

STUDY OF CYCLOREVERSION OF NITRONE-CYCLODIMERS

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Abstract

A series of 1,3-dipolar cycloaddition reactions are carried out using cyclodimers of simple nitrones and various dipolarophiles; substituted isoxazolidines are isolated and identified. It is proved that such cyclodimers, in solution, are in equilibrium with their corresponding nitrones and enamines. It is also concluded that aldocyclodimers are more potent than keto-cyclodimers in establishing a similar equilibrium.

Introduction

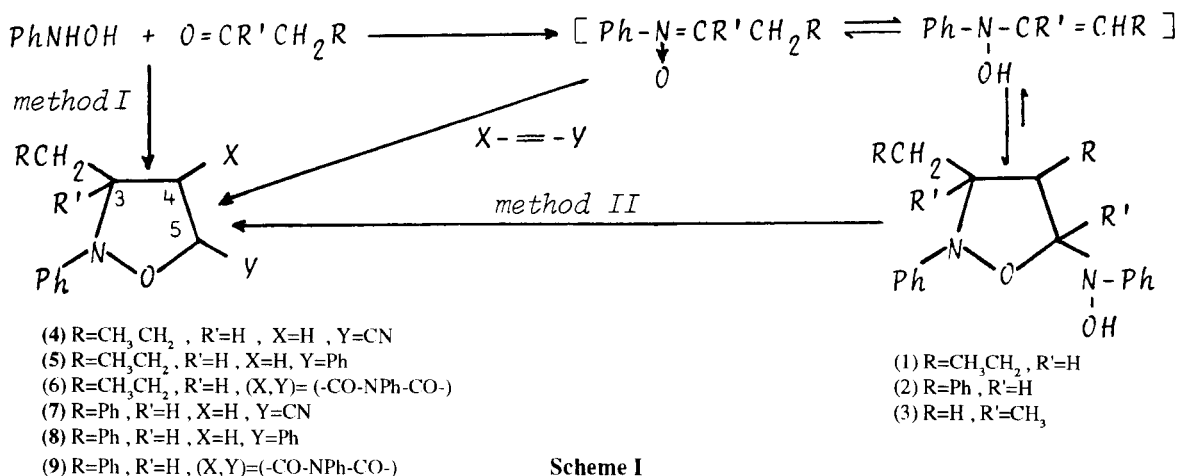
Reaction of hydroxylamines with aldehydes or ketones is a routine synthetic method of preparing nitrones. In recent years, however, more careful studies of the preparation of aldo- and keto-nitrones, containing α -hydrogens to the nitron moiety, have shown that the actual products of these reactions are the cyclodimers of these nitrones [1-5].

The formation of such cyclodimers is brought about by

the following cycloaddition reaction (Scheme I).

It is suggested that such cyclodimers are in equilibrium with their corresponding nitrones and enamines [6,7] the matter is not, however, conclusively settled.

The 1,3-dipolar cycloaddition reaction of nitrones leading to isoxazolidines has been widely reported and reviewed [8,9]. The corresponding cycloaddition reactions of cyclodimers, however, have not been investigated.



Scheme I

Keywords: Cycloreversion of nitron-cyclodimers

Results and Discussion

We intended to prove cycloreversion of the cyclodimers under investigation. To this end, we made use of dipolarophiles to trap the nitrones formed by the cycloreversion reaction. Two sets of reactions were carried out. In one set, the reaction of the cyclodimers with various dipolarophiles were studied. In the other, we examined the reaction of the same dipolarophiles with the nitrones, prepared *in situ*. We found the products of the two sets to be the same.

Since the cyclodimers could not have directly produced the substituted isoxazolidines obtained, the products must have been produced via an indirect pathway, i.e. a cycloreversion process. It is, therefore, reasonable to conclude that, in solution, the cyclodimers are in equilibrium with their corresponding nitrones and enamines (Scheme I).

Thus, *n*-butyraldehyde, phenylacetaldehyde, and acetone are reacted separately with phenylhydroxylamine to give the corresponding cyclodimers (1), (2) and (3), as previously described [2-5]. Cyclodimers (1) and (2) were reacted with acrylonitrile [10], styrene [11] and *N*-phenylmaleimide [12a, b] to give the corresponding substituted-isoxazolidines (4) - (9). Cyclodimer (3) failed to react with either of the named dipolarophiles; the inertness of this keto-cyclodimer shows that under the reaction conditions, it does not undergo cycloreversion. We carried out more experiments to test the extent of stability as well as the reactivity of (3) and similar keto-cyclodimers. The results are tabulated in Table I.

