Indian Journal of Chemistry
Vol. 37B, December1998; pp. 1239-1245

1,3-Dipolar reactions for the synthesis of new substituted isoxazolidines and isoxazoles

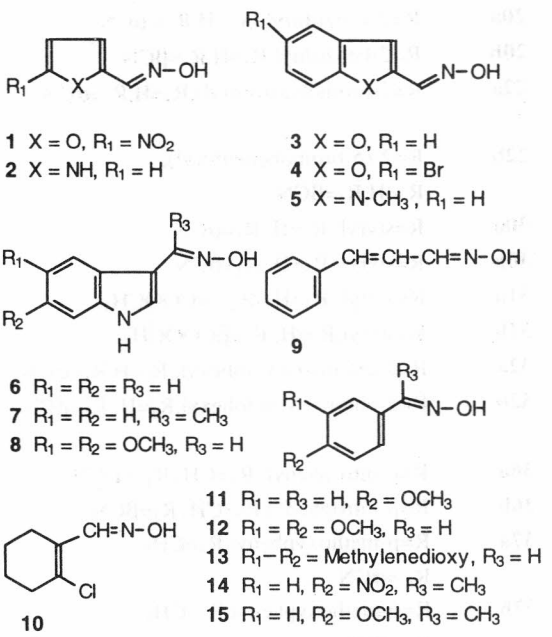
R S Kusurkar*, D K Bhosale, L A Gadre, J J Jain & H M Wadde
Department of Chemistry, University of Pune, Pune 411 007, India

Received 9 December 1997; accepted (revised) 25 September 1998

Unsaturated oximes are treated with dipolarophiles like acrylonitrile and methyl acrylate to furnish new 3,4-disubstituted and 3,5-disubstituted isoxazolidines. Reactions of unsaturated oximes with dimethylacetylene-dicarboxylate yield 3,4-disubstituted isoxazoles.

Isoxazolidines and isoxazoles are important intermediates in multistep synthesis of complex natural products[1]. Similarly isoxazoles are pharmacologically important and their derivatives exhibit antibacterial and antiviral activities[2]. The ring system in isoxazolidine and isoxazole is unique amongst the heterocyclic rings in the sense that though it is stable towards variety of reagents, it can be ring opened by N-O bond cleavage reactions. Moreover there are numerous possibilities of recyclizations arising from nitrogen nucleophilicity and from a suitable substituent at C-4 or C-5 of isoxazolidine ring, forming a new heterocyclic system.

In continuation with our studies[3] in cycloaddition reactions, we investigated reactions of unsaturated aldoximes as well as ketoximes with conventional olefinic and acetylenic dipolarophiles.The results obtained in these reactions are presented in this paper.



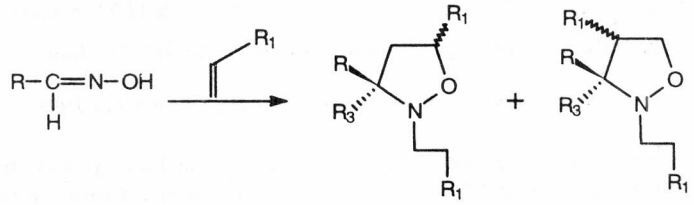
Scheme I—Unsaturated oximes used for 1,3-dipolar reactions

1,3-Dipolar reactions using unsaturated oximes 1-16 (Scheme I) with olefinic dipolarophiles. We have reported[3] earlier the reactions of furfuraldoxime and thiophene-2-aldoxime with conventional dipolarophiles which afforded 1,3-dipolar cycloadducts. To investigate the change in the reaction course by introducing a substituent, 5-nitrofurfuraldoxime **1** was treated with acrylonitrile at 120°C in a sealed tube. The product showed presence of cyano group and absence of hydroxyl group which indicated it to be formed by cycloaddition along with Michael addition. Chromatographic separation gave a isomeric mixture which when rechromatographed furnished two oily compounds. Amongst the expected four isomers, the above two were identified using ^{1}H NMR spectral data. One of the isomers showed a triplet at δ 4.9 and the other showed a dd at δ 5.0 for one proton. Both the isomers were shown to be 5-cyano isomers and the above signals were assigned to C_5-H which was expected to be the most downfield alicyclic signal amongst all the isomers. However due to the *cis* relationship of C_3-H with cyano group,*trans* isomer **16a** showed a downfield triplet (at δ 4.47) of C_3-H. In the *cis* isomer **16b** C_3-H was resonating as a triplet at δ 4.0. In both the spectra low intensity signals of

minor amount of 4-cyano isomers were also seen. Reaction with methyl acrylate furnished a isomeric mixture of cycloadduct **17,** from which 4-cyano isomers **17c** & **d** were isolated (Scheme II, Table I).

