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Research Article

A NOVEL METHOD FOR THE SYNTHESIS OF FORMYL PYRAZOLES USING VILSMEIER-HAACK REACTION

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ABSTRACT

A series of acetophenone substituted phenyl carbonyl hydrazones has been synthesized and their formylation was carried out by using Vilsmeier-Haack reaction. All the hydrazones and their formyl derivatives were screened for antibacterial activities.

Keywords: Vilsmeier-Haack reaction, Formylation, Hydrazones, N-formyl hydrazones.

INTRODUCTION

Pyrazole derivatives have attracted the attention of research scholars on account of their wide range of applications in medicine. Steroids containing pyrazole moiety are of interest as psychopharmacological agents[1]. Pyrimidino pyrazoles are being studied in the fight against cancer[2]. Pyrazole derivatives have been found to have antimalarial activity[3] and antihyperglycemic activity[4]. Some alkyl and aryl substituted pyrazoles have a sharp pronounced sedative action on the central nervous system[5]. Certain alkyl pyrazoles show significant bacteriostatic, bactericidal and fungicidal, analgesic and antipyretic activities[6].

Literature search reveals that formylation of hydrazones yield formyl pyrazoles. The Vilsmeier-Haack reaction is common method for the synthesis of 4-formyl pyrazoles[7].

The Schiff's bases of aldehydes and ketones on treatment with DMF and $POCl_3$ undergo cyclisation reactions forming pyrazole derivatives and undergo formylation on to the pyrazole ring[8].

Hydrazones of aliphatic and aromatic methyl ketones yield pyrazole-4-carboxaldehydes upon diformylation on treatment with Vilsmeier reagent[9]. Such type of cyclisation with formylation using Vilsmeier-Haack reaction is also reported by S. Selvi, P. T. Perumal[10], R. Sridhar et al[11], K. Hemanth Kumar et al[12], Sing, Karan et al[13] and D. B. Arunkumar et al[14].

By considering the wide range of application of formyl pyrazoles and in continuation of our interest in Vilsmeier-Haack reaction[15-20] we attempted formylation of acetophenone hydrazones using Vilsmeier-Haack reagent. It was planned to synthesize four different formyl pyrazole derivatives by reacting acetophenone hydrazones with Vilsmeier-Haack reagent DMF/$POCl_3$. With the hope of cyclisation with formylation of acetophenone hydrazones to form formylpyrazole. For this purpose we used hydrazones of aromatic ketones as starting compounds.

In the present work we have developed an efficient and general process involving performing activated ester followed by reaction with hydrazine for the preparation of hydrazides which gave desired hydrazides in excellent yield and purity under mild conditions.

The starting compounds acid hydrazides 3a-d required for the preparation of the target compounds were obtained by hydrazinolysis of esters 2a-d which in turn were prepared by refluxing carboxylic acids 1a-d with absolute methanol and conc. H_2SO_4. Compounds 2a-d on condensation with different acetophenones in methanol containing a catalytic amount of glacial acetic acid gave acetophenone hydrazones 4a-d – 7a-d. The hydrazones 4a-d – 7a-d on treatment with V.H. reagent (DMF/$POCl_3$) yielded formyl pyrazoles. (Scheme-I and Scheme-II)

RESULTS AND DISCUSSION

The ^{1}HNMR spectrum of the recrystallized samples showed the disappearance of the methylene proton signal and N-N-H signal. The proton signal for the newly formed pyrazole appears at δ7.2 ppm leaving the other proton signals almost unchanged. This confirmed the formation of the target molecules which was also characterized by elemental analysis.

A possible mechanism for the formylation of 4-formyl pyrazole is out lined in Scheme- III

Initial electrophilic attack of Vilsmeier-Haack reagent (a) on hydrazone (b) yielded the intermediate (c) which subsequently losses a molecule of HCl to provide intermediate (d). The nucleophilic attack by N-H group initiates the cyclisation and the resulting pyrazole intermediate losses Me_2NH to give the more stable pyrazole derivative (e). The pyrazole (e) reacts with another molecule of V.H. reagent (a) in an electrophilic substitution process giving an iminium salt (f), which is hydrolysed to corresponding 4-formyl pyrazole (g). The intermediate of pyrazole (e) is supported by earlier report[21]. This mechanism has following chief features:

- The electrophilic attack of first Vilsmeier-Haack complex at the probable attacking site of hydrazones results into cyclisation. While electrophilic attack of second V-H complex forms formyl product after hydrolysis.
- Intra molecular (1,5) hydrogen shift, and
- Cyclisation and elimination of $NHMe_2$ to give pyrazole derivative.

