Comparison of Catalytic Effect of Alkali and Alkaline Earth Metals Hydrogen Sulfate: As the Promoter for an Efficient Synthesis of 3,4-Dihydropyrimidin-2(1H)-ones under Solvent-Free Conditions

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ABSTRACT: Alkali and alkaline earth metals hydrogen sulfate catalyzed the one-pot three component condensation reactions of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea under solvent-free conditions leading to 3,4-dihydropyrimidin-2(1H)-ones in high yields at 80 °C. Our results showed that Biginelli reaction not only is pH dependent, but the cation of catalyst plays an important role.

KEY WORDS: Biginelli reaction, Dihydropyrimidinones, Catalytic effect, Lithium hydrogen sulfate, Sodium hydrogen sulfate, Potassium hydrogen sulfate, Magnesium hydrogen sulfate.

INTRODUCTION
In recent years, dihydropyrimidinones (DHPMs) and their derivatives occupy an important place in the realm of natural and synthetic organic chemistry because of their therapeutic and pharmacological properties [1,2]. They have emerged as integral backbones of several calcium channel blockers, antihypertensive agents, α1a-antagonists and neuropeptide Y(NPY) antagonists [3]. Therefore, many synthetic methods have been reported for preparing such compounds under classical reflux [4-10] or solvent free conditions [11-17] and microwave [18-21] or ultrasonic irradiation [22,23] using Lewis acids as well as protic acids as promoters. However, in spite of their potential utility, many of these methods involve low yields, long reaction times, high temperature and expensive reagents.

In continuation of our previous works on Biginelli reaction [15,24,25], herein we wish to report the results obtained from a study of the catalytic effect of lithium, sodium, potassium or magnesium hydrogen sulfate as a very cheap solid acid in preparation of DHPMs under solvent-free conditions at 80 °C (Scheme 1).

EXPERIMENTAL
Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. Mass spectra were recorded on a FINNIGAN-MAT 8430 mass spectrometer.
operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. $^1$H and $^{13}$C NMR spectra were recorded on a BRUKER DRX-500 AVANCE spectrometer at 500.13 and 125.77 MHz, respectively. NMR spectra were obtained on solutions in DMSO-d$_6$ using TMS as internal standard.

**Magnesium hydrogen sulfate catalyzed synthesis of 5-ethoxycarbonyl-6-methyl-4-(4-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one, under solvent-free conditions. A typical procedure**

**Small-Scale**

A mixture of 4-nitrobenzaldehyde (0.15 g, 1 mmol), ethyl acetoacetate (0.13 g, 1 mmol), urea (0.09 g, 1.5 mmol) and Mg(HSO$_4$)$_2$ (0.12 g, 0.5 mmol) were finely mixed together. The reaction mixture in a screw-capped vial containing a magnetic stirring bar was heated at 80 °C in a preheated oil bath for 4 hours. After cooling, the reaction mixture was poured onto crushed ice (40 g) and stirred for 5-10 min. The solid separated was filtered under suction, washed with cold water (40 mL) and then recrystallized from ethyl acetate:n-hexane (1:3) to afford the pure product 4d (0.25 g, 83%). Mp 206-208 °C.

IR (KBr): $\nu_{\text{max}}$ (cm$^{-1}$), 3215, 1731, 1707, 1641.

$^1$H NMR (DMSO-d$_6$): $\delta$(ppm), 1.07 (3H, t, $^3$J 6.8 Hz, CH$_3$), 2.26 (3H, s, CH$_3$), 3.97 (2H, q, $^3$J 5.4 Hz, OCH$_2$), 5.27 (1H, s, CH), 7.50 (2H, d, $^3$J 7.3 Hz, arom), 7.87 (1H, s, NH), 9.33 (1H, s, NH).

$^{13}$C NMR (DMSO-d$_6$): $\delta$(ppm), 14.5, 18.3, 54.2, 59.8, 98.7, 124.2, 128.1, 147.2, 149.8, 152.2, 152.5, 165.5.

