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Bromodimethyl Sulphonium Bromide Catalyzed Efficient One Pot Synthesis of 3,4-Dihydropyrimidine-2-(1*H*)-ones: An Improved High Yielding Simple Protocol for The Biginelli Reaction

SOMANATH D. BHINGE†, MD. SAIFUDDIN KHALID‡ and B. SUNIL KUMAR*
Department of Pharmaceutical Chemistry, NET Pharmacy College, Raichur-584 103, India
Fax: (91)(8472)253803; Tel: (91)(8472)271269; E-mail: sunil_bal1@yahoo.co.in

A novel one pot cyclocondensation of aldehyde, β-ketoester and urea or thiourea in acetonitrile by using bromodimethyl sulphonium bromide (BSB) under mild conditions affording 3,4-dihydropyrimidine-2-(1*H*) ones in excellent yield is described.

Key Words: Dihydropyrimidinones, Bromodimethyl sulphonium bromide, β-Ketoesters, Biginelli reaction.

INTRODUCTION

The wide range of pharmacological properties reported for pyrimidines and their derivatives prompted us to undertake the synthesis of the like compounds. These are one of the most important class of compounds possessing a wide spectrum of biological activities[1] such as antiviral, antibacterial and antitumour and antiinflammatory properties[2]. Many of these compounds act as α-1a-antagonist calcium channel[3], antihypertensive agent[4] and neuropeptide Y(NPV) antagonists[5]. Furthermore, several bioactive isolated marine alkaloids were found to contain the 2-amino-1,4-dihydropyrimidiones-5-carboxylate core[6]. The biological activities of some isolated alkaloids have also been attributed to the presence of dihydropyrimidinones moiety in the molecules[7]. Therefore the synthesis of this heterocyclic moiety has gained a immense importance in organic synthesis.

The core structure is commonly built by the reaction between aldehyde, β-ketoester and urea under acidic condition as proposed by Biginelli[8]. This reaction was reinvestigated by replacing the urea by thiourea, to give the 3,4-dihydropyrimidine-2(1*H*)-thione derivatives under the same Biginelli conditions[9]. Consequently, synthesis of these core compounds has gained and plethora of improved synthetic methodologies has recently been reported.

Synthetic strategies for the synthesis of dihydropyrimidinones, first reported by Biginelli, involves the one pot condensation of an aldehyde, β-ketoester and urea under stronger acidic conditions often suffer from low yields of the product

†Department of Pharmaceutical Chemistry, RMESs College of Pharmacy, Gulbarga-585 102, India.
‡Department of Pharmacology, Luqman College of Pharmacy, Gulbarga-585 102, India.

particularly in the case of substituted aromatic and aliphatic aldehyde. Several improved procedures for the synthesis of dihydropyrimidines have recently been reported. Hu *et al.*[10] and Kappe *et al.*[11] reported the use of BF_3,OEt_2/$CuCl_2$ and polyphosphate ester (PPE) medicated variation of the Biginelli reaction giving high yields of dihydropyrimidines, but the reaction requires 15-18 h.

Recently, several methods have been reported for preparing dihydropyrimidines using different Lewis acids such as $BF_3.OEt_2$, $LaCl_3$, $Ca(OTf)_3$, $InCl_3$, $LiClO_4$, $ZrCl_4$, $La(OTf)_3$, $NiCl_2{\cdot}6H_2O$, LiBr, $InBr_3$, $BiCl_3$, $CaCl_3$, CAN, $FeCl_3{\cdot}6H_2O$, TMSCl/NaI and ionic liquids[12] has been employed for this transformations. More recently microwave irradiation clays and I_2 are also reported[13].

However, in spite of their potential utility, some methods suffer from drawbacks like expensive, toxic reagent, longer reaction time and low yields and involve difficult product isolation procedures. Moreover, some of the methods are only practical for aromatic aldehydes. Thus there is still a need for a simple and general procedure for synthesis of dihydropyrimidinones and thiones under simple and mild conditions.

This is novel one pot condensation that are not only preservers the simplicity of Biginelli one pot reaction, but also consistently produces excellent yields of the dihydropyrimidine-2-(1*H*)-ones and thiones.

EXPERIMENTAL

Typical experiment procedure: A solution of aldehyde (1 mmol) β-ketoester (1 mmol), urea or thiourea (1.5 mmol) and bromodimethyl sulphonium bromide (0.1 mmol) in acetonitrile (10 mL) was stirred at 50-55 ºC for a certain period of time as required to complete the reaction (TLC). The solvent was removed under reduced procedure to yield a solid, which was washed thoroughly with water, filtered and recrystallized from ethanol to afford pure product.

