Studies Towards Diastereoselective Additions of 2,2-Dimethyl-3,4-dihydro-2*H*-pyrrole *N*-Oxide to Chiral Acrylates and Crotonates

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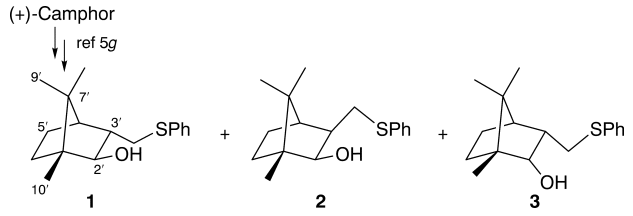
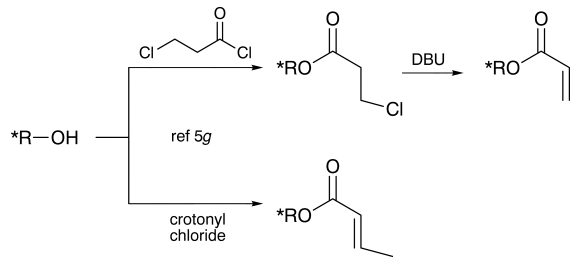
1,3-Dipolar additions of 2,2-dimethyl-3,4-dihydro-2*H*-pyrrole *N*-oxide (**5**) were studied with chiral acrylates **6**–**9** and chiral crotonates **10**–**12** derived from (+)-camphor.

Nitrone cycloaddition is a very important class of 1,3-dipolar cycloaddition reactions and has been utilized for the syntheses of a variety of natural products.[1] Many of these reports utilize either a non-asymmetric approach or an asymmetric approach wherein the nitrone is chiral.[3] Only a few reports describe the use of chiral dipolarophiles.[4] Recently, we reported 1,3-dipolar cycloadditions of nitrone[5c–e] and diazomethane[5f] to enantiomerically pure esters and lactones with an alkoxy-substituent in the γ-position leading to the regio- and stereo-selective formation of isoxazolidines and pyrazolines. We report here a study of the addition of 2,2-dimethyl-3,4-dihydro-2*H*-pyrrole *N*-oxide (**5**) to the chiral acrylates **6**–**9** and the chiral crotonates, **10**–**12** obtained from (+)-camphor and (−)-menthol. The preparations of chiral acrylates and crotonates are schematically represented in Schemes 1 and 2.[5g]



Scheme 1



Scheme 2

Addition of **5** to acrylates **6**–**9** were carried out in CH_2Cl_2 at ambient temperature (Scheme 3). The addition to **6** showed three spots on monitoring by TLC and the products were isolated by column chromatography. Whereas the two less polar and closely appearing fractions were due to individual cycloadducts, the more polar spot corresponded to two nonseparable adducts. ^{1}H and ^{13}C NMR spectra of all the four compounds were comparable and supported the adducts to have 2-alkoxycarbonyl substituents. 3-Substituted adducts were however, not detected.

