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Novel Selectfluor and Deoxo-Fluor-Mediated Rearrangements. New 5(6)-Methyl and Phenyl Methanopyrrolidine Alcohols and Fluorides

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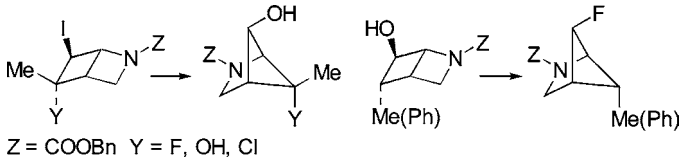
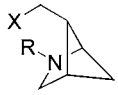
ABSTRACT

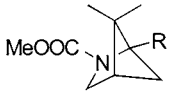


Stereoselective syntheses of novel 5,6-difunctionalized-2-azabicyclo[2.1.1]hexanes containing 5-*anti*-fluoro or hydroxyl in one methano bridge and a variety of *syn*- or *anti*-chloro, fluoro, hydroxy, methyl, or phenyl substituents in the other methano bridge have been effected. Rearrangements of iodides to alcohols were initiated using Selectfluor. Rearrangement of alcohols to fluorides was initiated using Deoxo-Fluor. Ring opening of 2-azabicyclo[2.2.0]hex-5-ene *exo*-epoxide with organocopper reagents is regioselective at C_5.

The 2-azabicyclo[2.1.1]hexane (methanopyrrolidine) ring system can be viewed as a conformationally constrained pyrrolidine.[1] As part of our efforts to prepare fluoro- and hydroxy-substituted methanopyrrolidines[2] with potential for library generation,[3] we are searching for efficient methods to introduce these functional groups in combination with other substituents onto stereochemically defined syn and anti orientations of the methano bridges. There are few reports of acyclic *syn*- or *anti*-alkyl substituents in the methano-bridges of 2-azabicyclo[2.1.1]hexanes. Huet et al. have disclosed a nine-step cyclobutane ring closure route to introduce 5-*syn*-aminomethyl substitution of **1**, and this was converted in six additional steps to the hydroxymethyl derivative **2**.[4] Pitrowski has utilized a photochemical ring closure method to introduce 5,5-dimethyl substituents in 1-aryl-substituted **3**.[5,6] There are no examples reported of 5-aryl substitution in 2-azabicyclo[2.1.1]hexanes.



1 R = BOC, X = NHBOC
2 R = Cbz, X = OH



3a R = Ph
3b R = 3-Cl-Pyridyl

We have reported efficient stereocontrolled rearrangement routes from 1,2-dihydropyridine photocyclization product **4** and species BrY (Y = Br, OH, OAc) in suitable solvents to prepare functionalized conformationally constrained 5-anti-6-anti-disubstituted methanopyrrolidines **6**.[2c−f,7] This one-step rearrangement method was found to apply only to the reactions of substrate **4** in which R = H.

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(1) For a review of synthetic approaches to 2-azabicyclo[2.1.1]hexanes, see: Krow, G. R.; Cannon, K. C. *Heterocycles* **2004**, *62*, 877.

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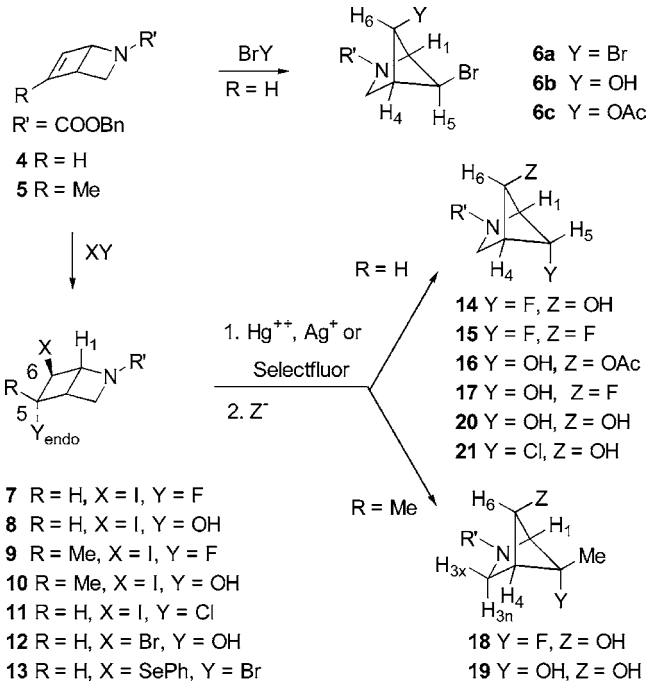

