One-pot, solvent-free synthesis via Biginelli reaction: Catalyst-free and new recyclable catalysts

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Abstract: Free catalyst one-pot three components coupling of aldehydes, \( \beta \)-dicarbonyl compounds, and urea was performed to afford both the corresponding 3,4-dihydropyrimidine-2-ones (DHPOs, (1–9)a) and their sulfur analogs 3,4-dihydropyrimidine-2-thiones (DHPTs, (1–9)b), synthesized in the presence of uranyl acetate (UA) and succinimide sulfonic acid (SuSA) as catalysts under the same conditions via Biginelli condensation protocol. Interestingly, the free catalyst reactions were performed for 4 h for DHPOs with the yields of high to excellent, while in the cases of DHPTs, the yield was lower. But when the UA or SuSA was used, the yields (both of DHPOs and DHPTs) were high to excellent and the reaction times were either 2.5 or 1 h, respectively. Also, these two catalysts were recyclable for four consecutive runs.

Subjects: Chemistry; Medicinal & Pharmaceutical Chemistry; Organic Chemistry

Key keywords: free catalyst; uranyl acetate; succinimide sulfonic acid; 3,4-dihydropyrimidine-2-one; 3,4-dihydropyrimidine-2-thione

1. Introduction

The Italian chemist Biginelli (1891a, 1891b), observed the reaction between an ammonia source and an aldehyde in equimolar ratio and urea in acidic alcoholic solution to obtain new compounds, well known as 3,4-dihydropyrimidine-2(1H)-ones (Kenner & Todd, 1957; Zaugg & Martin, 1965). After years from this discovery, emphasis was on understanding the course of reaction and some emphasis on structural variants as well. Subsequent to these academic developments, the Biginelli scaffold was shown to be of great value from a pharmaceutical point of view; because of this importance, investigations were very fast, and virtually every major journal was flooded with papers on the Biginelli reaction (Biginelli, 1893; Dallinger & Kappe, 2005; Dallinger, Stadler, & Kappe, 2004; Kappe, 1993, 2000a, 2000b, 2003, 2005; Kappe & Stadler, 2004; Kolosov, Orlov, Beloborodov, & Dotsenko, 2009; Phucho, 2000).

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PUBLIC INTEREST STATEMENT

Considerable attention has been paid to the synthesis of 3,4-3,4-dihydropyrimidine-2-ones (-thiones) owing to their significant biological activities. The search continues for better catalysts for the synthesis of and 3,4-dihydropyrimidines in terms of operational simplicity, reusability, economic viability, and greater selectivity. The current work reports efficient new catalysts (UA and SuSA) and compares these with catalyst free method in the preparation of such products.
Nongpiur, Tumtin, Nongrum, & Nongkhlaw, 2009; Singh, Arorea, & Singh, 2009; Vdovina & Mamedov, 2008; Wan & Liu, 2010). 3,4-Dihydropyrimidine-2-ones (DHPOs) were viewed in terms of operational simplicity, reusability, economic viability, and greater selectivity. Although different methods for the synthesis of Biginelli’s products were based on the use of strong protic acids such as H₂SO₄ (Folkers & Johnson, 1933a), HCl (Folkers & Johnson, 1933b) and zeolite (Radharani, Srinivas, Radha Kishan, Kulkarni, & Raghavan, 2001) metal triflates (Su, Li, Zheng, & Shen, 2005; Varala, Alam, & Adapa, 2003), varieties of other conditions such as ultrasonic (Gholap, Venkatesan, Daniel, Lahoti, & Srinivasan, 2004; Zhang, Li, Liu, & Wang, 2006), low melting acidic (Sangram, Sundarababu, & Bukhard, 2011) methods and ionic liquid (Valizadeh & Shockravi, 2009) media have been reported in the literature.

Uranyl acetate (UA) has been extensively used as a negative stain in the electron microscopy (Lewis & Knight, 1977).

But there are few references for UA as catalyst in organic reactions (Jha & Halada, 2011; Wang, Zhao, Li, Wang, & Zhang, 2001). In these works, the UA was used along with some other salts. It is vague that the original role is either because UA acts as Lewis catalyst or due to other accompanying salt. Also, the researches demonstrate that succinimide sulfonic acid (SuSA) efficiency promotes the rates of N-Boc protection of amines, trimethylsilylation of alcohols and phenols, and synthesis of xanthenes (Shirini & Ghaffari Khaligh, 2011, 2012a, 2012b).

