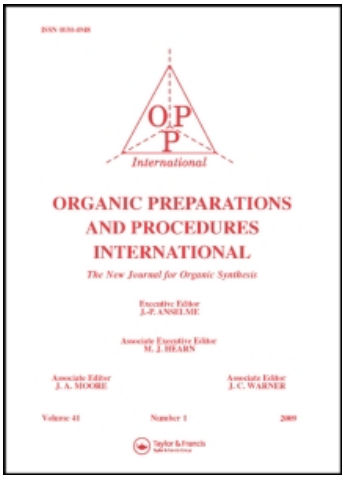

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SYNTHESIS OF NOVEL 5-SUBSTITUTED-6-METHYL-4-[5-CHLORO-3-METHYL-1-PHENYL-1*H*-PYRAZOL-4-YL]-3, 4-DIHYDROPYRIMIDIN-2(1*H*)-ONES

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SYNTHESIS OF NOVEL 5-SUBSTITUTED-6-METHYL-4-[5-CHLORO-3-METHYL-1-PHENYL-1*H*-PYRAZOL-4-YL]-3,4-DIHYDROPYRIMIDIN-2(1*H*)-ONES

Submitted by (06/16/06)

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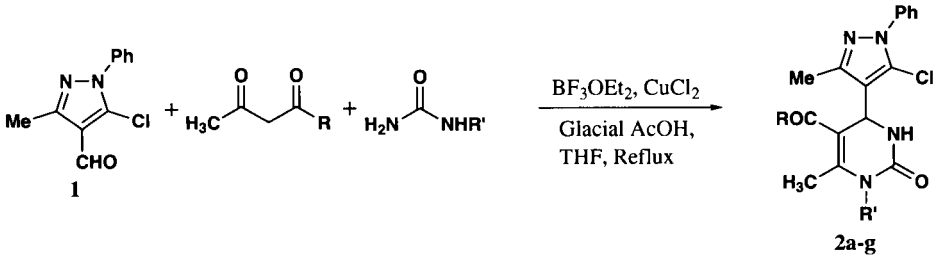
Derivatives of dihydropyrimidones (DHPMS) exhibit a wide range of biological activities and are antihypertensive, antitumor and anti-inflammatory agents.[1] Recently, appropriately functionalized DHPMs have emerged as orally active antihypertensive agents[2] or A_{1a} adrenoceptor-selective antagonists.[3] A very recent highlight in this context has been the identification of the structurally rather simple DHPM *monastrol* as a mitotic kinesin Eg5 motor protein

inhibitor and potential new lead for the development of anticancer drugs.[4] Apart from synthetic DHPM derivatives, several marine natural products with interesting biological activities containing the dihydropyrimidine-5-carboxylate core have recently been isolated.[5] In the past decade, 4-aryldihydropyrimidinones have attracted considerable attention owing to their high activity as calcium channel blockers. Similar compounds such as 4-aryl-1,4-dihydropyridines of the *nifedipine* type are already well established drugs because of their "Calcium ion" antagonistic and agonistic activities.[6] The effect of substitution on the 1,4-dihydropyridine ring on biological activity has been widely studied in the process of determining structure activity relationships. Although even the simple 2,6-dimethyl-3,5-dicarbalkoxy-1,4-dihydropyridines have some hypotensive activity in anesthetized animals, but better activity is generally observed with those compounds having a cyclic substituents (*ortho* or *meta*-substituted aryl or heteroaryl) at the 4-position.[7]

Our aim was to synthesize derivatives of dihydropyrimidines having a heterocyclic ring at the 4 position of the dihydropyrimidine ring. Thus, we combined the 1,4-dihydropyrimidine pharmacophore with the 5-chloropyrazole unit. It is well known that halogen derivatives of pyrazoles are used as materials for drugs and agrochemicals.[8] Strategies for the synthesis of the dihydropyrimidinone nucleus have varied from one-pot[9] to multistep approaches.[10] Biginelli's initial one-pot reaction of β-keto ester, aryl aldehyde and urea under strongly acidic conditions in a protic solvent frequently afforded low (20-50%) yields.[11] Subsequent multistep synthesis produced somewhat higher yields but lacked the simplicity of the one-pot synthesis.[12] More recently, several additional conditions for the synthesis of dihydropyrimidinones have been reported.[13] However, in spite of their advantage and potential utility, some of them suffer from drawbacks such as long reaction times, expensive catalysts or lower yields. We now report an efficient one-pot synthesis of new dihydropyrimidin-2(1*H*)-ones (*Table 1*) having a 5-chloropyrazole unit at position 4 of the dihydropyrimidine ring.

