Biginelli condensation of aliphatic aldehydes catalysed by zinc methanesulfonate

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Three-component condensation of an aliphatic aldehyde, 1,3-dicarbonyl compound and urea proceeds efficiently in absolute ethanol under refluxing temperature using zinc methanesulfonate as a catalyst to afford corresponding 3,4-dihydropyrimidinone. The catalyst can be reused for several times without distinct decrease in reaction yields. The procedure is very useful for the synthesis of dihydropyrimidinones with a wide range of aliphatic aldehydes.

Keywords: dihydropyrimidinones, zinc methanesulfonate, aliphatic aldehydes, green catalyst

Dihydropyrimidinones (DHPMs) are an important class of heterocyclic compounds having important biological activities. They are reported to serve as the integral backbones of several calcium channel blockers, antihypertensive agents and α_1-1-a-antagonists.[1] Most notably among these are the batzelladine alkaloids, which have been found to be potent HIVgp-120-CD4 inhibitors.[2] One of the most important methods for synthesising this class of compounds is one-pot condensation of 1,3-dicarbonyl compound with aldehydes and urea, first reported by Biginelli in 1893, using HCl as catalyst often affords unsatisfactory yields (20–50%).[3]

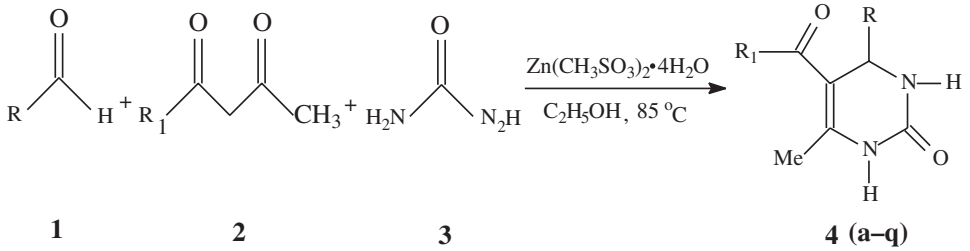
Because of the intense interest in the biological activity of these compounds, several improved procedures over the original Biginelli reaction were reported either by modifying the classical one-pot condensation or by extending the range of the reagents. Basically, the improved methods are all similar, using $LaCl_3{\cdot}7H_2O$,[4] $InBr_3$,[5] $Mn(OAc)_3{\cdot}2H_2O$,[6] $ZrCl_4$,[7] VCl_3,[8] LiBr,[9] $NbCl_5$,[10] $Sm(NO_3)_3{\cdot}6H_2O$,[11] $CdSO_4{\cdot}8H_2O$,[12] CAN[13] *etc*. as catalysts in a solvent such as CH_3CN, EtOH or HOAc. However, many of these methods are mainly concerned on aromatic aldehydes, there are few data relating to aliphatic aldehydes, whose DHPMs derivatives exhibit important biological activity. It is a pity that aliphatic aldehydes normally show poor yields in the Biginelli reaction. Therefore, to find a protocol for the preparation of DHPMs derived from a wide range of alkyl aldehydes in high yields is expected.

The catalysts that can be recovered and reused draw more attention in terms of environmental problems. We have reported Cu methanesulfonate catalysed esterification efficiently and can be reused for several times without any decrease in reaction yields.[14] In this paper, we describe a simple, convenient and high yielding protocol for the synthesis of DHPMs with a broad range of structurally diverse 1,3-dicarbonyl compounds (ethyl acetoacetate, methyl acetoacetate and pentanedione), urea and aliphatic aldehydes in presence of reusable $Zn(CH_3SO_3)_2{\cdot}4H_2O$ (10 mol%) in absolute ethanol under refluxing temperature (Scheme 1). The results are listed in Table 1.

In Table 1, all the three-component reactions proceeded smoothly and efficiently to give corresponding DHPMs. Both primary and secondary aldehydes participate well in the reactions. Besides β-keto esters, pentanedione was also employed to produce a variety of DHPMs. Most importantly, $Zn(CH_3SO_3)_2{\cdot}4H_2O$, the catalyst for the Biginelli reaction, can tolerate the presence of water in media with no sign of deactivation. For compounds **4a**, they derived from 36% aqueous formaldehyde and paraformaldehyde, respectively. The yields and purity of them are similar under the same experimental conditions. And for compound **4k**, it derived from 40% aqueous acetaldehyde. The results show the catalytic activity of $Zn(CH_3SO_3)_2{\cdot}4H_2O$ did not decrease in presence of water. Therefore, $Zn(CH_3SO_3)_2{\cdot}4H_2O$ is a water-tolerant catalyst for the Biginelli reaction.

