

1,3-Dipolar Cycloadditions Of C,N-diaryl nitrones to Methyl Cinnamate: Effect Of Reaction Conditions And Catalysts

Rina Saha, Avijit Banerji*,

Department of Chemistry, Government Maharani Sudarshan College, Bikaner, (Rajasthan).

Abstract

The present work describes the synthesis of isoxazolidines from the cycloaddition reaction between C-(4-chlorophenyl)-N-phenyl nitrone to methyl cinnamate under different reaction conditions. The effect of rare earth triflates as catalysts on 1,3-DC of nitrones has been reported in a limited number of publications, hence the effect of changing reaction conditions *viz.* reaction in the presence of solvent as well as in the absence of solvent and the presence of catalysts *viz.* ytterbium triflate, magnesium triflate, zinc triflate, lithium triflate, and also the reactions in the presence of montmorillonite clay K-10 and molecular sieves 4Å have been studied.

The reaction was performed by refluxing the nitrone with a three-molar excess of dipolarophile (methyl cinnamate) in 4–23 hours. The course of the reaction was monitored by TLC over silica gel using benzene-ethylacetate. The products were identified by IR, ¹H-NMR and ¹³C-NMR spectra. The reaction of C-(4-chlorophenyl)-N-phenyl nitrone with methyl cinnamate in different conditions gave the same major product 3,4-*trans*-4,5-*trans* [3-(4-chlorophenyl)-2,5-diphenyl-4-carbomethoxyisoxazolidine]. The catalytic reaction proceeded at the temperature about 65°C temperature at which the uncatalysed reaction hardly proceeds. Ytterbium triflate, lithium triflate and magnesium triflate played a greater role in enhancing the rates of reaction.

Key Words : 1,3-dipolar cycloaddition, nitrone, methyl cinnamate, reaction conditions, catalysts.

Introduction

The 1,3-dipolar cycloaddition is category of a organic chemical reaction belonging to the larger class of cycloadditions. It is the reaction between a 1,3-dipole and a dipolarophile, most of which are substituted alkenes, to form a five-membered ring. Cycloadditions of C-(4-chlorophenyl)-N-phenyl nitrone to methyl cinnamate were studied under different reaction conditions and catalysts.

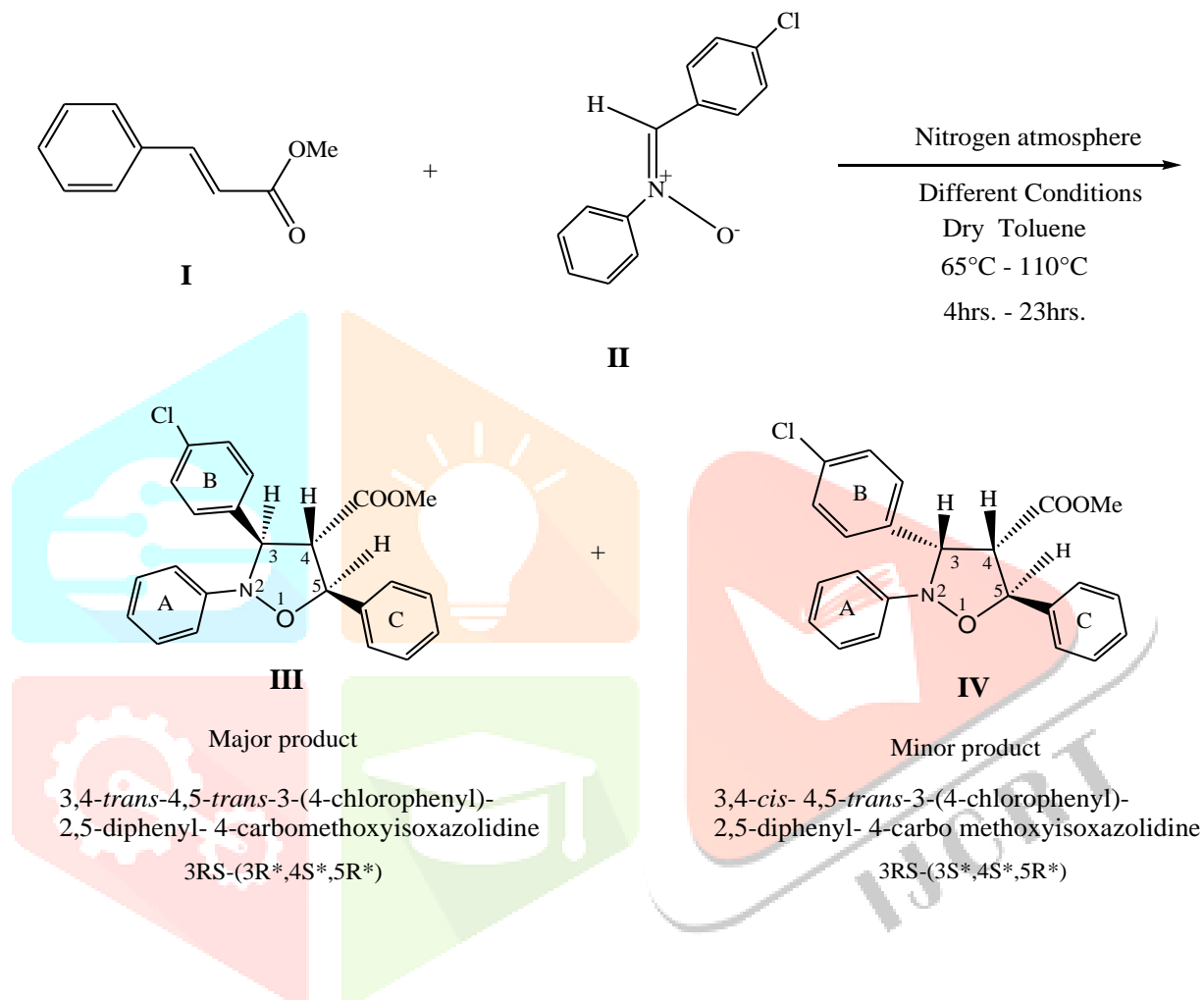
Reaction conditions: - (a) In refluxing toluene (~110°C); molar ratio of dipole: dipolarophile = 1:3. Time = 11 hrs.; Nitrogen atmosphere. (b) Solvent – free conditions; molar ratio of dipole: dipolarophile = 1:5. Temperature ~110°C. Time – 4 hrs. ; Nitrogen atmosphere. (c) In the presence of different catalysts, molar ratio of dipole : dipolarophile=1:3. Temperature ~65°C; Nitrogen atmosphere.

