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SYNTHESIS OF 1-(5-METHYLISOXAZOLE-3-YL)-5-ARYL-TETRAZOLES AND ITS PYROLYSIS

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ABSTRACT : 3-Aroylamino-5-methylisoxazoles (**2**) were obtained by the reaction of 3-amino-5-methylisoxazole (**1**) with different aroyl chlorides. These amides on reaction with phosphorous pentachloride followed by sodium azide yielded 1-(5-methylisoxazole-3-yl)-5-aryltetrazoles (**4**). Pyrolysis of the tetrazoles thus obtained resulted in the formation of 3-aryl-6-acetyl(1,2-4)triazines (**9**).

In continuation of our work [1-5] on the synthesis of fused heterocyclic systems from tetrazoles and with a view to synthesise the hitherto unknown isoxazolo(2,3-b) triazole ring systems, we report the synthesis and pyrolysis of 1-(5-methylisoxazole-3-yl)-5-aryltetrazoles.

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Reaction of 3-amino-5-methylisoxazle (**1**) wth aroylchloride (Ar =C_6H_5) in pyridine gave the corresponding amide [6] **2**.

Following the same procedure different 3-aroylamino-5-methylisoxazoles were prepared (Table I). The 3-benzamido-5-methylisoxazole **2** (Ar = C_6H_5) thus formed was treated with phosphorous pentachloride followed by sodium azide to yield a compound with mp. 85°C. The compound in its infrared (KBr) spectrum showed absorpbtion at 1600 cm^{-1} characteristic of C=N function. Absorption due to carbonyl (C=O) and azido(N_3) were not observed. In the mass spectrum M^+ appeared at m/z 227 and its ^{1} H-NMR ($CDCl_3$) , showed the following signals : δ 2.6 (s,3H, CH_3), 6.4 (s,1H, C-4 proton of the isoxazole ring), 7.2-7.6 (m, 5H,aromatic protons). Based on the above spectral data the compound was characterised as 1-(5-methylisoxazol-3-yl)-5- phenyltetrazole (**4a**; Ar=C_6H_5 ; R=CH_3).

Following the above procedure a number of tetrazoles were prepared by the reaction of 3-amino-5-methylisoxazoles with different acid chlorides as given in Table II.

Heating a mixture of **4a** and finely ground pure sand at 200°C for 2hr, and performing column chromotagraphy of the residue over neutral alumina with benzene as the eluant yielded a compound melting at 135°C in very low yield. Elemental analysis of the compound with mp.135°C suggested

TABLE - I

Melting points and yields of 3-aroylamino-5-methylisoxazoles **2**.

Compound	mp°C	Yield %	Elemental analysis % Found (Required)		
			C	H	N
a	163	85	reported [6]		
b	137	90	66.20 (66.66)	5.50 (5.55)	12.88 (12.96)
c	140	85	66.96 (66.66)	5.43 (5.55)	12.93 (12.96)
d	184	80	66.08 (66.66)	5.48 (5.55)	12.90 (12.96)
e	180	82	62.00 (62.06)	5.20 (5.17)	11.98 (12.06)
f	165	75	55.75 (55.81)	3.64 (3.87)	11.80 (11.83)
g	187	78	55.64 (55.81)	3.72 (3.87)	11.79 (11.83)
h	117	65	53.36 (53.44)	3.57 (3.64)	16.95 (17.00)

$C_{11}H_9N_3O$ composition. The molecular ion was observed at m/z 199 in its mass spectrum. Based on the above data from mass spectra, the compound with mp.135°C could be any of the structures **6**,**7**,**8** or **9** as depicted in the scheme. Interestingly the product **6**, expected by the loss of nitrogen

TABLE - II

Melting points and yields of 1(5-methylisoxazoles-3-yl) 5-aryltetrazoles **4**.

Compound	mp°C	Yield %	Elemental analysis % Found (Required)		
			C	H	N
a	85	65	58.10 (58.15)	3.92 (3.96)	30.78 (30.83)
b	90	70	59.68 (59.75)	4.52 (4.56)	29.00 (29.04)
c	85	68	59.59 (59.75)	4.46 (4.56)	28.96 (29.04)
d	112	60	59.64 (59.75)	4.53 (4.56)	28.90 (29.04)
e	115	75	56.00 (56.03)	4.20 (4.28)	27.18 (27.23)
f	105	70	50.20 (50.47)	2.91 (3.05)	26.73 (26.76)
g	150	72	50.22 (50.47)	2.95 (3.05)	26.96 (26.76)
h	160	55	48.48 (48.53)	2.92 (2.40)	30.80 (30.88)

4e : ^{1}H-NMR ($CDCl_3$), δ 2.6(s,3H, OCH_3), 6.7 (s,1H, C-4 isoxazole), 7.0-7.7 (two doublets, 4H aromatic protons). M^+ at m/z 257.

