SYNTHESIS OF 1, 3-DIKETONE AND ITS REACTION WITH DIFFERENT N-NUCLEOPHILES (PART I)

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ABSTRACT : Treatment of resorcinol with ethyl acetoacetate in presence of conc. sulphuric acid led to formation of 1,3-diketone **3** in several steps, which on reaction with ethylene diamine **4**, phenylene diamine **5**, hydroxylamine **8**, phenyl hydrazine **9** and hydrazine **10** led to formation of 1,4-diazepine **3**a, 1, 5-benzodiazepine **3**b, isoxazole **3**c and pyrazole **3**d derivatives respectively.

INTRODUCTION

The chemistry of heterocyclic compounds is very interesting and fascinating because of their great diversity and complexity. 1,3-diketones serve as precursors for the synthesis of versatile intermediates for obtaining a large number of biologically active heterocyclic compounds such as diazepines, benzodiazepines, isoxazoles, pyrazoles, imidazoles and benzimidazoles. Being potent psychotropic drugs (1-4) diazepine and its related compounds have attracted the attention of chemists in recent years. In our research programmes to develop new drugs it has been considered worth while to synthesize title compounds.

EXPERIMENTAL

Melting points of all the synthesized compounds are uncorrected. The purity of the compounds has been checked by thin layer chromatography using silica gel 'G' as adsorbent. The infra-red spectra were recorded on Perkin Elmer Infra cord spectrometer by using KBr pellets. ^{1}H NMR spectrum are recorded on JEOL-FTNMR-90 MHz spectrometer using TMS as internal standard.

1. Preparation of 1,3-diketone 3

(a) Preparation of 8-Acetyl-7-hydroxy-4-methylcoumarin
It was synthesised from resorcinol and ethyl acetoacetate as reported (5).

(b) Preparation of 7-Acetyl-6-hydroxy-3methyl benzofuran **1**
1 was synthesised from above coumarin derivative, by the earlier method (6).

(c) Preparation of 7-Acetyl-6-acetyloxy-3-methyl benzofuran **2**
On the basis of previous reports (7), **1** was acetylated leading to formation of **2**

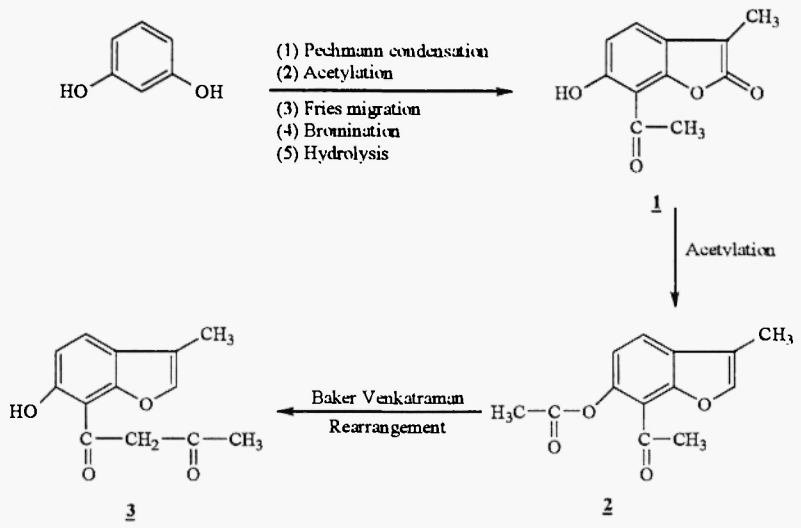
(d) Preparation of Butan-1-[7-(3-methyl-6-hydroxy)benzofuranyl]-1,3-dione **3**.

