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An Environmentally Friendly Solvent-free Synthesis of 3,4-Dihydropyrimidinones using a *p*-Aminobenzene Sulfonic Acid Catalyzed Biginelli Reaction

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ABSTRACT

Anhydrous *p*-aminobenzene sulphonic acid mediated solvent-free protocol is described for the synthesis of dihydropyrimidinones by the cyclocondensation of aldehydes, β-ketoesters and urea/thiourea. Yields obtained are significantly higher than those obtained utilizing classical Biginelli reaction conditions.

KEYWORDS

Anhydrous *p*-aminobenzene sulphonic acid, 3,4-dihydropyrimidinones, Biginelli reaction

1. Introduction

Multicomponent reactions (MCRs) occupy an outstanding position in organic and medicinal chemistry for their high degree of atom economy, applications in combinatorial chemistry, and diversity-oriented synthesis.[1] The Biginelli reaction,[2] one of the most useful multicomponent reactions, offers an efficient way to access multifunctionalized 3,4-dihydropyrimidinones(DHPMs) and related heterocyclic compounds.[3,4] Such heterocycles (Scheme 1) show a wide scope of pharmacological properties including antiviral, antitumor, antibacterial, and anti-inflammatory activities.[5] Several recently[6] isolated marine alkaloids with interesting biological activities also contain the dihydropyrimidinone-5-carboxylate core. Most notably among these are the batzelladine alkaloids, which have been found to be potent HIVgp-120-CD4 inhibitors.[7] Therefore, many synthetic methods for preparing such compounds have been developed. The first protocol to prepare the compounds of this type was presented by Biginelli in 1893 and involved a three-component, one-pot condensation.[2] A major drawback to Biginelli's original reactions, however, was poor to moderate yields.[8] Recently, many improved procedures have been reported using $InBr_3$,[9] $InCl_3$,[10] $LiClO_4$,[11] $FeCl_3{\cdot}6H_2O$ or $NiCl_2{\cdot}6H_2O$,[12] *p*-TsOH,[13] $LaCl_3{\cdot}7H_2O$,[14] $Bi(OTf)_3$,[15] $La(OTf)_3$,[16] $BF_3{\cdot}OEt_2$,[17] ionic liquids (BMIm·PF_6 and BMIm·BF_4),[18] natural HEU-type zeolite,[19] I_2,[20] *N*-bromosuccinimide (NBS),[21] polyanilinebismoclite complex[22] and other Lewis acids,[23] heteropoly acid,[24] sulphated zirconia,[25] $Sr(NO_3)_2$,[26] NH_2SO_3H,[27] *N*-butyl-*N*,*N*-dimethylphenylethylammonium bromide[28] and covalently anchored sulphonic acid onto silica,[29] CH_3SO_3H supported on Al_2O_3[30], etc. However, many of these reported methods suffer from drawbacks such as low yield of products, harsh reaction conditions, cumbersome experimental procedures, and use of moisture sensitive, toxic and costly catalysts. Therefore, there is a need to develop new catalysts which are easily available or prepared, cost-effective and environment-friendly. Moreover, the work-up procedure should be simpler.

2. Results and Discussion

Anhydrous *p*-aminobenzene sulphonic acid is a mild acid catalyst and this prompted us to use it in the synthesis of 3,4-dihydropyrimidinones from aldehydes with β-ketoester and urea/thiourea. Herein we wish to report the utilization of *p*-aminobenzene sulphonic acid as a catalyst in the one-pot, three-component Biginelli reaction under solvent-free conditions. This method (Scheme 1) not only preserved the simplicity of Biginelli's one-pot procedure but also remarkably improved the yields (>88 %) of dihydropyrimidinones in shorter reaction times (30–60 min) as opposed to the longer reaction times required for other catalysts. The results obtained are summarized in Table 1.

