Indian Journal of Chemistry
Vol. 46B, September 2007, pp. 1495-1500

1,3-Dipolar cycloadditions: part XIV – Highly selective cycloadditions of *C*, *N*-diaryl nitrones to diethyl aryl methylene malonates[1]

A Banerji*[a], S Sengupta[a], A Nayak[a], P K Biswas[a], B Bhattacharya[a], S Dasgupta (Mrs. Ray)[a], R Saha[a], Thierry Prangé[b] & Alain Neuman[b]

[a]Centre of Advanced Studies on Natural Products including Organic Synthesis, Department of Chemistry, University Colleges of Science and Technology, University of Calcutta, 92 Acharya Prafulla Chandra Road, Calcutta 700 009, India

E-mail: ablabcu@yahoo.co.uk

[b]Centre Universitaire, Paris-sud, Batiment 209D-BP34, 91898 Orsay Cedex, France

Received 13 June 2006; accepted (revised) 25 June 2007

Cycloaddition of nitrones to diethyl arylmethylene malonates occurred with very high selectivity to furnish 3,5-*trans*-2,3,5-triaryl-4,4-dicarbethoxy isoxazolidines. This is in contrast with the nitrone cycloadditions to other *α,β*-conjugated carbonyl derivatives where two diastereoisomeric (and on occasion regioisomeric) cycloadducts are generally obtained.

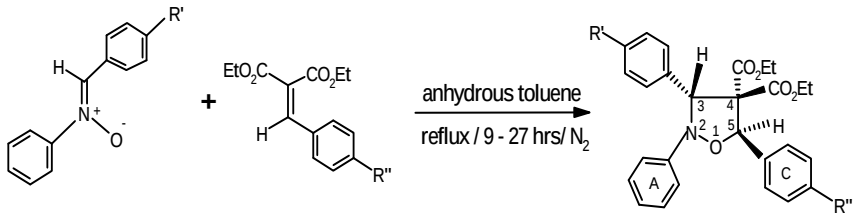
Keywords: 1,3-Dipolar cycloadditions, nitrones, cycloadducts, aryl methylene malonates, dipolarophile

1,3-Dipolar cycloadditions of nitrones to olefins constitute an important route to the isoxazolidine ring system[1-10]. The isoxazolidine cycloadducts correspond to masked 1,3-difunctionalised compounds, which may serve as synthetic templates for various types of molecules. Thus the degree of regioselectivity and stereoselectivity during the cycloaddition process is of utmost importance. A number of earlier studies of cycloadditions of 1,3-diaryl nitrones to double bonds conjugated with carbonyl functionalities showed that both regioselectivity and stereoselectivity depended upon the reactants chosen. Mostly, these reactions occurred with fairly high regioselectivity[1-4,8-10], but with variable diastereoselectivity. It was observed that with *C*-aryl-*N*-cinnamoyl piperidines[8,9], 2.3,5-triarylisoxazolidine cycloadducts were formed diastereo-selectively with the products having 3,4-*trans*-4,5-*trans* configurations predominating over the 3,4-*cis*-4,5-*trans* adducts (*de* 65 to 85%). In reactions where a *para*-nitro substituent was present on the dipolarophile, small amounts of the regioisomeric 2,3,4-triarylisoxazolidine cycloadducts were obtained.

The present work describes the cycloadditions of *C,N*-diaryl nitrones to arylmethylene malonates as an extension of the work on nitrone cycloadditions to α,β-unsaturated carboxylic acid derivatives. Introduction of an additional conjugated carbalkoxy group is expected to facilitate the cycloaddition reaction by polarising the double bond of the dipolarophile and depressing its LUMO energy. A remarkable increase in regio- and stereoselectivity compared to cinnamic acid derivatives is observed and exclusive formation of the *trans*-3,5-diaryl-4,4-dicarbethoxy isoxazolidines occurred in over 90% yields. No other products were detected within the limits of ^{1}H NMR analysis (<0.5%) of the reaction mixtures. Four nitrones and three dipolarophiles were investigated.

