Synthesis of some new Ethyl 4-(1,3-Diarylpyrazol-4-yl)-6-methyl-2-thioxo-1,3,4-trihydropyrimidine-5-carboxylates

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Abstract

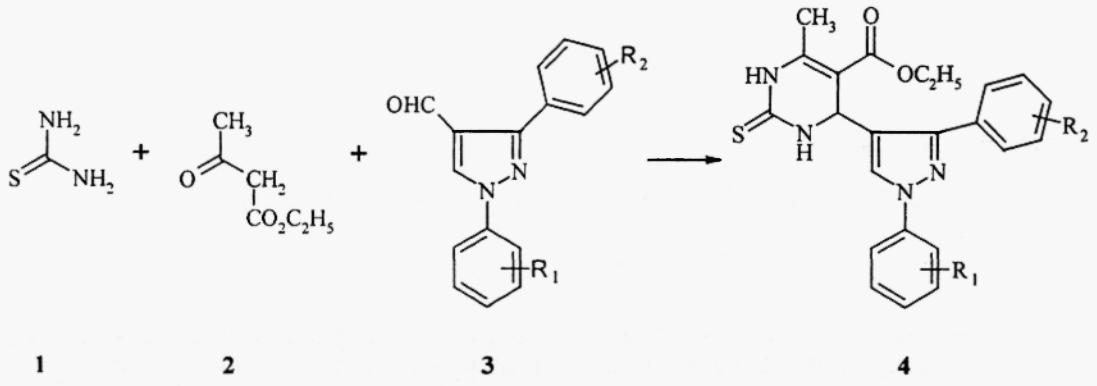
A series of some new 4-pyrazolyl-6-methyl-2-thioxo-1,3,4-trihydropyrimidine-5-carboxylates (**4**a-h) have been synthesised.

Introduction

Dihydropyrimidine esters (DHPM's) represent a partly reduced pyrimidine heterocyclic ring system with remarkable pharmacological properties. A variety of biological activities such as antiviral, antitumour, antibacterial and anti-inflammatory activities have been associated with these compounds[1]. These are structurally related to dihydropyridines and are known to exhibit antihypertensive and calcium channel blocking activities[2]. Dihydropyrimidine-5-carboxylate pharmacophore is also found in a number of marine products such as batzilladine alkaloids with potent HIV activity[3]. Furthermore, pyrazole nucleus has got wide application in medicinal chemistry[4]. This ring plays an important in many biological systems and many therapeutic agents like Celecoxib[5], Lonazolac[6] contain pyrazole ring. In continuation of our work on pyrazoles[7,8], it was considered of interest to synthesize some new dihydropyrimidine carboxylates incorporating this interesting heterocycle at C-4 position.

Results and Discussion

The key intermediates, various1,3-diarylpyrazole 4-carboxaldehydes (**3**) required in the present work were prepared by Vilsmeier-Haack reaction on substituted acetophenone phenylhydrazone derivatives in good yields[9]. These were reacted with ethylacetoacetate and thiourea in refluxing ethanol in presence of hydrochloric acid under Biginelli reaction condition[10] to give 4-pyrazolyl-2-thioxodihydropyrimidine-5-carboxylates in moderate yields (Scheme 1). The structures of compounds **4** is confirmed by ^{1}H NMR spectra by the presence of the characteristic signals around δ 7.9 (pyrazole H), 5.4 (C_4-H), 2.3 (CH_3) and two NH protons around δ 9.3 and 9.95 ppm. All the compounds reported in Table -1 were based on their correct elemental analyses IR and mass spectra of representative compounds.



1 2 3 4

SCHEME-1

Experimental Section

Melting points were determined in open capillaries and are uncorrected. IR spectra recorded in KBr pellets ^{1}H NMR spectra on a Varian 200 MHz instrument with TMS as internal standard, chemical shifts expressed in δ ppm and Mass spectra on Hewlett Packard Mass spectrometer operating at 70ev.

General procedure for the preparation of 1,3-diarylpyrazole-4-carboxaldehydes 3

Acetophenone phenylhydrazones were prepared by reaction of suitably substituted acetophenones with phenylhydrazines. These (0.1 mole) were dissolved in DMF and was added drop wise to a precooled Vilsmeier reagent prepared from Dimethylformamide (0.3 mol) and $POCl_3$ (0.3 mol) at 0-5°C, which was then carefully warmed to room temperature and heated slowly to 70° for 5 hrs. The reaction mixture was cooled to room temperature, basified with 25% NaOH solution at 5°C. The precipitate was filtered washed with water and recrystallised from ethylacetate - hexane to give pure **3** in good yields.

