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ECOFRIENDLY SYNTHESIS OF BIGINELLI PRODUCTS

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ABSTRACT:
A simple and efficient method has been devised for the synthesis of 2-[6-(4-chlorophenyl)-2-oxo-4-(substitutedphenyl)-1,3,4-trihydropyrimidine-5-yl]benzoic acid **(5)** and 2-[6-(4-chlorophenyl)-2-thioxo-4-(substitutedphenyl)-1,3,4-trihydropyrimidine-5-yl]benzoic acid **(6)**, by a one-pot three component cyclocondensation reaction of compound containing active methylene group**,** aromatic aldehydes and urea/thiourea using catalytic amount of fresh lemon juice in refluxing ethanol. The structures of the products were confirmed by IR, ^{1}H and ^{13}C NMR.

KEYWORDS: Aromatic aldehydes, Dihydropyrimidine, lemon juice.

INTRODUCTION:

Pyrimidone and their derivatives are considered to be important for drugs and agricultural chemicals. As it is a basic nucleus in DNA & RNA, it has been found to be associated with diverse biological activities [i]. Pyrimidone derivatives possess several interesting biological activities such as antitumor[ii], antiviral[iii], antifungal, anticancer[iv], antibacterial[v], antiinflammatory[vi], analgesic[vii], antagonist[viii], anti-HIV, antiplatelet, antithrombotic[ix] etc. Logically, we focused our attention on protonation of heteroatom in organic transformation by natural acids. Recently, it was reported that Fresh lemon juice as natural catalyst efficiently catalyzes the Knoevenagel and Biginelli reactions [x]. To our satisfaction we found that the use of stoichiometric amount of Lemon Juice resulted in quantitative yield of the corresponding pyrimidone derivative under reflux condition. However, no result was obtained when condensation is carried without employing catalyst [xi].The acid-catalyzed Biginelli reaction is a rapid and facile method for the synthesis of pyrimidones, which are interesting compounds with potential pharmaceutical applications. Now a day's multicomponent reactions (MCRs) are of increasing importance in organic and medicinal chemistry for various reasons [xii].MCR strategies offer significant advantages over conventional multistep organic synthesis [xiii]. MCR condensations involve three or more compounds reacting in a single event, but consecutively to form a new product, which contains the essential parts of all the starting materials [xiv].

EXPERIMENTAL

Melting points of all synthesized compounds were determined in open capillary tubes on an electro thermal apparatus and are uncorrected. The purity of the compounds was monitored by thin layer chromatography on silica gel coated aluminum plates (Merck) as adsorbent and UV light as visualizing agent. ^{1}H NMR and ^{13}C NMR spectra were recorded on Varian 500 MHz NMR spectrophotometer using $CDCl_3$/DMSO-d_6 as solvent and TMS as an internal standard (chemical shifts in δ ppm).

General Procedure:

Mixture of 2-[2-(4-Chlorophenyl)acetyl]benzoic acid (0.05 mol), Aromatic aldehydes (0.05 mol) and urea/thiourea (0.05 mol) was refluxed on a water bath in ethanol in the presence of catalytic amount of fresh lemon juice. The progress of the reaction was monitored by TLC. After completions of the reaction, the concentrated reaction mixture was cooled and poured onto ice-cold water, solid separated was filtered off, washed with water, dried, and recrystallized from aqueous alcohol to obtain pure compound.

2-[6-(4-chlorophenyl)-2-oxo-4-phenyl-1,3,4-trihydropyrimidine-5-yl]benzoic acid *(*5a)

Yield:68 %; m.p.=212-214 °C : IR (cm^{-1}): 1690(C=O), 1745(C=O), 3350(OH & NH)**,** ^{1}H NMR(δ ppm): 4.2 (1H,s, NH), 5.56 (1H,s,CH), 6.1 (1H,s, NH), 7.2-7.6 (13H, Ar- H), 10.8 (1H,s,OH), , ^{13}C NMR(δ ppm): 66.51(CH), 110.3-138.2 (Ar-C & C=C), 157.3 (C=O), 169.7 (C=O) .

2-[6-(4-chlorophenyl)-2-oxo-4-(p-chlorodphenyl)-1,3,4-trihydropyrimidine-5-yl]benzoic acid *(*5b).

Yield: 64%; m.p.=170-172°C ; IR (cm^{-1}): 1685(C=O), 1740(C=O), 3355(OH & NH)**,** ^{1}H NMR(δ ppm): 4.3 (1H,s, NH), 5.58 (1H,s,CH), 6.3 (1H,s, NH), 7.3-7.7 (12H, Ar- H), 10.9 (1H,s,OH), , ^{13}C NMR(δ ppm): 68.21(CH), 110.3-139.4 (Ar-C & C=C), 158.1 (C=O), 170.5 (C=O)

2-[6-(4-chlorophenyl)-2-thioxo-4-p-methoxyphenyl-1,3,4-trihydropyrimidin-5-yl]benzoic acid (6c)

Yield: 74%; m.p.=130-132°C ; IR (cm^{-1}): 1140 (C-O), 1310 (C=S), 3300 (O-H & N-H), 1750 (C=O), 1390-1620 (-Ar Ring) ^{1}H NMR(δ ppm): 3.0 (1H,s, NH), 3.73 (3H,s,OCH_3), 4.1 (1H,s, NH), 4.56 (1H,s, CH), 6.75-7.91 (12H, Ar- H), 11.0(1H,s,OH), ^{13}C NMR(δ ppm):, 55.70 (OCH_3),61.78(CH), 107.36-143.525 (Ar-C & C=C), 170.477 (C=O). 178.82 (C=S).

