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Note

An efficient, simple, one pot synthesis of dihydropyrimidine-2(1H)ones using phosphorus pentoxide

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Phosphorus pentoxide has been found to be a mild and efficient reagent for synthesis of dihydropyrimidones and its corresponding thio-analoges in refluxing ethanol.

Keywords: One pot synthesis, phosphorus pentoxide, dihydropyrimidones

The synthesis of dihydropyrimidones (DHPMs) and their thio-analogues have become popular in the world of synthetic organic chemistry due to their activities such as antibacterial, antiviral, anti-inflammatory, antihypertensive and antitumor[1]. They have been reported to serve as calcium channel blockers[2], as α-1-a antagonists and neuropeptide antagonists[14]. Recently, some marine alkaloids possessing dihydropyrimidine-5-carboxylate core have been shown to exhibit interesting biological activities such as potent HIV-gp-120-CD4 inhibitors as well as anti-HIV agents[13].

The first synthesis reported Biginelli involves a one-pot condensation of an aldehyde, ethyl acetoacetate and urea in ethanolic medium in the presence of strong mineral acid in 1893. However, this method suffered from drawbacks that the lower yields and longer reaction time especially with aliphatic as well as substituted aromatic aldehydes have been observed. The reaction remained ignored almost for a century but with the confirmation that dihydropyrimidones possess diverse and important biological properties, the interest in their synthesis has been greatly increased from last decades. A latter thing gave inspiration to organic chemist to find out more suitable protocol and simple methods for the synthesis of dihydropyrimidones.

Several protocols like PPA, $AlCl_3$, H_3BO_3, conc. HCl, $BF_3.OEt_2$, NH_4Cl, CAN, NBS, triflates of lanthanide compounds and In, Bi, Cu along with microwave irradiation etc. have been tried[6-10] to improve yields and conditions of Biginelli reaction. A few methods involve the use of ionic liquids[12]. However, the multi-step methods lack the simplicity of one-pot methods and are no longer used but for the improvements as one-pot procedures continue with use of different protocols.

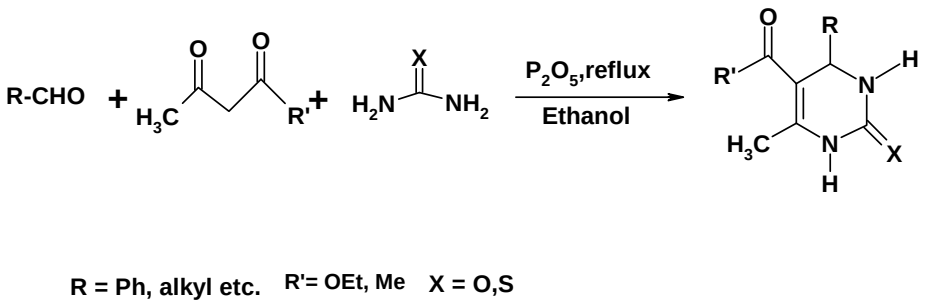
However, out of several methods and those involving different catalyst suffer from drawbacks that the use of expensive reagents like triflate of Bi, Cu, lanthanides etc., prolonged reaction times (Classical Biginelli reaction), and strongly acidic conditions, unsatisfactory yields and tedious workup procedures (e.g. acidic alumina) for the isolation of pure product in good yields. Many catalysts though are effective; their preparation procedures are difficult (e.g. ferric oxide nanocomposites). This requires the development of a new protocol for high yield and the use of inexpensive reagent, which requires shorter reaction time and with easier workup procedure.

Results and Discussion

In the presence of phosphorus pentoxide the Biginelli reaction satisfactorily fulfilled the entire above requirement. Phosphorus pentoxide is an inexpensive reagent, acts as an acid and dehydrating reagent. In Biginelli reaction water molecules formed during the progress of the reaction are absorbed by phosphorus pentoxide and get converted into phosphoric acid. This increases the acidic condition of the reaction mixtures and due to which the rate of the reaction is enhanced, which leads to shorter reaction time. Also, phosphorous pentoxide being soluble in water is easily removed.