Results & Discussion

Cycloaddition reactions of *C*-aryl-*N*-phenyl nitrones to the three diethyl arylmethylene malonates were investigated **(Scheme I)**. The reactions were performed with a threefold molar excess of the dipolarophile in refluxing toluene under nitrogen atmosphere for 9 to 27 hr. Only one series of cycloadducts, *viz*. the 3,5-*trans*-2,3,5-triaryl-4,4-dicarbethoxy isoxazolidines was obtained in all the reactions **(Scheme I)**. No signals for any diastereoisomeric or regioisomeric products could be detected by 300 MHz ^{1}H NMR analysis of the crude reaction mixtures. The structures and relative configurations of the products were established on the basis of spectroscopic data and X-ray analysis. IR spectra of all the cycloadducts showed the expected bands for an unconjugated ester at about 1730 cm^{-1}



R'	R''
(1) H	(5) H
(2) 4-Cl	(6) 4-Cl
(3) 4-NO_2	(7) 4-NO_2
(4) 3-NO_2	

	R'	R''
(8)	H	H
(9)	4-Cl	H
(10)	4-NO_2	H
(11)	4-Cl	4 -Cl
(12)	4-NO_2	4- Cl
(13)	4-Cl	4-NO_2
(14)	3-NO_2	H

Scheme 1

and the aromatic moieties. All the cycloadducts exhibited similar NMR characteristics. Complete ^{1}H and ^{13}C NMR assignment of the cycloadducts are given in **Tables I** and **II** respectively. These NMR assignments for the products were confirmed by two-dimensional NMR experiments. The ^{1}H NMR data of a typical cycloadduct, *viz*. **9**, is discussed below. The ^{1}H NMR spectrum of **9** showed two singlets at δ 5.46 (H-3) and 6.19 (H-5). Both H-3 and H-5 in **9** showed the expected long-range coupling to the *ortho*-protons of the aryl rings attached to the respective carbons in the COSY-LR spectra. Similar correlations were apparent in their two dimensional C-H correlation spectra. The two methylene protons in both carbethoxy groups in the cycloadducts were differentiated– for example in **14** one set of methylene protons appeared at δ 3.82 and 3.395, while the other set appeared at 3.84 and 3.385. These were coupled to the methyl groups appearing at δ 0.81 and 0.69 respectively, as shown by two-dimensional COSY experiments.

The relative configuration of the aryl substituents could be settled only from X-ray crystallographic analysis. X-ray analysis[11] of cycloadduct **9** (R=H, R'=4-Cl, R"=H) showed that the 3- and 5-substituents are *trans* to each other. The nitrogen lone pair is also *trans*- to H-3 **(Figure 1)**. The cycloaddition of *C,N*-diaryl nitrones to diarylmethylene malonates occured through a transition state in which the *C*-aryl group of the dipolarophile approaches *endo* to the nitrone **(Figure 2)**. This transition state is preferred over the alternative *exo*-transition state as 1,3-diaxial type interactions would occur between the nitrone *C*-aryl group with the aryl group on the dipolarophile.

Conclusion

The present work establishes a selective 1,3-dipolar cycloaddition route to 3,5-*trans*-2,3,5-triaryl-4,4-dicarbethoxy isoxazolidines without the formation of any isomeric products. Since isoxazolidines can be considered as masked 1,3-difunctionalised compounds which can serve as synthetic templates for various types of molecules, the present reaction is of importance in this respect.

Experimental Section

General. Melting points were determined in open capillary tubes on a Köfler block apparatus and are uncorrected. Neutral alumina was used for column chromatography, and silica gel G for TLC. Petroleum ether refers to the fraction having the boiling range 60-80°. IR spectra were recorded in KBr discs with a Perkin-Elmer RX-1 FT-IR, and UV spectra in spectral ethanol with a Hitachi U-3501. 300 MHz ^{1}H NMR, 75.5 MHz ^{13}C NMR and COSY-LR spectra were recorded in $CDCl_3$ solution with a Bruker AM-300L spectrometer (chemical shifts in δ ppm and *J* in Hz). 500 MHz ^{1}H NMR, 125 MHz ^{13}C NMR and COSY-LR, HMQC, HMBC spectra were recorded with a Bruker DRX 500. X-Ray crystallographic data were collected at the LURE DCI Synchrotron facility at Orsay, France; an Image Plate system (MAR 345) was used as the detector. Recording was done under cryo-temperature conditions at –160º. The CCDC no. for compound **9** is 235164.

