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A Facile Organocatalysis Protocol for One-pot Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-one Derivatives

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Abstract: A simple and efficient procedure has been described for the synthesis of 3,4-dihydropyrimidin-2-(1*H*)-ones, a multi-component Biginelli reaction from 1,3-dicarbonyl compound and urea with aromatic aldehydes at room temperature condition using organocatalyst N-(4-flourophenyl)-1-tosylpyrrolidine-2-carboxamide (FPTPC). The structures of the synthesized compounds were confirmed by analytical and spectral data.
Keywords: Aldehydes, 1,3-dicarbonyl compounds, Biginelli reaction, dihydropyrimidinones, organocatalyst.

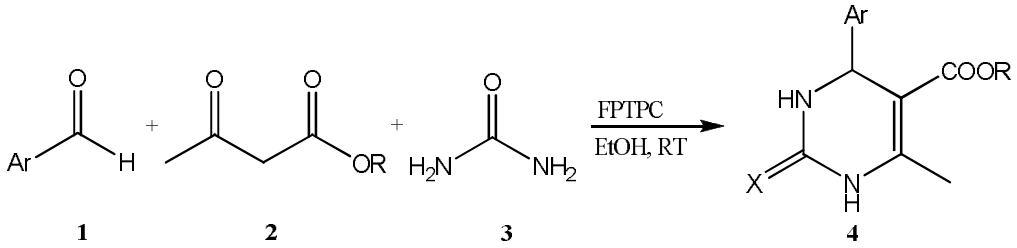
INTRODUCTION:

Dihydropyrimidinones (DHPMs) and their derivatives are one of the prime interest in industry because of their promising biological activities such as calcium channel blockers, antihypertensive agents, neuropeptide-Y (NPY) anatagonists and anticancer drugs.[1-2] Moreover, several marine alkaloids containing the DHPMs as core unit, most notably among them are batnazelladine alkaloid, which have been found to be potent HIV gp-120-CD inhibitors.[3-4]

In 1893 Italian chemist Biginelli synthesized dihydropyrimidinones through one-pot three-component condensation of β-ketoesters, aldehydes and urea in refluxing ethanol containing a catalytic amount of HCl.[5] Among the diversity of available methodologies in the literature that use lithium salts, TMSI, ionic liquids, solid phase, polymer-supported, heterogeneous catalysis by silicas and montmorillonites or activation by ultrasound and microwave energies as synthetic protocols to prepare DHPMs.[6-12]

Basically, most of the methods have been reported using catalyst like $Mn(OAc)_3$[13], $Cu(OTf)_2$[14], VCl_3[15], $Yb(OTf)_3$[16], $Al(HSO_4)_3$[17], $KHSO_4$[18], heteropolyacids[19] Lewis acids, polymer supported catalyst,[20] and Brönsted base (KOH)[21]. In spite of their potential utility some of these methods involve strongly acidic conditions, long reaction times, high temperature and unsatisfactory yields. Obviously, many of these catalysts and solvents are not at all acceptable in the context of green synthesis. Therefore, the discovery of new catalyst for the preparation of 3,4-dihydropyrimidin-2-ones under mild conditions is of prime importance.

Recently, paramount interest has been devoted to the organocatalysis reactions. Amino acid such as, *L*-proline can be regarded as the simplest "enzyme" and in addition to Hajos-Parrish-Eder-Sauer-Wiechert reaction and Aldol reaction, it has been successfully applied to many reactions. *L*-Proline has been also investigated in the catalysis of reduction, oxidation, electrophilic α-fluorination and amination.[22-25] Thus, as a part of our ongoing research towards green synthesis, we have revealed that Biginelli's reaction smoothly proceeds efficiently using *L*-proline derivative N-(4-flourophenyl)-1-tosylpyrrolidine-2-carboxamide (FPTPC) as organocatalyst and producing 3,4-dihydropyrimidin-2(1*H*)-ones in good to moderate isolated yields (Scheme-1).



Scheme 1: Synthesis of 3,4-dihydropyrimidin-2-(1H)-ones.

