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Photochemical Rearrangement of 2-Phenylthio-3-Aminocyclohexanols. New Access to Deoxyazasugars and their Derivatives.

Denis Gravel*, Ali Amoozadeh and Yuan Wang.
Département de chimie, Université de Montréal, C.P. 6128, Montréal, Québec, Canada, H3C 3J7.

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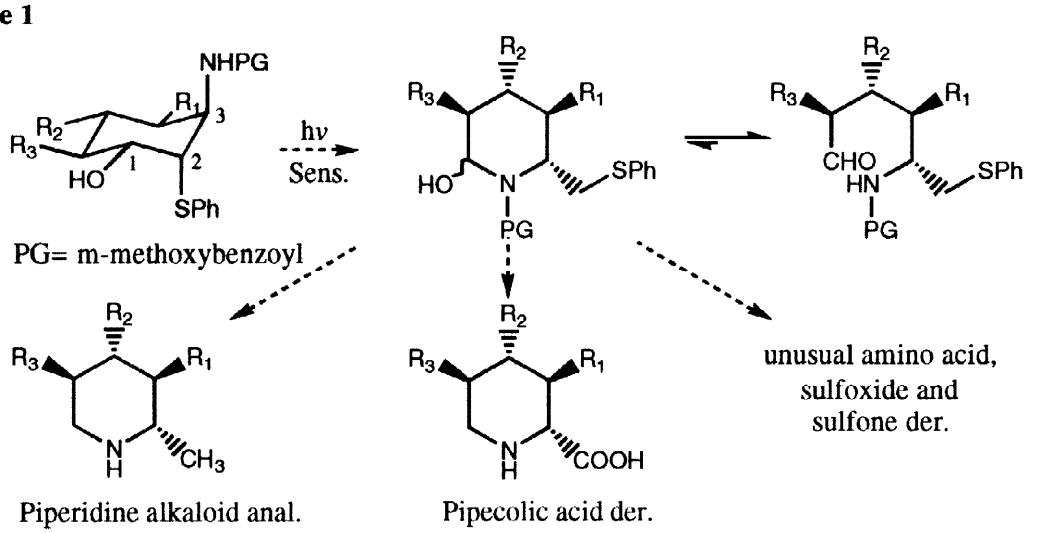
ABSTRACT: This paper reports the regioselective photorearrangement of 2-phenylthio-3-aminocyclohexanols to deoxyazasugars and their derivatives. These give access to variously substituted piperidines, amino-sulfones, -sulfoxides and -acids.

In the preceding communication[1] we illustrated a new synthetic methodology developed in our laboratory and pertaining to the photoinduced regioselective rearrangement of cyclic 2-phenylthio-1,3-diols to deoxysugars.[2] The latter allowed us to carry out a short stereospecific total synthesis of the fragrant oil (+)-cis-rose oxide, from R-(+)-3-methylcyclohexanone.[1]

In the present paper, we report the successful extension of the methodology to the case of 1,3-aminoalcohols i.e. 2-phenylthio-3-aminocyclohexanols, to gain access to deoxyazasugars[3] and their derivatives. The general strategy elaborated in this endeavor is illustrated in Scheme 1.

Scheme 1



As explained in the previous communication,[1] in order to preserve the 2,3-bond in the rearrangement and direct cleavage to the 1,2-bond, the relative stereochemistry of the starting carbocycle must be *trans*-diaxial for the phenylthio and amino groups which leaves a *cis* relationship for the phenylthioalcohol.

A short retrosynthetic analysis of the starting carbocycle shows that it should easily be accessible from a precursor enone as shown in Scheme 2.

