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Communications

1, 3-Dipolar cycloaddition reactions of N-cyclohexylnitrone

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1, 3-Dipolar cycloaddition reaction of nitrone **1**, derived from 2, 3-dihydro-4*H*-pyran with different dipolarophiles, have been studied. The reactions have been found to be highly regio- and stereo-selective.

Nitrones are versatile synthetic intermediates and excellent spin trapping reagents[1]. Nitrones are prepared either by condensation of aldehydes and ketones with hydroxylamines[1] or by oxidation of the corresponding N, N-disubstituted hydroxylamines[2].

In the present study the formation of nitrone **1** has been achieved (Scheme I) by refluxing N-cyclohexylhydroxylamine[3] and 2, 3-dihydro-4*H*-pyran in dry benzene which were then trapped *in situ* by different dipolarophiles in a 1, 3-dipolar cycloaddition reaction with high regio- and stereoselectivity giving **2** (cf. Table I). Dimerization of nitrone could also be controlled under this condition[4].

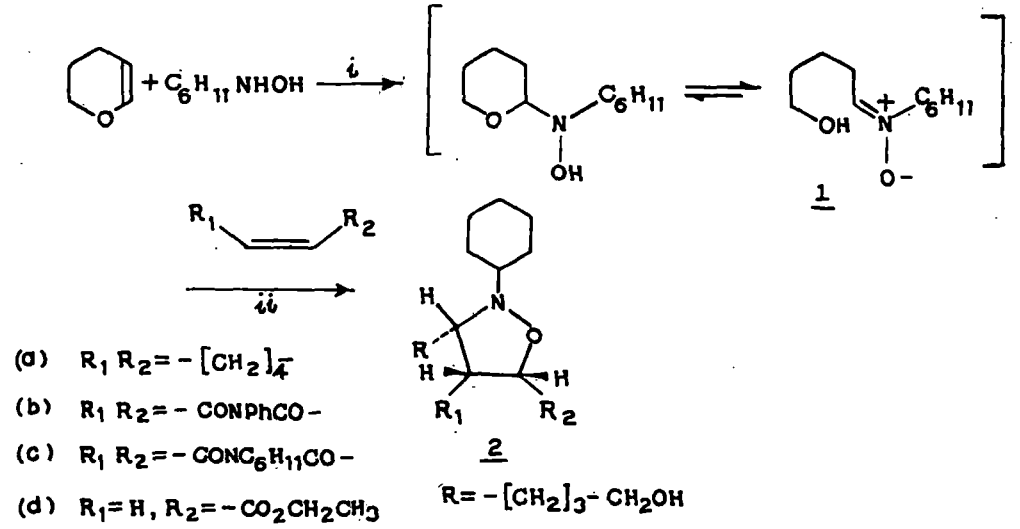
The concerted nature of these cycloaddition reactions with nitrone as 1, 3-dipole was generally accepted. The regioselectivity in these reactions was rationalized by using the frontier-orbital theory[5]. The ethyl acrylate adduct corresponded to this theory. Therefore, the 5-substituted adduct for ethyl acrylate is due to LUMO (nitrone)-HOMO (dipolarophile) interaction.

Cycloaddition of *Z*-nitrone via an *exo*-transition state results in the formation of *syn*-isoxazolidine[6]. The relative configurations of C-3, C-4 and C-5 in the adducts were in favour of the *exo*-transition state geometry. The proton at C-3 and C-4 were *syn* in **2b** and **2c** and their coupling constants ($J_{3,4}$ = 6 Hz) were also indicative of this stereochemical relationship, whilst a D_2O shake revealed the presence of one rapidly exchangeable proton at C-5. The stereochemical assignments of **2a** and **2d** at C-3, C-4 and C-5 on the isoxazolidine ring were also determined from ^1H NMR spectra. The coupling constant values ($J_{3,6}$ = 7.5-8.0 Hz) revealed the formation of *syn*-isoxazolidine in both the cases via *exo*-transition state.

Further study of the reaction in various systems is in progress.

Table I—Physical data of the cycloadducts (**2**)

Cycloadduct	Yield (%)	R_f	m.p. °C
2a	33.63	0.30	106
2b	26.01	0.34	132
2c	29.50	0.38	114
2d	55.94	0.41	Dark red gummy liquid



Scheme I

Experimental

General procedure for cycloaddition

N-Cyclohexylhydroxylamine (2.17 mmoles) was added to a solution of 2, 3-dihydro-4*H*-pyran (1 equivalent) in dry benzene (20 ml) under nitrogen atmosphere and the reaction mixture refluxed for 24 hr. The reaction was monitored by TLC [silica gel; ethyl acetate-benzene (1:10)]. Dipolarophiles were added (1 equivalent) at this stage and the reaction mixture was further refluxed for 24 hr. The solvent was evaporated off and the cycloadducts [cf., Table 1] were isolated by column chromatography using benzene-pet. ether (60°-80°) as eluant.

Compound 2a: MS: m/z 281 (M^+), 113, 98; IR ($CHCl_3$): 3264 (br), 2924, 2851, 1540, 1443, 1248 cm^{-1}; PMR ($CDCl_3$): δ 3.80-3.7 (d, 1H, J=4.5 Hz, C_5-H), 3.10-3.06 (br, 1H, >CH−N<), 2.63-2.46 (q, 1H, J=7.5 Hz, C_3-H), 2.36-2.16 (dd, 1H, J=4.5, J=7.5 Hz, C_4-H), 2.00-0.5 (m, 26H).

Compound 2b. MS: m/z 372 (M^+), 299, 289, 242, 173, 117, 113, 78; IR ($CHCl_3$): 3460 (br), 2940, 2840, 1780, 1700, 1690, 1480, 1395, 1190 cm^{-1}; PMR ($CDCl_3$): δ 7.80-7.30 (m, 5H, C_6H_5), 5.70-5.45 (br, 1H, C_5-H, exchangeable with D_2O), 4.50-4.26 (dd, 1H, J=6 Hz, C_4-H), 3.38-3.10 (dd, 1H, J=6 Hz, C_3-H), 3.00-2.83 (m, 1H, >CH−N<), 2.16-0.43 (m, 18H).

Compound 2c: MS: m/z 378 (M^+), 323, 305, 295, 277, 267, 251, 208, 196, 170, 114, 83; IR ($CHCl_3$): 3580, 2920 (br), 1775, 1690, 1440, 1390, 1140, 890 cm^{-1}; PMR ($CDCl_3$): δ 5.75-5.0 (br, 1H, C(5H)H, exchangeable, with D_2O), 4.15-3.93 (dd, 1H, J=6.06 Hz, J=6.06, C_4-H), 3.20-3.10 (m, 1H, >CH−N<), 3.06-2.94 (dd, 1H, J=6.06 Hz, C_3-H), 2.93-2.84 (m, 1H, >CH−N<O), 2.20-1.03 (m, 28H).

Compound 2d: MS: m/z 299 (M^+), 296, 242, 226, 204, 187, 142, 131; IR ($CHCl_3$): 3340 (br), 2930, 2850, 1725, 1440 cm^{-1}; PMR ($CDCl_3$): δ 4.77-4.64 (b, 1H, C(5)H, exchangeable with D_2O), 4.20 (q, 2H, $-OCH_2Me$), 3.10-2.98 (t, 1H, J=8.1 Hz, C_3-H), 2.98-2.80 (br, 1H, >CH−N<), 2.80-2.60 (q, 2H, J=8.1 Hz, C_4-H_2),, 2.35-0.60 (m, $-CH_3$ and remaining protons).

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