Species XY (X = I, Y = F, OH) react with alkene **4** to afford unrearranged addition products **7** and **8**. These have been shown to be useful precursors of 5-syn-6-anti-difunctional fluoro alcohol, difluoride, and hydroxyacetate structures **14**−**17** by "second chance" silver- or mercury salt-enhanced rearrangements.[2b,8] In this paper we describe several novel and major advances in the "second chance" rearrangement approach from unrearranged 6-*exo*-iodides that make it possible to introduce alkyl or aryl groups, in addition to fluoro and/or hydroxyl groups, onto the 5(6)-bridges of methanopyrrolidines in stereochemically defined syn and anti orientations. It is also possible to enhance the rearrangement of 6-*exo*-iodo-2-azabicyclo[2.2.0]hexanes to 6-hydroxymethanopyrrolidines with electrophiles other than silver or mercuric ions.

Our initial concern was to see if the mercury or silver ion-facilitated rearrangements could be extended to more crowded substrates, so the 6-*exo*-iodides **9** and **10** were prepared by addition of either IF or IOH to the alkene **5**.[2b,9] The ^{1}H NMR[10] of 6-*exo*-iodo-5-*endo*-fluoride **9**, shows no coupling between H_{6endo} (d, $J_{H,F} = 17$ Hz) at δ 4.85 and H_1 at δ 4.34 and 4.31 (rotamers).[2f] The 5-*exo* orientation of the C_5 methyl is shown by its positive NOE with H_4 at δ 3.05. Similarly, the ^{1}H NMR of 5-*endo*-hydroxyl-6-*exo*-iodide **10** shows as expected only minor coupling between H_6 (d, $J = 1.0$ Hz) at δ 4.62 and H_1 at δ 4.35. The 5-*exo* orientation of the C_5 methyl is shown by its positive NOE with H_4 at δ 2.95.

As shown in Table 1 (entry 1), treatment of the iodofluoride **9** with moist mercuric fluoride afforded a rearranged fluoro alcohol **18**. The ^{1}H NMR of fluoro alcohol **18** shows a large coupling for H_6 at δ 3.82 (d, $J_{H,F} = 27$ Hz) that indicates a W-plan syn,syn orientation for the F and H_6. A significant W-plan coupling between H_1 (d, $J = 7$ Hz) at δ 4.05 and H_4 at δ 2.63 is also characteristic of the 2-azabicyclo-[2.1.1]hexane system.[2b−e] The iodo alcohol **10** (entry 2) with moist mercuric fluoride gave the rearranged diol **19**. The ^{1}H NMR of **19** showed significant W-plan coupling between H_1 ($J = 7$ Hz) at δ 3.95 and H_4 at δ 2.4 and a singlet for H_6 at δ 3.85; consistent with a syn orientation for H_6 is its observed NOE with H_{3x} at δ 3.50. The stereochemistry of the methyl group follows from the absence of an observed NOE between the 5-methyl protons and H_{3n} at δ 3.25, as well as mechanistic considerations.[2b] Surprisingly, iodofluoride **9** and iodo alcohol **10** were unreactive toward mercuric chloride in nitromethane and mercuric acetate in nitromethane or acetic acid.[2b]

