Asymmetric 1,3-dipolar cycloaddition of nitrile oxides to chiral acryloyl esters bearing glucofuranose as auxiliary

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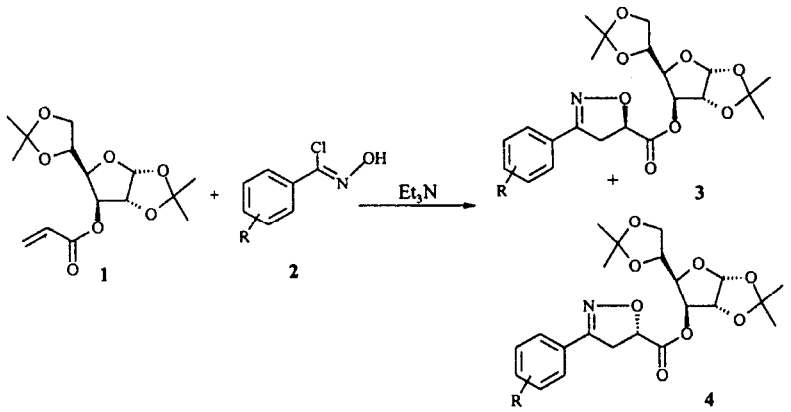
Asymmetric 1,3-dipolar cycloaddition of nitrile oxides to an acryloyl ester (1) derived from 1,2:5,6-di-*O*-isopropylidene glucose (6) was studied. Solvent and temperature effect was discussed. The single diastereoisomer was isolated with high diastereoselective excess.

Keywords 1,3-Dipolar cycloaddition, 2-isoxazoline, acryloyl ester, nitrile oxide

1,3-Dipolar cycloaddition reaction between a nitrile oxide and an olefinic dipolarophile affording isoxazoline ring is an important reaction in organic synthesis, which can create new stereogenic centre in one step.[1] In recent years, one of the most challenging tasks is to develop methodology for preparation of optically active isoxazoline.[2,3] Carbohydrates have gained much attention as auxiliaries in asymmetric organic reaction.[4a] The most successful application of carbohydrates as auxiliaries is in asymmetric Diels-Alder reaction, in which good to excellent stereoselectivity can be achieved.[4] It was also reported that carbohydrate nitrone derivatives as chiral dipole can be used in asymmetric 1,3-dipolar cycloaddition to induce the reaction stereoselectivity, but few examples of carbohydrate derivatives as chiral auxiliaries attached to an olefinic dipolarophiles were reported in asymmetric synthesis of isoxazolines.[3e,5,6] In this paper we wish to describe the regio- and stereoselectivity of 1,3-dipolar cycloaddition of nitrile oxides with chiral acryloyl ester (**1**) bearing glucofuranose as auxiliary (Scheme 1).

Scheme 1



As described in Scheme 1, acryloyl ester (**1**), which was readily derived from 1,2:5,6-di-*O*-isopropylidene glucose (**6**),[4d] was treated with aryl nitrile oxide generated from aryl hydroxyiminoyl chloride (**2**)[7] with

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triethyl amine to afford regioselective cycloaddition product (5*R*)-5-(1, 2: 5, 6-di-*O*-isopropylidene-glucofuranos-3-*O*-carbonyl)-3-aryl isoxazoline (**3**) and (5*S*)-5-(1, 2: 5, 6-di-*O*-isopropylidene-glucofuranos-3-*O*-carbonyl)-3-aryl isoxazoline (**4**) in good yields (Table 1). The stereoselectivity of the reaction depended on the solvent and temperature. For example, the reaction of **2a** with **1** was carried out in THF at 0℃ to afford cycloadduct **3a** and **4a** with diastereoisomeric ratio of 5:1 (Entry 7, Table 1), while unsatisfactory stereoselectivity was observed in dichloromethane, ether, toluene and other solvents or under low temperature (Entries 1—6). Reaction of **1** with aryl nitrile oxides containing an electron-donating group (Entries 7, 8) gave cycloadducts with good stereoselectivity, while nitrile oxide containing electron-withdrawing group gave poor stereoselectivity (Entries 10—12).

