Investigation of the Reactions of 2-Hydrazinobenzimidazoles with β-diketones: Synthesis of 2-(3,5-Disubstituted-1*H*-pyrazol-1-yl)benzimidazoles

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Reaction of 2-hydrazinobenzimidazoles with β-diketones in neutral and acidic media revealed that 2-(3,5-disubstituted-1*H*-pyrazol-1-yl)benzimidazoles are formed in the former case, whereas hydrazones are obtained in acidic medium. Further the alkylation of >NH of the title compound was investigated. Characterisation of these products have been done by elemental analysis, ir, pmr, ^{19}F nmr, ^{13}C nmr and mass spectral studies.

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Benzimidazole and pyrazole nuclei are found to be associated with various pharmacological activities [1-4]. In the course of the synthesis of bioactive benzimidazole derivatives, reactions of 2-hydrazinobenzimidazole with β-diketones were studied leading to the formation of compounds having both the benzimidazole and pyrazole nuclei. A literature survey revealed only two references on such compounds. However, one reports the synthesis by the reaction of 2-hydrazinobenzimidazole with α-cyanoacetophenone [5] and the other is a patent giving activity only with no synthetic details [6]. A detailed investigation of the reaction of 2-hydrazinobenzimidazole with β-diketones in different media was, therefore, undertaken. Such a reaction offers three different possibilities (Scheme 1) *viz*, formation of a pyrazole derivative **3** [7,8], hydrazone **4** [9] and triazepino derivative **5** [10]. We have observed that neutral medium afforded 2-(3,5-disubstituted-1*H*-pyrazol-1-yl)-benzimidazoles whereas acidic medium furnished 1,3-diketone-1-(benzimidazolyl-2-hydrazones).

Structure assignments to the products are based on spectral studies. In the ir spectrum of **3a** absorption band at 1620 cm^{-1} due to >C=N and at 3100 cm^{-1} due to >NH are observed. In its pmr spectrum, signal at δ 6.2 ppm due to pyrazolyl =CH- and at δ 9.4 ppm due to >NH of the imidazole ring and aromatic signals at δ 7.5-6.5 ppm are observed. The two $-CH_3$ groups appeared at δ 2.4 and 2.0 ppm. In the ^{13}C nmr spectrum of **3a** signals at δ 154 ppm (C-2), δ 149 (C-3'), δ 145 ppm (C-5') δ 128 ppm (C-4'), δ 140, 131, 120, 119, 117, 110 ppm's (aromatic carbons) and δ 12 ppm (two $-CH_3$) are observed. In the mass spectrum M^+ appears at m/z 212. ^{19}F nmr spectra of **3e**, shows a singlet at δ -111 ppm due to *p*-fluorophenyl group attached to pyrazolyl ring and another singlet at δ -80 ppm due to $-CF_3$ group attached to pyrazolyl carbon.

In case of compounds having different R^1 and R^2, the presence of the more electronegative group at 5'-position (R^1) and the other at position 3' (R^2) is explained by the fact that the diketones are in tautomeric form and the di-

