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Nucleophilic ring closure and opening of aminoiodohydrins

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Abstract

Enantiopure aminoiodohydrins obtained from α-aminoaldehydes and Sm/CH_2I_2 have been transformed into regioisomeric aminoiodohydrins, aminoepoxides, azetidines or 1,3-oxazolidines. The key step in these transformations is a nucleophilic opening–closing process.

Keywords: azetidines; epoxides; halohydrines; oxazolidines.

α-Aminoaldehydes have been widely used as chiral building blocks in organic synthesis. Their applications include organometallic addition to carbonyl groups,[1] aldol condensations,[2] cycloadditions with activated dienes[3] and transformations into other functionalities such as aminoalkenes[4] or α-aminoaldimines.[5]

We have recently published the use of α-aminoaldehydes **1** as valuable substrates for the preparation of various enantiomerically pure compounds, by iodomethylation using samarium diiodide.[6] Thus, aminoiodohydrins were prepared under mild conditions and in a diastereoselective manner (de ~80%) and were transformed into enantiopure azetidinium salts, allylamines, aminoalcohols or aminoepoxides. In this Letter we describe some new applications of these aminoiodohydrins **2**, which have been transformed into regioisomeric aminoiodohydrins **4**, aminoepoxides **5**, azetidines **8** or 1,3-oxazolidines **9**.

The aminoiodohydrins **4** were prepared starting from regioisomeric aminoiodohydrins **2** by an unexpected opening–closing process shown in Scheme 1.

So, when iodohydrins **2** were evaporated, a mixture of the azetidinium iodide **3** and a new iodohydrin **4** was obtained. Despite their instability, NMR spectra of compound **3** were recorded using a freshly prepared sample. However, signals corresponding to iodohydrin **4** began to appear some hours later. Transformation of **3** into **4** was complete within 72 hours, and pure iodohydrins **4** were thus obtained.

The optimised process to obtain compounds **4** was carried out by addition of KI at rt to a CH_2Cl_2 solution of the azetidinium salt, the final yields being 65–70%, based on the starting aminoaldehyde **1**.

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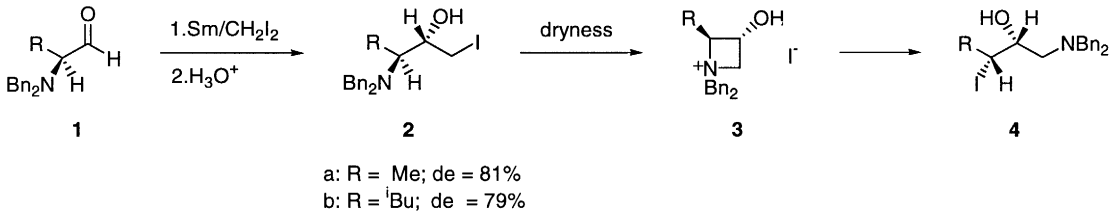


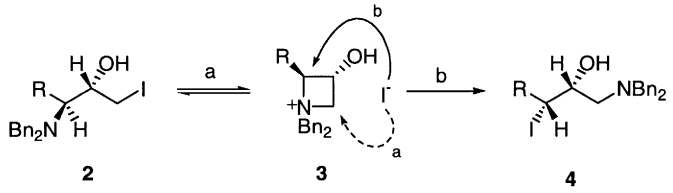
Scheme 1.

Diastereoisomeric excess was determined by examination of the ^{13}C NMR spectra, showing, as expected, similar values as starting compounds **2** (see Scheme 1).

The regiochemistry of iodohydrins **4** was established by means of ^{1}H NMR irradiation experiments (for a complete assignment of signals) and subsequent HMQC and HMBC experiments. They showed that iodide was incorporated into the molecule through position 2 of the azetidine ring, instead of position 4.