Table 1 Cycloaddition reaction of acryloyl ester **1** with nitrile oxides **2**

Entry	R	Solvent	*t* (℃)	Ratio of **3**:**4**[a]	Yield (%)[b]
1	4-methyl (**2a**)	CH_2Cl_2	0	4:3 (**3a**:**4a**)	79
2	4-methyl (**2a**)	Et_2O	0	5:3 (**3a**:**4a**)	80
3	4-methyl (**2a**)	Toluene	0	3:1 (**3a**:**4a**)	81
4	4-methyl (**2a**)	THF	-70	3:2 (**3a**:**4a**)	72
5	4-methyl (**2a**)	THF	-20	3:2 (**3a**:**4a**)	82
6	4-methyl (**2a**)	THF	r.t.	5:3 (**3a**:**4a**)	89
7	4-methyl (**2a**)	THF	0	5:1 (**3a**:**4a**)	80
8	4-methoxy (**2b**)	THF	0	4:1 (**3b**:**4b**)	89
9	H (**2c**)	THF	0	3:2 (**3c**:**4c**)	90
10	2,4-dichloro (**2d**)	THF	0	7:3 (**3d**:**4d**)	85
11	4-fluoro (**2e**)	THF	0	3:2 (**3e**:**4e**)	84
12	4-nitro (**2f**)	THF	0	3:2 (**3f**:**4f**)	87

[a] Isomeric ratios were determined by chiral HPLC analysis (Daicel chiralcel OD-H or OJ-H).

[a] All yields were isolated yields and all products gave satisfactory spectroscopic and analytical data.

Table 2 Diastereomeric excess of cycloadduct **3** after recrystallization

Entry	R	*d.e.* (%)[a]	$[\alpha]_D(CH_2Cl_2)$
1	4-methyl (**3a**)	99	-141.4(*c* 0.18)
2	4-methoxy (**3b**)	94	-151.0(*c* 0.50)
3	H (**3c**)	98	-110.2(*c* 0.75)
4	2,4-dichloro (**3d**)	92	-104.9(*c* 0.95)
5	4-fluoro (**3e**)	97	-124.7(*c* 0.60)

[a] Isomeric ratios were determined by chiral HPLC analysis (Daicel chiralcel OD-H or OJ-H).

It was difficult to separate the diastereoisomer **3** and **4** by column chromatography, however single optically pure isoxazoline **3** was easily obtained with up to 99% *d.e.* by recrystallizing from a mixture of CH_2Cl_2 and hexane (Table 2).

In order to determine the absolute configuration of cycloadducts, isoxazoline **3b** was treated with $NaBH_4$ to afford 3-(4′-methoxyphenyl)-5-hydroxymethyl isoxazoline (**5**) (Scheme 2) with specific rotation (-116.8°, *c* 0.6, MeOH), which was similiar to the reported specific rotation of *R*-configured isoxazoline **5** (-120°, *c* 0.4, MeOH).[8] Thus, the new resulting stereogenic center of cycloadduct **3b** was assigned to be R configuration. The stereochemistry of the cyclodition reaction can be explained in Fig. 1, in which the attacking of aryl nitrile oxide from the re-face of the olefinic double bond of **1** is more favorable than from the si-face with the bulky 5,6-isopropylidene group in glucose.

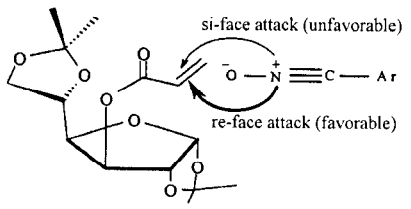
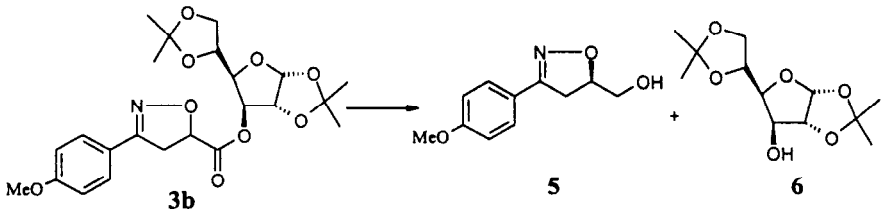