By changing the heteroatom, reactions were carried out using pyrrole-2-aldoxime **2** with acrylonitrile and methyl acrylate. These reactions furnished mixtures of isomers of 1,3-dipolar cycloadducts from which 4- substituted isomers were separated and identified as **18d** and **19c** & **d** using ^{1}H NMR spectral data.

Cycloaddition reactions using benzofuran-2-aldoxime **3** with acrylonitrile furnished all four



16a	R=2-(5-nitrofuryl),R_3=H,R_1=α CN	**17c**	R=2-(5-nitrofuryl)R_3=H,R_1=αCOOCH$_3$
16b	R=2-(5-nitrofuryl),R_3=H,R_1=βCN	**17d**	R=2-(5-nitrofuryl)R_3=H,R_1=βCOOCH$_3$
20a	R=2-benzofuryl, R_3=H,R_1= αCN	**18c**	R=2-(pyrrolyl),R_3=H, R_1=∝CN,
20b	R=2-benzofuyl,R_3=H,R_1=βCN	**18d**	R=2-(pyrrolyl),R_3=H, R_1=βCN
22a	R=2(bromobenzofuryl),R_3=H,R_1=αCN	**19c**	R=2-(pyrrolyl),R_3=H , R_1=∝COOCH$_3$
22b	R=2-(5-bromobenzofuryl), R_3=H,R_1=βCN	**19d**	R=2-(pyrrolyl), R_3=H , R_1=βCOOCH$_3$
30a	R=styryl, R_3=H, R_1=αCN	**20c**	R=2-benzofuryl ,R_3=H,R_1=∝CN
30b	R=styryl, R_3=H, R_1=βCN	**20d**	R=2-benzofuryl, R_3=H,R_1=βCN
31a	R=styryl, R_3=H , R_1= αCOOCH$_3$	**21c**	R=2-benzofuryl, R_3=H,R_1=∝COOCH$_3$
31b	R=styryl,R_3=H, R_1=βCOOCH$_3$	**21d**	R=2-benzofuryl, R_3=H,R_1=βCOOCH$_3$
32a	R=2-chloro-1-cyclohexyl, R_3=H,R_1=αCN	**23c**	R=2-(5-bromobenzofuryl) , R_3=H,R_1=αCOOCH$_3$
32b	R=2-chloro-1-cyclohexyl,R_3=H, R_1=βCN	**23d**	R=2-(5-bromobenzofuryl), R_3=H,R_1=βCOOCH$_3$
36a	R=p-nitrophenyl, R_3=CH$_3$,R_1 = αCN	**30c**	R=styryl ,R_3=H, R_1=αCOOCH$_3$
36b	R=p-nitrophenyl,R_3=CH$_3$,R_1=βCN	**30d**	R=styryl, R_3=H, R_1=βCOOCH$_3$
37a	R=p-methoxyphenyl,R_3=CH$_3$, R_1 =αCN	**31c**	R=styryl, R_3=H, R_1=αCOOCH$_3$
37b	R=p-methoxyphenyl,R_3=CH$_3$, R_1= βCN	**31d**	R=styryl, R_3=H, R_1=βCOOCH$_3$
38a	R=3,4-dimethoxyphenyl,R_3=H, R_1= αCN	**33c**	R=2-chloro-1-cyclohexyl,R_3=H, R_1=αCOOCH$_3$
38b	R=3,4-dimethoxyphenyl, R_3=H, R_1=βCN	**33d**	R=2-chloro-1-cyclohexyl,R_3=H, R_1=βCOOCH$_3$
39a	R=3,4-Methylenedioxy,R_3=H, R_1=αCN	**36c**	R=p-nitrophenyl,R_3=CH$_3$, R_1=αCN
39b	R=3,4-Methylenedioxy,R_3=H, R_1=βCN	**36d**	R=p-nitrophenyl,R_3=CH$_3$, R_1=βCN
		37c	R=p-methoxyphenyl,R_3=CH$_3$,R_1=αCN
		37d	R=p-methoxyphenyl,R_3=CH$_3$,R_1=βCN
		38c	R=3,4-dimethoxyphenyl,R_3=H, R_1= αCN
		38d	R=3,4-dimethoxyphenyl,R_3=H, R_1= βCN
		39c	R=3,4-Methylenedioxy,R_3=H,R_1=αCN
		39d	R=3,4-Methylenedioxy, R_3=H, R_1= βCN

Scheme II—1,3-Dipolar reactions using olefinic dipolarophiles.