EXPERIMENTAL:

Melting points were determined in open capillary tube and are uncorrected. The purity of the compounds has been checked by TLC. The IR spectra were recorded on Varian FTIR 640-IR spectrometer. ^{1}H NMR spectra were recorded on Burker 300 MHz spectrometer in $CDCl_3$ as a solvent and TMS as an internal standard. Mass spectra were recorded on Thermo Polaris Q GC/MS mass Spectrometer.

General Procedure for the Synthesis of 3,4-Dihydropyrimidin-2-(1*H*)-ones:

A mixture of benzaldehyde (2 mmol) , 1,3-dicarbonyl compound (2 mmol), urea (3 mmol) and N-(4-flourophenyl)-1-tosylpyrrolidine-2-carboxamide (FPTPC) (0.05 mol%) was stirred at room temperature for appropriate time (as given in Table 1). Reaction was monitored by thin layer chromatography (pet ether: ethyl acetate). After the completion of reaction as indicated by TLC, reaction mixture was poured into crushed ice and stirred well. The resulting precipitate was filtered and washed with water and crystallized from hot ethanol. The compounds are identified from their IR, ^{1}H NMR, ^{13}C NMR and GC-MS spectroscopic data and by comparing their melting points with those reported in literature.

Compound 4a: **IR** (KBr) (ν max, cm^{-1}) 3401, 2998, 2879, 1698, 1601, 1275, 679; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 1.56(t, 3H), 1.81(s, 3H), 4.62 (q, 2H),5.19 (s, 1H), 5.46 (d 1H), 5.89 (s, 1H, NH), 6.58(d, 2H), 6.98(d, 2H); **^{13}C NMR** (300 MHz, CDCl3) δ: 23.12, 24.01, 29.72, 50.00, 62.58, 117.56, 121.81, 127.65, 136.02, 145.14, 153.47, 169.54; **GC-MS** *m/z* 276.16 (M^+). **Elemental Analysis:** $C_{14}H_{16}N_2O_4$: C, 60.86; H, 5.84; N, 10.14; O, 23.16; found: C, 60.80; H, 5.75; N, 10.20; O, 23.18 ; C, 49.01; H, 2.48; N, 7.54.

Compound 4e: **IR** (KBr) (ν max, cm^{-1}) 3381, 3018, 2932, 1728, 1587, 1285, 729; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 1.91(s, 3H), 3.72 (s, 3H), 4.69(s, 1H), 5.69(d 1H), 6.35 (s, 1H, NH), 6.78(d, 2H), 7.13(d, 2H); **^{13}C NMR** (300 MHz, $CDCl_3$) δ: 16.7, 40.0, 54.6, 105.5, 116.9, 125.6, 133.8, 141.3, 147.6, 152.1, 157.1, 170.2; **GC-MS** *m/z* 262.20 (M^+). **Elemental Analysis:** $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68; O, 24.40; found: C, 59.50; H, 5.40; N, 10.72; O, 24.38.

Compound 4h: **IR** (KBr) (ν max, cm^{-1}) 3299, 3026, 2978, 1745, 1558, 1276, 776; **^{1}H NMR** (300 MHz, $CDCl_3$) δ: 1.65(s, 3H), 3.88 (s, 9H), 5.76(s, 1H), 6.03 (s, 1H, NH), 6.85-7.13(m, 3H),; **^{13}C NMR** (300 MHz, $CDCl_3$) δ: 12.16, 49.56, 50.01, 51.20, 63.15, 135.26, 103.26, 108.57, 116.13, 125.37, 135.59, 146.24, 152.26, 163.59, 177.26, 184.90; **GC-MS** *m/z* 306.39 (M^+). **Elemental Analysis:** $C_{15}H_{18}N_2O_5$: C, 58.82; H, 5.92; N, 9.15; O, 26.12; found: C, 58.87; H, 5.89; N, 9.20; O, 26.10.

