ORGANIC LETTERS

2003
Vol. 5, No. 15
2739−2741

Second-Chance Rearrangement Route to Novel 5(6)-Syn,anti-difunctional 2-Azabicyclo[2.1.1]hexanes

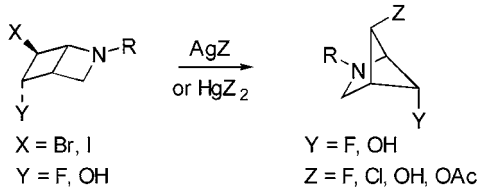
Grant R. Krow,* Guoliang Lin, Fang Yu, and Philip E. Sonnet

Department of Chemistry, Temple University, Philadelphia, Pennsylvania 19122

grantkrow@aol.com

Received May 31, 2003

ABSTRACT



The first syntheses of 5,6-difunctionalized-2-azabicyclo[2.1.1]hexanes containing *syn*-hydroxy and *syn*-fluoro substituents have been effected in a stereocontrolled manner. The key reactions are regioselective additions to the aziridinium ions formed from 6-*exo*-iodo(bromo)-5-*endo*-X-2-azabicyclo[2.2.0]hexanes (X = F, OH) upon silver or mercury salt enhancement of iodide nucleofugacity.

The 2-azabicyclo[2.1.1]hexane ring system **1** has now been generated by photochemical, ring closure, and rearrangement routes,[1] but there is a paucity of methods for introducing useful hydroxyl or halide functionality into the methano-bridges of **1**. A three-step rearrangement route introduces 5-*anti*-bromo-6-*anti*-hydroxy groups as in **2**, but this bromonium ion pathway does not allow for direct introduction of 5(6)-syn substituents.[2]

The nine-step cyclobutane ring closure route of Huet et al. has enabled a 5-*syn*-phenylselenyl group to be introduced as in **3**,[1d] but this group lacks the synthetic utility of a hydroxyl group or the biological utility of a fluoride. As part of our efforts to prepare fluoro- and hydroxy-substituted methanoprolines[3,4] and to generate methanopyrrolidine synthons for library generation,[5] we desired an efficient stereocontrolled method for introducing these functional groups into the methano bridges of azabicycle **1** in stereochemically defined syn and anti orientations.

In our initial attempts to prepare functionalized 2-azabicyclo-[2.1.1]hexanes, we showed that addition of BrOH to alkene **4** affords in 80% yield a 9:7 mixture of bromohydrin **7a**,

(1) For a leading reference to synthetic approaches to 2-azabicyclo[2.1.1]-hexanes, see: (a) Krow, G. R.; Yuan, J.; Lin, G.; Sonnet, P. E. *Org. Lett.* **2002**, *4*, 1259 and refs 5−7 therein. For additional nucleophilic ring closure approaches, see: (b) Rammeloo, T.; Stevens, C. V. *J. Chem. Soc., Chem. Commun.* **2002**, 250. (c) Rammeloo, T.; Stevens, C. V.; De Kimpe, N. *J. Org. Chem.* **2002**, *67*, 6509. (d) Lescop, C.; Mevellec, L.; Huet, F. *J. Org. Chem.* **2001**, *66*, 4187. (e) Rammeloo, T.; Stevens, C. V. *New J. Chem.* **2003**, *27*, 668. For additional photochemical approaches to 2-azabicyclo-[2.1.1]hexanes, see: (f) Kwak, Y.-S.; Winkler, J. D. *J. Am. Chem. Soc.* **2001**, *123*, 7429. (g) Toda, F.; Miyamoto, H.; Takeda, K.; Matsugawa, R.; Maruyama, N. *J. Org. Chem.* **1993**, *58*, 6208. (h) Vogler, B.; Bayer, R.; Meller, M.; Kraus, W. *J. Org. Chem.* **1989**, *54*, 4165.

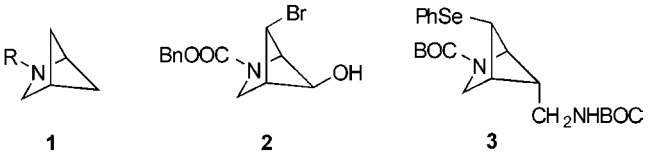
(2) (a) Krow, G. R.; Lee, Y. B.; Lester, W. S.; Christian, H.; Shaw, D. A.; Yuan, J. *J. Org. Chem.* **1998**, *63*, 8558. (b) Krow, G. R.; Lester, W. S.; Liu, N.; Yuan, J.; Hiller, A.; Duo, J.; Herzon, S. B.; Nguyen, Y.; Cannon, K. *J. Org. Chem.* **2001**, *66*, 1811.