Biological testing of the compounds

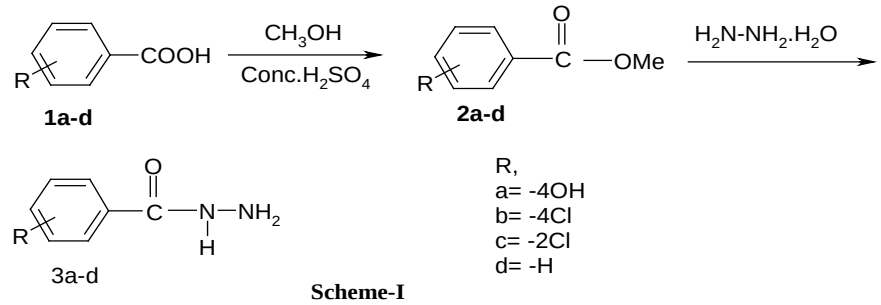
All the synthesized compounds 4 a-d, 6a-d, 7a-d, 8a-d and 11 a-d were evaluated *in-vitro* for antibacterial activity against bacterial strains *Proteus vulgaris, Staphylococcus aureus* and *Salmonella typhimurium* at the concentration 1mg/ml by paper disc diffusion method using DMF as solvent and nutrient agar was employed as culture media. the results were obtained in the form of clearing zone and were noted after the period of incubation (at 37^{0}C for 24-48 hrs). The zones of inhibitions were measured in mm and the data is presented in table I.

Similarly compounds 5 a-d and 9 a-d were evaluated *in-vitro* for antibacterial activity against bacterial strain *E. coli* and *S. aureus* at the conc. 1 mg/ml by paper disc diffusion method using DMF as solvent. The data is presented in table II.

RESULT

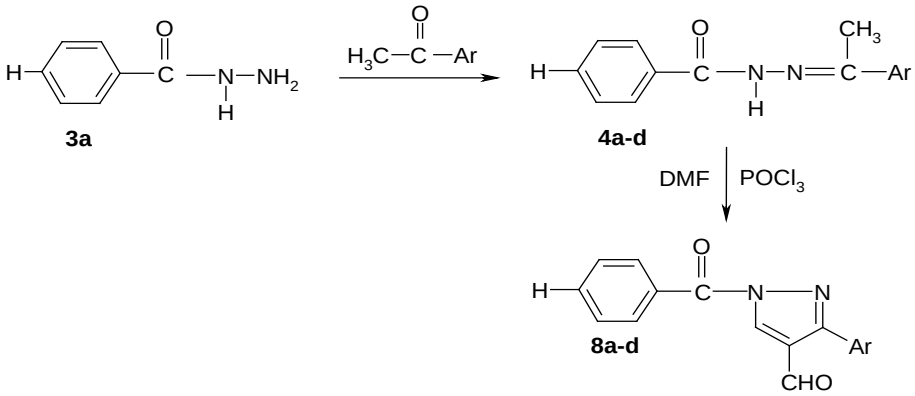
Most of the compounds were found to be active against *P. vulgaris*. Few compounds were founds active against *S. aureus* and all the above compounds were found inactive against *S. typhimurium*.

Table I and II summarizes the results of antibacterial activity of these compounds.