MS: $m/z$ (%), 305 (M$^+$, 25), 276 (92), 260 (20), 183 (100).

It is important to note that we have to close the cap of vial for low boiling aldehydes (4f, 4g). All the products (except 4l, 4s and 4t) are known compounds and were characterized by IR and $^1$H NMR spectroscopic data and their mps. Compared with reported literature values.

**Large-Scale**

A mixture of 4-nitrobenzaldehyde (1.50 g, 10 mmol), ethyl acetoacetate (1.30 g, 10 mmol), urea (0.90 g, 15 mmol) and Mg(HSO$_4$)$_2$ (1.20 g, 5 mmol) were finely mixed together. The reaction mixture in a 25 mL round-bottomed flask containing a magnetic stirring bar, was heated at 80 °C in a preheated oil batch for 4 hours. After cooling, the reaction mixture was poured onto crushed ice and stirred for 5-10 min. The solid separated was filtered under suction, washed with cold water and then recrystallized from ethyl acetate:n-hexane (1:3) to afford the pure product 4d (2.44 g, 80%).

4i: 5-Methoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one. Mp 280-282 °C.

IR (KBr): $\nu_{\text{max}}$ (cm$^{-1}$), 3340, 3200, 3088, 1690, 1631.

$^1$H NMR (DMSO-d$_6$): $\delta$(ppm), 2.27 (3H, s, CH$_3$), 3.53 (3H, s, OCH$_3$), 5.29 (1H, s, CH), 7.61-8.12 (4H, m, arom), 7.90 (1H, s, NH), 9.37 (1H, s, NH).

$^{13}$C NMR (DMSO-d$_6$): $\delta$(ppm), 18.4, 51.4, 53.8, 98.6, 121.4, 122.8, 130.7, 133.4, 147.2, 148.3, 150.1, 152.3, 166.1.

MS: $m/z$ (%), 292 (M$^+$+H, 25), 232 (92),169 (100).

4s: 5-Benzoyloxycarbonyl-6-methyl-4-(phenyl)-3,4-dihydropyrimidin-2(1H)-one. Mp 167-169 °C.

IR (KBr): $\nu_{\text{max}}$ (cm$^{-1}$), 3345, 3218, 3100, 1703, 1637.

$^1$H NMR (DMSO-d$_6$): $\delta$(ppm), 2.26 (3H, s, CH$_3$), 5.00 and 5.04 (2H, AB-system, $^3$J 12.7 Hz, OCH$_2$), 5.16 (1H, d, $^3$J 2.9 Hz, CH), 7.13-7.30 (10H, m, arom), 7.72 (1H, s, NH), 9.23 (1H, s, NH).

$^{13}$C NMR (DMSO-d$_6$): $\delta$(ppm), 18.3, 54.4, 65.3, 99.2, 126.7, 127.8, 128.0, 128.2, 128.7, 128.9, 137.0, 145.1, 149.7, 152.4, 165.5.

MS: $m/z$ (%), 322 (M$^+$, 45), 231 (19), 187 (20), 77 (100).

4t: 5-Benzyloxycarbonyl-6-methyl-4-(4-methoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one. Mp 187-189 °C.

IR (KBr): $\nu_{\text{max}}$ (cm$^{-1}$), 3340, 3210, 3100, 1695, 1630, 1603.

$^1$H NMR (DMSO-d$_6$): $\delta$(ppm), 2.25 (3H, s, CH$_3$), 3.71 (3H, s, OCH$_3$), 4.99 and 5.04 (2H, AB system, $^3$J 12.7 Hz, OCH$_2$), 5.12 (1H, s, CH), 6.83-7.27 (9H, m, arom), 7.68 (1H, s, NH), 9.21 (1H, s, NH).

$^{13}$C NMR (DMSO-d$_6$): $\delta$(ppm), 18.3, 53.8, 55.5, 65.2, 99.5, 114.2, 127.9, 128.0, 128.2, 128.7, 137.0, 137.3, 149.4, 152.4, 159.0, 165.6.

