

Note

Synthesis of 3,4-dihydropyrimidin-2(*IH*)-ones and 3,4,5,6,7,8-hexahydroquinazolin-2(*IH*)-ones *via* three component cyclocondensation

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3,4 Dihydropyrimidin-2(*IH*)-ones and 3,4,5,6,7,8-hexahydroquinazolin-2(*IH*)-ones have been synthesized from the condensation of ketones, aldehydes and urea/thiourea in the presence of sodium tertiary butoxide by the solventless microwave irradiation (MWI) process as well as the conventional process.

Keywords: Sodium tertiarybutoxide, dihydropyrimidinones, cyclohexanone, hexahydroquinazolinones

Beginelli dihydropyrimidines (DHPMs) are reported to be physiologically and pharmacologically important class of compounds which acquired special place in heterocyclic chemistry because of their diversified activities such as antibacterial, antiviral, anti-tumor and anti-inflammatory actions¹. They are also found in many natural products for which their synthesis has attracted a considerable attention in the recent years.

The original Biginelli synthesis was reported by P. Biginelli² which involves refluxing of aldehyde, diketone and urea in ethanolic HCl. Since then a number of improved variants employing new reagents, catalysts, methodologies and technique have emerged. Numerous synthetic methods for the preparation of these compounds have been reported using InCl₃ (ref. 3), lanthanide triflate (ref. 4), BF₃•OEt₂ (ref. 5), PPE (ref. 6a), KSF clay (ref. 6b), LaCl₃ (ref. 7), H₂SO₄ (ref. 8), ceric ammonium nitrate (CAN) (ref. 9), Mn(OAc)₃ (ref. 10), ion-exchange resin¹¹, InBr₃ (ref. 12), FeCl₃ (ref. 13), CdCl₂ (ref. 14), 1-*n*-butyl-3-methyl imidazolium tetrafluoroborate¹⁵, ytterbium triflates¹⁶, SiO₂/NaHSO₄ (ref. 17), BiCl₃ (ref. 18), LiClO₄ (ref. 19), ZrCl₄ (ref. 20), Cu(OTf)₂ (ref. 21), Bi(OTf)₃ (ref. 22), LiBr (ref. 23), NH₄Cl (ref. 24), SnCl₂.2H₂O (ref. 25a), AlCl₃/KI (ref. 25b),

CoCl₂/MnCl₂ (ref. 25c), AlCl₃/AlBr₃ (ref. 25d), P₂O₅ (ref. 26), BiOClO₄.x H₂O (ref. 27), CaCl₂ (ref. 28).

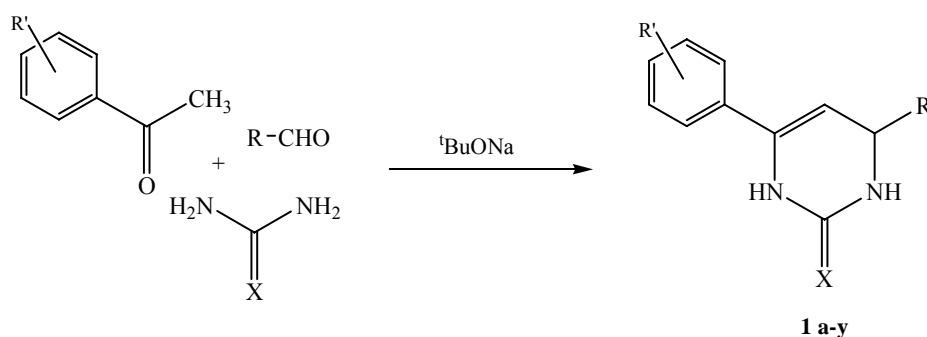
However, most of the reported methods for the preparation of DHPMs have limitations, like, expensive chemicals, tedious work-up, longer reaction time²⁹ and corrosive Lewis acid which required care in handling. Hence, there is need for a versatile, simple and environmentally friendly process for the synthesis of DHPMs, which would enhance the scope of their applications.