Table I— Characterisation data of individual stereo and regio isomers of isoxazolidines **16-39** and isoxazoles **40-42**

Compd	m.p. (°C)	Yield (%)	^{1}H NMR ($CDCl_3$, δ, ppm)
16a	Thick oil	45	2.55-2.75 (m, 3H, CH_2CN, C_4-H), 2.8-3.3 (m, 3H, NCH_2, C_4-H), 4.47 (t, *J*=6.2Hz, 1H, C_3-H), 4.9 (t, *J*=7.5Hz, 1H, C_5-H), 6.65 (d, *J*=3.7Hz, 1H, C3-H of furan ring), 7.32 (d, *J*=3.7Hz, 1H, C_4-H of furan ring).
16b	Thick oil	45	2.46-3.75 (2m, 6H, NCH_2CH_2, C_4H_2), 4.0 (t, *J*=7.5Hz, 1H, C_3-H), 5.0 (dd, *J*=3.7, 8.7Hz, 1H, C_5-H), 6.7 (d, *J*=3.7Hz, 1H, C_3-H of furan ring, 7.35 (d, *J*=3.7Hz, 1H, C_4-H of furan ring).
17c/d	Thick oil	40	2.45-2.8, 2.8-3.3 (2m, 5H, NCH_2CH_2, C_4-H), 3.57-3.8 (2s, 6H, 2COOMe), 4.0-4.8 (m, 3H, C_5H_2, C_3-H), 6.6 (m, 1H, C_3-H of furan ring), 7.3 (bs, 1H, C4-H of furan ring).
18d	115 M^+216	20	2.4-2.67 (m, 2H, CH_2CN), 2.67-3.12 (m, 2H, NCH_2), 3.45-3.78 (m, 1H, C_4-H), 3.9-4.48 (m, 3H, C_3-H, C_5H_2), 6.2-6.4 (m, 2H, C_3H, C_4-H of furan ring), 6.9-7.0 (m, 1H, C_5-H of furan ring), 8.6-9.0 (bs, 1H, NH).
19c & d	Thick oil	20	2.5-2.7, 2.8-3.1 (2m, 4H, NCH_2CH_2), 3.6-3.7 (2S, 6H, 2COOMe), 3.3-3.8 (m, 2H C_4-H, C_3-H), 3.9-4.2 (m, 2H C_5H_2), 6.0-6.2 (m, 1H, C_4-H of furan ring), 6.6- 6.8 (m, 2H, C_5-H, C_3-H of furan ring), 8.0-8.3 (bs, 1H, NH).
20a	Thick oil	30	2.54-2.77 (t.*J*=6.3Hz, 2H, CH_2CN), 2.9-3.3 (m, 4H, C_4H_2, NCH_2), 4.4 (t, *J*=7.5Hz, 1H, C_3-H), 4.95 (t, *J*=6.3 Hz, 1H, C_5-H), 7.7 (s, 1H, C_3-H of furan ring), 7.7-7.8 (m, 4H, benzofuryl protons).
20b	78-9	40	2.5-2.77 (t, *J*=7.5 Hz, 2H, CH_2CN), 2.9-3.3 (m, 4H, C_4H_2, NCH_2), 4.0 (t, *J*=7.5Hz, 1H, C_3-H), 4.95 (t, *J*=6.3Hz, 1H, C_5-H), 7.7 (s, 1H, C_3-H of furan ring), 7.2-7.8 (m, 4H, benzofuryl protons).