Experimental Section

General Techniques. ^1H NMR spectra (80 and 300 MHz) were recorded in CDCl_3 . Chemical shifts are reported in ppm relative to TMS as an internal reference. Coupling constants are given in hertz. Column and dry flash chromatography were used for purification of the products and were carried out on silica gel 60 (70-230 mesh). Mass spectra were recorded on a Kratos MS25 spectrometer. Purity of the products was checked by elemental analysis. Cyclodimers, used as starting materials, were prepared by previously reported methods and are not included in the experimental section.

General Procedures. Method I. A mixture of the cyclodimer, the appropriate dipolarophile, and solvent was magnetically stirred and refluxed. Removal of the solvent under reduced pressure gave a viscous residue which was further treated with ether-petroleum ether (60-80) mixture and was left in cold conditions overnight to give the cycloadduct isomers. Further purification of the cycloadducts was carried out by dry flash chromatography and recrystallization.

Method II. A mixture of phenylhydroxylamine, the carbonyl compound, the appropriate dipolarophile and solvent was magnetically stirred under reflux. Removal of the solvent under reduced pressure resulted in a gum. The gum was dissolved in ether-petroleum ether (60-80) mixture and was left overnight in cold conditions to give the corresponding cycloadducts. Subsequent purification of the products was done by recrystallization and chromatography.

Table I

Adduct	Method	Dipolarophile	Cyclodimer	Carbonyl compound	Solvent	Time (hr)	Yield (%)
(4)	I	acrylonitrile	(1)	---	acrylonitrile	4	66 ^a
	II	acrylonitrile	---	PrCHO	acrylonitrile	1.5	60
(5)	I	styrene	(1)	---	benzene	2.5	64 ^b
	II	styrene	---	PrCHO	styrene	1	-- ^c
(6)	I	<i>N</i> -phenylmaleimide	(1)	---	cyclohexane	4	89
	II	<i>N</i> -phenylmaleimide	---	PrCHO	ethanol	0.5	80
(7)	I	acrylonitrile	(2)	---	acrylonitrile	3	50
	II	acrylonitrile	---	PhCH_2CHO	acrylonitrile	1	-- ^c
(8)	I	styrene	(2)	---	benzene	2	60
	II	styrene	---	PhCH_2CHO	ethanol	1.5	-- ^c
(9)	I	<i>N</i> -phenylmaleimide	(2)	---	cyclohexane	0.5	96
	II	<i>N</i> -phenylmaleimide	---	PhCH_2CHO	ethanol	1.5	-- ^c

a: ratio isomer A/B = 3.6

b: ratio isomer A/B = 4.4

c: The reaction was followed by tlc, but successful separation was not attained.

5-Cyano-2-phenyl-3-propyl isoxazolidine (4)

Isomer A: Colorless solid, m.p. 31°C (Found C, 72.2; H, 7.5; N, 12.7. $C_{13}H_{16}N_2O$ requires C, 72.19; H, 7.46; N, 12.75); 1H NMR(300MHz) δ 1.0 (t,3H, CH_3); 1.66-2.0 (m,4H, CH_2); 2.35 (m,1H, H-4); 2.65 (m,1H, H-4); 3.8(m,1H, H-3) 4.85 (dd,1H, J=4.5 Hz, H-5); 7.0-7.4 (m,5H, C_6H_5); IR(KBr) 2270(CN), 1610 cm^{-1} ; m/z (e.i.) 216(M^+).

Isomer B: Yellow oil (Found C, 72.18; H, 7.42; N, 12.73. $C_{13}H_{16}N_2O$ requires C, 72.19; H, 7.46 N, 12.75); 1H NMR (300 MHz) δ 1.0 (t,3H, CH_3); 1.3-1.9 (m,4H, CH_2); 2.4 (m,1H, H-4); 2.63 (m,1H, H-4); 4.0 (m,1H, H-3); 4.85 (m,1H, H-5); 7.0-7.4 (m,5H, C_6H_5); IR(Neat) 2270(CN), 1610 cm^{-1} ; m/z (e.i.) 216(M^+).