Starting materials. The dipolarophile diethyl arylmethylene malonate was prepared by condensation of diethyl malonate with benzaldehyde[11]. The arylmethylene malonates were prepared from the

Table I — ^{1}H NMR Assignments of the products in $CDCl_3$ (δ, ppm)

Proton No.	**8**	**9**	**10**	**11**	**12**	**13**	**14**
H-3	5.51 (s, 1H)	5.46 (s, 1H)	5.61 (s, 1H)	5.44 (s, 1H)	5.59 (s, 1H)	5.47 (s, 1H)	5.62 (s, 1H)
H-5	6.26 (s, 1H)	6.20 (s, 1H)	6.23 (s, 1H)	6.16 (s, 1H)	6.19 (s, 1H)	6.26 (s, 1H)	6.22 (s, 1H)
$CO_2CH_2CH_3$ (I)	3.34,3.82 (m, 2H)	3.36,3.82 (m, 2H)	3.36,3.86 (m, 2H)	3.40,3.85 (m, 2H)	3.39,3.84 (m, 2H)	3.40,3.86 (m, 2H)	3.38,3.84 (m, 2H)
$CO_2CH_2CH_3$ (I)	0.69 (t, *J* =7.1, 3H)	0.69 (t, *J* =7.2, 3H)	0.69 (t, *J* =7.2, 3H)	0.73 (t, *J* =7.1, 3H)	0.77 (t, *J* =6.5, 3H)	0.71 (t, *J* =7.2, 3H)	0.69 (t, *J* =7.5, 3H)
$CO_2CH_2CH_3$ (II)	3.35,3.80 (m, 2H)	3.37,3.80 (m, 2H)	3.37,3.84 (m, 2H)	3.45,3.83 (m, 2H)	3.41,3.82 (m, 2H)	3.41,3.84 (m, 2H)	3.39,3.82 (m, 2H)
$CO_2CH_2CH_3$ (II)	0.79 (t, *J* =7.2, 3H)	0.81 (t,*J* =7.1, 3H)	0.82 (t, *J* =7.1, 3H)	0.84 (t, *J* =7.1, 3H)	0.82 (t, *J* =7.1, 3H)	0.84 (t, *J* =7.2, 3H)	0.81 (t *J* =7.5, 3H)
Aromatic protons of ring A							
(H-2,6, A)		7.07 (d, *J* =7.5, 2H)			7.03 (d, *J* =7.8, 2H)		7.08 (d, *J* = 7.5,2H)
(H-3,5, A)	6.99-7.58 (m, 15H)	7.21 (t, *J* =7.5, 2H)	7.02-7.52 (m, 5H)	7.01-7.49 (15H, m)	7.23 (t, *J* =7.5, 2H)	7.01-7.27 (m, 5H)	7.23 (t, *J* = 7.5, 2H)
(H-4, A)		7.01 (t, *J* =7.5, 1H)			7.06 (t, *J* =7.2, 2H)	--	7.04 (t, *J* = 7.5, 1H)
Aromatic protons of ring B							
(H-2, B)			7.70 (d, *J* =8.8, 2H)		7.73 (d, *J* =8.7, 2H)	7.34 (d, *J* =8.4, 1H)	8.40 (s, 1H) 7.95 (d, *J* = 7.5, 1H)
(H-6, B)		7.23-7.35 (m, 5H)					
(H-3,5, B)			8.21 (d, *J* =8.8, 2H)		8.21 (d, *J* =8.7, 2H)	7.47 (d, *J* =8.4, 1H)	7.54 (t, *J* = 8.0, 1H)
(H-4, B)			--		--	--	8.18 (dd, *J* =8.2, 1.2, 1H)
Aromatic protons of ring C							
(H-2,6, C)		7.48-7.51 (br. s, 5H)	7.02-7.51 (m, 5H)		7.02-7.51 (m, 4H)	7.71 (d, *J* =8.7, 2H)	7.49 (d, *J* =8.6, 2H)
(H-3,5, C)						8.22 (d, *J* =8.7, 2H)	7.34 (m, 3H)
(H-4, C)					--	--	

Note: (i) ^{1}H NMR were recorded at 300 MHz, except for **14**, which was recorded at 500 MHz.
(ii) Multiplicities and *J* values (in Hz) are given in brackets.

appropriate aldehydes by the same procedure. The nitrones were prepared as described in our early communications[8-10].

General procedure for the cycloaddition reactions. The nitrone (3 mmole) and a threefold molar excess of the dipolarophile (9 mmole) in toluene solution (20 cm^3) was refluxed for a period of 9 to 27 hr. The reaction were monitored by TLC and by 300 MHz ^{1}H NMR. After completion of the reaction the solvent and excess dipolarophile were removed from the crude reaction mixture *in vacuo* using a Büchi rotary evaporator. The residue was analysed by 300 MHz ^{1}H NMR. Usually the product separated on concentrating the solution, occasionally it was necessary to purify the substance from a small amount of decomposed material by passage through a short column of neutral alumina.

