Large scale Biginelli reaction via water-based biphasic media: a green chemistry strategy

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Abstract—An important stage in process development is kilo scale preparation of the target compound. For this reason, a procedure involving water-based biphasic reaction media has been developed for conducting some exothermic reactions on a large scale. This protocol is illustrated by the energy-efficient and rapid preparation of dihydropyrimidinones by a solvent-free, green chemistry procedure applied to the Biginelli reaction using p-toluenesulfonic acid as catalyst.

Organic reactions belong to two classes: exothermic and endothermic. Traditional synthetic procedures, however, do not appear to make any distinction between these two types. As a rule, most conventional organic reactions involve a solvent that is selected usually on the basis of the boiling point to match the preferred temperature for the reaction of interest. Endothermic reactions need input of energy by heating, microwave irradiation or other methods such as the use of ultrasound. For exothermic reactions, however, external supply of energy would be unnecessary. In this context we have redesigned the Biginelli reaction.

The century-old Biginelli reaction (Scheme 1) has been attracting a great deal of attention in recent years partly because of the diverse types of physiological activity associated with the 3,4-dihydropyrimidin-2(1H)-ones produced by this reaction. This reaction involves the interaction of an aldehyde (1), a β ketoester (2), and urea or thiourea (3) in presence of an acid catalyst to produce the dihydropyrimidinone (4). Some of the interest in this heterocyclic synthesis is also due to the challenge of redesigning and improving an old but useful preparative method. Most of the recent work describes synthesis on a small scale. In contrast, we have been studying this reaction with the aim of devising kilogram scale procedures that would be helpful to process development programs.

One of the most recent publications on the Biginelli reaction reports the use of acetonitrile as a solvent, substantial amounts of iodine as a catalyst and a reaction period of reflux for 6–8 h under nitrogen to produce very high yield of the desired dihydropyrimidinones. A solvent-free method has been described that uses zinc chloride as the catalyst and reaction for 20 min at 80 °C. Glycol has been used as a solvent with potassium hydrogen sulfate as the promoter and a reaction time of 2 h at 100 °C. Earlier publications have reported other variations of the reaction conditions. A microwave-promoted modification used polyphosphate ester as the reaction medium.

Keywords: Biginelli reaction; Biphasic media; Dihydropyrimidinones; p-TSA as catalyst.

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In a recent publication we have reported observations on the solvent-free Biginelli reaction when it was initiated by grinding (known as Grindstone Chemistry in our laboratory). The temperature profile of the reaction established that this reaction is strongly exothermic. In connection with a project we became interested in the preparation of dihydropyrimidinones on several hundred grams scale. The highly exothermic nature of the reaction therefore presented a problem for which we have devised a simple green chemistry and energy-efficient solution that is described below.

Water is a medium that is fully compatible with green chemistry. Also, because of its large specific heat capacity, water is very efficient in removing thermal energy from reaction mixtures. After some experimentation with a few widely used reactions, a water-based procedure has been developed in our laboratory that has proved very convenient for conducting on a large scale several exothermic reactions involving liquid reagents.

This procedure consists of the following steps: (1) water immiscible, organic reagents for an exothermic reaction are added to a large volume of water; (2) an efficient mechanical stirrer is used next for mixing intimately these two separate layers; (3) the appropriate (acid or base) catalyst—if required for the reaction—is added to this biphasic liquid mixture. As stirring is continued the temperature of the reaction mixture rises indicating the start of an exothermic reaction. If the temperature rise is too rapid, cold water or crushed ice can be added to keep the temperature of the reaction mixture at the desired low level (usually 50 °C or lower to minimize evaporation).

There are several useful aspects of this water-based biphasic medium for conducting exothermic reactions. The apparatus required is simple: a large enough reaction vessel and an efficient stirrer are adequate. In our experience, most reactions take less than 20 min for completion on a molar scale of reactants. The solid reaction product that separates is usually crystalline and of high purity. In almost all cases the yield is very high. All these positive aspects make the reaction very compatible with green chemistry requirements. This procedure does not apply to endothermic reactions.

For a test of this procedure the acetylation of various amines that are immiscible with water was studied. It may be noted that a standard conventional method for N-acylation is the Schotten–Baumann reaction, which may be conducted by the interaction of an acid chloride and an amino compound that are added to an aqueous alkali solution and agitated vigorously. Traditionally, acetylation of amines is also conducted by the treatment of the solution of an amino compound (in a solvent such as dichloromethane or ether) with an acid anhydride or acid chloride in presence of pyridine (or a tertiary amine such as triethylamine).