Result and Discussion

The reaction were performed by refluxing the nitrone with a three-molar excess of dipolarophile (methyl cinnamate) in 4–23 hours. The course of the reaction was monitored by TLC over silica gel using benzene-ethylacetate (4:1). The 300 MHz ¹H-NMR analysis of the crude product, obtained after removal of the solvent in a Büchi rotary evaporator under reduced pressure, showed the presence of two diastereoisomeric products (III) and (IV). From a

comparison of chemical shifts and coupling constants of the isoxazolidine ring protons, with those of established similar cycloadducts, it was found that the major product has structure (III) Type1, with the 3,4-*trans*-4,5-*trans* configuration. The corresponding ¹H-NMR chemical shifts and coupling constants of the isoxazolidine ring protons, indicated the diastereoisomeric 3,4-*cis*-4, 5-*trans* structure (IV) Type 2 for the minor product. The relative proportions of the products could be ascertained from the integration of the isoxazolidine ring protons.

The reactants as well as the products obtained are listed in Scheme 1.



Scheme 1: Cycloaddition Reactions of C, N-Diarylnitrones to Methyl cinnamate

Complete characterisation of structure as well as the regio- and stereochemistry of the major cycloadduct were possible by analysing the NMR spectra. 300 MHz ¹H-NMR; (2.) 75.5 MHz ¹³C-NMR (a) fully decoupled, (b) DEPT.

Elemental analyses and the mass spectrometrically derived molecular weights gave results which were in agreement with those expected for the cycloadducts. The EIMS mass spectrum of compound (III) showed a peak at 393 in accordance with the molecular formula C₂₃H₂₀NO₃Cl. The important fragments were at m/z 231[C₁₃H₁₀NOCl], 215[C₁₃H₁₀NCl], 162[C₁₀H₁₀O₂], 147[C₉H₇O₂], 131[C₉H₇O], 103[C₈H₇], 91 [C₇H₇], 77[C₆ H₅]. The IR spectrum (recorded in KBr disc) of compound (III) showed strong absorption bands at 1737 cm⁻¹ indicating the presence of an unconjugated carbonyl group. Medium intensity bands in the region 2954, 2850 cm⁻¹ indicated the presence of aliphatic -CH- stretching. Band at 834 cm⁻¹ indicated the presence of 1,4-disubstituted benzene ring. Medium intensity bands at 757, 695 cm⁻¹ indicated the presence of monosubstituted benzene ring(s).

The complete ¹H-NMR and ¹³C-NMR assignments of Compound (III) are given in Table I.

Table I : 300 MHz. ^1H NMR and 75.5 MHz ^{13}C NMR Assignments of Compound III.

Proton no.	Chemical shift (δ , ppm)	Multiplicity (J, Hz)	Carbon no.	Chemical shift (δ , ppm)	Multiplicity from DEPT
H-3	5.13	d (6.6)	C-3	73.2	>CH-
H-4	3.49	dd (6.6),(8.6)	C-4	66.2	>CH-
H-5	5.31	d (8.6)	C-5	82.9	>CH-
-CO-O-CH ₃	3.56		-CO-O-CH ₃	170.7	
			-CO-O-CH ₃	52.5	
Ring A			Ring A		
H-2,6	6.95	d (7.7)	C-1	150.8	Quarternary
H-3,5	7.19	t (7.5)	C-2,6	114.3	=CH-
H-4	6.89	t (7.3)	C-3,5	126.9	=CH-
			C-4	122.1	=CH-
Ring B			Ring B		
H-2,6	7.39–7.46	m	C-1	136.5	Quarternary
H-3,5			C-2,6	130.2	=CH-
			C-3,5	129.1	=CH-
			C-4	134.3	Quarternary
Ring C			Ring C		
H-2,6	7.33-7.37	m	C-1	139.8	Quarternary
H-3,5			C-2,6	128.0	=CH-
			C-3,5	128.7	=CH-
H-4			C-4	127.8	=CH-