In this communication, we report the use of phosphorus pentoxide for the one pot synthesis of **3**, 4-dihydropyrimidones.

As a trial case, benzaldehyde (1.06 g, 10 mmoles) ethyl acetoacetate (1.30 g, 10 mmoles) urea (1.80 g, 30 mmoles) and phosphorus pentoxide (0.5 g, 3.54 mmoles) were mixed thoroughly and the reaction mixture refluxed on the water-bath. After the completion of reaction, the mixture was poured on the crushed ice (100 g), after the stirring the desired dihydropyrimidones separated out as a white solid in quantitative yield (**Scheme I**). The same reaction was



R = Ph, alkyl etc. R'= OEt, Me X = O,S

Scheme I

then attempted with variable quantities of phosphorous pentoxide. However, excess addition of phosphorous pentoxide does not increase the yield of product.

Effect of amount of phosphorous pentoxide on the yield of 3,4-dihydropyrimidin-2(1H)-ones was investigated by using the various amount of phosphorus pentoxide. As per our observation 100 mg of phosphorus pentoxide gives 30-40% yield, 200 mg of phosphorus pentoxide gives 55-60% yield, 300 mg gives 65-70 % yield, 400 mg gives 75-80% yield while 500 mg of phosphorus pentoxide gives 85-95% yield in refluxing ethanol.

Using the optimized quantity of phosphorous pentoxide the reaction was extended to a variety of aldehydes including aromatic, aliphatic as well as heterocyclic aldehydes to afford corresponding dihydropyrimidones in excellent yields.

The versatility of the method was then checked by using thiourea instead of urea to prepare dihydrothiopyrimidones and by replacing ethyl acetoacetate with acetyl acetone, which gave corresponding DHPMs. Both these variations did not affect appreciably the yield as well as ease of workup procedure. All these results are summarized in **Table I**.

Experimental Section

All the compounds are reported one and their melting points are matched with reported value. All the above products have been characterized by proton NMR, IR and ^{13}C. The ^{1}H NMR and ^{13}C NMR spectra were recorded by using DMSO-d_6 solvent on a Brucker 300 MHz spectrometer with tetra methyl silane as an internal standred and IR on a FTIR spectrophotometer. The reaction was monitored by TLC using silica gel 60-F 254 plates.

General procedure

The mixture of an aldehyde (10 mmoles), urea/thiourea (30 mmoles), ethyl acetoacetate/acetyl acetone (10 mmoles) and phosphorous pentoxide (0.5 g, 3.54 mmoles) in 250 mL round bottom flask refluxed on water bath, cooled and the reaction mixture was poured on crushed ice. The separated solid was then filtered, washed with pet ether, dried and recrystallised using ethanol.

Spectroscopic data of representative DHPMs

5-Ethoxycarbonyl-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one (entry-1): m.p 203-204°C (Lit m.p. 204°C) [5c] ; IR (KBr): 3244, 1724, 1647 cm^{-1}; PMR(DMSO-d_6,): δ 1.16 (3H, t, J = 8 Hz, $CO_2CH_2CH_3$), 2.34 (3H, s, CH_3), 4.05 (2H, q, J = 8 Hz, $CO_2OCH_2CH_3$), 5.30(1H, bs, CH), 7.39 (5H, m, ArHs), 6.01 (1H, bs, NH), 8.24 (1H, bs, NH); CMR (DMSO-d_6,): δ 165.33, 152.11, 148.19, 144.78, 128.37,126.22, 99.27, 59.19, 53.83, 38.96, 17.67, 14.02.

