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Synthesis of N-1substituted acylpyrazolones

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ABSTRACT

A series of acylpyrazolones, 1-(2-hydroxybenzoyl)-3-methyl-pyrazol-5-one, 1-(2-aminobenzoyl)-3-methyl-pyrazol-5-one, 1-benzoyl-3-methyl-pyrazol-5-one have been synthesized from ethylacetoacetate and substituted hydrazide at lower temperature. Reaction conditions are important features of this synthesis. At higher temperature, migration of acyl group takes place. The products possess antibacterial activities.

KEYWORDS

N-1 substituted acylpyrazolones;
Ethylacetoacetate;
Substituted hydrazide.

INTRODUCTION

Pyrazolone represent an important class of compound for their number of application in diverse area[1-3]. The pyrazolones derivatives have great importance in medicinal chemistry as analgesic[4], anti-pyretic[5], and anti-inflammatory agents[6]. Such properties of pyrazolones encourage in the search of new pyrazolone derivatives. Pyrazolones compounds possess anti-bacterial[7], anti-fungal[8], anti-tumor[9], anti-convulsants[10], anti-oxidant[11], neuro-protectives[12], anti-hyperglycemic[13], insecticides[14].

Besides pharmaceutical applications, the pyrazo lones are uses in photography as colour coupler and sensitizers[15], in solvent extraction of metal ions[16], in the synthesis of dyes[17], in chromatography[18] and in photochemical industries[19].

A number of methods for the synthesis of pyrazolones have reported in literature. However, one of most frequently used is a classical method for synthesis of pyrazolones is that condensation of β-ketoester with hydrazine[20].

Lecher et al.[21] have been reported the synthesis of pyrazol-5-one by reacting ketene with phenyl hydrazine.

Pyrazolones containing a group other than phenyl in the 1-position are far from common.

The groups different to the phenyl-ring is introduced in N-1 position by using different starting hydrazine in the synthesis of N-1 substituted pyrazolone.

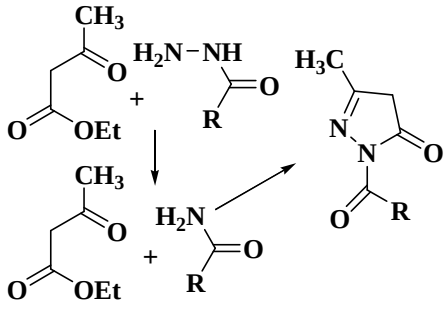
The pyrazolone having are CH_3, $-C_6H_4NO_2$, $C_5H_4CF_3$, $-C_5H_4N$ as substituent at N-1 have been reported[22]. N.A.Evans[23] have been reported the synthesis of 1-acetyl-3-methyl-pyrazol-5-one by adding acetic-anhydride to the solution of 3-methyl-pyrazol-5-one in pyridine.

H.A.Torrey et al.[24] has been synthesized 1-benzoylphenyl-3-methylpyrazol-5-one from the hydrochloride of parahydrazinobenzophenone and acetoacetic ester with a few drops of hydrochloride acid.

N-1 substituted thiocarbamoyl-3,5-diphenyl pyrazol-5-one has anti-amoebic activity and it synthesized by base catalyzed Claisen-Schmidt condensation of benzaldehyde with acetophenone followed by cyclisation with various thiosemicarbazide[25].

In the present paper, novel synthesis of substituted acylpyrazolones has been described.

Short Communication



Where R=PhOH, $PhNH_2$, Ph

SCHEME 1

EXPERIMENTAL

Melting points are uncorrected. IR spectra of the ligand and of the complexes were recorded on Shimadzu IR spectrophotometer in the range 400-4000cm^{-1} using KBr discs. ^{1}HNMR and ^{13}CNMR spectra in $CDCl_3$ were recorded, using TMS as internal standard. The antibacterial activity of the compounds under investigation was tested by the well diffusion method, using Muller-Hinton agar as the nutrient medium and ampicillin was used as the standard.