In an effort to avoid metal salts in these reactions, an alternative reagent to enhance the leaving ability of iodide was sought. Selectfluor or F-TEDA-BF_4 [1-fluoro-4-chloromethyl-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)] has good oxidant and electrophilic properties.[11] While there is evidence that methanolic solutions of iodides can be stable in the presence of Selectfluor,[12] it has been shown by Wong and co-workers that Selectfluor in wet acetonitrile can be used in the cleavage of electron-rich thioglycoside,[13]

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Table 1. 5-*anti*-Methyl-2-azabicyclo[2.1.1]hexanols by Mediated Iodide Rearrangements

no.	reactant	R	X	Y	reagents/temp/time	product	Z	Y	yield (%)
1	**9**	Me	I	F	HgF_2 moist/$MeNO_2$/60 °C/16 h[a]	**18**	OH	F	53
2	**10**	Me	I	OH	HgF_2 moist/$MeNO_2$/60 °C/16 h[a]	**19**	OH	OH	37
3	**9**	Me	I	F	F^+ [b]/CH_3CN/H_2O/60 °C/20 h	**18**	OH	F	71
4	**9**	Me	I	F	6:5 CH_3CN/H_2O/60 °C/20 h	nr			
5	**10**	Me	I	OH	F^+ [b]/CH_3CN/H_2O/60 °C/20 h	**19**	OH	OH	62

[a] No reaction was observed with $Hg(OAc)_2$ or $HgCl_2/MeNO_2$/80 °C/16 h. No reaction was observed with $Hg(OAc)_2$/HOAc/80 °C/16 h. [b] Selectfluor; nr = no reaction

Table 2. 2-Azabicyclo[2.1.1]hexanols by Mediated Rearrangement of Iodides

no.	reactant	R	X	Y	reagents/temp/time	product	Z	Y	yield (%)
1	**7**	H	I	F	F^+ [a]/CH_3CN/H_2O/25 °C/12 h	**14**	OH	F	84
2	**7**	H	I	F	HgF_2 moist/$MeNO_2$/60 °C/24 h	**14**	OH	F	60[b]
3	**7**	H	I	F	AgF/$MeNO_2$/60 °C/16 h	**15**	F	F	67[b]
4	**8**	H	I	OH	AgOAc/HOAc/60 °C/36 h	**16**	OAc	OH	60[b]
5	**8**	H	I	OH	$HgF_2/MeNO_2$/60 °C/24 h	**17**	F	OH	65[b]
6	**8**	H	I	OH	F^+ [a]/CH_3CN/H_2O/25 °C/12 h	**20**	OH	OH	68
7	**11**	H	I	Cl	F^+ [a]/CH_3CN/H_2O/25 °C/12 h	**21**	OH	Cl	75
8	**11**	H	I	Cl	CH_3CN/H_2O[c]	nr			
9	**11**	H	I	Cl	HOAc/H_2O 1:1/95 °C/48 h	nr			
10	**12**	H	Br	OH	F^+ [a]/CH_3CN/H_2O/80 °C/16 h	nr			
11	**12**	H	Br	OH	AgF/$MeNO_2$/85 °C/12 h	**17**	F	OH	20[b]
12	**13**[d]	H	PhSe	Br	F^+ [a]/CH_3CN/H_2O/80 °C/16 h	nr			

[a] Selectfluor/1:1 CH_3CN/H_2O. [b] Ref 2b. [c] Added NH_4Cl (3 equiv)/60 °C/1 day or H_2SO_4 (pH = 1)/35 °C/12 h. [d] Ref 2c; nr = no reaction.

tetrahydropyranyl, *p*-methoxybenzylidene, and 1,3-dithiane[14] protecting groups under mild conditions. We here report that Selectfluor in water/acetonitrile can be substituted for mercury or silver salts in the rearrangement of the iodides in Table 1. Iodofluoride **9** with Selectfluor at 60 °C for 20 h (entry 3) afforded the fluoro alcohol **18**. No reaction of iodide **9** was observed in acetonitrile/water in the absence of Selectfluor (entry 4). Similarly, iodo alcohol **10** with Selectfluor (entry 5) afforded diol **19**.

