RESEARCH LETTER

Deep eutectic solvents and glycerol: a simple, environmentally benign and efficient catalyst/reaction media for synthesis of N-aryl phthalimide derivatives

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Deep eutectic solvents (DES) and glycerol have been successfully employed as efficient catalysts/reaction media in the synthesis of N-aryl phthalimide derivatives from phthalic anhydride and primary aromatic amines. The DES prepared from choline chloride and malonic acid proved to be an efficient catalyst whereas glycerol and the DES of choline chloride and urea played a dual role of catalyst and solvent. These mixtures are biodegradable, nontoxic, and cost-effective thereby providing a good industrial alternative to conventional methods. These methods gave products in moderate to high yields with good recyclability of catalyst/solvent at least up to five consecutive runs.

Keywords: deep eutectic solvents; glycerol; choline chloride; phthalimide; phthalic anhydride; urea

Introduction

N-phenylphthalimide and its derivatives possess beneficial pharmacological properties that include anticonvulsant (1) and anti-inflammatory activities (2, 3), and some imide derivatives are also used in tuberculosis therapy, as well as a growth stimulant for plants (4, 5). Phthalimide derivatives are also widely used in polymer and synthetic chemistry (6, 7). Hence, such imide derivatives are significant, especially with respect to industrial and pharmaceutical applications. A screening of phthalimide derivatives for anticonvulsant activity test in mice by Vamecq and co-workers (8) led to the selection of compounds of the type 5i as shown in Figure 1 for oral maximal electroshock-induced seizure (MES) evaluation in rats.

N-phenylphthalimide derivatives have been synthesized by many methods, including condensation of an anhydride with an amine in acetic anhydride medium catalyzed by acids (9), N-alkylation of phthaloyl dichloride with azide in the presence of triphenylphosphine (10), and N-alkylation of imides in alcohol media (11). However, these methods have obvious disadvantages, like longer reaction times, use of acids, volatile organic solvents and toxic catalysts at stoichiometric levels, and recovery in small quantities.

Apart from conventional methods, phthalimide synthesis has also been reported in ionic liquids like [bmim][PF6] (12) and [bmim][BF4] (13) or nonionic liquid solvents like polyethylene glycol (14). Although these methods showed improved yields, however, they still hold some limitations like longer reactions times, use of organic solvents during work-up, difficulty in recovery of reaction media or higher reaction temperatures. In addition, ionic liquids especially based on imidazole with fluorinated anions suffer from the demerits of being non-biodegradable, toxic, commercially expensive and their production is also related to the use of large amounts of unsafe and volatile organic solvents (15).

Therefore, it is essential to develop a cost-effective and environmentally benign catalytic system which is of utmost importance in contemporary organic synthesis. Owing to this, we planned the synthesis of N-aryl phthalimide derivatives in efficient, biodegradable, and economical alternatives such as deep eutectic solvents (DES) and glycerol. DES include simple eutectics made from a combination of quaternary ammonium salts, like choline chloride, with hydrogen bond donors like urea and glycerol, or with Lewis acids like zinc chloride. Such eutectic mixtures possess many significant properties (16) similar to conventional ionic liquids, such as low vapor pressure, and low flammability. Their cost-effectiveness is owing to the large scale commercial production of choline chloride as a chicken feed additive. In addition, the manufacture of choline chloride is done through a simple and efficient gas phase reaction between trimethylamine, ethylene oxide, and HCl. The Roger Sheldon E factor (17)
for this salt is close to zero because almost no waste products are formed during this reaction. The same can also be applicable for preparation of DES since no by-products are generated during its formation. The ability of DES to act as catalysts or solvents, however, has not been explored adequately in the field of synthetic organic chemistry, except for some reactions like Fischer indole synthesis (18), acetylation of carbohydrates and cellulose (19), selective N-alkylation (20), and Knoevenagel condensation (21). Glycerol is a polar, nontoxic, biodegradable, recyclable, highly inert, and stable solvent manufactured on a large scale from renewable sources. It has been utilized as an alternative for organic solvents in several reactions like asymmetric reductions of prochiral ketones catalyzed by baker’s yeast (22), hydrogenation, C-C coupling, and kinetic resolution of racemates (23). A review relating to the use of glycerol as a solvent has been published recently (24). Also, a recent paper shows the effectiveness of eutectic solvents of choline chloride and glycerol in esterification reaction (25).

Herein, we present N-aryl phthalimide synthesis in glycerol and two different DES prepared from choline chloride and malonic acid/urea.