Reaction of *C,N*-diphenyl nitrone 1 with ethyl benzylidene malonate 5–Synthesis of 3*RS(3R*, 5R*)*–2,3,5-triphenyl-4,4-dicarbethoxyisoxazolidine 8 ($C_{27}H_{27}NO_5$). Reaction time - 9.5 hr. White crystals, m.p. 102-104°C; yield: 1.29 g (90%); IR (KBr): 1728 (s, ester C=O), 2978 (m, aryl C-H), 751, 697 (m, mono-substituted benzene ring) cm^{-1}; Anal Calcd for $C_{27}H_{27}NO_5$: C, 72.6; H, 6.0; N, 2.9; Found: C, 72.8; H, 6.1; N, 3.1%.

Table II — ^{13}C NMR Assignments of the products in $CDCl_3$ (δ, ppm)

Carbon No.	**8**	**9**	**10**	**11**	**12**	**13**	**14**
C-3	75.5	74.8	74.5	74.8	74.5	75.0	74.7
C-4	74.9	74.9	74.9	74.8	74.8	74.9	75.0
C-5	83.2	83.3	83.6	82.6	82.8	82.4	83.6
$CO_2CH_2CH_3$ (I, II)	167.9, 167.4	167.8, 169.3	167.5, 166.9	167.2, 167.6	167.4, 166.9	167.6, 167.4	167.9, 167.3
$CO_2CH_2CH_3$ (I, II)	61.5, 61.2	61.7, 61.4	61.9, 61.6	61.6, 61.9	62.1, 61.8	62.4, 62.3	62.4, 62.0
$CO_2CH_2CH_3$ (I, II)	13.2, 13.1	13.3, 13.2	13.1, 13.3	13.3, 13.3	13.4, 13.3	13.7, 13.7	13.8, 13.6
(C-1, A)	149.1	148.8	148.2	148.6	148.0	148.6	148.6
(C-2,6, A)	118.1	118.5	118.8	118.5	11.8	118.7	118.9
(C-3,5, A)	129.0	130.4	130.0	130.4	130.0	129.2	129.2
(C-4, A)	123.4	123.9	124.4	124.1	124.6	124.7	124.7
(C-1, B)	137.8	136.3	148.1	136.1	148.1	136.0	-
(C-2 B) (C-6, B)	-	-	123.4	-	123.5	-	123.2 135.2
(C-3, B) (C-5, B)	128.4	128.6	128.8	128.7	128.6	128.6	148.1 129.4
(C-4, B)	128.3	134.4	144.9	134.5	144.7	130.7	123.9
(C-1, C)	135.5	135.4	135.1	133.9	133.6	142.8	135.3
(C-2,6, C)	127.3	127.3	127.3	127.9	128.4	123.6	127.6
(C-3,5, C)	128.0	128.1	128.2	128.3	128.9	-	129.2
(C-4, C)	-	-	-	134.6	134.8	135.0	128.6

Note: — ^{13}C NMR spectra were recorded at 75.5 MHz, except those of **13** and **14**, which were recorded at 125.5 MHz.