(3) (a) Bretcher, L. E.; Jenkins, C. L.; Taylor, K. M.; DeRider, M. L.; Raines, R. T. *J. Am. Chem. Soc.* **2001**, *123*, 777. Also, see refs 1b−e and: (b) Piela, L.; Nemethy, G.; Scheraga, H. A. *J. Am. Chem. Soc.* **1987**, *109*, 4477. (c) Montelione, G. T.; Hughes, P.; Clardy, J.; Scheraga, H. A. *J. Am. Chem. Soc.* **1986**, *108*, 6765. (d) Mapelli, C.; van Halbeek, H.; Stammer, C. H. *Biopolymers*, **1990**, *29*, 407. (e) Juvvadi, P.; Dooley, D. J.; Humblet, C. C.; Lu, G. H.; Lunney, E. A.; Panek, R. L.; Skeean, R.; Marshall, G. R. *Int. J. Pept. Protein Res.* **1992**, *40*, 163. (f) Bell, E. A.; Qureshi, M. Y.; Pryce, R. J.; Janzen, D. H.; Lemke, P.; Clardy, J. *J. Am. Chem. Soc.* **1980**, *109*, 1409. (g) Talluri, S.; Montelione, B. T.; van Duyne, G.; Piela, L.; Clardy, J.; Scheraga, H. A. *J. Am. Chem. Soc.* **1987**, *109*, 4473. (h) Pirrung, M. C. *Tetrahedron Lett.* **1980**, *21*, 4577. (i) Hughes, P.; Martin, M.; Clardy, J. *Tetrahedron Lett.* **1980**, *21*, 4579. (j) Kite, G. C.; Ireland, H. *Phytochemistry* **2002**, *59*, 163.

(4) Krow, G. R.; Herzon, S. B.; Lin, G.; Qiu, F.; Sonnet, P. E. *Org. Lett.* **2002**, *4*, 3151.

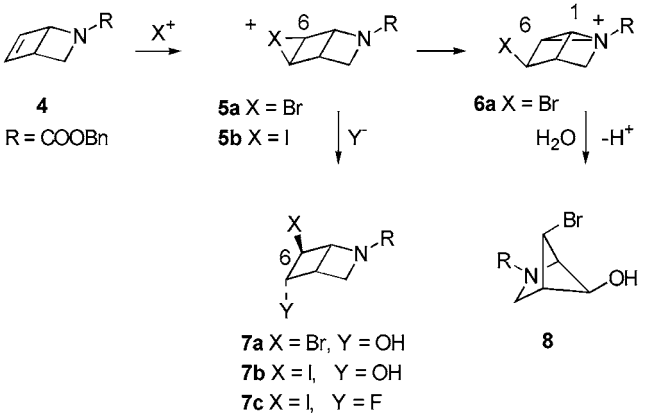
(5) For a library based upon 4-hydroxyproline, see: Goldberg, M.; Smith, L., II; Tamayo, N.; Kiselyov, A. S. *Tetrahedron* **1999**, *55*, 13887. For a library based upon amide diols, see: Lee, C. E.; Kick, E. K.; Ellman, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 9735.

10.1021/ol0349662 CCC: $25.00
Published on Web 07/01/2003



1 **2** **3**

derived from bromonium ion **5a**, and 5-*anti*-bromo-6-*anti*-hydroxy **8** from the rearranged aziridinium ion **6a**.[2a−b,6] By contrast IOH affords only the unrearranged iodohydrin **7b** in nearly quantitative yield.[6] Similarly, addition of iodine/mercuric fluoride to alkene **4** afforded in 68% yield unrearranged iodofluoride **7c**.[6]