20c	110-3	10	2.5-2.8 (t, *J*=7.5 Hz, 2H, CH_2CN), 2.9-3.2 (t, *J*=7.5 Hz , 2H, NCH_2), 3.6 (m, 1H, C_4-H), 4.2-4.5 (m, 3H, C_5H_2,C_3-H), 6.8 (s, 1H, C_3-H of furan ring), 7.23-8.0 (m, 4H, benzofuryl protons).
20d	108-10	10	2.5-2.7 (t, *J*=6.3 Hz, 2H, CH_2CN), 2.9-3.2 (t, *J*=6.3 Hz , 2H, NCH_2), 3.8 (m, 1H, C_4-H) 4.2-4.5 (m, 3H, C_5H_2, C_3-H), 6.8 (s, 1H, C_3-H of furan ring), 7.23-7.4 (m, 4H, benzofuryl protons).
21c/d	Thick oil M^+333	20	2.5-2.8 (t, *J*=7.5 Hz, 2H, CH_2COOMe), 3.0-3.3 (m, 3H, C_4-H, NCH_2) , 3.5, 3.6 (2s, 6H, 2COOMe), 4.2-4.5 (m, 3H C_5H_2, C_3-H), 6.7 (s, 1H, C_3-H), 7.1-7.8 (m, 4H, benzofuryl protons).
22b	120-1 M^+346	80	2.5-2.7 (m, 2H, CH_2CN), 2.8-3.3 (m, 4H, NCH_2, C_4H_2), 4.07 (t, *J*=8.7Hz, 1H, C_3-H), 5.0 (dd, *J*=7.5, 3.7Hz, 1H, C_5-H), 6.8 (s, 1H, C_3-H of furan ring), 7.4 (s, 1H, C4-H of furan ring), 7.7 (bs, 2H, benzofuryl protons).
23c/d	Thick oil	20	2.5-2.7 (t, *J*=6.3Hz, 2H CH_2COOMe), 3.0-3.4 (m, 3H, C_4-H, NCH_2), 3.6-3.7 (2s, 6H, 2COOMe), 4.2-4.4 (m, 3H, C_3-H, C_5H_2), 6.7 (s, 1H, C_3-H), 7.1-7, 7 (m, 3H, benzofuryl protons).
24 mixture of isomers	88-92	60	2.59-2.82, 2.91-3.22, 3.27-3.66 (3m, alicyclic & aliphatic protons), 3.74, 3.93, 4.0 (3s, 3H, NCH_3), 4.0-4.8, 4.9-5.2 (2m, alicyclic protons), 6.61, 6.65, 6.72, 6.82 (4s, 1H, C_3-H of indole ring), 7.28-7.7 (m, 3H, aromatic protons), 7.74 (d, *J*=7.5Hz, 1H, aromatic protons).
25 mixture of isomers	Thick oil	72	1.08-1.41 (2t, *J*=7.7Hz, 2$COOCH_2CH_3$), 3.86-4.2 (2q, *J*=7.7Hz, 2$COOCH_2CH_3$), 2.5-2.75, 2.76-3.08 (2m, alicyclic protons), 3.61-3.86 (s, NCH_3), 4.25-4.8 (m, C_5-H), 6.41, 6.5 (2s, C_3-H of indole ring), 6.91-7.16 (m, aromatic protons), 7.5 (d, *J*=7.5Hz, aromatic protons).