In continuation of our investigations on the synthesis of (DHPOs and DHPTs) via Biginelli protocols (Shockravi, Kamali, Sharifi, Nategholeslam, & PahlavanMoghanlo, 2013), here in, we report efficient new catalysts (UA and SuSA) and compare with catalyst free method in the preparation of such products.

2. Experimental

2.1. Chemicals and apparatus
All reactions were carried out in an efficient hood. The starting materials were purchased from Merck and Fluka chemical companies. Melting points were determined with a Branstead Electrothermal model 9200 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer RX 1 Fourier transform infrared spectrometer. The ¹H and ¹³C NMR spectra were recorded in DMSO-d₆, Acetone-d₆, and CDCl₃ on Bruker Avance 300 MHz spectrometers. Elemental analyses were carried out by a Perkin Elmer 2400 series II CHN/O analyzer. In continuation of our investigations on the synthesis of (DHPOs and DHPTs) via Biginelli protocols, here in, we report efficient new catalysts (UA and SuSA) and compare with catalyst free method in the preparation of such products.

2.2. Synthesis of 1a as general procedure
A mixture of benzaldehyde (2 mmol, 0.21 g), ethyl acetoacetate (2 mmol, 0.26 g), urea (3 mmol, 0.18 g) and UA, 2H₂O, (1 mol %, 8.5 mg) or SuSA (1 mol %, 3.6 mg) (or without catalyst) was heated in an oil bath with stirring at 90°C for corresponding hours (Tables 1 and 2). After cooling, the

| Temperature (°C) | Time (h) | Product yield (%) |
|-----------------|----------|-------------------|
| 50              | 5        | 30                |
| 60              | 5        | 35                |
| 70              | 5        | 55                |
| 80              | 5        | 67                |
| 90              | 5        | 95                |
| 100             | 5        | 95                |
| 90              | 4        | 95                |
| 90              | 3        | 85                |
Table 2. Synthesis of 7b under different conditions for optimization of reactions

| Temperature of reaction (°C) | Catalyst (mol %) | UA as catalyst | SuSA as catalyst |
|------------------------------|------------------|----------------|------------------|
|                              |                  | Time (h)       | Product yield (%)| Time (h) | Product yield (%)|
| 80                           | 20               | 4              | 75               | 4        | 75               |
| 90                           | 20               | 4              | 95               | 4        | 95               |
| 100                          | 20               | 4              | 95               | 4        | 93               |
| 90                           | 10               | 4              | 95               | 4        | 95               |
| 90                           | 5                | 4              | 95               | 4        | 95               |
| 90                           | 1                | 4              | 95               | 4        | 95               |
| 90                           | 0.5              | 4              | 87               | 4        | 85               |
| 90                           | 2.5              |               |                  |          |                  |
| 90                           | 2                | 2              | 87               | 1.5      | 95               |
| 90                           |                  | –              | –                |          | 1                | 95               |

Table 3. Details of Biginelli synthesis

| Entry | Ar         | Urea | Thiourea | Product yield (%) without catalyst | Product yield (%) with UA | Product Yield (%) with SuSA | mp (°C) | Found | Lit.  |
|-------|------------|------|----------|------------------------------------|---------------------------|-----------------------------|---------|-------|-------|
| 1a    | C₆H₅       | ✓    |          | 80                                 | 95                        | 90                          | 205-207 | 204–205<sup>a</sup> |
| 1b    |            | ✓    |          | 45                                 | 86                        | 85                          | 206-208 | 206–208<sup>h</sup> |
| 2a    | 2-Cl-C₆H₅  | ✓    |          | 95                                 | 85                        | 88                          | 221–223 | 222–224<sup>c</sup> |
| 2b    |            | ✓    |          | 62                                 | 80                        | 85                          | 216-218 | –     |
| 3a    | 4-Cl-C₆H₅  | ✓    |          | 85                                 | 84                        | 83                          | 212-214 | 214–215<sup>c</sup> |
| 3b    |            | ✓    |          | 25                                 | 81                        | 80                          | 177–180 | 178–179<sup>d</sup> |
| 4a    | 3-(NO₂)-C₆H₄| ✓  |          | 70                                 | 92                        | 92                          | 227–229 | 227–228<sup>e</sup> |
| 4b    |            | ✓    |          | 45                                 | 90                        | 90                          | 210-212 | 210-212<sup>q</sup> |
| 5a    | 4-(NO₂)-C₆H₄| ✓  |          | 84                                 | 81                        | 84                          | 205-207 | 207-208<sup>f</sup> |
| 5b    |            | ✓    |          | 51                                 | 65                        | 75                          | 203-205 | 204–205<sup>d</sup> |
| 6a    | 4-F-C₆H₅   | ✓    |          | 85                                 | 90                        | 95                          | 176-178 | –     |
| 6b    |            | ✓    |          | 75                                 | 85                        | 91                          | 188-190 | –     |
| 7a    | 3-HO-C₆H₅  | ✓    |          | 60                                 | 95                        | 96                          | 187-189 | 187–189<sup>n</sup> |
| 7b    |            | ✓    |          | 60                                 | 95                        | 95                          | 182–184 | 183–185<sup>c</sup> |
| 8a    | 4-MeO-C₆H₄ | ✓    |          | 77                                 | 81                        | 88                          | 198-200 | 199–201<sup>c</sup> |
| 8b    |            | ✓    |          | 52                                 | 80                        | 81                          | 216–218 | –     |
| 9a    | 2-Furyl    | ✓    |          | 64                                 | 78                        | 85                          | 189–192 | –     |
| 9b    |            | ✓    |          | 42                                 | 70                        | 80                          | 182–184 | 185<sup>n</sup> |

