SHORT PAPER

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A simple and efficient synthesis of 3,4-dihydropyrimidin-2-ones catalysed by amidosulfonic acid†

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A general and practical route for the synthesis of dihydropyrimidines by the one-pot cyclocondensation of aldehydes, β-ketoesters and urea is described using NH_2SO_3H as catalyst. Yields and selectivities are significantly better than under classical Biginelli reaction conditions.

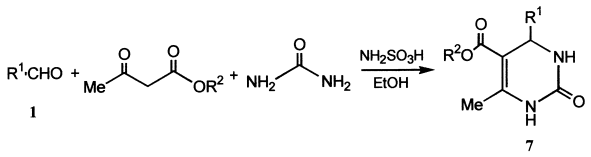
Keywords: Biginelli reaction, dihydropyrimidinones, aminosulfonic acid, synthesis

In the past decade dihydropyrimidines have been the focus of considerable due to their therapeutic and pharmacological properties[1,2]. A wide range of biological effects in the areas of antimicrobial, antiviral, antitumor, antiinflammatory and cardiovascular activities has been established for Biginelli compounds. For example, several functionalised derivatives are used as calcium channel modulators, antihypertensive agents and α_{1a}-antagonists.[3] So, currently the original cyclocondensation reaction has been extended to include variations in all three components allowing access to a large number of multifunctionalised dihydropyrimidine derivatives, and many publications and patents deal with their synthesis.[2-16]

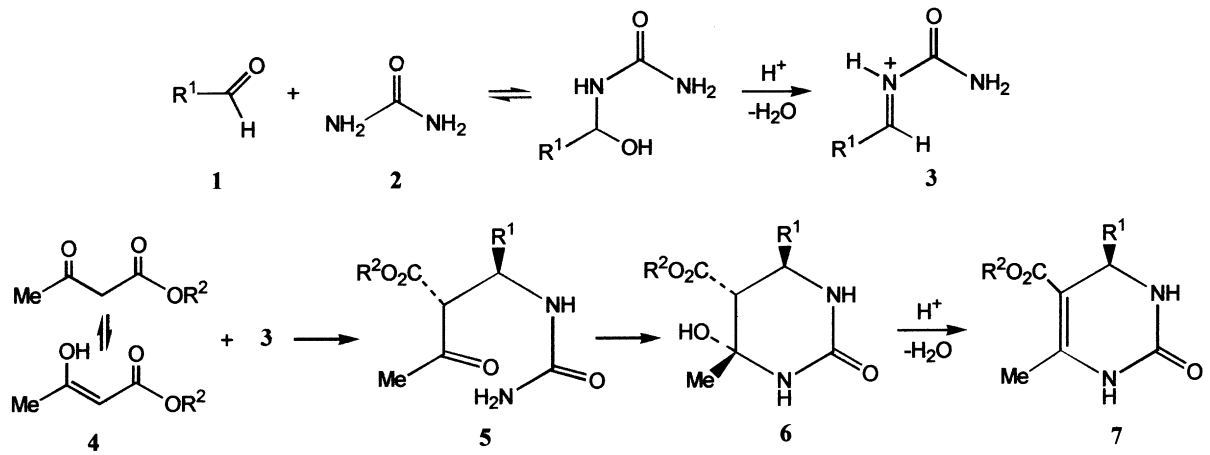
The most simple and straightforward procedure, first reported by Biginelli, involves the one-pot cyclocondensation of a β-ketoester with an aldehyde and urea under strongly acidic conditions.[1,4] One major drawback of this so-called Biginelli reaction is the moderate yields (25–60%) that are frequently encountered when using substituted aromatic and aliphatic aldehydes.[1-6] Although high yields could be achieved by complex multi-step procedures, these methods lack the simplicity of original one-pot Biginelli protocol.[6-8] Within the past few years several modified and improved procedures for the one-step synthesis of dihydropyrimidines have been published. Hu[9] and Kappe[10] reported the use of BF_3. OEt_2/CuC1 and PPE (polyphosphate ester)-mediated variations of the Biginelli reaction, giving high yields of dihydropyrimidines, but the reaction requires 15–18h of reaction time. More recently, montmorillonite-KSF[11], iron(III)[12], and Nafion-H[13] have been employed for this transformation. In addition, there are some other methods such as microwave-assisted[13] and solid-phase synthesis[14]. However, in spite of their potential utility, some methods suffer from drawbacks like longer reaction times, unsatisfactory yields, lower selectivity, and cumbersome product isolation procedures.

Amidosulfonic acid (sulfamic acid, NH_2SO_3H) has been found to be an extraordinarily efficient acid catalyst. This prompted us to use it in the synthesis of 3,4-dihydropyrimidin-2-ones from aldehydes with β-ketoester and urea. In this paper we report a practical and simple approach to this cyclocondensation catalysed by NH_2SO_3H in refluxing ethanol. (Scheme 1).