Reaction of aldehyde **1** with a β-keto ester or β-diketone and urea (or substituted urea) in the presence of $CuCl_2$/acetic acid/$BF_3.(OEt)_2$ in dry THF at reflux temperature afforded the corresponding dihydropyrimidin-2(1H)-one derivatives (**2a-g**) in good yields (50-71%) (*Scheme 1*).



a) R = OEt, R' = H; b) R = OMe, R' = H c) R = Me, R' = H; d) R = OEt, R' = Me;
e) R = OMe, R' = Me; f) R = OEt, R' = Ph; g) R = OMe, R' = Ph

Scheme 1

Aldehyde **1**[14] was prepared by the Vilsmeier-Haack[15] reaction of the corresponding pyrazolone[16] with phosphorus oxychloride in dimethylformamide.

We studied several conditions for DHMP formation such as (i) I_2 in toluene, (ii) acetic acid/catalytic HCl, (iii) refluxing in ethanol containing catalytic HCl or H_2SO_4 and (iv) $BiNO_3$/acetonitrile. The reaction was rapid and produced good yields when $BF_3.(OEt)_2$ was used in slight excess (1.3 equiv) and $CuCl_2$ and acetic acid were used in catalytic amounts. Copper ion and BF_3•$(OEt)_2$ were chosen as additives for their known carbonyl-activating abilities.

Table 1. Yields, mps and Elemental Analysis of Compounds **2**

Cmpd[a]	Yield (%)	mp (°C)	Time (h)	Elemental Analysis (Found) C	H	N
2a	71	234-236	12	57.75 (57.45)	5.08 (5.12)	14.97 (14.81)
2b	60	245-246	10	56.67 (56.84)	4.72 (4.84)	15.56 (15.26)
2c	55	237-239	10	59.30 (59.45)	4.94 (4.80)	10.17 (10.01)
2d	59	184-186	10	58.76 (58.56)	5.41 (5.50)	14.43 (14.25)
2e	54	180-182	11	57.75 (57.50)	5.08 (4.81)	14.97 (14.71)
2f	50	Oil	12	63.94 (63.78)	5.14 (5.28)	12.38 (12.15)
2g	55	Oil	11	62.99 (63.09)	5.24 (5.01)	12.78 (13.01)

a) All compounds are light yellow in color

EXPERIMENTAL SECTION

All reagents used were AR grade. THF was distilled from sodium/benzophenone prior to use. Melting points were determined using a Thomas-Hoover melting point apparatus and are uncorrected. ^1H (300 MHz) and ^{13}C NMR (75MHz) spectra were recorded on a Bruker 300 NMR spectrometer in DMSO-d_6 (with TMS for ^1H and chloroform-*d* for ^{13}C as internal references) unless otherwise stated. MS were recorded on Agluent 1100 ES-MS Karlsrhue Germany. Column chromatography was performed on silica gel (230-400 mesh). Microanalyses were obtained with an Elemental Analysensysteme GmbH VarioEL V3.00 element analyzer. The reactions were monitored by thin layer chromatography (TLC) using aluminium sheets with silica gel 60 F_{254} (Merck). All reactions were carried out under nitrogen atmosphere.

5-Ethoxycarbonyl-6-methyl-4-[5-chloro-3-methyl-1-phenyl-1*H*-pyrazol-4-yl]-3,4-dihydropyrimidin-2(1*H*)-one (2a). Typical Procedure.- A mixture of 0.85 g (0.386 mmol) of aldehyde **1**, of ethyl acetoacetate 0.542 g (0.386 mmol) and of urea 0.348 g (0.579 mmol) was refluxed in dry THF (20 mL) in the presence of BF_3•OEt_2 (0.56 g, 0.502 mmol), of glacial acetic acid (0.040 g) and of $CuCl_2$ (0.0514 g) for 18-24 h. The resulting mixture was then neutralized with aq. 10% Na_2CO_3 solution and the product was extracted into ethyl acetate (3 x 50 mL). After removal of solvent, the compound was then purified by column chromatography using ethyl acetate and hexane (3:7) to give pure **2a** (1.03 g, 71%).