4 R = COOBn

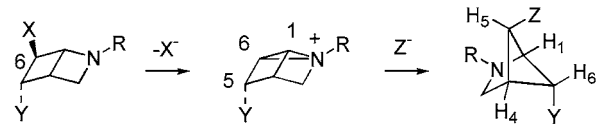
5a X = Br
5b X = I

6a X = Br

7a X = Br, Y = OH
7b X = I, Y = OH
7c X = I, Y = F

8

Although we were at first disappointed that conditions could not be found to induce the iodonium ion **5b** to rearrange, it was noted that, unlike aziridinium ion **6a**, the functional groups in unrearranged **7** are ideally situated to afford 5-syn substituents in azabicycle **10**. The X group at C_6 is antiperiplanar to the ring nitrogen, and the Y group at C_5 is syn to the nitrogen-containing bridge. The experimental problem then is this: can the halides at C_6 of **7a**−**c** be induced to ionize by a k_Δ process or with subsequent nitrogen participation in preference to either an alternative k_Δ process involving 5-*endo*-hydroxyl group participation[7] or to a k_{Nu} process in which there is external nucleophilic attack at C_6?[8] And if, given this second chance after failing to intercept iodonium ion **5b**, the nitrogen does participate to form aziridinium ions **9**, will these ions be attacked by nucleophiles at C_1 in preference to C_6?[8] If all of these conditions can be met, then a route to 5(6)-*syn*-fluoro- and 5-*syn*-hydroxy-2-azabicyclo[2.1.1]hexanes **10** will have been achieved.



7a X = Br, Y = OH
7b X = I, Y = OH
7c X = I, Y = F
R = COOBn

9a Y = OH
9b Y = F

10a Y = OH, Z = F
10b Y = OH, Z = OAc
10c Y = OH, Z = Cl
10d Y = Z = F
10e Y = F, Z = OH
10f Y = F, Z = OAc
10g Y = F, Z = Cl

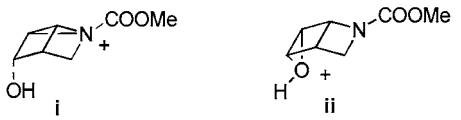
Herein we describe how the classical use of silver or mercury salts to enhance the nucleofugacity of the bromide and iodide ions results in successful solutions to the posed problem.[9] A variety of previously unavailable 5,6-difunctional-2-azabicyclo[2.1.1]hexanes can now be made that have *syn*-fluoro or *syn*-hydroxy groups in one methano bridge of **10** and *anti*-fluoro, *anti*-hydroxy, *anti*-acetoxy, or *anti*-chloro substituents in the other.

Syntheses of the precursors 5-*endo*-hydroxy-6-*exo*-bromo-, 5-*endo*-hydroxy-6-*exo*-iodo-, and 5-*endo*-fluoro-6-*exo*-iodo-2-azabicyclo[2.2.0]hexanes **7a**−**c** from pyridine have been described.[6] The substrates **7a**−**c** were heated in nitromethane or acetic acid in the presence of a silver or mercury salt for at least 24 h to give the results shown in Table 1.[9] Our initial efforts to react bromohydrin **7a** with AgF in nitromethane were sluggish at 60 °C, and only at 85 °C was a low yield of fluoro alcohol **10a** obtained (entry 1). The related iodide **7b** was more reactive and gave better yields of **10a** with either AgF (entry 2) or HgF_2 (entry 3) at 60 °C. Structure **10a** was characterized by the large coupling for syn proton H_5 at δ 4.55 (d, $J = 59$ Hz). The absence of W-plan coupling of this proton with anti proton H_6 defines the syn orientation of the hydroxyl group. The 2-azabicyclo[2.1.1]hexane structure was confirmed by the characteristic W-plan coupling of bridgehead protons H_1 and H_4 ($J = 6.8$ Hz) and the pair of nonequivalent geminal H_3 protons that appeared as two doublets ($J = 9$ Hz), not further coupled to H_4.[2a,b]

Other nucleophiles can be introduced into the anti position beside fluoride. Silver acetate in acetic acid reacts with halohydrin **7b** to afford hydroxy acetate **10b** (entry 4), and mercuric chloride in nitromethane affords chlorohydrin **10c** (entry 5). The pair of doublets for the H_3 protons and the W-plan coupling of H_1 and H_4 confirmed the azabicyclic ring structure. The trans relationship of the functional groups was again characterized by the absence of long-range W-plan

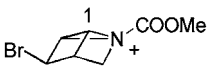
(6) Krow, G. R.; Lin, G.; Rapolu, D.; Fang, Y.; Lester, W.; Herzon, S. B.; Sonnet, P. E. *J. Org. Chem.* **2003**, *68*, 5292−5299.

