

Research Letter

Cs₂CO₃/[bmim]Br as an Efficient, Green, and Reusable Catalytic System for the Synthesis of N-Alkyl Derivatives of Phthalimide under Mild Conditions

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Aza-conjugate addition of phthalimide to α,β -unsaturated esters efficiently achieves in the presence of catalytic amount of Cs₂CO₃ and ionic liquid 1-butyl-3-methylimidazolium bromide ([bmim]Br) under mild reaction conditions (70°C) to afford N-alkyl phthalimides in high yields and relatively short reaction times.

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1. Introduction

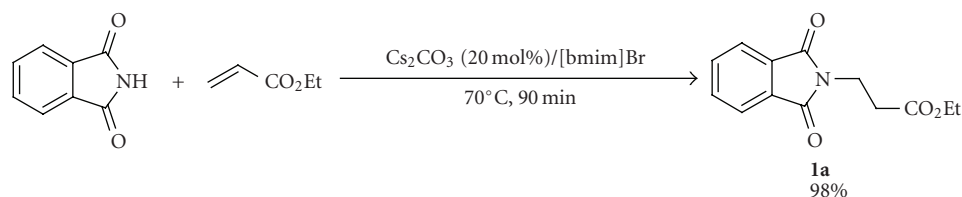
Over the past decade, room temperature ionic liquids have been emerged as a new class of stable and inert solvents. They exhibit high thermal stability, high polarity due to their ionic nature and a great ability to solubilize polar and nonpolar organic compounds. To date, various organic reactions have been carried out and investigated in ionic liquids, such as conjugate addition of sulfonamides [1, 2], azide ion [3], amines and N-heterocycles [4, 5], indoles [6], thiocyanide ion [7], active methylenes [8, 9], and thiols [10] to electrophilic alkenes, and other carbon-carbon, carbon-nitrogen, carbon-oxygen as well as carbon-sulfur bonds formation [11, 12].

N-alkyl derivatives of phthalimide have attracted much interest due to their potential use as antipsychotic [13], anti-inflammatory [14], hypolipidemic [15], agents and receptors [16], and so on. Moreover, these compounds are very useful intermediates in organic synthesis as they can be easily converted to primary amines (Gabriel synthesis) [17]. Therefore, there is a great deal of interest in the synthesis of this class of compounds. The aza-conjugate addition of phthalimide to electrophilic alkenes can be used as a useful synthetic route toward N-alkylated

phthalimides [18–21]. Several catalysts have been applied to achieve this transformation such as Na/EtOH [18], AlMe₂Cl [19], ZnO [20], and 1,4-diazabicyclo[2,2,2]octane [21]. However, these reported methods are associated with one or more of the following drawbacks: (i) moderate yield, (ii) relatively long reaction time, (iii) harsh conditions, (iv) the use of more reactive phthalimide salts instead of phthalimide, (v) difficult experimental procedure, and (vi) the necessity of stoichiometric amount of catalyst. Moreover, the aza-conjugate addition reaction of phthalimide has been scarcely studied. Therefore, it seems highly desirable to find an efficient new protocol for this reaction.

Cesium carbonate is a commercially available, heterogeneous, and environmentally benign basic catalyst that has been used in various organic transformations [22–28].

Considering the above subjects and also in continuation of our previous studies on green organic synthesis [20, 21, 29–32], we report here an efficient, green, and simple method for the preparation of N-alkyl phthalimides via aza-conjugate addition of phthalimide to α,β -unsaturated esters in the presence of catalytic amount of Cs₂CO₃ in [bmim]Br at 70°C (Scheme 1). This present method has none of the above disadvantages at all.



SCHEME 1

TABLE 1: Comparing the reaction of phthalimide with ethyl acrylate in conventional solvents versus [bmim]Br.

| Entry | Solvent | Time (min) | Yield (%) ^a |
|-------|--------------------|------------|------------------------|
| 1 | [bmim]Br | 90 | 98 |
| 2 | CH ₃ CN | 180 | 49 |
| 3 | EtOH | 120 | 61 |
| 4 | H ₂ O | 120 | 37 |
| 5 | DMSO | 120 | 89 |
| 6 | DMF | 120 | 86 |
| 7 | HMPTA | 120 | 75 |
| 8 | Solvent-free | 240 | 13 |

^aIsolated yield.

2. Results and Discussion

We have found previously Cs₂CO₃ acts as an efficient basic reagent for N3-alkylation of N1-substituted pyrimidines [22], and N-arylation of nucleobases [23]. Moreover, this base has been frequently applied for alkylation and arylation reactions [24–28]. These subjects encouraged us to use Cs₂CO₃ as catalyst for N-alkylation of phthalimide via aza-conjugate addition reaction. Therefore, firstly we used different amounts of Cs₂CO₃ to accomplish aza-conjugate addition of phthalimide (2 mmol) to ethyl acrylate (2.4 mmol) in [bmim]Br (1 g) at range of 25–100°C to provide compound **1a** (Scheme 1). The results showed that the reaction proceeded efficiently in the presence of 20 mol% of Cs₂CO₃ at 70°C and the product was obtained in 98% yield after 90 minutes. We also examined the reaction in the presence of sodium and potassium carbonate in which the product was produced in 59 and 82% within 240 and 180 minutes, respectively. Thus, we selected Cs₂CO₃ as catalyst for our reaction.

To compare the efficiency of ionic liquid versus the conventional solvents, we examined the reaction between phthalimide (2 mmol) and ethyl acrylate (2.4 mmol) using Cs₂CO₃ (20 mol%) in some conventional solvents (10 mL) at 70°C (Table 1). As it can be seen from Table 1, higher yield and shorter reaction time were obtained in [bmim]Br. The reaction was also tested in solvent-free conditions; however, these conditions were not efficient (Table 1). Therefore, ionic liquid is an essential factor to promote our reaction.

