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Synthesis of Protected Chiral Vicinal Diaminoalcohols by Diastereoselective Intramolecular Benzylic Substitution from Bistrichloroacetimidates

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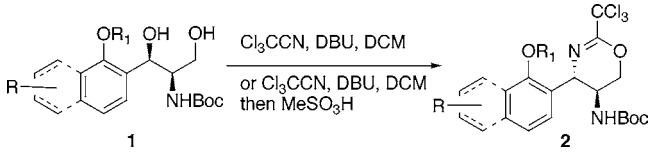
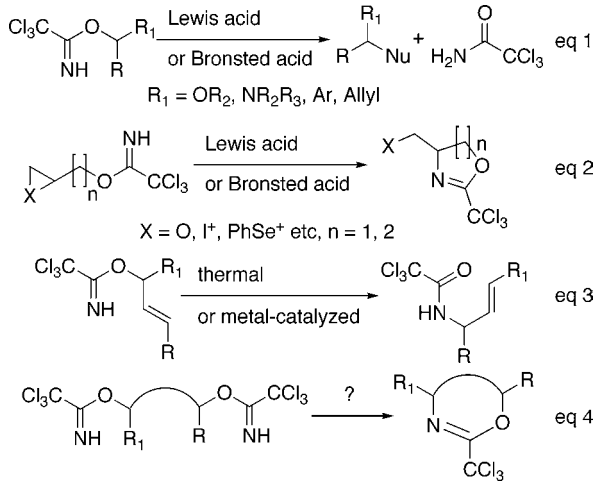
ABSTRACT



An efficient synthesis of chiral dihydrooxazines (2) from 1-aryl-2-amino-propane-1,3-diols (1) via the corresponding bistrichloroacetimidate intermediates has been developed. In this transformation, one trichloroacetimidate acts as a leaving group and the other acts as a nucleophile. The cyclization proceeds through an S_N1 mechanism to provide *trans*-dihydrooxazines with complete diastereoselectivity irrespective of the absolute configuration of the benzylic alcohol. The transformation of 2 into other selectively protected aminodiols is also documented.

Trichloroacetimidate is known to be a good leaving group under acidic conditions especially if the putative carbenium intermediate is stabilized by a neighboring heteroatom, aryl, allyl, or oxyallyl group, etc.[1] Thus, *O*-glycosyl trichloroacetimidates are efficient glycosyl donors for the synthesis of glycoconjugates,[2] whereas benzyl trichloroacetimidates are proven to be versatile benzylation reagents for hydroxy groups under acidic conditions (eq 1, Scheme 1).[3] On the other hand, the nitrogen atom of trichloroacetimidates can also act as an efficient nucleophile for intramolecular ring opening of halonium salts,[4] epoxides,[5] and dioxolanyliums (eq 2, Scheme 1).[6] The Overman rearrangement,[7] a [3,3]-sigmatropic rearrangement that combines the dual reactivities

Scheme 1. Trichloroacetimidate as a Leaving Group and as a Nucleophile



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(2) (a) Schmidt, R. R. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 212−235. (b) Roussel, F.; Knerr, L.; Grathwohl, M.; Schmidt, R. R. *Org. Lett.* **2000**, *2*, 3043−3046. (c) Zhang, J.; Schmidt, R. R. *Synlett* **2006**, 1729−1733.

(3) (a) Iversen, T.; Bundle, D. R. *J. Chem. Soc., Chem. Commun.* **1981**, 1240−1241. (b) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247−2250. (c) Zhang, J.; Schmidt, R. R. *Synlett* **2006**, 1729−1733.

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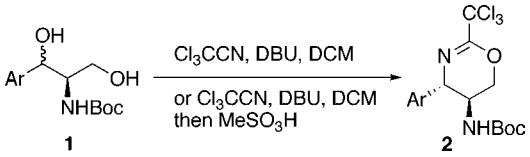
of trichloroacetimidates, has also found widespread application in organic synthesis (eq 3). Interestingly, the transformation shown in eq 4 (Scheme 1) wherein one trichloroacetimidate acts as a nucleophile while the other acts as a leaving group has rarely been investigated. Aside from the stereochemical issue, a potential pitfall of this otherwise attractive approach is the regioselectivity of the reaction. Indeed, two examples reported in the literature involving intramolecular vinylogous Schmidt glycosidation showed disparate regioselectivities.[8,9] We reasoned that by varying the electronic nature of the R and R_1 groups we should be able to push the reaction to proceed through an S_N1 mechanism and consequently to control the regioselectivity of the cyclization by modulating the relative stability of the incipient carbenium intermediate. Because the resulting oxazoline (five-membered ring) or oxazine (six-membered ring) is easily hydrolyzed, this route would constitute an efficient way to synthesize amino alcohols and derivatives thereafter from 1,2- or 1,3-diols. Nicolaou and co-workers have recently reported an elegant synthesis of sulfamidate from styrene-derived 1,2-diols using the Burgess reagent on the basis of the same principle.[10,11]

