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An Efficient, Green synthesis of Ethyl/Methyl 4-(3-Aryl-1-Phenl-1H-Pyrazol-4-yl)-6-Methyl-2-oxo-1,2,3,4-Tetrahydropyrimidine-5-Carboxylates

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Abstract : An efficient, green heterogeneous catalyst was developed for one-pot three component synthesis of Ethyl/methyl 4-(3-aryl-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives by the condensation of aldehydes, acetoacetate, and urea in the presence of 5% WO_3/ZrO_2 heterogenous catalyst under solvent-free condition.

Keywords : One-pot multi componant synthesis, Dihydropyrimidones, pyrazoles, heterogeneous catalyst and WO_3/ZrO_2.

Introduction:

Dihydropyrimidones (DHPMs) and their derivatives have gained importance in medicinal chemistry due to their pharmacological applications such as antimicrobial[1,2], anticancer[3], anti-inflammatory[4], analgesic[4], anti-HIV[5], antihypertensive[6], antimalarial[7] activities. DHPMs were also screened as neuro peptide antagonists[8] for treating anxiety[9], optic nerve dysfunction[10] and antioxidant agents[11]. The DHPMs are most recently emerged as an integral backbone of several drugs used as orally active antihypertensive agents[12-14], calcium channel blockers[15], adrenoceptor selective antagonists[16,17]. Monastrol is a derivative of DHPM, a novel cell-permeable molecule that blocks normal bipolar spindle assembly in mammalian cells and therefore causes cell cycle arrest. On the other hand, Biginelli reaction has been known as an efficient one-pot reaction protocol to preparing Dihydropyrimidinones. The Biginelli reaction was attracted renewed attention and many improved procedures were made towards good reaction conditions, and they involved the use of catalysts/reagents, transition metal–based reagents, ionic liquids, polymer-immobilized reagents, microwaves, and ultrasound irradiation. Despite all of the improved methods, organic synthesis methods still have many drawbacks, such as the use of organic solvents, long reaction times, high costs, low yields, nonsustainable catalysts, and purification issues. Keeping in view the above DHPM biological importance and catalytical procedure, our research group has been making considerable efforts for synthesis of DHPM by using more innovative synthetic protocol, it adopting more eco-friendly approach. Owing the facts mentioned above we haves synthesized ethyl/methyl 4-(3-aryl-1-phenyl-

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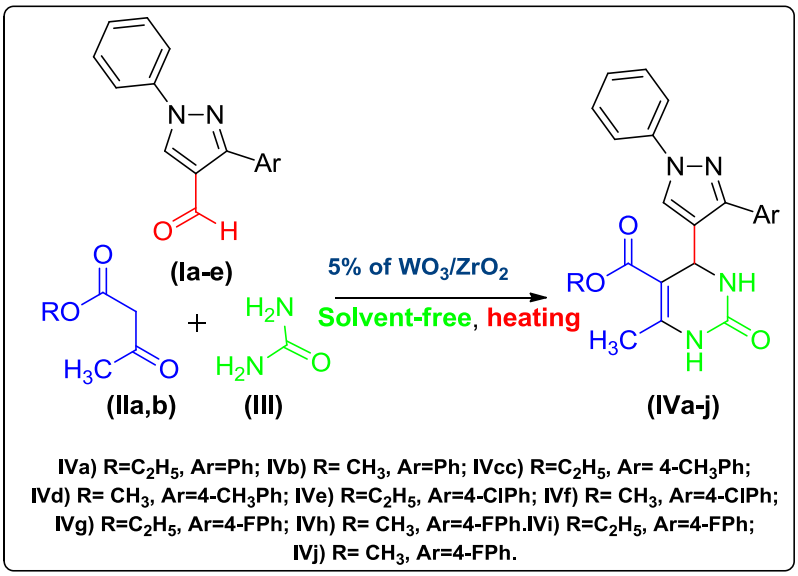
1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate derivatives by the condensation of aldehydes, aceto acetate, and urea in the presence of 5% WO_3/ZrO_2 heterogenous catalyst under solvent-free condition.



Scheme-1: Synthesis of Alkyl4-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVa-n)

Material and method:

The purity of the compounds was checked by TLC using precoated silica gel plates 60254(Merck). ^{1}H NMR spectra were recorded on Bruker Avance II 400 MHz spectrometer using tetramethylsilane as an internal standard. Mass spectra were recorded on a GCMS-QP 1000 EX mass spectrometer.

