1,3-Dipolar Cycloaddition Reactions of Nitrones with Unsaturated Methylsulfones and Substituted Crotonic Esters†

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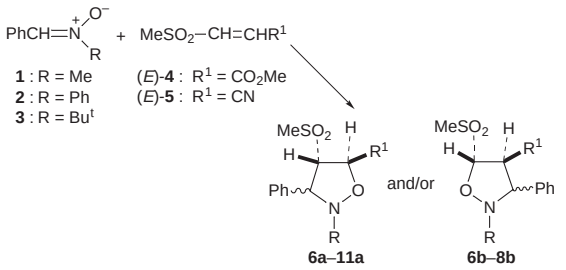
The cycloaddition reaction of nitrones to unsaturated methylsulfones and substituted crotonic esters gives a sole product or a mixture of tri- or tetra-substituted isoxazolidines, such that with disubstituted dipolarophiles the regiochemistry is dependent upon the nitrone and the vicinal electron-withdrawing group (CN or CO_2Me) but with trisubstituted olefins, regiospecific cycloadditions are observed.

1,3-Dipolar cycloaddition reactions to alkenes are a valuable and versatile synthetic methodology for the synthesis of polyfunctionalized organic molecules.[1] The transfer of the stereochemical information of the olefin to the stereocenters of the heterocyclic ring is an advantage in cycloaddition reactions with α,β-unsaturated esters,[2a,b] for the stereocontrolled synthesis of key intermediates of β-lactams.[2c]

In view of our interest in evaluating the factors affecting the regioselectivity in the cycloaddition of nitrones to various alkenes[3] we investigated the synthesis of new isoxazolidines starting from unsaturated methylsulfones possessing vicinal electron-withdrawing (CN or CO_2Me) substituents since the number of papers on the use of unsaturated sulfones is limited.[4]



Scheme 1

We have examined the reactions of nitrones **1**–**3** with methylsulfones **4**,**5**. The reactions were carried out in benzene solution for the times given in Table 1. As shown in Scheme 1, the reactions lead to a single product or a mixture of 3,4,5-trisubstituted isoxazolidine regioisomers **6**–**11a**,**b**; the diastereoisomeric ratios **a** : **b** were determined by ^{1}H NMR. In all cases the 4-sulfonyl isomer **a** is the sole or dominant cycloadduct and both of the regioisomers **a** and **b** could be separated by column chromatography. The assignment of regiochemistry, structure and relative configuration were established by analytical and spectroscopic data. Thus treatment of **1** with **4** afforded a mixture of **6a**,**b**. The ^{13}C NMR spectrum of **6b** shows the C-5 resonance at lower field (δ 92.39) than observed for **6a** (δ 75.76) attributable to a deshielding effect of the neighbouring oxygen atom and sulfonyl group characterizing regioisomer **b**. Reaction of **1** with **5** gave a mixture of **7a**,**b**. In this case, however, the isolated solid **7b** was in fact a non-separable mixture of adducts **7b$_1$** and **7b$_2$** in the ratio 70 : 30. The ^{13}C NMR spectrum of mixture **7b** showed the C-5 resonances resulting from the same regiochemistry for **7b$_1$** and **7b$_2$**. The ^{1}H NMR spectrum of **7b** exhibited a doublet for H-3 at δ 4.20 (**7b$_1$**) and 4.08 (**7b$_2$**). The small coupling constant $J_{3,4}$ 6.21 Hz compared to $J_{3,4}$ 9.50 Hz indicated its *trans* relationship with the H-4 proton in **7b$_1$** according to $J_{trans} < J_{cis}$.[5] All these data indicate that **7b$_1$** and **7b$_2$** are epimers at the carbon atom bearing the phenyl group. Reaction of **2** with **4** gave a mixture **8a**,**b** while **2** with **5** led to the sole product **9a**. Only one cycloadduct **10a** or **11a** was isolated when **3** reacted with **4** or **5**, respectively. Since nitrone cycloaddition takes place with retention of configuration, H-4 and H-5 protons are *trans* to each other in cycloadducts **6**–**11a**,**b** whatever the coupling constants $J_{4,5}$. The relationship between H-3 and H-4 can be deduced from the values of $J_{3,4}$ by comparison with literature results.[5,6] For isoxazolidines **6**–**11a and 7b$_1$**, the coupling constant $J_{3,4}$

Table 1 Reaction time, physical data and yields for compounds **6**–**11a**,**b** and **16**–**20**[a]

Compound	R	R^1	R^2	R^3	R^4	Reaction conditions	*t*/h	Mp/°C	**a**:**b**	Yield[b] (%)
6a	Me	CO_2Me	—	—	—	[c]	72	121–122	65 : 35	26
6b	Me	CO_2Me	—	—	—	[c]	72	104–105		13
7a	Me	CN	—	–	—	[c]	72	146–147	50 : 50	45
7b	Me	CN	—	—	—	[c]	72	124–126		33
8a	Ph	CO_2Me	—	—	—	[c]	72	135–136	60 : 40	42
8b	Ph	CO_2Me	—	—	—	[c]	72	144–146		14
9a	Ph	CN	—	–	—	[c]	48	116–117	100 : 0	73
10a	But	CO_2Me	—	—	—	[d]	144	160–161	100 : 0	44
11a	But	CN	—	—	—	[d]	96	184–185	100 : 0	45
16a	Me	—	Me	$MeSO_2$	H	[c]	120	108–109	100 : 0	45
17a	Ph	—	Me	$MeSO_2$	H	[c]	168	140–141	100 : 0	47
18b	Me	—	Cl	Me	H	[c]	96	43–44	100 : 0	52
19b	Ph	—	Cl	Me	H	[c]	96	Oil	100 : 0	48
20	Me	—	—	—	—	[c]	168	Oil	—	41

[a]Satisfactory elemental analyses were obtained for all products. [b]Isolated yield. [c]In benzene at room temperature. [d]In refluxing benzene.

