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Regio and Stereocontrolled Synthesis of Aryl Cis Aminoalcohols From Cis Glycols

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Abstract: Reaction of aryl substituted cis diols with α-acetoxyisobutyryl chloride results in the formation of trans vicinal chlorohydrin acetates where the halide is benzylic. Displacement of chloride with azide ion, deprotection of the ester and reduction of the azide furnishes the requisite cis aminoalcohols. This facile four-step procedure results in the exclusive replacement of a benzylic hydroxyl with an amino group, with a net retention of stereochemistry. This set of transformations is generally applicable to a wide variety of cis diols, and the overall yields are excellent.
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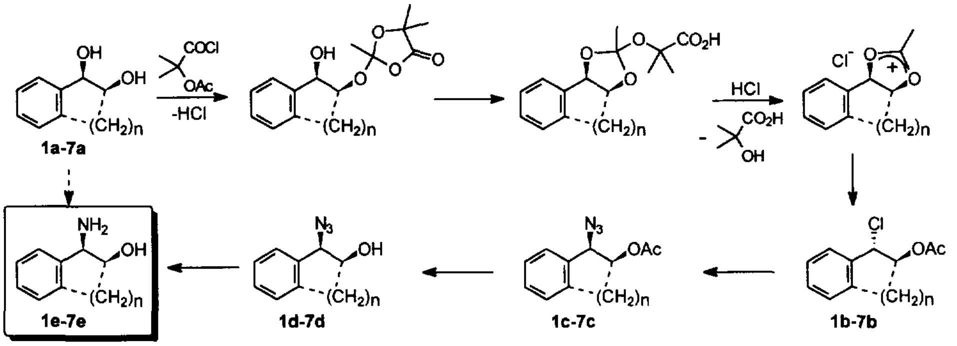
Over three decades ago Mattocks reported an unusual reaction of ethylene glycol with 2-acetoxy-2-methylbutyryl chloride which yielded 2-chloroethyl acetate.[1] Subsequently, α-acetoxyisobutyryl halides have been utilized for the conversion of vicinal cis diols in nucleosides to halohydrin acetates,[2,3] and these compounds have now become key intermediates in the synthesis of deoxynucleosides.[4-6] Although nucleoside[6-8] and other oxiranes[9,10] have been prepared through the use of α-acetoxyisobutyryl halides, there are virtually no applications of these acyl halides to the preparation of other classes of compounds. As part of our program in polynuclear aromatic hydrocarbon induced carcinogenesis, we have been developing methods for regio and stereoselective construction of cis and trans vicinal aminoalcohols, which contain a benzylic amine functionality. Among these, the trans aminoalcohols can be easily prepared through an S_N2 ring-opening of benzylic oxiranes by either azide ion followed by reduction,[11] or by a direct aminolysis.[12] On the other hand, access to the corresponding cis derivatives is significantly more difficult. Although syntheses of specific cis aminoalcohols have been reported,[13] a general route to this important class of compounds is lacking. Herein, we report a convenient, highly regio and stereocontrolled route to cis aminoalcohols from aryl substituted cis glycols through the use of α-acetoxyisobutyryl halides.

Of the two commercially available α-acetoxyisobutyryl halides (chloride and bromide) the chloro derivative was chosen for the present study. This is primarily because a benzylic halogeno intermediate is formed in the reaction (Scheme), and extreme lability of a benzylic bromine was expected in extended aromatic systems. Benzylic chlorides on the other hand, should be less reactive, and correspondingly more amenable to isolation procedures. The basis for the regio and stereochemical outcome of this approach is the formation of an acetoxonium species produced by elimination of α-hydroxyisobutyric acid from the orthoester intermediate,[2] that is formed *in situ* from the cis glycol. This acetoxonium ion undergoes trans chloride addition at the most stable carbocationic site, resulting in the formation of a vicinal chlorohydrin acetate. These halohydrin acetates can also be prepared in an overall two-step procedure, where the glycol is first converted to a cyclic orthoester with trimethyl orthoacetate followed by its fragmentation with trityl chloride,[14] trimethylsilyl chloride[15] or acetyl halide.[16] Although we have previously utilized the orthoester route for the synthesis of one cis aminoalcohol,[17] we have found that the present approach using commercially available α-acetoxyisobutyryl chloride is by far more convenient.