### Results and discussion

In order to compare the efficiency of our method with conventional routes, we conducted N-phenylphthalimide synthesis in different organic solvents and biodegradable media like glycerol and DES, as summarized in Table 1. It is interesting to observe that the reaction gave poor yields in organic solvents. However, DES (ChCl:urea) gave best yields when used as a reaction media at 80 °C that could be owing to lesser viscosity of DES or greater solubility of phthalic anhydride at higher temperatures. On the contrary, the DES of choline chloride and malonic acid gave best yields when used in catalytic amounts. It is also observable that the deep eutectic of choline chloride and glycerol gave poorer yields under all conditions.

The 1H NMR spectra of the DES (ChCl:malonic acid) without and with (30% v/v) dilution using deuterated methanol confirmed that the DES remains in its original form even on dilution. The fact that the reaction did not proceed with malonic acid as catalyst in methanol (Table 1, entry 17) suggests that the

| S. no. | Solventsa | Catalyst | Reaction temperature (in °C) | Yield (%)b |
|-------|-----------|----------|-----------------------------|------------|
| 1     | Methanol  | –        | 65                          | 30         |
| 2     | Dichloromethane | –     | 40                          | –          |
| 3     | Toluene   | –        | 80                          | 40         |
| 4     | Acetonitrile | –     | 80                          | 38         |
| 5     | Glycerol  | –        | 80                          | 65         |
| 6     | DES       | –        | 80                          | 56         |
| 7     | DES (ChCl:glycerol) | –   | 80                          | 81         |
| 8     | DES (ChCl:urea) | –    | 80                          | 67         |
| 9     | Glycerol  | –        | 65                          | 56         |
| 10    | DES       | –        | 65                          | 40         |
| 11    | DES (ChCl:urea) | –   | 65                          | 60         |
| 12    | DES (ChCl:malonic acid) | – | 65                          | 62         |
| 13    | Methanolf | Glycerol | 65                          | 52         |
| 14    | Methanolf | DES      | 65                          | 45         |
| 15    | Methanolf | DES      | 65                          | 69         |
| 16    | Methanolf | DES      | 65                          | 84         |
| 17    | Methanolf | Malonic acid | 65 | 15         |
| 18    | Glycerol  | –        | Room temperature            | –          |
| 19    | DES (ChCl:urea) | –    | Room temperature            | –          |

aDES, Deep eutectic solvent.

bIsolated yields.

cReaction conditions: phthalic anhydride (1.0 g, 7 mmol), aniline (0.6 ml, 7 mmol), reaction media (10 vol), Reaction time – 2.5 hrs.

dReaction conditions: phthalic anhydride (1.0 g, 7 mmol), aniline (0.6 ml, 7 mmol), Catalyst (30% v/v), reaction media (10 vol), Reaction time – 2.5 hrs.

Figure 1. Compound 5i: 2-(2,6-dimethylphenyl)isoindoline-1,3-dione.
reaction occurs because of DES and not due to its individual components.

After screening different methods for synthesis of N-phenylphthalimide, three best and efficient systems were chosen for further studies that included reactions of functionalized aniline derivatives as shown in Scheme 1. As summarized in Table 2, the reaction gave good results by all the three different methods for a variety of functional groups that include both electron-donating as well as electron-withdrawing groups. The reaction was faster in the presence of electron-donating substituents (Table 2, entries 5b–5f), with relatively better yields. The reaction offered moderate to good yields even in the case of electron-withdrawing aromatic amines (Table 2, entry 5h) and ortho-substituted amines (Table 2, entry 5i). The reaction times were comparatively shorter than many reported methods in the literature.

The synthesis of N-aryl phthalimide derivatives from phthalic anhydride and primary aromatic amines in imidazolium ionic liquids has been reported earlier in the literature (12). In these studies, the ionic liquid was recycled by heating with ethanol to extract the ionic liquid. In the present method, glycerol/DES (ChCl:urea) was recovered by simply evaporating water (added during work-up) from the reaction mass after filtration of the solid product. In case of the other DES (ChCl:malonic acid), the filtrate, obtained after separation of solid product, was subjected to removal of methanol by distillation under vacuum. We tried the reaction of phthalic anhydride with aniline in fresh media/catalyst, as well as in those recovered from the successive runs as summarized in Figure 3. The yields did not show much decrease in activity, even after five successive runs. Thus, these methods employing glycerol and DES are environmentally benign, both with respect to synthesis and work-up, since it prevented much use of organic solvents especially due to the simplification of procedure. Moreover, the catalyst/media are biodegradable and nontoxic.

**Experimental section**

**General**

The progress of the reaction was monitored by thin layer chromatography (TLC) on silica gel plates. All compounds were characterized by Mass spectrometry, FT-IR, UV, 1H NMR, and 13C NMR spectroscopy. The compounds were also checked for their melting points which were in well accordance with the literature values (Table 2). Also, the 1H NMR and 13C NMR for DES (ChCl:urea) along with the 1H NMR spectra of the DES (ChCl:malonic acid) in its actual and diluted forms is provided. FT-IR spectra were recorded on a Bomem Hartmann and Braun MB-Series FT-IR spectrometer. 1H NMR spectra were recorded on Varian 300 MHz mercury plus spectrometer and mass spectral data were obtained with a micromass-Q-TOF (YA105) spectrometer. Common reagent grade chemicals were procured from M/s S.D. Fine Chemical Ltd., India, and were used without further purification.

