Diastereoselectivity of nitrone 1,3-dipolar cycloaddition to Baylis-Hillman adducts

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Dedicated to Professor Branko Stanovnik on the occasion of his 65th birthday
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Abstract
1,3-Dipolar cycloadditions of *C*-phenyl-*N*-methylnitrone to Baylis-Hillman adducts (β-hydroxy-α-methylene esters) proceed with complete regioselectivity in good yields to afford the corresponding diastereomeric 3,5,5-trisubstituted isoxazolidines. Attack of the dipole from the less sterically hindered side of the dipolarophiles affords C-3/C-5 *cis* isoxazolidines as the predominant isomers. Addition of Lewis acids and microwave irradiation produce only a small effect on the diastereoisomeric product ratio. Microwave irradiation accelerates the reaction.

Keywords: Dipolar cycloaddition, diastereoselection, nitrones, microwave heating, isoxazolidines

Introduction

The nitrone-olefin 1,3-dipolar cycloaddition is a powerful reaction in that it can create as many as three new contiguous stereogenic centres in a single step.[1] Based on an evaluation of the nitrone cycloaddition, it was felt that the stereochemistry of these new centers could be controlled if the reaction system were properly designed.[1-3] Regio- and stereoselective nitrone cycloaddition, followed by reduction of the N-O bond to produce both an amino and a hydroxy function, allows the synthesis of many products of potential interest. Diastereoselectivity of the cycloadditions depends mainly upon the nature of dipole and dipolarophile; several models that allow the prediction of the major product diastereomer, have been published.[4]

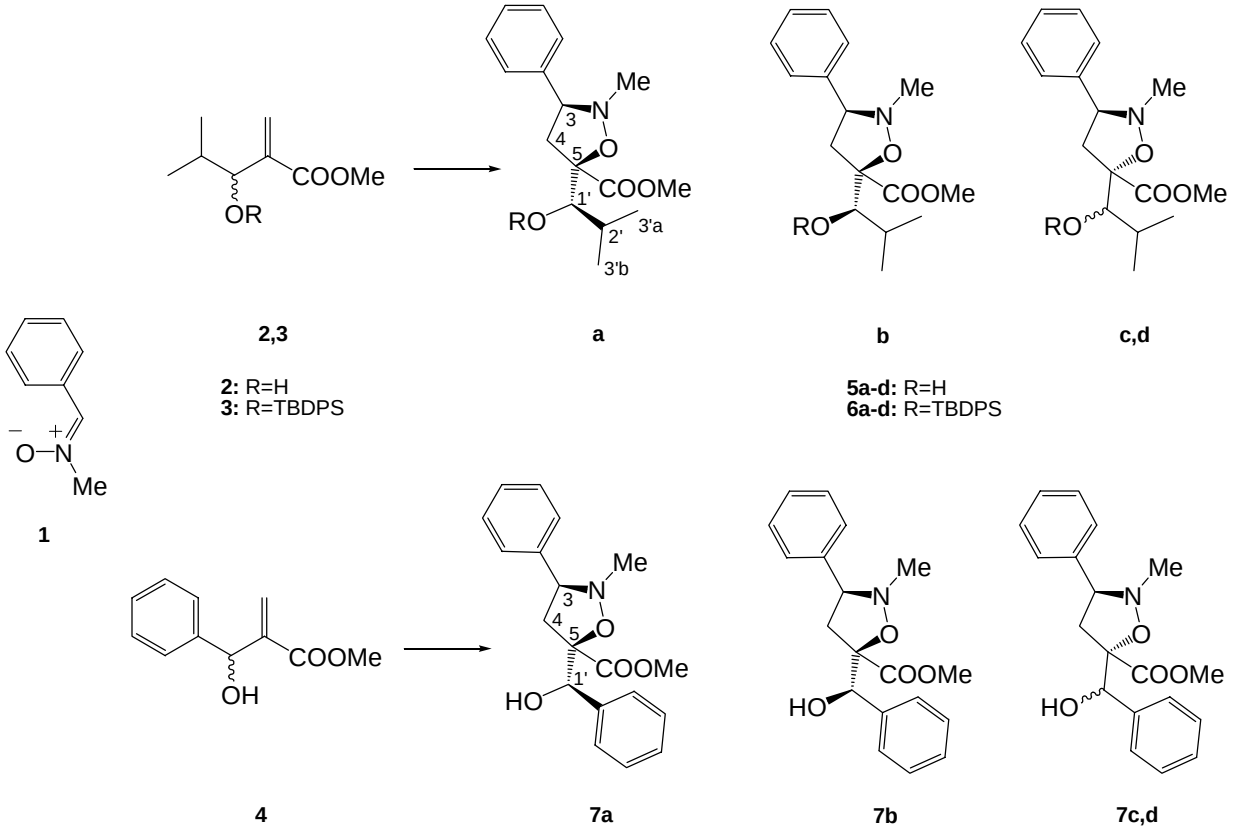
When 1,3-dipolar cycloaddition is to be used in any synthesis of a complex target molecule, a method that accommodates change or even reversal of the ratio of diastereoisomers would be a