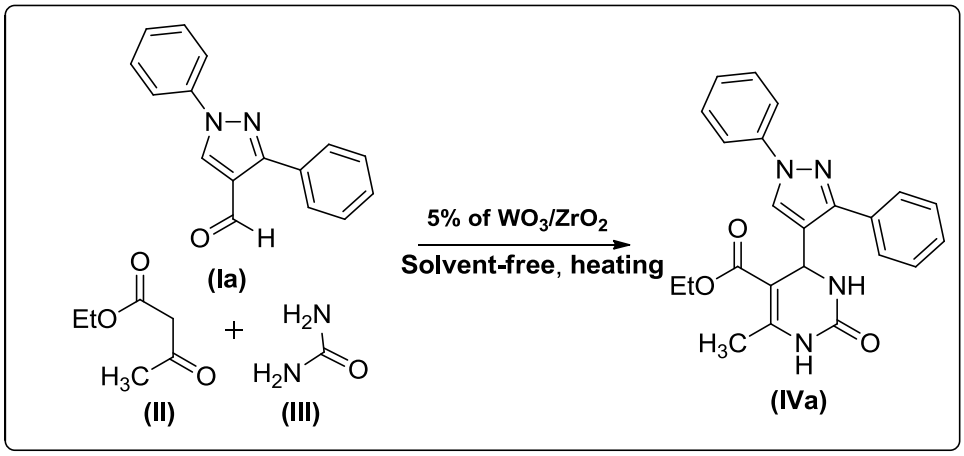
General procedure for the synthesis of Dihydropyrimidines (**IVa-j**):.

A mixture of aldehydes (**Ia-j**) (1 mmol), acetoacetate (**II**) (1mmol), urea (**III**) (1 mmol) and 5% WO_3/ZrO_2 (5 mmol) was taken into round bottom flask and stirring at room temperature for 20-30 min. The progress of the reaction monitored by TLC, after completion of the reaction the crude extracted with dichloromethane twice and the catalyst was separated out. The dichloromethane solvent concentrated under reduced pressure and the compound purified by column chromatography to afford pure Dihydropyrimidines (**IVa-j**)

Result and discussion:

Dihydropyrimidines were synthesized previously by using different reaction methods and catalysts which were associated various drawbacks such as long reaction times, work up complexity, tedious reaction conditions, highly economical with low yields. Hence, the development of new synthetic procedures are essential taking view of this aspect we have developed a new reusable catalyst for the synthesis of Dihydropyrimidines. After several attempt to made synthesis of DHPM more eco-friendly we optimized the catalyst, that resulted 5% WO_3/ZrO_2 under neat condition gave better yields. Generally the DPHM were synthesized by one-pot reaction of aldehyde, ethyl acetoacetate and urea. Initially, our research group was reacted the reactant by using WO_3 and ZrO_2 indifendenlty but gave very low yields of DHPMs. After that our research group focused on synthesis these compound by using heterogeneous catalyst of WO_3/ZrO_2 under different solvent medium like Acetonitrile, water, Chloroform, acetic acid, ethanol, *t*-butanol at room temperature with stirring but the reaction did not give satisfactory yields. Surprisingly, the reaction in solvent-free condition it led to a remarkable improvement in the yield (Table 1). Further, the catalyst was optimized with three different concentrations such as 1%, 5% and 10% of WO_3/ZrO_2 with same reaction condition, higher yields were observed by using 5% WO_3/ZrO_2 (Table 1). As expected, an improvement in the yield and reduction

in the reaction time by increasing reaction temperature but no remarkable change was observed. The synthetic methodology and catalyst has received considerable attention as an inexpensive, eco-friendly, high reactive, easy to handle and nontoxic, affording the corresponding products in excellent yields with high selectivity. The catalyst was active after ten successive reactions.



Scheme-2: Optimization reaction of compound IVa

Table-1: Optimization of catalysts and reaction condition

Entry	Reagent	solvent	Raction time	Yield[a]
1	WO_3	Neat	12	40%
2	ZrO_2	Neat	5	55%
3	WO_3/ZrO_2	Acetonitrile	2.5	60%
4	WO_3/ZrO_2	water	2.5	65%
5	WO_3/ZrO_2	Chloroform	3	62%
6	WO_3/ZrO_2	Acetic acid	2	68%
7	WO_3/ZrO_2	Ethanol	1	64%
8	WO_3/ZrO_2	*t*-butanol	1	62%
9	1% WO_3/ZrO_2	Neat	30 min.	78%
10	**5% WO_3/ZrO_2**	**Neat**	**20 min.**	**88%**
11	10% WO_3/ZrO_2	Neat	20 min.	82%

[a] isolated yield

Spectral data:

Ethyl 4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine -5-carboxylate (IVa): Yield: 88%; m.p. 106 °C; ^{1}HNMR: δ 1.12-1.15 (t, 3H, CH_3), 2.37 (s, 3H, CH_3), 4.07-4.11 (q, 2H, O-CH_2), 5.76 (s, 1H, CH), 7.28-7.31 (m, 3H, ArH), 7.42-7.80 (m, 8H, ArH), 8.09 (s,1H, ArH), 9.15 (s, 1H, NH); MS m/z=403 $[M+H]^+$.

Methyl 4-(1,3-diphenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine -5-carboxylate (IVb): Yield: 85%; m.p. 111 °C; ^{1}HNMR: δ 2.37 (s, 3H, CH_3), 4.08 (s, 3H, OCH_3), 5.57 (s, 1H, CH), 7.27-7.30 (m, 3H, ArH), 7.44-7.82 (m, 6H, ArH), 8.09 (s, 1H, ArH), 9.16 (s, 1H, NH); MS m/z=389 $[M+H]^+$.