Contd—

Table I— Characterisation data of individual stereo and regio isomers of isoxazolidines **16-39** and isoxazoles **40-42**—*Contd*

Compd	m.p. (°C)	Yield (%)	^{1}H NMR ($CDCl_3$, δ, ppm)
26 mixture of isomers	Thick oil	62	2.5-2.77, 2.88-3.25 (2m, 4H, NCH_2CH_2CN, C_4-H), 3.41-3.75, 3.83-4.55, 4.9 (2m, dd, *J*=7.7, 4.1Hz, together 4H, C_5-H, C_3-H, NCH_2- CH_2CN), 7.05-7.5 (m, aromatic protons, C_2-H), 7.55-8.0 (m, C_4-H of indole ring), 8.27 (bs, NH).
27 mixture of isomers	Thick oil	75	2.38-2.8, 2.86-3.3 (2m, alicyclic & aliphatic protons), 3.52, 3.63, 3.77 (3s, 2COOMe), 4.08-4.41, 4.55-4.86 (2m alicyclic protons, C_5-H), 6.88-7.47 (m, C_2H of indole ring, aromatic protons), 7.5-7.86 (m, C_4-H of indole ring), 8.19 (bs, 1H, NH).
28 mixture of isomers	175-8	65	2.41-2.75, 2.75-3.25 (2m, alicyclic &aliphatic protons), 3.88, 3.92, 3.94 (3s, 2OMe), 4.0-4.47 (m, alicyclic protons), 4.9 (bt, *J*=7.7Hz, C_5-H), 6.75, 7.36 (2s, C_7-H, C_4-H of indole ring), 6.97-7.27 (m, C_2-H of indole ring), 8.0 (bs, NH).
29 mixture of isomers	Thick oil	70	2.44-2.77, 2.77-3.19 (2m, alicyclic and aliphatic protons), 3.5-4.0 (bs, 2OMe and 2COOMe), 4.16-4.36 (m, alicyclic protons), 4.5-4.8 (m, C_5-H), 6.72 (s, C_7-H of indole ring) 6.92-7.0 (m, C_2-H and C_4-H of indole ring), 7.88 (bs, NH).
30a+b*	Thick oil	—	2.4-2.88, 2.88-3.12, 3.12-3.64 (3m, alicyclic & aliphatic protons), 4.99 (dd, *J*=3.8, 5.14Hz, 1H, C_5-H), 6.28 (dd, *J*=7.7, 15Hz, 1H, olefinic protons), 6.84 (d, *J*=15Hz, 1H, olefinic protons), 7.4-7.84 (m, 5H, aromatic protons).
30c/d*	76	—	2.64-3.04, 3.16-3.88, 4.08-4.64 (3m, 8H, aliphatic & alicyclic protons), 6.4 (dd, *J*=7.7, 15Hz, 1H, olefinic proton), 6.86 (d, *J*=15Hz, 1H, olefinic proton), 7.4-7.82 (m, 5H, aromatic protons).
31a/b*	Thick oil	—	2.5-2.89, 3.0-3.42 (2m, 7H, aliphatic & alicyclic protons), 3.76 (s, 3H, COOMe), 3.86 (s, 3H, COOMe), 4.78 (t, 1H, C_5-H), 6.24 (dd, *J*=7.7, 15Hz, 1H, olefinic proton), 6.8 (d, *J*=15Hz, 1H, olefinic proton), 7.2-7.84 (m, 5H, aromatic protons).
31c/d*	Thick oil	—	2.64-3.6 (m, 6H, aliphatic & alicyclic protons), 3.84 (s, 3H, COOMe), 3.88 (s, 3HCOOMe), 4.04-4.40 (m, 2H, aliphatic protons), 6.36 (dd, *J*=7.7, 15Hz, 1H, olefinic proton), 7.92 (d, *J*=15Hz, 1H, olefinic proton), 7.4-8.0 (m, 5H aromatic protons).
32a+b†	Thick oil	—	1.53-1.98, 2.36-2.58, 2.58-2.84, 2.84-3.50 (4m, aliphatic & alicyclic protons), 4.12 (t, *J*=9Hz C_3-H), 4.52 (t, *J*=9Hz, C_3-H), 4.68-5.10 (m, C_5-H).
33c/d	Thick oil	67	1.92-2.22, 2.28-3.16, 3.16-3.48, (3m, 14H, aliphatic & alicyclic protons), 3.86 (s, 6H, 2COOMe), 4.04-4.82 (m, 2H, alicyclic protons).
34 mixture of isomers	Thick oil	52	1.72 (s, 3H, CH_3), 1.8 (s, 3H, CH_3) 2.06-2.5, 2.6-3.36, 3.54-3.8, 3.96-4.84 (m, 13H, aliphatic and alicyclic protons), 4.84-5.26 (m, 1H C_5-H), 7.2-7.86 (m, 8H, indole ring protons), 8.0-8.4 (m, 2H C_4-H of indole ring), 8.4-8.88 (m, 2H, NH of indole ring).
35 mixture of isomers	Thick oil	45	2.36-2.42 (m, CH_3 & aliphatic protons), 2.42-3.08, 3.08-3.40 (2m, alicyclic protons), 3.76 (s, 4COOMe), 4.04-4.34, 4.52-4.78 (2m, alicyclic protons), 7.36-7.72, 8.0-8.24 (2m, indole ring protons), 8.5-8.82 (m, NH, exchangeable with D_2O).
36a/b†	138-9	—	1.7 (s, 3H, CH_3), 2.68-3.30 (m, 6H, alicyclic & aliphatic protons), 4.8 (t, *J*=7.71Hz, 1H, C_5-H), 7.9 (d, *J*=9Hz, 2H, aromatic protons), 8.44 (d, *J*=9Hz, 2H, aromatic protons).