In the case of products **4a** and **4d**, the m.p. of them are different from the literature reports. In order to ascertain the proper m.p., products **4a** and **4d** were synthesised using other catalysts such as $(NH_4)_2Ce(NO_3)_6$, praseodymium methanesulfonate and neodymium methanesulfonate under the same conditions. The results show the m.p. of the products are still in the range 256–258 °C and 179–180 °C, respectively. The molecular weight of the compound **4a** and **4d** measured by vapour pressure osmometry are 181 and 230, which are close to the calculated value 184 and 226. And the characterisation of IR, ^{1}H NMR and elemental analysis described below also confirms the formation of products. So we consider the proper m.p. of compound **4a** and **4d** are 256–258 °C and 179–180 °C, respectively.

Taken the synthesis of product **4c** as example, the reusability of $Zn(CH_3SO_3)_2{\cdot}4H_2O$ in the Biginelli reaction has been tested. Firstly, the experiment was carried out under refluxing conditions without catalyst for 2h. No reaction proceeds almost. When the reaction was catalysed by $Zn(CH_3SO_3)_2{\cdot}4H_2O$ under identical conditions, the yield of the product **4c** raised up to 77%. After reaction, the mixture was poured into ice water. The product **4c** precipitated was isolated by simple filtration. The catalyst remaining in the aqueous phase could be recovered



1 **2** **3** **4 (a–q)**

Scheme 1

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Table 1 $Zn(CH_3SO_3)_2{\cdot}4H_2O$ catalysed synthesis of dihydropyrimidinones

DHPMs	R	R_1	Time/h	Yield/%[a]	M.p./ °C	
(**4**)					Found	Reported
4a	H[b]	C_2H_5O	7	64	256–258	242–244 (dec.)[5]
	H[c]	C_2H_5O	7	66	256–258	242–244 (dec.)[5]
4b	CH_3	C_2H_5O	9	78	185–187	186–188[15]
4c	CH_3CH_2	C_2H_5O	2	77, 75, 74, 71[d]	179–181	179–181[11]
4d	$CH_3(CH_2)_2$	C_2H_5O	2	82	179–180	153–155[16]
4e	$(CH_3)_2CH$	C_2H_5O	2	60	195–197	195–196[17]
4f	$CH_3(CH_2)_5$	C_2H_5O	2	60	154–155	152–153[18]
4g	$CH_3(CH_2)_6$	C_2H_5O	2	81	118–119	–
4h	CH_3	CH_3	9	55	186–188	–
4i	CH_3CH_2	CH_3	5	50	173–175	–
4j	$CH_3(CH_2)_2$	CH_3	5	63	151–152	151–152[11]
4k	H[c]	CH_3O	9	52	253–255	–
4l	CH_3	CH_3O	9	56	167–169	–
4m	CH_3CH_2	CH_3O	7	75	184–185	184–185[11]
4n	$CH_3(CH_2)_2$	CH_3O	3	74	174–175	174–175[11]
4o	$(CH_3)_2CH$	CH_3O	7	63	216–218	–
4p	$CH_3(CH_2)_5$	CH_3O	4	72	149–151	149–151[18]
4q	$CH_3(CH_2)_6$	CH_3O	4	76	128–130	–

[a]Isolated yields after recrystallisation.
[b]Using 36% aqueous formaldehyde.
[c]Using paraformaldehyde.
[d]Catalyst was reused four times.

by evaporating the filtrate. Then the recovered catalyst was reused for subsequent reactions, little decrease in catalytic activity was observed, demonstrating that $Zn(CH_3SO_3)_2{\cdot}4H_2O$ is a "green" catalyst for the Biginelli condensation.

