SYNTHESIS OF 1-ACETYL-2-METHYL-3-THIOXO-4-(1-AZA-2-ARYLVINYL)-5-OXO-6-(ARYL METHYLENE)1,2,4-TRIAZAPERHYDROINES

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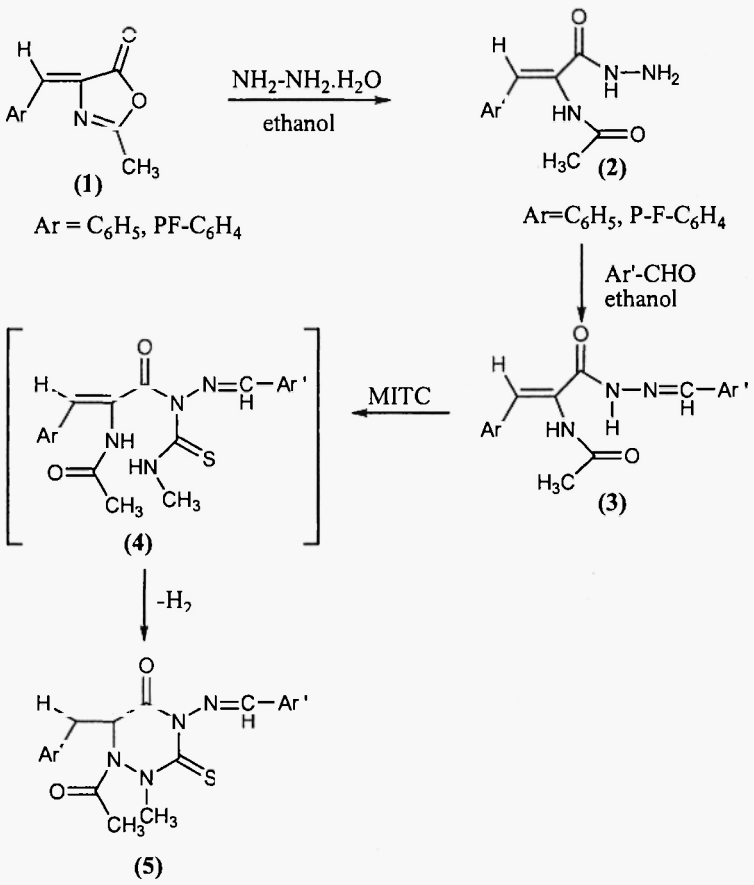
Abstract: Treatment of α–acetamido-cinnamhydrazides with aromatic aldehydes produces N-(1-aza-2-arylvinyl)-2-(acetylamino)-3-aryl prop-2-enamides. These on treatment with methyl isothiocyanate yielded the novel unknown title compounds.

A large number of applications 1,2,4-triazine ring system were recorded in the literature as antimicrobial, antitumor activity[1], antiviral[2], anticancer[3], antimalarial[4], antiinflammatory[5], herbicides[6], antihypertensive[7] and antiarthritics[8]. 1,2,4-Triazine ring systems were also significant as pesticides, synthetic high polymers, chemical coatings, photographic fogging agents and in dyes. In continuation of our studies on the synthesis of nitrogen containing heterocycles using methylisothiocyanate[9,10,11] now we wish to report the simple synthesis of 1-acetyl-2-methyl-3-thioxo-4-(1-aza-2-arylvinyl)5-oxo-6-(aryl methylene)-1,2,4-triazaperhydroines (**5**) employing 2-oxazolin-5-ones (**1**).

Synthesis of the title compounds (**5**) has been envisaged by the reaction of N-(1-aza-2-arylvinyl)-2-acetylamino-3-aryl-prop-2-enamides (**3**) with methyl isothiocyanate (MITC) in the presence of 1:1 methanol-acetic acid mixture. The required (**3**) was synthesized from 2-methyl-oxazolin-5-one (**1**) through two step synthetic sequence. Refluxing an equimolar mixture of (**3a**) and MITC in methanol, acetic acid mixture yielded 1-acetyl-2-methyl-3-thioxo-4-(1-aza-2-methyl phenyl vinyl)-5-oxo-6-(phenyl methylene)-1,2,4-triazaperhydroine (**5a**) characterized based on its mass, IR, ^{1}H NMR and ^{13}C NMR spectral data. To test its generality the method has been extended to seven other enamides [**3(b-h)**] and in all the cases the corresponding 1,2,4-triazoperhydroines **5(b-h)** were isolated in good yield.