Scheme

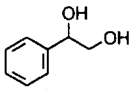
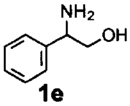
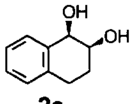
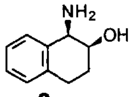
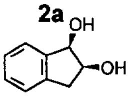
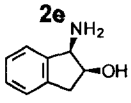
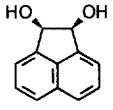
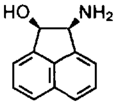
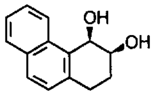
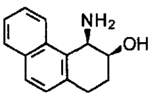
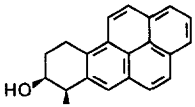
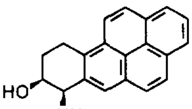
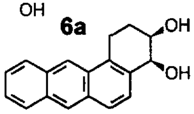
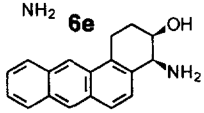


Note: Although the scheme represents the initial reaction occurring at the non-benzylic hydroxyl, the overall outcome would be identical if the benzylic hydroxyl participated in this initial step. However, based on steric differences it could be argued that the former is less-hindered and thus more reactive than the latter.

A brief investigation of optimal solvents for this transformation revealed that these reactions barely progressed in Et_2O or THF, and although these reactions proceeded in $CHCl_3$ they were not clean. However, rapid and clean formation of chlorohydrin acetates (**1b-7b**) was observed with three molar equivalents of α-acetoxyisobutyryl chloride in anhydrous MeCN, within about 1 hour at 0 °C to room temperature.[18] To avoid decomposition of the chlorohydrin acetates, which were obtained by a simple extractive workup, these were immediately converted to the azides without further purification. Displacement of chloride could be achieved in a facile manner with the soluble lithium azide in DMF at 50 °C, and the azidoacetates (**1c-7c**, see Table) were obtained in excellent yields after chromatography. Since, we and others have previously encountered an *O*→*N* acyl migration upon reduction of α-acyloxyazides,[11a,17,19] the hydroxyls were deprotected with NaOMe in 1:1 THF-MeOH or with NH_3-MeOH (85-98% yield). Finally, catalytic reduction of the azidoalcohols (**1d-7d**) with 5% Pd on carbon in 1:1 THF-MeOH provided the aminoalcohols (**1e-7e**, see Table) in yields ranging from 64-83% after chromatographic purification.

Certain specific cases are worthy of comment. (a) The reaction of 1-phenyl-1,2-ethanediol (**1a**), the only aryl substituted glycol investigated by Greenberg and Moffatt,[2] with α-acetoxyisobutyryl chloride results in halogen substitution exclusively at the benzylic position with no substitution at the less-hindered non-benzylic site. Thus, the present route allows for the regioselective preparation of a single phenylglycinol isomer (**1e**). This is not possible through a direct ring-opening of styrene oxide by azide ion followed by reduction, since, azide addition occurs at both the benzylic and the non-benzylic sites.[20] (b) Although **2e** and **3e** have recently been prepared,[13] the acidic media utilized in these syntheses may be incompatible with substrates that undergo rearrangement or decomposition under these conditions. The present strategy therefore, offers a relatively mild and general route to a variety of cis aminoalcohols. (c) The cis aminoalcohol of acenaphthene (**4e**) is reported as a minor isomer in the $NaBH_4$ reduction of amino acenaphthenone with the trans stereoisomer being the predominant component.[21] However, our procedure provides a facile route to **4e** exclusively, and compounds of this type are important intermediates in the preparation of DNA oligomers adducted with the metabolites of environmentally prevalent carcinogenic cyclopentahydrocarbons. (d) Among the cis diols studied, the tetrahydrophenanthrene derivative (**5a**) is particularly interesting due to steric constraints in the bay region. In **5a**, in contrast to other diols where a certain degree of conformational flexibility exists, the benzylic hydroxyl is forced into an axial orientation. However, despite this conformational rigidity the transformations proceed smoothly and **5e** is obtained in very good overall yield.

Table: ***Structures of glycols, the product amines[a] and yields.[b]***

Diol	2-step % yield of azido acetate	Amine	4-step overall % yield
 **1a**	**1c**: 81	 **1e**	62
 **2a**	**2c**: 70	 **2e**	56
 **3a**	**3c**: 69	 **3e**	48
 **4a**	**4c**: 89	 **4e**	48
 **5a**	**5c**: 76	 **5e**	54
 **6a**	**6c**: 64	 **6e**	52
 **7a**	**7c**: 79	 **7e**	60

[a] All compounds were characterized by proton NMR and HRMS.
[b] Isolated yields of pure products.

In this report we have described a general and concise route for the preparation of aryl substituted cis aminoalcohols from the corresponding cis glycols. Therefore, several biologically relevant aminoalcohols can now be easily accessed through this route.[22] Additionally, this strategy when coupled with asymmetric dihydroxylation procedures,[23] provides an effective route for the facile, regioselective preparation of enantiopure aminoalcohols.

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