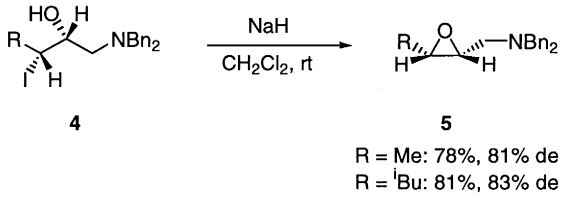
The opening–closing process mentioned above is unusual, and it is determined by the capability of iodide to act both as a leaving and as a nucleophilic group. Similar closing processes have been reported previously,[7] including examples taking place on aminochlorohydrins,[8] but the azetidinium salt formed is stable. However, in this case, iodide is nucleophilic enough to attack the ring.[9]

Although nucleophilic attack at a secondary centre is disfavoured by steric hindrance (Scheme 2, path b), the charged leaving group allows the nucleophilic substitution to occur. The expected position of attack (carbon 4) should lead to the initial iodohydrin **2**, which could be in equilibrium with the azetidinium iodide (Scheme 2, path a). The observed non-epimerisation of this carbon dismisses an S_N1 mechanism (through carbocations), and an S_N2 mechanism could explain the diastereospecificity of the process. Once the attack takes place on carbon 2, the obtained compound **4** is unable to undergo further closure.



Scheme 2.

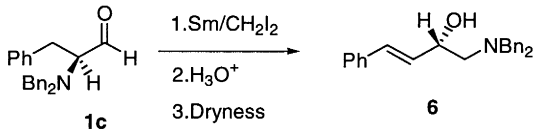
The chiral aminoalcohols **4** so obtained could be transformed, taking advantage of the iodide function. For example, we have prepared aminoepoxides (which are important compounds because of their biological properties[10] and synthetic applications) by simple treatment of iodohydrins with NaH (Scheme 3).



Scheme 3. Synthesis of aminoepoxides

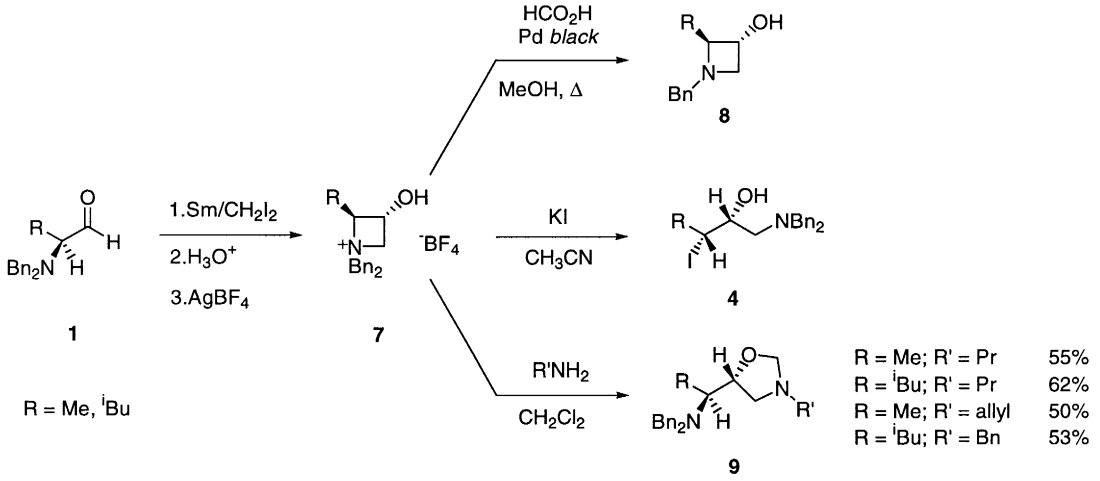
Moreover, synthesis of compounds **5** served to determine the relative configuration of the chiral centres and to prove the proposed stereochemistry of compounds **4** and **5**. Analysis of the coupling constants of the oxirane ring and NOE experiments showed a *cis* arrangement of substituents.