Selectfluor is also an alternative for mercury and silver salts in the rearrangement of less substituted iodofluoride **7**, iodo alcohol **8**, and iodochloride **11** (Table 2). Iodofluoride **7** rearranges with Selectfluor at room temperature in high yield to give fluoro alcohol **14** (entry 1).[2b] The reaction of iodofluoride **7** with Selectfluor gives higher yields of fluoro alcohol **14** than when enhanced by moist HgF_2 (entry 2), but difluoride **15** is better obtained with AgF (entry 3), because of the difficulty of keeping HgF_2 dry.[2b] Iodo alcohol **8** has been shown to react with silver acetate/acetic acid (entry 4) to give hydroxyacetate **16**, while dry mercuric fluoride affords a fluoro alcohol **17** (entry 5). Iodo alcohol **8** reacts at room temperature with Selectfluor to give the diol **20** (entry 6). As expected for a 5-anti/6-syn arrangement of the hydrogens in diol **20**, there is no symmetry plane and no W-plan coupling for H_5 at 4.65 and H_6 at δ 3.82 in the ^{1}H NMR spectrum.

Olefin **4** reacted with iodine monochloride to afford 5-*endo*-chloro-6-*exo*-iodide **11**, whose stereochemical assignment was made on the basis of its ^{1}H NMR. The 6-proton is endo based upon its lack of coupling with bridgehead proton H_1. Proton H_5 is exo (dd, J = 7, 6 Hz) based upon its large 7 Hz coupling with bridgehead proton H_4. With iodochloride **11**, only the iodide and not the chloride reacts with Selectfluor to give a rearranged 5-*syn*-chloro-6-*anti*-alcohol **21** (entry 7). Proton H_5 in chloro alcohol **21** is not coupled to H_6, as is expected for a structure that lacks a W-plan arrangement of these protons.

Is Selectfluor a necessary reagent for effecting iodide rearrangements in acetonitrile/water? Control experiments show that Selectfluor, an *N*-fluoro ammonium salt, is required. There was no reaction of iodochloride **11** observed in acetonitrile/water with or without added ammonium chloride. Nor does proton catalysis cause rearrangement, since iodochloride **11** did not react in acetonitrile/water with added acid (entry 8). Iodochloride **11** was also unreactive in aqueous acetic acid (entry 9).[15]

A 6-*exo*-bromide is a less efficient leaving group than iodide, and reaction of bromo alcohol **12** with Selectfluor was not observed (entry 10). Forcing conditions are required to rearrange bromo alcohol **12** to fluoro alcohol **20** (entry 11). Conditions were not found for phenylselenide **13** to react with Selectfluor (entry 12).

We next turned our attention to alcohols as substrates for rearrangement. It is known that alcohols are easily converted to fluorides using Deoxo-Fluor [bis(2-methoxyethyl)amino-

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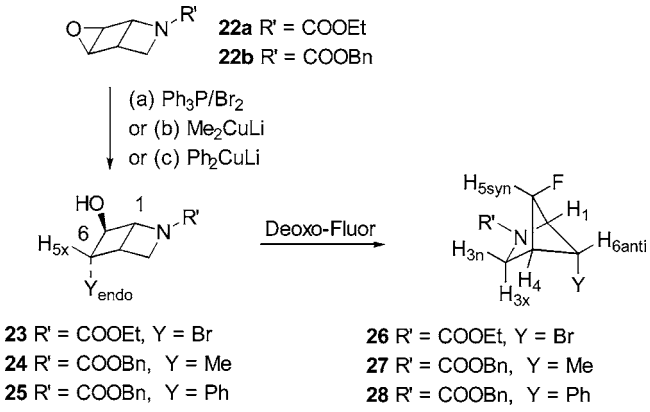
Table 3. 5(6)-Fluoro-2-Azabicyclo[2.1.1]hexanes by Mediated Alcohol Rearrangements

no.	reactant	R	Y	reagents/temp/time	product	Y	yield (%)
1	**23**	H	Br	R_2NSF_3/CH_2Cl_2/heat/12 h[a]	**26**	Br	60
2	**24**	H	Me	R_2NSF_3/CH_2Cl_2/25 °C/9 h	**27**	Me	75
3	**24**	H	Me	$F^+/CH_3CN/H_2O$/80 °C, 2 days[b]	nr		
4	**25**	H	Ph	R_2NSF_3/CH_2Cl_2/25 °C/2 h	**28**	Ph	77

