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Solution- and Solid-Phase Synthesis of 4-Hydroxy-4,5-dihydroisoxazole Derivatives from Enantiomerically Pure *N*-Tosyl-2,3-aziridine Alcohols

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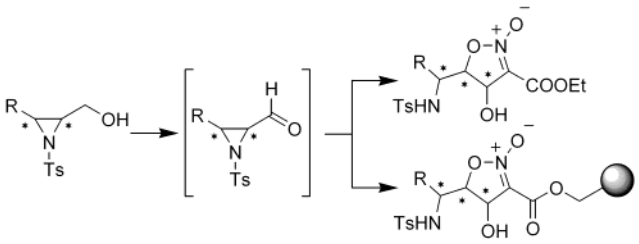
ABSTRACT



Enantiomerically pure *N*-tosyl-2,3-aziridine alcohols are directly converted into 4-hydroxy-4,5-dihydroisoxazole 2-oxides through oxidation to the corresponding aldehydes followed by in situ tandem nitroaldol-intramolecular cyclization. This study was concerned with (i) the selection of a suitable aziridine activation, (ii) the preparation of the target 4-hydroxy-4,5-dihydroisoxazole derivatives in solution, and (iii) the elaboration of a solid-phase process using hydroxy Merrifield-supported nitroacetic acid ester.

In recent years we have been investigating new methodologies for the preparation of 4-hydroxy-4,5-dihydroisoxazoles.[1] This is an interesting class of substrates that can lead to expeditious preparations of aminopolyhydroxylated compounds, which often exhibit therapeutical properties.[1,2] However, these heterocycles cannot be prepared directly by nitrile oxide cycloaddition to alkenes,[3] and, to the best of our knowledge, no solid-phase synthesis of 4-hydroxy-4,5-dihydroisoxazoles has yet been reported.[4]

We developed a new approach to the synthesis of 4-hydroxy-4,5-dihydroisoxazole 2-oxides[5,6] based on the tandem[7,8] nitroaldol-intramolecular cyclization reaction between an activated primary nitroalkane and an aldehyde bearing a leaving group on the α-position. When enantiomerically pure starting materials are employed, this process affords enantiopure 4,5-dihydroisoxazoles.[9] We recently

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(1) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, p 1069. Vogel, P.; Schaller, C. *Synlett* **1999**, 1219. Schaller, C.; Vogel, P.; Jäger, V. *Carbohydr. Res.* **1998**, *314*, 25. Wade, P. A.; Shah, S. S.; Govindarajan, L. *J. Org. Chem.* **1994**, *59*, 7199. Jäger, V.; Schröter, D. *Synthesis* **1990**, 556. Schwab, W.; Jäger, V. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 603.

(2) It has been found that a 4-oxygenated-4,5-dihydroisoxazole derivative is itself biologically active: Schaller, C.; Demange, R.; Picasso, S.; Vogel, P. *Bioorg. Chem. Med. Lett.* **1999**, 277.

(3) When vinyl ethers are employed, 5-oxygenated rather than 4-oxygenated heterocycles are obtained, with cycloaddition to furans being an exception.

(4) Solid-supported 4-unoxygenated derivatives are routinely obtained via the cycloaddition route; see, for example: Zou, N.; Jiang, B. *J. Comb. Chem.* **2001**, *2*, 6 and refs cited therein.

(5) Rosini, G.; Marotta, E.; Righi, P.; Seerden, J.-P. *J. Org. Chem.* **1991**, *56*, 6258. Rosini, G.; Galarini, R.; Marotta, E.; Righi, P. *J. Org. Chem.* **1990**, *55*, 781.

(6) Righi, P.; Marotta, E.; Rosini, G. *Chem. Eur. J.* **1998**, *4*, 2501. Righi, P.; Marotta, E.; Landuzzi, A.; Rosini, G. *J. Am. Chem. Soc.* **1996**, *118*, 9446.

(7) Tietze, L. *Chem. Rev.* **1996**, *96*, 115.

(8) Hudlicky, T. *Chem. Rev.* **1996**, *96*, 3−30.