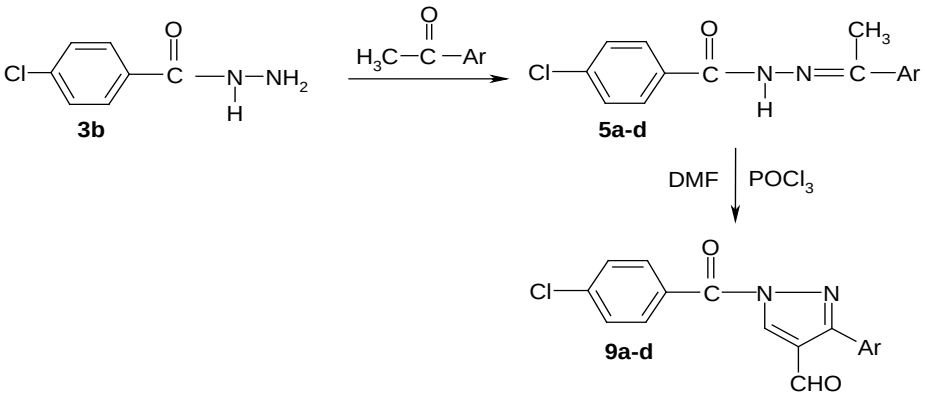


1a-d **2a-d** 3a-d

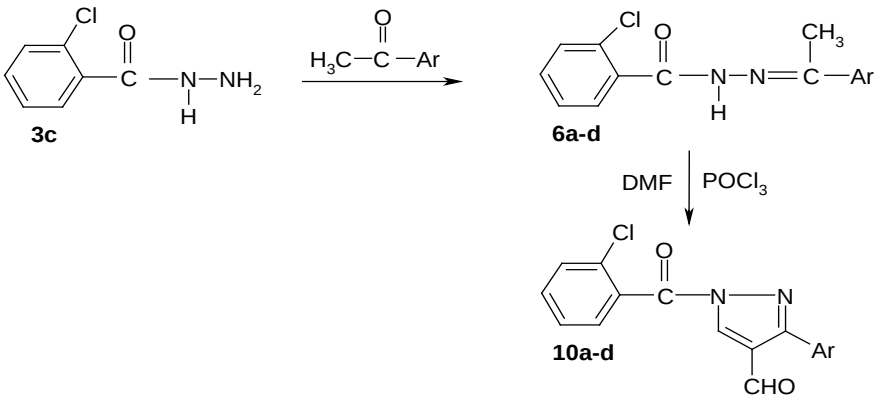
Scheme-I



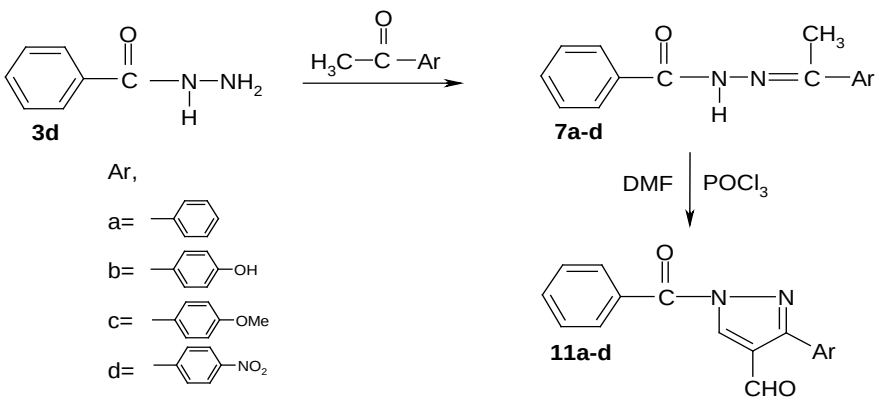
3a **4a-d** **8a-d**



3b **5a-d** **9a-d**

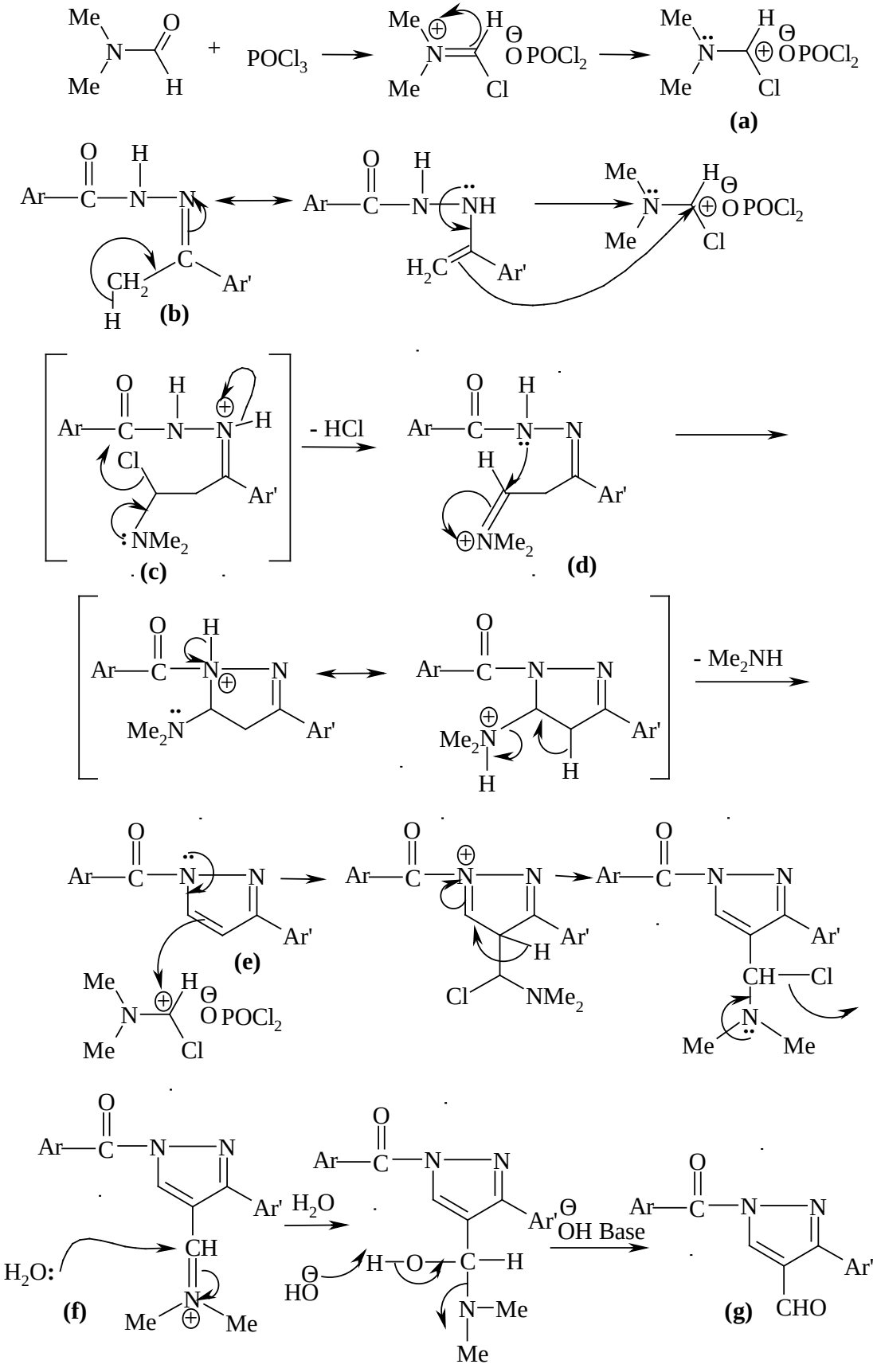


3c **6a-d** **10a-d**



3d **7a-d** **11a-d**

Scheme-II



Cyclisation along with formylation (Scheme-III)

Table I: Antibacterial activity of compounds 4a-d, 6a-d, 7a-d, 8a-d and 11a-d Zone of inhibition (m.m.) Antibacterial activity of compounds

Compound	*P.vulgaris*	*S.aureus*	*S. typhimurium*
4a	10	-	-
4b	04	-	-
4c	12	-	-
4d	06	-	-
6a	10	-	-
6b	05	-	-
6c	10	-	-
6d	-	-	-
7a	-	-	-
7b	-	-	-
7c	-	-	-
7d	-	-	-
8a	09	12	-
8b	-	-	-
8c	08	13	-
8d	07	-	-
10a	05	-	-
10b	-	-	-
10c	12	-	-
10d	-	-	-
11a	07	-	-
11b	08	-	-
11c	12	-	-
11d	12	-	-

Table II: Antibacterial activity of compounds 5a-d and 9a-d, Dzone of inhibition (mm)

Compound	*E. coli*	*S. aureus*
5a	-	-
5b	-	08
5c	-	10
5d	-	-
9a	12	10
9b	06	08
9c	10	07
9d	-	05

Experimental section

Preparation of acetophenone-4-hydroxyphenyl-1-carbonyl hydrazone (4a)

A mixture of 4-hydroxybenzhydrazide (0.01 mole) and acetophenone (0.01 mole) in methanol (30 ml) containing a drop of glacial acetic acid was refluxed for 30 minutes. The separated colorless solid was filtered and crystallized from ethanol.

