

# Imidazolium-Based Phosphinite Ionic Liquid as Reusable Catalyst and Solvent for One-Pot Synthesis of 3,4-Dihydropyrimidin-2(1*H*)-(thio)ones

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**ABSTRACT:** A mild and efficient procedure for the synthesis of 3,4-dihydropyrimidin-2(1*H*)-(thio)ones in phosphinite ionic liquid is described. This ionic liquid plays a dual role as both the reaction media and also a catalyst, which can be easily recovered and reused in several runs. © 2009 Wiley Periodicals, Inc. *Heteroatom Chem* 20:284–288, 2009; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20549

## INTRODUCTION

Ionic liquids are a new class of solvents, which have attracted growing interest over the past few years due to their unique physical and chemical properties [1]. They usually consist of poorly coordinating ion pairs, and a classical example is the readily accessible 1-butyl-3-methylimidazolium tetrafluoroborate [bmim][BF<sub>4</sub>], which is a colorless mobile but nonvolatile liquid with no smell [2]. Since such solvents easily dissolve metal salts and transition metal catalysts, interesting developments have recently appeared in synthesis using organometallic reagents [3]; some applications of these solvents in organic

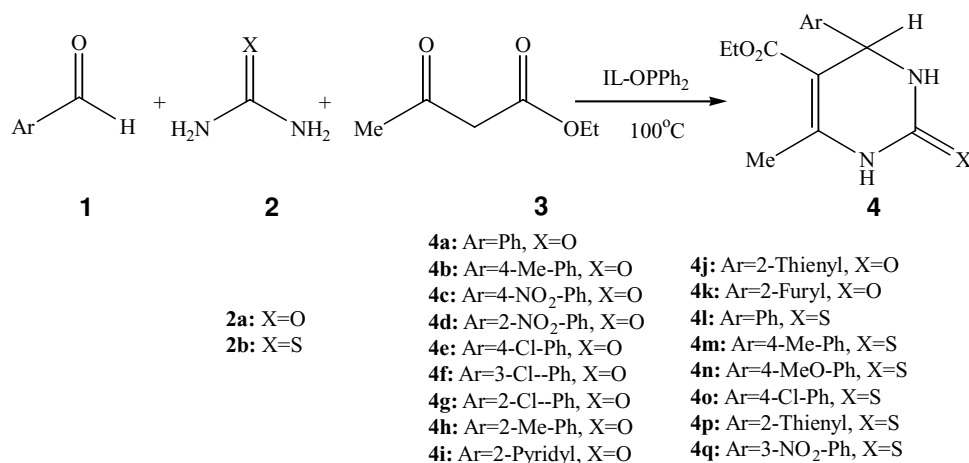
chemistry have also been reported, for instance in alkylations [4], benzoin condensation [5], and Diels–Alder [6], and Friedel–Crafts [7] type reactions. Furthermore, their possible use for selective extraction of organic compounds has been noted recently [8].

Dihydropyrimidinones (DHPMs) have attracted considerable attention because of their wide spectrum of biological and therapeutic activities. Functionalized DHPMs have been used as potent calcium channel blockers [9], antihypertensive agents [10], and neuropeptide Y antagonists [11]. The Biginelli reaction is a well-known, simple, and straightforward procedure for the synthesis of DHPMs by the three-component condensation of aliphatic or aromatic aldehyde, acetoacetate ester, and urea [12]. There is a variety of suitable reaction conditions, traditionally with strong Bronsted acid, but nowadays, more frequently, with Lewis acids [13] for the synthesis of DHPMs via the Biginelli reaction. Many novel and useful adaptations of the Biginelli reaction have been described in the literature, including those employing microwaves [14], solid-phase synthesis [15], ionic liquids [16], silica gel supported sodium hydrogensulfate [17], and polymer-supported catalysts [18]. In recent years, there has been an increasing interest in reactions that proceed in task-specific ionic liquids (TSILs) as a powerful alternative to conventional molecular organic solvents or catalysts due to their particular properties, such as undetectable vapor pressure, wide liquid range, as well as the ease of recovery