5-Ethoxycarbonyl-4-(4-methoxyhenyl)-6-methyl -3,4-dihydropyrimidin-2(1H)-one (entry-2): m.p. 200-201°C (Lit m.p. 199-201°C)[10] ; IR (KBr): 3242, 1705, 1650, 1513, 1340 cm^{-1}; PMR (DMSO-d_6): δ 1.19 (3H, t, J = 7 Hz, $CO_2CH_2CH_3$), 2.32 (3H, s, CH_3), 3.79 (3H, s, OCH_3), 4.06 (2H, q, J = 7 Hz, $CO_2CH_2CH_3$), 5.33(1H, bs, CH), 6.80-6.90 (2H, dd, ArHs), 7.21-7.26 (2H, dd, ArHs), 8.39 (1H, bs, NH), 5.92 (1H, bs, NH) ; CMR (DMSO-d_6): δ 168.37,165.46, 154.57, 150.58, 148.54, 148.41, 129.72, 128.59, 97.77, 38.98, 23.86, 17.60, 13.98

5-Methylcarbonyl-4-(phenyl)-6-methyl-3,4-dihydropyrimidin-2(1H)-thiones (entry-7): m.p. 221-222°C (Lit m.p. 220-22°C) [10] ; IR (KBr): 3247, 3115, 2928, 1720, 1701, 1652 cm^{-1}; PMR (DMSO-d_6): δ 2.42 (3H, s, $COCH_3$), 1.98 (3H, s, CH_3), 5.23 (1H, bs, CH), 7.10-7.8(m, 5H, ArHs), 8.87 (1H, bs, NH), 9.04 (1H, bs, NH).

In conclusion, we have developed a simple, quick and efficient method for the synthesis of

Table I — Data for the synthesis of dihydropyrimidinones in the presence of phosphorus pentoxide

Entry	R	R'	X	Time (hrs)	Yield* (%)	m.p. Obs. (lit)°C
1	C_6H_5	OEt	O	1.0	95	203-204 (204)[5c]
2	4-(CH_3O)-C_6H_4	OEt	O	1.5	94	200-201(199-201)[10a]
3	4-(CH_3O)-C_6H_4	Me	O	1.5	89	166-167(166-168)[10a]
4	4-(CH_3O)-C_6H_4	OEt	S	1.5	92	149-150(150-152)[10a]
5	C_6H_5	OEt	S	1.0	92	206-208 (208-209)[5c]
6	C_6H_5	Me	O	1.2	91	243 (242-244)[4b]
7	C_6H_5	Me	S	1.3	88	221-222(220-222)[10a]
8	2-(Cl)-C_6H_4	OEt	O	1.2	85	215-218(215-218)[4]
9	4-(Cl)- C_6H_4	OEt	O	0.5	94	217-218(216-217)[8c]
10	C_6H_5-CH=CH	OEt	O	1.5	90	231-232 (232)[12b]
11	C_6H_5-CH=CH	OEt	S	1.7	86	224-225(223-225)[8c]
12	4-(NMe_2)-C_6H_4	OEt	O	1.5	87	250-251(250-252)[9a]
13	2-furyl	OEt	O	2.0	75	210-211 (209-211)[8c]
14	nC_3H_7	OEt	O	3.5	76	152 (152-153)[4a]
15	nC_5H_{11}	OEt	O	3.0	73	162-163 (163)[12b]
16	2-(OH)-C_6H_4	OEt	O	2.0	82	200-201(201-203)[10a]
17	4-(NO_2)-C_6H_4	OEt	O	0.5	95	208-209 (207-210)[12c]
18	C_6H_5	OMe	O	1.2	92	206-207(207-210)[12c]

*Yields refer to pure isolated products

Biginelli dihydropyrimidones using phosphorus pentoxide. Apart from its simplicity, the important advantage of the present protocol is the ability to tolerate variations in all the three components of the reaction. To the best of our knowledge, this is one of the quickest, economical and simple alternatives towards the synthesis of 3,4-dihydropyrimidones. This introduces another important use of phosphorous pentoxide in synthetic Organic Chemistry.

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