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LETTERS

Enantioselective Preparation of 3,4,5-Trisubstituted-4,5-dihydroisoxazoles and 4-Substituted-5,6-dihydro-4*H*-[1,2]-oxazines by Nitrile Oxide Cycloaddition to α-Silyl Allyl Alcohols

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Abstract: Regio- and stereoselective 1,3-dipolar cycloaddition of nitrile oxide to optically active α-silyl allyl alcohol provides a useful preparation of 3,4,5-trisubstituted 4,5-dihydroisoxazoles, which are readily converted into chiral 4-substituted 5,6-dihydro-4*H*-[1,2]-oxazines in 73-100% yields on treatment with TBAF. © 1999 Elsevier Science Ltd. All rights reserved.

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4,5-Dihydroisoxazoles are regarded as useful synthetic building blocks for open-chain aliphatic compounds because they can be readily converted into γ-amino alcohols or β-hydroxy ketones through reductive N-O bond cleavage.[1] Despite their promising potential, however, they have not been utilized widely in organic synthesis because of the existence of several crucial problems in preparing 4,5-dihydroisoxazoles. Although 1,3-dipolar cycloaddition of nitrile oxides to alkenes is the most direct way to access 4,5-dihydroisoxazoles, this strategy sometimes incurs problems in the yield and/or regio- or stereoselectivity of the reaction.[2] For example, benzonitrile oxide undergoes the 3 + 2 cycloaddition with methyl crotonate to give a mixture of two regioisomeric 4,5-dihydroisoxazoles in about 2:1 ratio.[3] To overcome these drawbacks of the reaction,[4] we have recently discovered a good solution, in which the nitrile oxide cycloaddition to allylic alcohols was accelerated in the presence of a magnesium ion, and the regio/stereoselectivity was effectively controlled to give a single isomer of 4,5-dihydroisoxazoles.[5] On the other hand, optically active α-silyl alcohols have been often used as a chiral equivalent of achiral primary alcohol since protiodesilylation induced by the fluoride anion regenerates non-silylated alcohols in the retention of configuration.[6] In this paper, we report a facile method to prepare non-racemic 4,5-dihydroisoxazoles from optically active α-silyl allyl alcohols with this methodology. A novel preparation of optically active 5,6-dihydro-4*H*-[1,2]-oxazines induced by the fluoride anion is also described.

Optically active α-silyl allyl alcohols **1** were prepared in three steps from allyl alcohols: first of all, allyl alcohols were converted into α-silyl allyl alcohols *via* retro-Brook rearrangement.[7] The resulting alcohols were

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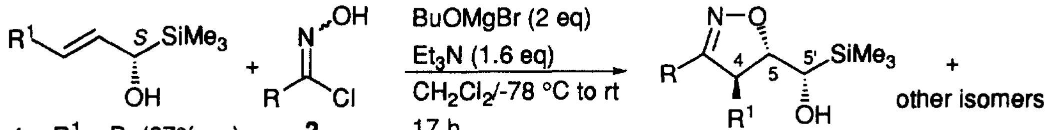
oxidized to acylsilane, which were then reduced with (+)-DIP-Cl to give (*S*)-1 in 85-87% ee.[8] Our present method is shown in Scheme 1. The cycloaddition was examined in a procedure we had reported previously and the desired optically active 4,5-dihydroisoxazoles **3** were isolated in almost diastereomerically pure form. The results are summarized in Table 1.



1a; R^1 = Pr (87% ee) **2**

1b; R^1 = Me (85% ee) (5*S*,5'*S*)-**3**

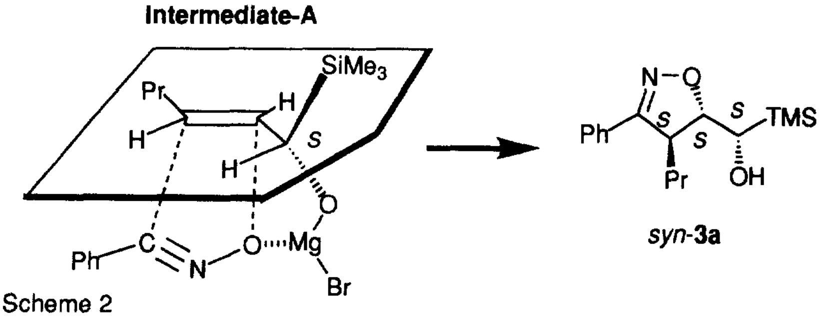
Scheme 1

Table 1 Preparation of optically active 4,5-dihydroisoxazoles **3** from chiral α-silyl allyl alcohols **1**.

Entry	R^1	R	Product	Yield (%)[a]	Ratio[b]	$[\alpha]_D$
1	C_3H_7-	Ph	**3a**	75	94:6	+130.4
2	C_3H_7-	*p*-Cl-C_6H_4-	**3b**	52	97:3	+124.8
3	C_3H_7-	$PhCH_2CH_2$-	**3c**	40	99:1	+91.0
4	C_3H_7-	*p*-CF_3-C_6H_4-	**3d**	32	98:2	+124.9
5	Me	Ph	**3e**	59	94:6	+113.3
6	Me	*p*-Cl-C_6H_4-	**3f**	58	95:5	+121.9
7	Me	*p*-CF_3-C_6H_4-	**3g**	45	99:1	+99.0

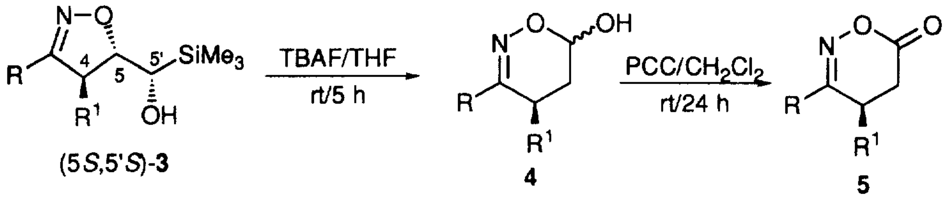
[a] Isolated yield. [b] Determined by HPLC analysis with ChiralCel OD-H or ChiralPak AD.