desirable. However, one cannot change the dipole and/or the dipolarophile (except changing the protecting group in the suitable dipolarophile), since they are determined by the structure and the strategy of the synthesis of the target molecule.

Lewis acids are often used as catalysts in 1,3-dipolar cycloadditions of nitrones.[5] Recently we have described (i) the reversal of diastereoselectivity of mesitonitrile oxide 1,3-dipolar cycloadditions to Baylis-Hillman adducts that is brought about by added Mg(II) as well (ii) the acceleration of this cycloaddition by microwave irradiation.[6] In the present communication, we report the investigation of the effect of the addition of Mg(II) additive upon the stereoselectivity of reactions of *C*-phenyl-*N*-methylnitrone (**1**) with Baylis-Hillman adducts **2-4**.

Results and Discussion

Baylis-Hillman adducts **2-4** were chosen as electron deficient dipolarophiles. Adducts **2** and **4** were prepared *via* Baylis-Hillman reactions by using an appropriate aldehyde and methyl acrylate.[7,8] Dipolarophile **3** was obtained by the silylation of **2**. The cycloadditions of nitrone **1** with **2-4** are completely regioselective; only the 5-substituted isoxazolidines **5-7** are isolated irrespective of the presence or absence of Mg(II). Change of solvent, alteration of reaction temperature or microwave irradiation have no influence on the regioselectivity of the reaction.



The cycloadditions were first carried out in the absence of any Lewis acid. Reaction of nitrone **1** and isopropyl Baylis-Hillman adduct **2** formed mixtures of diastereoisomers (Table 1). Isoxazolidine **5a** was formed as a major product. It is noterworthy to mention that at room temperature no cycloaddition has been observed; after 14 days only the unreacted starting materials were detected (entry 1, Table 1).

Table 1. 1,3-Dipolar cycloaddition of nitrone **1** to Baylis-Hillman adducts **2-4**

Entry	Olefine	Reaction conditions	Lewis acid	Yield [%]	*cis:trans*	a	b	c	d
1	**2**	CH_2Cl_2, rt, 14 d	-		-				
2	**2**	CH_2Cl_2, rt, 14 d	MgI_2-I_2	28	98:2	94	4	2	-
3	**2**	CCl_4, reflux, 7 d	-	81	96:4	87	9	3	1
4	**2**	CCl_4, mw, 1000W, 1 h	-	68	97:3	89	8	3	-
5	**2**	CCl_4, reflux, 7 d	MeMgBr	69	87:13	76	11	5	8
6	**2**	toluene, reflux, 18 h	-	68	79:21	67	12	14	7
7	**2**	toluene, reflux, 19 h	MeMgBr	62	81:20	67	14	11	9
8	**3**	toluene, reflux, 14 d	-	14	100:0	100	-	-	-
9	**4**	CCl_4, reflux, 7 d	-	84	93:7	78	15	5	2
10	**4**	CCl_4, mw, 1000W, 1 h	-	74	94:6	79	15	6	-
11	**4**	CCl_4, reflux, 7 d	MeMgBr	72	88:12	66	22	7	5
12	**4**	toluene, reflux, 18 h	-	71	86:14	61	25	11	3
13	**4**	toluene, reflux, 19 h	MeMgBr	66	89:11	65	24	7	4