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SCHEME 1

and reuse [19]. Zuliang et al. used room temperature TSILs, 3-trialkylammoniopropanesulfonate, for the synthesis of DHPMs [19c]. Shaabani and Rahmati [20] used room temperature ionic liquid 1,1,3,3-tetramethylguanidinium trifluoroacetate as catalyst, Li et al. [21] reported ionic liquid (BMImSac) as catalyst, Zheng et al. [22] synthesized and used ionic liquid CMIHSO<sub>4</sub> as catalyst for the Biginelli reaction. Our recent interest is in the area of green synthesis under conventional heating as well as microwave conditions [23]. In this paper, a task-specific ionic liquid (phosphonite ionic liquid, IL-OPPh<sub>2</sub>), with weak Lewis basic character, was synthesized and used as catalyst for the one-pot synthesis of 3,4-dihydropyrimidinones or their sulfur analogues via the Biginelli reaction (Scheme 1).

## EXPERIMENTAL

### General Information

Task-specific ionic liquid was prepared according to the procedure reported in the literature [24,25]. All chemicals were purchased from Merck and used as received. <sup>1</sup>H NMR spectra (400 MHz) were recorded on a Bruker Avance spectrometer using TMS as internal standard. Infrared spectra were recorded in KBr and were determined on a Perkin Elmer FT-IR spectrometer. Elemental analyses were carried out on a Perkin-Elmer 240C elemental analyzer and are reported in percent atomic abundance. All melting points are uncorrected and measured in an open glass-capillaries using Stuart melting point apparatus.

### Synthesis of 3,4-Dihydropyrimidin-2(1H)-(thio)-ones (4a-q): General Procedure

A mixture of arylaldehyde (5 mmol), 1,3-dicarbonyl compound (6.25 mmol), urea or thiourea (5.75 mmol), and IL-OPPh<sub>2</sub> (5 mmol) was heated at 100°C under stirring. The reaction was monitored by TLC using ethyl acetate/hexane (2:5) as eluent. After cooling to room temperature, the reaction mixtures were extracted with ether and ethylacetate (8 mL × 3). The organic layers were collected and concentrated in vacuum. The residual solid was recrystallized from ethyl acetate or ethanol to afford pure product.

### Recyclability of IL-OPPh<sub>2</sub>

After carrying out the reaction, the mixture was extracted with the mixture of ether and ethyl acetate (8 mL × 3) to remove all adsorbed organic substrates. Then the remained ionic liquid (IL) was dried in a vacuum oven and reused in the next cycle directly without further purification.

## RESULTS AND DISCUSSION

We have recently introduced an imidazolium-based phosphinite ionic liquid for the Horner–Wadsworth–Emmons type reaction [26]. In this report, the ionic liquid plays a dual role both as a reagent via its phosphinite-carrying group and also as the reaction media. Here, we report a new application of this ionic liquid as solvent and catalyst for the mild and efficient synthesis of Biginelli products in the absence of any acid catalyst (Scheme 1). The

**TABLE 1** Synthesis of Dihydropyrimidin-2(*H*)-ones and Thiones in IL-OPPh<sub>2</sub> at 100°C

| Entry | X | Ar                    | Product <sup>a</sup> | Time (h) <sup>b</sup> | Mp °(C) |                 | Yield <sup>c</sup> (%) |
|-------|---|-----------------------|----------------------|-----------------------|---------|-----------------|------------------------|
|       |   |                       |                      |                       | Found   | Reported [Ref.] |                        |
| 1     | O | Ph                    | <b>4a</b>            | 2.5                   | 205–207 | 206–208 [27]    | 91                     |
| 2     | O | 4-Me-Ph               | <b>4b</b>            | 3                     | 204–206 | 205–206 [27]    | 89                     |
| 3     | O | 4-NO <sub>2</sub> -Ph | <b>4c</b>            | 1.5                   | 210–212 | 211–213 [28]    | 95                     |
| 4     | O | 2-NO <sub>2</sub> -Ph | <b>4d</b>            | 3                     | 220–221 | 221 [29]        | 90                     |
| 5     | O | 4-Cl-Ph               | <b>4e</b>            | 1.3                   | 212–213 | 212–213 [30]    | 89                     |
| 6     | O | 3-Cl-Ph               | <b>4f</b>            | 1.5                   | 192–194 | 193–195 [31]    | 91                     |
| 7     | O | 3-NO <sub>2</sub> -Ph | <b>4g</b>            | 3                     | 228–229 | 229–231 [13e]   | 92                     |
| 8     | O | 4-MeO-Ph              | <b>4h</b>            | 1.4                   | 202–204 | 202–204 [32]    | 93                     |
| 9     | O | 2-Pyridyl             | <b>4i</b>            | 2.5                   | 193–195 | 194–195 [30]    | 94                     |
| 10    | O | 2-Thienyl             | <b>4j</b>            | 2                     | 214–216 | 215–217 [32]    | 88                     |
| 11    | O | 2-Furyl               | <b>4k</b>            | 1.5                   | 206–208 | 206–208 [22]    | 89                     |
| 12    | S | Ph                    | <b>4l</b>            | 2                     | 204–206 | 205–206 [33]    | 90                     |
| 13    | S | 4-Me-Ph               | <b>4m</b>            | 2.1                   | 192–195 | 192–194 [32]    | 91                     |
| 14    | S | 4-MeO-Ph              | <b>4n</b>            | 3.5                   | 148–149 | 150–152 [32]    | 92                     |
| 15    | S | 4-Cl-Ph               | <b>4o</b>            | 3                     | 179–182 | 180–182 [33]    | 93                     |
| 16    | S | 4-OH-Ph               | <b>4p</b>            | 2.5                   | 193–195 | 193–194 [34]    | 94                     |
| 17    | S | 3-NO <sub>2</sub> -Ph | <b>4q</b>            | 2                     | 206–208 | 206–207 [27]    | 90                     |