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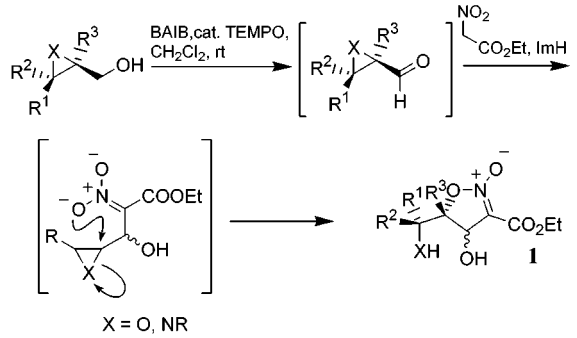
disclosed that enantiopure 2,3-epoxy alcohols can be directly converted to the corresponding 4,5-dihydroisoxazoles of type **1**,[10] without the need to isolate or even manipulate the intermediate aldehyde (Scheme 1, X = O).

Scheme 1. One-Pot Conversion of 2,3-Epoxy Alcohols into 4,5-Dihydroisoxazoles **1**



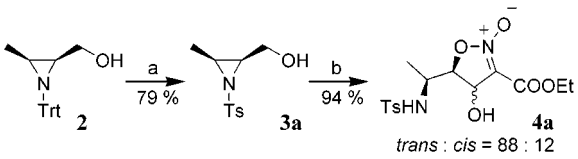
In this paper, we wish to report the extension of this one-pot multibond-forming process to the use of enantiomerically pure aziridine alcohols as the starting materials. A solid-phase version of this reaction will also be discussed.

2,3-Aziridine alcohols are valuable building blocks for diastereoselective reactions and can be obtained in either enantiomeric configuration from a variety of convenient sources, including 2,3-epoxy alcohols.[11] Moreover, the 4,5-dihydroisoxazole derivatives that would arise from 2,3-aziridine alcohols will give, after N-deoxygenation[9,10] and reductive ring cleavage,[1] linear polyhydroxylated 2,5-diaminoalkanes, some of which are known to be selective inhibitors of the HIV-1 protease.[12]

i. Selection of a Suitable N-Substitution. The use of aziridines, instead of epoxides, poses the question of how to fill the additional valence on nitrogen.[13] By studying this, we will also have a better understanding of the driving force involved in the final step of the one-pot procedure, the 4,5-dihydroisoxazole ring closure with concomitant opening of the three-membered ring (Scheme 1).

Initially, we focused on nonactivated *N*-trityl-2,3-aziridine alcohols. Following a known methodology,[14] (*S*)-threonine methyl ester hydrochloride was converted into aziridine alcohol **2** (Scheme 2).

Scheme 2. Direct Conversion of *N*-Tosyl Aziridine Alcohol **3a** to the Corresponding 4,5-Dihydroisoxazole **4a**[a]



[a] (a) TFA, −78 °C, then TsCl, Et_3N −40 to 0 °C; (b) BAIB, catalytic TEMPO, rt, 5 h, then ethyl nitroacetate, ImH, 20 h, rt.

When alcohol **2** was subjected to the same one-pot reaction conditions depicted in Scheme 1 (X = NTrt), the monitoring of the reaction by TLC revealed the formation of the corresponding aldehyde and its subsequent consumption upon addition of the base and ethyl nitroacetate. However, no 4,5-dihydroisoxazole was detected in the reaction mixture. This is probably due to the failure of the final ring-closure step, indicating that a nonactivated aziridine nitrogen atom cannot act as a leaving group. Therefore, we decided to try the *N*-tosyl group as a more activating N-substitution, performing the direct switch from the *N*-trityl to the *N*-tosyl group.[15] Application of the reaction conditions depicted in Scheme 1 to *N*-tosyl aziridine alcohol **3a** furnished the desired 4,5-dihydroisoxazole **4a** in a 94% yield as an 88:12 mixture of 4,5-trans:4,5-cis isomers (Scheme 2). This observation thus demonstrates that activation of the heteroatom of the aziridine ring is needed for it to serve as a leaving group in the final 4,5-dihydroisoxazole ring closure.

We also investigated whether N-activation alone (without aziridine ring strain) is sufficient for 4,5-dihydroisoxazole ring formation. In fact, we knew that the intramolecular cyclization step does take place with the oxygenated equivalent when linear α-tosyloxyaldehydes are employed as the starting materials.[9] For this purpose, we prepared the (*S*)-phenylalaninol derivatives **5a**−**c**[16] (Figure 1) with increasing electron-withdrawing substitutions on the nitrogen atom. However, under the same conditions, all of these substrates failed to give the corresponding 4,5-dihydroisoxazoles.