Since nitrone **1** shows no reactivity in the non-catalyzed reactions at room temperature, higher reaction temperatures are needed to effect complete reaction. On the other hand, when the reaction was performed in the presence of MgI_2-I_2 catalyst, a mixture of cycloadducts **5a-c** was formed in 28% yield in diastereomeric ratio of 94 : 4 : 2 (entry 2, Table 1). The lowest diastereomeric ratio has been achieved by the performing the reaction in boiling toluene (entries 6 and 7, Table 1). Reaction of nitrone **1** and phenyl Baylis-Hillman adduct **4** proceeded in analogous fashion; isoxazolidine **7a** was formed as major product (entry 9, Table 1). A complete selectivity is observed with compound **3** in which the silyl protected hydroxy group prevents the possible coordination. The low chemical yield in this case may be due to steric reasons.

The addition of a Grignard reagent (MeMgBr) as a Lewis acid in contrast to mesitonitrile oxide cycloaddition exerts a slight influence on the stereoselectivity of the reaction (entries 3 and 5, Table 1). The observed reversal of the stereoselectivity of the mesitonitrile oxide cycloaddition with dipolarophile **2** has been rationalised in terms of the presence of a chelated transition state with a geometry different from a "nonchelated" transition state.[6] We have presumed that Mg(II) coordinates with alcoholate as well as with the methoxycarbonyl group, and therefore the conformation of a magnesium alcoholate differs from that of the corresponding free Baylis-Hillman adduct.[6]

On the other hand, the stereoselectivity was not improved in the reaction between nitrone **1** and dipolarophile **2** even under catalyzed conditions, a result that suggests insufficient co-ordination between the Lewis acid and the dipolarophile **2**. A Lewis acid catalyst can be incorporated both in nitrone **1** and bidentate ester **2**. It is clear that the catalyst is mostly incorporated in the dipole complex rather than the dipolarophile complex.[5a] Yields of the cycloaddition in the presence of Mg(II) additive are lower when compared with the yields of the reaction performed without the Mg(II) additive (Table 1).

Our attempts to accelerate the cycloaddition by microwave irradiation were successful. For example, the reaction of Baylis-Hillman adduct **2** was complete in seven days when performed in refluxing CCl_4 without irradiation, whereas the same cycloaddition under microwave irradiation could be completed in only 1 h (entries 3 and 4, Table 1). In this case, the diastereomeric excess was nearly unchanged. Dipolarophile **4** reacted under microwave irradiation reacted analogous fashion and the corresponding reaction time also decreased from 7 days to 1 hour (entries 9 and 10, Table 1).

Purification by flash chromatography allowed the isolation of the pure major diastereoisomers **5a, 6a, 7a** as well as minor isomer **7b**, while the isolation and/or characterization of the other minor isomers was not possible. All structures described were characterized *via* analysis of their respective ^{1}H- and ^{13}C- NMR spectra. The ratio of diastereoisomers was determined from quantitative ^{13}C NMR spectra, by integration of the peaks from C-5 of the isoxazolidines.

Moreover, no thermal interconversion among cycloadducts occurred in refluxing toluene, thus indicating that the cycloaddition proceeded irreversibly under the reaction conditions to give the kinetically controlled products **5-7**. The structural assignments of the products are based on analysis of NMR spectra. The stereochemistries of the cycloadducts were deduced by n.O.e. experiments. The most important and decisive information obtained from these experiments is the presence or absence of the n.O.e. interaction between the protons H-4/H-3, H-4/H-1′ and H-3/H-1′ in the corresponding cycloadducts. For instance the *cis* relationship of the phenyl substituent at C-3 and methoxycarbonyl substituent at C-5 in **7a** has been assigned on the basis of NOEDS. The enhancement on signal H-4_B and the enhancement on signal H-3 and H-1′ following saturation of signal H-4_A show a *cis* relationship between the aforementioned substituents at C-3 and C-5; irradiation of H-4_B causes only enhancement on H-4_A. Moreover, the missing interactions between H-4_B and H-3 and between H-4_B and H-1′ confirm this *cis* relationship.