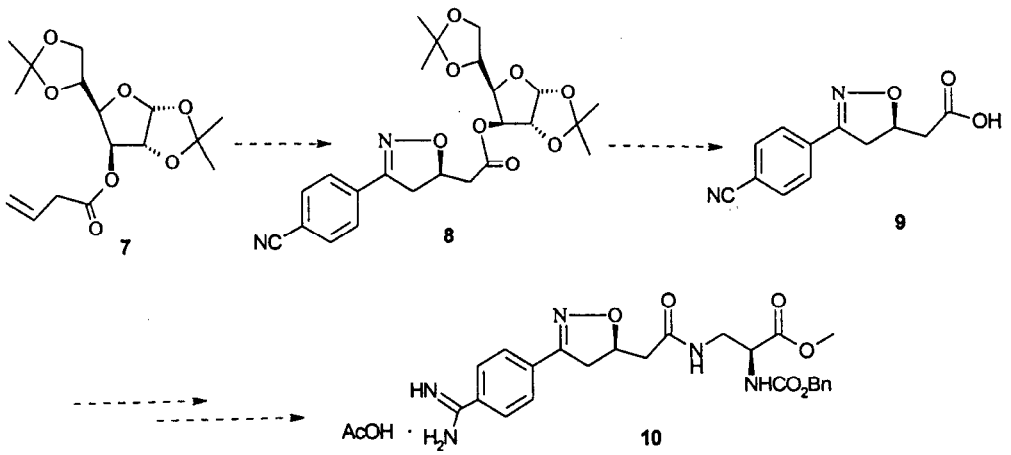
Fig. 1 Attacking process of nitrile oxide **2** to acryloyl ester **1**.

Because 1,2:5,6-di-*O*-isopropylidene glucose (**6**) is a useful auxiliary attached to dipolarophile in 1,3-dipolar cycloaddition, the optically pure isomer is accessible simply by recrystallization. So perhaps it can provide an alternative sugar-induced asymmetric 1,3-dipolar cycloaddition process to afford chiral acid (**9**) with R configuration, which is the key intermediate to synthesize the nonpeptide GPIIb/IIIa binding antagonist (**10**)[9-11] (Scheme 3). Currently the preparation of 3-butenoic ester (**7**) and its asymmetric 1,3-dipolar cycloaddition reaction are in progress and the results will be reported in due course.

Scheme 2



Scheme 3



Experimental

General methods

Melting points were determined on a Digital Melting Apparatus WRS-1A. NMR spectra were recorded as $CDCl_3$ solutions on a VXL-300 instrument. The ^1H NMR (300 MHz) chemical shifts were reported as δ values in parts per million relative to tetramethylsilane ($\delta_{TMS} = 0.0$) as internal standard. Infrared spectra were recorded on a Perkin-Elmer 983 FT-IR spectrometer. Mass spectral measurements were performed on a Fining 4021 or Fining MAT 8403 gas chromatography/mass spectrometer at 70 eV and mass data were tabulated as m/z. Elemental analyses were carried out on a MOD-1106 elemental analyzer. All solvents were purified and dried by standard techniques just before use. All reactions were monitored by thin layer chromatography (TLC) using silica gel GF254. Products were purified by column chromatography on silica gel manufactured in Qingdao Marine Chemical Factory, eluted with solvent mixture of petroleum ether (bp 60—90℃) and ethyl acetate. Optical rotations were measured using a Shanghai WZZ-1S automatic polarimeter.

