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

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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 6, hydroxylamine 8, phenyl hydrazine 9 and hydrazine 10 led to formation of 1,4 diazepine 3a, 1, 5-benzodiazepine 3b, isoxazole 3c and pyrazole 3d, 3e derivatives respectively.

INTRODUCTION

The reaction of different N-nucleophiles with 1,3-diketones has attracted considerable attention as a convenient tool for synthesizing a wide variety of novel drugs. Our interest in the synthesis of novel heterocyclic compounds like diazepines, benzodiazepines, isoxazoles, pyrazoles, imidazoles and benzimidazoles, is justified by their biological activity which might render such compounds as valuable pharmaceuticals etc.

The diazepines are useful as anticancer (1), anti-asthamatic, anti-inflammatory or bronchodilating agents (2) and in the treatment of Alzheimer's disease (3). Pharmacologically active (4) benzodiazepines have been proved to be an useful anti-epileptic drug (5,6) acting on specific neurotransmitter receptors or ion channels. Isoxazole derivatives show diuretic and hypolipemic activity. Pyrazole derivatives are useful as insecticides, fungicides as well as anticonvulsant and antimicrobial agents.

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 (7).

(b) Preparation of 7-Acetyl-6-hydroxy-3-methyl benzofuran 1

1 was synthesised from above coumarin derivative, by the earlier method (8).

(c) Preparation of 7-Acetyl-6-benzoyloxy-3-methyl benzofuran 2

Compound1 (1g,0.0043M) is suspended in 5% sodium hydroxide solution (20ml) in a small conical flask and benzoyl chloride (2ml at a time) is added with constant vigorous shaking for 5-10 minutes, until the odour of benzoyl chloride disappears, resulting in the alkaline nature of the mixture. The solid benzoyl derivative is filtered and is washed with a small amount of cold water. It is crystallized from aqueous alcohol. (m.p. = 110°, yield= 0.83g, 83%, R_f = 0.51) Purity is checked through TLC (System Petroleum ether: Acetone, 8: 2).

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

A mixture of 7-Acetyl-6-benzoyloxy-3-methyl benzofuran (2.94 g, 0.01 M), dry pyridine (20 ml) and powdered KOH (2.94 g, 0.04 M) undergoes Baker-Venkatraman Rearrangement as mentioned in our earlier publication (9). A yellow coloured precipitate is obtained. It is filtered and is crystallised from acetone (m.p. = 184°, yield =2.49g, 85% $R_f = 0.39$). Purity is checked through TLC (System Petroleum ether: acetone, 8: 2)

IR(cm^{-1}) = 1200(-OH), 1630(-C=O), 1450($-CH_3$), 1520(-C=C-), 1220(-C-H), 3030($-C_6H_5$)

^{1}H NMR(δ, $CDCl_3$) = 7.25-7.64 (7H, Ar-H, m) 2.23 (3H, $-C-CH_3-$, s) 6.86,6.95 (2H, $-C-CH_2-$, s), 12.71 (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 Propan-1- [7-(3-methyl-6-hydroxy) benzofuranyl]-3-phenyl-1, 3-dione.

2. General procedure for synthesis of diazepines

The reaction of 1,3-diketone 3 (2.0 g, 6.8 mM) with 4 (1.2 ml, 0.02M) or 6 (2.16 g, 0.02 M) led to the formation of light brown coloured 3a and deep violet coloured 3b powdered mass, along with isoimidazole and/or benzimidazole derivatives. This procedure is similar to the one mentioned in the part I of this paper (9).

3a = 6H-7-[7-(3-methyl-6-hydroxy)benzofuranyl]-5-phenyl-1,4-diazepine
3b = 3H-4-[7-(3-methyl-6-hydroxy)benzofuranyl]2-phenyl-1,5-benzodiazepine.

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

According to part I of this paper (9), 3c is prepared by refluxing 1,3-diketone 3 (2.94g, 0.01M) with hydroxylamine hydrochloride (1.38g, 0.02M).

4. General procedure for synthesis of Pyrazoles.

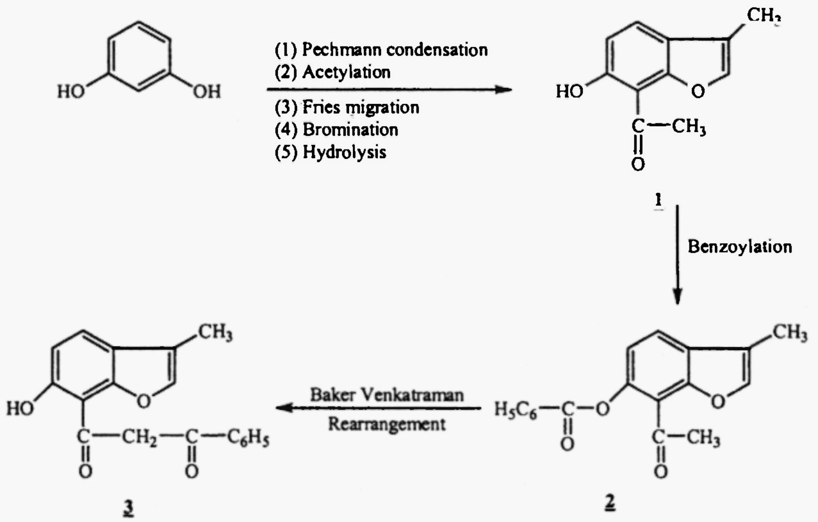
3d and 3e are prepared by refluxing a mixture of 1,3-diketone 3(14.5g, 0.493M) and phenyl hydrazine 9 (10.8g, 0.1M) or hydrazine hydrate **10** (4.9g, 0.1M) in absolute ethanol (80ml). This method was given by Grandberg et al (10), similar to the earlier procedure (9).