In conclusion, 1,3-dipolar cycloadditions of *C*-phenyl-*N*-methylnitrone to Baylis-Hillman adducts (β-hydroxy-α-methylene esters) proceed with complete regioselectivity in good yields to afford the corresponding diastereomeric 3,5,5-trisubstituted isoxazolidines. Attack of the dipole from the less sterically hindered side of the dipolarophiles affords C-3/C-5 *cis* isoxazolidines as major products. Addition of Lewis acids and microwave irradiation produce only a small effect on the diastereoisomeric product ratio, moreover the microwave irradiation accelerates the reaction.

Experimental Section

General Procedures. All starting materials and reagents are commercially available (Fluka, Merck, Avocado or Aldrich) and were used without further purification. Solvents were dried before use. Thin-layer chromatography (TLC glass plates coated with silica 60 F_{254} Merck) was used for monitoring of reaction courses, eluents are given in the text. For column chromatography the flash chromatography technique was employed using silica 60 (0.040-0.063 mm, Merck). Melting points (mp) were determined on a Kofler hot plate apparatus and are uncorrected.

IR spectra were recorded on FTIR NICOLET MAGNA 750 instrument. The ^{1}H and ^{13}C NMR spectra of deuterochloroform solutions were obtained using Varian VXR-300 (300 MHz) and Bruker DRX-400 (400 MHz) instruments, tetramethylsilane (TMS) being the internal reference.

C-Phenyl-*N*-methylnitrone (**1**) was prepared from the benzaldehyde by the reaction with *N*-methylhydroxylamine according to the procedure already described in the literature.[9] The Baylis-Hillman alkenes **2, 4** were prepared by the reaction of isobutyraldehyde and benzaldehyde with methylacrylate in the presence of catalytic amount of DABCO respectively.[7,8] Alkene **3** was obtained by the silylation of **2** with TBDPSCl and imidazole in CH_2Cl_2. MeMgBr as 1.4M solution in THF used for cycloadditions is commercially available reagent. The MgI_2-I_2 was freshly prepared prior to use.

General procedures

Method A. To the round-bottom flask equipped with magnetic stirring bar were nitrone **1**, corresponding alkene **2-4** (1 eq) and solvent added. The appropriate solvent, reaction time and temperature for each reaction are listed in Table 1. The reaction mixture was stirred until complete conversion of nitrone **1** (monitored by TLC) alternatively, when the conversion was not complete, the reaction was stopped after 14 days. The solvent was evaporated and quantitative ^{13}C NMR of crude reaction mixture was recorded. The reaction mixture was then column chromatographed. The yields of the isolated mixtures of cycloadducts for each experiment are given in Table 1.

Method B. Cycloadditions in the presence of Lewis acids. The reactions were carried out under argon atmosphere. To the dry round-bottom flask equipped with magnetic stirring bar and rubber septum was alkene **2** or **4** (1 eq) added. The solution of Lewis acid (1 eq) was at room temperature dropwise added and the mixture was stirred for 15-30 min at the same temperature. The solution of nitrone **1** (1 eq) was then with syringe dropwise added. The appropriate solvent, reaction time and temperature are listed in Table 1. The mixture was stirred until complete conversion of nitrone **1** (monitored by TLC). The reaction was quenched with saturated NH_4Cl water solution, extracted with CH_2Cl_2 (in the case of MgI_2-I_2 mediated cycloadditions the

collected organic layers were washed with 10% $Na_2S_2O_7$ water solution to remove I_2), dried over Na_2SO_4 and the solvent was removed by rotary evaporation.

Method C. Microwave mediated cycloadditions. The reactions were carried out in conventional kitchen microwave oven at the rate of 1000 W. The equimolar solution of nitrone **1** and alkene **2** or **4** in CCl_4 was put into the 100 ml Erlenmayer flask, cooled to 0 °C, flask was inserted to microwave oven and the mixture was irradiated for 5 min. The flask was than taken out and the reaction course was monitored. The mixture was again cooled down to 0 °C and whole sequence was repeated until complete conversion of nitrone **1** (12 times). The solution was then transferred to the round-bottom flask and the solvent was removed by rotary evaporation.

