2011 International Conference on Chemistry and Chemical Process
IPCBEE vol.10 (2011) © (2011) IACSIT Press, Singapore

Synthesis of Ethyl 2-((E)-3-(E) benzylideneamino)-4-(2-(4`-substituted phenyl)hydrazono)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)Acetate Derivatives

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Abstract. Pyrazolones, pyrazoles and related heterocycles possess various types of biological activities. A good deal of importance is given to pyrazoline derivatives. It is due to their wide use in medicinal chemistry and some of them possess antituberculosis antineoplastic, antidiabetic anti fertility and anti thyroid activity. The antibacterial activity of Mannich bases has been well established. In view of these observations, it appeared of interest,that`s why we have utilised easily accessible, easily ongoing,cost effective, easily reproducible and feasible synthetic routs for synthesis of some novel Mannich bases bearing azomethine pyrazoline-5-one, oxophenylazetidine and Indole moieties.In our present investigation we have synthesised the Ethyl 2-((E)-3-(E) benzylideneamino)-4-(2-(4`substitutedphenyl) hydrazono)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)acetate derivatives,these derivatives are purified by simple purification techniques, and characterised by ^{1}HNMR,IR and Mass spectroscopy. Further to this scope, we committed to innovate new, synthetically most important and active molecules towards targeted diagnostic diseases. Many of these newly synthesised molecules exhibit antibacterial, anticonvulsant, anticancer activities and are used to fight infections involving AIDS. They are also used in agriculture as herbicides, fungicides or insecticides

Keywords: Mannich Reaction, 1,2-Diazole, Oxophenylazetidine.

1. Introduction

Mannich bases and their derivatives have many attractive applications, in paint and polymer chemistry as hardeners, cross linkers, reaction accelerations[1-2] etc. However, the most important applications are in the field of pharmaceutical products[3-4].Studies on antineoplastic drugs, analgesic drug, antibiotic drugs etc[5-9], including labelled molecules[10-12] have received particular attention in the recent past. Various 3-bromo -4-methyl-8-(substituted amino methyl)umbelliferone and have been synthesized by the Mannich reaction of 3-bromo-4-methylumbelliferone with various primary/secondary amines. These compounds have been tested for their antibacterial-activity[13] In present attempt we have synthesised pyrazoline derivatives of mannich bases**(9 a-h),**characterised by ^{1}HNMR,IR and Mass Spectral data.

