Reactions of Cinnamylideneamino Isoxazoles with Dimethyl Acetylenedicarboxylate

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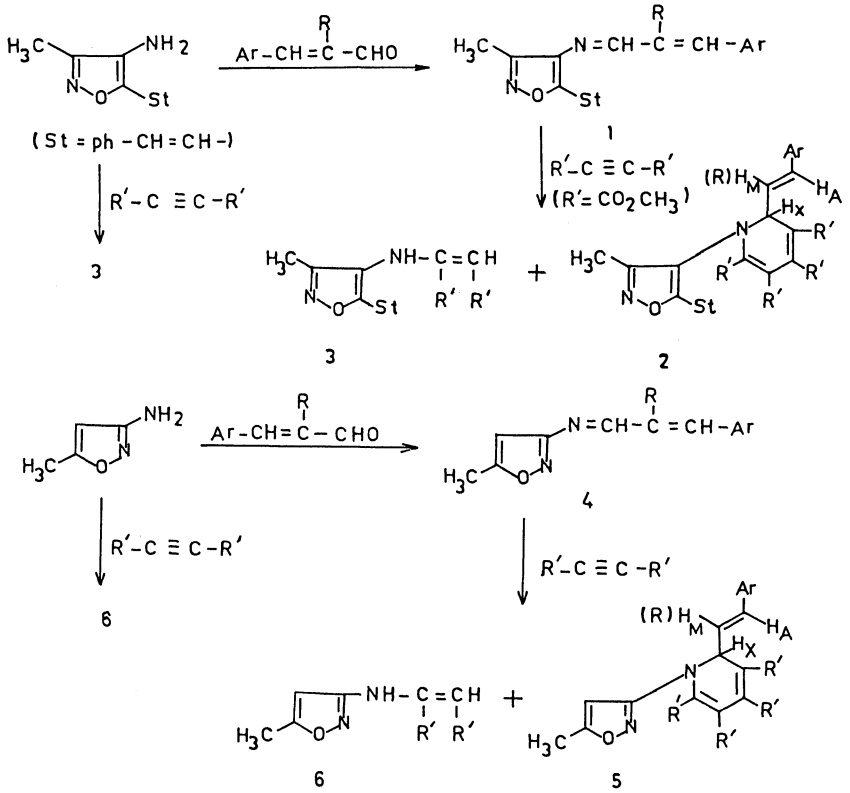
Synopsis. The interaction of 4-cinnamylideneamino-3-methyl-5-styrylisoxazoles (**1**) with dimethyl acetylenedicarboxylate has given an isoxazolyldihydropyridine (**2**) as major and an isoxazolylaminofumarate (**3**) as minor products respectively. 3-Cinnamylideneamino-5-methylisoxazoles (**4**) behave similarly. Isoxazolylaminofumarates (**3** and **6**) have been identified by unambiguous synthesis.

Interaction of the Schiff's bases of aminoisoxazoles with benzonitrile oxide, naphthols, benzoxazinones and light studied in our laboratories, led to the formation of oxadiazolines,[1] naphthoxazines,[2] quinazolinones,[3] and imidazoles[4] respectively as substituents on isoxazoles. In continuation of the work in this direction, we investigated reaction of cinnamylideneaminoisoxazoles with dimethyl acetylenedicarboxylate (DMAD). Gagan[5] was the first to assign a definite structure to the products from reaction of benzylidenemethylamine and cinnamylideneaniline with DMAD. Later, Murphy et al.[6] who used benzylideneanisidine and anisylideneaniline in this reaction made some unusual observations. The reactions in this field have been reviewed twice.[7,8] Though the interaction of this versatile synthon with aromatic and a few heteroaromatic Schiff's bases is known, the isoxazole counterparts have not been utilized so far in this reaction. Here, we report the results of the reaction of cinnamylidene Schiff's bases of 3-amino and 4-aminoisoxazoles with DMAD.

4-Cinnamylideneamino-3-methyl-5-styrylisoxazoles (**1**) have been synthesized starting from 3,5-dimethylisoxazole by nitration and regiospecific styrylation.[9] 3-Metyl-4-nitro-5-styrylisoxazole thus obtained, on reduction with tin(II) chloride-hydrochloric acid[10] and subsequent reaction with cinnamaldehydes gave the conjugated Schiff's bases.



compound	R	Ar
a	H	C_6H_5-
b	H	C_6H_4-OCH_3-(O)
c	H	C_6H_4-NO_2-(O)
d	CH_3	C_6H_5-