This is a novel proton source that not only preserves the simplicity of Biginelli's one-pot reaction but also consistently produced 80–90% yields of the dihydropyrimidin-2-ones. The



Scheme 1



Scheme 2

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† This is a Short Paper. There is therefore no corresponding material in *J Chem. Research (M).*

Table 1 Dihydropyrimidines (DHPMs): synthesis catalysed by NH_2SO_3H

Entry	R^1	R^2	Reaction time/h	Selectivity/ %[c]	Yields/%[d] A[a]	B[b]	M.P./°C Found	Reported[4]
1	C_6H_5	Et	3	95	90	78[4]	203–204	202–204[4]
2	4-$OCH_3C_6H_4$	Et	1	94	91	61[4]	201–203	201–203[4]
3	4-OHC_6H_4	Et	4	92	79	66[4]	225–227	227–229[4]
4	3-$NO_2C_6H_4$	Et	4	85	86	51[4]	226–228	226–227[4]
5	4-$NO_2C_6H_4$	Et	2	89	86	58[4]	209–210	208–211[4]
6	3-ClC_6H_4	Et	1.5	93	87	56[17]	193–194	192–193[17]
7	4-ClC_6H_4	Et	2	91	80	56[9]	212–214	213–215[9]
8	3,4-$(OCH_2O)C_6H_3$	Et	2	92	72	49[4]	187–188	187–188[4]
9	3-OCH_3-4-OH-C_6H_3	Et	2	88	84	42[4]	232–233	232–233[4]
10	$CH_3CH_2CH_2$	Et	3	92	87	15[15]	154–156	153–155[15]
11	$CH_3(CH_2)_4CH_2$	Et	3	90	89	–	152–153	–
12	C_6H_5	Me	2.5	94	86	49[9]	210–212	209–212[9]
13	4-(OCH_3)-C_6H_4	Me	0.5	98	96	28[9]	194–195	192–194[9]
14	4-(Cl)-C_6H_4	Me	3	92	78	56[9]	203–205	204–207[9]
15	4-(NO_2)-C_6H_4	Me	4	84	73	41[9]	236–238	235–237[9]
16	$CH_3CH_2CH_2$	Me	3	96	92	–	165–166	–
17	$CH_3(CH_2)_4CH_2$	Me	3	91	88	–	149–151	–

[a]Method A, new reaction conditions (NH_2SO_3H in EtOH).
[b]Method B, classical Biginelli conditions (HCl in EtOH)[1,18].
[c]Selectivity (%)= (**7** yield / **1** conversion) × 100%.
[d]Yields (%), pure isolated products based on aldehydes.

various dihydropyrimidinones which have been prepared are listed in Table 1, and are under examiniation to ascertain their physiological behaviour.

We consider that the mechanism is similar to that of Kappe[5] for the classical Biginelli reaction (Scheme 2) regarding an *N*-acyliminium ion of type **3** as the key intermediate. Interception of iminium ion **3** by β-ketoester **4** produces open-chain ureide **5**, which subsequently cyclises to the dihydropyrimidine (**5** → **6** → **7**). The first step in this mechanism evidently involves the acid-catalysed formation of an N-acyliminium ion precursor of type **3** from an aldehyde and urea component. The second step (**3** → **5**) can be regarded as addition of a π-nucleophile, *i.e.* the enol tautomer of acetoacetate **4**, to the electrodeficient *N*-acyliminium species **3**. In order to promote conditions that would favour the formation and interception of such an iminium ion in the Biginelli reaction, thereby minimising side reactions, we have investigated a variety of reaction conditions (such as ZrO_2–$S_2O_7^{2-}$/EtOH, ZrO_2–SO_4^{2-}/EtOH, $TiC1_4$–K–10/EtOH), and one of the most efficient reagents tested proved to be NH_2SO_3H. The success of the NH_2SO_3H/EtOH method may be the result of specific interaction of NH_2SO_3H with the *N*-acyliminium ion intermediates of type **3** that is well established.

In order to drive the reaction to completion, generally an excess of two of the three components has to be employed. We utilise 1 : 1.2 : 1.5 ratio of aldehyde, β-ketoester and urea in a one-pot condensation using refluxing EtOH as solvent which has previously been employed successfully in the Biginelli reaction.[3a,6,12,15,16] The presence of 0.5mol of NH_2SO_3H as a reaction mediator per mol of the reaction provided higher yields. After the reaction was completed the dihydropyrimidinones precipitated from the reaction mixture. Even for aliphatic aldehydes (*e.g.*, butyraldehyde) which normally show extremely poor yields (15%) in the standard Biginelli reaction[15], the product could be obtained easily in good yield (87%).