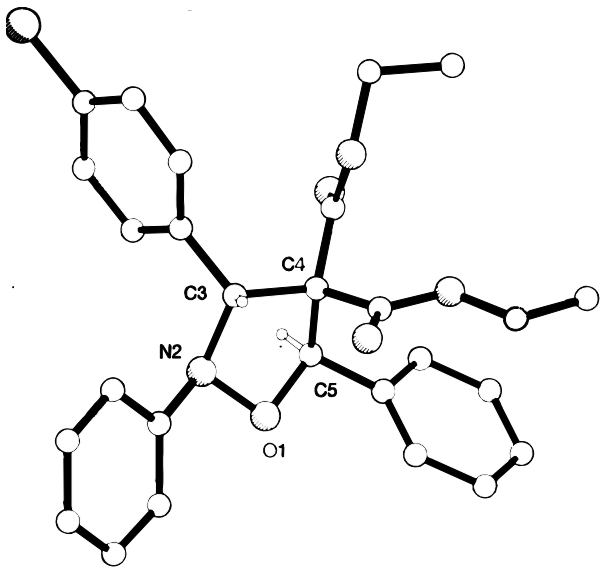


Figure 1

Reaction of *C*-(4-chlorophenyl)-*N*-phenyl nitrone 2 with ethyl benzylidene malonate 5 – Synthesis of 3*RS(3R*,5R*)*-2,5-diphenyl-3-(4-chlorophenyl)-4,4-dicarbethoxyisoxazolidine 9 ($C_{27}H_{26}NO_5Cl$). Reaction time – 14 hr. White crystals, m.p. 120°C; yield: 1.28g (89%); IR (KBr): 1726 (s, ester C=O), 2980 (w, aryC-H), 1064 (m, aryl Cl) 753, 693 (m, mono substituted benzene ring) cm^{-1}; Anal Calcd for $C_{27}H_{27}NO_5Cl$: C, 67.5; H, 5.4; N, 2.9; Found: C, 67.2; H, 5.2; N, 2.8%.

The crystal structure data for compound **9** was recorded at the LURE DCI Synchrotron facility in Orsay, France. Crystal data for compound **9**: The crystals were monoclinic, one molecule in the asymmetric unit, space group $P2_{1/C}$, parameters of unit cell are a = 15.860 (3) Å, b = 10.780 (2) Å, c = 16.430 (2) Å, β = 118.93(7)°, R = 7.36% for 2385 F obs. The crystal structure data for compound **9** was recorded at the LURE DCI Synchrotron facility in Orsay, France. An Image Plate system (MAR345) was used as the detector. Recording was done under cryotemperature condition, at –160°C. Crystallographic data for **9** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 235164. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail:deposit@ccdc.cam.ac.uk).

Reaction of *C*-(4-nitrophenyl)-*N*-phenyl nitrone 3 with ethyl benzylidene malonate 5 – Synthesis of 3*RS(3R*,5R*)*-2,5-diphenyl-3-(4-nitrophenyl)-4,4-dicarbethoxy isoxazolidine 10 ($C_{27}H_{26}N_2O_7$). Reaction time – 27 hr. Pale yellow crystals, m.p.

Figure 2

146-48°C; yield: 1.32g (90%); IR (KBr): 1727 (s, ester C=O), 2986 (m, aryl C-H), 754, 689 (m, mono substituted benzene ring), 854 (m, 1, 4-disubstituted benzene ring) cm^{-1}; Anal Calcd for $C_{27}H_{26}N_2O_7$: C, 66.1; H, 5.3; N, 5.7; Found: C, 65.9; H, 5.5; N, 5.5%.

Reaction of *C*-(4-chlorophenyl)-*N*-phenyl nitrone 2 with 4-chloro- ethyl benzylidene malonate 6 – Synthesis of 3*RS(3R*,5R*)*-2-phenyl-3-(4-chlorophenyl)-5-(4-chlorophenyl)-4,4-di-carbeth-oxy-isoxazolidine 11 ($C_{27}H_{25}NO_5Cl_2$). Reaction time – 10 hr. White crystals, m.p. 99-101°C; yield: 1.41 g (92%); IR (KBr): 1727 (s, ester C=O), 2986 (m, aryl C-H), 754, 689 (m, mono substituted benzene ring), 854 (m, 1, 4-disubstituted benzene ring), 1090, 1061 (m, aryl C-Cl) cm^{-1}; Anal Calcd for $C_{27}H_{25}NO_7Cl_2$: C, 63.0; H, 4.9; N, 2.7; Found: C, 62.8; H, 4.7; N, 2.6%.

Reaction of C-(4-nitrophenyl)-*N*-phenyl nitrone 3 with 4-chloro- ethyl benzylidene malonate 6 – 3*RS(3R*,5R*)* -2-phenyl-3-(4-nitrophenyl)-5-(4-chlorophenyl)-4,4-dicarbethoxy-isoxazolidine 12 ($C_{27}H_{25}N_2O_7Cl$). Reaction time – 15 hr. Pale yellow crystals, m.p. 166-67°C; yield: 1.44 g (92 %); IR: ν_{max} (KBr): 1727 (s, ester C=O), 2988, (m, aryl C-H), 756, 692 (m, mono substituted benzene ring), 854 (m, 1, 4-disubstituted benzene ring), 1523, 1347 (s, aromatic – NO_2 group) cm^{-1}; Anal Calcd for $C_{27}H_{25}NO_7Cl_2$: C, 61.8; H, 4.7; N, 5.3; Found: C, 61.6; H, 4.5; N, 5.2%.