molecule from **4** through the formation of a nitrene intermediate **5**, was not the isolated compound as inferred from its infrared spectrum. The compound in its IR (KBr) spectrum showed absorption at 1690 cm^{-1} due to carbonyl (C=O) , and at 1600 cm^{-1} (C=N) functions respectively. The

presence of the carbonyl function in the infrared spectrum rules out the structure **6** for the compound obtained on pyrolysis. The structures **7, 8** and **9** could be differentiated on the basis of ^{1}H-NMR spectra. The proton on the triazine in **9** being aromatic will resonate around δ 7-8 ; olefinic proton in case of **8** will be observed around δ 6; the proton attached to a saturated carbon (sp^3) as in **7** in the bicyclic system would appear between δ 3-4 [7]. The compound with mp.135°C obtained on the pyrolysis of **4a** in its ^{1}H NMR ($CDCl_3$) showed the following signals, δ 2.5 (s,3H, CH_3), 7.2-8.1 (m,6H, aromatic protons (5H) and a the proton of the triazine ring). Based on these values we assign structure **9** to the compound.

Rearrangement of the isoxazoles carrying an amino function in the 3-position has been reported [8-11]. In the present case loss of a nitrogen molecule during the pyrolysis of **4** gives nitrene intermediate (**5**) which is essentially a substituent in the 3-position of the isoxazole ring. It undergoes cyclisation to give **6** which was not isolated. The cleavage of N-O bond in the isoxazolo(2,3-b) triazole (**6**) followed by rearrangement results in the formation of **7**. The bicyclic ring system **7** is the intermediate which in the present reaction condition undergoes further rearrangement to give **9**. The tetrazoles mentioned in table II were subjected to pyrolysis to yield the corresponding triazines **9** (Table III).

TABLE - III

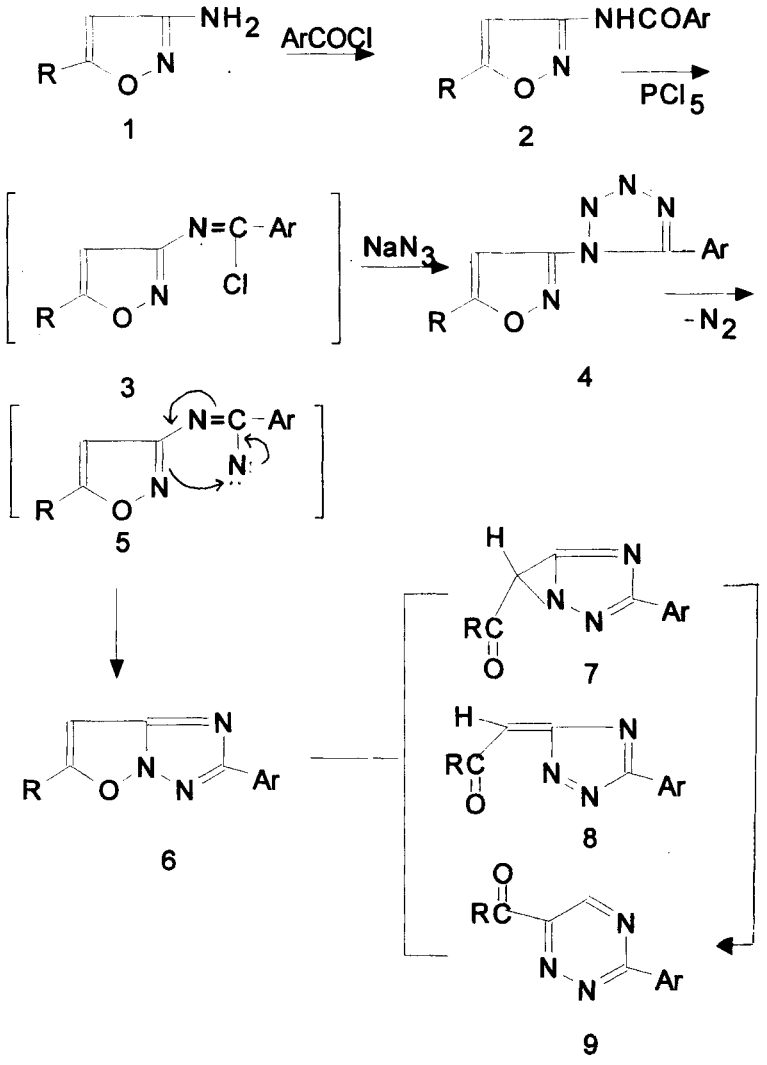
Melting points and yields of 3-aryl-6-acetyl(1,2-4) triazines **9**