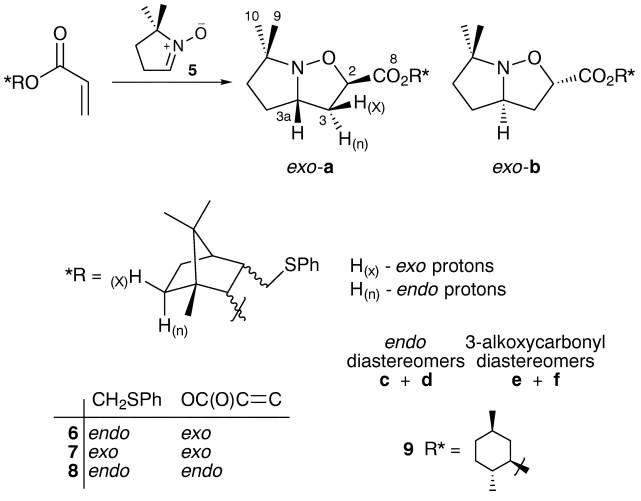
It was not possible to determine the orientation of the 2-alkoxycarbonyl substituents in the above molecules only on the basis of ^{1}H and ^{13}C NMR spectra. This problem was resolved by assignment of the various protons in these molecules by COSY sequence and their relative disposition (especially of the 2-, 3- and 3a-protons) by NOESY experiments. The diastereoselectivity (Table 1) was determined by integration in ^{1}H NMR spectra. In order to improve the diastereoselectivity, **7** and **8** were reacted in micellar media (0.1 M SDS solution). The reactions were found to be sluggish and did not go to completion even after 15 d. The sluggishness of reaction could be due to poor participation of nitrone in the hydrophobic environment of the misceles, unlike the acrylates. The major reaction seem to occur in the aqueous phase. The selectivity observed in SDS solution was better compared to that in CH_2Cl_2. To check if this improvement is due to change of solvent, the cycloaddition of **5**–**7** was carried out in water as well. As expected, the reaction was sluggish as in SDS solution and here again an improvement in diastereoselectivity of the 2-*exo*-carboxylate adduct was observed.

Table 1 Diastereomeric ratio and effect of solvents

Acrylates	**a**:**b**, (**a**+**b**) (%)	**c**:**d**[a], (**c**+**d**) (%)
6[b]	1.1:1, (85)	–, (15)
7[b]	1.5:1, (82)	–, (18)
7[c]	1.8:1, (85)	–, (15)
7[d]	2.1:1, (76)	–, (24)
8[b]	1.3:1, (84)	–, (16)
8[c]	1.8:1, (85)	–, (15)
9[b]	1.3:1, (78)	–, (16)[e]

[a]Not determined; [b]In dichloromethane; [c]In 0.1 M SDS solution; [d]In water; [e]6% of a 1:1 ratio of 3-alkoxycarbonyl diasteromers **e** and **f** was observed.

Earlier we reported[5d] the cycloaddition of menthyl crotonate with **5** and observed the formation of a single product. In continuation of these studies, we performed 1,3-dipolar cycloaddition of crotonates **10**–**13** with **5**. Additions of **5** to crotonates **10**–**12** were done in refluxing benzene solution



Scheme 3

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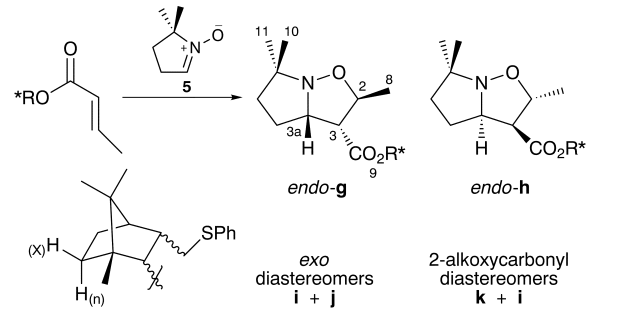
Table 2 Diastereomeric ratio due to π-facial selectivity and percentage composition of adducts

Crotonates	**g**:**h**, (**g** + **h**) (%)	**i**:**j**, (**i** + **j**) (%)	**k**:**l**, (**k** + **l**) (%)
10	–[a], (79)	1.1:1, (9)	1.2:1[b], (12)
11	1.6:1[c], (69)	1.1:1, (5)	1.4:1, (26)
12	2.3:1[b], (71)	–[a], (9)	1.3:1, (20)
13[d]	–, (88)	–, (4)	–, (8)

[a]Not assigned; [b]Peaks not resolved to base line; [c]From ^{13}C NMR; [d]**g** = **h**, **i** = **j**, **k** = **l**.

