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Diastereoselective Additions of Organolithium and Organomagnesium Reagents to the C=N Bond of A Chiral, Cyclic Nitrone Derived from Erythrulose

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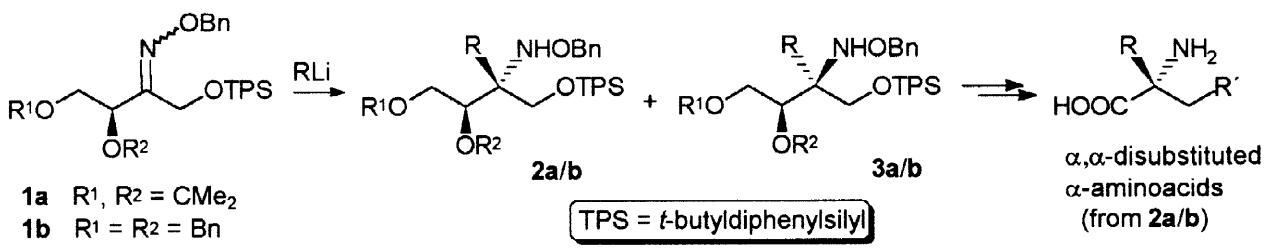
Abstract: The reaction of the 3,4-O-isopropylidene-L-(S)-erythrulose with hydroxylamine, followed by treatment of the resulting mixture of (E)- and (Z)-oximes with acetone and an acid catalyst, afforded two crystalline chiral compounds. Through X-ray diffraction analysis, these products were identified as a double acetonide derived from the (E)-oxime and a cyclic nitrone derived from the (Z)-oxime. The additions of organolithium and organomagnesium reagents to the C=N bond of the nitrone were found to be diastereoselective. The addition products are useful intermediates for the preparation of α,α-disubstituted α-aminoacids and other nitrogen-containing compounds in enantiopure form.

The addition of carbon nucleophiles to C=N bonds[1] is a synthetically important method of preparing various types of compounds of pharmacological utility. Among these, amino polyols[2] and non-proteinaceous amino acids[3] have attracted a particular interest. The latter, for example, are needed for the synthesis of enzyme inhibitors and peptidomimetics.[4] We have recently reported on the diastereoselective addition of organolithium reagents to the C=N bond of chiral ketoxime ethers **1a/1b**, where the differentially protected amino polyols **2a/b** and/or **3a/b** are formed.[5] We have then shown that these can be converted into enantiopure α,α-disubstituted α-amino acids,[6] a particularly interesting type within the non-proteinaceous amino acids.



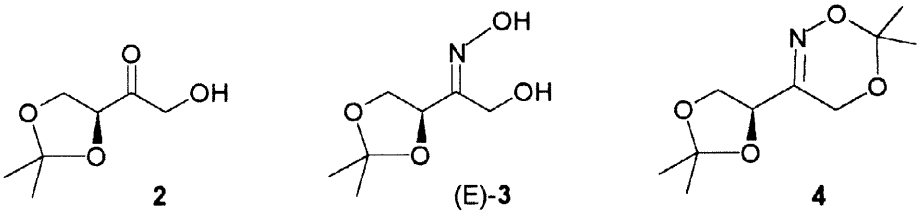
1a R^1, R^2 = CMe_2
1b R^1 = R^2 = Bn

2a/b **3a/b**

TPS = *t*-butyldiphenylsilyl

α,α-disubstituted α-aminoacids (from **2a/b**)

In search of an alternative way of obtaining compounds of this structural type, we wondered whether oxime (E)-**3**, to be prepared from erythrulose acetonide **2**,[7] would react with acetone to yield dioxazine **4**, which is a formal double acetonide of erythrulose (E)-oxime. This compound might be a cheaper surrogate of the somewhat expensive O-benzyl oximes (E)-**1a** or (E)-**1b**.