Compound	mp°C	Yield %	Elemental analysis % Found (Required)		
			C	H	N
a	135	45	66.28 (66.33)	4.50 (4.52)	21.00 (21.10)
b	230	55	67.28 (67.60)	5.10 (5.16)	19.68 (19.72)
c	215	57	67.45 (67.60)	5.02 (5.16)	19.64 (19.72)
d	140	43	67.50 (67.60)	5.04 (5.16)	19.60 (19.72)
e	160	58	62.62 (62.88)	4.72 (4.80)	18.30 (18.34)
f	143	58	56.50 (56.53)	3.29 (3.43)	17.73 (17.99)
g	180	60	56.42 (56.53)	3.32 (3.43)	17.89 (17.99)
h	215	48	54.00 (54.09)	3.20 (3.27)	22.93 (22.95)

9e : ^{1}H-NMR ($CDCl_3$), δ 2.7(s,3H, OCH_3), 7.2-8.0 (m, 5H aromatic and triazine protons). M^+ at m/z 229.

Thermal decomposition of 1-(5-methylisoxazole-3-yl)-5-aryltetrazole by the elimination of a molecule of nitrogen to give **9**, occurs only above 150°C. The high temperature of decomposition rules out a concerted process. Elimination of nitrogen molecule from **4** and formation of **9** occurs in

SCHEME



R=CH_3

Ar : a = C_6H_5 ; b = o-$H_3CC_6H_4$; c = m-$H_3CC_6H_4$; d = p-$H_3CC_6H_4$
e = p-$CH_3OC_6H_4$; f = o-ClC_6H_4 ; g = p-ClC_6H_4 ; h = p-$O_2NC_6H_4$

stages. In this reaction nitrene (**5**) initialy formed as a result of loss of a nitrogen molecule is the key intermediate. Electrocyclisation involving nucleophilic attack of the isoxazole ring nitrogen on the nitrene nitrogen and formation of C-N bond between C-4 and N of isoxazole ring along with a simultaneous fission of C-N bond in **6**, reasonably explains the formation of **7**. The compound **7** undergoes further rearrangement to give **9**. To minimise the intermolecular reaction and to improve the yields the reaction was carried out in different solvents . The most suitable solvent was found to be decalin.

EXPERIMENTAL

Preparation of 3-aroylamino-5-methylisoxazole (2):

To a solution of 3-amino-5-methylisoxazole (**1**) in pyridine was added equimolar amount of aroyl chloride with constant stirring. After the addition is complete the mixture was poured into ice cold water.The product separated was filtered , washed with 10% sodium bicarbonate solution then with water and dried. The crude product thus obtained was recrystallised from benzene. Characterstics of compound **2a**: (R = CH_3 ; Ar = C_6H_5), melting point 163°C (reported 162°C) [6]. IR (KBr) cm^{-1} : 3250 (NH), 1670 (C=O). ^1H NMR ($CDCl_3$): δ 2.4 (s, 3H, CH_3), 6.9 (s,1H,C-4 of isoxazole ring), 7.2-8.0 (m,5H, aromatic protons) and 10.2 (broad, 1H, (NH) D_2O exchangeable).

Preparation of 1-(5-methylisoxazole-3-yl)-5-aryltetrazoles (4):

3-Aroylamino-5-methylisoxazole (0.005mole) was heated with phosphorous pentachloride (0.005 mole) at 100°C for 0.5hr. After the evolution of hydrochloric acid fumes ceased , traces of phosphorous oxychloride were removed from the reaction mixture . The imidoyl chloride thus obtained was directly treated with a cold solution of sodium azide (0.005 mole) and excess of sodium acetate trihydrate in aqueous acetone and stirred for 12 hr at room temperature.The aqueous solution was extracted with chloroform and the extract was concentrated and chromatographed over a column of neutral alumina. The desired compound was obtained in pure form in petroleum ether-benzenz (10:1) eluant.

Pryolysis of 1-(5-methylisoxazole-3-yl)-5-aryltetrazoles (4):

A. Neat Pryrolysis:

A mixture of **4a** and finely ground pure sand at 200°C for two hours, cooling the mixture and extracting the residue with chloroform and passing it over a column of neutral alumina yielded a compound melting at 85°C in benzeze-petroleum ether (10:1) fraction. The compound was identified as 1-(5-methylisoxazole-3-yl)-5-phenyltetrazole. The desired triazine **9** was obtained in benzene fraction. Further elution with benzene-ethyl acetate (1:1) fraction gave only a gummy material.

B. Solvent Pyrolysis -General Procedure:

1-(5-methylisoxazole -3-yl) -5-aryltetrazole (0.0025mole) in decalin (20 ml) was refluxed for 2 hr. The solvent was removed under reduced pressure. The residue thus obtained was chromatographed over a column of neutral alumina to give the desired triazine in benzene fraction.

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