The three-component, cyclocondensation reaction may be performed under relatively simple reaction conditions by heating together the three components, an aldehyde **1**, β-ketoester **2** and urea/thiourea **3**. In order to drive the reaction to completion, generally an excess of one or two of the three components has to be employed. We utilized a 1:1:3 ratio of aldehyde, β-ketoester and urea/thiourea which has previously been employed successfully in the Biginelli reaction.[27] The presence of 0.1 mol of anhydrous p-aminobenzene sulphonic acid as a reaction mediator per mol of the reaction provided higher yields. After the completion of the reaction, as indicated by TLC, the reaction mixture was poured into cool water from which the dihydropyrimidinones were isolated by filtration and recrystallized from methanol or ethanol as indicated in Table 1.

The results presented in the Table 1 indicate the scope and generality of the method, which is efficient for urea or thiourea. An important feature of this method is that electron releasing or withdrawing groups on the aromatic aldehydes give excellent yields. Even for aliphatic aldehydes (e.g. isobutyraldehyde) which normally show extremely poor yields (15 %) in the standard Biginelli reaction, the product could be obtained easily in good yield (88 %).

In summary, this paper discloses a rapid and simple protocol of the Biginelli dihydropyrimidinones synthesis through the use of the readily available *p*-aminobenzene sulphonic acid as catalyst under solvent free conditions. Moreover, excellent yields with short reaction times, no side reactions and easy experimental and product isolation procedures make this an important alternative to other catalysts commonly used in the Biginelli reaction.

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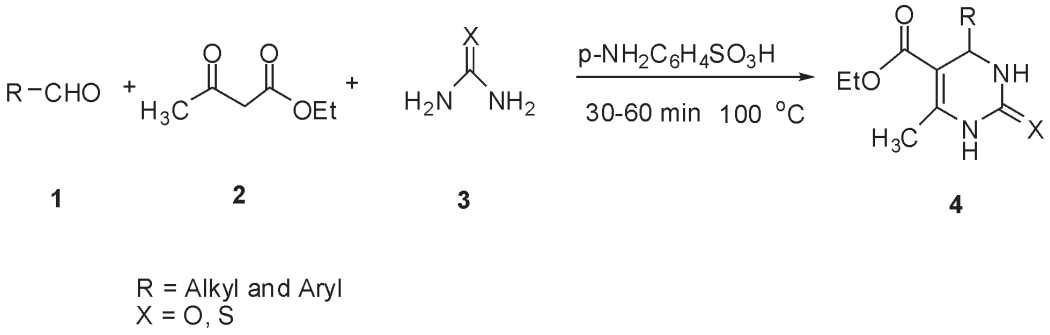

Scheme 1.

3. Experimental

All melting points were determined on a Yanaco apparatus and they are uncorrected. NMR spectra were measured on a Brucker 400 NMR instrument in d_6-DMSO and chemical shifts are expressed as units, TMS being used as an internal standard for ^{1}H NMR, and ^{13}C NMR. IR spectra were determined as KBr pellets on Avatar360 FT-IR spectrophotometer. Elemental analysis was carried out with a Yanaco Chncorder MT-3 Analyzer.

3.1 Preparation of Dihydropyrimidinones 4a–n: General Procedure

A typical procedure is as follows: A mixture of benzaldehyde (1 mmol), ethyl acetoacetate (1 mmol), urea /thiourea (3 mmol), and anhydrous *p*-aminobenzene sulphonic acid (0.1 mmol) was stirred at 100 °C, for an appropriate time (Table 1). On completion of reaction (TLCs, ethyl acetate/hexane), water (30 mL) was slowly added to the reaction mixture and stirring continued for 10 min. The solid that separated was filtered off, washed with hexane, water, and then recrystallized from hot ethanol or methanol to afford pure dihydropyrimidinone, which was characterized by spectroscopic methods. The spectroscopic data for representative 3,4-dihydropyrimidinones are summarized below.