2 (E)-**3** **4**

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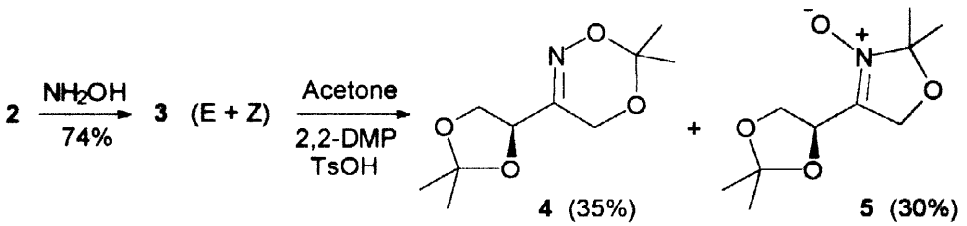
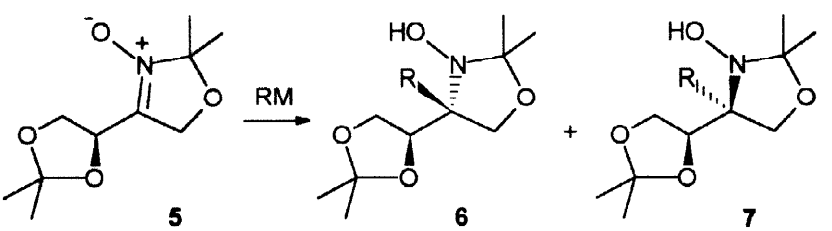
In fact, acetonide **2** was treated with hydroxylamine to yield oxime **3** as a mixture of (E) and (Z) stereoisomers. Reaction of this mixture with acetone/2,2-dimethoxypropane in the presence of an acid catalyst and chromatographic separation furnished two crystalline compounds, **4** and **5**, with the molecular formula $C_{10}H_{17}NO_4$. As a result of X-ray diffraction analyses,[8] the less polar compound was shown to be the expected dioxazine **4**, obviously derived from oxime (E)-**3** by formation of a second O,O-acetal ring. The more polar compound was nitrone **5**, the formation of which is explained by formation of a N,O-acetal ring in oxime (Z)-**3**.

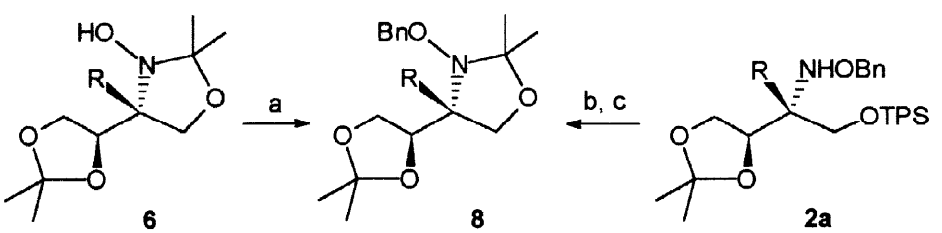


We then investigated the reactivity of the imino carbon atom of these compounds towards organometallic reagents. In contrast with our expectations, the cyclic oxime **4** proved completely unreactive towards all organometallic reagents we essayed, either in the presence or absence of Lewis acids. Fortunately, nitrone **5** displayed a synthetically useful reactivity. Not only organolithium but also organomagnesium reagents reacted with the C=N bond of **5** to yield mixtures of the heterocyclic derivatives **6** and **7**. Table 1 shows the results of these organometallic additions. The hindered reagent *tert*-butylmagnesium bromide did not react with **5**. *Tert*-butyllithium caused decomposition, in contrast with that observed with oxime (E)-**1a**.[5] It is noteworthy that stereoisomer **6** is the major or exclusive isomer formed in all cases.



The configuration of the newly formed stereocentre was deduced from the chemical correlations depicted in Scheme 1. Benzylation of the N-hydroxy group of **6** afforded compounds of general formula **8**. The same compounds were also obtained from products **2a** of known configuration[5] by desilylation followed by N,O-acetal ring formation.

Scheme 1



Reaction conditions. a) NaH, THF, then BnBr, TBAI, RT, 12 h. b) TBAF, THF, RT, 12 h. c) Me_2CO, 2,2-dimethoxypropane, TsOH, RT, 12h.