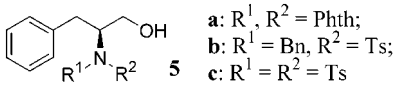


Figure 1.

Thus, contrary to what we found for oxygen, in the case of nitrogen, both the three-membered ring strain and het-

(9) Marotta, E.; Baravelli, M.; Maini, L.; Righi, P.; Rosini G. *J. Org. Chem.* **1998**, *63*, 8235.

(10) Marotta, E.; Micheloni, L. M.; Scardovi, N.; Righi, P. *Org. Lett.* **2001**, *3*, 727.

(11) (a) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Tetrahedron Lett.* **1999**, *40*, 981. (b) Andres, J. M.; de Elena, N.; Pedrosa, R.; Perez-Encabo, A. *Tetrahedron* **1999**, *55*, 14137. (c) Nayak, S. K.; Thijs, L.; Zwanenburg, B. *Synlett* **1998**, 1187. (d) Hwang, G. I.; Chung, J. H.; Lee, W. K. *J. Org. Chem.* **1996**, 6183.

(12) Kohl, N. E.; Emini, E. A.; Schleif, W. A.; Davis, L. J.; Heimbach, J. C.; Dixon, R. A: F.; Scolnick, W. M.; Sigal, I. S. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 4686. Schreiner, E. P.; Gstach, H. *Synlett* **1996**, 1131. Ettmayer, P.; Hübner, M.; Gstach, H. *Tetrahedron Lett.* **1994**, *35*, 3901.

(13) Unprotected aziridine alcohols or aldehydes are rather unstable.

(14) Okawa, K.; Nakajima, K. *Biopolymers* **1981**, *20*, 1811. cf.: Willems, J. G. H.; Hersmis, M. C.; de Gelder, R.; Smits, J. M. M.; Hammink, J. B.; Dommerholt, J.; Thijs, L.; Zwanenburg, B. *J. Chem. Soc., Perkin Trans. 1* **1997**, 963.

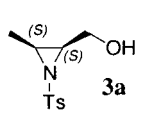
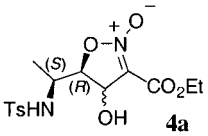
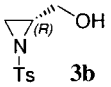
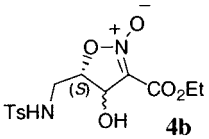
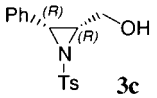
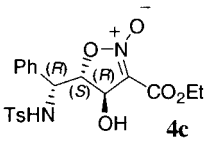
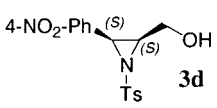
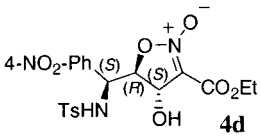
(15) Fujii, N.; Nakai, K.; Habashita, H.; Hotta, Y.; Tamamura, H.; Otaka, A.; Ibuka T. *Chem. Pharm. Bull.* **1994**, *42*, 2241.

(16) Compounds **5a**−**c** were prepared by adapting the procedures found in the following references. **5a**: Backer, Y.; Eisenstadt, A.; Stille, J. K. *J. Org. Chem.* **1980**, *45*, 2145. **5b**: Jurczak, J.; Gryko, D.; Kobrycka, E.; Gruza, H.; Prokopowicz, P. *Tetrahedron* **1998**, *54*, 6051. **5c**: DeChristopher, P. J.; Adamek, J. P.; Lyon, G. D.; Klein, S. O.; Baumgarten, R. J. *J. Org. Chem.* **1974**, *39*, 3525.

eroatom activation are necessary for the final step of the process to occur.

ii. Solution-Phase Process. After these preliminary results, we prepared three more aziridine alcohols **3b**−**d** (see Table 1) from commercially available (*S*)-serine methyl ester

Table 1. One-Pot Formation of 4,5-Dihydroisoxazoles **4**

starting material	products	yield[a] (%)	*trans:cis* ratio
 **3a**	 **4a**	94	88:12
 **3b**	 **4b**	75	42:58
 **3c**	 **4c**	92	100:0
 **3d**	 **4d**	55	100:0