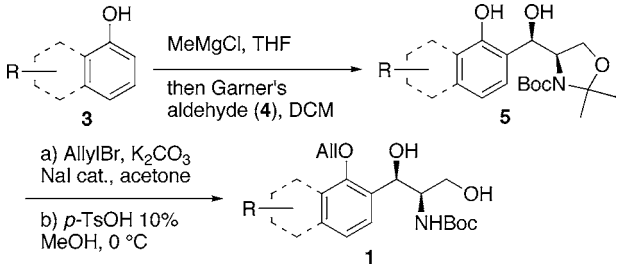
In connection with our ongoing project, we were interested in the synthesis of chiral diamines.[12,13] As a continuation of this research program, we report in this letter an efficient synthesis of oxazine **2** from readily accessible 1-aryl-2-amino-propane-1,3-diol (**1**) via a bistrichloroacetimidate intermediate and document that the overall process is highly regio- and stereoselective irrespective of the absolute configuration of the benzylic alcohol (Scheme 2).[14]

Scheme 2. Synthesis of Diaminoalcohol by Intramolecular Cyclization of Bistrichloroacetimidate



The required amino diol **1** was synthesized as shown in Scheme 3. Phenolic aldol condensation between phenol **3** and Garner's aldehyde **4** mediated by methyl magnesium chloride afforded the syn adduct **5** in excellent yield and diastereoselectivity (cf. Supporting Information for details).[15] The syn selectivity was taken for granted on the basis of Casiraghi's work and was confirmed by X-ray analysis in our related studies.[16] Allylation of phenol followed by cleavage of oxazolidine with *p*-toluenesulfonic acid generated the desired amino diol **1** (Scheme 3).

Scheme 3. Synthesis of 1-Aryl-2-aminopropane-1,3-diols **1**



To our delight, attempted synthesis of bistrichloroacetimidates by reaction of aminodiol **1a** with 3 equiv of trichloroacetonitrile in dichloromethane in the presence of DBU afforded directly the *trans*-dihydrooxazine **2a** in 62% yield (Scheme 4). The hypothetic bistrichloroacetimidate was not isolable in this case. The structure of **2a** was assigned without ambiguity by X-ray analysis. The ^{1}H NMR spectrum of **2a** displayed a coupling constant ($J_{H4-H5} = 5.6$ Hz) characteristic of the trans relationship of these two protons.[4b,c] By applying the same one-pot protocol, compounds **2b** and **2c** were prepared from the corresponding aminodiols with complete regio- and stereoselectivity.

When diol **1d** was reacted with trichloroacetonitrile in dichloromethane in the presence of DBU, the corresponding bistrichloroacetimidate **6d** was isolated in 50% yield (Scheme 5). Although **6d** was not very stable, it was isolated by column chromatography and was fully characterized. In the presence of a catalytic amount of methanesulfonic acid (0.05 equiv of $MeSO_3H$ in CH_2Cl_2, $C = 0.03$ M), **6d** cyclized

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(11) Rinner, U.; Adams, D. R.; Santos, M. L. D.; Abboud, K. A.; Hudlicky, T. *Synlett* **2003**, 1247−1252.

(12) For reviews, see: (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. (b) Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121−1162.

(13) For diastereoselective and stereodivergent three-component phenolic Mannich reactions, see: Rondot, C.; Zhu, J. *Org. Lett.* **2005**, *7*, 1641−1644.

(14) The bistrichloroacetimidates of olefinic 1,3-diols and olefinic 1,2-diols have been prepared and used in iodine-promoted cyclization. Under these conditions, these bistrichloroacetimidates displayed completely different reactivity from that shown in the present study. See: (a) Kang, S. H.; Kim, J. S.; Youn, J.-K. *Tetrahedron Lett.* **1998**, *39*, 9047−9050. (b) Kang, S. H.; Kim, C. M.; Youn, J.-K. *Tetrahedron Lett.* **1990**, *40*, 3581−3582.