The formation of the 1,2,4-triazaperhydroines can be rationalized as follows. Addition of MITC over more nucleophilic amide group of (**3**) would lead the formation of stable intermediate (**4**), which finally undergoes intramolecular cyclisation to yield 1,2,4-triazaperhydroines (**5**) by the elimination of the hydrogen molecule (Scheme 1). The intermediate **4a** (Ar=C_6H_5, Ar1=C_6H_4-OCH_3) KBr showed peaks at 3258 cm^{-1} (NH), 1762 cm^{-1} (C=O), 1562 cm^{-1} (C=N) and 1250 cm^{-1} (C=S). The ^{1}H NMR in $CDCl_3$ has shown peaks at 1.2 (s, 3H, CH_3), 1.5 (s, 3H, $COCH_3$), 4.0 (s, 3H, OCH_3), 7.0 (s, 1H, =CH-Ar), 7.4-7.5 (m, 9H, aromatic), 8.0 (s, 1H, Ar-CH=N), 9.4 (s, 1H, D_2O exchangeable), 11.2 (s, 1H, NH, D_2O exchangeable).



3 & 5	-	a	b	c	d	e	f	g	h
	Ar-	C_6H_5	C_6H_5	C_6H_5	C_6H_5	p-F-C_6H_4	p-F-C_6H_4	p-F-C_6H_4	p-F-C_6H_4
	Ar'	$C_6H_4OCH_3$	o-NO_2-C_6H_4	C_6H_5	OCl-C_6H_4	C_6H_5	p-CH_3-C_6H_4	p-Cl-C_6H_4	o-OH-C_6H_4

Scheme-1

Experimental

The melting points were uncorrected and taken in sulphuric acid bath. IR spectra were recorded on KBr with Niodel 740 spectrometer FTIR and ^1H and ^{13}C NMR spectra on a Varian-Gemini-200 and 50 MHz with TMS as internal standard and mass spectra were recorded on MSPC SCIEX API 3000 instrument.

Elemental analysis was measured by Yamaco C,H,N MT-3 apparatus [and the purity of all the compounds was checked on silica gel G TLC plates using Iodine vapours as visualizing agent].

Synthesis of α –acetamido-cinnamhydrazides (2)

General Procedure

To a solution of arylidine-2-methyl-oxazolene-5-ones (**1**) (0.01 mole) in ethanol (20 ml) was added a solution of hydrazine hydrate (99%, 0.02 mole) in ethanol (5 ml). The deep yellow colour of the solution immediately changed to light yellow and the ocmpound that separated out was filtered and recrystallised from ethanol with 85% yield. MP 160, (Lit. 158)[12].

Synthesis of N-(1-aza-2-arylvinyl)-2-(acetylamino)-3-arylprop-2-enamides (3)

General Procedure

Equimolar quantities of α–acetamidocinnam hydrazides (**2**) and aromatic aldehydes were dissolved in ethanol with few drops of acetic acid. The reaction mixture was heated on steam bath for about 1 hour and cooled to 10^{0}C. The solid that separated was filtered washed with ethanol and dried. The compounds [**3(a-h)**], (Table-I) thus prepared gave single spot on TLC (benzene-ethyl acetate, 2:8).

Synthesis of 1-(acetyl)-2-methyl-3-thio-4-(1-aza-2-aryl vinyl)-5-oxo-6-(aryl methylene)-1,2,4-triazaperhydroine (5)

General Procedure

Equimolar quantities of enamides (**3**) (0.001 ml) and methyl isothiocyanate (MITC) were dissolved in 1:1 mixture of methanol-acetic acid and refluxed for 4 hours. The solvent was distilled under reduced pressure and the solids that separated out was filtered, washed with ethanol and dried. The compound gave single spot on TLC (benzene-ethyl acetate, 2:6).

