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Synthesis of Some New Isoxazolidines by 1,3-Dipolar Cycloaddition Reaction of Nitrones and Olefins

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A series of new isoxazolidines **5a-j** were synthesized by 1,3-dipolar cycloaddition reaction of different nitrones with substituted olefins under reflux condition. The yields of products following recrystallization from absolute ethanol were of the order of 40%-66%. IR, NMR and mass spectroscopies were used for identification of these compounds.

Key Words: Isoxazolidine, Nitrones, 1,3-Dipolar, Cycloaddition.

Introduction

Nitrones are important synthetic intermediates that have been used extensively in organic chemistry[1−7]. Some nitrones have been used for the trapping and identification of free radicals[7], particularly in biological studies[4]. Various synthetic approaches for the synthesis of nitrones have been reported by several groups[8−18]. The most general approach for the preparation of nitrones is the condensation reaction between aldehydes or ketones with N-monosubstituted hydroxylamines[8]. Nitrones can react as 1,3-dipolar species with a large variety of dipolarophiles to give different products. One of the most synthetic applications of nitrones is their use as 1,3-dipoles in cycloaddition reactions to olefins for preparation isoxazolidines[19]. Isoxazolidines are known to possess antibacterial activity[20]. The purpose of the present work is to synthesis some new isoxazolidines by 1,3-dipolar cycloaddition reaction of nitrones and olefins.

Experimental

Melting points (mp) were determined with an electrothermal digital melting point apparatus. IR spectra were obtained using a Galaxy series FT-IR 5000 spectrophotometer using KBr pellets. ^{1}HNMR spectra were recorded on Bruker 400 and 500 MHz spectrometers, using Me_4Si (TMS) as an internal standard. Mass spectra were measured with an EI (70 eV)+Q1MSLMR up LP spectrometer. Reaction courses and product mixtures were monitored using thin layer chromatography.

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General procedure for preparation of nitrones

Nitrones **3a-e** were synthesized using the condensation reaction between corresponding aldehydes and N-phenylhydroxylamine in ethanolic solution[8].

General procedure for preparation of isoxazolidines

The appropriate nitrone **3** (0.01 mol) was dissolved in dry benzene or toluene (3 mL) and the corresponding olefin **4** (0.01 mol) was added. The reaction mixture was refluxed for 10-30 h. Concentration of the solution under vacuum gave the crude product, which was then recrystallized from ethanol.

5-(4-Chlorophenyl)-2,3-diphenyl-isoxazolidine (5a)

mp 91-93 °C
IR (KBr): υ = 3100, 2900, 1600, 1487, 1300, 1100, 821, 765 cm^{-1}
^{1}HNMR ($CDCl_3$): δ (ppm) = 2.3 (m, 2H, H-4), 3.0 (dd, J = 9.1, 7.9 Hz, 1H, H-3), 4.7 (dd, J = 9.1, 7.9 Hz, 1H, H-5), 7.4 (m, 14H, H_{arom}).
^{13}CNMR ($CDCl_3$): δ (ppm) = 40.1, 64.3, 85.5, 116.2, 122.5, 126.9, 128.0, 128.2, 132.6, 133.8, 142.0, 146.1.
Ms: (m/z %) = 311 (M^+, 32%), 222 (6%), 194 (18%), 180 (42%), 131 (23%), 90.7 (100%), 76.2 (38%).

2,3-Diphenyl-4-ethoxycarbonyl-5-methylisoxazolidine (5b)

IR (KBr): υ = 3086, 2980, 1732, 1599, 1489, 1030, 754, 698 cm^{-1}
^{1}HNMR ($CDCl_3$): δ (ppm) = 1.0 (t, J = 7.5 Hz, 3H, CH_3, ester), 1.3 (d, J = 7.0 Hz 3H, CH_3), 3.1 (m, 1H, H-4), 4.0 (q, J = 7.5 Hz, 2H, CH_2O), 4.5 (dd, J = 9.1, 7.8 Hz, 1H, H-3), 5.0 (d, 1H, J = 8.0 Hz, H-5), 7.1 (m, 10H, H_{arom}).
^{13}CNMR ($CDCl_3$): δ (ppm) = 14.2, 17.0, 54.4, 60.6, 67.5, 76.6, 124.9, 125.1, 125.2, 126.4, 127.9, 128.1, 130.9, 144.5, 170.4.
Ms: (m/z %) = 311 (M^+, 32%), 222 (6%), 194 (18%), 180 (42%), 131 (23%), 90.7 (100%), 76.2 (38%).