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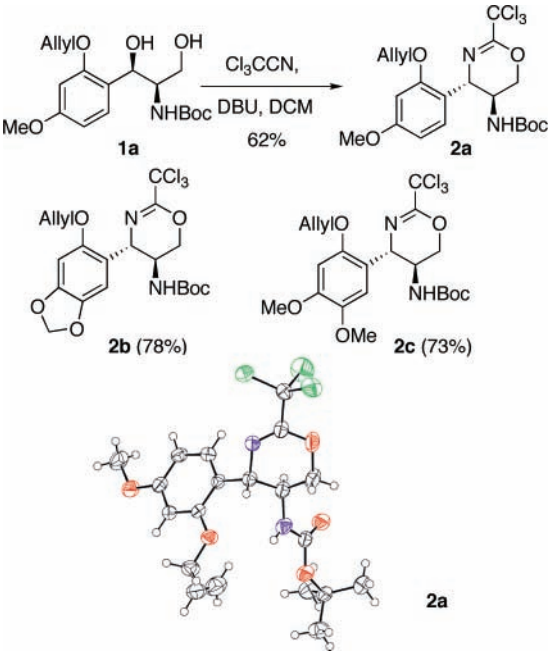
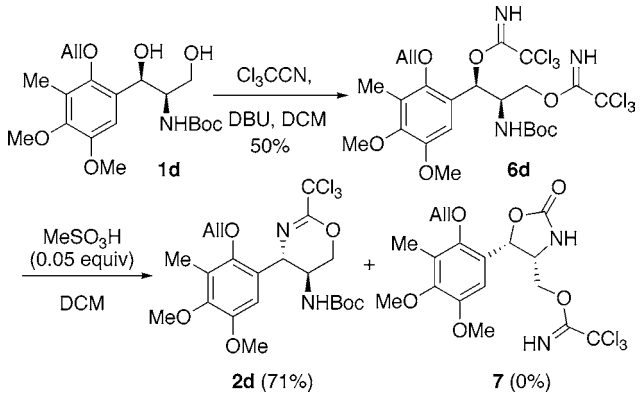
Scheme 4. One-Pot Synthesis of Dihydrooxazines **2a**−**c**



smoothly to afford the *trans*-dihydrooxazine **2d** in 71% yield. Lewis acids such as $BF_3{\cdot}OEt_2$ and Et_2AlCl were less effective as catalysts for this reaction. It is interesting to note that the alternative cyclization mode leading to oxazolidinone **7** was

Scheme 5. Two-Step Synthesis of Dihydrooxazine **2d**



not observed indicating the higher nucleophilicity of the trichloroacetimidate over the *tert*-butyloxycarbonyl function under these reaction conditions.[17] The scope of this two-step process was found to be quite general, and other dihydrooxazines synthesized are listed in Figure 1. At the present time, we have no clear-cut explanation on the different reactivity of the bistrichloroacteimidates derived from **1a**−**c** and **1d**−**i**.

To evaluate the importance of using the bistrichloroacetimidate as the cyclization precursor, the benzyl alcohol **8**

(17) De Paolis, M.; Blankenstein, J.; Bois-Choussy, M.; Zhu, J. *Org. Lett.* **2002**, *4*, 1235−1238.

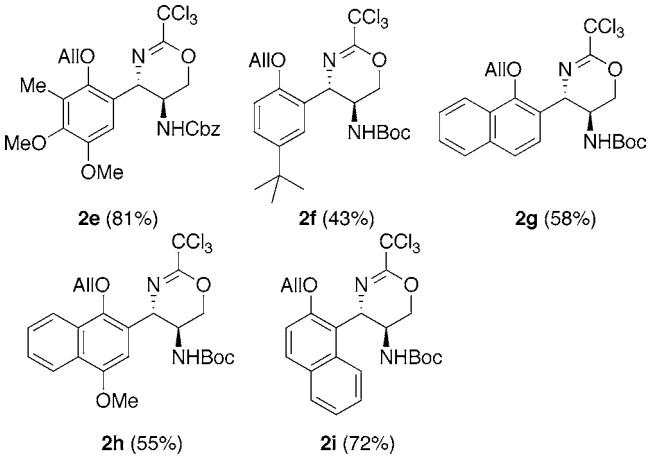
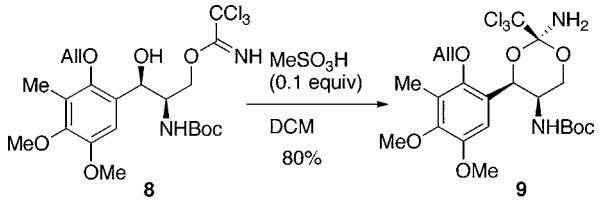


Figure 1. Yields of dihydrooxazines **2e**−**i** from a two-step synthesis.

was synthesized by reacting the diol with 1 equiv of trichloroacetonitrile. When **8** was submitted to the same reaction conditions as those described for **6d**, the 1,3-dioxane **9**, instead of the desired oxazine, was produced (Scheme 6).