Results and Discussion

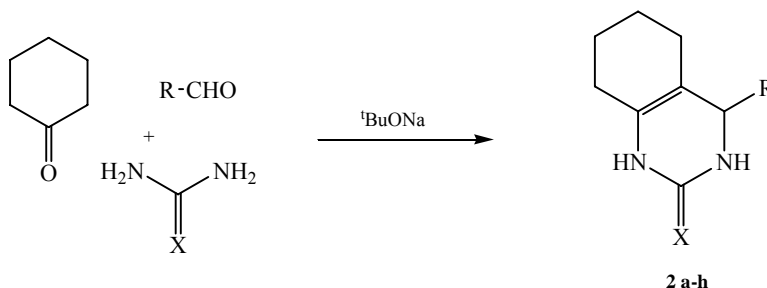
Our literature survey revealed that in almost all the reported methods, DHPMs have been synthesized using diketones or ketoesters as starting materials and the reaction were carried out in acidic medium or in the presence of acid catalysts. A convenient route has been developed for the synthesis of 3, 4-dihydropyrimidin-2(*IH*)-ones or thiones (**Scheme I**) and 3,4,5,6,7,8-hexahydroquinazolin-2(*IH*)-one or thiones (**Scheme II**) starting from enolisable ketones (substituted acetophenones or cyclohexanone) and aromatic aldehydes. The one pot-synthesis of the title compound is achieved *via* chalcone formation, which is generated *in situ* by the condensation of ketones with aromatic aldehydes in the presence of sodium tertiary butoxide followed by the cyclisation with urea or thiourea to give the products in good to excellent yields (**Tables I and II**). The reaction was also carried out under microwave irradiation without using solvent. The results of the conventional process and the MWI process were compared which revealed that the latter gave comparatively higher yields in shorter reaction time (**Table III**).

Experimental Section

The melting points were determined in open capillaries with Kumar's melting point apparatus and are uncorrected. ¹H NMR spectra were recorded on a 400 MHz Varian Mercury Plus instrument using TMS as internal standard in CDCl₃ (chemical shifts in δ, ppm are expressed as downfield from TMS). Mass spectra were recorded on Joel D-30 at an ionization potential of 70 eV. IR spectra were recorded on a Nicolet-410 and spectrum BX spectrometer using



Scheme I



Scheme II

KBr pellet. Elemental analyses were performed on a Hitachi 026 CHN analyzer. All the compounds gave satisfactory elemental analysis within $\pm 0.5\%$ of the theoretical values. All reactions were monitored by TLC on glass plates coated with silica gel (ACME's) containing 13% calcium sulphate as binder and visualization of compounds was accomplished by exposure to iodine vapour or by spraying acidic potassium permanganate solution or by UV Chamber (Labco). Column chromatography was carried out using ACME's silica gel (60-120 mesh).

General Procedure

Conventional Method

To a well stirred solution of sodium tertiarybutoxide (1 g) in acetonitrile or THF, ketone (1 mmole) was added, followed by aldehyde (1 mmole). The mixture was stirred for about 5 min and then urea/thiourea (1.5 mmole) in ethanol was added and the mixture was refluxed for about three to six hrs till the reaction was complete (monitored by TLC). The mixture was then cooled to RT and poured into water with continuous stirring when the solid product separated out. The crude solid product was purified by repeated recrystallisation from alcohol or by column chromatography to give the pure products. (Tables I and II).

Microwave method

A mixture of ketone (1 mmole), aldehyde (1 mmole), urea/thiourea (1.5 mmole) and sodium tertiary butoxide (1 g) was grinded thoroughly and irradiated in a microwave oven at 300 W for about 3 to 4 min at an interval of 30 sec. After the completion of the reaction, (monitored by TLC) the reaction mixture was cooled to room temperature and water was added with stirring when the solid product precipitated out, which was then filtered. The crude product was washed with water and recrystallised from alcohol or purified by column chromatography to give the pure products in good to excellent yields.


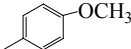
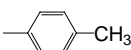
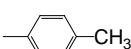


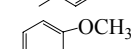
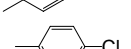
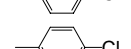
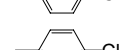
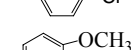



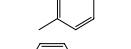
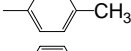
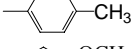
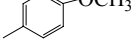
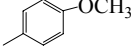






All the products were characterised by melting point, ^1H NMR, IR, mass spectra and CHN analysis.

Spectral data

4-(4-Methoxyphenyl)-6-phenyl-3,4-dihydropyrimidin-2(1H)-one 1b. m.p. 250-53°C; IR: 3337, 1650, 1534 cm^{-1} ; MS (EI): m/z 280 (M^+); ^1H NMR (CDCl_3): δ 3.69 (s, 3H, OCH_3), 5.27 (d, 1H, CH), 5.83 (d, 1H, =CH), 7.11-7.73 (m, 9H, ArH), 8.07 (s, 1H, NH), 9.21 (s, 1H, NH); Anal. Calcd. For $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}$; C, 72.84; H, 5.75; N, 9.99. Found: C, 72.82; H, 5.78; N, 10.02%.