General procedure

Cycloaddition of acryloyl ester (**1**) *with aryl hydroxyiminoyl chloride* (**2**)

To a solution of acryloyl ester **1** (200 mg, 0.63 mmol) in dried THF (15 mL) was added aryl hydroxyiminoyl chloride **2** (0.89 mmol), then Et_3N (0.125 mL, 0.89 mmol) was dropped slowly. The reaction mix-

ture was stirred at room temperature overnight. The resulting suspension was filtered by celite and the filtrate was concentrated under reduced pressure. The crude product was subjected to flash chromatography (petroleum: ethyl acetate = 4:1) to afford the mixture of **3** and **4**. Single diastereomer **3** was obtained by recrystallizing the mixture from hexane and dichloromethane.

3a and **4a** ν_{max}: 2989, 2938, 1749, 1610, 1517, 1456, 1374, 1259, 1215, 1076, 1024, 846 cm^{-1}. $\delta_H(CDCl_3)$: 7.5(d, J = 8 Hz, 2H), 7.1(d, J = 8 Hz, 2H), 5.8—6.0(m, 1H), 5.4(d, J = 2 Hz, 1H), 5.0—5.2(m, 1H), 4.42—4.62(m, 1H), 4.05—4.25(m, 2H), 3.9—4.1(m, 2H), 3.5—3.6 (m, AB system, 2H), 2.3(s, 3H), 1.3—1.4(m, 4 × CH_3, 12H). m/z(%): 448(M^+ + 1, 14.64), 432 (63.47), 390(29.86), 332(12.97), 206(19.17), 160(80.83), 101(100), 132(32.01), 43(67.24). Anal. $C_{23}H_{29}NO_8$. Calcd: C, 61.74; H, 6.48; N, 3.13. Found: C, 61.43; H, 6.63; N, 2.83.

3b and **4b** ν_{max}: 2986, 2937, 1748, 1609, 1517, 1548, 1373, 1214, 1075, 1023, 839 cm^{-1}. δ_H ($CDCl_3$): 7.5—7.7(m, 2H), 6.8—6.9(m, 2H), 5.8—6.0(m, 1H), 5.3(d, J = 3 Hz, 1H), 5.1—5.2(m, 1H), 4.4—4.6(m, 1H), 4.1—4.2(m, 4H), 3.75(s, 3H), 3.6—3.7(m, AB system, 2H), 1.2—1.4(m, 12H, 4 × CH_3). m/z(%): 464(M^+ + 1,4.18),463(M^+,4.18),448(M^+ − CH_3,41.76), 406(8.22), 348(5.92), 176(80.39), 101(100), 43 (71.29). Anal. $C_{23}H_{29}NO_9$. Calcd: C, 59.61; H, 6.26; N, 3.02. Found: C, 59.15; H, 6.35; N, 2.74.

3c and **4c** ν_{max}: 2989, 2939, 1751, 1571, 1449, 1382, 1374, 1216, 1164, 1077, 1025, 889 cm^{-1}. $\delta_H(CDCl_3)$: 7.5—7.7(m, 2H), 7.3—7.5(m, 3H), 5.85—6.0(m, 1H), 5.35(d, J = 3 Hz, 1H), 5.15—5.3(m, 1H), 4.42—4.7(m, 1H), 4.0—4.2 (m, 4H), 3.5—3.65(m, AB system, 2H), 1.52(s, 3H), 1.38(s, 3H), 1.3(s, 6H). m/z(%): 434 (M^+ + 1, 2.53), 433(M^+, 0.13), 418(42.96), 375(6.60), 299(3.49), 192(12.92), 174(6.37), 146(67.92), 118(33.07), 101(100), 77(26.53), 43(82.96). Anal. $C_{22}H_{27}NO_8$. Calcd: C, 60.96; H, 6.23; N, 3.23. Found: C, 60.46; H, 6.34; N, 3.02.