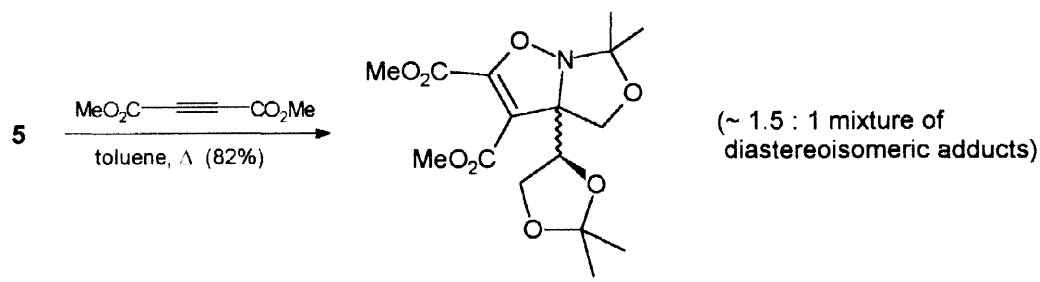
Table 1. Stereoisomer Distribution in the Addition of Organometallic Reagents to Nitrone **5**.[a]

Entry	RM	T[b]	Yield[c]	**6** / **7**[d]
1	MeLi	—78	80	91 : 9
2	MeLi	0	78	91 : 9
3	*n*BuLi	—78	74	90 : 10
4	*t*BuLi	—78	Dec.	
5	PhLi	—78	75	85 : 15
6	allylLi	—78	60	70 : 30
7	MeMgCl	—78	70	75 : 25
8	EtMgCl	—78	79	87 : 13
9	vinylMgCl	—78	68	90 : 10
10	HC≡CMgCl	0	72	90 : 10
11	HC≡CMgCl	—78	No r.	
12	allylMgBr	—78	50	70 : 30
13	PhMgBr	—78	76	>95 : 5
14	BuMgBr	—78	75	83 : 17
15	*t*BuMgBr	25	No r.	

[a]All reactions were performed in Et_2O. The reaction time was 1 hour in all cases. [b]In degrees (°C). [c]Overall yield (%) of both stereoisomers. [d]Determined by $^1H/^{13}C$ NMR.

It turns out therefore that the nucleophillic additions of either organolithium or Grignard reagents to the C=N bond of **5** take place with the same steric course as that observed in the reactions of (E)-**1a** with organolithium derivatives. As a matter of fact, nucleophillic additions to chiral nitrones have often been used for the synthesis of many types of nitrogen-containing compounds.[9] Various mechanistic models have been proposed to explain the stereochemical outcome of such additions, which have in most cases been performed on *nitrones derived from α- and/or β-oxygenated aldehydes*. It has been suggested that the mechanistic models developed for stereoselective reactions in alkenes and enolates are more suitable than those normally used for carbonyl additions.[9] Some of these models involve chelation of the metal with the nitrone oxygen and a proximal oxygen atom. A similar chelation mechanism might also be invoked here in order to account for the observed results in nucleophilic additions to **5**, *a nitrone formally derived from a ketone*. However, we cannot provide any sound experimental proof to support this or any other mechanistic proposal. Computational studies on nucleophillic additions to **5** are currently being performed in order to ascertain the origin of the stereoselectivity.

Nitrone **5** can be expected to undergo 1,3-dipolar cycloadditions to suitable dipolarophiles.[10] Although only preliminary results are available as yet, **5** has been found to react with dimethyl acetylene dicarboxylate in refluxing toluene to yield a mixture of both possible cycloadducts (see next scheme). The process displayed, however, a low stereoselectivity, as both stereoisomeric adducts were obtained in a 1.5:1 ratio. The configurations of the individual adducts have not yet been assigned. Further cycloadditions of **5** to other dipolarophiles are being currently investigated. Their results will be published in due course, together with the corresponding theoretical calculations.



The methodology we describe in this communication represents an useful alternative to our previous protocol[5] for the preparation of α,α-disubstituted α-amino acids and related chiral, nitrogen-containing compounds. Work in this direction is now underway.

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