[a] R_2NSF_3 = Deoxo-Fluor. [b] F^+ = Selectfluor; nr = no reaction.

sulfur trifluoride].[16] It was not clear that this reagent could be used to effect our desired rearrangement;[17] however, as shown in Table 3 (entry 1), treatment of bromo alcohol[2f] **23**, prepared from epoxide **22a**, with Deoxo-Fluor successfully led to the rearranged fluorobromide **26**; there is no W-plan F/H_6 or H_5/H_6 coupling in this structure.[10]



Since, the epoxides **22** are easily prepared from pyridine,[2f,9] we envisioned ring opening of epoxides **22** as a convenient source of 5-(*endo*)-alkyl(aryl)-6-*exo*-alcohol substrates. Indeed, epoxide **22b** undergoes a regioselective ring opening at C_5 with lithium dimethylcopper[18] to afford 5-*endo*-methyl-6-*exo*-alcohol **24**. As expected for this stereochemical arrangement, endo proton H_6 is a doublet at δ 4.17 ($J_{5,6}$ = 5 Hz) coupled to the trans H_{5x} at δ 2.74. Similarly, epoxide **22b** and lithium diphenylcopper afforded the alcohol **25**, whose 6-*exo*-hydroxy-5-*endo*-phenyl stereochemistry is characterized by the absence of coupling between H_1 at δ 4.48 and H_6 at δ 4.72 (d, $J_{5,6}$ = 6 Hz) and by large couplings for H_{5x} at δ 3.80 ($J_{5,4}$ = 7 Hz, $J_{5,6}$ = 6 Hz) with H_6 and with H_4 at δ 3.26.

Treatment of alcohol **24** with Deoxo-Fluor (Table 3, entry 2) gave the desired 6-*syn*-methyl-5-*anti*-fluoride **27**. As expected for structure of 6-*syn*-methyl stereochemistry, the ^{1}H NMR showed no long-range W-plan coupling between the protons or fluorine atoms on H_5 and H_6, but W-plan coupling was observed between H_1 at δ 4.33 (d, J = 7 Hz) and H_4 at δ 2.75. Positive NOE effects are observed for the 6-*syn*-methyl group with H_{3x} and for H_{5syn} with H_{3n}.[10] The alcohol **24** was unreactive with Selectfluor (entry 3). Deoxo-Fluor and alcohol **25** (entry 4) gave the novel 6-*syn*-phenyl isomer **28** in which neither H_{5syn} at δ 4.87 (d, J = 62 Hz) nor fluorine is in position to show W-plan coupling with H_{6anti}.

A four-step stereoselective rearrangement route from 4-methylpyridine has been developed to prepare 2-azabicyclo-[2.1.1]hexanols **18** and **19** with a 6-*anti*-methyl in a methano bridge. The key step is an iodide solvolysis mediated by silver or mercuric salts or with most novelty by Selectfluor, whose use should be of broader applicability because of ease, cost, and safety. Additionally, a five-step stereoselective rearrangement route from pyridine to 5-*anti*-fluoro-6-*syn*-alkyl(aryl)-2-azabicyclo[2.1.1]hexanes has been achieved. The key steps include a regioselective opening of epoxide **22b** to provide access to useful 6-*exo*-alcohols **24** and **25** having strategically placed 5-*endo*-methyl or 5-*endo*-phenyl groups. These alcohols rearrange under the influence of Deoxo-Fluor to give 5-*anti*-fluoro-6-*syn*-methyl(phenyl)-2-azabicyclo[2.1.1]hexanes. The first synthesis of a methanopyrrolidine with a *syn*-Ph group in the 5(6)-methano bridge has been described.

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

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