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

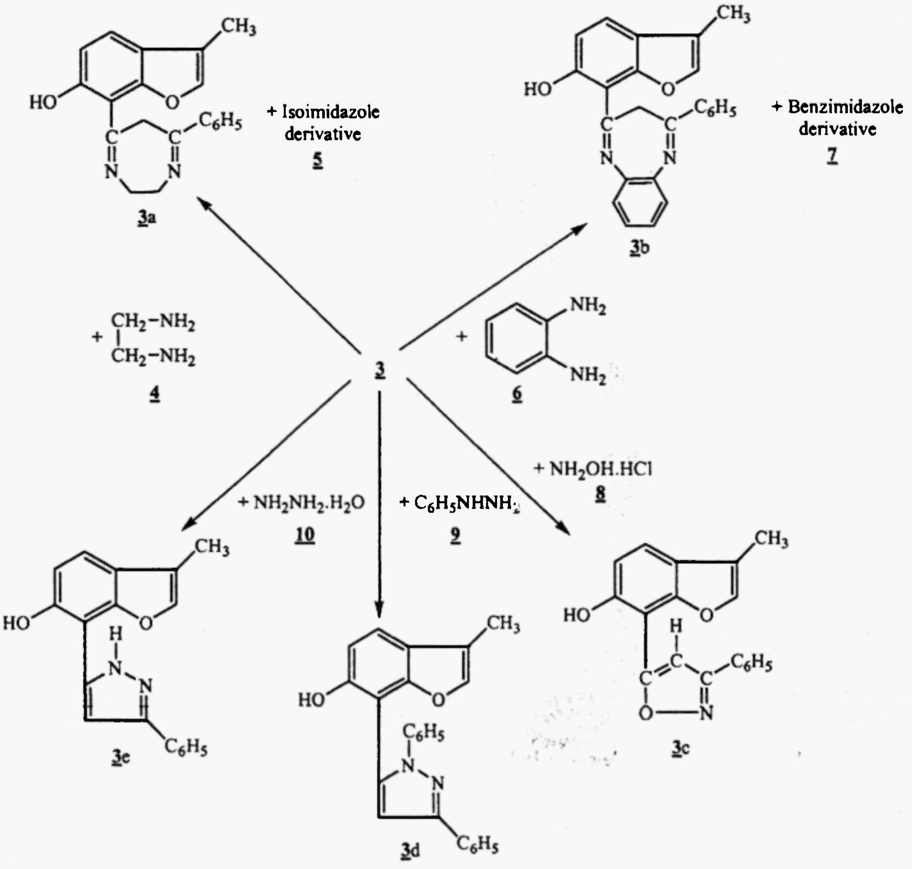
Analytical data of synthesized compounds is tabulated in table 1. IR and ^{1}H NMR data of synthesized heterocyclic compounds are included in table 2 and 3 respectively.

Table 1 : Physical data of compounds

Compound 3	(%) Yield	M.P. (°C)	Rf	Molecular formula	Found (Calcd)% N
a	35	230	0.63	$C_{20}H_{18}N_2O_2$	8.9(8.805)
b	26	160	0.53	$C_{24}H_{18}N_2O_2$	7.27(7.65)
c	57	110	0.41	$C_{18}H_{13}NO_3$	4.23(4.81)
d	52	140	0.52	$C_{24}H_{18}N_2O_2$	8.32(7.65)
e	45	184	0.43	$C_{18}H_{14}N_2O_2$	9.21(9.65)



Scheme 1



Scheme 2

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

Comd. 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	-	-	3030	1200	-	-	-	-
b	-	3310, 3235, 3115, 1640, 1610, 1540, 1525, 1270, 1235, 1160, 1130	1440	3030	1200	-	-	-	-
c	-	-	1070	3030	-	1150	-	-	-
d	-	-	-	3030	-	-	1650	-	1410
e	-	-	-	3030	-	-	1610	3150	-

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

Compd. 3	Ar-H	$-C-CH_3$	$-N=C-CH_3$	$=N-CH_2\cdot CH_2-N$	-OH	=CH	$-CH_2$	-NH
a	6.7-8.3(m)	2.1(s)	-	2.9-3.80(s)	-	-	4.28(s)	-
b	7.0-7.9(m)	1.85(s)	-	-	-	6.2(s)	2.21(s)	-
c	6.9-8.2(m)	2.0(s)	-	-	-	6.25(s)	-	-
d	7.3-7.8(m)	2.0 (s)	-	-	-	6.7(s) 7.0(s)		
e	6.8-7.8	2.0(s)	-	-	-	-	4.28(s)	11.0(s)

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