. Chem.* **2001**, *66*, 1811. (c) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Liu, N.; Yuan, J.; Duo, J.; Herzon, S. B.; Nguyen, Y.; Zacharias, D. *J. Org. Chem.* **2001**, *66*, 1805.

(8) Krow, G. R.; Yuan, J.; Fang, Y.; Meyer, M. D.; Anderson, D. J.; Campbell, J. E.; Carroll, P. J. *Tetrahedron* **2000**, *56*, 9227.

(9) Dalton, D. R.; Rodebaugh, R. K.; Jefford, *J. Org. Chem.* **1972**, *37*, 362.

(10) Neighboring group participation by the double-bonded oxygen of a tosylate has been postulated. Boyle, P. H.; Coy, J. H. *J. Org. Chem.* **1973**, *38*, 826.

Scheme 1. Mechanistic Analysis



formation of structure **5** by aryloxy migration (entry 3). In the alternative (path c), if the oxygen atom on the methylene has a sufficiently electron withdrawing substituent, aziridinium ion **8** can favorably compete; attack of water at C_1 of this intermediate affords the desired structure **6** (entries 4−5).

To assess qualitatively the relative energies of the inferred intermediate bridged bromonium ions **3**, oxonium ions **7**, and aziridinium ions **8**, calculations were performed using the Gaussian 98 suite of computations (Table 2).[12] The

Table 2. Calculated Energies of Bridged Reaction Intermediates **6**−**8**

			relative energies (kcal/mol)[a]		
no.	reactant	R	bromonium ion **3**	oxonium ion **7**	aziridinium ion **8**
1	**2a**	H	+22.7	0.0	+13.3
2	**2b**	$Si(CH_3)_3$[b]	+34.4	0.0	+24.6
3	**2c**	2-Cl-5-pyridyl	+27.0	0.0	+13.3
4	**2d**	SO_2Ph-*p*-NO_2	+27.2[c]	+3.8	+7.7
				0.0 (7-ring) **9**	

[a] These were optimized with B3LYP/6-31G(d)//RHF/6-31G(d).[12] Energies are relative to the lowest energy structure of each set. [b] Replacement for $OSi(CH_3)_2(t$Bu). [c] No bromonium ion minimum was located in the potential energy surface of the tosylate analogue of **2d**. Calculated values for the tosylate were 0.0 (7-ring), 3.7 (oxonium ion), and 12.2 (aziridinium ion).

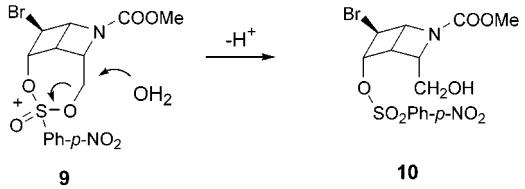
substituted oxonium ions **7a**−**d** are energetically favored over the aziridinium ions (entries 1−5). As expected, the aziridinium ion **8d** (entry 4), bearing the strongly electron withdrawing nosylate group at C_7, is closest in energy to its corresponding oxonium ion **7d**. Surprisingly, the calculations predict seven-membered bridged species **9** to be most stable (entry 4).[13] With the calculations as a guide, the preferential formation of rearranged nosylate **6** appears to be the result of a kinetically controlled process favoring aziridinium ion **8d**, rather than an oxonium ion species **7** or **9**. Our success in isolating the bicyclic nosylate **6** in useful yield has been quite fortunate.

The utility of nosylate **6** can be shown by the synthesis of the first reported *N*-BOC-3-aminomethyl-2-azabicyclo[2.1.1]-hexane **12**,[14] a protected diamine desired for preparation of new fluoroquinolones.[2] Reaction of the nosylate **6** with sodium azide in DMF afforded azide **11** in 55% yield.[15] Hydrogenation of **11** over Pd/C in methanol in the presence of $(BOC)_2O$ gave the protected diamino alcohol **12** in 73% yield.[16] Further synthetic applications of nosylate **6** will be reported shortly.

(11) Sulfur−oxygen cleavage under nucleophilic solvolytic conditions is known. (a) Gassman, P. G.; Hornback, J. M.; Pascone, J. M. *Tetrahedron Lett.* **1971**, *12*, 1425. (b) Xu, C.-L.; Chen, Z.-C, *Tetrahedron Lett.* **1991**, *32*, 2933. (c) Precedent for sulfur−oxygen bond cleavage of tosylates in other than strongly nucleophilic solvolytic conditions is sparse. See ref 10. In the solvolysis of fluorinated alkyl tosylates, which contain electron-poor alkyl groups, no measurable cleavage of the alkyl−oxygen bond occurred in 98% sulfuric acid. Drabicky, M. J.; Myhre, P. C.; Reich, C. J.; Schmittour, E. R. *J. Org. Chem.* **1976**, *41*, 1472.

(12) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B. G.; Chen, W.; Wong, M. W.; Andres, J. L.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, revision A.9; Gaussian, Inc.: Pittsburgh, PA, 1998.

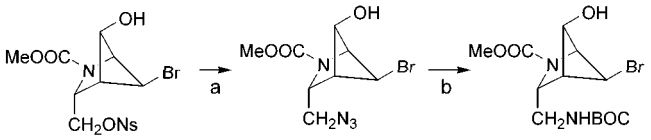
(13) Intermediate **9** might be expected to ring open by attack of water at C_7 to give nosylate **10**, which we did not observe.



(14) For synthesis of a 4-aminomethyl-2-azabicyclo[2.1.1]hexane, see ref 2. For synthesis of a 5-aminomethyl-2-azabicyclo[2.1.1]hexane, see ref 6c.

(15) Fleming, P. R.; Sharpless, K. B. *J. Org. Chem.* **1991**, *56*, 2869.

(16) Sakaitani, M.; Hori, K.; Ohfune, Y. *Tetrahedron Lett.* **1988**, *29*, 2983.



6 **11** **12**

(a) NaN_3, (b) H_2/Pd/$(BOC)_2O$

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, the National Science Foundation (CHE 0111208), and the Temple University Research Incentive Fund for support of this research. We also thank Yuhong Fang and George Kemmerer.

Supporting Information Available: All experimental procedures, spectroscopic data, and ^1H NMR and ^{13}C NMR for compounds **2b**, **2d**, **4**−**6**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL020007G