The mechanism of the Zn(II)-catalysed Biginelli condensation is proposed in Scheme 2, which regards the *N*-acyliminium ion as the key intermediate. The first step in this reaction is the formation of acylimine intermediate (formed by reaction of the aldehyde with urea) that is stabilised by the zinc ion. And the subsequent addition of the β-carbonyl compound to the acylimine, followed by cyclisation and dehydration, affords the corresponding DHPMs

In conclusion, the present procedure described a useful protocol for the Biginelli condensations of aliphatic aldehydes catalyzed by $Zn(CH_3SO_3)_2{\cdot}4H_2O$. The catalyst can be easily recovered and reused without distinct decrease in reaction yields. Excellent reaction yields, reusable catalyst and aqueous media are important features of this new protocol for preparing DHPMs.

Experimental

All melting points were determined by using RY-1 micro melting point apparatus and were uncorrected. IR spectra were recorded on Spectrum GX series Fourier Transform instrument of Perkin Elmer. ^{1}H NMR spectra were recorded on Bruker AVANCE 600 spectrometer in DMSO-d_6 using TMS as an internal standard. Elemental analyses were carried out on EA 2400II elemental analyzer (Perkin-Elmer). Molecular weight determination was performed on K-7000 Vapor Pressure OSMO meter (Germany).

General procedure for the $Zn(CH_3SO_3)_2{\cdot}4H_2O$ catalysed synthesis of DHPMs (**4**): A solution of aliphatic aldehyde (30 mmol), 1,3-dicarbonyl compounds (35 mmol), urea (45 mmol) and $Zn(CH_3SO_3)_2{\cdot}4H_2O$ (3 mmol) in absolute ethanol (10 ml) was refluxed for the required time in a 100 ml conical flask. After cooling to room temperature, the reaction mixture was then poured onto crushed ice. The solid products were filtered under suction, washed thoroughly with cold water and 20% ethanol (v), and subsequently dried and recrystallised from ethanol (except **4a** and **4k** were recrystallised from 50% ethanol: dimethyl sulfoxide) to give pure DHPMs. All the pure products were characterised by m.p., IR, ^{1}H NMR. Spectral data for selected new compounds:

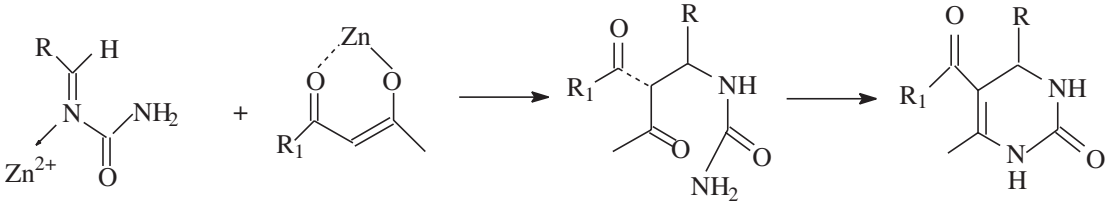
4a: IR (KBr): 3258, 3138, 2954, 1741, 1709, 1666 cm^{-1}; ^{1}H NMR (DMSO-d_6): 8.86 (s, 1H, NH), 7.01 (s, 1H, NH), 4.07 (q, 2H, *J*=7.0 Hz, OCH_2CH_3), 3.88 (s, 2H, CH_2), 2.15 (s, 3H, CH_3), 1.20 (t, 3H, *J*=7.0 Hz, OCH_2CH_3); Anal. Calc. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.58; N, 15.21. Found: C, 52.09; H, 6.45; N, 15.33%.

4d: IR (KBr): 3250, 3120, 2958, 1720, 1646 cm^{-1}; ^{1}H NMR (DMSO-d_6): 8.93 (s, 1H, NH), 7.33 (s, 1H, NH), 4.10 (q, *J*=4.7 Hz, 3H, H-4 and $O\underline{CH_2}CH_3$), 2.16 (s, 3H, CH_3), 1.40 (m, 4H, $\underline{CH_2CH_2}CH_3$), 1.21 (t, *J*=4.7 Hz 3H, OCH_2CH_3), 0.87 (t, 3H, $CH_2CH_2CH_3$); Anal. Calcd for $C_{11}H_{18}N_2O_3$: C, 58.38; H, 8.03; N, 12.38. Found: C, 58.71; H, 8.01; N, 12.29%.