Cycloadducts **3** were obtained in moderate to good yields. In all cases, the major isomers of **3**, which were formed with more than 94:6 diastereoselectivity, were purified through simple chromatographic treatment. All cycloadducts **3** showed positive optical rotation. HPLC analyses on ChiralCel OD-H or ChiralPak AD indicated that enantiomeric excesses of the starting dipolarophies **1** and the major adducts **3** were almost identical. The stereochemistry of the cycloadduct **3a** proved to be 5*S*,5'*S* which was clearly determined by X-ray crystallographic analysis.[9] Consequently, the stereochemical course of the cycloaddition is analogous to the results we have reported, in which the allylic alkoxide and the nitrile oxide coordinate to the magnesium ion to form intermediate A, which undergoes cycloaddition to give 5*S*,5'*S*-**3a** selectively (Figure 1).



Scheme 2

The obtained chiral isoxazoline **3** should be a potentially useful synthetic building block. We next attempted to remove the silyl group to convert to 5-hydroxymethyl-4,5-dihydroisoxazoles (Scheme 3). The results are summarized in Table 2.



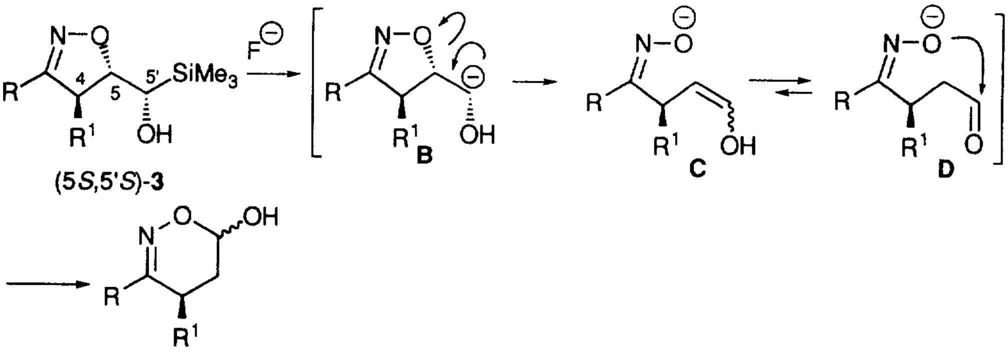
Scheme 3

Table 2 Conversion of 4,5-dihydroisoxazoles **3** to 5,6-dihydro-4*H*-[1,2]-oxazines **4** and **5**.

Entry	R^1	R	4;	Yield (%)^a	5	Yield (%)^a	[α]$_D$
1	C_3H_7-	Ph	**4a**	100	**5a**	67	+55.1
2	C_3H_7-	*p*-Cl-C_6H_4-	**4b**	92	**5b**	80	+37.1
3	C_3H_7-	$PhCH_2CH_2$-	**4c**	73	**5c**	56	+65.8
4	C_3H_7-	*p*-CF_3-C_6H_4-	**4d**	82	**5d**	72	+33.1
5	Me	Ph	**4e**	86	**5e**	56	+33.7
6	Me	*p*-Cl-C_6H_4-	**4f**	89	**5f**	86	+21.6
7	Me	*p*-CF_3-C_6H_4-	**4g**	76	**5g**	77	+18.3

a. Isolated yield.

Standard reaction conditions (TBAF/dry THF/room temp.) were examined for adducts **3a**. To our surprise, however, none of the desired desilylated alcohol was observed in the reaction mixture, but optically active 5,6-dihydro-4*H*-[1,2]-oxazine **4a** was isolated in a quantitative yield instead. Use of wet THF resulted in complete recovery of the starting **3**. A hemiacetal unit in compound **4a** produced a mixture of two diastereomers, whose ratio was about 2:1. To check the optical purity of **4a**, PCC oxidation was carried out; oxazinone **5a** was isolated in good yield. HPLC analysis for **5a** in ChiralPak-AD revealed that the enantiomeric excess of **5a** was 81% ee, which was almost identical to the ee value for **3a**, 82% ee.



Scheme 4 **4**

We assume the reaction pathway to be as follows (Scheme 4); initially, the fluoride anion generates an α-anion of hydroxymethyl group **B**, from which an oximate anion eliminates to give enol intermediate **C**. Through the keto-enol tautomerism, intermediate C isomerizes to aldehyde **D**, which is then intramolecularly attacked by the oximate anion to give oxazine acetal **4**.

In conclusion, optically active 4,5-dihydroisoxazoles are readily prepared from chiral α-silyl allyl alcohol *via* 1,3-dipolar cycloaddition of nitrile oxide in the presence of a magnesium ion. Treatment of the adducts with a fluoride anion provides a novel preparation of optically active 5,6-dihydro-4*H*-[1,2]-oxazines in 73-100% yield.[10] Further conversion and application for these compounds are now under investigation in our laboratory.

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