Regiocontrol of Nitrile Oxide Cycloadditions to Allyl Alcohols. Synthesis of 4-Substituted and 4,4-Disubstituted 5-Hydroxymethyl-2-isoxazolines

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Abstract: The first regiocontrol of nitrile oxide cycloadditions is described. Reaction of benzonitrile oxide with (E)-2-butenol is highly accelerated by the presence of a magnesium alkoxide, and this reaction proceeds in an exclusively regioselective manner to produce 5-hydroxymethyl-4-methyl-3-phenyl-2-isoxazoline as the sole cycloadduct. Synthetic applications to other substituted allyl alcohols are discussed.

The well established high synthetic utility of 2-isoxazolines is due to their synthetic equivalency of a wide variety of important functionalized building blocks such as β -hydroxy ketones, β -amino alcohols, α , β -unsaturated ketones, and related functionalities.¹ Nitrile oxide cycloaddition offers the most useful access to 2-isoxazoline skeletons in which one carbon-carbon bond forming process is involved. Cycloadditions of nitrile oxides with terminal olefins (monosubstituted olefins) proceed readily and in an exclusively regioselective manner, regardless of the nature of the substituent (electron-withdrawing, -donating, alkyl, aryl, heteroatom type substituents, etc), leading to the 5-substituted 2-isoxazoline derivatives.² However, reactions with 1,2-disubstituted olefinic dipolarophiles are disappointingly decelerated and besides the regioselectivity is extremely lowered even when these substituents are electronically different types, e.g. an alkyl or aryl vs an acyl or ester group.³ Situation is worse in the reactions with 1,1,2-trisubstituted ethenes.

We have recently reported the chelation-controlled highly diastereoselective cycloadditions of nitrile oxides to allyl alcohol derivatives;⁴ this offered the first example of the Lewis acid-assisted stereocontrol of 1,3-dipolar cycloadditions. The nitrile oxide/Lewis acid complexes, generated from hydroximoyl chlorides and organometallics, undergo *syn*-selective cycloadditions to the allyl alcohols bearing an α -chirality. The present communication describes an efficient rate acceleration and an exclusively high regiocontrol, that have been discovered in the study of nitrile oxide cycloadditions to allyl alcohol derivatives.



Scheme 1

Reaction of (E)-2-butenol (1a, X = H) with benzonitrile oxide (3) produces a mixture of regioisomeric cycloadducts 4a and 5a (Scheme 1).⁵ Both the regioselectivities and the yields of products were very poor when (1) 1a (X = H) was reacted with 3 generated from benzohydroximoyl chloride (2)/NEt₃ (Table 1, Entry 1) or 2/EtMgBr (Entry 2), (2) alkoxides 1a (X = Li, EtZn, Et₂Al) were reacted with 3 generated from 2/NEt₃ (Entries 3, 5, 6), or (3) alkoxide 1a (X = Li) was reacted with 3 generated from 2/n-BuLi (Entry 4). It was surprising that reaction of magnesium alkoxide 1a (X = MgBr) with the nitrile oxide 3 generated from 2/NEt₃ resulted in a satisfactory yield and a high regioselectivity (Entry 7).

Entry	X of 1a (equiv)	Base (equiv)	Additive (equiv)	Temp/°C	Time/h	Yield/%b	4a:5ac
1	H (1)	NEt ₃ (1)	_	rt	1.5	46	46:54
2	H (1)	EtMgBr (1)	LORGE	30	17	20	55:45
3	Li (1)	NEt ₃ (1)		rt	0.5	10	49:51
4	Li (1)	<i>n</i> -BuLi (1)	-	n	0.5	13	60:40
5	EtZn (1)	NEt ₃ (1)		rt	0.5	9	46:54
6	$Et_2Al(1)$	NEt ₃ (1)		rt	0.5	14	48:52
7	MgBr (1)	NEt ₃ (1)	_	rt	0.5	62	96:4
8	MgBr (1)	_		гt	27	9	88:12
9	MgBr(2)	-		-30	66	63	98:2
10	MgBr (2)			rt	0.5	82	99:1
11	MgBr (2)		<i>i</i> -PrOH (2)	rt.	0.5	92	97:3
12	MgBr (2)		<i>n</i> -BuOH (2.2)	rt	3.5	75	98:2
13	MgCl(1)	t-BuMgCl (1)	-	rt	0.5	47	96:4
14	MgBr(1)	EtMgBr (1)	_	rt	0.5	62	96:4
15	MgI (1)	MeMgI (1)		T!	0.5	10	98:2
16	MgBr (1)	n BuLi (1)	-	rt	0.5	55	95:5
17	MgBr (1)	<i>i</i> -PrOLi (1)		rt	0.5	62	96:4
18	Li (1)	EtMgBr (1)		rt	2.5	66	>99:1
<u>19</u>	Li (1)	EtMgBr (1)	с	rt	5	41	9 <u>3:7</u>

Table 1. Cycloadditions of Benzonitrile Oxide to (E)-2-Buten-1-ol Leading to 4a and 5a^a

^aAll reactions were performed in dichloromethane. ^bIsolated yield. ^cDetermined on the basis of ¹H NMR of the crude product. ^cSolvent: THF.