Reaction of **1** with DMAD has been carried out in dry toluene under reflux for 12 h. After the removal of solvent the residue was passed through a column of silica gel. Two products have been isolated by eluting with varying proportions of benzene-ethyl acetate. The first compound from chromatographic separation has been identified as dimethyl 2-(3-methyl-5-styryl-4-isoxazolyl) aminofumarate (**3**). The presence of NH is indicated by IR (3410 cm^{-1}) and ^1H NMR (δ 9.0 and exchanged with D_2O) spectra. In ^1H NMR the vinyl proton resonates as a sharp singlet at δ 5.5. The mass spectrum showing a molecular ion at m/z 342 supports the structure of the product, formed as a result of the reaction of aminoisoxazole with DMAD. The aminoisoxazole is presumably formed by the action of traces of moisture. The presence of cinnamaldehyde (from **1**) in the reaction mixture has been detected by Tollen's reagent ($AgNO_3$+1 M NaOH+aq NH_3) (1 M=1 mol dm^{-3}). The structure of the fumarate (**3**) has been authenticated by a separate reaction of 4-amino-3-methyl-5-styrylisoxazole with DMAD in ether. This reaction has afforded a product identical in all respects (TLC, IR, and mixed mp) with **3**. The second product which is major, has been identified as the cycloadduct whose molecular weight is recorded at m/z 598 corresponding to the 1 : 2 reaction of the cinnamylidene Schiff's base with DMAD. Based on ^1H NMR and mass spectra the product is shown to be tetramethyl 1-(3-methyl-5-styryl-4-isoxazolyl)-2-styryl-1,2-dihydropyridine-3,4,5,6-tetracarboxylate (**2**) similar to the product reported by Gagan (loc. cit.). Two protons of styryl group on dihydropyridine and another proton on dihydropridine ring show up as AMX system between δ 5.1—6.0 (J_{AM}=15.6, J_{AX}=0, and J_{MX}=5.1 Hz). The trans geometry of this styryl double bond is clearly indicated by the coupling (15.6 Hz) between the two hydrogens.

The reaction of 3-cinnamylideneamino-5-methylisoxazole (**4**) with DMAD under similar conditions gave the analogous results. Chromatographic separation of the product mixture gave dimethyl 2-(5-methyl-3-isoxazolyl)aminofumarate (**6**) and tetramethyl 1-(5-methyl-3-isoxazolyl)-1,2-dihydropyridine-3,4,5,6-tetracarboxylate (**5**). The starting material **4** required for the above reaction has been made by interaction of 3-amino-5-methylisoxazole (purchased from market) with cinnamaldehyde in ethanol. The fumarate (**6**) shows NH proton as a broad peak at δ 9.8 (exchangeable with D_2O) and vinylic proton at δ 5.4 in ^1H NMR. The mass spectrum showing the molecular ion at m/z 240 is in confirmity with the structure. The structure of **6** was further proved by unambiguous synthesis. The dihydropyridine (**5**) shows, in ^1H NMR, an AMX pattern for the two styryl protons and another on the pyridine ring in the region between 5.6—6.7 (J_{AM}=15.6 Hz, J_{AX}=0, and J_{MX}=5 Hz). Molecular weight of **5** is given by the mass spectrum which shows a weak signal at m/z 496. All the compounds prepared have been included in the table along with the characterization data.

Experimental

All the melting points are uncorrected. The purity of the compounds was checked by TLC. The IR spectra were recorded on a Perkin-Elmer 283 model as KBr discs. ^1H NMR spectra were run on a Varian AD 100 spectrometer using TMS as internal reference (chemical shifts in δ scale). Mass spectra were recorded on a Hitachi model RMU 6E at 70 eV. Silica gel was used for both TLC and column chromatography.

4-Cinnamylideneamino-3-methyl-5-styrylisoxazoles (1). 4-Amino-3-methyl-5-styrylisoxazole (0.01 mol) and cinnamaldehyde (0.01 mol) were refluxed in ethyl alcohol (20 ml) for 2 h. The compound separated on cooling was filtered and recrystallized from benzene (Table 1).

Reaction of 4-Cinnamylideneamino-3-methyl-5-styrylisoxazole with DMAD. A mixture of 4-cinnamylideneamino-3-methyl-5-styrylisoxazole (0.01 mol) and DMAD (0.02 mol) was refluxed in dry toluene for 12 h. After the removal of solvent, the residue was passed over a column of silica gel. Elution with benzene-ethyl acetate (5%) gave fumarate (**3**), whereas benzene-ethyl acetate (20%) gave dihydropyridine (**2**) (Table 1). Fumarate (**3**): mp 80 °C, Yield 5% [Found: C, 64.06; H, 5.23; N, 8.15%. Calcd for $C_{18}H_{18}N_2O_5$: C, 63.15; H, 5.26; N, 8.18%]. IR (KBr): 3410(NH), 1750 cm^{-1}