<sup>a</sup>Products were characterized by comparison of their spectroscopic data (<sup>1</sup>H NMR and IR) and melting points with those reported in the literature.

<sup>b</sup>Determined by TLC.

<sup>c</sup>Yields of recrystallized products.

reaction between benzaldehyde, urea **2a**, and ethylacetoacetate in IL-OPPh<sub>2</sub> leads to the formation of related dihydropyrimidine **4a**. The reaction mixture was stirred at 100°C in a preheated oil bath. Next, to improve the yields, we performed the reactions using different quantities of reagents. The best results were obtained with a 1:1.15:1.25:1 ratio of aldehyde, urea, β-ketoester, and IL-OPPh<sub>2</sub>, respectively. Several DHPMs were successfully synthesized in high yields by following the above method. The products can be separated from the ionic liquid system by simple extraction with ether and ethyl acetate in all examined cases. The results of the transformation of differently substituted aryl aldehydes to DHPM derivatives **4a–q** are presented in Table 1. Aromatic aldehydes bearing both electron-donating and electron-withdrawing groups readily undergo the reaction, giving fair yields of the corresponding Biginelli compounds. All products are known compounds, characterized by mp, IR, <sup>1</sup>H NMR spectra, and elemental analysis.

To exhibit the catalytic effect of IL-OPPh<sub>2</sub>, the condensation of two arylaldehydes (4-nitrobenzaldehyde and 4-methoxybenzaldehyde) with ethylacetoacetate and urea was studied by using different imidazolium-based ILs including [bmim] Cl, [bmim] Br, and [bmim] BF<sub>4</sub> at 100°C. It was found that these ILs were no more effective, and poor yield of the corresponding

3,4-dihydropyrimidinones were recorded in these conditions.