Yield (57.08%), m.p. 240-241^{0}C. m.f. $C_{15}H_{14}O_2N_2$

I.R. (KBr): 1670, 1535, 3174, 3375cm^{-1}

4-hydroxy acetophenone-4-hydroxyphenyl-1-carbonyl hydrazone (4b)

Yield (61.11%), m.p. 274-276^{0}C. m.f. $C_{15}H_{14}O_3N_2$

I.R. (KBr): 1608, 1553, 3072, 3290cm^{-1}

4-methoxy acetophenone-4-hydroxyphenyl-1-carbonyl hydrazone (4c)

Yield (51.92%), m.p. 212-213^{0}C. m.f. $C_{16}H_{16}O_3N_2$

I.R. (KBr): 1649, 1591, 1249, 3149 and 3269cm^{-1}

4-nitro acetophenone-4-hydroxyphenyl-1-carbonyl hydrazone (4d)

Yield (51.57%), m.p. 220-221^{0}C. m.f. $C_{15}H_{13}O_4N_3$

I.R. (KBr): 1650, 1514, 1346, 3100 and 3300cm^{-1}

Preparation of acetophenone-4-chlorophenyl-1-carbonyl hydrazone (5a)

A mixture of 4-chlorobenzhydrazide (0.01 mole) and acetophenone (0.01 mole) in methanol (30 ml) containing a drop of glacial acetic acid was refluxed for 30 minutes. The separated solid was filtered and crystallized from ethanol.

Yield (85.15%), m.p. 175-176^{0}C. m.f. $C_{15}H_{13}ON_2Cl$

I.R. (KBr): 1660, 1589, 3060cm^{-1}

4-hydroxy acetophenone-4-chlorophenyl-1-carbonyl hydrazone (5b)

Yield (85.80%), m.p. 170-171^{0}C. m.f. $C_{15}H_{13}O_2N_2Cl$

I.R. (KBr): 1637, 1506, 3006, and 3181cm^{-1}

4-methoxy acetophenone-4-chlorophenyl-1-carbonyl hydrazone (5c)

Yield (87.61%), m.p. 250-252^{0}C. m.f. $C_{16}H_{15}O_2N_2Cl$

I.R. (KBr): 1641, 1596, 1270, and 3205cm^{-1}

4-nitro acetophenone-4-chlorophenyl-1-carbonyl hydrazone (5d)

Yield (90.0%), m.p. 225-226^{0}C. m.f. $C_{15}H_{12}O_2N_3Cl$

I.R. (KBr): 1660, 1575, 1344, and 3286cm^{-1}

Preparation of acetophenone-2-chlorophenyl-1-carbonyl hydrazone (6a)

A mixture of 2-chlorobenzhydrazide (0.01 mole) and acetophenone (0.01 mole) in methanol (30 ml) containing a drop of glacial acetic acid was refluxed for 30 minutes. The separated solid was filtered and crystallized from ethanol.

Yield (49.68%), m.p. 124-125^{0}C. m.f. $C_{15}H_{13}ON_2Cl$

I.R. (KBr): 1666, 1545, 3200cm^{-1}

4-hydroxy acetophenone-2-chlorophenyl-1-carbonyl hydrazone (6b)

Yield (90.%), m.p. 150^{0}C. m.f. $C_{15}H_{13}O_2N_2Cl$

I.R. (KBr): 1630, 1513, 3100, and 3250cm^{-1}

4-methoxy acetophenone-2-chlorophenyl-1-carbonyl hydrazone (6c)

Yield (90.0%), m.p. 152-153^{0}C. m.f. $C_{16}H_{15}O_2N_2Cl$

I.R. (KBr): 1670, 1601, 1520, and 3206cm^{-1}

4-nitro acetophenone-2-chlorophenyl-1-carbonyl hydrazone (6d)