Table 2. Spectroscopic Data of Compound **2a-g**

Cmpd	IR (cm^{-1})	^1H NMR (δ)	^{13}C NMR (δ)
2a	3398, 3281, 1703	9.29 (s, 1H), 7.56-7.4 (m, 6H), 5.31 (s, 1H), 3.98 (q, 2H), 2.35 (s, 3H), 2.19 (s, 3H), 1.07 (t, 3H)	165.1, 151.163, 148.3, 147.0, 137.7, 129.2, 128.16, 124.7, 120.8, 95.3, 67.9, 59.0, 45.95, 17.64, 14.15, 12.39
2b	3319, 3243, 1703, 1644	9.3 (s, 1H), 7.4-7.5 (m, 6H), 5.315 (s, 1H), 3.512 (s, 3H), 2.23 (s, 3H), 2.20 (s, 3H)	166, 151, 148.69, 148.3, 138.04, 129.8, 128.8, 125.2, 121.1, 96.07, 70.2, 51.42, 46.3, 18.01, 12.717
2c	3319, 3243, 1703, 1644	9.27 (s, 1H), 7.64 (d, 1H), 7.5-7.4 (m, 5H), 5.38 (d, 1H), 2.25 (s, 3H), 2.22 (s, 3H), 2.13 (s, 3H)	196, 153, 151, 148, 138, 130, 129, 125, 120, 107.3, 70.52, 46.67, 31.016, 19.44, 12.9
2d	3219.74, 1702.8, 1684.59	7.8-7.79 (d, 1H), 7.43-7.56 (m, 5H), 5.29 (d, 1H), 3.9-4.0 (q, 2H), 3.18 (s, 3H), 2.49 (s, 3H), 2.17 (s, 3H), 1.07-1.2 (t, 3H)	165, 152, 150, 147.6, 137, 129, 128, 124, 120.25, 98.56, 59.45, 44.75, 29.415, 16.011, 14.08, 12.46
2e	3335.09, 1706.20, 1688.83, 1628.27	7.78 (s, 1H), 7.53-7.47 (m, 5H), 5.303 (s, 1H), 3.59 (s, 3H), 3.18 (s, 3H), 2.49 (s, 3H), 2.17 (s, 3H)	166, 153.2, 151.4, 148.5, 138.05, 129.99, 129.148, 125.5, 120.8, 99.31, 70.38, 51.89, 45.23, 30.23, 16.68, 12.86
2f	3401.7, 2961.7, 2918.3, 2849.7, 1692.5, 1635	7.98 (s, 1H), 7.52-7.43 (m, 10H), 5.47 (s, 1H), 3.6 (t, 2H), 2.3 (s, 3H), 2.0 (s, 3H), 1.07-1.09 (q, 3H)	166, 152.3, 151, 147.7, 140.1, 138.4, 129.2, 128.7, 127.1, 124.2, 119, 118.1, 60.2, 33.2, 14.71, 13.7
2g	3245.8, 2924.1, 2852.3, 1695.6, 1594.6	7.99 (s, 1H), 7.54-7.46 (m, 10H), 5.47 (s, 1H), 3.64 (s, 3H), 2.34 (s, 3H), 2.02 (s, 3H)	165.4, 152.4, 151, 147.8, 139.9, 137.2, 129.5, 128.2, 126.3, 124.1, 128.5, 120, 119.0, 104.4, 58.8, 34.2, 15.2, 8.1

IR (KBr) cm^{-1}: 3398, 3281, 1703; ^{1}HNMR (300 MHz, DMSO-d_6, ppm) δ: 9.29 (s, 1H), 7.56-7.4 (m, 6H), 5.31 (s, 1H), 3.98 (q, 2H), 2.35 (s, 3H), 2.19 (s, 3H), 1.07 (t, 3H); ^{13}C (300 MHz , DMSO-d_6, ppm) δ: 165.1, 151.163, 148.3, 147.0, 137.7, 129.2, 128.16, 124.7, 120.8, 95.3, 67.9, 59.0, 45.95, 17.64, 14.15, 12.39; MS (m/z): 374 (M^+);

Anal. Calcd. for $C_{18}H_{19}N_4O_3$: C, 57.75; H, 5.08; N, 14.97. Found: C, 57.45; H, 5.12; N, 14.81.

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