2,5-Diphenyl-3-propyl isoxazolidine (5)

Isomer A: Colorless solid, m.p. 10-12°C (Found C, 80.9; H, 8.05; N, 5.1. $C_{18}H_{21}NO$ requires C, 80.86; H, 7.92; N, 5.24); 1H NMR (300 MHz) δ 1.05 (t,3H, CH_3); 1.4-2.0 (m,4H, CH_2); 2.05 (m,1H, H-4); 2.85 (m,1H, H-4); 3.95 (m,1H, H-3) 5.09 (dd,1H, J=7Hz, H-5); 6.9-7.5 (m,10H, C_6H_5); IR(KBr) 1600 cm^{-1} ; m/z (e.i.) 267(M^+).

Isomer B: Yellow oil (Found C, 80.82; H, 7.88; N, 5.3. $C_{18}H_{21}NO$ requires C, 80.86; H, 7.92 N, 5.24); 1H NMR (300 MHz) δ 1.05 (t,3H, CH_3); 1.5-2.0 (m,4H, CH_2); 2.54 (m,2H, H-4); 3.79 (m,1H, H-3); 5.29 (t,1H, J=8Hz, H-5); 6.98-7.0 (m,10H, C_6H_5); IR(Neat) 1600 cm^{-1} ; m/z (e.i.) 267(M^+).

2-Phenyl-3-propyl isoxazolidine-4,5-cis-dicarboxylic acid N-phenylimide (6)

Colorless needles, m.p. 95-6°C from cyclohexane (lit, 12a,b) colorless flakes, 106.5- 107.5 °C, from ethanol (Found C, 71.47; H, 6.0; N, 8.2. $C_{20}H_{20}N_2O_3$ requires C, 71.41; H, 5.99; N, 8.33); 1H NMR (300 MHz) δ 1.05 (t,3H, CH_3); 1.4-1.9 (m,4H, CH_2); 3.6 (d, 1H, J=7Hz, H-4); 4.68 (m, 1H, H-3); 5.07 (d,1H, J= 7Hz, H-5); 6.4-7.4 (m,10H, C_6H_5); IR(KBr) 1710, 1778(C=O), 1598 cm^{-1} m/z (e.i.) 336(M^+).

3-Benzyl-5-cyano-2-phenyl isoxazolidine (7)

Colorless needles, m.p. 92-93°C (Found C, 76.8; H, 6.0; N, 10.2. $C_{17}H_{16}N_2O$ requires C, 77.25; H, 6.1; N, 10.60); 1H NMR(300 MHz) δ 2.5 (m,2H, H-4); 2.9 (dd,1H, J=7.5Hz, CH_2 -Ph); 3.25 (dd,1H, J=7Hz, CH_2 -Ph); 4.09

(m,1H, H-3); 4.9 (dd,1H, J=5Hz, H-5); 6.9-7.4 (m,10H, C_6H_5); IR(KBr) 2250(CN), 1610 cm^{-1} ; m/z(e.i.) 265(M^+).

3-Benzyl-2,5-diphenyl isoxazolidine (8)

Colorless crystals, m.p. 56-8°C (Found C, 83.4; H, 6.7; N, 4.3. $C_{22}H_{21}NO$ requires C, 83.78; H, 6.71; N, 4.44); 1H NMR (300 MHz) δ 2.15, 2.78 (m,2H, H-4); 2.95 (dd,1H, J=5.5Hz, CH_2 -Ph); 3.3 (dd,1H, J=7Hz, CH_2 -Ph); 4.14 (m,1H, H-3); 5.1 (dd,1H, J= 7.5Hz, H-5); 6.9-7.4 (m,15H, C_6H_5); IR(KBr) 1600 cm^{-1} ; m/z (e.i.), 315(M^+).

3-Benzyl-2-phenyl isoxazolidine-4,5-cis-dicarboxylic acid N-phenylimide (9)

Colorless crystals, m.p. 192-4°C (Found C, 75.4; H, 5.3; N, 7.2. $C_{24}H_{20}N_2O_3$ requires C, 74.98; H, 5.24 N, 7.29); 1H NMR (300 MHz) δ 2.91 (dd,1H, J=6.5Hz, CH_2 -Ph); 3.19 (dd,1H, J= 8.5Hz, CH_2 -Ph); 3.71 (d,1H, J= 7.5Hz, H-4); 4.9 (t,1H, H-3); 5.09 (d,1H, J= 7.5Hz, H-5); 6.4-7.4 (m,15H, C_6H_5) IR(KBr) 1720, 1800(C=O), 1610 cm^{-1} ; m/z (e.i.) 384(M^+).

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