Scheme 1

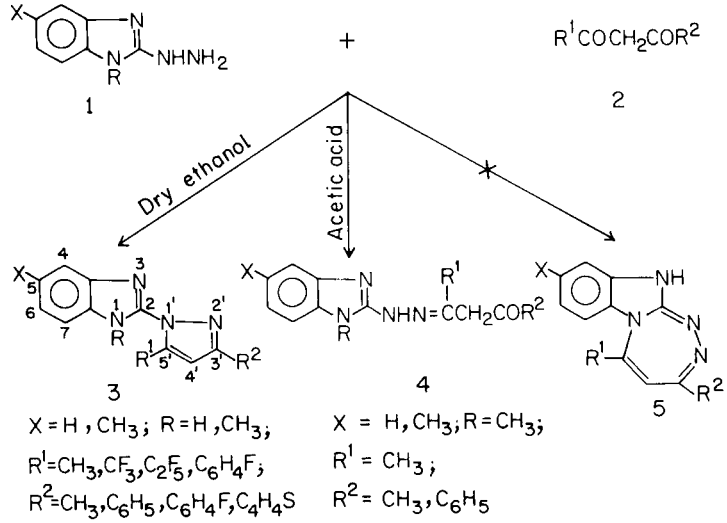

Table I

Analytical Data of 2-(3,5-Disubstituted-1*H*-pyrazol-1-yl)benzimidazoles and 1,3-Diketone-1-(benzimidazolyl-2-hydrazones)

Compound No	X	R	R^1	R^2	Yield %	MP °C	Formula	Analysis % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N
3a	H	H	CH_3	CH_3	86	>300	$C_{12}N_{12}N_4$	67.92	5.60	21.69	67.99	5.67	21.71
3b	H	H	C_6H_5	CH_3	76	185-186	$C_{17}H_{14}N_4$	74.45	5.19	20.43	74.72	5.20	20.23
3c	H	H	C_6H_4F	CH_3	80	179-181	$C_{17}H_{13}FN_4$	68.95	4.39	18.80	69.00	4.37	18.79
3d	H	H	CF_3	C_6H_5	82	190-191	$C_{17}H_{11}F_3N_4$	62.19	3.35	17.07	62.21	3.40	16.99
3e	H	H	CF_3	C_6H_4F	83	220-221	$C_{17}H_{10}F_4N_4$	58.95	2.89	16.18	58.99	2.91	16.00
3f	5-CH_3	H	CF_3	C_4H_4S	70	162-163	$C_{16}H_{10}F_3N_4S$	55.33	2.88	16.13	55.39	2.91	16.21
3g	H	H	C_6H_4F	C_6H_4F	69	310-311	$C_{22}H_{14}F_2N_4$	70.96	3.76	15.05	70.98	3.80	15.01
3h	5-CH_3	H	C_6H_4F	CH_3	71	145-146	$C_{18}H_{15}FN_4$	70.58	4.90	18.30	70.60	4.92	18.28
3i	H	CH_3	C_2F_5	C_6H_4F	74	159-161	$C_{19}H_{12}F_6N_4$	55.60	2.92	13.65	55.62	3.00	13.59
4a	H	H	C_6H_5	CH_3	70	179-180	$C_{17}H_{16}N_4O$	69.86	5.47	20.43	69.89	5.51	20.39
4b	H	H	CH_3	CH_3	73	>300	$C_{12}H_{14}N_4O$	62.60	6.08	24.34	62.68	6.11	24.41

rection of enolization is towards the more electonegative substituted acyl group. In the case of hydrazones, the position of alkyl group (R^1) is explained on the basis of high reactivity of less enolized carbonyl group [11].

The formation of hydrazone **4a** was confirmed by their ir spectrum which shows an absorption band at 1680 cm^{-1} due to the remaining >C=O group of the diketone. This is further confirmed by the pmr spectrum, in which a singlet at δ 4.2-3.8 ppm due to $-CH_2-$ appeared. The other peaks appeared at δ 9.3 ppm due to >NH, 7.5-6.5 ppm due to aromatic protons and at δ 2.0 ppm due to $-CH_3$. In the mass spectrum of the **4a** parent peak appears at m/z 292.

The possibility of the formation of triazepine derivative **5** was ruled out in both the media by the absence of a signal near δ 5.8 ppm reported for the triazepino =CH- [10].

Thus, as reported [7,12] in neutral medium cyclisation takes place directly leading to the formation of a pyrazole ring except in the case of the reaction with benzoylacetone which gave both the products *viz*, pyrazolyl and hydrazone in the ratio 3:1 which was separated by plc in benzene:-ethyl acetate (80:20).