Cycloaddition of nitrone 1 with alkene 2

The reaction between nitrone **1** (1 g, 7.4 mmol) and alkene **2** (1.17 g, 7.4 mmol) in CCl_4 (50 ml) was carried out according to the method C. The mixture of three diastereoisomers (89:8:3) was purified and separated by flash column chromatography on silica gel (250 g, 25x4.5 cm) eluting with EtOAc/hexanes 20:80 to give a mixture of three diastereoisomers **5a-c** (487 mg, 23%) and 993 mg (45%) of single major diastereoisomer **5a**. Combined yield 1.48g (68%).

***cis*-5-(1-Hydroxy-2-methylpropyl)-2-methyl-3-phenylisoxazolidine-5-carboxylic acid methyl ester (5a).** colourless solid, R_f = 0.24 (EtOAc/hexanes 30:70), mp 80-81 °C (EtOAc/hexanes); ν_{max} (KBr) 3503, 2988, 2959, 2871, 1721, 1277, 1205, 1059, 1012 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.37-7.28 (m, 5H, H_{Ph}), 3.86 (s, 3H, H-CO_2CH_3), 3.82 ("dd", 1H, *J* = 4.4 Hz, H-1'), 3.45 (dd, 1H, *J* = 9.1, 8.5 Hz, H-3), 2.99 (dd, 1H, *J* = 12.9, 8.5 Hz, H-4a), 2.91 (dd, 1H, *J* = 12.9, 9.1 Hz, H-4b), 2.58 (s, 3H, H-NCH_3), 2.52 (d, 1H, *J* = 3.8 Hz, OH), 1.75-1.67 (m, 1H, H-2'), 1.00, 0.94 (2xd, 3H, 3H, *J* = 6.7, 6.7 Hz, H-3'a, H-3'b); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 173.9 (C=O), 138.2, 128.6, 128.1, 128.0 (6C, C_{Ph}), 87.6 (C-5), 76.3 (C-1'), 74.6 (C-3), 52.7 (C-CO_2CH_3), 42.8 (C-NCH_3), 42.1 (C-4), 29.8 (C-2'), 20.7 (C-3'a), 16.4 (C-3'b).

Cycloaddition of nitrone 1 with alkene 4

The reaction of nitrone **1** (0.162 g, 1.2 mmol) with alkene **4** (0.230 g, 1.2 mmol) in toluene (10 ml) was carried out according to the method A. The mixture of four diastereoisomers (61:25:11:3) was purified and separated by flash column chromatography on silica gel (25 g, 12.5x2 cm) eluting with EtOAc/hexanes 20:80 to give a mixture of four diastereoisomers **7a-d** (137 mg, 35%), 21 mg (5%) of single diastereoisomer **7b** and 142 mg (36%) of single major diastereoisomer **7a**. Combined yield 0.300 g (76%).

***cis*-5-(Hydroxy-phenylmethyl)-2-methyl-3-phenylisoxazolidine-5-carboxylic acid methyl ester (7a).** colourless solid, R_f = 0.32 (EtOAc/hexanes 30:70), mp 113-115 °C (EtOAc/hexanes); ν_{max} (KBr) 3535, 3062, 2983, 2954, 2849, 1726, 1452, 1278, 1052, 1030, 1021 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.43-7.24 (m, 10H, H_{Ph}), 5.13 (s, 1H, H-1'), 3.83 (s, 3H, CO_2CH_3-H), 3.13 (dd, 1H, *J* = 8.3, 8.2 Hz, H-3), 2.91 (dd, 2H, *J* = 13.2, 7.9 Hz, H-4a, OH), 2.71 (dd, 1H, *J* = 13.0, 9.6 Hz, H-4b), 2.60 (s, 3H, NCH_3-H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 173.4

(C=O), 137.6, 137.5, 128.6, 128.2, 127.9, 127.4 (12C, 2xC_{Ph}), 87.5 (C-5), 75.4 (C-1'), 73.7 (C-3), 52.7 (CO_2CH_3-C), 42.9 (NCH_3-C), 42.6 (C-4).