General procedure for the preparation of 4

A mixture of 1,3-diarylpyrazole-4-carboxaldehyde (0.01 mol), ethylacetoacetate (0.01 mol) and thiourea (0.012 mol) in ethanol (30 ml) containing catalytic amount of hydrochloric acid was refluxed for 3-4 hrs. The progress of the reaction was monitored by TLC. At the end of the reaction, solvents were distilled off, the separated solid was filtered washed with methanol and subjected to column chromatography (Silica gel – DCM) to give pure **4** as crystalline solids.

Ethyl-4-(1,3-Diphenylpyrazol-4-yl)-6-methyl-2-thioxo-1,3,4-trihydropyrimidine-5-carboxylate 4a

A mixture of 1,3-diphenylpyrazole-4-carboxaldehyde (**3**, 2.48 g, 0.01 mol), ethyl acetoacetate (**2**, 1.30 g, 0.01 mol), thiourea (**1**, 1.06 g, 0.012 mol), ethanol (30 ml), conc.

Table 1: Characterization data of compounds **4**

Compd	R_1	R_2	M.p °C	Yield %	Mol. Formula	^{1}H NMR (δ ppm) 200 MHz (DMSO-d_5), MS (70ev) m/z
4a	H	H	197	62	$C_{23}H_{22}N_4O_2S$	0.9(t, 3H), 2.35(s, 3H), 3.8(g, 2H), 5.55(s, 1H), 7.35(m, 6H), 7.75(m, 4H), 7.95(s, 1H), 9.3(bs, 1H), 9.95(bs, 1H)
4b	H	4Br	243	59	$C_{23}H_{21}BrN_4O_2S$	0.9(t, 3H), 2.3(s, 3H), 3.82(q, 2H), 5.43(s, 1H), 7.2-7.7(m, 9H), 7.92(s, 1H), 9.4(bs, 1H), 10.0(bs, 1H)
4c	H	4-F	239	64	$C_{23}H_{21}FN_4O_2S$	0.9(t, 3H), 2.3(s, 3H), 3.8(q, 2H), 5.42(s, 1H), 7.2(m, 3H), 7.35(m, 2H), 7.75(m, 4H), 7.95(s, 1H), 9.4(bs, 1H), 9.95(bs, 1H)
4d	H	2,4-diCl 5-F	207	67	$C_{23}H_{19}Cl_2FN_4O_2S$	1.0(t, 3H), 2.34(s, 3H), 3.75(q, 2H), 5.4(s, 1H), 7.2-7.5(m, 7H), 7.9(s, 1H), 9.4(bs, 1H), 9.9(bs, 1H)
4e	4-F	4-Cl	259	63	$C_{23}H_{20}ClFN_4O_2S$	0.9(t, 3H), 2.3(s, 3H), 3.8(q, 2H), 5.4(s, 1H), 7.2-7.7(m, 8H), 7.9(s, 1H), 9.35(bs, 1H), 10.02(bs, 1H)
4f	2,4-diF	2,4-diCl 5-F	192	69	$C_{23}H_{17}Cl_2F_3N_4O_2S$	0.9(t, 3H), 2.3(s, 3H), 3.8(q, 2H), 5.4(s, 1H), 7.2-7.5(m, 5H), 7.9(s, 1H), 9.3(bs, 1H), 10.0(bs, 1H)
4g	2,4-diF	4-F	217	71	$C_{23}H_{19}F_3N_4O_2S$	0.95(t, 3H), 2.3(s, 3H), 3.8(q, 2H), 5.4(s, 1H), 7.2-7.5(m, 7H), 7.9(s, 1H), 9.3(bs, 1H), 9.95(bs, 1H)
4h	2,4-diF	4-Cl	211	68	$C_{23}H_{19}ClF_2N_4O_2S$	0.9(t, 3H), 2.3(s, 3H), 3.8(q, 2H), 5.42(s, 1H), 7.2-7.5(m, 7H), 7.92(s, 1H), 9.3(bs, 1H), 9.95(bs, 1H)

HCl (10 drops) was refluxed for 4-5 hrs. It was worked up according to general procedure described for **4** to give **4a** as crystalline solid. Yield: 2.59 gm (62%); m.p: 197°; IR: 1617cm^{-1}; ms (70ev) m/z (%): 418 (M^+,); ^{1}H NMR (DMSO-d_6): δ 0.9 (t, 3H), 2.35 (s, 3H), 3.8(q, 2H), 5.5 (s, 1H), 7.35 (m, 6H), 7.75 (m, 4H), 7.95 (s, 1H), 9.3 (bs, 1H), 9.95 (bs, 1H). (Found: C, 66.24; H, 5.47; N, 13.56 $C_{23}H_{22}N_4O_2S$ requires C, 66.02, H, 5.26; N, 13.39%)

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