3d and **4d** ν_{max}: 2989, 2937, 1749, 1589, 1479, 1384, 1259, 1216, 1164, 1077, 1025, 867 cm^{-1}. $\delta_H(CDCl_3)$: 7.6(d, J = 9 Hz, 1H), 7.4(d, J = 2 Hz, 1H), 7.25(dd, J = 2, 8 Hz, 1H), 5.80—6.05(m, 1H), 5.30—5.50(m, 1H), 5.20—5.35 (m, 1H), 4.55(d, J = 4 Hz, 1H), 4.20—4.35(m, 2H), 4.10—4.16(m, 1H), 3.90—4.06(m, 1H), 3.72—3.86(m, AB system, 2H), 1.52(s, 3H), 1.41(s, 3H), 1.30(s, 3H), 1.25(s, 3H). m/z (%): 504(M^+ + 2, 2.53), 502(M^+, 2.02), 486 (24.10), 488(16.79), 444(4.93), 446(3.30), 385 (4.72), 214(28.29), 186(19.65), 101(100), 73 (17.84), 43(74.94). Anal. $C_{22}H_{25}NO_8Cl_2$. Calcd: C, 52.59; H, 4.98; N, 2.78. Found: C, 52.50; H, 5.01; N, 2.64.

3e and **4e** ν_{max}: 2990, 2939, 1752, 1605, 1515, 1383, 1220, 1162, 1077, 1025, 841 cm^{-1}. δ_H ($CDCl_3$): 7.46—7.65(m, 2H), 7.06—7.14(m, 2H), 5.89—5.96(m, 1H), 5.35(d, J = 2 Hz, 1H), 5.12—5.28(m, 1H), 4.6(t, J = 8 Hz, 1H), 4.01—4.12(m, 4H), 3.70—3.76(m, AB system, 2H), 1.5(s, 3H), 1.15—1.30(m, 3 × CH_3, 9H). m/z(%): 452(M^+ + 1, 6.68), 436(36.99), 393 (22.80), 370(24.04), 353(23.30), 335(16.64), 278(19.65), 252(9.00), 210(28.92), 164(100), 136(39.90), 101(73.78), 43(58.32). Anal. $C_{22}H_{26}NO_8F$. Calcd: C, 58.53; H, 5.76; N, 3.10. Found: C, 58.24; H, 5.93; N, 2.79.

3f and **4f** ν_{max}: 2992, 2936, 1768, 1610, 1523, 1373, 1344, 1197, 1164, 1081, 1021, 848 cm^{-1}. $\delta_H(CDCl_3)$: 8.25(d, J = 9 Hz, 2H), 7.80(d, J = 9 Hz, 2H), 5.85—5.96(m, 1H), 5.24—5.45 (m, 1H), 5.18—5.35(m, 1H), 4.51(dd, J = 4,6 Hz,1H), 3.87—4.09(m, 4H), 3.52—3.64(m, AB system, 2H), 1.5(s, 3H), 1.14—1.36(m, 3 × CH_3, 9H). m/z(%): 463(M^+ − CH_3, 34.02), 464 (8.21), 362(2.85), 344(3.34), 237(3.61), 191 (31.05), 163(11.43), 127(13.38), 117(12.26), 101(100), 43(65.09). Anal. $C_{22}H_{26}N_2O_{10}$. Calcd: C, 55.23; H, 5.44; N, 5.86. Found: C, 55.33; H, 5.72; N, 5.87.

Reduction of the cycloadduct **3b** *by* $NaBH_4$

To a stirred solution of cycloadduct **3b** (0.322 mmol) in the mixture solvents of methanol (2 mL) and THF (2 mL) was added $NaBH_4$ (19 mg, 0.5 mmol). The stirring was continued overnight at room temperature, then quenched by adding 3 drops of water. The mixture was filtered with a pad of celite. After evapora-

tion of the solvent, the residue was column chromatographed (petroleum ether: ethyl acetate 2:1) to afford 3-(4′-methoxyphenyl)-5-(hydroxymethyl) isoxazoline **5** quantitively. δ_H(CD_3COCD_3): 7.42—7.59(m, 2H), 6.88—7.04(m, 2H), 4.57—4.72(m, 1H), 3.9(s, 3H), 3.46—3.67(m, 2H), 3.40(dd, AB system, J = 11, 16 Hz, 1H), 3.3(s, 1H, -OH), 3.15(dd, AB system, J = 7, 16 Hz, 1H).

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