Spectral and Analytical Data

3(a) M.P. 165 ^{0}C, % yield 85, IR (KBr) cm^{-1} 3248, 3058 (NH), 1771 (C=O), 1680 (C=N), H NMR ($CDCl_3$) : δ 2 (s, 3H, $COCH_3$), 3.9 (s, 3H, OCH_3), 6.7 (s, H, C_6H_5CH=), 7.1-7.9 (m, 9H, Ar), 8.4 (s, H, =CH-Ar), 9.5 (br, H, NH-D_2O-exchangeable), 11.3 (br, H, NH, D_2O-exchangeable). Mass m/z M$^+$ 337; Anal. calcd. for $C_{19}H_{19}N_3O_3$: C 67.77, H 5.64, N 12.46%.

3(b) M.P. 170 ^{0}C, % yield 90, IR (KBr) cm^{-1} 3249, 3176 (NH), 1889 (C=O), 1593 (C=N), H NMR ($CDCl_3$) : δ 2.1 (s, 3H, $COCH_3$), 6.8 (s, H, C_6H_4CH=), 7.2-7.9 (m, 9H, Ar), 8.4 (s, H, N=CH-Ar), 9.4 (br, H, NH, D_2O-exchangeable), 11.8 (br, H, NH, D_2O- exchangeable). Mass m/z M$^+$ 352; Anal. Calcd. for $C_{19}H_{16}N_4O_4$: C 61.36, H 4.54, N 15.9%.

3(c) M.P. 154 ^{0}C, % yield 91, IR (KBr) cm^{-1} 3340-3240 (NH), 1760 (C=O), 1600 (C=N), H NMR ($CDCl_3$) : δ 2 (s, 3H, CH_3), 6.8 (s, H, Ar), 7.2-7.9 (m, 10H, Ar), 8.4 (s, H, N=CH-Ar), 9.4 (s, H, NH- D_2O exchangeable), 11.4 (s, H, NH-D_2O exchangeable). Mass m/z M$^+$ 307, Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C 69.45, H 5.47, N 13.5%.

3(d) M.P. 164 ^{0}C, % yield 55, IR (KBr) cm^{-1} 3379, 3201 (NH), 1696 (C=O), 1630 (C=O), 1620 (C=N), H NMR ($CDCl_3$) : δ 2 (s, 3H, CH_3), 6.9 (s, H, =CH-Ar), 7.2-7.9 (m, 9H, Ar), 8.4 (s, H, N=CH-Ar), 9.4 (s, H, NH-D_2O exchangeable), 11.4 (s, H, D_2O exchangeable). Mass m/z M$^+$ 342, Anal. Calcd. for $C_{18}H_{18}N_3O_2Cl$: C 63.15, H 4.68, N 12.3%.

3(e) M.P. 188 ^{0}C, % yield 69, IR (KBr) cm^{-1} 3256, 3152 (NH), 1619 (C=N), 1696 (C=O), H NMR ($CDCl_3$) : δ 2.2 (s, 3H, $COCH_3$), 6.9 (s, H, =CH-Ar), 7.2-7.9 (m, 9H, Ar), 8.4 (s, H, Ar-CH=N), 9.4 (s, H, NH-D_2O exchangeable), 11.4 (s, H, D_2O exchangeable), Mass m/z M$^+$ 326, Anal. Calcd. for $C_{18}H_{16}N_3O_2F$: C 66.26, H 5.2, N 12.88%.

3(f) M.P. 192 ^{0}C, % yield 68, IR (KBr) cm^{-1} 3162, 3362 (NH), 1681 (C=O), 1599 (C=N), HNMR ($CDCl_3$) : δ 2 (s, 3H, $COCH_3$), 2.9 (s, 3H, CH_3), 6.9 (s, H, =CH-Ar), 7.2-7.9 (m, 8H, Ar), 8.3 (s, H, CH=Ar), 9.9 (s, H, NH-D_2O exchangeable), 10.1 (s, H, NH-D_2O exchangeable), Mass m/z M$^+$ 339, Anal. Calcd. for $C_{18}H_{18}N_2O_2F$: C 67.3, H 5.3, N 12.5%.