3.1.1. *Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate* (**4a**)

IR (KBr)/cm^{-1} 3244, 3115, 2931, 1719, 1650, 1450, 658, 785; δ_H (d_6-DMSO, 400 MHz): 1.15 (t, 3H, J=7.2 Hz, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.93 (q, 2H, J=7.1 Hz, OCH_2), 5.14 (s, 1H, C*H*), 7.25–7.12 (m, 5H, arom C*H*), 7.74 (s, 1H, N*H*), 9.06 (s, 1H, N*H*); δ_C (d_6-DMSO, 100 MHz): 173.2, 164.1, 142.9, 144.4, 128.4 (2C), 127.5, 126.4 (2C), 100.9, 59.4, 53.6, 17.2, 13.9; Found: C, 64.66; H, 6.21; N, 10.78 %. Anal. Calcd for $C_{14}H_{16}N_2O_3$ (260.29); C, 64.60; H, 6.20; N, 10.76 %.

3.1.2. *Ethyl 6-methyl-4-(3-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate* (**4b**)

IR (KBr)/cm^{-1} 3281, 3116, 2980, 1685, 1650, 1450, 798; δ_H (d_6-DMSO, 400 MHz): 1.07 (t, J=7.2 Hz, 3H, OCH_2CH_3), 2.25 (s, 3H, CH_3), 3.96 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.09 (s, 1H, C*H*), 7.61–7.70 (m, 2H, arom C*H*), 7.87 (s, 1H, N*H*), 8.07–8.36 (m, 2H, arom C*H*), 9.34 (s, 1H, N*H*); δ_C (d_6-DMSO, 100 MHz): 175.3, 165.4, 147.3, 146.6, 146.2, 135.5, 131.9, 123.3, 122.6, 100.6, 60.4, 54.2, 17.6, 14.5; Found: C, 55.06; H, 4.91; N, 13.71 %. Anal. Calcd for $C_{14}H_{15}N_3O_5$ (305.10); C, 55.08; H, 4.95; N, 13.76 %.

3.1.3. *Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate* (**4i**)

IR (KBr)/cm^{-1} 3328, 3174, 2931, 1670, 1650, 1450; δ_H (d_6-DMSO, 400 MHz) 1.10 (t, 3H, J=7.2 Hz, OCH_2CH_3), 2.29 (s, 3H, CH_3), 4.03 (q, 2H, J=7.0 Hz, OCH_2), 5.17 (s, 1H, C*H*), 7.21–7.36 (m, 5H, arom C*H*), 9.64 (s, 1H, N*H*), 10.03 (s, 1H, N*H*); δ_C (d_6-DMSO, 100 MHz): 174.2, 165.1, 144.9, 143.4, 128.5 (2C), 127.6, 126.3 (2C), 100.7, 59.5, 54.0, 17.1, 13.9; Found: C, 60.76; H, 5.81; N, 10.08 %. Anal. Calcd for $C_{14}H_{16}N_2O_2S$ (276.09); C, 60.85; H, 5.84; N, 10.14 %.

3.1.4. *Ethyl 6-methyl-4-(4-methoxyphenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate* (**4j**)

IR (KBr)/cm^{-1} 3314, 3170, 2983, 1668, 1650, 653, 766, 819; δ_H

Table 1 *p*-Aminobenzene sulphonic acid catalyzed synthesis of dihydropyrimidinones under solvent-free conditions.

Entry	R	X	Time/min	Yield/%		m.p./°C
				A	B[b]	Found (reported)
4a	C_6H_5	O	30	96	78 [3]	204–204 (202–204) [3]
4b	3–$NO_2C_6H_4$	O	50	90	51 [3]	226–228 (226–227) [3]
4c	4–$OCH_3C_6H_4$	O	40	95	61 [3]	201–202 (201–202) [3]
4d	4–Cl C_6H_4	O	30	89	56 [17]	212–214 (213–215) [17]
4e	4–$CH_3C_6H_4$	O	50	98	–	170–171(172–173) [17]
4f	3–Cl C_6H_4	O	60	94	56 [17]	192–194 (192–193) [17]
4g	4–$N(CH3)_2C_6H_4$	O	50	98	–	251–254 –
4h	4–OH C_6H_4	O	50	95	66 [3]	224–225 (227–229) [3]
4i	C_6H_5	S	60	88	–	207–209 (208–210) [9]
4j	4–$OCH_3C_6H_4$	S	40	94	–	153–155 –
4k	4–$CH_3C_6H_4$	S	45	90	–	204–206 –
4l	3–$NO_2C_6H_4$	S	60	90	–	205–206 (206–208) [30]
4m	$(CH_3)_2CH$	S	60	88	–	176–178 (176–177) [20]
4n	$CH_3CH_2CH_2$	O	60	90	15 [3]	153–155 (154–156) [27]