(Scheme 4). TLC of the reaction mixture in each case showed two spots and these components were separated by column chromatography. The major fraction showed the presence of four diastereomers and the minor fractions of two diastereomers by ^{1}H NMR spectra. With the aid of a COSY experiment and the ^{1}H NMR spectra it was concluded that all the minor fractions were composed of two 3-alkoxycarbonyl adducts and the major fractions had a pair of 2-alkoxycarbonyl adducts and a pair of 3-alkoxycarbonyl adducts. ^{13}C NMR assignments were done on the basis of chemical shifts and assignments of similar molecules.[6] Table 2 sums up the various selectivities obtained.

The results obtained above can be explained by FMO theory. Accordingly, for acrylates the HOMO (dipole)-LUMO (dipolarophile) interaction is energetically favour-



	CHSPh	OC(O)C=CMe
10	*endo*	*exo*
11	*exo*	*exo*
12	*endo*	*endo*

13 R* = Me (methyl crotonate)

Scheme 4

able. This leads to the formation of 2-substituted adducts. Since there is a small difference between the terminal coefficients in the nitrone HOMO, it has been indicated that LUMO (dipole)–HOMO (dipolarophile) interaction determines the regioselectivity.[7] Likewise, it has been reported[8] that addition of 3,4-dihydro-2*H*-pyrrole *N*-oxide to methyl acrylate leads to preferential formation of 2-methoxycarbonyl adducts. The formation of 3-methoxycarbonyl products in 20% yield were also noticed. In comparison, the addition of **5** to **6**–**8** led to the formation of 2-alkoxycarbonyl adducts only, and, in the case of **9** only, 6% 3-alkoxycarbonyl adducts were obtained. This observation is accountable for by the large bulk in the alkoxy groups in the dipolarophiles **6**–**9**. The geometry of approach of **5** to the dipolarophiles **6**–**9** in the formation of 3-substituted adducts involve larger steric interaction compared to the formation of 2-substituted adducts, and hence the latter products are favored in line with stereoelectronic factors. The diastereomeric excess (de) of 2-*endo*-alkoxycarbonyl adducts formed in these reactions could not be determined where as the de of 2-*exo*-alkoxycarbonyl adducts were determined by ^{1}H NMR. The obtained selectivity was poor. This was due to a very low conformational energy difference between the s-*cis* and s-*trans* enoate conformers based on a calculation done on methyl acrylate using the PCMODEL program. Therefore the nitrone additions could occur from both π faces of the acrylates without much discrimination.

Regioselectivity of addition of **5** to crotonates **10**–**12** is also in line with the earlier observation.[7] In contrast to high regioselectivity obtained on cycloaddition to acrylates **6**–**9**, there is a loss of regioselectivity with considerable formation of 2-alkoxycarbonyl products. The formation of 2-alkoxycarbonyl adducts in the present case is large (12–26%, Table 2) and is favoured due to the large steric bulk of the alkoxy groups. These results are in accordance with an increase in the formation of 2-substituted alkoxycarbonyl adducts on increasing the bulk of the crotonates from methanol to isopropanol to *tert*-butanol on addition of 3,4-dihydro-2*H*-pyrrole *N*-oxide.[11]

The diastereoselectivity obtained was determined wherever possible by NMR analysis (Table 2). Unfortunately, the selectivity obtained is not high, and is attributed to free conformational mobility between the s-*cis* and s-*trans* orientation of the enoate moiety at the reaction temperature. The product distribution seems to depend on the approach of nitrone to dipolarophile and the conformation of the enoate moiety in the transition state during the addition (see full text version for discussion of the transition state).

The involvement of *synperiplanar* geometries of enoates during uncatalysed cycloadditions have precedence in the addition of nitrile oxide to chiral acrylates and crotonates and in the Diels-Alder addition of cyclopentadiene to chiral acrylates.[14] For crotonates also, better selectivity was achieved with the use of auxiliaries **2** and **3** than **1**. The best 3-*endo* selectivity obtained was for the crotonates **12** (39% de).

Techniques used: IR, ^{1}H and ^{13}C NMR, 2D (^{1}H-^{1}H) COSY

References: 14; Schemes: 4; Figs: 1; Tables: 3

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