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Rapid And Facile One Pot Synthesis Of Dihydropyrimidin-2-Ones

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ABSTRACT

A rapid and solvent free , three component one pot synthesis of dihydropyrimidin-2-ones in the presence of catalytic amounts of(bromodimethyl)sulfonium bromide at ambient temperature in high yields is reported in a shortest time.

KEYWORDS

Dihydropyrimidinones;
(bromodimethyl)
sulfoniumbromide;
Biginelli reaction.

INTRODUCTION

In the main stream of the current interest in one-pot multicomponent reactions that permit a rapid access to combinatorial libraries of organic molecules for efficient lead structure identification and optimization in drug discovery[1], the acid–catalysed condensation of aldehyde, β-ketoester, and urea(or thiourea), known as the Biginelli reaction from the name of its inventor[2] is receiving increased attention[3]. The considerable interest for DHPM-type products stems from their structural similarities to dihydro pyiridines with remarkable pharmacological properties as calcium channel blocker, antihypertensive agents, α_1-1-antagonists. Even marine alkaloids having DHPM core unit were found to show interesting biological activities such as anti-viral, anti-tumor, anti-bacterial and anti-inflammatory activities[5].

A plethora of improved protocols using various types of catalysts[6]and conditions[7] have been reported with the aim of overcoming the main drawbacks of the Biginelli reaction. Yet, these strategies suffer from use of expensive reagents, low yields.

Normally many of these protocols required prolonged reaction times and refluxing conditions.

Therefore, there is a scope for the improvement in terms of yield, time, environmental benignness, inexpensive catalyst and simple conditions. Guided by these points we wish to report a simple, rapid and efficient method for the synthesis of 3,4-dihydro pyrimidin -2(1H)-ones with (bromodimethyl) sulfonium bromide as the catalyst.

The reaction of aldehyde, β-ketoester and urea was carried out in a solvent-less environment in the presence of 10 mol%(bromodimethyl)sulfonium bro-

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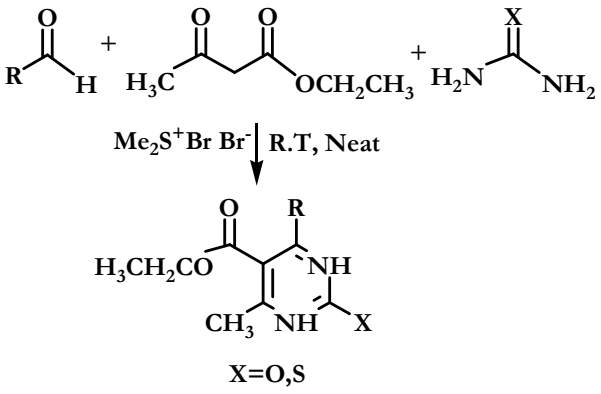

mide at room temperature gave the corresponding dihydropyrimidinones in excellent yields. While preserving the simplicity of the biginelli reaction, the method offers very much-improved yields in a shortest possible time. Many pharmacologically important moieties may be substituted on the aromatic ring with high efficiency under (bromodimethyl) sulfonium bromide[8] catalyzed conditions. Aromatic aldehydes carrying either electron-donating or withdrawing substituents afforded high yields of products in high purity. Acid sensitive aldehydes such as furfural worked well without the formation of any side products. Another important aspect of this method is the survival of a variety of functional groups such as ether, nitro, hydroxy, halide groups under the reaction conditions. Another important feature being that no bromination occurred in aromatic ring as well as on double bond.

Thus, this procedure offers easy access to substituted dihydropyrimidin-2-ones with a variety of substitution patterns under solvent free conditions and catalytic amount of (bromodimethyl)sulfonium bromide at room temperature.

In conclusion we have developed a simple and efficient protocol for the synthesis of dihydro pyrimidin-2-ones using(bromodimethyl) sulfonium bromide which offers several advantages over the other reported catalysts. Other advantages of this method is that it is environmentally benign (solventless) with very short reaction times involving simple workup procedure and no heat energy required which makes it an efficient method for the synthesis of dihydropyrimidinones.

General procedure

A mixture of β-ketoester(2mmol), aldehyde (2mmol), urea or thiourea and(bromodimethyl) sulfonium bromide(10mol%) were stirred for appropriate time(TABLE) at room temperature. After completion of the reaction as indicated by TLC, the reaction mixture was washed with water, the solid obtained was filtered and recrystallised from ethanol to yield pure product.

TABLE

Product	R	X	M.p(oC)	Time(min)	Yield(%)
4a	C_6H_5	O	201	10	93
4b	4-(Me)-C_6H_4	O	171	15	90
4c	4-(OMe)-C_6H_4	O	201	15	97
4d	2,5-$(OMe)_2$-C_6H_4	O	210	15	96
4e	3,4,5-$(OMe)_3$-C_6H_4	O	205	20	94
4f	4-(Cl)-C_6H_4	O	212	10	95
4g	4-(NO_2)-C_6H_4	O	207	20	91
4h	4F-CF_3-C_6H_3	O	202	15	87
4i	4F- C_6H_4	O	175	20	95
4j	4-OH- C_6H_4	O	200	20	95
4k	C_6H_5CH=CH	O	205	20	87
4l		O	204	20	87
4m		O	198	20	85
4n	C_6H_5	S	164	15	92
4o	4F- C_6H_5	S	198	20	88
4p	4-OH- C_6H_5	S	194	20	90

All products gave satisfactory spectral data and are in full agreement with the assigned structures. However few selected new compounds data is provided here under.

Spectroscopic data

4o: M.p. 198^{0}c; ^{1}H-NMR(400MHz) (DMSO-d_6):δ1.18(3H,t, J=7.5Hz, CH_3), 4.00(2H, q, J=7.5Hz, OCH_2), 2.28(3H, s,CH_3), 5.2(1H,s), 6.0(2H, d, J=9.0Hz, Ar-H), 7.40(2H,d, J=9.0Hz Ar-H), 8.80 and 9.4(NH, 2H, S, br)Anal.Calcd.for $C_{14}H_{15}FN_2O_2S$: C, 57.14; H, 5.10 ; N, 9.52 %; found. C, 57.04; H, 4.99; N, 9.50%.

4m: M.p. 204^{0}c; ^{1}H-NMR(400 MHz) (DMSO-d_6) : 1.18(3H, t, J=7.5Hz, CH_3), 4.01 (2H,q, J=7.5Hz, OCH_2), 2.28(3H,s,CH_3,), 5.25 (1H,S) ,6.82-7.45(3H, m, thio-ring), 8.99 (2H, br, NH). Anal. Calcd.for $C_{12}H_{14}N_2O_3S$: C, 54.14; H, 5.26; N, 10.53%; found. C, 54.10 ; H, 5.33 ; N, 10.56%

4h: M.p.202^{0}c; ^{1}H-NMR(400 MHz)(DMSO-d_6): 1.18(3H, t, J=7.5Hz, CH_3), 4.00(2H, q, J=7.5Hz, OCH_2), 2.27(3H, s, CH_3), 5.45(1H, s), 6.98-6.73 (3H,m, Ar-H). Anal.Calcd.for $C_{15}H_{14}F_4N_2O_3$: C, 52.02; H, 4.05; N, 8.09%; found. C, 52.00; H, 4.09;

N, 8.12 %

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