5-Cyano- 2,3-diphenyl isoxazolidine (5c)

IR (KBr): υ = 3061, 2361, 1597, 1280, 1100, 781, 760 cm^{-1}
^{1}HNMR ($CDCl_3$): δ (ppm) = 2.7 (m, 2H, H-4), 4.2 (t, J = 7.9 Hz, 1H, H-3), 4.8 (t, J = 7.9 Hz, 1H, H-5), 7.2 (m, 10H, H_{arom}).
^{13}CNMR ($CDCl_3$): δ (ppm) = 34.1, 64.7, 67.1, 116.9, 121.9, 123.2, 127.2, 128.2, 129.9, 130.2, 140.3, 146.7.
Ms: (m/z %) = 250 (M^+, 100%), 224 (28%), 196 (28%), 180 (30%), 105 (22%), 90.7 (5%).

3-(2-Hydroxyphenyl)- 5-methoxycarbonyl -2-phenylisoxazolidine (5d)

IR (KBr): υ = 3061, 2361, 1751, 1570, 1468, 1280, 1033, 784 cm^{-1}
^{1}HNMR ($CDCl_3$): δ (ppm) = 2.8 (m, 2H, H-4), 3.6 (s, 3H, -OCH_3), 4.6 (m, 2H, H-3 and H-5), 6.9 (m, 9H, H_{arom}).

^{13}CNMR ($CDCl_3$): δ (ppm) = 39.9, 51.5, 57.8, 75.3, 117.1, 118.6, 116.5, 122.0, 128.2, 128.3, 128.9, 147.4, 157.7, 171.9.
Ms: (m/z %) = 299 (M^+, 22%), 267 (3%), 210 (4%), 198 (34%), 196(13%), 90.7 (100%).

4-Ethoxycarbonyl-3-(2-hydroxyphenyl)-5-methyl-2-phenylisoxazolidine (5e)

mp 108-110 °C
IR (KBr): υ = 3352, 2982, 2868, 1705, 1597, 1487, 1300, 1100, 766 cm^{-1}
^{1}HNMR ($CDCl_3$): δ (ppm) = 1.1 (t, J = 7.5 Hz, 3H, CH_3 ester), 1.5 (d, J = 7.0 Hz 3H, CH_3), 3.4 (m, 1H, H-4), 4.1 (q, J = 7.5 Hz, 2H, -CH_2O), 4.6 (d, J = 8.0 Hz, 1H, H-3), 5.1 (d, J = 8.0 Hz, 1H, H-5), 7.1 (m, 9H, H_{arom}).
^{13}CNMR ($CDCl_3$): δ (ppm) = 14.3, 16.9, 55.6, 59.9, 60.6, 75.6, 120.2, 117.5, 119.0, 125.0, 125.1, 127.7, 128.0, 128.6, 145.8, 157.5, 170.4.
Ms: (m/z %) = 327 (M^+, 52%), 210 (11%), 196 (100%), 131 (36%), 90.7(4%), 44.6 (17%).

2,5-Diphenyl-3-(4-nitrophenyl)isoxazolidine (5f)

mp 120-122 °C
IR (KBr): υ = 3047, 1597, 1470, 1348, 1028, 850, 692 cm^{-1}
^{1}HNMR ($CDCl_3$): δ (ppm) = 2.4 (m, 2H, H-4), 3.2 (dd, J = 9.1, 7.8 Hz, 1H, H-3), 5.1 (dd, J = 9.1, 7.8 Hz, 1H, H-5), 7.6 (m, 14H, H_{arom}).
^{13}CNMR ($CDCl_3$): δ (ppm) = 38.7, 64.5, 85.8, 116.4, 121.8, 124.8, 124.0, 128.7, 129.3, 132.9, 137.4, 145.9, 147.2.
Ms: (m/z %) = 346.5 (M^+, 1%), 192 (5%), 90.7 (100%), 76.3 (63%).

5-Methoxycarbonyl-3-(4-nitrophenyl)-2-phenylisoxazolidine (5g)

IR (KBr): υ = 2955, 1730, 1597, 1529, 1340, 1207, 1109, 856, 758 cm^{-1}
^{1}HNMR ($CDCl_3$): δ (ppm) = 2.5 (m, 2H, H-4), 3.8 (s, 3H, -OCH_3), 4.4 (t, J = 8.1 Hz, 1H, H-3), 5.0 (t, J = 8.1 Hz, 1H, H-5), 7.7 (m, 9H, H_{arom}).
^{13}CNMR ($CDCl_3$): δ (ppm) = 35.6, 51.4, 64.2, 75.3, 116.7, 121.7, 128.3, 136.8, 145.9, 146.0, 146.1, 171.9.
Ms: (m/z %) = 328 (M^+, 84%), 312 (71%), 241 (2%), 225 (9%), 101(12%), 90.7 (100%), 76.3 (61%).