Table 1. The Physical Properties and Elemental Analysis of the Products

Compound	Mp	Yield	Formula	Found/%			Calcd/%		
	°C	%		C	H	N	C	H	N
1a	115	90	$C_{12}H_{18}N_2O$	80.32	5.71	8.87	80.25	5.73	8.91
1b	110	85	$C_{22}H_{20}N_2O_2$	76.71	5.83	8.12	76.74	5.81	8.13
1c	150	85	$C_{21}H_{17}N_3O_3$	70.18	4.74	11.66	70.19	4.73	11.69
1d	88	80	$C_{22}H_{20}N_2O$	80.43	5.98	8.49	80.48	6.09	8.53
2a	92	55	$C_{33}H_{30}N_2O_9$	66.10	4.98	4.72	66.22	5.01	4.68
2b	83	45	$C_{34}H_{32}N_2O_{10}$	65.06	5.12	4.53	64.96	5.09	4.45
2c	135	50	$C_{33}H_{29}N_3O_{11}$	61.62	4.72	6.48	61.58	4.51	6.53
2d	85	35	$C_{34}H_{32}N_2O_9$	66.63	5.12	4.61	66.66	5.22	4.57
4a	130	85	$C_{13}H_{12}N_2O$	74.01	5.59	13.19	73.58	5.66	13.20
4b	95	80	$C_{14}H_{14}N_2O_2$	70.12	5.65	11.46	69.42	5.78	11.57
4c	90	90	$C_{13}H_{11}N_3O_3$	59.98	4.17	16.29	60.70	4.28	16.34
4d	82	82	$C_{14}H_{14}N_2O$	74.41	6.21	12.29	74.33	6.19	12.38
5a	90	50	$C_{25}H_{24}N_2O_9$	61.02	4.92	5.59	60.48	4.83	5.64
5b	85	40	$C_{26}H_{26}N_2O_{10}$	60.12	5.01	5.24	59.31	4.94	5.32
5c	120	45	$C_{25}H_{23}N_3O_{11}$	55.36	4.12	7.67	55.45	4.25	7.76
5d	78	35	$C_{26}H_{26}N_2O_9$	62.07	4.99	5.51	61.17	5.09	5.49

(CO_2CH_3); ^1H NMR ($CDCl_3$): δ=2.2 (s, 3H, isoxazole-CH_3), 3.6, 3.8 (2s, 6H, $COOCH_3$), 5.5 (s, 1H, vinylic -H) 6.7—7.2 (AB_q, 2H, Ph-CH=CH), 7.2—7.5 (m, 5H, Ph-H), 9.0 [s(broad), 1H, NH]. dihydropyridine (**2a**): mp 92 °C, ^1H NMR ($CDCl_3$): δ=2.1 (s, 3H, isoxazole-CH_3), 3.5, 3.6, 3.7, 3.9 (4s, 12H, $COOCH_3$), 5.1 (d, 1H, H_X, J_{XM}=5.1 Hz), 5.6 (dd, 1H, H_M), 6.0 (d, 1H. H_A, J_{AM}=15.6 Hz), 6.6—7.0 (AB_q, 2H, isoxazole-CH=CH-) 7.0—8.0 (m. 10H, Ph-H).

3-Cinnamylideneamino-5-methylisoxazole (4). 3-Amino-5-methylisoxazole (0.01 mol) and cinnamaldehyde (0.01 mol) were refluxed in ethyl alcohol (20 ml) for 2 h. The compound separated in the reaction mixture was filtered and recrystallized from benzene (Table 1).

Reaction of 3-Cinnamylideneamino-5-methylisoxazole with DMAD. A mixture of **4** (0.01 mol) and DMAD (0.02 mol) was heated in dry toluene for 24 h. The residue obtained after removal of solvent was passed over column of silica gel. Elution with benzene-ethyl acetate (5%) gave the fumarate (**6**) and benzene-ethyl acetate (20%) gave dihydropyridine (**5**) (Table 1). Fumarate (**6**): mp 70 °C, Yield 5% [Found: C, 49.91; H, 5.11; N, 11.59%. Calcd for $C_{10}H_{12}N_2O_5$: C, 50.0; H, 5.0; N, 11.66%]. IR (KBr): 3420 (NH), 1760 cm^{-1} (CO_2CH_3): ^1H NMR ($CDCl_3$): δ=2.1 (s, 3H, isoxazole-CH_3), 3.5. 3.7 (2s, 6H, $COOCH_3$), 5.4 (s, 1H, vinylic H), 5.7 (s, 1H, isoxazole-H), 9.8 [s(broad). 1H, NH]. dihydropyridine (**5a**): mp 90 °C: ^1H NMR ($CDCl_3$): δ=2.3 (s, 3H, isoxazole-CH_3) 3.5, 3.6, 3.7, 3.9 (4s, 12H, $COOCH_3$), 5.9 (s, 1H, isoxazole-H), 5.6 (d, 1H, H_X, J_{XM}=5 Hz), 6.1 (dd, 1H, H_M), 6.7 (d, 1H, H_A, J_{AM}=15.6 Hz), 7.2—7.6 (m, 5H, Ph-H).

Unambiguous Synthesis of Fumarate (3): 4-Amino-3-methyl-5-styrylisoxazole (0.01 mol) and DMAD (0.01 mol) were stirred at room temperature in dry ether for 12 h. The compound separated was filtered and passed through silica gel. Elution with benzene-ethyl acetate (5%) gave the product identical in all respects with **3**.

Unambiguous Synthesis of (6): Similar reaction was conducted between 3-amino-5-methylisoxazole and DMAD which gave the fumarate, found to be identical with **6**.

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