3(g) M.P. 196 ^{0}C, % yield 69, IR (KBr) cm^{-1} 3362, 3162 (NH), 1681 (C=O), 1591 (C=N), H NMR ($CDCl_3$): δ 2.2 (s, 3H, $COCH_3$), 6.9 (s, H, CH-Ar), 7.2-7.8 (m, 9H, Ar) 7.8 (s, H, N-CH-Ar), 8.2 (s, H, CH-Ar D_2O exchangeable), 9.8 (s, H, NH-D_2O exchangeable). Mass m/z M$^+$ 362, Anal. Calcd. for $C_{18}H_{15}N_3O_2FCl$: C 61.3, H 4.3, N 11.29%.

3(h) M.P. 228 ^{0}C, % yield 69, IR (KBr) cm^{-1} 3307 (NH), 3002 (br, OH), 1711 (C=O), 1691 (C=N), H NMR ($CDCl_3$) : δ 2.21 (s, 3H, $COCH_3$), 5.4 (s, H, OH), 6.8 (s, H, CH-Ar), 7.79 (m, 8H, Ar), 8.4 (s, H, NH-D_2O exchangeable), 11.4 (s, H, NH-D_2O exchangeable), Mass m/z M$^+$ 342, Anal. Calcd. for $C_{18}H_{16}N_3O_3F$: C 64.6, H, 4.54, N 11.9%.

5(a) M.P. 170 ^{0}C, % yield 50, IR (KBr) cm^{-1} 1762 (C=O), 1662 (C=N), 1250 (C=S), HNMR ($CDCl_3$) : δ 1.2 (s, 3H, CH_3), 1.5 (s, 3H, $COCH_3$), 4 (s, 3H, NCH_3), 7 (s, H, =CH-Ar), 7.4-7.5 (m, 9H, Ar), 8 (s, H, -CH=N), ^{13}C NMR ($CDCl_3$) : δ 8 (C-CH_3), 21 (N-CH_3), 55 (O-CH_3), 115 (Ar-C=C), 127-130 (Ar), 135 (Ar-C=N), 148 (C=O), 161 (C=S), 170 (O=C-N), Mass m/z M$^+$ 408, Anal. Calcd. for $C_{21}H_{20}N_4O_3S$: C 61.77, H 4.9, N 13.73, S, 7.84%.

5(b) M.P. 180 ^{0}C, % yield 90, IR (KBr) cm^{-1} 1751 (C=O), 1567 (C=N), 1250 (C=S), HNMR ($CDCl_3$) : δ 2 (s, 3H, CH_3), 4.5 (s, 3H, NCH_3), 7.7 (m, 9H, -Ar), 8.2 (s, H, Ar-CH=), 8.4 (s, H, Ar-CH=N), ^{13}C NMR ($CDCl_3$) : δ 8 (c-CH_3), 21 (N-CH_3), 115 (Ar-C=C), 128-131 (Ar), 162 (C=S), 170 (O=C-N), Mass m/z M$^+$ 423, Anal. Calcd. for $C_{20}H_{17}N_5O_4S$: C 55.7, H 4.02, N 16.5, S 7.5%.

5(c) M.P. 175 ^{0}C, % yield 74, IR (KBr) cm^{-1} 1698 (C=O), 1573 (C=N), 1250 (C=S), HNMR ($CDCl_3$) : δ 1.9 (s, 3H, CH_3), 4 (s, 3H, NCH_3), 6.9-7.2 (m, 10H, -Ar), 7.8 (s, H, Ar-CH=), 8.2 (s, H, Ar-CH=N), ^{13}C NMR ($CDCl_3$) : δ 9 (C-CH_3), 22 (N-CH_3), 115 (Ar-C=C), 127-130 (Ar), 163 (C=S), Mass m/z M$^+$ 378, Anal. Calcd. for $C_{20}H_{18}N_4O_2S$: C, 63.49, H 4.76, N 14.81, S 8.46%.

