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1,3-Dipolar Cycloaddition of 1-Carboxynitrone: Different Stereoselectivity Caused by Salt Effect

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Abstract: *Treatments of 1-carboxynitrone 1 with monosabstituted olefins 2 caused a 1,3-dipolar cycloadditions to give cis-isoxazolidines 3 with high stereoselection. On the other hand, reactions of 1 with olefins in the presence of triethylamine afforded trans-isomers 4 predominantly.*

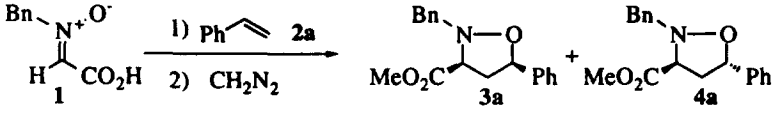
Since γ-hydroxy-α-amino acids are very important parts of biological active compounds such as theonellamide F,[1] neopolyoxins,[2] WS-43708A,[3] and scytonemin A,[4] the developments of various methods that provide stereoselective approaches to this class of compounds are needed to research the bioactive area.[5] Therefore, we have studied 1,3-dipolar cycloaddition of 1-carboxynitrone **1** as a dipolar with some olefins as diporalophiles.

Recently, a number of stereocontrolled intermolecular 1,3-dipolar cycloadditions of nitrone have been reported. For example, Wilcox and his group[6] recorded salt effects in nitrone-olefin cyclization reaction. Kansui and Kunieda[7] found a high *endo*-selectivity in the smectic-phase [3+2] cycloaddition. Kanemasa and his co-workers[8] developed a metal ion-mediated 1,3-dipolar cycloaddition using allylic alcohols as dipolarophiles. Gilbertson et al.[9] discovered an *endo*-selective reaction of α,β-unsaturated hexacarbonyldiiron bridging acyl complexes with nitrones. We now report a novel methodology for the stereoselective production of isoxazolidines, which are useful precursors for γ-hydroxy-α-amino acids, utilizing nitrone **1**[10] possessing carboxyl group at the 1-position.

Reaction of nitrone **1** with styrene (**2a**) proceeded at room temperature to give a 93 : 7 mixture of the 3,5-*cis*- **3a** and *trans*-isoxazolidines **4a** (Table 1, entry 1). On the other hand, treatment of **1** with **2a** in the presence of triethylamine provided a 12 : 88 mixture of **3a** and **4a** (entry 2).[11] No formation of regioisomers was observed under both conditions. Results of the 1,3-dipolar cycloaddition of nitrone **1** and styrene (**2a**) in the presence of various amines are summarized in Table 1. Yields and stereoselectivities of cycloadditions were

determined after esterification using diazomethane. Although the use of butylamine as additive gave a poor yield (entry 5), the addition of bulky amines was favorable for the cycloaddition and resulted in similar stereoselectivity (entries 2 - 4) except for addition of pyridine (entry 6). Stereostructures of **3a** and **4a** were determined by NOE experiments.

Table 1. Effect of Amine on the 1,3-Dipolar Cycloaddition



entry	amine	yield (%)[a]	ratio (**3a** : **4a**)[b]
1	none	75	93 : 7
2	Et_3N	73	12 : 88
3	*i*-Pr_2NH	61	23 : 77
4	*t*-$BuNH_2$	60	9 : 91
5	$BuNH_2$	13	28 : 72
6	Pyridine	67	62 : 38

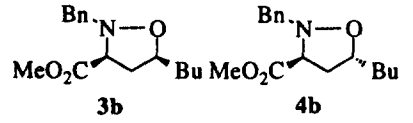
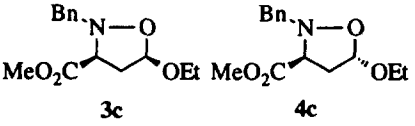
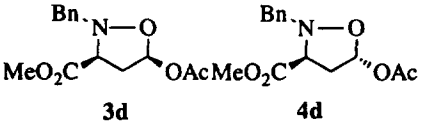
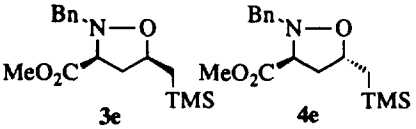
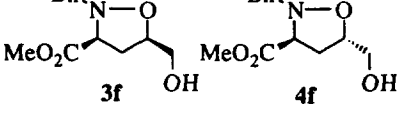
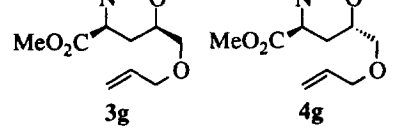
[a] Isolated yields.
[b] Determinded by ^1H NMR integration.