2-[6-(4-chlorophenyl)-2-thioxo-4-p-hydroxyphenyl-1,3,4-trihydropyrimidin-5-yl]benzoic acid (6d)

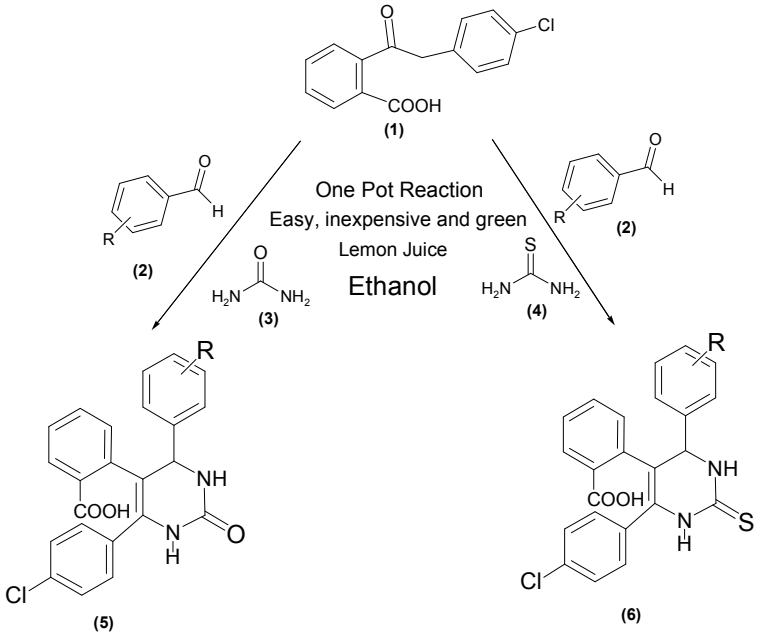
Yield: 76%; m.p.=180-181°C ; IR (cm^{-1}): 1670 (C=O), 1230(C=S), 3330(NH),3450(OH)**,** ^{1}H NMR(δ ppm):, 3.2 (1H,s, NH), 3.8 (1H,s, NH), 4.46 (1H,s, CH), 5.75 (1H,s,OH), 6.95-7.82 (12H, Ar- H), 10.9(1H,s,OH), ^{13}C NMR(δ ppm):, 60.78(CH), 108.35-142.621 (Ar-C & C=C), 171.371 (C=O), 176.73 (C=S).

TABLE I : Characterization data of compounds **5 (Urea derivative)** and **6 (Thiourea derivative)**

Compounds	R	Mol. Formula	m.p. °C	Yield %	Color
5a	H	$C_{23}H_{17}N_2O_3Cl$	212-214	68	White
5b	4-Cl	$C_{23}H_{16}N_2O_3Cl_2$	170-174	64	White
5c	4-OCH_3	$C_{24}H_{19}N_2O_4Cl$	130-132	77	Pale Green

5d	4-OH	$C_{23}H_{17}N_2O_4Cl$	214-216	71	Dark Yellow
5e	3-OCH_3, 4-OH	$C_{24}H_{19}N_2O_5Cl$	145-148	79	Orange
6a	H	$C_{23}H_{17}N_2O_2SCl$	200-202	69	Cream
6b	4-Cl	$C_{23}H_{16}N_2O_2SCl_2$	156-160	80	Light Yellow
6c	4-OCH_3	$C_{24}H_{19}N_2O_3SCl$	130-132	74	Green
6d	4-OH	$C_{23}H_{17}N_2O_3SCl$	150-151	76	Buff
6e	3-OCH_3, 4-OH	$C_{24}H_{19}N_2O_4SCl$	131-133	70	Yellow

Reaction Scheme



RESULTS AND DISCUSSION

The target molecules 2-[6-(4-chlorophenyl)-2-oxo-4-(substitutedphenyl)-1,3,4-trihydropyrimidine-5-yl]benzoic acid **(5) (a-e)** and 2-[6-(4-chlorophenyl)-2-thioxo-4-(substitutedphenyl)-1,3,4-trihydropyrimidine-5-yl]benzoic acid **(6) (a-e)**,were synthesized in good yield by the one pot reaction of aromatic aldehydes, 2-[2-(4-Chlorophenyl)acetyl]benzoic acid and urea/thiourea in refluxing ethanol using few drops of fresh lemon juice as catalyst.

CONCLUSIONS

A number of new pyrimidones were prepared in good yield over a short reaction time, following a facile work-up process. The catalyst is inexpensive, easily available and environmental friendly.

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