<sup>a</sup>Kumar, Kasthuraiah, Reddy, and Reddy (2001).
<sup>b</sup>Ghosh, Maiti, and Chakrabarty (2004).
<sup>c</sup>Fu et al. (2002).
<sup>d</sup>Wang, Qian, Tian, and Ma (2003).
<sup>e</sup>Kumar, Shanmugam, and Babu (2011).
<sup>f</sup>Chari, Shobha, Kumar, and Dubey (2005).
<sup>g</sup>Shaabani, Bazigar, and Teimouri (2003).
<sup>h</sup>Russowsky et al. (2006).
<sup>i</sup>Ranu, Hajra, and Jana (2000).
reaction mixture was poured in ice (10 mL) water and the precipitated solid was collected by filtration, washed with distilled water, and dried. The crude product was recrystallized from ethanol to give the corresponding pure product (1a). White solid, (Table 3) mp 205–207°C; IR (KBr) ν: 3233, 3101, 2940, 1718, 1697, 1595, 1218 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ: 1.22 (t, J = 7.0 Hz, 3H), 2.36 (s, 3H), 4.07 (q, J = 7.0 Hz, 2H), 5.29 (s, 1H), 5.91 (s, 1H), 7.09–7.21 (m, 5H), 8.28 (s, 1H); ¹³C NMR (75 MHz, CDCl₃) δ: 14.1, 18.2, 54.5, 61.1, 102.0, 126.4, 127.3, 128.2, 143.0, 146.5, 163.2 ppm; Anal. Calcd for C₁₄H₁₆N₂O₃: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.25; H, 5.99; N, 10.98.

3. Results and discussion
To the best of our knowledge, our first finding was that the free-solvent reaction of benzaldehyde and urea with ethyl acetoacetate without any catalyst afforded the desired DHPO in 70% yield (Scheme 1). We then optimized the reaction conditions by conducting the reaction at different temperatures and times. The results are summarized in Table 1, whereby better yields were obtained when the temperature was at 90°C with 4 h reaction time.

Several activated and deactivated aromatic aldehydes underwent the reaction to give the corresponding DHPOS in good to excellent yields. The experimental procedure was very simple, convenient, and had the ability to tolerate a variety of other functional groups such as methoxy, nitro, hydroxy, halides, and nitros under the reaction conditions (Table 3).

Our experimental works demonstrated that in the case of DHPTs, the yields were generally much lower compared to the reactions which were carried out without a catalyst (Table 3). Therefore, the results, UA as Lewis acid and SuSA as Brønsted–Lowry acid catalysts, are summarized in Table 2, which clearly indicate the generality and scope of the reaction with respect to various aromatic and heterocyclic aldehydes (Table 3).

Interestingly, both of the catalysts can be recycled for four consecutive runs without significant loss of activity (Table 4).

![Scheme 1. Biginelli-type reaction.](image)

### Table 4. Recycled UA and SuSA in the synthesis of Biginelli reactions

| Catalyst type | Runs |   |   |   |   |
|---------------|------|---|---|---|---|
|               | 1    | 2 | 3 | 4 | 5 |
| Product yield (%) with UA | 95   | 88| 88| 76| 45|
| Product yield (%) with SuSA | 95   | 95| 90| 75| 50|
4. Conclusion

In conclusion, we have successfully developed a quick, convenient, and efficient method for the synthesis of DHPs under solvent-free conditions. The environmental advantages include omitting organic solvent, generality and simplicity of procedure, shorter reaction time, simple workup, catalyst-free and reusable catalysts conditions, and pure products in good to excellent yields.

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