Compound **2** undergoes Baker – Venkatraman rearrangement. A mixture of 7-Acetyl-6-acetyloxy-3-methyl benzofuran (2.32 g, 0.01 M), dry pyridine (20 ml) and powdered KOH (2.24 g, 0.04 M) is stirred for about 20 min. and is allowed to stand for 0.5 hrs. The mixture is acidified with dil. HCl when a yellow product is precipitated. It is filtered and is crystallised from aq. alcohol (mp 105°, yield 2.01g, 87% R_f = 0.53). Purity is checked by TLC (system $CHCl_3$: CH_3OH, 9 : 1)

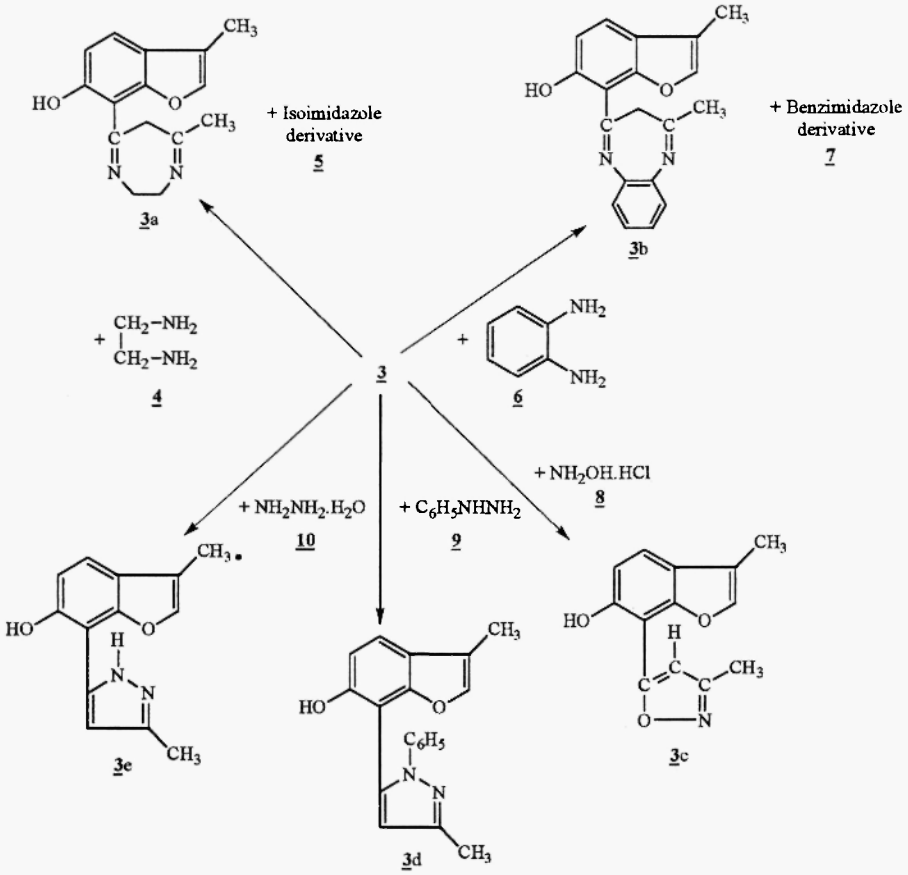
IR(cm^{-1}) = 1200(-OH), 1590(-C=O), 1460(-CH_3), 1520(-C=C-), 1210(-C-H)

^{1}H NMR(δ, $CDCl_3$) = 7.26-7.61 (3H, Ar-H, d) 2.22, 2.87 (6H, -C-CH_3-, s) 6.8 (2H, -C-CH_2-, s), 12.81 (1H, -OH [enolic], s) 15.59 (1H, -OH [aromatic], s)

On the basis of above data, formula of the above compound **3** has been given as Butan-1- [7-(3-methyl-6-hydroxy) benzofuranyl]-1,3-dione.



SCHEME 1



SCHEME 2

2. General procedure for synthesis of diazepines

1,3-diketone 3 (2.0 g, 6.8 mM) is refluxed in dry ethanol (15 ml) for 4 hours. The reaction mixture is cooled and 20 ml of glacial acetic acid is added followed by dropwise addition of 4 (1.2 ml, 0.02M) or 6 (2.16 g, 0.02 M). The reaction mixture is refluxed at 120°C and cooled to room temperature and kept overnight, a solid separated. An additional crop of this compound is obtained on ether addition. Both these compounds are found to be same in TLC and m.p.'s determination. Crystallisation from ethanol afforded compound which may be an isoimidazole derivative 5 (m.p. 107°, yield 0.05g, R_f = 0.32) and benzimidazole derivative 7 (m.p. 120°, yield 0.2g, R_f = 0.33) respectively.From the mother liquor the solvent is distilled off under reduced pressure. The residue is thoroughly washed with dry ether. A dry powdered mass is obtained (3 a or 3 b). Crysatllisation with acetone gave a crystalline residue (3a or 3b).

