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Reversal of Stereoselectivity of Mg(II) Catalysed 1,3-Dipolar Cycloaddition. Acceleration of Cycloaddition by Microwave Irradiation.

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Abstract: 1,3-Dipolar cycloadditions of mesitonitrile oxide to Baylis-Hillman adducts (β-hydroxy-α-methylene esters) proceed regioselectively in good yields. Addition of a Grignard reagent reverses the diastereoselectivity of the cycloaddition. Microwave irradiation strongly accelerates the reaction with only a small effect on its diastereoisomeric excess.

Keywords: Cycloadditions, Diastereoselection, Nitrile oxides, Microwave heating

Isoxazolines, products of 1,3-dipolar cycloaddition reactions of nitrile oxides and olefins, are important intermediates in organic synthesis. Various products, such as 1,3-diols, 1,3-aminoalcohols, aminocarbonyls and α,β-unsaturated carbonyls can be prepared from isoxazolines.[1]

If a chiral alkene is used as the dipolarophile, two diastereoisomers can be formed by 1,3-dipolar cycloaddition. Several models have been published which predict the structure of the major diastereoisomer.[2] However, if a 1,3-dipolar cycloaddition is to be used in a synthesis of a complex target molecule, it may be neccessary to change or even reverse the ratio of diastereoisomers. The 1,3-dipole and/or dipolarophile (except for changing the protecting group in suitable dipolarophile) cannot be changed because they are determined by the structure and strategy of the synthesis of target molecule. However a change of solvent usually has little or no effect on the diastereoisomeric excess.[2] Although Lewis acids are often used as catalysts in Diels-Alder cycloadditions, the effective use of Lewis acids in 1,3-dipolar cycloaddition of nitrile oxides is the subject of only a few reports to date.[3]

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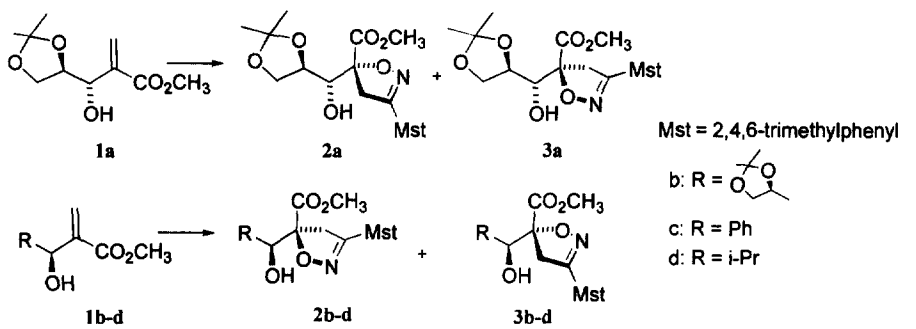
In the present communication, we report an investigation into the effect of the addition of methylmagnesium bromide on the stereoselectivity of reactions of mesitonitrile oxide with the Baylis-Hillman adducts **1a-d.**[4] The reactions are completely regioselective with only the 5-substituted isoxazolines being isolated - irrespective of the presence or absence of the Mg(II) additive. The cycloadditions were first carried out in the absence of any Lewis acid (entries 1, 4, 6 and 11) - a single isomeric product (entry 11) or mixture of isomers (de ranging from >90% to 4%) were formed, with the compounds **3a-d** being obtained as the main products. The stereocenter in the β-position has little effect on the diastereoisomeric ratio (22:78 for **1a** and 26:74 for **1b**).

Table 1. 1,3-Dipolar Cycloaddition of Mesitonitrile oxide to Baylis-Hillman adducts 1a-d.



entry	comp.	solvent[a]	Lewis acid[b]	r. time	r. temp.	yield (%)	ratio **2:3**[c]
1.	**1a**	TOL	-	2 h	80°C	89	22 : 78
2.	**1a**	DCM	MeMgBr	48 h	r.t.	50	>95 : <5
3.	**1a**	CLB	MeMgBr	4 min	MW[d]	34	78 : 22
4.	**1b**	TOL	-	2 h	80°C	92	26 : 74
5.	**1b**	DCM	MeMgBr	43 h	r.t.	62	85 : 15
6.	**1c**	TOL	-	4 h	80°C	92	42 : 58
7.	**1c**	DCM	MeMgBr	24 h	r.t.	57	61 : 39
8.	**1c**	DCM	-	24 h	r.t.	96	48 : 52
9.	**1c**	CLB	MeMgBr	4 min	MW[d]	40	70 : 30
10.	**1c**	CLB	-	1.5 min	MW[d]	99	43 : 57
11.	**1d**	TOL	-	2 h	80°C	99	<5 : >95
12.	**1d**	DCM	MeMgBr	78 h	r.t.	35	>95 : <5

[a]TOL: toluene, CLB: chlorobenzene, DCM: dichloromethane; [b]One equivalent of the MeMgBr was employed. The reaction were allowed to reach completion. [c]Determined from ^{1}H and/or ^{13}C-NMR of crude reaction mixture; [d]Microwave irradiation