2. Results

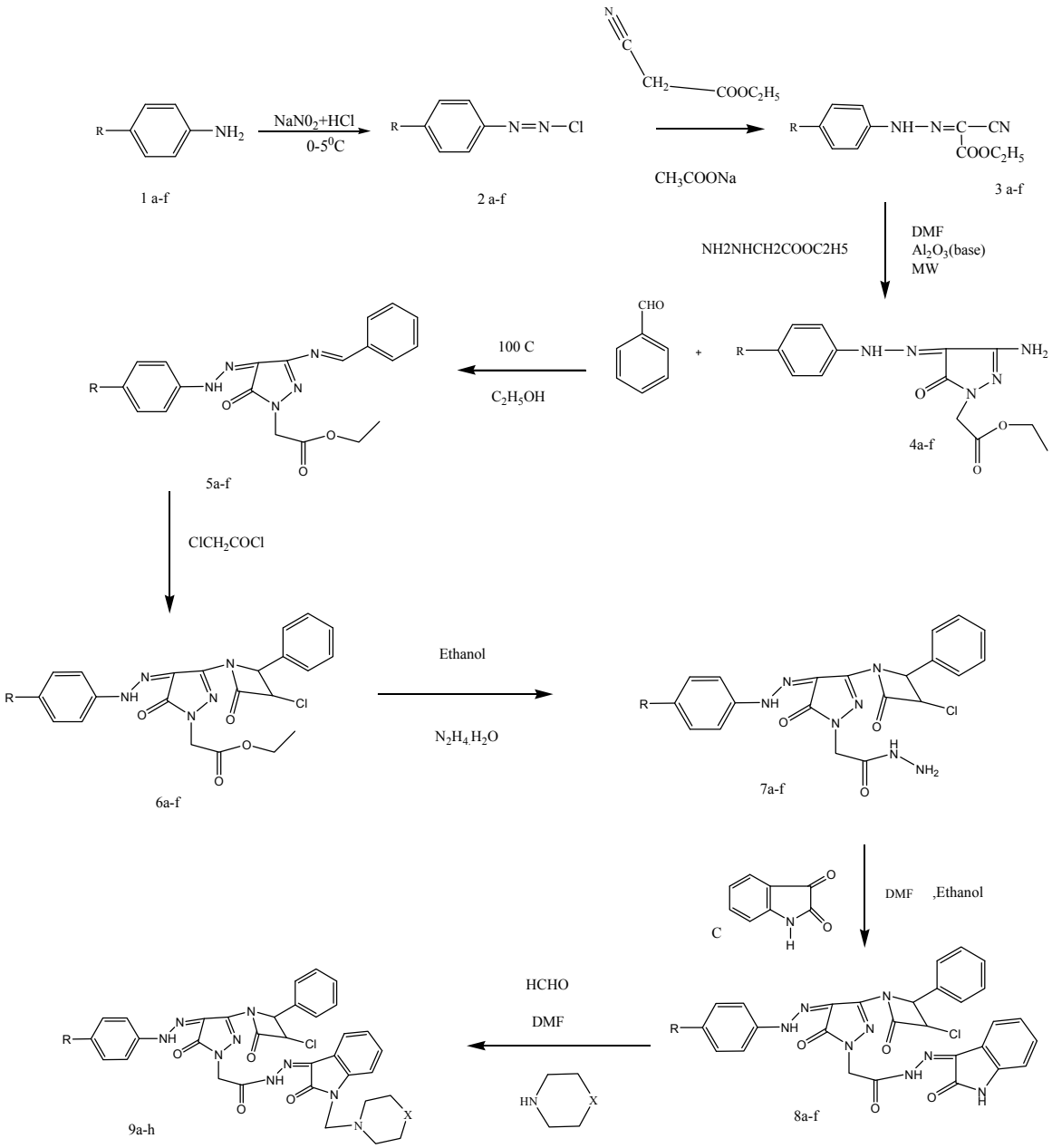
Our preparation of (Z)-2-((Z)-3-(3-chloro-2-oxo-4phenylazetidin-1-yl)-4-(2-(4`-chlorophenyl) hydrazono)-5oxo-4,5-dihydro-1H-pyrazol-1-yl)-N`-(2-oxo-1-(piperidin-1-ylmethyl) indolin-3-ylidene) acetohydrazide 9(a-h) followed the classic synthesis of 8(a-f),utilising the coupling of the isatin[14] with 7(a-f).The pyrazol acetate 6(a-f) and hydrazine hydrate, both required for preparation of precursor 7(a-f),were prepared as follows. Starting from commercially available p-substituted aniline moieties 1(a-f), the pyrazol acetate 6(a-f) were prepared by diazotisation of 1(a-f) with HCl/$NaNO_2$,followed by in-situ coupling with ethyl 2-cyanoacetate and sodium acetate mixture at 0-5°c in minimum amount of water and ethanol to afford cyanoacetate 3(a-f) (in 89% yield),followed by condensation with ethyl 2-hydrazinyl acetate and DMF under

microwave conditions intermittently at 30 sec intervals for 2-4 min to give 78% -85% of 4(a-f).The coupling of 4(a-f) with benzaldehyde and ring formation with 2-chloro acetyl chloride afforded 6(a-f) with 43%-61% yield.The precursor 7(a-f) was prepared by the reaction of hydra zine hydrate with pyrazol acetate 6(a-f) at 100°c with 61-73% yield. Coupling of the acetohydrazide 7(a-f) with the isatin,followed by mannich condensation to afford required mannich bases 9(a-h) with good yields.