Ethyl 6-methyl-2-oxo-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro pyrimidine-5-carboxylate(IVc): Yield: 86%; m.p. 118°C; ^{1}HNMR: δ 0.84-0.88 (t, 3H, CH_3), 2.25 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.88 (q, 2H, OCH_2), 5.37 (s, 1H, CH), 7.39-7.44 (m, 3H, ArH), 7.57-7.59 (d, 2H, ArH), 7.64-7.66 (d, 2H, ArH), 7.70 (s, 1H, NH), 7.78-7.80 (d, 2H, ArH), 8.34 (s, 1H, ArH), 9.18 (s, 1H, NH); MS m/z=417 $[M+H]^+$.

Methyl 6-methyl-2-oxo-4-(1-phenyl-3-(p-tolyl)-1H-pyrazol-4-yl)-1,2,3,4-tetrahydro pyrimidine-5-carboxylate(IVd): Yield: 85%; m.p. 109°C; ^{1}HNMR: δ 2.25 (s, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.92 (s, 3H,

OCH_3), 5.36 (s, 1H, CH), 7.38-7.41 (m, 3H, ArH), 7.55-7.57 (d, 2H, ArH), 7.63-7.65 (d, 2H, ArH), 7.79-7.81 (d, 2H, ArH), 8.35 (s, 1H, ArH), 9.16 (s, 1H, NH); MS m/z=413 $[M+H]^+$.

Ethyl 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVe): Yield: 90%; m.p. 176°C; ^{1}HNMR: δ 0.83-0.86 (t, 3H, CH_3), 2.26 (s, 3H, CH_3), 3.78-7.83 (q, 2H, OCH_2), 5.36 (s, 1H, CH), 7.32-7.36 (m, 2H, ArH), 7.49-7.56 (m, 4H, ArH), 7.77-7.90 (m, 4H, ArH), 8.36 (s,1H, ArH), 9.18 (s,1H, NH); MS m/z=437 $[M+H]^+$.

Methyl 4-(3-(4-chlorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVf): Yield: 88%; m.p. 182°C; ^{1}HNMR: δ 2.26 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.36 (s, 1H, CH), 7.30-7.34 (m, 2H, ArH), 7.45-7.53 (m, 4H, ArH), 7.72-7.85 (m, 4H, ArH), 8.35 (s,1H, ArH), 9.16 (s,1H, NH); MS m/z=424 $[M+H]^+$.

Ethyl 4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVg): Yield: 90%; m.p. 167°C; ^{1}HNMR: δ 0.91-0.95 (t, 3H, CH_3), 2.27 (s, 3H, CH_3), 3.84-3.88 (q, 2H, O-CH_2), 5.42 (s, 1H, CH), 7.17-7.20 (d, 2H, ArH), 7.30-7.36 (m, 3H, ArH), 7.55-7.69 (m, 5H, ArH), 8.89 (s, 1H, ArH) 9.16 (s, 1H, NH); MS m/z=481 $[M+H]^+$.

Methyl 4-(3-(4-bromophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (IVh): Yield: 89%; m.p. 167°C; ^{1}HNMR: δ 2.28 (s, 3H, CH_3), 3.85 (s, 3H, OCH_3), 5.41 (s, 1H, C_4H), 7.18-7.20 (d, 2H, ArH), 7.29-7.34 (m, 3H, ArH), 7.54-7.68 (m, 5H, ArH), 8.86 (s, 1H, ArH) 9.16 (s, 1H, NH); MS m/z=467 $[M+H]^+$.

Ethyl 4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(IVi): Yield: 86%; m.p. 108°C; ^{1}HNMR: δ 0.87-0.91 (t, 3H, CH_3), 2.37 (s, 3H, CH_3), 3.82-3.84 (q, 2H, O-CH_2), 5.37 (s, 1H, CH), 7.19-7.21 (d, 2H, ArH), 7.29-7.33 (m, 3H, ArH), 7.63-7.80 (m, 5H, ArH), 8.65 (s,1H, ArH), 9.18 (s,1H, NH); MS m/z=421 $[M+H]^+$.

Methyl 4-(3-(4-fluorophenyl)-1-phenyl-1H-pyrazol-4-yl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate(IVj): Yield: 85%; m.p. 104°C; ^{1}HNMR: δ 2.36 (s, 3H, CH_3), 3.86 (s, 3H, OCH_3), 5.35 (s, 1H, CH), 7.19-7.21 (d, 2H, ArH), 7.30-7.35 (m, 3H, ArH), 7.59-7.77 (m, 5H, ArH), 8.67 (s, 1H, ArH), 9.17 (s, 1H, NH); MS m/z=407 $[M+H]^+$.

Conclusion:

In conclusion, we have successfully synthesised a series dihydropyrimidines by using an efficient heterogeneous catalyst such as 5% WO_3/ZrO_2 under solvent-free condition. The synthetic method proved to be an easy, simple, gaves higher yields with shorter reaction times, and also more eco-friendly.

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