When 2 equivalents of magnesium alkoxide $\mathbf{1a}$ (X = MgBr) were used also as a base for the generation of nitrile oxide 3, higher yields of $\mathbf{4a}$ resulted, essentially as a single regioisomer (Entries 9, 10). This makes a striking contrast with the result obtained in a similar reaction using one equivalent of $\mathbf{1a}$ (X = MgBr, Entry 8). The complex 3•MgBrCl was certainly generated as reacting intermediate in the case of Entry 10,⁴ and they underwent competitive cycloadditions with two dipolarophiles $\mathbf{1a}$ (X = H and MgBr). By comparison with the extremely poor regioselectivity observed in Entry 2, the followings are concluded: (1) the reaction of 3 to magnesium alkoxide $\mathbf{1a}$ (X = MgBr) proceeds much more rapidly than that to $\mathbf{1a}$ (X = H), (2) this reaction is very clean and exclusively regioselective, (3) the high regioselectivity is not affected by the presence of $\mathbf{1a}$ (X = H) of the free alcohol type. Actually, no significant decrease of regioselectivity was observed by addition of an alcohol additive, both primary and secondary (Entries 11, 12). Instead, the reaction became much cleaner to give a higher yield of $\mathbf{4a}$ (92%) in the presence of *i*-PrOH.

Screening of various reaction conditions concluded that the use of magnesium alkoxides 1a (X = MgX) was essential for the exclusively high regioselectivity (Entries 13-17). However, reaction of the nitrile oxide 3 generated from 2/EtMgX with the lithium alkoxide 1a (X = Li) was also highly regioselective (Entry 18), and surprisingly, no decrease of regioselectivity in THF was observed (Entry 19).⁶ Such high selectivities seem to be inconsistent with the results of Entries 3, 4. An explanation is as follows: The high selectivities in

reactions of the complex 3•LiCl generated from 2/n-BuLi or 2/i-PrOLi with 1a (X = MgBr, Entrics 16, 17) are understanding. Both 1a (X = Li) and the complex 3•MgBrCl generated from 2/FtMgBr must be less reactive than the combination of 1a (X = MgBr) and 3•LiCl,⁷ and hence, they have an opportunity to undergo acid/base reaction to form 1a (X = MgBr) and 3•LiCl (Scheme 2).⁸ As a result, the reaction always proceeds via 3•LiCl and 1a (X = MgBr) regardless of the kinds of starting substrates.



Scheme 2

When a mixture of **1a** (X = MgBr) and **1b** (X = H), each 2 equivalents, was reacted with nitrile oxide **3** generated from 2/NEt₃, a 53:47 mixture of regioselective cycloadducts **4a** and **4b** was obtained in 98% of total yield (Scheme 2). This indicates that the alkoxide **1a** (X = MgBr) rapidly equilibrates with the free alcohol **1b** (X = H) and the alkoxides **1a,b** (X = MgBr) predominantly react with **3**. On the basis of these results and the fact that the free nitrile oxide **3** is more reactive than the complex **3**•MX (MX: Lewis acid),⁷ simplification of the procedure was performed as follows.

Table 2. Reactions of **3** with 1a (X = H) in the Presence of *n*-BuOMgBr^a

Entry	n-BuOMgBr	Time/h	Yield/%b	4a:5a ^c
1	0.1 equiv	24	37	57:43
2	0.3	24	29	68:32
3	0.5	24	59	82:18
4	0.8	12	53	97:3
5	1.1	2.5	83	4a only
6	1.3	1	87	4a only

^aSolvent: dichloromethane, ^bIsolated yield, ^bBased on ¹H NMR of the crude product.

The nitrile oxide 3 generated from $2/NE_{13}$ was reacted with the free alcohol 1a (X = H) and *n*-BuOMgBr (Scheme 2). When more than one equivalent of *n*-BuOMgBr was employed, only 4a was obtained in high yields (Table 2, Entries 5, 6). Both the selectivity and the yield were found to depend upon the equimolar amount of *n*-BuOMgBr (Entries 1-3) so that the catalytic reaction could not be attained.

Finally, the nitrile oxide cycloadditions with a variety of substituted allyl alcohols were performed under the reaction conditions that **3**

generated from $2/NEt_3$ was allowed to react with 1a-e (X = H) in dichloromethane in the presence of *n*-BuOMgBr (1.3 equiv). The results are listed in Table 3. To be emphasized are (1) the exclusively high

regioselectivities producing 2-isoxazoline-5-methanols **4a-e** (Entries 1-5) (2) the excellent yields of **4** (Entries 1-4), (3) the effective acceleration of cycloadditions (Entries 3 and 5), (4) the reversed regioselectivity in reactions with (E)-3-phenyl-2-propenol (**1d**) (Entry 4) and 3-methyl-2-butenol (**1e**) (Entry 5).