[a]Method **A**: new reaction conditions (anhydrous *p*-aminobenzene sulphonic acid).
[b]Method **B**: classical Biginelli conditions (HCl in EtOH).

(d_6-DMSO, 400 MHz): 1.10 (t, 3H, J=7.2 Hz, OCH_2CH_3), 2.29 (s, 3H, CH_3), 3.72 (s, 3H, OCH_3), 4.01 (q, 2H, J=7.2 Hz, CH_2), 5.13 (s, 1H, C*H*), 6.89 (d, 2H, arom C*H*), 7.12 (d, 2H, arom C*H*), 9.59 (s, 1H, N*H*), 1.02 (s, 1H, N*H*); δ_C (d_6-DMSO, 100 MHz): 174.0, 165.1, 158.7, 144.6, 135.6, 127.5 (2C), 113.8 (2C), 100.9, 59.5, 55.0, 53.4, 17.1, 14.0; Found: C, 58.76; H, 5.82; N, 9.21 %. Anal. Calcd for $C_{15}H_{18}N_2O_3S$ (306.10); C, 58.80; H, 5.92; N, 9.14 %.

3.1.5. *Ethyl 6-methyl-2-thioxo-4-p-tolyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate* (**4k**)

IR (KBr)/cm^{-1} 3225, 3174, 2980, 1675, 1650, 1450; δ_H (d_6-DMSO, 400 MHz): 1.10 (t, J=7.3 Hz, 3H, OCH_2CH_3), 2.26 (s, 3H, CH_3), 2.29 (s, 3H, CH_3), 4.01 (q, J=7.0 Hz, 2H, OCH_2CH_3), 5.14 (s, 1H, C*H*), 7.09–7.15 (m, 4H, arom C*H*), 9.60 (s, 1H, N*H*) , 10.29 (s, 1H, N*H*); δ_C (d_6-DMS O, 100 MHz): 174.1, 165.1, 144.8, 140.5, 136.8, 129.0 (2C), 126.2 (2C), 100.8, 59.3, 53.7, 20.6, 17.1, 14.0; Found: C, 61.89; H, 6.24; N, 9.51 %. Anal. Calcd for $C_{15}H_{18}N_2O_2S$ (290.11); C, 62.04; H, 6.25; N, 9.65 %.

3.1.6. *Ethyl 6-methyl-4-(3-nitrophenyl)-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate* (**4l**)

IR (KBr)/cm^{-1} 3177, 2988, 1715, 1650, 1450; δ_H (d_6-DMSO, 400 MHz): 1.12 (t, J=7.2 Hz, 3H, OCH_2CH_3), 2.33(s, 3H, CH_3), 4.03 (q, J=7.2 Hz, 2H, OCH_2CH_3), 5.35 (s, 1H, C*H*), 7.68–8.18 (m, 4H, arom C*H*), 9.78 (s, 1H, N*H*), 10.52 (s, 1H, N*H*); δ_C (d_6-DMSO, 100 MHz): 175.0, 165.3, 148.3, 146.5, 146.0, 133.5, 130.9, 123.2, 121.6, 100.3, 60.3, 54.0, 17.7, 14.4; Found: C, 52.36; H, 4.81; N, 13.01 %. Anal. Calcd for $C_{14}H_{15}N_3O_4S$ (321.08); C, 52.33; H, 4.70; N, 13.08 %.

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