Reaction of *C*-(4-chlorophenyl)-*N*-phenyl nitrone 2 with 4-nitro ethyl benzylidene malonate 7 – Synthesis of 3*RS(3R*,5R*)*-2-phenyl-3-(4-chlorophenyl)-5-(4-nitrophenyl)-4,4-dicarbethoxy-isoxazolidine 13 ($C_{27}H_{25}N_2O_7Cl$). Reaction time – 19 hr. Yellow crystals, m.p. 104-106°C; yield: 1.42 g (90%); IR (KBr): 1727 (s, ester C=O), 2982 (m, aryl C-H), 750, 690 (m, mono-substituted benzene ring), 857 (m, 1, 4-disubstituted benzene ring), 1526, 1346 (s, aromatic–NO_2 group) cm^{-1}; Anal Calcd for $C_{27}H_{25}NO_7Cl_2$: C, 61.8; H, 4.7; N, 5.3; Found C, 61.6; H, 4.6; N, 5.2%

Reaction of *C*-(3-nitrophenyl)-*N*-phenyl nitrone 4 with ethyl benzylidene malonate 5 - Synthesis of 3*RS(3R*,5R*)*-2-phenyl-3-(3-nitrophenyl)-5-phenyl-4,4-dicarbethoxy-isoxazolidine 14 ($C_{27}H_{26}N_2O_7$). Reaction time – 24 hr. Pale yellow crystals, m.p. 106°C; yield: 1.36 g (91.83%); IR (KBr): 1728 (s, ester C=O), 2987, (m, aryl C-H), 753, 691 (m, mono substituted benzene ring), 1526, 1349 (s, aromatic –NO_2 group) cm^{-1}. Anal Calcd for $C_{27}H_{26}N_2O_7$: C, 66.1; H, 5.3; N, 5.7; Found: C, 65.8; H, 5.0; N, 5.4%.

Acknowledgements

The authors thank the CSIR (JRFs to SSG and BB), Calcutta University (JRFs to AN and SDG), ICCR (JRF to PKB) and UGC (TRF to RS) for financial assistance.

References

1 (a) Banerji A, Biswas P K, Sengupta P, Dasgupta S & Gupta M; *Indian J Chem*, 43B, **2004**, 880.
(b) Banerji A, Bandyopadhyay D, Prangé T & Neuman A; *Tetrahedron Letters*, 46 (15), **2005**, 2619.
(c) Banerji A, Bandyopadhyay D, Sengupta P, Basak B, Prangé T & Neuman A; *Tetrahedron Letters*, 47, **2006**, 3827.
(d) Banerji A, Biswas P K, Bandyopadhyay D, Gupta M, Prangé T & Neuman A; *J Heterocyclic Chemistry*, 44 (1) **2007**, 137.

2 Torsell K B G, in *Nitrile oxides, Nitrones and Nitronates in Organic Synthesis*, (VCH, New York, Weinheim), **1988.**

3 Tufariello J J, in *1,3-Dipolar cycloaddition chemistry; Edited by A Padwa*, (Wiley International, NY), **1984**, Vol. 2, p.83.

4 *Synthetic applications of 1,3-dipolar cycloaddition chemistry toward heterocycles and natural products*; edited by A

Padwa & W H Pearson, (John Wiley & Sons, NY), **2002**, Ch. 1.

5 Banerji A, Banerji J, Haldar S, Maiti K K, Basu S, Prangé T & Neuman A. *Indian J Chem*, 37B (2), **1998**, 105.

6 Banerji A, Maiti K K, Haldar S, Mukhopadhyay C, Banerji J, Prangé T & Neuman A, *Monatshefte für Chem*, 131**, 2000,** 901.

7 Banerji A, Dasgupta S, Sengupta P, Prangé T & Neuman A, *Indian J Chem*, 43B, **2004**, 1925.

8 Sridharan V, Muthusubramanian S, Sivasubramanian S & Polborn K, *Tetrahedron*, 60, **2004**, 8881.

9 Blanáriková-Hlobilová I, Kubánová Z, Fisera K, Cyranski M K, Salanski P, Jurczak J & Prónayová N, *Tetrahedron*, 59, **2003**, 3333.

10 Saito T, Yamada T, Miyazaki S & Otani T, *Tetrahedron Letters*, 45, **2004**, 9581, 9585.

11 Vogel A I, *Practical Organic Chemistry*, 4th edn, (Longman, London), **1978**, 402.