SYNTHESIS OF DIHYDROPYRIMIDINONES: AN IMPROVED CONDITIONS FOR THE BIGINELLI REACTION

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Abstract: A mild and selective method for the synthesis of dihydropyrimidinones using CBr_4 in methanol in the Biginelli three component cyclocondensation reactions has been developed. Yields are significantly higher than utilizing classical Biginelli reaction conditions.

In the past decades broad ranges of biological activities have been ascribed to partly reduced pyrimidine derivatives[1]. Among these 4-aryl-dihydropyrimidinone derivatives are pharmacologically very important as calcium channel blockers[2], anti hypertensive agents[3], and α_{1a}-adrenergic antagonists[4] and neuropeptide Y (NPY) antagonists[5]. In addition dihydropyrimidinone-5-carboxylate core unit is found in many marine natural products[6] including batzelladine alkaloids, which are found to be potent-HIV gp-120-CD_4 inhibitors. Biginelli reported the first synthesis of various 4-aryl-dihydropyrimidinone derivatives more than a century ago[7] by a simple one-pot condensation reaction of β-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of catalytic amount of acid. However, this one-step protocol often suffers from low to moderate yields (20-50 %) of the desired target molecules, particularly in case of substituted aromatic aldehydes or thiourea is employed[1, 8-11]. This has lead to the recent disclosure of several improved reaction protocols for the synthesis of dihydropirimidinones such as BF_3-OEt_2 in combination with transition metal salts with a proper proton source[12], polyphosphateester[13], acidic clay montmorillonite KSF[14], $Yb(OTf)_3$[15], $InCl_3$[16], $FeCl_3$[17], $LiClO_4$[18] and microwave assisted the Biginelli three component cyclo condensation reaction[19]. However, many of these one-pot procedures are generally required strong protic or Lewis acids, prolonged reaction times and high temperature. Thus, the present study explore the use of CBr_4 in methanol is an alternative method for one-pot Biginelli reaction for the synthesis of dihydropyrimidinones.

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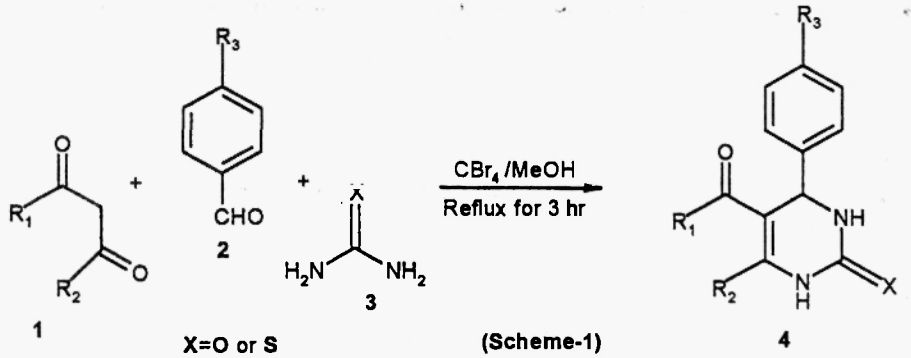
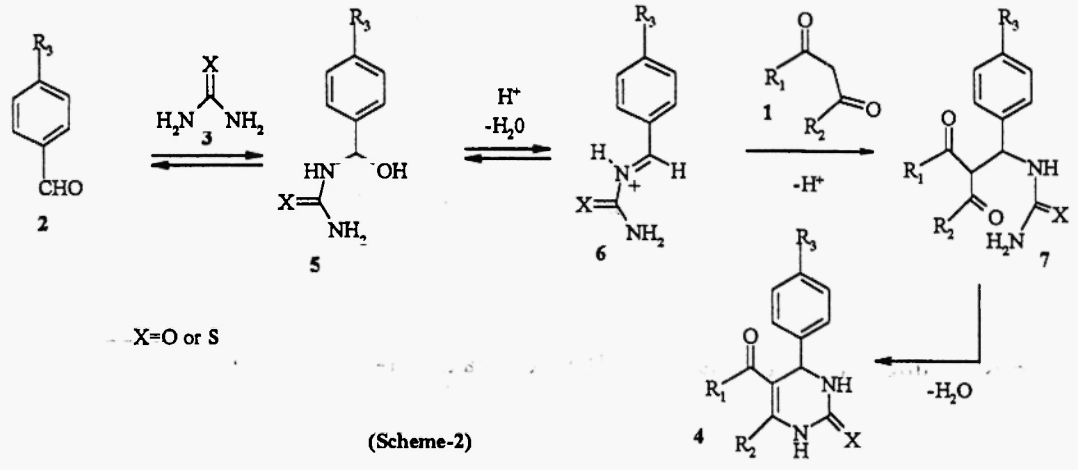
In recent years CBr_4 in protic/non-protic solvent has received considerable attention as a powerful reaction medium for effecting various transformations[20] like chemoselective desilylation of tertiary butyl dimethylsilylethers, chemoselective esterification, deprotection of acetals, ketals, thiols hemithiols and alcohols to alkyl halides. CBr_4 in methanol provides a convenient procedure to carry out the reactions and workup conditions. The occurrence of this reaction may be attributed to the in situ formation of catalytic amount of HBr from CBr_4 in refluxing methanol. In addition, CBr_4 in methanol found to retain its activity even in the presence of nitrogen containing compounds. These special inherent properties of CBr_4 in methanol prompted us to



explore this as an acid catalyst for the synthesis of dihydropyrimidinones.