3. Discussion

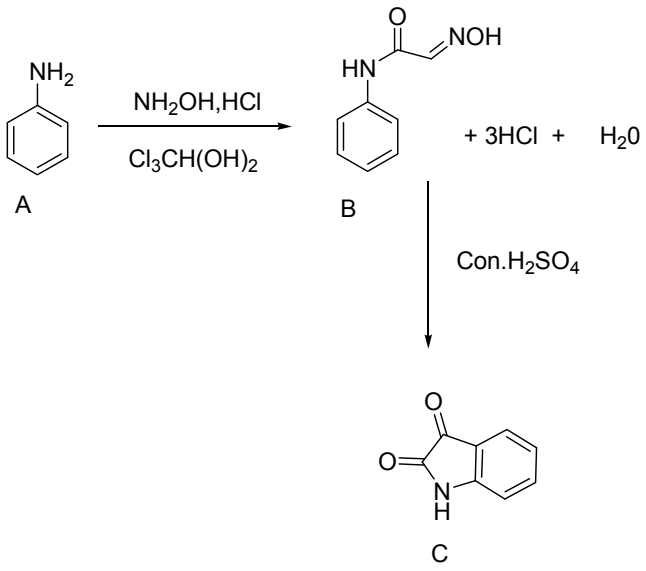
The maintenance of 0-5°c in diazotisation step is very important and also critical, because diazonium salt won`t form if we cooled the reaction mass to < -10°c, and slow addition of ethyl 2-cyanoacetate is preferable.The yield of the precursor 7(a-f) could be increased with substituted benzaldehyde moieties.

Sl no	**R**	**X**	**Compound**	Time(h)	**Temp °C**	**Yield(%)**
1	H	-------	5a	2	100	92
2	CH_3	-------	5b	5	100	89
3	OCH_3	------	5c	5	80	95
4	OC_2H_5	------	5d	**5**	90	96
5	Cl	------	5e	4	100	91
6	Br	------	5f	4	95	85
7	H	------	6a	72	rt	47
8	CH_3	-----	6b	72	rt	43
9	OCH_3	-----	6c	72	rt	38
10	OC_2H_5	------	6d	72	rt	56
11	Cl	--------	6e	72	rt	61
12	Br	--------	6f	72	rt	46
13	H	--------	7a	5	95	61
14	CH_3	-------	7b	4-5	95	64
15	OCH_3	--------	7c	3	95	73
16	OC_2H_5	-------	7d	4	95	70
17	Cl	-------	7e	5	95	72
18	Br	--------	7f	4	95	68
19	H	-------	8a	2	95	64
20	CH_3	-------	8b	2.5	95	71
21	OCH_3	--------	8c	3-4	95	60
22	OC_2H_5	--------	8d	3-4	95	70
23	Cl	------	8e	1	95	65
24	Br	-------	8f	1	95	70
25	H	-CH2	9a	16	0-rt	70
26	CH3	-CH2	9b	16	0-rt	70
27	OCH3	-CH2	9c	16	0-rt	70
28	OC2H5	-CH2	9d	16	0-rt	75
29	Cl	-CH2	9e	16	0-rt	75
30	Br	$-CH_2$	9f	16	0-rt	80
31	Cl	-O-	9g	16	0-rt	85
32	Cl	$-N-CH_3$	9h	16	0-rt	80



R = H, CH3, OCH3, OC2H5, Cl, Br

X= CH2, -O, -N-CH3



4. Experimental Section

Melting points were determined in open capillary tubes and are uncorrected (in degree Celsius).The Infrared spectra were recorded in KBr discs on Perkin-Elmer FT-IR(Spectrum ONE) spectrophotometer(ν_{max} in cm^{-1}).The ^{1}HNMR spectra were rcorded on a Bruker AMX (200 MHz) spectro photometer in DMSO-d_6 with TMS as an internal standard (chemical shifts in δ).Mass Spectra were recorded on a mass spectrophotometer JOEL sx-102(FAB) instrument (m/z in %).Silica gel chromatography using Merck silica gel 60ASTM(60-120 &230-400)mesh.