**Preparation of DES**

In this study, two DES were prepared by combining choline chloride with urea/malonic acid (Figure 2) according to the procedures reported in the literature (16). Choline chloride (100 g, 714 mmol) and urea (86 g, 1.43 mol) were placed and heated at 74°C, until a clear solution began to form. The DES 1 thus formed (186 g, 100%) was cooled and used in reactions without any purification. The DES 2 was prepared similarly by mixing choline chloride (100 g, 714 mmol) and malonic acid (75 g, 714 mmol) at 100°C.

Scheme 1. Synthesis of N-phenylphthalimide derivatives from phthalic anhydride and primary aromatic amines using glycerol or deep eutectic solvents.
The atom efficiency of this reaction is 100% since all the atoms present in the starting materials were incorporated in the products.

**General procedure for synthesis of N-arylphthalimides in biodegradable media including glycerol/DES (ChCl:urea)**

To a mixture of phthalic anhydride 3 (1.0 g, 7.0 mmol) in reaction media (glycerol/DES) (10 ml, 10 vol), primary aromatic amine 4 (7.0 mmol) was added in two equal portions with a time interval of 10 minutes and the reaction mixture was stirred at 80°C for an appropriate time as indicated in Table 2. The product formation was monitored by TLC. After cooling, the reaction mixture was poured in water (10 ml) and the solid product 5 obtained was filtered off, washed with water (3–6 ml), dried in air, and further purified by silica gel column chromatography using toluene as an eluent. The mother liquor obtained from filtration was subjected to evaporation of water under vacuum to recover reaction media.

**General procedure for synthesis of N-arylphthalimides using catalytic amounts of DES (ChCl:malonic acid)**

To a solution of phthalic anhydride 3 (1.0 g, 7.0 mmol) in methanol (10 ml, 10vol), the catalyst (DES of ChCl:malonic acid) was added in 30% v/v quantity with respect to methanol. Then primary aromatic amine 4 (7.0 mmol) was added in two equal portions with a time interval of 10 minutes and the reaction mixture was stirred at 65°C for an appropriate time as indicated in Table 2. The product formation was monitored by TLC. After cooling, the reaction mixture was distilled under vacuum partially to remove excess of methanol and then filtered off to separate the

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**Figure 2. Deep eutectic solvent of (a) choline chloride and urea (b) choline chloride and malonic acid.**

**Table 2. Synthesis of N-arylphthalimides in glycerol and deep eutectic solvent (DES) (ChCl:urea) as reaction media and DES (ChCl:malonic acid) as catalyst at 80 and 65°C, respectively.**

| Entry | -Ar     | Time (h) | Glycerol | ChCl:urea | ChCl:malonic acid |
|-------|---------|----------|----------|-----------|------------------|
| 5a    | -C₆H₅   | 2.5      | 65       | 81        | 84               |
| 5b    | p-MeOC₆H₅ | 2        | 71       | 86        | 89               |
| 5c    | m-MeOC₆H₅ | 2.5      | 70       | 84        | 87               |
| 5d    | p-MeC₆H₅  | 2.5      | 72       | 85        | 85               |
| 5e    | m-MeC₆H₅  | 2.5      | 70       | 84        | 88               |
| 5f    | o-MeC₆H₅  | 2.5      | 68       | 79        | 83               |
| 5g    | p-CIC₆H₅  | 3.5      | 70       | 77        | 81               |
| 5h    | p-NO₂C₆H₅ | 4.5      | 63       | 74        | 77               |
| 5i    | 2,6-diMeC₆H₅ | 3.5 | 61       | 78        | 82               |

*a* Isolated yields.  
*b* Reaction conditions: phthalic anhydride (1.0 g, 7 mmol), aromatic amine (7 mmol), reaction media (10 vol); reaction temperature = 80°C.  
*c* Reaction conditions: phthalic anhydride (1.0 g, 7 mmol), aromatic amine (7 mmol), Catalyst (30% v/v), methanol (10 vol); reaction temperature = 65°C.
solid product 5 which was further separately washed with water, dried in air, and purified by silica gel column chromatography using toluene as an eluent. The mother liquor was subjected to evaporation of methanol under vacuum to recover the catalyst.

This reaction was also scaled up to 50 g of phthalic anhydride with aniline thus producing N-phenylphthalimide with a yield of 67% in glycerol, yield of 80% in DES (ChCl:urea), and 85% in DES (ChCl:malonic acid). The recovered biodegradable media was used for recycling studies.