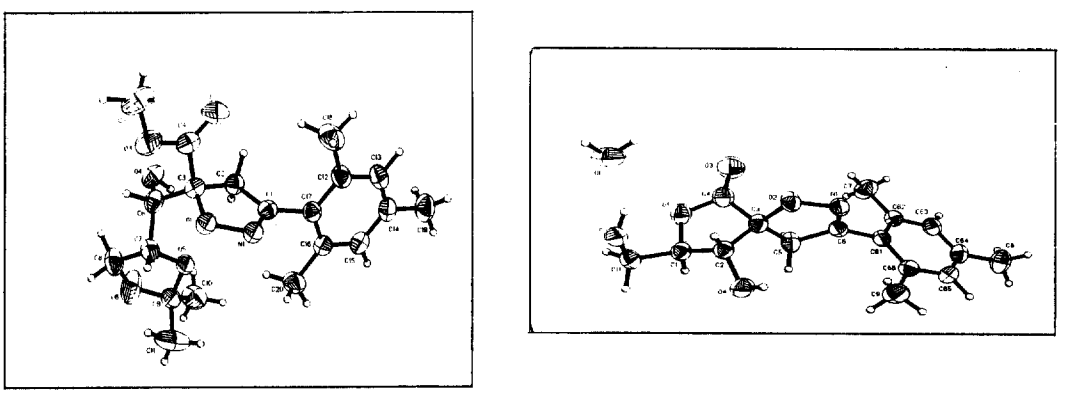
The addition of a Grignard reagent (MeMgBr)[5] as a Lewis acid affects and can even reverse the sense of induced stereoselectivity: >95:<5 for **1a** and **1d** (entry 2 and 12) or 85:15

for **1b** (entry 5). The stereochemical outcome of the cycloaddition in the absence of Grignard reagent has been rationalised in terms of the presence of hydrogen bonding in a Felkin-Anh-Houk model[6] (Fig. 1). The reversal of the stereoselectivity presumably results from the imposition of a chelated transition state with a geometry different from a "nonchelated" transition state. The chelated transition state may arise from the coordination of both the 1,3-dipole and the dipolarophile by the same magnesium cation (Fig. 1). These results are very similar to those already reported by Kanemasa.[3]

Nonchelated Chelated

Figure 1. Nonchelated and chelated transition states

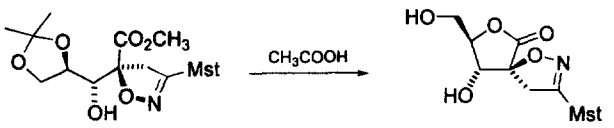
Attempts to accelerate the cycloaddition by microwave irradiation were successful (the reaction time decreased from days to less than 5 min) in both the chelated and nonchelated cycloadditions without any loss of stereoselectivity for non-catalysed cycloadditions (entry 6, 10) and with only a small change of stereoselectivity in the case of the chelated reactions (entry 2, 3 and 7, 9 respectively).



2b **4**

Fig. 3. A view of **2b** and **4** respectively. Ellipsoids are drawn at the 50% probability level.

The structure of the cycloadduct **2b**[7] was determined by X-ray analysis and that of cycloadduct **3a** from X-ray diffraction of the product of lactonisation **4**.[8]



3a **4**

Structures of cycloadducts **2c-d** and **3c-d** were assigned by analogy. The ^{13}C-NMR shift of carbon in position 5 of the isoxazoline ring is shifted to lower values in the case of diastereoisomers **2a-d** when compared to those of **3a-d**.[9]

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7. Spectroscopic data for **2b**: ^{1}H-NMR (300 MHz, $CDCl_3$) δ 1.39 (s, 3H), 1.45 (s, 3H), 2.25 (s, 6H), 2.29 (s, 3H), 3.67 (d, *J*=18.3 Hz, 1H), 3.77 (d, *J*=18.3 Hz, 1H), 3.89 (s, 3H), 3.92 (dd, *J*=8.2, 7.7 Hz, 1H), 4.18 (dd, *J*=8.3, 6.7 Hz, 1H), 4.21 (d, *J*=2.2 Hz, 1H), 4.43 (ddd, *J*=7.6, 6.7, 2.2 Hz, 1H), 6.90 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 19.5, 21.1, 25.5, 26.2, 43.1, 53.2, 67.3, 70.1, 73.4, 88.9, 110.3, 125.1, 128.5, 136.6, 139.1, 158.3, 171.1
8. Crystallises with one water molecule. Spectroscopic data for **4**: ^{1}H-NMR (300 MHz, DMSO) δ 2.18 (s, 6H), 2.25 (s, 3H), 3.32 (d, *J*=19.2 Hz, 1H), 3.64 (m, 1H), 3.76 (m, 1H), 3.77 (d, *J*=16.8 Hz, 1H), 4.10 (m, 1H), 4.41 (t, *J*=5.9 Hz, 1H), 5.23 (t, *J*=5.2 Hz, 1H), 6.46 (d, *J*=5.4 Hz, 1H), 6.94 (s, 2H); ^{13}C-NMR (DMSO) δ 19.1, 20.7, 40.0, 58.9, 69.5, 82.5, 87.9, 125.0, 128.2, 136.3, 138.6, 156.8, 173.3
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