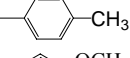
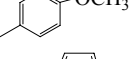


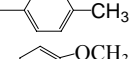
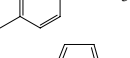

4,6-Diphenyl-3,4-dihydropyrimidin-2(1H)-thione 1q. m.p. 227-31°C; IR: 3300, 3098, 1678, 1577 cm^{-1} ;

Table I — Preparation of 4,6-disubstituted-3,4-dihydropyrimidin-2(*1H*)-ones

Entry	R	R'	X	Product	Yield [#] (%)	m.p. Found (Reported){°C}
1		H	O	1 a	76	233-34 (233-36) ^[25d]
2		H	O	1 b	82	247-49 (248-50) ^[25d]
3		H	O	1 c	79	247-49 (248-50) ^[25d]
4		4-OCH ₃	O	1 d	80	237-40
5		4-CH ₃	O	1 e	81	202-03
6		4-OCH ₃	O	1 f	76	210-13
7		4-Cl	O	1 g	69	260-62
8		4-CH ₃	O	1 h	68	251-52
9		4-OCH ₃	O	1 i	68	263-65
10		H	O	1 j	68	267-68 (267-69) ^[25d]
11		4-OCH ₃	O	1 k	74	229-31
12		H	S	1 l	73	205-07
13		4-CH ₃	S	1 m	66	195-97
14		4-OCH ₃	S	1 n	68	203-04
15		H	S	1 o	74	197-98
16		4-OCH ₃	S	1 p	76	118-19
17		H	S	1 q	78	227-31
18		4-CH ₃	S	1 r	76	116-17
19		4-Cl	S	1 s	68	241-43
20		H	O	1 t	71	224-25
21		4-CH ₃	O	1 u	67	226-28
22		4-OCH ₃	O	1 v	69	253-55
23		4-CH ₃	S	1 w	65	211-13
24		4-OCH ₃	S	1 x	67	242-45
25		H	S	1 y	68	207-09

[#]Yields refer to the pure solid products

Table II — Preparation of 3,4,5,6,7,8-hexahydroquinazolin-2(*IH*)-ones

Entry	R	X	Product	Yield (%) [#]	m.p. (°C)
26		O	2 a	75	163-65
27		O	2 b	64	184-86
28		O	2 c	71	210-13
29		O	2 d	65	190-91
30		S	2 e	69	150-53
31		S	2 f	64	173-75
32		S	2 g	68	197-99
33		S	2 h	70	169-70

[#] Yields refer to the pure solid products

Table III — Comparison between conventional and MWI process

Product	Reaction time		Yield (%)	
	Conventional heating (hr)	Microwave heating (sec)	Conventional heating	Microwave heating
1a	4	180	76	83
1l	4.5	180	73	81
1n	6	240	68	80
1q	6	240	65	78
1y	5	180	67	80
2f	6	240	65	72
2h	6	240	68	75

MS (EI): m/z 296 (M^+); 1H NMR ($CDCl_3$): δ 8.72 (s, 1H), 7.91 (s, 1H), 7.02-7.40 (m, 10H, ArH), 5.89 (s, 1H), 5.48 (s, 1H); Anal. Calcd. For $C_{17}H_{16}N_2O$: C, 72.18; H, 5.26; N, 10.53. Found: C, 72.16; H, 5.23; N, 10.49%

4-(4-Methoxy Phenyl)-3,4,5,6,7,8-hexahydroquinazolin-2(*IH*)-thione 2g. m.p. 197-99°C; IR: 3342, 3016, 1652, 1534, 1213 cm^{-1} ; MS (EI): m/z 274 (M^+); 1H NMR ($CDCl_3$): δ 1.68 (m, 4H, CH_2), 1.96 (m, 4H, $-CH_2-$), 3.89 (s, 3H, OCH₃), 5.82 (s, 1H, CH), 9.97-7.48 (m, 4H, ArH), 7.98 (s, 1H, NH), 9.47 (s, 1H, NH); Anal. Calcd. For $C_{15}H_{18}N_2OS$: C, 65.66; H, 6.61; N, 10.21. Found: C, 65.62; H, 6.65; N, 10.23%.

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