3-(4-Bromophenyl)-2,5-diphenylisoxazolidine (5h)

mp 119-121 °C
IR (KBr): υ = 3100, 2900, 2342, 1487, 1257, 1000, 758, 500 cm^{-1}
^{1}HNMR ($CDCl_3$): δ (ppm) = 2.3 (m, 2H, H-4), 3.1 (dd, J = 9.1, 7.8 Hz, 1H, H-3), 5.0 (dd, J = 9.1, 7.8 Hz, 1H, H-5), 7.2 (m, 14H, H_{arom}).
^{13}CNMR ($CDCl_3$): δ (ppm) = 36.2, 64.7, 78.6, 116.1, 122.6, 123.7, 124.6, 125.7, 126.9, 128.5, 129.5, 129.7, 133.1, 139.1.
Ms: (m/z %) = 379 (M^+, 0.5%), 273 (25%), 192.1 (10%), 90.7 (100%), 76.2 (58%).

3-(4-Bromophenyl)-5-(4-chlorophenyl)-2-phenylisoxazolidine (5i)

IR (KBr): υ = 3100, 1595, 1487, 1300, 1010, 817 cm^{-1}

^{1}HNMR ($CDCl_3$): δ (ppm) = 2.45 (m, 2H, H-4), 3.3 (dd, J = 9.0, 7.8 Hz, 1H, H-3), 5.1 (dd, J = 9.0, 7.8 Hz, 1H, H-5), 7.3 (m, 13H, H_{arom}).

^{13}CNMR ($CDCl_3$): δ (ppm) = 40.3, 64.4, 85.6, 116.3, 122.0, 123.7, 127.0, 128.5, 129.7, 130.4, 131.6, 132.7, 134.0, 141.1, 146.1.

Ms: (m/z %) = 414.9 (M^+, 4.3%), 306.9 (4%), 273.9 (3.8%), 226 (1.1%), 191 (10%), 168 (6.6%), 139 (6.5%), 103 (6.8%).

5-(4-Chlorophenyl)-2-phenyl-3-thienylisoxazolidine (5j)

mp 103-105 °C

IR (KBr): υ = 3086, 2939, 1597, 1486, 1300, 1093, 821, 760 cm^{-1}

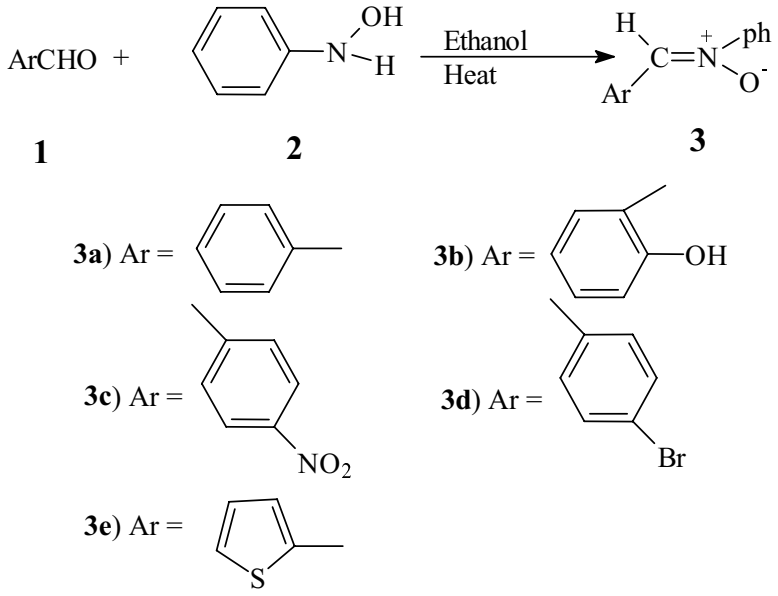
^{1}HNMR ($CDCl_3$): δ (ppm) = 2.4 (m, 2H, H-4), 3.2 (dd, J = 9.0, 7.8 Hz, 1H, H-3), 5.2 (t, J = 8.0 Hz, 1H, H-5), 7.4 (m, 12H, H_{arom}).

^{13}CNMR ($CDCl_3$): δ (ppm) = 33.7, 65.1, 88.2, 116.0, 122.6, 127.2, 127.6, 128.0, 129.6, 131.1, 133.9, 135.0, 148.6.