Contd—

Table I— Characterisation data of individual stereo and regio isomers of isoxazolidines **16-39** and isoxazoles **40-42**—*Contd*

Compd	m.p. (°C)	Yield (%)	^{1}H NMR ($CDCl_3$, δ, ppm)
36c/d†	122-3	—	1.84 (s, 3H, CH_3), 2.64-3.16 (m, 4H, aliphatic protons), 3.72 (m, 1H, C_4-H), 4.18-4.64 (m, 2H, C_5-H), 8.0 (d, *J*=9Hz, 2H, aromatic protons), 8.52 (d, *J*=9Hz, 2H aromatic protons).
37a&b‡	Thick oil	—	1.5 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 2.62-3.52 (m, 12H, aliphatic & alicyclic protons), 3.9 (s, 6H, $2OCH_3$), 4.08-5.08 (s, 2H, alicyclic protons), 7.0-7.24 (m, 4H aromatic protons), 7.44-7.8 (m, 4H, aromatic protons).
37c‡	128-9	—	1.6 (s, 3H, CH_3), 2.64-3.04.3.34-3.72 (m, 4H, & m, 1H aliphatic & alicyclic protons), 3.92 (s, 3H, OCH_3), 4.12-4.60 (m, 2H, alicyclic protons), 7.16 (d, *J*=9Hz, 2H, aromatic protons), 7.76 (d, *J*=9Hz, 2H, aromatic protons).
38a/b	Thick oil	49	2.25-2.8, 2.8-3.3 (2m, 7H, aliphatic and alicyclic protons), 3.6, 3.74 (2s, 6H, 2COOMe), 3.81 (2s, 6H, 2OMe), 4.36-4.83 (m, 1H, C_5-H), 6.47-7.1 (m, 3H, aromatic protons).
38c/d	Thick oil	44	2.3-2.78, 2.78-3.19, 3.19-3.45 (3m, 7H, aliphatic and alicyclic protons), 3.51, 3.52 (2s, 6H, 2COOMe), 3.85 (s, 6H, 2OMe), 4.0-4.25 (m, 1H, C_5-H), 6.61-7.05 (m, 3H, aromatic protons).
39a/b	Thick oil	56	2.22-2.75, 2.75-3.33, 3.91-4.15 (3m, 7H, aliphatic and alicyclic protons), 3.53, 3.72 (2s, 6H, 2COOMe), 4.17-4.69 (m, 1H, C_5-H), 5.86 (s, 2H, OCH_2O), 6.45-6.89 (m, 3H, aromatic protons).
39c/d	Thick oil	18	2.25-2.67, 2.67-3.0, 3.0-3.42 (3m, 6H, aliphatic and alicyclic protons), 3.50-3.58 (2s, 6H, 2COOMe), 3.89-4.19 (m, 2H, C_5H_2), 5.83 (s, 2H, OCH_2O), 6.42-6.94 (m, 3H, aromatic protons).
40	100-102	62	4.05 (s, 3H, COOMe),7.27-8.1 (m, 6H, aromatic & olefinic), 8.5 (m, 2H, olefinic & C_5-H).
41	124	66	3.79(s, 3H, COOMe), 3.90 (s, 3H, OMe), 7.0 (d, *J*=7.5 Hz, 2H, aromatic protons), 8.5 (d, *J*=7.5 Hz, 2H, aromatic protons), 8.6 (s, 1H, C_5-H).
42	167-170	68	3.81(s, 3H, COOMe), 6.1 (s, 2H , OCH_2O), 6.91(d, *J* = 7.7 Hz, 1H, aromatic protons), 7.81 (dd, *J* =7.7, 1.4 Hz, 1H, aromatic proton), 8.6 (d, *J*=1.4 Hz, 1H, aromatic proton), 8.65 (s, 1H, C_5-H).

*Total yield of **30a/b/c/d** and **31a/b/c/d** is 72% & 71% respectively
†Total yield of **32a/b/c/d** and **36a/b/c/d** is 65 & 78% respectively.
‡Total yield of **37a/b/c/d** is 76%

isomers **20a-d** of the cycloadduct which were isolated and characterised. The regioisomers were differentiated on the basis of the most downfield signal of C_5-H. In **20a** and **20b** it appeared at δ 4.95 and in **20c** and **20d** two protons at C-5 appeared at δ 4.2-4.5. Discrimination between **20a** and **20b** was carried out on the basis of chemical shift of C_3-H. Because of the *cis* relationship of C_3-H and cyano group, C_3-H was expected to resonate downfield (δ 4.4)in *trans* isomer as compared to that in *cis* isomer(δ 4.0). Isomers **20c** and **20d** were differentiated on the basis of the chemical shift of C_4-H which being *cis* to benzofuran ring, was expected to be more shielded. Thus the compound having signal at δ 3.6 was the *trans* isomer **20c** and the other having signal at δ 3.8 was the *cis* isomer **20d** (Scheme II, Table I).