***cis*-5-(Hydroxy-phenylmethyl)-2-methyl-3-phenylisoxazolidine-5-carboxylic acid methyl ester (7b).** colourless oil, R_f = 0.45 (EtOAc/hexanes 30:70); ν_{max} (KBr) 3466, 3063, 3031, 2954, 2850, 1741, 1495, 1455, 1435, 1256, 1200, 1118, 1051, 1028, 1018 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.48-7.23 (m, 10H, H_{Ph}), 5.07 (s, 1H, H-1'), 3.78 (s, 3H, CO_2CH_3-H), 3.04-2.88 (m, 3H, OH, H-3, H-4a), 2.81 (dd, 2H, *J* = 12.6, 9.9 Hz, H-4b), 2.57 (s, 3H, NCH_3-H); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 173.8 (C=O), 138.6, 137.5, 128.6, 128.4, 128.1, 128.0, 127.8, 127.5 (12C, 2xC_{Ph}), 86.1 (C-5), 75.2 (C-1'), 73.5 (C-3), 52.7 (CO_2CH_3-C), 44.8 (C-4), 42.9 (NCH_3-C).

Cycloaddition of nitrone 1 with alkene 3

The reaction between nitrone **1** (0.200 g, 1.5 mmol) and alkene **3** (0.587 g, 1.5 mmol) in toluene (10 ml) was carried out according to the method A. The crude reaction mixture which contained only one diastereoisomer **6a,** unreacted nitrone **1** and dipolarophile **3**, was purified and separated by flash column chromatography on silica gel (20 g, 19x1.5 cm) eluting with EtOAc/hexanes 10:90 to give 107 mg (14%) of single major diastereoisomer **6a** and 117 mg (59%) of unreacted nitrone **1** was recovered.

***cis*-5-[1-(*tert*-Butyl-diphenylsilanyloxy)-2-methylpropyl]-2-methyl-3-phenylisoxazolidine-5-carboxylic acid methyl ester (6a).** colourless viscous oil, R_f = 0.61 (EtOAc/hexanes 30:70); ^{1}H NMR (400 MHz, $CDCl_3$/TMS): δ 7.84-7.83 (m, 4H, H_{Ph}), 7.48-7.28 (m, 11H, H_{Ph}), 4.20 (d, 1H, *J* = 1.8 Hz, H-1'), 3.77 (s, 3H, CO_2CH_3-H), 3.40 (dd, 1H, *J* = 8.8, 8.5 Hz, H-3), 3.18 (dd, 1H, *J* = 12.3, 9.4 Hz, H-4a), 3.00 (dd, 1H, *J* = 12.3, 8.2 Hz, H-4b), 2.40 (s, 3H, NCH_3-H), 1.53 (m, 1h, H-2'), 1.19 (s, 9H, Si(C(CH_3)$_3$-H), 0.76, 0.73 (2xd, 3H, 3H, *J* = 7.0, 7.0 Hz, H-3'a, H-3'b); ^{13}C NMR (100 MHz, $CDCl_3$/TMS): δ 174.1 (C=O), 136.5, 136.3, 129.5, 129.4, 128.4, 128.2, 127.8, 127.3 (15C, 3xC_{Ph}), 89.1 (5-C), 76.6 (1'-C), 73.5 (3-C), 52.4 ($CO_2\underline{C}H_3$-C), 41.9 (NCH_3-C), 41.1 (4-C), 31.7 (C-2'), 27.4 (3C, C-Si(C(CH_3)$_3$), 20.0 (2C, C-Si(C(CH_3)$_3$, C-3'a), 16.1 (C-3'b).

Desilylation of 6a. To the solution of **6a** (0.077 g, 0.1 mmol) in THF (10 ml) at 0 °C the solution of TBAF.xH_2O (0.049 g, 0.2 mmol) was dropwise added. The mixture was allowed to warm to room temperature and stirred for 8 hours. Saturated $NaHCO_3$ was added, mixture was extracted with $CHCl_3$, dried over Na_2SO_4 and the solvent was evaporated. The product was isolated by flash column chromatography on silica gel (8 g, 7x1.5 cm) eluting with EtOAc/hexanes 10:90 to give 19 mg (45%) of **5a**.

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