3a = 6H-7-[7-(3-methyl-6-hydroxy)benzofuranyl]5methyl-1,4-diazepine, light brown compound.
3b = 3H-4-[7-(3-methyl-6-hydroxy)benzofuranyl]2-methyl-1,5-benzodiazepine, deep violet coloured compound.

3. Synthesis of 4H-5-[7-(3-methyl-6-hydroxy)benzofuranyl]3-methyl isoxazole 3c

1,3-diketone 3 (2.32g, 0.01M) is refluxed with hydroxylamine hydrochloride (1.38g, 0.02M) in pyridine for 25 hrs. The mixture is poured into crushed ice and washed several times with acetic acid (15%) to remove pyridine. The semisolid obtained is then triturated with ethanol (95%) and recrystallised from aq. ethanol.

4. General procedure for synthesis of Pyrazoles.

A mixture of 1,3-diketone 3(14.5g; 0.0625M) and phenyl hydrazine 9 (10.8g, 0.1M) or hydrazine hydrate 10 (4.9g, 0.1M) is refluxed in absolute ethanol (80ml) for four hours on a steam bath. The mixture is cooled and filtered. Crystallisation with ethanol yields the crystalline product (3d or 3e). Purity of compounds (3c, 3d, 3e) is checked by TLC using ($CHCl_3$: CH_3OH, 9:1) as mobile phase.

3d = 5-[7-(3-methyl-6-hydroxy)benzofuranyl]3-methyl-1-phenyl pyrazole.

3e = 5-[7-(3-methyl-6-hydroxy)benzofuranyl]3-methyl pyrazole.

Analytical data of synthesized compounds is tabulated in table 1. IR and ^1H NMR data of synthesized heterocyclic compounds are included in table 2 and 3 respectively.

Table 1 : Physical data of compounds

Compound 3	(%) Yield	M.P. (°C)	R_f	Molecular formula	Found (Calcd)% N
a	36	100	0.64	$C_{15}H_{16}N_2O_6$	11.42(10.93)
b	24	104	0.51	$C_{19}H_{16}N_2O_2$	10.15(9.21)
c	55	164	0.46	$C_{13}H_{11}NO_3$	6.02(6.11)
d	60	108	0.46	$C_{19}H_{16}N_2O_2$	10.11(9.21)
e	47	103	0.37	$C_{13}H_{12}N_2O_2$	11.83(12.28)

Table 2 : IR data of compounds (cm^{-1})

Compd. 3	1,4-diazepine moiety	1,5-benzodiazepine moiety	$-CH_3$	$-C_6H_5$	-OH	-CH	-C=N	-NH	-CN
a	3310, 2905, 1660, 1515, 1505, 1420, 1370, 1295, 1085	-	-	-	1250	-	-	-	-
b	-	3310, 3235, 3115, 1640, 1610, 1540, 1525, 1270, 1235, 1160, 1130	1450	-	1200	-	-	-	-
c	-	-	940	-	-	1130	-	-	-
d	-	-	1440	-	1200	-	1660	-	1420
e	-	-	1430	-	1200	-	1670	3200	-

Table 3 : ^1H NMR data of compounds (δ ppm, $CDCl_3$)

Compd. 3	Ar-H	$-C-CH_3$	$-N=C-CH_3$	$=N-CH_2-CH_2-N$	-OH	=CH	$-CH_2$	-NH
a	7.4-7.8	1.8(s)	2.2(s)	2.9(s)	12.9(s)	6.9(s)	-	-
b	7.0-8.40(m)	2.21(s)	1.6(s)	-	12..93	-	2.28(s)	-
c	6.9-7.8(m)	1.95(s) 1.95(s)	2.25(s)	-	-	6.2(s)	-	-
d	6.7-8.25(m)	2.05(s)	-					
e	6.8-7.8	1.95(s) 2.4(s)	-	-	11.0(s)	-	4.28(s)	8.1-8.4(s)

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Received on September 11, 2001