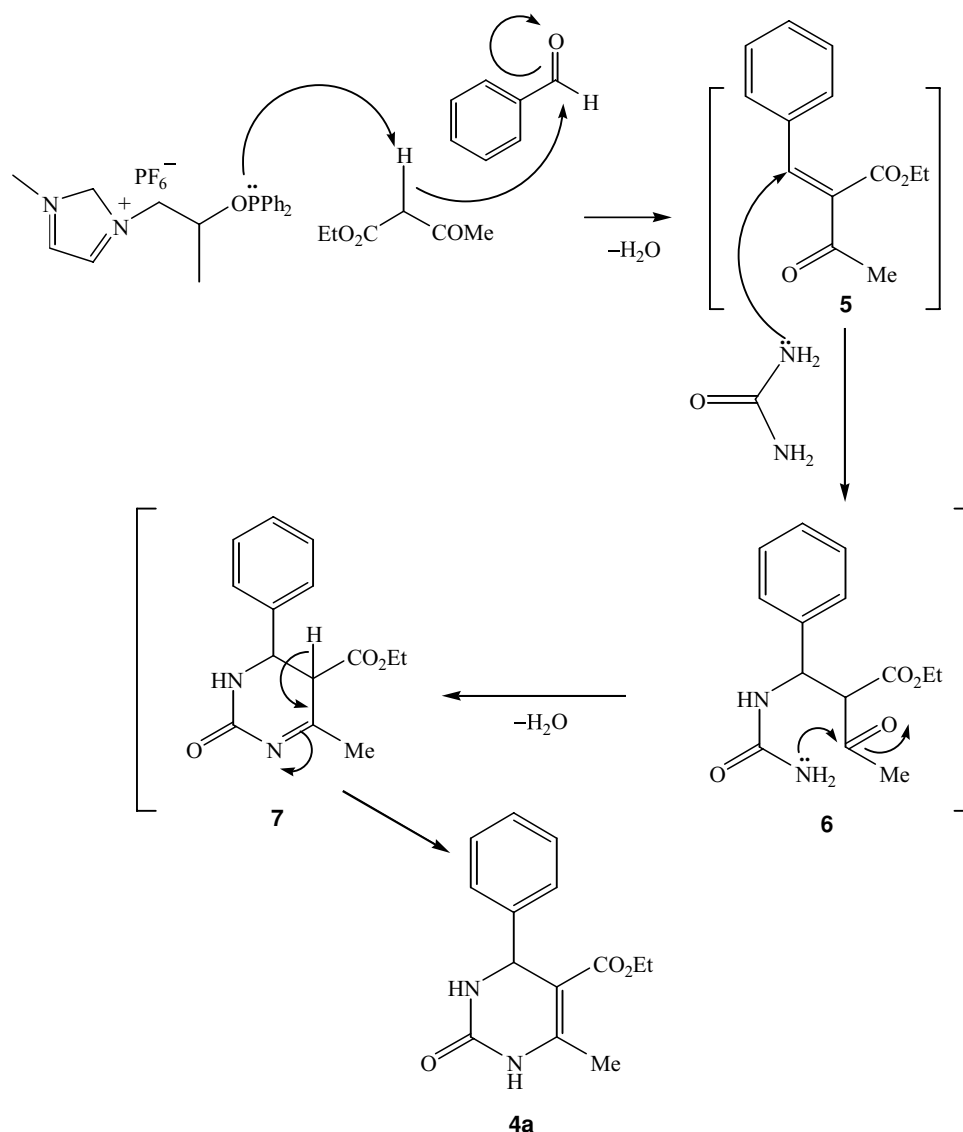
A plausible mechanism for the formation of the selected product **4a** in the presence of IL-OPPh<sub>2</sub> as a weak base catalyst is outlined in Scheme 2. Intermediate **5** apparently results from the initial Knoevenagel condensation of ethylacetoacetate with benzaldehyde in the presence of IL-OPPh<sub>2</sub> as a Lewis base catalyst. Michael addition of urea to the **5** yields the intermediate **6**, which cyclizes to cyclic imine **7** via the intramolecular condensation reaction. Compound **7** is converted to stable enamine product.

A noteworthy feature of ILs is their recyclability. In the present study, we investigated that IL-OPPh<sub>2</sub> can be recycled. After removal of the mixture of product, possible impurities and unreacted materials, the remaining IL was reused for consecutive three cycles without loss in their efficiency (Table 2).

**TABLE 2** The Comparison of Efficiency of IL-OPPh<sub>2</sub> in Synthesis of Biginelli Products **4a** and **4l** after Three Times

| Run | Yield(%) <sup>a</sup> |           |
|-----|-----------------------|-----------|
|     | <b>4a</b>             | <b>4l</b> |
| 1   | 91                    | 90        |
| 2   | 90                    | 90        |
| 3   | 91                    | 89        |

<sup>a</sup>Yields of recrystallised product.



SCHEME 2

## CONCLUSION

Task-specific Lewis basic ionic liquid has been shown to facilitate the Biginelli condensation reaction of a range of aryl aldehydes. Using the IL-OPPh<sub>2</sub> without solvent produced a homogeneous reaction system and showed high initial activity and overall conversion. In addition, IL-OPPh<sub>2</sub> can be easily recycled and reused with the same efficacies for three cycles. The merit of this methodology is that it is simple, mild, and efficient. Therefore, we believe that the work reported here provides a more practical alternative to the existing methodologies.

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