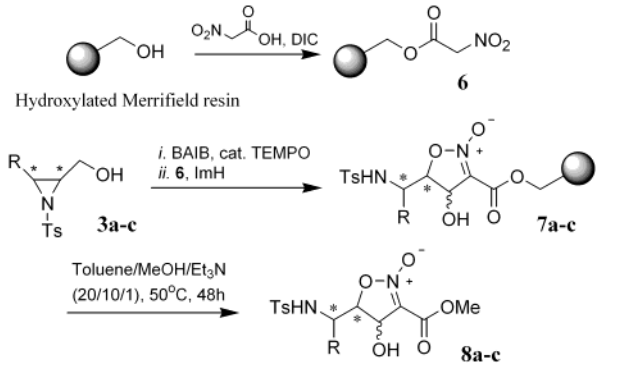
[a] Conditions: BAIB, catalytic TEMPO, rt, 5 h, then ethyl nitroacetate, ImH, 20 h, rt.

hydrochloride, (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol, and (1*R*,2*R*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol (the free base of choramphenicol), respectively. The one-pot conditions applied for the reaction shown in Scheme 1 for the epoxy alcohols were used for the aziridine alcohols. According to this methodology, oxidation[17] of the alcohol moiety, employing bisacetoxyiodobenzene (BAIB) as the stoichiometric oxidant and tetramethylpiperidinyloxy radical (TEMPO) as the catalyst, smoothly converted 2,3-aziridine alcohols **3** to the corresponding aldehydes in 4−5 h at room temperature. Upon in situ addition of imidazole and ethyl nitroacetate, the corresponding 4-hydroxy-4,5-dihydroisoxazole 2-oxides **4** were obtained after stirring for 20 h at room temperature. The results of this one-pot three-bond-forming process are reported in Table 1. The overall yields of this one-pot direct conversion of 2,3-aziridine alcohols into enantiomerically pure 4,5-dihydroisoxazole derivatives are more than satisfactory, except for that of the product **4d**. This lower yield is probably due to the extremely low solubility of **4d** in all the common organic solvents. The only way we found to isolate it was by direct crystallization from the crude reaction mixture. The final 4,5-dihydroisoxazole ring closure is completely regiospecific and proceeds through a 5-*exo* nucleophilic attack on the 2-position of the aziridine ring. The process is increasingly trans selective as the steric hindrance of the C^3-substituent of the aziridine alcohol increases, becoming stereospecific for substrates **3c** and **3d**.[18]

In the case of the pair of products **4a**, the diastereoisomers could be separated directly by flash column chromatography. However, products **4b** could not be separated as such or as their corresponding *tert*-butyldimethylsilyl ether.[9]

iii. Solid-Phase Process. A solid-phase version of the above methodology requires the immobilization of one of the two starting materials. Because product variation in the target compounds results from the different aziridine alcohols employed, the logical starting material to immobilize is the nitroacetic ester. The polymer-bound nitroacetate **6** was prepared in high yield by reacting nitroacetic acid[19,20] with hydroxymethyl polystyrene[21] in the presence of diisopropylcarbodiimide (DIC)[22] (Scheme 3).

Scheme 3. Solid-Phase Approach to the One-Pot Nitroaldol-Cyclization Procedure



The formation of the polymer-bound nitroacetate was monitored by the infrared absorptions at 1565 cm^{-1} (nitro group) and 1755 cm^{-1} (ester). Moreover, completion of the coupling reaction could be observed by the disappearance of hydroxyl absorption (3572 cm^{-1}, free; 3446 cm^{-1}, hydrogen bonded).

N-Tosyl aziridine alcohols **3a**−**c** were selected for the parallel solid-phase approach. According to the solution-phase approach, the aziridine alcohols were converted into the corresponding aldehydes by TEMPO/BAIB oxidation. Subsequent treatment of the aziridine aldehyde with polymer-bound nitroacetate in the presence of imidazole resulted in the formation of the polymer-supported nitroaldol-cyclization reaction (Scheme 3). The course of this reaction was followed

(17) Piancatelli, G.; Margherita, R.; De Mico, A.; Parlanti, L.; Vescovi, A. *J. Org. Chem.* **1997**, *62*, 6974.

