Cycloadditions of Chiral Nitrones

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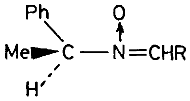
Summary 1,3-Dipolar cycloaddition of chiral nitrones to prochiral olefins or phenyl isocyanate yields diastereoisomeric non-racemic 2,3,5-substituted isoxazolines or 2,3,4-substituted 2,4-oxazolidin-5-ones, the formation of one of the diastereoisomers being preferred; the composition of the mixtures was determined.

IT is generally accepted that 1,3-dipolar cycloadditions are single-step, four-centre, concerted reactions in which two new σ-bonds are formed. The 1,3-dipolar cycloaddition of nitrones is also a kinetically controlled *cis*-stereospecific reaction[1–3] and has been reviewed.[4]

Monosubstituted alkenes form addition products with nitrones regioselectively in such a way that the substituent at the ethylenic carbon atom becomes the substituent in the 5-position of the resulting isoxazolidine ring.[2] The highest degree of stereoselectivity was observed in the case of nitrones with pronounced steric hindrance such as *C,N*-diphenylnitrone, but in other cases there was also considerable stereoselectivity.

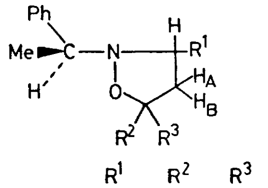
We have now studied a series of cycloadditions of this type using *N*-chirally substituted nitrones and we have examined the asymmetric induction in the isoxazolidines obtained.

We have studied the cycloadditions of the (*S*)-nitrones (I) and (II) with various dipolarophiles; the results are given in Tables 1 and 2. The chemical yields of the cycloadditions were high (60—100%). For compounds (III)—(VI), a mixture of four optically active products was generally obtained as pairs of diastereoisomers (A),(B) and (C),(D) arising from *cis*- and *trans*-addition, respectively. The mixtures of diastereoisomers (A),(B) and (C),(D) in some, but not all, cases could be separated by preparative t.l.c. and the composition of the mixtures was also determined by integration of signals in their ^{1}H n.m.r. spectra.

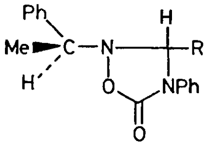


(I); R = Ph, $[\alpha]_{578}^{20}$ +83·4° (*c* 1, CH_2Cl_2)

(II); R = Bu^t, $[\alpha]_{578}^{20}$ −6·3° (*c* 1, CH_2Cl_2)



	R^1	R^2	R^3
(III)	Ph	H	Ph
(IV)	Ph	Me	CO_2Me
(V)	Ph	H	CO_2Me
(VI)	Bu^t	H	Ph



(VII) R = Ph

(VIII) R = Bu^t

It was possible to assign the *cis*- or *trans*-configuration to the pairs of diastereoisomers of (III)—(VI) from their n.m.r. spectra, in particular from the positions of the 4-H_A and 4-H_B signals. It has been shown[5] that for isoxazolidines

TABLE 1. Cycloadditions of the nitrones (I) and (II) with dipolarophiles to give diastereoisomeric products (III)—(VI).

Nitrone	Dipolarophile	Product	% Chemical yield	Diastereoisomer composition (%) *cis*[a] (A)	(B)	% e.e.[b]	*trans*[a] (C)	(D)	% e.e.[b]
(I)	$PhCH{=}CH_2$	(III)	90	76[c]	11[d]	75	8	5	5
(I)	$MeO_2CCMe{=}CH_2$	(IV)	90	62[e]	20	51	18	0	100
(I)	$MeO_2CCH{=}CH_2$	(V)	60	40[f]	23	27	29[g]	7	61
(II)	$PhCH{=}CH_2$	(VI)	85	42[h]	24[i]	27	22[j]	12	34

[a] *cis* and *trans* refer to the relative positions of the R^1 and R^3 substituents. [b] Enantiomeric excess, *e.g.* = [%(A) − %(B)]/[%(A) + %(B)]. The compounds indicated have been isolated pure; physical constants (m.p./°C, $[\alpha]_{578}^{20}$, *c* 1 in CH_2Cl_2). [c] 87, + 54·4°. [d] Oil, −104·4°. [e] Oil, +10·7°. [f] Oil, −21·6°. [g] Oil, −19·2°. [h] 89—92, −55·0°. [i] (83% pure) oil, −27·5°. [j] 130, −58·3°.

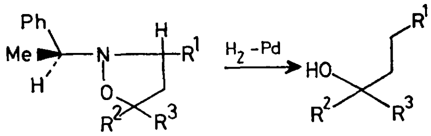
having the *cis*-configuration the multiplets due to these protons are broader than those of the *trans*-isomers. The ratio of the sum of the yields of (A) and (B) to that of the yields of (C) and (D) is a measure of the *cis*-stereoselectivity of the cycloaddition. Within the pairs of diastereoisomers, the enantiomeric excess of the asymmetric synthesis can be calculated (Table 1). Cycloadditions with PhN=C=O to give the isoxazolidinones (VII) and (VIII) also showed asymmetric induction (see Table 2 for e.e. values).

In some cases we have also hydrogenolysed (H_2-Pd) the *cis*-diastereoisomer (A) which is formed in excess, after purification by preparative t.l.c. Compound (III)-(A) gave $PhCH_2CH_2CH(OH)Ph$ (IX), $[\alpha]^{20}_{578}$ −25·7° (*c* 1, CH_2Cl_2) while (IV)-(A) gave $PhCH_2CH_2C(Me)(OH)CO_2Me$, $[\alpha]^{20}_{578}$ −38·2° (*c* 1, CH_2Cl_2).

Table 2. Cycloadditions of the nitrones (I) and (II) with PhN=C=O to give the diastereoisomeric products (VII) and (VIII).

Nitrone	Product	% Chemical yield	Diastereoisomer composition (%) (A)	(B)	% e.e.[a]
(I)	(VII)	72	67[b]	33[c]	34
(II)	(VIII)	100	60[d]	40[e]	20

[a] See footnote[b] to Table 1. [b] Isolated pure, m.p. 165 °C, $[\alpha]^{20}_{578}$ +27·6° (*c* 1 in CH_2Cl_2). [c] Isolated pure, m.p. 189—192 °C, $[\alpha]^{20}_{578}$ −123° (*c* 1 in CH_2Cl_2). [d] m.p. 182 °C, $[\alpha]^{20}_{578}$ +12°. [e] m.p. 160 °C, $[\alpha]^{20}_{578}$ − 23·6° (*c* 1 in CH_2Cl_2).



The optical purity of the alcohol (IX) was evaluated from the n.m.r. spectrum of its ester with ω-(−)-camphanic acid measured in the presence of $Eu(fod)_3$.[6] The signals of all three methyl groups of the acyl group of the ester were measured. In the case of the ester obtained from the racemic alcohol, all three methyl singlets underwent magnetic differentiation on addition of $Eu(fod)_3$ and changed into three pairs of equivalent singlets. Under the same conditions there was no resolution of the same set of signals for the ω-(−)-camphanic acid ester of the optically active 1,3-diphenylpropan-1-ol obtained by hydrogenolysis, within the accuracy of measurement of the n.m.r. spectra.

Thermodynamic studies on the mixture of diastereoisomers (VI) have shown that as the reaction temperature increases, the equilibrium of the *cis*- and *trans*-diastereoisomers is shifted from an initial value of 65 : 35 *cis* : *trans* to 52 : 48 after 60 h at 100 °C.

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