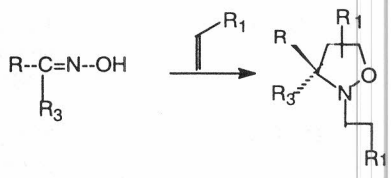
Reaction of acrylonitrile with 5-bromobenzofuran-2-aldoxime **4**, furnished only 5-cyano isomer **22b** in high yield. In the reactions using methyl acrylate both **3** and **4** oximes furnished mixtures of isomers of cycloadducts (**21** and **23**) from which **21c/d** and **23c/d** were separated.

Indole 2-aldoxime **5**, indole-3-aldoxime **6** and 5,6-dimethoxyindole-3-aldoxime **8** also gave mixtures of isomers of the cycloadducts **24**, **25**, **26**, **27**, **28**, and **29** respectively with acrylonitrile as well as ethyl acrylate or methyl acrylate which were not separated into individual isomers (Scheme III, Table I).

Cinnamaldoxime **9** and 2-chloro-1-cyclohexene-aldoxime **10** when used in these reactions gave initially mixtures of isomers. In the case of cinnamaldoxime with acrylonitrile as well as methyl acrylate, 4- and 5-cyano isomers were separated and identified as **30a/b**, **30c/d** and **31a/b** **3 1c/d**. In the case of oxime **10** with acrylonitrile, stereoisomeric mixture of 5-isomers was isolated in 2:5 ratio of *cis*(**32b**):*trans*(**32a**)as shown by ^{1}H NMR. With methyl acrylate, mixture of isomers of **33** was obtained from which **33c/d** was separated into pure form. Veratraldoxime **12** and piperonal oxime **13** furnished mixtures of isomers **38** and **39** with methyl acrylate (Scheme II,Table I).

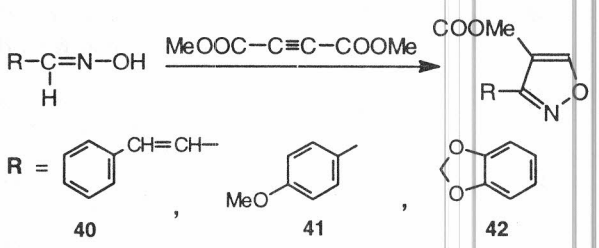
In the last part of this work, ketoximes **7**,**14**, and **15** when treated with dienophiles gave mixtures of isomers of the adducts **34**, **35**, **36**, **37.**

1,3-Dipolar reactions using unsaturated oximes with acetylenic dipolarophile (DMAD). Recently we have reported[3] a reaction of thiophene–2-aldoxime with DMAD which furnished directly 3-substituted isoxazole-4-methyl ester. In connection with this work, ∝,β-unsaturated oximes **9**, **11** and **13** were treated with DMAD. The products obtained were 4-carbo-methoxy isoxazoles **40**-**42** (Scheme IV, Table II). The probable mechanism can be shown as initial cycloaddition with Michael addition to give 4-isoxazoline which can isomerise to 3-isoxazoline. The two carbomethoxyl groups can be differentiated on the basis of the fact that, C_4-COOMe is vinylogous amide while C_5-COOMe is a saturated ester. Hydrolysis and decarboxylation of C_5-COOMe might be furnishing the products as shown in Scheme V. The position of –COOMe group was confirmed from the ^{1}H NMR spectral data in which most downfield proton C_5-H was seen around δ 8-9. In each case dehydrated products were obtained in around 20% yield.