4g: IR (KBr): 3239, 3112, 2926, 1702, 1652 cm^{-1}; ^{1}H NMR (DMSO-d_6): 8.94 (s, 1H, NH), 7.33 (s, 1H, NH), 4.10 (m, 3H, H-4 and $O\underline{CH_2}CH_3$), 2.15 (s, 3H, CH_3), 1.39 (m, 15H, $(CH_2)_6CH_3$), 0.86 (t, 3H, $OCH_2\underline{CH_3}$); Anal. Calc. for $C_{15}H_{26}N_2O_3$: C, 63.80; H, 9.30; N, 9.92. Found: C, 63.69; H, 9.21; N, 9.97%.

4h: IR (KBr): 3301, 3089, 2971, 1693, 1610 cm^{-1}; ^{1}H NMR (DMSO-d_6): 9.01 (s, 1H, NH), 7.29 (s, 1H, NH), 4.22 (m, 1H, $CHCH_3$), 2.20 (s, 3H, OCH_3), 2.18 (s, 3H, CH_3), 1.07 (t, 3H, $CHCH_3$); Anal. Calc. for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19; N, 16.65. Found: C, 57.31; H, 7.21; N, 16.52%.

4i: IR (KBr): 3246, 3122, 2974, 1707, 1682, 1615 cm^{-1}; ^{1}H NMR (DMSO-d_6): 8.94 (s, 1H, NH), 7.40 (s, 1H, NH), 4.08 (t, 1H, $CHCH_2CH_3$), 2.20 (d, 6H, OCH_3 and CH_3), 1.39 (m, 2H, *J*=7.4 Hz, CH_2CH_3), 0.81 (t, 3H, *J*=7.4 Hz, CH_2CH_3); Anal. Calc. for $C_9H_{14}N_2O_2$: C, 59.32; H, 7.76; N, 15.38. Found: C, 59.20; H, 7.71; N, 15.42%.



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Scheme 2

4k: IR (KBr): 3258, 3141, 2955, 1712, 1664 cm^{-1}; ^1H NMR (DMSO-d_6): 8.90 (s, 1H, NH), 7.04 (s, 1H, NH), 3.89 (s, 2H, CH_2), 3.59 (s, 3H, OCH_3), 2.15 (s, 3H, CH_3); Anal. Calc. for $C_7H_{10}N_2O_3$: C, 49.40; H, 5.93; N, 16.49. Found: C, 49.52; H, 5.90; N, 16.35%.

4l: IR (KBr): 3246, 3114, 2952, 1709, 1656 cm^{-1}; ^1H NMR (DMSO-d_6): 9.01 (s, 1H, NH), 7.20 (s, 1H, NH), 4.13 (q, 1H, $CHCH_3$), 3.61 (s, 3H, OCH_3), 2.16 (s, 3H, CH_3), 1.15 (t, 3H, $CHCH_3$); Anal. Calc. for $C_8H_{12}N_2O_3$: C, 52.16; H, 6.58; N, 15.21. Found: C, 52.05; H, 6.53; N, 15.29%.

4o: IR (KBr): 3239, 3118, 2955, 1702, 1649 cm^{-1}; ^1H NMR (DMSO-d_6): 8.93 (s, 1H, NH), 7.30 (s, 1H, NH), 3.95 (t, 1H, CH), 3.59 (s, 3H, OCH_3), 2.17 (s, 3H, CH_3), 1.68 (m, 1H, $\underline{CH}(CH_3)_2$), 0.82 (d, 3H, $CH(\underline{CH_3})_2$), 0.73 (d, 3H, $CH(\underline{CH_3})_2$); Anal. Calc. for $C_{10}H_{16}N_2O_3$: C, 56.58; H, 7.61; N, 13.20. Found: C, 56.35; H, 7.67; N, 13.08%.

4q: IR (KBr): 3242, 3120, 2927, 1706, 1652 cm^{-1}; ^1H NMR (DMSO-d_6): 8.95 (s, 1H, NH), 7.33 (s, 1H, NH), 4.04 (q, 1H, CH), 3.60 (s, 3H, OCH_3), 2.16 (s, 3H, CH_3), 1.38 (m, 12H, $(\underline{CH_2})_6CH_3$), 0.86 (t, 3H, $(CH_2)_6\underline{CH_3}$); Anal. Calc. for $C_{14}H_{24}N_2O_3$: C, 62.65; H, 9.03; N, 10.44. Found: C, 62.49; H, 9.01; N, 10.56%.

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