5(d) M.P. 185 ^{0}C, % yield 73, IR (KBr) cm^{-1} 1755 (C=O), 1613 (C=N), 1251 (C=S), HNMR ($CDCl_3$) : δ 2 (s, 3H, CH_3), 3.4 (s, 3H, NCH_3), 6.9 (s, H, CH-Ar), 7-7.9 (m, 9H, -Ar), 9 (s, H, Ar-CH=), ^{13}C NMR ($CDCl_3$) : δ 9 (C-CH_3), 21 (N-CH3), 129-131 (Ar-C=C), 165 (C=S), 170 (C-N), Mass m/z M$^+$ 413, Anal. Calcd. for $C_{20}H_{17}N_4O_2SCl$: C 58.11, H 4.11, N 13.56, S 7.75%.

5(e) M.P. 168 ^{0}C, % yield 57, IR (KBr) cm^{-1} 1709 (C=O), 1650 (C=N), 1251 (C=S), HNMR ($CDCl_3$) : δ 2 (s, 3H, CH_3), 2.4 (s, 3H, NCH_3), 6.9 (s, H, CH-Ar), 7.3-7.9 (m, 9H, -Ar), 8.2 (s, H, Ar-CH=), ^{13}C NMR ($CDCl_3$) : δ 8 (CH_3), 23 (N-CH_3), 115 (Ar-C=C), 128-131 (Ar), 162 (C=S), Mass m/z M$^+$ 396, Anal. Calcd. for $C_{20}H_{17}N_4O_2SF$: C 59.11, H, 4.19, N 13.79, S 7.14%.

5(f) M.P. 198 ^{0}C, % yield 60, IR (KBr) cm^{-1} 1694 (C=O), 1595 (C=N), 1249 (C=S), HNMR ($CDCl_3$) : δ 1.4 (s, 3H, CH_3), 1.8 (s, 3H, CH_3), 4 (s, 3H, NCH_3), 6 (s, H, =CHAr), 6.8-7.4 (m, 8H, -Ar), 7.8 (s, H, N=CH), ^{13}C NMR ($CDCl_3$) : δ 9 (C-CH_3), 23 (N-CH_3), 115 (Ar-C=C), 127-130 (Ar), 163 (C=S), 171 (O=C-N), Mass m/z M$^+$ 410, Anal. Calcd. for $C_{21}H_{19}N_4O_2SF$: C 60.0, H 4.5, N 13.3, S 7.6%.

5(g) M.P. 210 0C, % yield 56, IR (KBr) cm^{-1} 1706 (C=O), 1586 (C=N), 1251 (C=S), HNMR ($CDCl_3$) : δ 1.4 (s, 3H, CH_3), 2.1 (s, 3H, CH_3), 7.7.9 (m, 8H, -Ar), 8.1 (s, H, Ar-CH), 9.3 (s, H, N=CHAr), ^{13}C NMR ($CDCl_3$) : δ 8 (C-CH_3), 22 (N-CH_3), 25 (C-Cl), 115 (Ar-C=C), 127-132 (Ar), 163 (C=S), 171 (O=C-N), Mass m/z M$^+$ 431, Anal. Calcd. for $C_{20}H_{16}N_4O_2SClF$: C 60.0, H 4.5, N 13.3, S 7.6%.

5(h) M.P. 250 ^{0}C, % yield 70, IR (KBr) cm^{-1} 1712 (C=O), 1562 (C=N), 1252 (C=S), HNMR ($CDCl_3$) : δ 1.4 (s, 3H, CH_3), 3 (s, 3H, NCH_3), 5 (s, H, OH), 7.1 (s, H, CH-Ar), 7.2-7.9 (m, 8H, Ar), 8.8 (s, H, ArCH=N), ^{13}C NMR ($CDCl_3$) : δ 9 (C-CH_3), 22 (N-CH_3), 115 (HO-C), 127-138 (Ar), 163 (C=S), 170 (O=C-N), Mass m/z M$^+$ 413, Anal. Calcd. for $C_{20}H_{17}N_4O_3SF$: C 58.1, H 4.35, N 13.5, S 7.75%.

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