RESULTS AND DISCUSSION

One pot reactions of benzaldehyde (**1**) (1 mmol) with β-ketoester (**2**) (1 mmol) and urea or thiourea (**3**) (1.5 mmol) in the presence of bromodimethyl sulphonium bromide in acetonitrile as a solvent at 50-55 ºC resulted in the formation of corresponding dihydropyrimidine (**4a**) (yields 96 %). The reaction was spontaneous, the product precipitating immediately from the reaction medium and complete conversion being achieved within 0.5 to 1.5 h as monitored by TLC. Many pharmacologically relevant substitution patterns on the aromatic ring could be introduced with the high efficiency. Most importantly, all aromatic aldehyde carrying either electron withdrawing or electron donating substituted reacted very well, giving good to excellent yields (Table-1). Aliphatic aldehyde also reacted well with β-dicarbonyl compounds and urea giving the corresponding dihydropyrimidine in good yields.

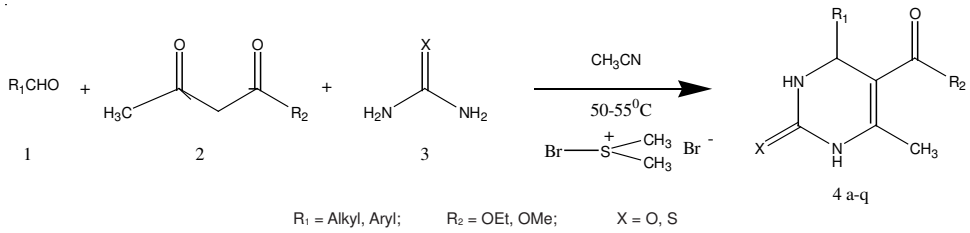

TABLE-1
BROMODIMETHYL SULPHONIUM BROMIDE (BSB)-CATALYZED EFFICIENT SYNTHESIS OF DIHYDROPYRIMIDINE-2-(1*H*)-ONES AND THIONES*

Entry	R_1	R_2	X	Product	Time (min)	Yields (%)**	Ref.
1	C_6H_5	OEt	O	**4a**	30	96	12e
2	C_6H_5	OEt	S	**4b**	40	90	12e
3	4-$NO_2C_6H_4$	OEt	O	**4c**	50	87	12e
4	C_6H_5CH=CH	OEt	O	**4d**	45	80	12e
5	2-Furyl	OEt	O	**4e**	60	75	12e
6	4-$(CH_3)C_6H_4$	OMe	O	**4f**	40	89	12e
7	4-ClC_6H_4	OEt	S	**4g**	60	91	12e
8	4-ClC_6H_4	OEt	O	**4h**	90	93	12e
9	$(CH_3)CH$	OEt	O	**4i**	45	81	12m
10	C_5H_{12}	OEt	O	**4j**	50	80	12e
11	$(CH_3)CH$	OMe	S	**4k**	50	83	13d
12	C_5H_{12}	OEt	S	**4l**	60	80	13d
13	C_6H_5	OMe	S	**4m**	35	93	12o
14	4$(CH_3)C_6H_4$	OEt	O	**4n**	45	91	12e
15	C_6H_5	OMe	O	**4o**	40	94	12e
16	4-$NO_2C_6H_4$	OEt	S	**4p**	70	92	12e
17	2-$(OH)C_6H_4$	OEt	O	**4q**	50	76	12m
18	4-ClC_6H_4	OEt	S	**4r**	45	91	12e

*Yields refer to pure products and all products were characterized by comparison of their physical and spectral data with those of authentic samples.
**All the compounds are known, Structure of the product were confirmed from their spectral (IR ^{1}H NMR and MS) data.

Thiourea has been used with similar success to provide the corresponding dihydropyrimidine-2-(1*H*)-thiones which are also of much interest because of their pharmacological activity.

In conclusion, a simple modification of the Biginelli reaction for the synthesis of dihydropyrimidines and thiones using bromodimethyl sulphonium bromide as an efficient catalyst is developed. The methods offers several advantages including high yields, short reaction times and a simple experimental work-up procedure and direct product isolation in pure form. The product procedure is equally effective for both urea and thiourea and are for aromatic, aliphatic, aldehydes and compatibility with various functional groups are some of the advantage of the present procedure.

The mildness of the method together with ease of operation should largely extend the scope of this, as an alternative reagent system, which is safe, environmentally friendly and inexpensive for the three component Biginelli reaction.

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