Ms: (m/z %) = 341 (M^+, 0.05%), 233 (0.47%), 111 (9%), 90.7 (100%), 76.2 (64%).

Results and Discussion

Nitrones **3a-e** were prepared according to the published method as far as possible[8] (Scheme 1). The condensation reaction between the appropriate aldehyde and phenylhydroxylamine offered the desired nitrones in good yields. In each case only the *Z*–isomer was detected using NOE experiments (Table 1). An enhancement was observed in the difference spectra upon irradiation of the azomethine proton of the nitrone and the phenyl ring protons.



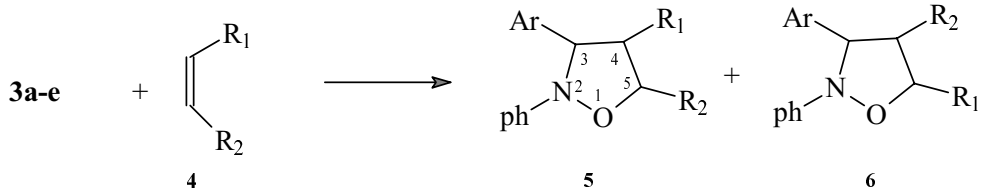
Scheme 1

Table 1. Reaction time and yields on the formation of nitrones.

1	Nitrone **3**	Rt (h)	Yield (%)
benzaldehyde	C,N-diphenylnitrone **3a**	12	78
salicylaldehyde	C-(2-hydroxyphenyl)-N-phenylnitrone **3b**	2	47
p-nitrobenzaldehyde	C-(4-nitrophenyl)-N-phenylnitrone **3c**	2	85
p-bromobenzaldehyde	C-(4-bromophenyl)-N-phenylnitrone **3d**	2	89
2-thiophenecarboxaldehyde	C-(2-thiophenyl)-N- phenylnitrone **3e**	2	78

Rt = reaction time

1,3-Dipolar cycloaddition reaction of nitones to olefins (Scheme 2), which was carried out under reflux condition and different times, afforded isoxazolines **5a-j** in average yield and high selectivity (Table 2).



4 5 6

5a) Ar= Ph, R_1=H, R_2= 4-ClPh
5b) Ar= Ph, R_1= CO_2Et, R_2= Me
5c) Ar= Ph, R_1= H, R_2= CN
5d) Ar= 2-OHPh, R_1= H, R_2= CO_2Me
5e) Ar= 2-OHPh, R_1= CO_2Et, R_2= Me
5f) Ar= 4-NO_2Ph, R_1= H, R_2= Ph
5g) Ar= 4-NO_2Ph, R_1= H, R_2= CO_2Me
5h) Ar= 4-BrPh, R_1= H, R_2= Ph
5i) Ar= 4-BrPh, R_1= H, R_2= 4-ClPh
5j) Ar= 2-thienyl, R_1= H, R_2= 4-ClPh

Scheme 2

Table 2. Reaction time and yields on the formation of isoxazolidines.

Nitrone **3**	Olefin **4**	Isoxazolidine **5**	Rt (h)	M.P• (°C)	Yield (%)
3a	*p*-chlorostyrene	**5a**	10	91-93	60
3a	ethyl crotonate	**5b**	23	-	43
3a	acrylonitrlile	**5c**	21	-	63
3b	methyl acrylate	**5d**	30	-	40
3b	ethyl crotonate	**5e**	10	108-110	57
3c	styrene	**5f**	13	120-122	66
3c	methyl acrylate	**5g**	21	-	50
3d	styrene	**5h**	27	119-121	48
3d	*p*−chlorostyrene	**5i**	27	-	55
3e	*p*−chlorostyrene	**5j**	25	103-105	64

Rt = reaction time

•Compound with no m.p was an oily product

Yields of the products were in the order of 40%-66%, as summarized in Table 2. The selectivity of most nitrone cycloadditions to mono-substituted olefins was such that the 5-substituted isoxazolidine **5** was

preferentially formed as the major isomer. However using 1,2-disubstituted olefin such as ethyl crotonate in reaction with **3b** gave the isoxazolidine **5e** with the more electron-withdrawing substituent, CO_2Et, on the 4 position. The stereoselectivity of this 1,3- dipolar cycloaddition reaction may be influenced by both electronic and steric effects[21]. In the reactions where electron-withdrawing groups were present on the nitrone, isoxazolidine **6** was also formed as the minor product, which was separated by flash column chromatography. Such an isomer was found in the 1,3- dipolar cycloaddition reaction of C-(4-nitrophenyl)-N-phenylnitrone **3c** with methyl acrylate.

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