Synthesis of (E)-2-(3-(3-chloro-2-oxo-4-phenylazetidin-1-yl)-4-(2-(4`-substitutedphenyl) hydrazono)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)acetohydrazide 7(a-f). The required primary amine 1(a-f) is dissolved in a suitable volume of water containing 3.0 equivalents of hydrochloric acid (or sulphuric acid) by the applica tion of heat if necessary.The solution thus obtained is cooled to 0ºC when the amine hydrochloride (or sulphate) usually crystallizes. The temperature is maintained at 0-5ºC, and the aqueous sodium nitrite solution is added drop-wise till there is no free nitrous acid. The solution is tested later with an external indicator (moist potassium iodide starch paper).Excess acid is harmful; the concentration of the acid is reduced to optimum value.An excess of acid is always minimized to stabilize the diazonium salt. The similar procedure is adopted for the preparation of other substituted phenyl diazonium hydrochlorides 2(a-f)

A solution of sodium acetate (0.2 mol) in 100ml of aqueous alcohol (50%) is added to a solution of ethyl 2-cyanoacetate (0.1 mol) in 50 ml of ethanol and the mixture is cooled to 0ºC.This cold mixture is added gradually to the corresponding diazonium chloride 2(a-f)(0.1 mol) till turbidity is observed. The addition is continued till yellow crystals separated out. These crystals are filtered, washed with water and dried to afforded 3(a-f).Condensation of (z)-ethyl-2-(2-(4`-substitutedphenyl)hydrazono)-2-cyanoacetate 3(a-f) with ethyl 2-hydrazinyl acetate in the presence of catalytic amount of dimethyl formamide under microwave irradiation afforded (Z) ethyl 2-(3-amino-4-(2-(4`-subtitutedphenyl)hydrazono)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]acetate 4(a-f). In a typical experimental procedure, a mixture of (Z)-ethyl 2-cyano-2-(2-phenylhydrazono acetate(1.0 mol) 3a(R=H),ethyl hydrazinyl acetate(1.0 mol) and dimethyl formamide (10 drops) was subjected to microwave irradiation at 150W intermittently at 30 sec intervals for 2 minutes. After complete conversion as indicated by TLC, the reaction mixture was cooled and treated with cold water.The precipitate was filtered,recrystalized from ethanol to afforded 78% of 4a(R=H).

Equimolar quantity of (Z) 2-(3-amino-4-(2-(4`-subtitutedphenyl)hydrazono)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl]acetate 4(a-f) and benzaldehyde were dissolved in absolute alcohol. Added a drop of acetic acid and then heated on a steam bath for 2h at 100°C.After standing for 24h at room temperature, the crude mass concentrated as such to remove ethanol. The product was recrystallised from warm ethanol with 85%-92% yield 5(a-f).The 2-chloro acetyl chloride (0.01 mol) was added dropwise to Ethyl 2-((E)-3-(E)benzylideneamino)-4-(2-(4`substitutedphenyl)hydrazono)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)acetate5(a-

f) (0.01 mol) and triethylamine (0.02 mol) in dioxane (25ml) at room temperature. The mixture was refluxed for 8h and left at room temperature for 3 days. Poured the reaction contents on crushed ice.The product thus formed was filtered and washed with sodium bicarbonate solution. The dried product 6(a-f) was recrystallised from absolute alcohol with 43%-61% yield.

A solution of 6(a-f) (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (20 ml) was refluxed for 5 hours. The reaction mixture was cooled and poured on to ice cold water with stirring. The separated solid was filtered, washed with water and recrystallized from ethanol to afford 7(a-f) with 61%-73% yield. IR spectra ν_{max} (KBr)in cm^{-1}: 677-C-Cl,778-810-Aromatic, 1634,1645-C=N, 1695,1710-C=O, 3447-NH2, 1658,3305-NH ^{1}HNMR ($CDCl_3$&DMSO-d_6 δppm),8a**:**6.67(s,1H,Ar-NH),7.10(t,2H,Ar-H),6.97(t,1H,Ar-H),6.63(d,2H,Ar-H), 7.18 (m,5H,Ar-H),3.97(s,2H,$COCH_2$),5.54(d,1H,4-CH),5.89(d,1H,3-CH), 4.98(t,1H, COONH), 3.42 (d,2H,-NH_2). ^{13}CNMR(CDCl3,δppm): 46.8,56.6,63.2, 117.4(2), 118.9 ,127.8(3), 129.6,143.8, 156.6 (2),168.2, 169.9, 179.8.EI ms:m/z:455.85;found:456.8(M+1).Anal calcd for $C_{20}H_{18}ClN_7O_4$(455.85)C:52.70; H:3.98;O:14.04; found:C:52.59; H:3.75; O:13.06.