After optimization of the reaction conditions, we reacted phthalimide with different α,β -unsaturated esters. The results are summarized in Table 2. As Table 2 indicates, all reactions proceeded efficiently and the N-alkyl phthalimides

were produced in excellent yields and relatively short reaction times.

The interesting behavior of [bmim]Br/Cs₂CO₃ system lies in the fact that it can be reused after simple washing with Et₂O, rendering this process more economical. The yields of compound **1a** (model compound) in the 2nd and 3rd uses of the [bmim]Br/Cs₂CO₃ were almost as high as in the first use (see Table 3).

3. Experimental

All chemicals were purchased from Merck, (Germany) or Fluka, (Switzerland) Chemical Companies. The ¹H NMR (250 MHz) and ¹³C NMR (62.5 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Mass spectra were recorded on a Shimadzu GC MS-QP 1000 EX apparatus. Melting points were recorded on a Büchi B-545 apparatus in open capillary tubes.

3.1. General Procedure for the Synthesis of N-Alkyl Phthalimides

To a well-ground mixture of phthalimide (0.294 g, 2 mmol) and Cs₂CO₃ (0.130 g, 0.4 mmol) in a 10 mL round-bottomed flask connected to a reflux condenser [bmim]Br (1 g) and α,β -unsaturated ester (2.4 mmol) were added. The resulting mixture was stirred in an oil bath (70°C) for the times reported in Table 1. Afterward, the reaction mixture was cooled to room temperature and was extracted with Et₂O (3 × 50 mL). The organic extracts were then combined. After removal of the solvent, the crude product was purified by short column chromatography on silica gel eluted with EtOAc/*n*-hexane (1/3). After isolation of the product and evaporation of the remaining Et₂O in ionic liquid, the ionic liquid containing the catalyst (Cs₂CO₃/[bmim]Br) was used for the next run under identical reaction conditions.

3.2. Selected Physical and Spectral Data

Ethyl 3-Phthalimido Propanoate (**1a**)

Colorless solid; mp 59–60°C (Lit. [20] mp 60–61°C); IR (KBr): 3051, 2968, 1774, 1716 cm⁻¹; ¹H NMR (CDCl₃): δ 1.11 (t, 3H, *J* = 7.1 Hz, CH₃), 2.57 (t, 2H, *J* = 7.2 Hz, O=CCH₂), 3.86 (t, 2H, *J* = 7.2 Hz, NCH₂), 4.06 (q, 2H, *J* = 7.1 Hz, OCH₂), 7.57–7.70 (m, 4H); ¹³C NMR (CDCl₃): δ 13.8, 32.7, 33.5, 64.3, 122.9, 131.7, 133.8, 167.5, 170.6; MS (*m/z*): 247 (M⁺).

TABLE 2: Synthesis of N-alkyl phthalimides using Cs₂CO₃/[bmim]Br catalytic system.

| R | Product ^a | Time (min) | Yield (%) ^b |
|--------------------------------------------------------------------------------------------------|----------------------|------------|------------------------|
| CH ₃ CH ₂ | 1a | 90 | 98 |
| CH ₃ (CH ₂) ₂ CH ₂ | 1b | 90 | 98 |
| CH ₃ (CH ₂) ₄ CH ₂ | 1c | 90 | 97 |
| C ₆ H ₅ CH ₂ | 1d | 100 | 96 |
| C ₆ H ₅ CH ₂ CH ₂ | 1e | 100 | 96 |
| C ₆ H ₅ CH=CHCH ₂ | 1f | 100 | 95 |
| <i>o</i> -CH ₃ O-C ₆ H ₄ OCH ₂ CH(OH)CH ₂ | 1g | 130 | 93 |
| C ₆ H ₅ | 1h | 70 | 96 |
| | 1i | 70 | 94 |

^aAll compounds are known and their structures were identified by comparison of their melting points and spectral data with those in the authentic samples.

^bIsolated yield.

TABLE 3: Aza-conjugate addition of phthalimide to ethyl acrylate in the presence of recycled Cs₂CO₃/[bmim]Br.

| Entry | Cycle | Time (min) | Yield (%) ^a |
|-------|---------|------------|------------------------|
| 1 | 1st use | 90 | 98 |
| 2 | 2nd use | 90 | 96 |
| 3 | 3rd use | 100 | 95 |

^aIsolated yield.

2-Hydroxy-3-(2-Methoxyphenoxy)Propyl 3-Phthalimido Propanoate (**1g**)

Pale yellow oil (Lit. [21] oil); IR (neat): 3480, 3049, 2948, 1770, 1715 cm⁻¹; ¹H NMR (CDCl₃): δ 2.63 (t, 2H, *J* = 7.0 Hz, O=CCH₂), 3.67 (s, 3H, CH₃), 3.80–3.90 (m, 5H), 4.11–4.19 (m, 3H), 6.73–6.80 (m, 4H), 7.54 (m, 2H), 7.68 (m, 2H); ¹³C NMR (CDCl₃): δ 32.8, 33.6, 55.7, 65.7, 67.9, 70.5, 111.9, 114.2, 120.9, 121.8, 123.2, 131.7, 134.0, 147.8, 149.3, 168.0, 170.8; MS (*m/z*): 399 (*M*⁺).

4. Conclusions

In summary, we have developed a new method for the synthesis of N-alkyl phthalimides as biologically interesting compounds via aza-conjugate addition reaction. This new strategy has the advantage of high yield, short reaction time, mild conditions, ease of product isolation, potential for recycling of the catalytic system, and compliance with the green chemistry protocols.

Acknowledgments

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