Table II: 300 MHz. ^1H NMR Assignments of Compound IV

Proton no.	Chemical shift (δ , ppm)	Multiplicity (J, Hz)
H-3	4.98	10.5
H-5	5.75	9.6

Table III : Yield of cycloadduct obtained from methyl cinnamate in different conditions:

Except for Serial No. 2, molar ratio of dipole: dipolarophile was 1: 3. For serial no.2, the molar ratio was 1: 5

S. No.	Nitrones	Dipolarophiles	Reaction condition	Time & Temperature of the reaction	Overall yield %	Diastereo-isomeric ratio III : IV
1.	<i>C</i> -(4-chlorophenyl)- <i>N</i> -phenylnitron	Methyl Cinnamate	Refluxing toluene	11 hrs. 110 °C	86	90.5 : 9.5
2.	<i>C</i> -(4-chlorophenyl)- <i>N</i> -phenylnitron	Methyl Cinnamate	Absence of solvent	4 hrs. 110 °C	84	94 : 6
3.	<i>C</i> -(4-chlorophenyl)- <i>N</i> -phenylnitron	Methyl Cinnamate	Ytterbium triflate	14 hrs. 65 °C	77	94 : 6
4.	<i>C</i> -(4-chlorophenyl)- <i>N</i> -phenylnitron	Methyl Cinnamate	Lithium triflate	19 hrs. 65°C	87	92 : 8
5.	<i>C</i> -(4-chlorophenyl)- <i>N</i> -phenylnitron	Methyl Cinnamate	Lithium perchlorate	12 hrs. 65 °C	53	85 : 15
6.	<i>C</i> -(4-chlorophenyl)- <i>N</i> -phenylnitron	Methyl Cinnamate	Magnesium triflate	16 hrs. 65 °C	89	91 : 9
7.	<i>C</i> -(4-chlorophenyl)- <i>N</i> -phenylnitron	Methyl Cinnamate	Zinc triflate	22 hrs. 65 °C	22	84 : 16
8.	<i>C</i> -(4-chlorophenyl)- <i>N</i> -phenylnitron	Methyl Cinnamate	Montmorillonite clay K-10	23 hrs. 65 °C	67	95 : 5
9.	<i>C</i> -(4-chlorophenyl)- <i>N</i> -phenylnitron	Methyl Cinnamate	Molecular sieve 4 Å	5 hrs. 110 °C	65	89 : 11

The reaction of *C*-(4-chlorophenyl)-*N*-phenyl nitron with methyl cinnamate in different conditions gave the same major product 3,4-*trans*-4,5-*trans* [3-(4-chlorophenyl)-2,5-diphenyl-4-carbomethoxyisoxazolidine]. The catalytic reaction proceeded at the temperature about 65°C temperature at which the uncatalysed reaction hardly proceeds. Ytterbium triflate, lithium triflate and magnesium triflate played a greater role in enhancing the rates of reaction.

Conclusions

The reaction of *C*-(4-chlorophenyl)-*N*-phenyl nitron with methyl cinnamate in different conditions gave the same major product 3,4-*trans*-4,5-*trans* [3-(4-chlorophenyl)-2,5-diphenyl-4-carbomethoxyisoxazolidine].

The use of different catalysts *viz* ytterbium triflate, lithium triflate and magnesium triflate played a role in enhancing the rates of reaction. . The products could be formed at the temperature about 65°C, temperature at which the uncatalysed reaction hardly proceeds. Thus there is a significant gain as these cycloaddition

reactions can be carried out under milder condition. Moreover there is some increase in the selectivity of process. Lithium perchlorates were less effective than the three other triflates.

Zinc triflate was not suitable as it gave lower yields than the other catalysts, and also did not increase the diastereoselectivity of the process.

The presence of molecular sieves 4Å did not significantly alter reaction rates or diastereoselectivity from the normal reactions.

References

1. Kobayashi,S; Akiyama,R; *Tetrahedron Letters*, 1998 **39**, 9211.
2. Kobayashi,S; Jørgensen, K.A.; *Cycloaddition Reactions in Organic Synthesis*. WILEY-VCH Verlag GmbH, Weinheim (Germany), 2002 323-326.
3. Ewing, D. E. *Organic Magnetic Resonance*, 1979 **12**(9), 499.
4. Liard, A. *Chemistry – A European Journal*., 2003 **9**(4), 1000.
5. Vogel A. I. *A Text Book of Practical Organic Chemistry*, 4th Ed., Longmann Group Ltd., 722, 1978.
6. Banerji A.; Biswas P K.; Bandyopadhyay D.; Gupta M.; Prangé T.; Neuman A.; *Journal of Heterocyclic Chemistry*, 44, 2007, 137.