Yield (88.0%), m.p. 146-147^{0}C. m.f. $C_{15}H_{12}O_2N_3Cl$

I.R. (KBr): 1664, 1580, 1348, and 3230cm^{-1}

Preparation of acetophenone phenyl-1-carbonyl hydrazone (7a)

A mixture of benzhydrazide (0.01 mole) and acetophenone (0.01 mole) in methanol (30 ml) containing a drop of glacial acetic acid was refluxed for 30 minutes. The separated solid was filtered and crystallized from ethanol.

Yield (88.0%), m.p. 150-151^{0}C.

I.R. (KBr): 1645, 1584,3200

4-hydroxy acetophenone phenyl-1-carbonyl hydrazone (7b)

Yield (78.74.%), m.p. 228-229^{0}C.

I.R. (KBr):1635,1540,3100,3250

4-methoxy acetophenone phenyl-1-carbonyl hydrazone (7c)

Yield (88.0%), m.p. 158-159^{0}C.

I.R. (KBr):1660 , 1565, 3206

4-nitro acetophenone phenyl-1-carbonyl hydrazone (7d)

Yield (94.0%), m.p. 180-187^{0}C.

I.R. (KBr):1665, 1585,1345, 3200.

Preparation of formyl pyrazoles

1-(3-phenyl-4-formyl pyrazole-1-carbonyl) 4-hydroxybenzene (8a)

To the Vilsmeier-Haack reagent prepared from DMF (10 ml) and $POCl_3$ (1.1 ml, 0.012 mole) at 0 ^{0}C, hydrazone 4a (1.016 gm, 0.004 mole) was added in small aliquots at a time and the reaction mixture was stirred at 60-65 ^{0}C for 4 hrs and poured into ice cold water. The solid separated on neutralization with $NaHCO_3$ was filtered, washed with water and crystallized from aq. Methanol which formed 8a.

Yield 1.016 gm (45.33%), m.p. 99-100 ^{0}C,

I.R (KBr): 3235, 2854, 1685, 1607, 1465 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ 8.62 (1H, S, -CHO), 7.61 (1H, S, -CH), 9.40 (1H, S, -OH), 6.40-6.34 (5H, M, -Ar), 6.62-6.45 (4H, M, -Ar)

Elemental analysis calculated for $C_{17}H_{12}N_2O_2$, C 73.91, H 4.34, N 10.14, found C 73.80, H 3.62, N 13.10%

Other compounds **8a-e - 11 a-e** were prepared according to above mentioned method.

1-(3-4-methoxyphenyl-4-formyl pyrazole-1-carbonyl) 4-hydroxybenzene (8b)

Yield 1.136 gm (24.0%), m.p. 108-110 ^{0}C,

I.R (KBr): 3200, 2855, 1665, 1607, 1461, 1253 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ 7.76 (1H, S, -CHO), 3.8 (3H, S, -OCH_3), 7.2 (1H, S, -CH), 9.32 (1H, S, -OH), 6.58-6.54 (4H, M, -Ar), 6.76-6.72 (4H, M, -Ar)

Elemental analysis calculated for $C_{18}H_{14}N_2O_2$, C 67.02, H 4.34, N 8.69, found C 66.92, H 4.34, N 8.57%

1-(3-4-hydroxyphenyl-4-formyl pyrazole-1-carbonyl) 4-hydroxybenzene (8c)

Yield 1.06 gm (65.38%), m.p. 120-121 ^{0}C,

I.R (KBr): 3018.78, 2925, 1648.08, 1605.64, 1460.27 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ 7.76 (1H, S, -CHO), 7.12 (1H, S, -CH), 9.4 (1H, S, -OH), 6.87-6.77 (4H, M, -Ar), 6.68-6.64 (4H, M, -Ar)

1-(3-4-nitrophenyl-4-formyl pyrazole-1-carbonyl) 4-hydroxybenzene (8d)