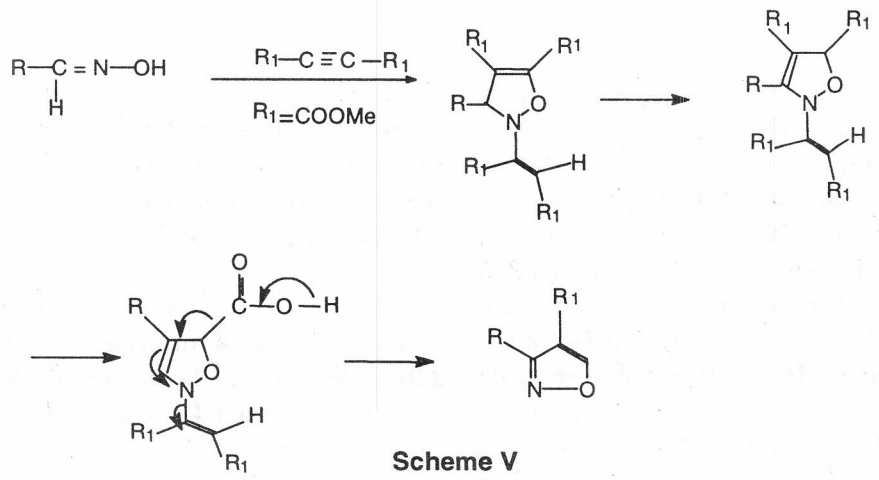


24 R=2-(N-methylindolyl),R_3=H,R_1=CN
25 R=2-(N-methylindolyl),R_3=H,R_1=COOEt
26 R=3-indolyl,R_3=H,R_1=CN
27 R=3-indolyl,R_3=H,R_1=$COOCH_3$
28 R=3-(5,6-dimethoxyindolyl),R_3=H,R_1=CN
29 R=3-(5,6-dimethoxyindolyl),R_3=H,R_1=$COOCH_3$
34 R=3-indolyl,R_3=Me,R_1=CN
35 R=3-indolyl,R_3=Me,R_1=$COOCH_3$

Scheme III—1,3-Dipolar reactions using olefinic dipolarophiles



Scheme IV – 1,3 Dipolar reactions using DMAD



Scheme V

Conclusion

Reactions of unsaturated oximes **1-10** and **12-15** with double bonded dipolarophiles furnished new substituted isoxazolidines while those of **9**, **11** and **13** with DMAD furnished substituted isoxazoles.

Experimental Secion

IR spectra were recorded in nujol on Perkin Elmer–337 spectrometer and ^{1}H NMR spectra on a Jeol FX 90Q spectrometer at 90 MHz in $CDCl_3$ using TMS as internal standard. Carbon/hydrogen analyses were carried out on Hosli C/H analyser .

Preparation of unsaturated oximes. ∝,β–Unsaturated oximes **1-15** were prepared using reported procedures.

General procedure for 1,3-dipolar reactions. To the unsaturated oxime **1-15** was added an excess of the dipolarophile (acrylonitrile, methyl acrylate, ethyl acrylate or DMAD) and a pinch of hydroquinone. After passing dry nitrogen gas, the reaction mixture was heated (for 12-120 hr) in a sealed tube at 120°C. Excess of the dipolarophile was removed. The reaction mixture was chromatographed on silica gel using pet ether–ethyl acetate (2-10%) which furnished the product as a thick oil (few are solids).The isoxazolidines obtained as thick oils were mixtures of regio- and stereoisomers. In some cases the thick oil was rechromatographed on silica gel using pet ether-ethyl acetate to furnish single isomer. IR spectra of all isoxazolidines obtained in the reactions with acrylonitrile showed bands in the range of 2250-2260 cm^{-1} for –CN and with methyl acrylate showed bands in the range of 1730-1770 cm^{-1} for –COOMe along with the other bands. All isoxazoles showed bands in the range of 1747-1755 cm^{-1} for -COOMe. All products showed satisfactory microanalysis within the range of C 0.3%, H 0.2%.

Acknowledgement

We thank Mr A P Gadgil and Mrs J P Chaudhari for analytical and spectral data. One of us (HMW) thanks the UGC, New Delhi, for the award of teacher fellowship under FIP.

References

1 Grunanger P & Funzi P V, *The Chemistry of Heterocyclic Compounds, Isoxazoles*, Vol 49, Part I, (John Wiley, New York) **1991**, 391,753.

2 Devi V U, Ashok K, Rao K R K M, *Indian J Chem* 29B,**1990**, 898.

3 Kusurkar R S, Wadia M S, Bhosale D K, Tavale S S & Puranik V G, *J Chem Res (S)*, **1996**, 478 *J Chem Res(M)*, **1996**, 2701