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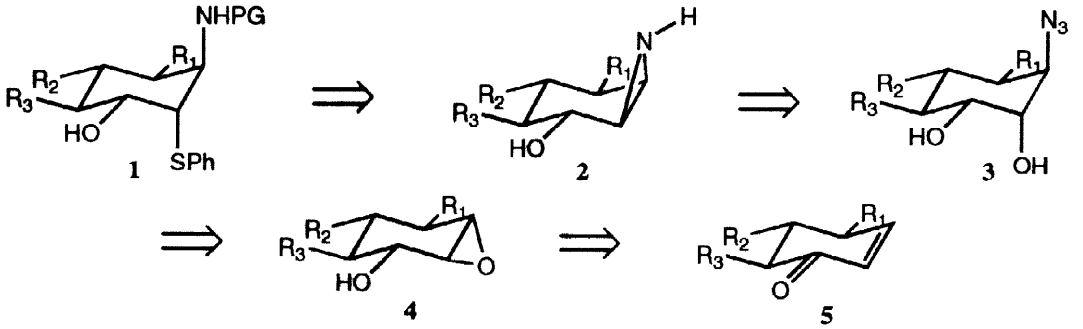
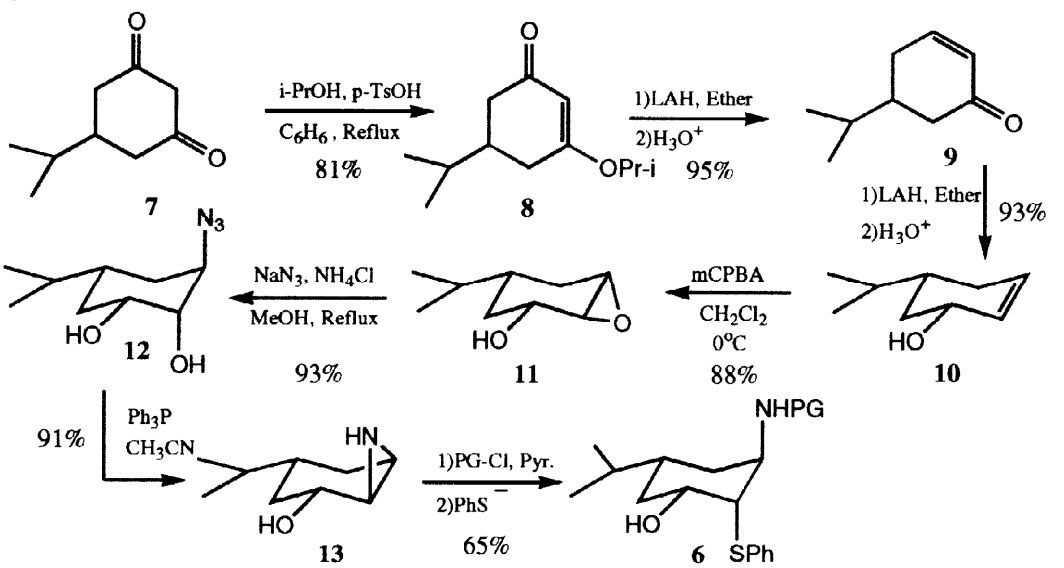
Scheme 2



Indeed, *trans*-diaxial ring opening of the precursor aziridino alcohol **2** with thiophenoxide should yield the desired starting carbocycle. The aziridine, on the other hand, could originate from the reduction of an appropriate *trans*-diaxial azido alcohol **3** which, in turn, should be accessible from a *cis*-epoxy alcohol **4**. Finally, the latter is easily derived from a precursor enone **5**.[1] The literature is extremely rich in methods to access various substituted cyclohexanones and cyclohexenones, and new methods are constantly appearing for their preparation in enantiomerically pure form.[4]

Scheme 3 represents a specific example of the elaboration of a starting carbocycle **6** where R_1=R_3=H and R_2=isopropyl. An identical sequence was carried out for R_2=phenyl and it can be anticipated that a variety of starting carbocycles could be accessed following this general strategy.

Scheme 3



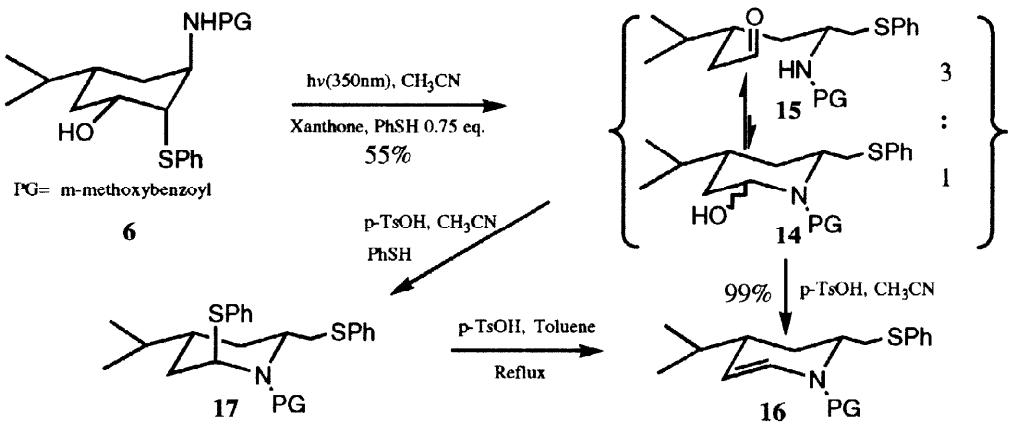
Indeed, β-diketone **7** is commercially available and its preparation follows a broadly applicable scheme.[5] Its further transformation *via* enol ether **8** to the corresponding enone **9** is also accessible *via* a general methodology.[6,7] The rest of the sequence follows well established stereoselective procedures, beginning with reduction[8] of the enone **9** to the *cis* allylic alcohol **10** followed by *cis* epoxidation[9] to **11**. Opening of the latter with azide[10] yields **12** which upon reduction[11] furnishes **13**. Protection of aziridino alcohol **13** followed by thiolate opening yields the required carbocyclic 2-phenylthio aminoalcohol **6**.