RESULT AND DISCUSSION:

Herein we report one-pot synthesis of DHPMs using catalytic amount organocatalyst N-(4-chlorophenyl)-1-tosylpyrrolidine-2-carboxamide. The advantage of organocatalysis brought the prospect of a complementary mode of catalysis, with the potential for savings in cost, time and energy, an easier experimental procedure, and reductions in chemical waste. These benefits arise from factors; a) organic molecules are generally insensitive to oxygen and moisture in the atmosphere, so there is no need for special reaction vessels, storage containers and experimental techniques, or for ultra-dry reagents and solvents. b) A wide variety of organic reagents can be used such as amino acids, carbohydrates and hydroxy acids are naturally available from biological sources as single enantiomers.

Furthermore to find the optimal reaction conditions we have performed a model reaction; 4-hydroxybenzaldehyde (2 mmol), ethylacetoacetate (2 mmol) and urea (3 mmole) was stirred at room temperature in the presence of organocatalyst N-(4-flourophenyl)-1-tosylpyrrolidine-2-carboxamide (FPTPC) (0.05 mole%) employing various solvents such as dichloromethane, chloroform, acetonitrile, dimethylformamide and dimethyl sulfoxide but these were found to be less effective (Table 1). It is remarkable that the reaction carried out in ethanol gives excellent yield (89 %) (Entry 4, Table 1).

Table 1: Optimization of reaction using various solvent.

Entry	Solvent	Time (hrs.)	Yield (%)[a]
1	DCM	No reaction	-
2	Chloroform	7.00	trace
3	Acetonitrile	8.00	42
4	**Ethanol**	**4.30**	**89**
5	DMF	6.00	63
6	DMSO	12.00	23

[a]Isolated yield.

In order to compare different catalyst with present organocatalyst, we have done the reaction in ethanol using other Lewis acid such as $ZnCl_2$, $AlCl_3$, Montmorillonite, phenylboronic acid and L-proline; to our surprise we found good result with organocatalyst N-(4-flourophenyl)-1-tosylpyrrolidine-2-carboxamide (FPTPC) (Table 2).

The products obtained were isolated in satisfactory yields by conventional work up. This methodology was effective in the preparation of dihydropyrimidones with uniformly good yields (Table 3). Both analytical and spectroscopic data of all synthesized compounds are in full agreement with the proposed structures.

Table 1: Effect of the different catalyst on synthesis.

Entry	Catalysts	mole%	Time (hrs.)	Yield(%)[a]
1	$ZnCl_2$	0.05	9.00	42
3	$AlCl_3$	0.05	11.30	21
4	Montmorillonite	0.05	8.00	trace
5	Phenylboronic acid	0.05	-	-
6	L-Proline	0.05	6.00	70
7	**FPTPC**	**0.05**	**4.30**	**89**

[a]Isolated yield.

Table 3: Synthesis of 3,4-dihydropyrimidin-2(1*H*)-ones.

Entry	Ar	R	Product	Time (h)	Yield (%)[a]	M. P. (^oC)	
						Obs.	Lit.
01	4-OH-C_6H_4	Et	4a	4.30	89	220	220[4]
02	4-OCH_3-C_6H_4	Et	4b	4.00	83	200	201[4]
03	4-OH, 3-$OCH_3C_6H_3$	Et	4c	4.30	81	255	256[4]
04	3,4-OCH_3-C_6H_3	Et	4d	5.00	80	173	175[4]
05	4-OH-C_6H_4	Me	4e	5.00	87	190	-
06	4-OCH_3-C_6H_4	Me	4f	5.00	79	192	192[12]
07	4-OH, 3-$OCH_3C_6H_3$	Me	4g	4.30	86	225	-
08	3,4- OCH_3-C_6H_3	Me	4h	4.30	78	217	-

[a] Isolated yield.

CONCLUSION:

In summary, we have demonstrated N-(4-flourophenyl)-1-tosylpyrrolidine-2-carboxamide (FPTPC) a organocatalyst can promote the multicomponent Biginelli's reaction efficiently. Besides its simplicity, neutral reaction conditions and use of commercial solvents without previous purifications or drying, this method was effective with a variety of substituted aromatic aldehydes independently of the nature of the substituent in the aromatic ring, representing an improvement to the classical Biginelli's methodology.

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