The Biginelli Condensation: A Novel and Efficient Regioselective Synthesis of Dihydropyrimidin-2(1*H*)-ones Using Lithium Bromide

Partha P. Baruah, Sunil Gadhwal, Dipak Prajapati, and Jagir S. Sandhu*
Regional Research Laboratory, Jorhat 785006, Assam, India

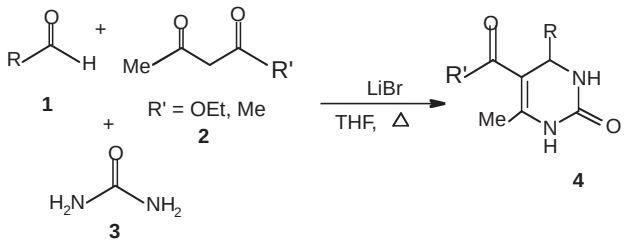
(Received June 17, 2002; CL-020507)

Various substituted 3,4-dihydropyrimidin-2(1*H*)-ones were synthesised in one-pot reaction of aldehydes, β-ketoesters and urea using LiBr in tetrahydrofuran in excellent yields without any side reactions as observed by Biginelli and others.

In recent years attention has been focused particularly on dihydropyrimidinones (DHPMs) which are an important class of compounds due to their therapeutic and pharmacological properties.[1] They have emerged as integral backbones of several calcium channel blockers (e.g., nifedipine), antihypertensive agents and alpha$_1$-a-antagonists,[2] Moreover, alkaloids containing the dihydropyrimidine unit have been isolated from marine sources[3] and among these are the batzelladine alkaloids which were found to be potent HIV gp-120-CD4 inhibitors.[4] This is an impressive profile that bodes well for the interaction of this heterocyclic building block with a variety of biological targets of interests in medicinal chemistry. Thus synthesis of this heterocyclic nucleus is of continuing interest. The most convenient Biginelli's one-pot reaction for the synthesis of DHPMs, first described more than a century ago[1a] (1893) and reviewed[1b] recently, involves condensation of β-dicarbonyl compounds with aldehydes and ureas or thioureas. The reaction is commonly performed in refluxing ethanolic HCl or THF. However the main drawback of Biginelli reaction is low yields in case of substituted aromatic and aliphatic aldehydes[5] and sensitive functional groups are lost during the reaction.[6] Several improvements including combination of Lewis acids with transition metal salts or $BF_3{\cdot}OEt_2$[7] or KSF[8] or $InCl_3$[9] and polyphosphate ester[10] recently mediated Biginelli reaction to greatly improve the yield of the process.[11] But the practical application of these methods suffer from disadvantages such as the use of expensive or less easily available reagents, vigorous reaction conditions, prolonged standing or heating at moderately high temperatures and tedious manipulations in the isolation of the pure products. Consequently there is a need for the development of protocol using readily available and safer reagents which lead to high yields of dihydropyrimidinone derivatives.

Herein we report an efficient advancement of Biginelli reaction using lithium bromide as promoter for the one-pot conversion of 1,3-dicarbonyl compound, aldehyde and urea to dihydropyrimidin-2-(1*H*)-ones. The reaction is complete within 4–6.5 h, workup is simple, the reagents are readily available, the yields are excellent and the method is applicable to aliphatic, aromatic and heterocyclic aldehydes.

In a typical case, a solution of ethyl acetoacetate (1.30 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol) and urea (0.6 g, 10 mmol) in THF (25 ml) was stirred for 5 min at room temperature. To this solution lithium bromide (1.72 g, 20 mmol) was added and the resulting mixture was heated under reflux for



1 2 3 4

Scheme 1.

4 h under nitrogen atmosphere. After completion (monitored by TLC), the reaction was cooled to room temperature and poured into water (200 ml). The solid separated was filtered, washed with water and then recrystallized from isopropanol to afford pure product **4a**, mp 201–202 °C (lit.[12] mp 202 °C) in 96% yield. Similarly other substituted aldehydes, β-dicarbonyl compound and urea are reacted together by this procedure to produce the corresponding dihydropyrimidin-2(1*H*)-ones. The results are summarised in the Table 1. Under this condition, the yields were significantly improved to 80–96% for the classical Biginelli method, and the reaction time was reduced. A number of substituted aromatic, aliphatic and heterocyclic aldehydes have been employed successfully. Acetylacetone has also been employed with similar success as ethyl acetoacetate. This condensation procedure is fairly general and several functional-

Table 1. LiBr-mediated synthesis of dihydropyrimidin-2-(1*H*)-ones

Entry	Product	R	R′	Reaction time/h	Yield[a]/%
1	**4a**	Ph	OEt	4	90
2	**4b**	4-(OCH_3)C_6H_4	OEt	4.5	82
3	**4c**	4-(OH)-C_6H_4	OEt	4	80
4	**4d**	4-(NO_2)-C_6H_4	OEt	4	83
5	**4e**	3-(NO_2)	OEt	6	80
6	**4f**	2,3-(Cl_2)-C_6H_3	OEt	6.5	84
7	**4g**	3,4-(OCH_3)$_2$-C_6H_3	OEt	4	85
8	**4h**	4-(Cl)-C_6H_4	OEt	4.5	80
9	**4i**	Ph	Me	6	95
10	**4j**	4-(Cl)-C_6H_4	Me	6.5	85
11	**4k**	PhCH = CH	OEt	6	80
12	**4l**	2-Furyl	OEt	5	82
13	**4m**	2-Pyridyl	OEt	5	80
14	**4n**	n-Pr	OEt	6	82

[a]Yields refer to pure isolated products, characterised by mp and spectral (IR, ^{1}H NMR, and MS) data.

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ities including nitro, chloro, hydroxy, methoxy and conjugated carbon-carbon double bond do survive during the course of the reaction. Attempts to perform this reaction using β-keto aldehyde in THF for 4 h was fruitless even when a large excess of LiBr was used under refluxing conditions. Further increase of reaction time gave no significant improvement, rather decomposition of starting materials occurred. Also the reaction did not proceed in the absence of lithium bromide. The reaction proceeds effectively with $AlCl_3$, or $CeCl_3$, but do not give comparable results to LiBr. Similarly other salts like KBr or NaBr or LiCl do not give satisfactory results (yield hardly 30–40%). In case of $MgSO_4$ and Na_2SO_4 the reaction does not proceed even after 33 h of refluxing. Roughly 1.5 equivalent of LiBr was found to be sufficient for these reactions and use of less than 1.5 equivalent is not optimal one. The use of large amount of LiBr is also found to be not fruitful i.e. it does not increased the yields. All the compounds obtained were characterised fully by comparison of spectral data (IR, ^{1}H NMR, Mass) and mp with those of authentic samples. Although the detailed mechanism of this reaction is not clear at this stage, it is likely that the reaction may proceed through the acylimine intermediate formed in situ and the subsequent addition of the β-keto ester enolate to the acylimine followed by cyclisation and dehydration as proposed using Lewis-acids.[7,9] Further investigations of the scope and mechanism of the reaction are under way.

In conclusion the present method employing LiBr for the synthesis of various dihydropyrimidine-2(1*H*)-ones provides an efficient advancement of Biginelli's reaction. In addition to its simplicity and selectivity this reaction has one salient feature in its ability to tolerate a variey of aldhydes and constitute a useful alternative to the commonly accepted procedures.

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