We find that the present procedure gives reproducibly high yields and needs much shorter reaction times than with KSF (10–48h)[11] or other catalysts, the reaction being completed within 0.5–4h. For example, entry **1**, with KSF catalyst and heating for 48h, the product was obtained in 72% yield. However, our procedure with NH_2SO_3H catalyst and heating for 3h gave it in 90% yield. The crude products could be easily obtained by filtration or evaporation of the solvent and washed with EtOH and water, and no crystallisation or chromatographic purification is necessary.

Another benefit of the NH_2SO_3H process is that in the reaction system there is no other side reaction, compound **7** being obtained with high selectivity (84-98%).

In summary, this paper discloses a rapid and simple protocol of the Biginelli dihydropyrimidine synthesis through the use of the readily available NH_2SO_3H as reaction mediator. Moreover, excellent yields with short reaction times, no side reaction, a non-corrosive medium, and easy experimental and product isolation procedures make this an important alternative to the classical catalyst.

Experimental

^{1}H NMR spectra of the products were measured on a Varian VXR-300S spectrometer using $CDC1_3$ or CD_3SOCD_3 as solvent. Melting points were determined using a Thomas-Hoover capillary melting point apparatus.

General procedure for the synthesis of dihydropyrimidinones: A 25ml round-bottom flask fitted with a reflux condenser was charged with aldehyde (1 mmol), β-ketoester (1.2 mmol), urea (1.5 mmol), NH_2SO_3H (0.5 mmol), and EtOH (10ml). The mixture was heated to reflux (78°C) for 0.5–4 h and the progress of the reaction was monitored by TLC. After completion of the reaction the solution was cooled to room temperature and the resulting suspension was filtered. The collected solid was rinsed with toluene and water, then dried in vacuum at 40°C to afford the desired product as a white crystalline solid.

Data for entry **5:** IR (KBr) 3230, 3109, 2977, 1701, 1641, 1591, 1520 cm^{-1}; ^{1}H NMR (300Hz, DMSO-d_6) δ9.37 (s,N*H*), 8.20 (d, 2H, *J* = 8.7 Hz), 7.91 (d, 1H, *J* = 2.5 Hz), 7.50 (d, 2H, *J* = 8.7 Hz), 5.27 (d, 1H, *J* = 1.6 Hz), 3.98 (q, 2H, *J* = 7.1 Hz), 2.25 (s, 3H), 1.09 (t, 3H, *J* = 7.1 Hz); HRMS calcd for $C_{14}H_{15}N_3O_5$ (M^+) 305.1012, found 305.0980.

For entry **11:** IR (KBr) 3249, 3156, 2789, 1728, 1707, 1656 cm^{-1}; ^{1}H NMR (300Hz, $CDC1_3$) δ8.50 (1H, s, N*H*), 7.31 (1H, s, N*H*), 4.1–4.4 (1H, m, C*H*), 3.58 (3H, s, CH_3O), 2.34 (3H, s, CH_3), 1.10–1.48 (10H, m, $CH_3(CH_2)_4CH_2$), 0.90 (3H, t, $CH_3(CH_2)_4CH_2$); Anal. Calcd for $C_{14}H_{24}N_2O_3$: C 62.66, H 9.01, N 10.44: found C 62.54, H 9.10, N 10.31.

For entry **16:** IR (KBr) 3249, 3160, 2782, 1732, 1707, 1493 cm^{-1}; ^{1}H NMR (300Hz, $CDC1_3$) δ7.89 (1H, s, N*H*), 7.16 (1H, s, N*H*), 5.6 (1H, m, C*H*), 3.68 (3H, s, CH_3O), 2.25 (3H, s, CH_3), 1.27–1.56 (4H, m, $CH_3CH_2CH_2$), 0.86 (3H, t, $CH_3(CH_2)_4CH_2$); Anal. Calcd for $C_{10}H_{16}N_2O_3$ C 56.59, H 7.60, N 13.20; found C 56.47, H 7.56, N 13.11.

For entry **17:** IR (KBr) 3251, 3178, 2803, 1707, 1654, 1489 cm^{-1}; ^{1}H NMR (300Hz, $CDC1_3$) δ7.87 (1H, s, N*H*), 7.19 (1H, s, N*H*), 5.62

(1H, m, C*H*), 3.64 (3H, s, CH_3O), 2.26 (3H, s, CH_3), 1.29–1.58 (10H, m, $CH_3(CH_2)_4CH_2$), 0.87 (3H, t, $CH_3(CH_2)_4CH_2$); Anal. Calcd for $C_{13}H_{22}N_2O_3$: C 61.39, H 8.72, N 11.01; found C 6121,m H 8.79, N 10.92.

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