In contrast, we have found that when an aqueous mixture of a water immiscible amine (5a–b) (e.g., a substituted aniline or benzyl amine) is stirred vigorously with acetic anhydride (6), an exothermic reaction ensues (as shown by the temperature rise of the reaction mixture) and in a matter of minutes the insoluble amide starts to precipitate. It may be noted that the rate of hydrolysis of acetic anhydride under these conditions is quite slow as shown by our reaction temperature profile for a mixture of acetic anhydride and water. In most cases the amide is of high purity and produced in more than 90% yield. Successful preparations of substituted acetonilide (including acetaminophen or tylenol (7a) and phenacetin (7b)) were conducted on molar (or multiple molar) quantities of amines. The purity of the amides was very high without recrystallization (see Scheme 2).

Encouraged by the above findings, the Biginelli reaction was conducted on 50 mmol scale: benzaldehyde (5.3 g), ethyl acetooctoate (6.5 g), and urea (100 mmol, 6 g, dissolved in 15 mL of water) were mixed together and the resulting biphasic mixture was stirred vigorously. In about 5 min a white crystalline solid started to separate. This solid was collected by filtration, washed with water and dried. The product was found to be essentially pure Biginelli product in 93% yield. This protocol was also applied to several other substituted benzaldehydes (see Scheme 1). In all cases the corresponding N-heterocycles (Biginelli products) were obtained in essentially pure form and in more than 90% yield.

For further testing our protocol, the Biginelli reaction was conducted successfully starting with 250 g of the following aldehydes: benzaldehyde, salicylaldehyde, p-chlorobenzaldehyde, p-nitrobenzaldehyde, and o-chlorobenzaldehyde. About 100 mL of water was used for these reactions. The condensation reaction with separation of crystalline product appeared to be complete in less than 30 min (Table 1). Another experiment, with

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<td>81</td>
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Scheme 2.
0.5 kg of benzaldehyde as the starting material, also gave very satisfactory yield of 93%.

In one experiment a very large volume (1 L) of water was used when conducting the reaction with 250 g of benzaldehyde. The reaction appeared to be very slow with no visible separation of solids in more than 2 h. But, on standing overnight the reaction was found to be complete. It was noted that the product that had separated was highly crystalline and colorless; the melting point indicated that the compound was pure. Thus, there was no need for recrystallization; washing with cold water followed by drying provided more than 95% yield of pure material. The purity was confirmed by GC–MS.

In summary, water-based biphasic reactions with immiscible organic reagents (for several exothermic reactions) were conducted on a large scale under vigorous agitation; the final temperature of the reaction mixture could be controlled by adjusting the quantity of water (or, by adding crushed ice). Water insoluble solid products that crystallized out in a short time were thus obtained in essentially pure condition and in very high yield.10 This protocol was energy-efficient and it ensured high atom economy.11

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References and notes

2. For extensive citations of diverse types of physiological activities, see literature cited in Ref. 4.
3. Previously reported reactions were conducted on a few hundred milligram scale.
5. Sun, Q.; Wang, Y.-q.; Ge, Z.-m.; Cheng, T.-m.; Li, R.-t. Synthesis 2004, 1047.
7. For extensive citation of earlier literature, see Ref. 4.
10. (a) Typical experimental procedure for the Biginelli reaction: An aromatic aldehyde (1 mol) was added to 150 mL of water with vigorous stirring. Then to this mixture was added urea/thiourea (2 mol) followed by the addition of ethylacetoacetate (1 mol), with constant stirring. Finally 5 g of p-toluenesulfonic acid was added to the above reaction mixture. During stirring a white crystalline solid separated out. After 15 min of stirring, this solid was filtered, washed with water and dried. It was recrystallized from methanol/ethyl acetate. The yields and melting points of the products are reported in Table 1. (b) Typical experimental procedure for N-acetylation: An aromatic amine (1 mol) was added to 110 mL of water with vigorous stirring. Then to it was added 102 mL (1 mol) of acetic anhydride. During stirring a white crystalline solid separated out. After 15 min of stirring the reaction mixture was allowed to cool and filtered. The solid product was washed with ice cold water and dried.
11. This is Green Chemistry Part 2. For the previous paper, see: Bose, A. K.; Pednekar, S.; Ganguly, S. N.; Chakraborty, G.; Manhas, M. S. Tetrahedron Lett. 2004, 45, 8351.