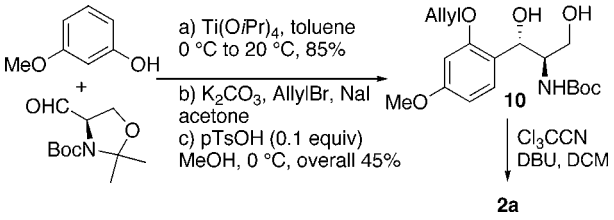
Scheme 6. Cyclization of Hydroxy Trichloroacetimidate



The intramolecular nucleophilic addition of the hydroxy group to the protonated imine (6-exo-trig cyclization) could account for the formation of dioxane **9**. We emphasize that the reaction is highly diastereoselective due to the favorable steric and stereoelectronic effects to generate only one single isomer **9** whose structure was determined by X-ray analysis (cf. Supporting Information).

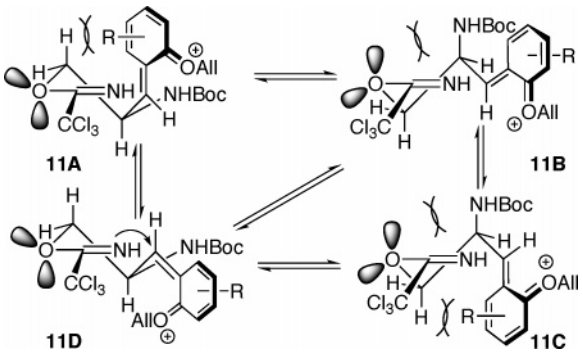
The inversion of stereochemistry at the benzylic center was observed from **1** to **2** in all cases examined. To probe if the substitution reaction went through the S_N2 mechanism as these results might suggest, an *anti*-aminodiol **10** was synthesized by a Ti-mediated phenolic aldol condensation process (Scheme 7).[15] When **10** was submitted to reaction conditions identical to those described for its syn diastereomer, the same *trans*-dihydrooxazine **2a** was isolated in 74% yield. These results indicated that the cyclization might proceed through an S_N1 rather than an S_N2 mechanism. Supposing that the reaction went through an *ortho*-quinone methide intermediate **11**,[18] the stereochemical outcome may be explained on the basis of conformational analysis. Considering the relative stability of the four conformers (Scheme 8), **11D** with all substituents in the *pseudoequatorial*

Scheme 7. Stereochemical Issue of the Cyclization



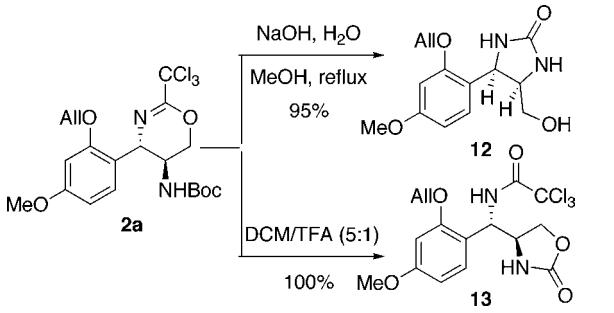
position may predominate over others. Cyclization by a 6-exo-trig mode afforded then the observed *trans*-dihydrooxazine.

Scheme 8. Stereochemical Consideration



Although the dihydrooxazine can be hydrolyzed under acidic conditions, we have found two interesting transformations that lead to the selectively protected form of the diamino alcohol (Scheme 9). Thus, heating to reflux a methanol solution of **2a** in the presence of NaOH (20 equiv) afforded

Scheme 9. Derivatization of Dihydrooxazine **2a**



the imidazolidinone **12** in 95% yield. On the other hand, stirring a solution of **2a** in CH_2Cl_2 and TFA (v/v = 5:1) at room temperature generated the oxazolidinone **13** in quantitative yield. The structure of **13** was confirmed by X-ray analysis (cf. Supporting Information).

In conclusion, we have developed an efficient synthesis of the selectively protected diamino alcohol unit that is of considerable interest in terms of both synthetic application and catalyst design.[19] The key to our approach is the exploitation of the dual reactivities of bistrichloroacetimidates. The application of this chemistry to the total synthesis of bioactive natural products such as bioxalomycin[20] is in progress.

Acknowledgment. Financial support from the CNRS and a doctoral fellowship from this institute to C.R. are gratefully acknowledged.

Supporting Information Available: Experimental details and physical data for compounds **1**−**13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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