Futher, the 1-methyl derivative of **3d** was prepared in two ways. In the first method, *N*-methyl-2-hydrazinobenzimidazole was reacted with trifluoromethylbenzoylacetone while in the second case, methylation was done after the preparation of **3d**. The low yield and the formation of sticky product by the first method appears to be probably due to some degree of polymerization of *N*-methyl-2-hydrazinobenzimidazole by being in contact with alcohol.

The formation of *N*-methyl-2-(5-trifluoromethyl-3-phenyl-1*H*-pyrazol-1-yl)benzimidazole was confirmed by the ir spectrum in which no absorption band in the region 3410-3100 cm^{-1} due to >NH is observed. Further, in the pmr spectrum it gives an extra signal δ 3.7 ppm due to $>N-CH_3$ and in the mass spectrum M^+ appears at m/z 342.

EXPERIMENTAL

Melting points are uncorrected. Infrared spectra were recorded using a Perkin-Elmer 557 spectrophotometer. The ^1H nmr spectra were recorded on a Jeol (Model FX90Q) at 89.55 MHz using TMS as the external reference and on a Perkin Elmer RB-12 (at 60 MHz) using DMSO-d_6 or TFA as solvents. The ^{13}C nmr and ^{19}F nmr spectra were recorded on a Jeol (Model FX90Q) and taken in DMSO-d_6 at 22.49 MHz and 84.25 MHz respectively. Hexafluorobenzene (at δ -162.9 ppm) was used as external reference in the latter case. The mass spectra were recorded on MS-30 and MS-50 Kratos mass spectrometer operating at an ionisation potential of 70 eV.

2-Hydrazinobenzimidazoles **1**.

These were prepared following the method of Bednyagina *et al* [13].

Fluorinated 1,3-Diketones **2**.

Fluorinated 1,3-diketones were prepared following the method of Joshi *et al* [14].

2-(3,5-Disubstituted-1*H*-pyrazol-1-yl)benzimidazoles **3a-i**.

2-Hydrazinobenzimidazole (0.01 mole) was refluxed with 1,3-diketone (0.01 mole) in dry ethanol (40 ml) for 5 hours. The solution on cooling gave a white compound. It was filtered and recrystallised from ethanol. Analytical data for all the compounds which were synthesized are given in Table I.

1,3-Diketone-1-(benzimidazolyl-2-hydrazones) **4a,b**.

2-Hydrazinobenzimidazole (0.01 mole) was refluxed with β-diketone (0.01 mole) in glacial acetic acid (40 ml) for 5 hours. On cooling a coloured compound was obtained which was recrystallised from ethanol. The analytical data of the compounds prepared are recorded in Table I.

N-Methyl-2-(5-trifluoromethyl-3-phenyl-1*H*-pyrazol-1-yl)benzimidazole.

It was prepared by two methods.

(a) *N*-Methyl-2-hydrazinobenzimidazole (0.01 mole) was refluxed with trifluoromethylbenzoylacetone (0.01 mole) in dry ethanol (40 ml) for 5 hours. On cooling it was filterd when a sticky mass was obtained which solidified on repeated washing with petroleum ether and the solid finally recrystallised from benzene-ethyl acetate, mp 149-151°, yield 45%.

Anal. Calcd. for $C_{18}H_{13}F_3N_4$: C, 63.15; H, 3.80; N, 16.37. Found: C, 63.09; H, 3.83; N, 16.28.

(b) To, 2-(5-trifluoromethyl-3-phenyl-1*H*-pyrazol-1-yl)benzimidazole (0.01 mole) was added 10 ml of 30% sodium hydroxide, alcohol (30 ml) and methyl iodide (0.01 mole) and the mixture stirred for one day. After stirring, the alcohol was removed by distillation, the residue poured into cold water, filtered and recrystallised from alcohol-benzene mixture, mp 150-151°, yield 87%.

Anal. Calcd. for $C_{18}H_{13}F_3N_4$: C, 63.15; H, 3.80; N, 16.37. Found: C, 63.20; H, 3.82; N, 16.30.

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