(7) Calculations using the restricted Hartree−Fock method with the 6-31G(d) basis set show that the aziridinium ion **i** is 34.6 kcal/mol more stable than the protonated epoxide **ii**. See Supporting Information.



i **ii**

(8) Attack of the nucleophile occurs at C_1 in 5-*exo*-bromoaziridinium ions. See refs 1a, 2b,c, and 6. Although the ion **iii** has a larger LUMO at C_1, there is a bromine atom steric effect for nucleophilic attack at C_6 not present in **9**. See ref 6.



iii

(9) Silver and mercury salts accelerate substitution reactions of iodides and bromides. (a) Filippo, J. S., Jr.; Romano, L. J. *J. Org. Chem.* **1975**, *40*, 782. (b) March, J. *Advanced Organic Chemistry*, 3rd ed.; Wiley-Interscience: New York, 1985; p 318. (c) Pocker, Y.; Wong, Y.-H. *J. Am. Chem. Soc.* **1975**, *97*, 7105. (d) Zamashchikov, V. V.; Rudakov, E. S.; Bezbozhnaya, T. V. *React. Kinet. Catal. Lett.* **1984**, *24*, 65. (e) Carreno, M. C.; Carretero, J. C.; Garcia Ruano, J. L.; Rodriguez, J. H. *Tetrahedron* **1990**, *46*, 5649−64. (f) Sandler, S. R. *J. Org. Chem.* **1967**, *32*, 3876.

Table 1. Metal-Enhanced Rearrangements of Azabicycles **7a**−**c**

no.	reactant	X	Y	reagent and temp[a]	product	Y	Z	yield (%)
1	**7a**	Br	OH	$AgF/MeNO_2$/85 °C[b]	**10a**	OH	F	20
2	**7b**	I	OH	$AgF/MeNO_2$/60 °C	**10a**	OH	F	58
3	**7b**	I	OH	$HgF_2/MeNO_2$/60 °C	**10a**	OH	F	65
4	**7b**	I	OH	AgOAc/AcOH/60 °C[c]	**10b**	OH	OAc	60
5	**7b**	I	OH	$HgCl_2/MeNO_2$/60 °C	**10c**	OH	Cl	74
6	**7c**	I	F	$AgF/MeNO_2$/60 °C	**10d**	F	F	67
7	**7c**	I	F	$HgF_2/MeNO_2$/60 °C[d]	**10d**	F	F	54
8	**7c**	I	F	$HgF_2/MeNO_2$/60 °C[e]	**10e**	F	OH	60
9	**7c**	I	F	$Hg(OAc)_2$/HOAc/60 °C	**10f**	F	OAc	73
10	**7c**	I	F	$HgCl_2/MeNO_2$/60 °C	**10g**	F	Cl	63

[a] $t = 24$ h. [b] At 60 °C, **7a** was recovered unchanged (92%). [c] $t = 36$ h. [d] New bottle of HgF_2 was used. [e] Previously opened bottle of moisture-sensitive HgF_2 was used.

coupling between H_5 and H_6. Attempted reactions with mercuric bromide and mercuric iodide in nitromethane were unsuccessful, apparently because of insolubility of these halide salts.

The iodo fluoride **7c** serves as a precursor for several novel *syn*-fluorides. Reaction with silver fluoride (entry 6) or mercuric fluoride (entry 7) affords the difluoride **10d**.[9] The trans stereochemistry was assigned from the appearance of H_5 (dd, $J = 58.1$ Hz, 22.8 Hz); the smaller W-plan coupling of this proton is with the *syn*-fluoro group on C_6. Reaction of **7c** with mercuric fluoride that had been exposed to the air afforded fluoro alcohol **10e** and not difluoride **10d**, which is indicative of a large amount of moisture in the hygroscopic salt (entry 8). The related fluoro acetate **10f** was more rationally prepared by reaction of **7c** with mercuric acetate in acetic acid (entry 9). The H_6 protons adjacent to oxygen in **10e** (d, $J = 23$ Hz) and **10f** (d, $J = 21.5$ Hz) again enabled assignment of trans sterochemistry to the two 5,6-substituents. Mercuric chloride reacted with **7c** to form *trans*-fluoro chloride **10g** with H_6 (d, $J = 21.3$ Hz) defining the stereochemistry (entry 10).

A stereoselective route has been achieved to prepare 2-azabicyclo[2.1.1]hexanes **10** having *syn*-fluoro or *syn*-hydroxyl groups in one methano bridge and a fluoro, chloro, hydroxy, or acetoxy substituent in the remaining methano bridge. These new methanopyrrolidines are now available for preparation of new fluoro- and hydroxymethanoprolines.[4]

Acknowledgment. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (CHE 0111208) for support of this research and to Scott Sieburth for helpful comments.

Supporting Information Available: All experimental procedures, spectroscopic data, and copies of ^1H NMR and ^{13}C NMR for compounds **10a**−**g**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0349662