MS: $m/z$ (%), 351 (M$^+$, 37), 321 (59), 216 (20), 77 (100).

**RESULTS AND DISCUSSION**

The results of the three component condensation of aldehydes, 1,3-dicarbonyl compounds and urea or thiourea which to lead 3,4-dihydropyrimidin-2(1H)-one derivatives catalyzed by LiHSO$_4$(LiHS), NaHSO$_4$(NaHS), KHSO$_4$(KHS), or Mg(HSO$_4$)$_2$(MgHS) are summarized.
in Table 1. The procedures give the products in moderate to good yields and avoid problems associated with solvent use (cost, handling, safety and pollution).

It is natural to suppose that metal-enolate ion pairs and metal-\(N\)-acylimine species are key intermediate in the Biginelli reaction. On the other hand, the Biginelli reaction not only is pH dependent, but the cation of catalyst play an important role in stabilizing \(N\)-acylium intermediate or in increasing enolate reactivity (Scheme 2).

We have found that LiHSO\(_4\), NaHSO\(_4\) or KHSO\(_4\) are more efficient catalysts than Mg(HSO\(_4\))\(_2\) for the Biginelli reaction with acetylacetone (Entries 4m-o). This can be explained by the fact that Mg\(^{2+}\) coordinates strongly with acetylacetone and decreases the activity of \(\pi\)-nucleophile of the enol tautomer of acetlyacetone in reaction with electron deficient \(N\)-acylimine species. However, Mg(HSO\(_4\))\(_2\) relative to LiHSO\(_4\), NaHSO\(_4\) or KHSO\(_4\) is the preferred catalyst for aliphatic aldehydes which normally find extremely poor yields in the Biginelli reaction [19] (Entries 4f and 4g). This may be explained by the fact that Mg\(^{2+}\) coordinates strongly with \(N\)-acylium intermediate.
and stabilizes it more than what alkali metals do in the LiHS, NaHS and KHS.

In addition, due to hardness and low polarizability trend of Li$^+$ > Na$^+$ > K$^+$ [26] in coordination with enolate, LiHSO$_4$ usually leads to low yields with respect to NaHSO$_4$ and KHSO$_4$, so the yield of reactions follows the opposite order, namely KHSO$_4$ > NaHSO$_4$ > LiHSO$_4$.

In order to improve the yields we have tested a variety amount of each catalyst with model reaction using anisaldehyde (1 mmol), ethyl acetoacetate (1 mmol) and urea (1.5 mmol) at 80 °C for 4 hours. The best results have been obtained with a 1:1:1.5:0.5 and 1:1:1.5:0.7 ratio of aldehyde, β-dicarbonyl, urea and catalyst for Mg(HSO$_4$)$_2$ and KHSO$_4$, respectively. However, the amount of catalyst is increased to 1:1:1.5:1 for LiHSO$_4$ and NaHSO$_4$. 

\[ \text{Scheme 1} \]

\[ \text{Scheme 2} \]
Importantly, aromatic aldehydes carrying either electron donating (-OMe) or electron withdrawing (-NO2) substituents all reacted very well, giving moderate to excellent yields of the desired products using these catalysts. Decreased reaction times are also realized because of the increased reactivity of the reactant in the solid state and the fact that the other reaction product, water, evaporates at the reaction temperature of 80 °C.

Also we scale up the reaction to the level producing multi-grams of product without any problems (see Experimental Section).

CONCLUSION

a) Alkali and alkaline earth metals hydrogen sulfate as a very cheap and stable solid acid capable to catalyze the Biginelli reaction under solvent-free conditions at 80 °C.

b) The Biginelli reaction not only is pH dependent, but the cation of catalyst play an important role.

c) Mg(HSO4)2 relative to LiHSO4, NaHSO4 or KHSO4 is the practical catalyst for the Biginelli reaction especially with aliphatic aldehydes, which normally find extremely poor yields in the Biginelli reaction.

Acknowledgment

Financial support from the Research Council of Shahid Beheshti University is acknowledged.

Received : 26th January 2005 ; Accepted : 8th March 2005

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