Yield 1.196 gm (44.51%), m.p. 110-112 ^{0}C,

I.R (KBr): 3238.81, 2855.07, 1629.57, 1607.12, 1461.81, 1515.60, 1345.59 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ 8.9 (1H, S, -CHO), 7.6 (1H, S, -CH), 9.2 (1H, S, -OH), 7.44-7.38 (4H, M, -Ar), 6.99-6.80 (4H, M, -Ar)

1-(3-phenol-4-formyl pyrazole-1-carbonyl) 4- chlorobenzene 9a)

Yield 0.16 gm (40.26%), m.p. 126 ^{0}C,

I.R (KBr): 1691, 1650, 1689, 2836 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ 9.9 (1H, S, -CHO), 7.2 (1H, S, -CH), 7.5-7.4 (4H, M, -Ar), 7.9-7.8 (1H, M, -Ar)

1-(3-4-methoxyphenyl-4-formyl pyrazole-1-carbonyl) 4-chlorobenzene (9b)

Yield 0.6 gm (55.30%), m.p. 110 ^{0}C,

I.R (KBr): 1671, 1640, 1506, 1261, 2952 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ 8.7 (1H, S, -CHO), 7.3 (1H, S, -CH), 3.8 (3H, S, -OCH_3), 8.1-7.8 (4H, M, -Ar), 7.6-7.5 (4H, M, -Ar)

1-(3-4-hydroxyphenyl-4-formyl pyrazole-1-carbonyl) 4-chlorobenzene (9c)

Yield 0.61 gm (55.30%), m.p. 133 ^{0}C,

I.R (KBr): 1678, 1640, 1511, 3210, 2849 cm^{-1}.

^{1}H-NMR (DMSO-d6): δ 8.91 (1H, S, -CHO), 7.3 (1H, S, -CH), 9.9 (4H, S, -OH), 8.1-7.9 (4H, M, -Ar), 7.6-7.5 (4H, M, -Ar)

1-(3-4-nitrophenyl-4-formyl pyrazole-1-carbonyl) 4-chlorobenzene (9d)

Yield 0.42 gm (35.57%), m.p. 98 ^{0}C,

I.R (KBr): 1631, 1654, 1587, 2837, 1344, 1536 cm^{-1}.

1-(3-phenyl-4-formyl pyrazole-1-carbonyl) 2-chlorobenzene (10a)

Yield 23%, m.p. 110 ^{0}C,

I.R (KBr): 1687,1652, 1587, 2852 cm^{-1}.

1-(3, 4-methoxyphenyl-4-formyl pyrazole-1-carbonyl) 2-chlorobenzene (10b)

Yield 20%, m.p. 92 ^{0}C,

I.R (KBr): 1679,1652, 1556, 1278, 2887 cm^{-1}.

1-(3, 4-hydroxyphenyl-4-formyl pyrazole-1-carbonyl) 2-chlorobenzene (10c)

Yield 37%, m.p. 100 ^{0}C,

I.R (KBr): 1684,1658, 1628, 3240, 2558 cm^{-1}.

1-(3, 4-nitrophenyl-4-formyl pyrazole-1-carbonyl) 2-chlorobenzene (10d)

Yield 22%, m.p. 82 ^{0}C,

I.R (KBr): 1690, 1648, 1578, 1532, 1354, 2850 cm^{-1}.

1-(3-phenyl-4-formyl pyrazole-1-carbonyl) benzene (11a)

Yield 32%, m.p. 88-90 ^{0}C,

I.R (KBr): 2840, 1668, 1615, 1515 cm^{-1}.

1-(3, 4-methoxyphenyl-4-formyl pyrazole-1-carbonyl) benzene (11b)

Yield 30%, m.p. 98-100 ^{0}C,

I.R (KBr): 2856, 1662, 1610, 1517, 1261 cm^{-1}

1-(3, 4-hydroxyphenyl-4-formyl pyrazole-1-carbonyl) benzene (11c)

Yield 36%, m.p. 96-97 ^{0}C,

I.R (KBr): 2857, 1649, 1604, 1458 cm^{-1}

1-(3, 4-nitrophenyl-4-formyl pyrazole-1-carbonyl) benzene (11d)

Yield 42.05%, m.p. 82-83 ^{0}C,

I.R (KBr): 2848, 1691, 1612, 1456, 1554, 1349 cm^{-1}

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