Entry	Allyl alcohol	R1	R ²	Time/h	Product	Yield/%b	4:5 ^c	
1	1a (X = H)	Me	Н	1	4a	90	Single	(46:54)
2	1b (X = H)	<i>n</i> -Pr	Н	1	4 b	90	Single	(55:45)
3	$\mathbf{le} (\mathbf{X} = \mathbf{H})$	Н	n-Pr	1.5	4c+5c	100	98:2	(–) ^d
4	1d (X = H)	Ph	Н	1.5	4 d	92	Single	(20:80)
5	1e(X = H)	Me	Me	13	4e+5e	47	99:1	(1:99) ^e

Table 3.	Cycloadditions	of Nitrile Ox	ide 3 to S	ubstituted A	Ilyl Alcohols	$la-e (X = H)^a$
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^aSolvent: dichloromethane. ^bIsolated yield. ^cDetermined on the basis of ¹H NMR of the crude product. The ratio in parenthesis is that observed in the reaction of **3** generated from 2/NEt₃. ^dNo cycloadduct was formed. ^eYield: 15% (15 h, at rt).

In conclusion, the highly effective regiocontrol to produce 2-isoxazoline-5-methanol derivatives has been accomplished by the reactions of nitrile oxides, generated through a usual method using hydroximoyl chloride precursors and triethylamine, with substituted allyl alcohols *in the presence of more than one equimolar amount of a magnesium alkoxide*. It is no doubt that the chelated transition state A (Scheme 2) is responsible for the high regiocontrol.

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References and Note

- D. P. Curran, "Advances in Cycloaddition," ed by D. P. Curran, JAI Press, Greenwich (1988), Vol 1, pp 129-89; S. Kanemasa and O. Tsuge, *Heterocycles*, 30, 719 (1990). See also references cited therein.
- P. Caramella and P. Grünanger, "Nitrile Oxides and Imines," as Chapter 3 of Vol 1 of "1,3-Dipolar Cycloaddition Chemistry," ed by A. Padwa, John Wiley & Sons, New York (1984), pp 291-392.
- The regioselectivities (4-acyl:5-acyl or 4-ester:5-ester) observed in the cycloadditions of benzonitrile oxide arc: 68:32 with (E)-1-phenyl-2-buten-1-one and 59:41 with (E)-4-phenyl-3-buten-2-one (G. Bianchi, C. De Micheli, R. Gandolfi, P. Grünanger, P. Vita. Finzi, and O. Vajna de Pava, J. Chem. Soc., Perkin Trans. 1, 1973, 1148); 32:68 with methyl crotonate (M. Christl and R. Huisgen, Chem. Ber., 106, 3345 (1973).
- 4. S. Kanemasa, S. Kobayashi, M. Nishiuchi, H. Yamamoto, and E. Wada, Tetrahedron Lett., 32, 6367 (1991).
- 5. All new compounds discussed here were fully characterized on the basis of spectral and analytical data. As an example, **4a**: Colorless liquid; IR (neat) 3400, 2950, 1450, 1350, 1080, 880, and 770 cm⁻¹; ¹H NMR (CDCl₃) $\delta = 1.30$ (3H, d, $J_{Mc-4} = 7.0$ Hz, 4-Me), 2.80 (1H, br, OH), 3.63 (1H, dq, $J_{4.5} = 5.1$ and $J_{4-Me} = 7.0$ Hz, H-4), 3.66 (1H, dd, $J_{gem} = 12.1$ and $J_{CH_{2-5}} = 5.1$ Hz, one of CH₂OH), 3.75 (1H, dd, $J_{gem} = 12.1$ and $J_{CH_{2-5}} = 5.1$ Hz, one of CH₂OH), 3.75 (1H, dd, $J_{gem} = 12.1$ and $J_{CH_{2-5}} = 4.0$ Hz, the other of CH₂OH), 4.42 (1H, dt, $J_{5-CH_{2}} = 5.1$, $J_{5.4} = 5.1$, and $J_{5-CH_{2}} = 4.0$ Hz, H-5), 7.37-7.42 (3H, m, Ph), and 7.62-7.68 (2H, m, Ph); ¹³C NMR (CDCl₃) $\delta = 17.62$ (4-Me), 43.63 (C 4), 63.25 (CH₂OH), 88.69 (C-5), 127.07, 128.43, 128.85, 130.02 (each Ph), and 161.35 (C-3).
- 6. Such unconcern of the regioselectivity to the polarity of reaction solvent differs from the sharp decrease of diastereoselectivity observed in the nitrile oxide cycloadditions to the allyl alcohols bearing an α -chirality (Ref. 4).
- 7. The nitrile oxide complex 3•MX is less reactive than the free dipole 3. When a stronger Lewis acid is incorporated in the complex, its reactivity decreases (Ref. 4).
- 8. The lithium alkoxide 1a (X = Li) as a stronger Lewis base reacts with MgBrCl as a stronger Lewis acid to produce 1a (X = MgBr) and LiCl, both weaker acid and base. This acid/base reaction must be quite rapid.