Next, 1,3-dipolar cycloadditions of nitrone **1** with a variety of olefins were examined. The results of the cyclization are presented in Table 2. Almost the same outcomes as above were obtained by reactions utilizing alkyl olefin **2b** (entries 1 and 2), enols **2c** and **2d** (entries 3, 4, 5, and 6), and allylsilane (**2e**) (entries 7 and 8). Namely, *cis*-isoxazolidines **3b** - **e** were produced as major products in the absence of amine. By contrast, the addition of triethylamine provided mainly *trans*-isoxazolidines **4b** - **e**. But mixtures of *cis*- **3f** and *trans*-isoxazolidines **4f** were formed in similar ratios by reactions with allyl alcohol (**2f**) in the absence and in the presence of triethylamine (entries 9 and 10). The low stereoselectivities would be caused by the neighboring hydroxyl group, because the cycloadditions of nitrone with diallyl ether (**2g**) stereoselectively proceeded under both reaction conditions (entries 11 and 12).

^1H NMR spectra of **1** only showed the presence of *Z*-isomer, on the other hand, it was found to be a mixture of *Z*- and *E*-isomers (*Z* : *E* = 1 : 1.6) in the presence of triethylamine.[12] It is considered that, *cis*-isoxazolidine would be predominantly formed from *Z*-nitrone **1**, and *trans*-isomer would be produced mainly

from *E*-isomer.[13] Since the ratio of *E*- and *Z*-nitrone was not parallel to the ratio of products, the reactivity of *E*-nitrone would be higher than that of *Z*-nitrone in the presence of triethylamine.

Table 2. Stereoselectivity in the 1,3-Dipolar Cycloaddition of Nitrone **1** with Various Olefins

entry	olefin	additive	products (*cis*, *trans*)	yield	ratio (*cis* : *trans*)
1		none		71	94 : 6
2	**2b**	Et_3N	**3b** **4b**	37	10 : 90
3		none		~20	74 : 26
4	**2c**	Et_3N	**3c** **4c**	68	14 : 86
5		none		54	93 : 7
6	**2d**	Et_3N	**3d** **4d**	16	32 : 68
7		none		74	98 : 2
8	**2e**	Et_3N	**3e** **4e**	34	12 : 88
9		none		80	65 : 35
10	**2f**	Et_3N	**3f** **4f**	87	60 : 40
11		none		65	76 : 24
12	**2g**	Et_3N	**3g** **4g**	63	15 : 85

In conclusion, we have developed the synthesis of *cis*- and *trans*-3-carboxyisoxazolidines which are masked γ-hydroxy-α-amino acids. As each isomers are prevalently obtained, respectively, this methodology is applicable to the synthesis of a variety types of γ-hydroxy-α-amino acids.

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11. Typical procedure: Nitrone **1** (33.2 mg, 0.185 mmol) and triethylamine (0.15 g, 1.43 mmol) in chloroform (1 ml) were stirred at room temperature for 1 h. To the reaction mixture was added styrene (0.45 g, 4.36 mmol) at the same temperature. After being stirred for 32 h, volatile materials were evaporated. The residue in THF (3 ml) was allowed to react with excess amount of CH_2N_2 in ether at room temperature for 30 min. The solvents were removed by evaporation. The residue was purified by chromatography on a silica gel (eluent AcOEt : hexane = 1 : 4). The separable mixture of isoxazolidines (**3a** : **4a** = 12 : 88, 40.6 mg, 73%) were obtained. **3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.61 (ddd, 1H, *J* = 12.6, 8.0, 6.4 Hz), 2.97 (ddd, 1H, *J* = 12.6, 8.4, 7.7 Hz), 3.69 (s, 3H), 3.87 (dd, 1H, *J* = 8.4, 6.4 Hz), 4.16 (d, 1H, *J* = 12.0 Hz), 4.24 (d, 1H, *J* = 12.0 Hz), 5.26 (dd, 1H, *J* = 8.0, 7.7 Hz), 7.23-7.47 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.0, 52.4, 61.6, 66.9, 78.9, 126.9, 127.8, 128.1, 128.57, 128.60, 129.5, 136.4, 139.8, 171.8; IR (neat) 1740 cm^{-1}. **4b** : ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.42 (ddd, 1H, *J* = 12.5, 9.3, 8.4 Hz), 2.88 (ddd, 1H, *J* = 12.5, 7.3, 5.8 Hz), 3.67 (s, 3H), 3.73 (dd, 1H, *J* = 9.3, 5.8 Hz), 4.16 (d, 1H, *J* = 13.3 Hz), 4.24 (d, 1H, *J* = 13.3 Hz), 5.15 (dd, 1H, *J* = 8.4, 7.3 Hz), 7.23-7.46 (m, 10H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 41.0, 52.3, 62.2, 66.8, 79.1, 126.6, 127.7, 128.1, 128.4, 128.6, 129.7, 136.2, 139.8, 171.4; IR (neat) 1745 cm^{-1}.
12. Signals due to methylene protons of *Z*- and *E*-nitrones were resonated at δ 4.86 and 5.84 ppm as singlet, respectively.
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