Here with, we wish to report a simple procedure with high yields using CBr_4 in methanol under reflux conditions (Scheme-1). In order to be able to carry out such Biginelli condensation, we investigated the reaction of β-keto ester (**1**), arylaldehyde (**2**), urea or thiourea- (**3**), employed in a ratio (1.2: 1: 3) using CBr_4 (3.01mmol) in methanol, (10mL) refluxing for 3h to provide dihydropyrimidinones in good to excellent yields. After completion of the reaction, methanol was removed under reduced pressure and water was added to the reaction mixture to precipitate dihydropyrimidinones. The products thus obtained were crystallized from ethyl acetate and characterized by ^{1}H-



NMR, IR and mass spectral data. Apart from its simplicity and less reaction times, this protocol is able to tolerate variations in all of the three building blocks. Several examples illustrating this novel and general method for the synthesis of dihydropyrimidinones are summarized in **Table-I**.

On the basis of these experimental results, it has been suggested that CBr_4 in methanol may generate HBr in situ, which is more acidic than HCl, [20(e)] for utilizing in fast and better efficiency and high purity of the products. The following mechanism has been proposed for the classical Biginelli reaction under acidic conditions (Scheme 2). Addition of urea /thiourea (**3**) to aryl -aldehyde (**2**) leads to hemiaminals of type (**5**) via standard nucleopholic addition[21]. This hemiaminal expected to undergo dehydration in the presence of acid (HBr) to a carbenium ion, which may be formulated as a highly reactive N- acyl iminium ion (**6**). The presence of β-keto ester (**1**) in the reaction medium lead to react with N- acyl iminium ion (**6**) to furnish intermediate (**7**), which than cyclized to the dihydropyrimidinones (**4**).

Table 1. **CBr_4 Catalyzed synthesis of different Dihydropyrimidinones**

Entry	R_1	R_2	R_3	X	Product	Yield (%)[$]
1	C_2H_5O	CH_3	H	O	4a[12]	90
2	C_2H_5O	CH_3	CH_3	O	4b[18]	77
3	C_2H_5O	CH_3	NO_2	O	4c[12]	80
4	C_2H_5O	CH_3	OCH_3	O	4d[12]	92
5	C_2H_5O	CH_3	Cl	O	4e[12]	75
6	CH_3O	CH_3	OCH_3	O	4f[12]	88
7	CH_3	CH_3	OCH_3	O	4g[15]	80
8	CH_3O	CH_3	H	O	4h[12]	83
9	C_2H_5O	CH_3	OCH_3	S	4i	81
10	CH_3O	CH_3	OCH_3	S	4j	86

[$] Isolated yields and all compounds were characterized by study of their ^1H NMR, IR and mass spectral studies.

In conclusion, we have described a novel and improved protocol for the synthesis of dihydropyrimidinones by using CBr_4 in methanol, in the three component condensation of β-ketoester, aldehyde and urea/thiourea reactions which allows the rapid assembly of structurally diverse dihydropyrimidinone derivatives in a good to excellent yields (75-92%).

Experimental section

^1H (200 and 400 MHz) NMR spectra were recorded (in $CDCl_3$+ DMSO- d_6) using TMS as internal standard. IR spectra were recorded on Perkin-Elmer RXI FT-IR spectrophotometers. Mass spectra were recorded on a VG Auto Spec-M instrument.

Typical experimental procedure for 4a: A mixture of benzaldehyde (4.72 mmol), ethylacetoacetate (5.66 mmol) and urea (14.15 mmol) was added to a solution of CBr_4 (3.01 mmol) in methanol (10 ml). The reaction mixture was refluxed for 3h, solvent was removed under reduced pressure, water was added and extracted into ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under vacuum. The crude solid thus obtained was crystallized from ethyl acetate to yield **4a** (1.1 g, 90%). All products were studied under the same reaction condition.

5-(Ethoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine (4i): mp 152-154°C; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): 9.89 (br s, 1H, NH), 9.21 (br s, 1H, NH), 7.18 (d, J =8.6 Hz, 2H arom 2H), 6.8 (d, J =8.6 Hz, 2H, arom 2H), 5.19 (d, J =2.78 Hz, 1H, CH), 4.02 (q, J =7.1 Hz, 2H, OCH_2), 3.78 (s, 3H, arom OCH_3), 2.3 (s, 3H, CH_3), 1.19 (t, J =7.1 Hz, 3H, CH_3); IR (neat) $\nu_{(max)}$: 3210, 1710, 1640, 1540, 1500 cm^{-1}; EIMS *m/z* (%) 306 (M^+, 67), 277 (95), 233 (80), 199 (37), 171 (18), 115 (10), 77(11), 59 (16), 42 (76); Anal. Calcd for $C_{15}H_{18}N_2O_3S$: C, 58.80; H, 5.92; N, 9.14. Found: C, 58.95; H, 5.86; N, 9.25.

5-(Methoxycarbonyl)-4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine (4j): mp 168-170°C; ^1H NMR (400 MHz, $CDCl_3$+DMSO-d_6): 9.15 (br s, 1H, NH), 7.8 (br s, 1H, NH), 7.16 (d, J= Hz, 2H, arom 2H), 6.95 (d, J= Hz, 2H, arom 2H), 5.18 (d, J= Hz, 1H, CH), 3.82 (s, 3H, arom OCH_3), 3.71 (s, 3H, OCH_3), 2.24 (s, 3H, CH_3); IR (neat) $\nu_{(max)}$: 3221, 1705, 1647, 1560, 1495 cm^{-1}; EIMS *m/z* (%)

292(M^+, 2), 251 (71), 172 (29), 76 (99), 59 (7), 42 (72); Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58. Found: C, 57.68; H, 5.48; N, 9.65.

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