The development of satisfactory conditions for the photoinduced rearrangement as pertains to the nature of the amine protecting group required some optimization (see scheme 4). Indeed, the original amine protecting groups used such as Boc or Cbz led to complex reaction mixtures. Optimization of the

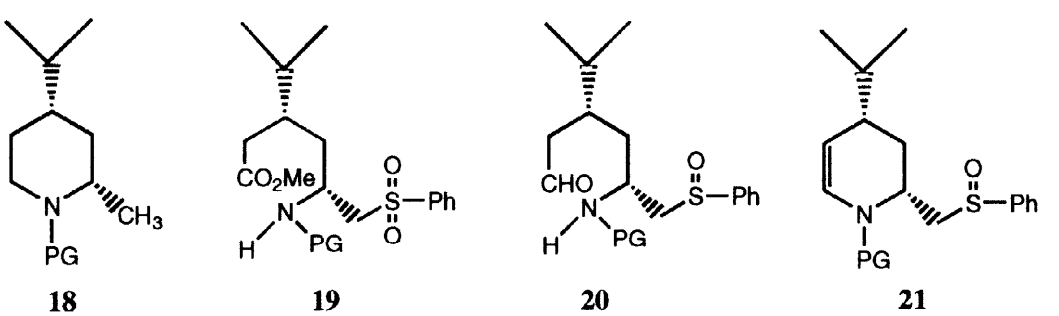
thiophenol/carbocycle ratio as well as evaluation of numerous amide-type protecting groups eventually showed that the m-methoxybenzoyl group gave a clean reaction mixture as well as reproducible results. Under these conditions, the desired deoxyazasugar (a carbinolamide derivative **14**), in equilibrium with its open form, (an aldehydo-amide **15**) is isolated. The optimum yield for the photoinduced rearrangement is 55% which corresponds to 65% based on consumed starting carbocycle. Under acidic dehydration conditions, the N-protected dehydropiperidine derivative **16** is obtained, while under the same conditions but in presence of 1 eq. of thiophenol, the 2-phenylthiopiperidine derivative **17** is obtained. The latter derives from the addition of thiophenol to the intermediate iminum ion in the dehydration process of **14**. In retrospect, it turns out that the usual amine protecting groups such as Boc and Cbz, which are carbamates, are probably too basic and therefore easily lead to dehydration of the deoxyazasugar which initiates the addition of different nucleophiles to the corresponding iminium ion.

Scheme 4 illustrates the photoinduced rearrangement reaction leading to the desired deoxyazasugar product **14** and its subsequent **controlled** acid catalyzed reactions which enhance the synthetic possibilities of the methodology.

Scheme 4



As further illustration of the possibilities, we report herein the preparation of compounds **18-21**. These are easily obtained from the deoxyazasugar derivative produced by the photolysis of **6**. Piperidine derivative **18** is obtained in 75% yield by treating enamide **16** with Raney Nickel in 60°C ethanol for two hours. Amino acid derivative **19**, on the other hand, is formed in 70% yield by first oxidizing photoproduct **14** with 10 eq. of $NaClO_2$ in presence of NaH_2PO_4 buffer and then esterifying with diazomethane.[12] Amino sulfoxide derivative **20**, is produced in 93% yield as a separable 3:2 mixture of two diastereoisomers, by reacting photoproduct **14** with mCPBA in CH_2Cl_2 at -78°C, while dehydropiperidine sulfoxide **21** results in 96% yield, also as a separable 3:1 mixture of two diastereoisomers, when enamide **16** is treated with mCPBA in CH_2Cl_2 at -78°C.



Finally, one application which remains elusive at this point, is the preparation of various α-amino acid derivatives by oxidation of the phenylthio group to the corresponding carboxylic acid. Our first attempt *via* the Pummerer[13] strategy led to low yields (5-10%) of the desired α-amino acids. This, it appears, could be due to internal participation by the neighboring amide group[14] thus preventing the normal course of the Pummerer rearrangement from taking place.

Efforts to circumvent this problem are underway and results will be reported in due course.

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