RESULT AND DISCUSSION

The methanolic solution of ethylacetoacetate (0.01mmol) was added slowly with stirring to the ice cold methanolic solution of 2-hydroxy-benzoic acid hydrazide (0.01mmol) for HBMP, 2-amino-benzoic acid hydrazide (0.01mmol) for ABMP, benzoic acid hydrazide (0.01mmol) for BMP (scheme 1). The mixture was kept in an ice-bath for 12 hours with occasional stirring. A solid was filtered and washed with water, followed by passing through column of silica gel (60-120 mesh) using benzene-ethyl acetate (80:20) as eluent. The product was recrystallised from hot methanol. The purity of the isolated product was checked by TLC.

The spectral analysis of the products is given below:

1-(2-Hydroxybenzoyl)-3-methyl-2-pyrazol-5-one

Colourless solid, M.P.136^{0}C, Composition: C-60.55 % (60.52), H-4.62 %(4.59), N-12.84 % (12.87), IR (KBr, cm^{-1}):33478-3100 cm^{-1} (broad, OH stre.), 1718 cm^{-1}(C=O stret), 1639 cm^{-1}(C=O stre. of pyrazolone), 1600cm^{-1} (C=N stre.), 1552 cm^{-1}, 1500 cm^{-1} and 1450 cm^{-1} (aromatic C=C stre.), 1280 cm^{-1}(phenolic C-O stre.), 756 cm^{-1}(1,2 disubstituted benzene). ^{1}HNMR ($CDCl_3$): δ2.1 (s, 3H, CH_3), 2.3 (s, 2H, CH_2), 5.5 (s, 1H, OH), 6.8 (d, 1H, ArH), 7.1 (d, 1H, ArH), 7.2 (t, 1H, ArH), and 7.8 (t, 1H, ArH). Mass spectrum of HBMP shows an intense peak (M^+) at 218.06 less intense peaks (M+1) at 219.07 and (M+2) at 220.07.

1-(2-Aminobenzoyl)-3-methyl-2-pyrazol-5-one

Crystalline brown solid, M.P148^{0}C, Composition: C-60.82 %(60.80), H-5.10 % (5.09), N-19.34 % (19.33) IR (KBr,cm^{-1}):33287-3190cm^{-1} (doublet), 1713cm^{-1} (C=O str), 1649cm^{-1} (C=O str of pyrazole), 1600cm^{-1}(C=N stre.), 1557cm^{-1}, 1555cm^{-1} and 1465cm^{-1}(aromatic C=C stretching), 745 cm^{-1}(ortho substituted benzene). ^{1}HNMR ($CDCl_3$): δ2.1 (s, 3H, CH_3), 2.4 (s,2H, CH_2), 4.3 (s, 2H, NH_2), 6.7 (d,1H, ArH), 6.8(d, 1H, ArH), 7.3 (t,1H, ArH), and 7.7 (t, 1H, ArH)

1-Benzoyl-3-methyl-2-pyrazol-5-one

Colourless solid, M.P.162^{0}C,Composition: C-60.55 %(60.52), H-4.62 %(4.59), N-12.84 %(12.87). IR: 1723cm^{-1} (C=O str,), 1683cm^{-1} (C=O str, of pyrazole), 1597cm^{-1}(C=N stre.), 1557cm^{-1}, and 1466cm^{-1} (aromatic C=C stretching), 719cm^{-1} and 761cm^{-1} (ortho substituted benzene). ^{1}HNMR ($CDCl_3$): δ1.4 (s, 3H, CH_3), 2.3 (s,2H, CH_2), 5.5 (s, 1H, OH), 7.1 (t, 1H, ArH), 7.4 (d,2H, ArH), and 7.6(d,1H, ArH)

Antibacterial activity

The synthesized acylpyrazolones were tested for antibacterial activity. Mueller-Hinton agar was used for testing the susceptibility of microorganisms by cup-plate agar diffusion method[26] using methanol as solvent, at a concentration of 1mg/mL of methanol against gram positive *(Staphylococcus aureus)* and gram negative *(Escherichia coli and Salmonella typhi)* bacteria. The zone of inhibition against the growth of microorganisms was determined at the end of an incubation period of 24 h at 37^{0}C. Activity was determined by measuring the diameter of zones showing complete inhibition (mm). Growth inhibition was compared with the standard Ampicillin trihydrate as antibacterial agent.

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