(18) The assignment of relative stereochemical configuration 4,5-trans or 4,5-cis is based on the value of the coupling constant between C^4H and C^5H in the ^1H NMR spectrum (J_{cis} = 6.5−6.6 Hz, J_{trans} = 1.9−3.0 Hz). The evaluation of the relative amount of the two isomers is based on the integration of the C^5H signal and on HPLC analysis of the mixtures.[5]

(19) Zen, S.; Koyama, M.; Koto, S. *Org. Synth.* **1976**, *55*, 77.

(20) Armarego, W. L. F. *J. Chem. Soc. C* **1969**, 986.

(21) Hydroxymethyl polystyrene (100−200 mesh, 1% DVB, loading 0.68 mequiv/g) was purchased from Novabiochem and used as received.

(22) A similar procedure was recently reported for Wang resin: Kuster, G. J.; Scheeren, H. W. *Tetrahedron Lett.* **2000**, *41*, 515. See also: Sylvam, C.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* **1999**, *40*, 875.

by the disappearance of the infrared nitro absorption at 1565 cm^{-1}. The presence of a typical band at 1625 cm^{-1} (C═N) in the final product confirmed the successful formation of the five-membered heterocyclic target compound on the solid support (**7**). Fortunately, no large excess of the solution component (the aldehyde) is necessary to drive the process to completion since only a 0.1 equiv excess is needed to observe complete disappearance of the IR nitro group absorption in a reasonable reaction time.

Detachment of the 4,5-dihydroisoxazole derivatives from the resin was achieved by means of base-induced transesterification with methanol to give the free methyl esters **8**. In all cases, triethylamine was used as the base. Fine-tuning of the conditions for cleavage demonstrated that the most efficient transesterification was achieved in a 20/10/1 toluene/methanol/triethylamine mixture. In this solvent system, complete detachment took place at 50 °C within 48 h (Scheme 3). It is worth noting that the same reaction using ethanol, instead of methanol, did not go to completion under these optimized conditions, even after a reaction time of 6 days. Complete removal of the target compound from the resin was ascertained by infrared spectroscopy. No absorption at 1625 and 1737 cm^{-1} could be detected in the resulting polymer. The overall yields of this solid-phase nitroaldol-cyclization reaction and cleavage steps range from good (72%, R = H) to very good (quantitative yield, R = Me). The trans:cis ratios are, to some extent, different from those observed for the solution-phase counterparts. For R = H, the trans:cis ratio amounts to 66:34, as opposed to the 42:58 trans:cis ratio found in solution. For R = Me or Ph, the resulting trans:cis ratios are practically the same as those found in solution (see Table 2).

In conclusion, we have shown that our one-pot tandem procedure reported in Scheme 1 can be further extended to enatiomerically pure *N*-tosyl 2,3-aziridine alcohols, leading to a new class of enantiopure 4-hydroxy-4,5-dihydroisoxazole 2-oxides in solution. The starting aziridine alcohols can be obtained in a few steps from natural amino acids or readily available chiral amino alcohols. The overall yields of the sequence from the commercially available starting chiral building blocks are in the range of 33−63%. Moreover, we have shown that this procedure can also be used in a solid-phase approach, with no modification even in the stoichiometry of the reactants. This solid-phase procedure is a convenient way to rapidly prepare solid-supported 4,5-dihydroisoxazole derivatives and offers an attractive starting point for further on-resin elaboration of the enantiopure 5-aminoalkyl-4-hydroxy-4,5-dihydroisoxazole 2-oxides.

Table 2. Solid-Phase One-Pot Formation of Isoxazoles **8**

starting material	yield (%)	trans:cis ratio
3a	Quant.	92:8
3b	72	66:34
3c	82	100:0

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Supporting Information Available: Experimental procedures for the preparation of compounds **2**, **3a**−**d**, **4a**−**d**, **6**, **7a**−**c**, and **8a**−**c**; actual ^{1}H and ^{13}C NMR spectra of 4,5-dihydroisoxazoles **4a**−**d**; and actual IR spectra of solid-supported 4,5-dihydroisoxazoles **7a**−**c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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