Different behaviour was observed when the aminoiodohydrin **2c** (R=Bn), derived from phenylalaninal **1c**, was used. Instead of the iodohydrin **4c**, the *E*-allylic alcohol **6**[11] was obtained (Scheme 4). This can be explained by assuming that the corresponding azetidinium salts undergo a spontaneous β-elimination, after abstraction of a benzylic proton, affording only the *E*-diastereoisomer.[12] This reaction was optimised by adding aqueous NaOH to a CH_3CN solution of the concentrate obtained after the iodomethylation of **1c**, at rt, affording the aminoalcohol in 75% yield. The enantiomeric excess of this compound was determined by chiral HPLC analysis of the corresponding *O*-benzoylated compound[13] and the obtained value (84% ee) was in agreement with the diastereoisomeric excess of *O*-acetylated iodohydrin **2c** (81%), derived from phenylalanine.[6]



Scheme 4.

On the other hand, the azetidinium salt could be stabilised using a counterion less nucleophilic than iodide. So, treatment of crude and unconcentrated iodohydrins **2** with $AgBF_4$ afforded the azetidinium tetrafluoroborate salts **7**, as stable compounds.[6] These compounds were monodebenzylated via a hydrogenolysis process[8] (Scheme 5), to afford the azetidines **8** in almost quantitative yields.



Scheme 5. Transformation of azetidinium salts

When compounds **7** were treated with KI, the expected iodohydrins **4** were obtained again. When amines were added to a CH_2Cl_2 solution of the azetidinium tetrafluoroborate, irreversible nucleophilic attack took place at the favoured carbon 4. The obtained diaminoalcohols reacted in situ with dichloromethane[14] affording 1,3-oxazolidines **9**[15] (Scheme 5).

The experimental procedure to obtain these compounds involved addition of an excess of the amine to a CH_2Cl_2 solution of the tetrafluoroborate **7**, at room temperature. The solution was allowed to stand for 48 h, the solvents removed in vacuo (0.1 mmHg, 70°C)[16] followed by extraction. Products were obtained in 50–62% yields (from starting aminoaldehyde **1**). ^1H NMR irradiations, HMQC and HMBC experiments identified the products as depicted in Scheme 5.

In conclusion, we have developed some new applications of iodohydrins **2**, obtaining other enantiopure regioisomeric aminoiodohydrins **4**, aminoepoxides **5**, azetidines **8** or 1,3-oxazolidines **9**, using simple methodology.

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9. The ratio of closure product to 3-amino-1-haloalkan-2-ols and derivatives is very dependent on the substitution pattern in the structure. For example, we have described that the iodohydrins **2** can be stabilised by acetylation of the alcohol group (Ref. 6). Substitution on the amine group or at C2 can also be an important effect. See: Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem*. **1995**, *60*, 6696–6699 and Ref. 8.
10. Chiral aminoepoxides are highly useful intermediates in the synthesis of protease inhibitors and other pharmaceutically interesting compounds. See, for example: Luly, J. R.; Dellaria, J. F.; Plattner, J. J.; Soderquist, J. L.; Yi, N. *J. Org. Chem.* **1987**, *52*, 1487–1492.
11. For some applications of the allylic alcohols, see: (a) Reich, H. J.; Wollowitz, S. *J. Am. Chem. Soc.* **1982**, *104*, 7051–7059. (b) Yamamoto, Y.; Yatagai, H.; Saito, Y.; Maruyama, K. *J. Org. Chem.* **1984**, *49*, 1096–1104.
12. Although thermodynamic control could be assumed, an *anti* elimination in the most stable conformer could not be counted upon.
13. Chiral HPLC analysis (Chiralcel OD-H) was carried out using, for comparison, a racemic mixture of the corresponding compound, to exclude the possibility of co-elution of both enantiomers. Aminoalcohol **6** could not be resolved using the chiral column Chiralcel OD-H; HPLC analysis was carried out with the corresponding benzoic ester, prepared by reaction of **6** with benzoyl chloride.
14. For other examples of CH_2Cl_2 as an alkylating agent, see: Spillane, W. J.; Burke, P. O. *Synthesis* **1986**, 1021–1024.
15. Oxazolidines have been extensively used as intermediates in the synthesis of several compounds with biological activity: Marshall, J. A.; Beaudoin, S. *J. Org. Chem.* **1996**, *61*, 581–586.
16. A by-product in these reactions results from condensation of the amine with CH_2Cl_2, easily removed and purified by distillation.