Synthesis of Isatin (C). The required Isatin (C) was prepared by the procedure described by Marvel and Heirs[14]

Synthesis of (Z)-2-((Z)-3-(3-chloro-2-oxo-4-phenylazetidin-1-yl)4-(2-(4`-substitutedphenyl)hydrazono) -5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-N`-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazi de 9(a-h). Equimolar quantities (0.01 mol) of Isatin (C) and the corresponding amino compound 7(a-f) were dissolved in warm ethanol (40 ml) containing DMF (0.5 ml). The reaction mixture was refluxed for 1-4 hours and then kept at room temperature for overnight. The resulting solid was filtered and washed with ethanol, dried and recrystallized from ethanol to afford Compounds 8(a-f) with 60%-71% yield**.** A mixture of (8e) (0.1 mol), piperidine (0.15 mol) and water (20 ml) was stirred to obtain a clear solution. To this solution, HCHO (0.05 mol) and DMF (2ml)were added in ice-cold condition and stirred for 2 hours in an ice-bath and left overnight at room temperature. The obtained white solid was isolated and recrystallized from ethanol,to give Compound (9e) with 75% yield**.**The reaction procedure leading to 9e was then extended to the synthesis of 9(a-h)

In a typical example, a mixture of hydrazone (8e) with aqueous formaldehyde and piperidine in DMF for 6 hours at room temperature yielded a single product which was identified as (Z)-2-((Z)-3-(3-chloro-2-oxo-4phenylazetidin-1-yl)-4-(2-(4`-chlorophenyl)hydrazono)-5oxo-4,5-dihydro-1H-pyrazol-1-yl)-N`-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide 9(e) on the basis of its spectral data. 9e**:**IR spectra ν_{max} (KBr)in cm^{-1}: 648,678-C-Cl;710,778,797,834-Aromatic;1615,1636,1647-C=N; 1697, 1705,1715C=O;3308-NH;1625-CO-NH.^{1}HNMR($CDCl_3$&DMSO-d_6 δppm): 6.68(s,1H,Ar-NH),7.10 (t,2H,Ar-H),6.63(d,2H,Ar-H),7.20(m,5H,Ar-H),7.41(t,2H,Indole-Ar-H),7.86 (d,2H,Indol Ar-H) ,3.97(s,2H,-$COCH_2$), 5.54(d,1H,4-CH),5.92(d,1H,3-CH),6.98(s,1H,-CONH), 5.68(S,2H,-NCH_2),1.62 (m,6H, Piperidine) 2.56 (m,4H,Piperidine).^{13}CNMR(CDCl3,δppm):25.7(2), 26.2,52.8(2),55.4(2), 63.2,71.2, 117.9 (3), 121.9,124.7(2), 127.7(3),128.8 (2),129.5,129.9 (2), 131.8, 133.4, 142.2, 143.8, 148.4, 153.2 (2), 164.9 (2),168.7, 174.8.EI ms: m/z:700.57; found:701.02 (M+1), Anal calcd for C34H31Cl2N9O4 (700.57): C:58.29;H:4.46,O:9.14.Found:C:58.09;H:4.67;O:9.02.

Similar treatment of hydrazones 8(a-f) with Piperidine, Morpholine, N-methyl piperazine in presence of formaldehyde in DMF at room temperature afforded the (Z)-2-((Z)-3-(3-chloro-2-oxo-4phenylazetidin-1-yl)4-(2-(4`-substitutedphenyl)hydrazono)-5-oxo-4,5-dihydro-1H-pyrazol-1-yl)-N`-(2-oxo-1-(piperidin-1-ylmethyl)indolin-3-ylidene)acetohydrazide 9(a-h) with 70%-85% yield.

5. Acknowledgements

We are greatly thankful to the Sri Krishnadevaraya University,anantapur,India for instrumental supporting.

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