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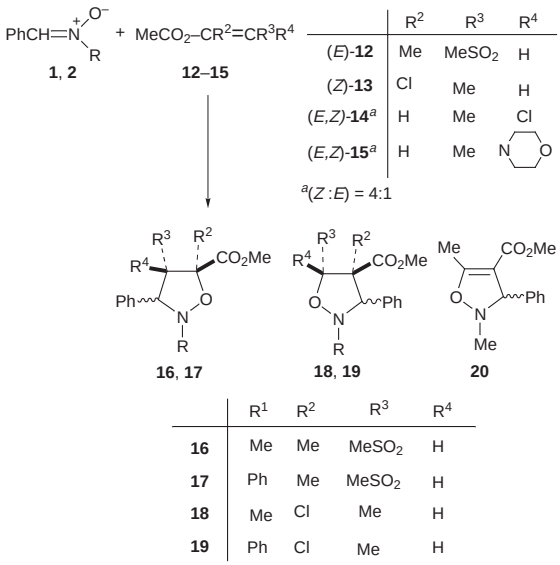

	R^1	R^2	R^3	R^4
16	Me	Me	$MeSO_2$	H
17	Ph	Me	$MeSO_2$	H
18	Me	Cl	Me	H
19	Ph	Cl	Me	H

Scheme 2

of *ca*. 6–8 Hz indicated a *trans* relationship between H-3 and H-4, in agreement with literature results.[5,6] NOE experiments carried on **6a** confirmed this attribution: indeed 5% enhancements were observed for H-5 and H-3 upon saturation of $MeSO_2$ which suggested that these protons are on the same side of the ring. For cycloadducts **6b** and **7b$_2$** the coupling constant values $J_{3,4}$ of *ca*. 9 Hz indicated a *cis* relationship between H-3 and H-4. For compound **8b** the coupling constant value of $J_{3,4}$ 8.4 Hz does not permit unequivocal establishment of the relative stereochemistry at C-3/C-4. We attempted to evaluate if steric effects may be at the origin of the different stereoselectivities observed in reactions of various esters with nitrones. With this purpose we introduced an electron donating substituent α or β to the ester group, so called captodative olefins,[7] to study the chemical behaviour of such cycloaddition reactions. The reactions of methylsulfonyl-, chloro- and morpholino-crotonic esters **12**–**15** with nitrones **1**, **2** can be compared with the experimentally observed regioselectivities in the corresponding cycloadditions to olefins **4**, **5** (Table 1). As shown in Scheme 2, the cycloadditions took place with complete regioselectivity, affording tetrasubstituted isoxazolidines **16**–**19** or 3,4,5-trisubstituted isoxazoline **20**. Their structures and regiochemistries were established by analytical and spectroscopic data. The presence of the methyl group increases the regioselectivity of the reactions compared with that for **4** with the same nitrones **1**, **2**. In the ^{1}H NMR spectra of **16** and **17** the presence of two doublets (1H for each) for **16** and **17**, attributed to H-3 and H-4, characterize their structures unequivocally. The cycloaddition reactions of **1**, **2** with **13** invert the regiochemistry and lead to isoxazolidine **18** or **19**, respectively. The presence of a singlet (1 H) and a quartet (1 H) for **18** and **19**, attributed to the C-3 and C-5 protons, respectively, characterizes their structures unequivocally. The reaction of **14** and **15** with **1** gave unstable isoxazolidines which through elimination of HCl or morpholine afforded the same isoxazoline **20** which has been previously prepared by Black *et al*.[8]

In conclusion, the studied cycloaddition reactions have been found to occur with high regioselectivity and lead to a sole or dominant heterocycle substituted at position 4 by an electron-withdrawing group; the results compare very well with similar literature data.[4]

A judicious choice of substituents in the trisubstituted alkenes is crucial to achieve high or complete selectivity in favour of 4- or 5-carbomethoxy-substituted isoxazolidines. Apart from selectivity aspects, the isoxazolidines formed should be of interest as precursors for the synthesis of a variety of aminoalcohol derivatives which could be readily converted into β-lactams.[2,9]

Experimental

The ^{1}H NMR spectra (300.13 MHz) and ^{13}C NMR spectra (75 MHz) were recorded on a Brücker MLS 300 spectrometer. Chemical shifts are expressed in ppm downfield from internal $SiMe_4$. Column chromatography was performed with Merck silica gel 60 (70–230 mesh) or silica gel (35–70 mesh) for flash chromatography. Elemental analyses were performed by the Microanalytical Laboratory, operated by the Department of Analyses of Vernaison (France). Starting dipolarophiles **4**, **5**, **12**[10] and **13**,[11] **14**,[12] **15**[13] were prepared according to known methods.

Procedure for Cycloaddition Reactions.—A solution of nitrone (0.01 mol) and olefin (0.01 mol) in benzene (50 ml) was stirred at room temperature or at reflux for the requisite time. The solvent was removed and the crude product purified by chromatography on silica gel with hexane–ethyl acetate as eluent, or by recrystallization.

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