Spectroscopic data for compounds (5a–5i)

2-phenylisoindoline-1,3-dione 5a

m.p. 202°C (205°C Lit. (26)); λ<sub>max</sub> (methanol)/nm 214 and 292; IR (KBr): v<sub>max</sub> (in cm<sup>-1</sup>) = 3071, 1736, 1707, 1593, 1495, 1358, and 1261; 1H NMR (δ in ppm, CDCl<sub>3</sub>): δ = 7.25–7.96 (9H, m, aromatic CH); 13C NMR (δ in ppm, CDCl<sub>3</sub>): δ = 123.8, 126.6, 128.1, 129.1, 131.8, 134.4, 167.3; m/z (EI) 224.0 (M + 1); C<sub>14</sub>H<sub>11</sub>NO<sub>2</sub> calculated m/z: 223.0.

2-(3-methoxyphenyl) isoindoline-1,3-dione 5c

m.p. 122°C (128°C Lit. (27)); λ<sub>max</sub> (methanol)/nm 226 and 228; IR (KBr): v<sub>max</sub> (in cm<sup>-1</sup>) = 2843, 1781, 1720, 1608, 1497, 1463, 1379, 1225; 1H NMR (δ in ppm, CDCl<sub>3</sub>): δ = 6.98–7.96 (8H, m, aromatic CH); 3.84 (3H, s, OCH<sub>3</sub>); 13C NMR (δ in ppm, CDCl<sub>3</sub>): δ = 55.51, 112.45, 114.19, 118.95, 123.82, 129.86, 131.83, 132.76, 134.46, 160.13, 167.27; m/z (EI) 254.1 (M + 1); C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub> calculated m/z: 253.1.

2-4-methylphenyl) isoindoline-1,3-dione 5d

m.p. 200°C (204°C Lit. (26)); λ<sub>max</sub> (methanol)/nm 235 and 292; IR (KBr): v<sub>max</sub> (in cm<sup>-1</sup>) = 3040, 2916, 2864, 1747, 1714, 1514, 1464, 1383, 1219; 1H NMR (δ in ppm, CDCl<sub>3</sub>): δ = 7.31–7.95 (8H, m, aromatic CH); 2.41 (3H, s, CH<sub>3</sub>); 13C NMR (δ in ppm, CDCl<sub>3</sub>): δ = 21.27, 123.73, 126.52, 129.07, 129.83, 131.91, 134.35, 138.21, 167.47; m/z (EI) 238.0 (M + 1); C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub> calculated m/z: 237.0.

2-(2-methylphenyl) isoindoline-1,3-dione 5f

m.p. 180°C (182°C Lit. (26)); λ<sub>max</sub> (methanol)/nm 234 and 294; IR (KBr): v<sub>max</sub> (in cm<sup>-1</sup>) = 3090, 2924, 2851, 1745, 1712, 1496, 1463, 1379, 1225; 1H NMR (δ in ppm, CDCl<sub>3</sub>): δ = 7.23–7.94 (8H, m, aromatic CH); 2.42 (3H, s, CH<sub>3</sub>); 13C NMR (δ in ppm, CDCl<sub>3</sub>): δ = 21.40, 123.68, 127.28, 128.93, 129.02, 131.56, 131.80, 134.34, 139.10, 167.35; m/z (EI) 238.0 (M + 1); C<sub>15</sub>H<sub>11</sub>NO<sub>3</sub> calculated m/z: 237.0.

2-(4-methoxyphenyl) isoindoline-1,3-dione 5g

m.p. 194°C (192°C Lit. (28)); λ<sub>max</sub> (methanol)/nm 218 and 292; IR (KBr): v<sub>max</sub> (in cm<sup>-1</sup>) = 3061, 1742, 1715, 1496, 1389, 1121; 1H NMR (δ in ppm, CDCl<sub>3</sub>): δ = 7.26–7.96 (8H, m, aromatic CH); 13C NMR (δ in ppm, CDCl<sub>3</sub>): δ = 123.89, 127.71, 129.34, 130.28, 131.67, 133.84, 134.60, 167.01; m/z (EI) 258.0 (M + 1); C<sub>14</sub>H<sub>11</sub>ClNO<sub>2</sub> calculated m/z: 257.0.
2-(4-nitrophenyl)isoindoline-1,3-dione 5h

m.p. 268°C (267°C Lit. (26)); \( \lambda_{\text{max}} \) (methanol)/nm 225, 270, and 345; IR (KBr); \( v_{n\text{max}} \) (in \( \text{cm}^{-1} \)) = 3118, 1782, 1728, 1517, 1342, 1594, 1494, 1377, 1224; \(^1\text{H} \) NMR (in ppm, CDCl3): \( \delta = 7.26-8.40 \) (8H, m, aromatic CH); \(^{13}\text{C} \) NMR (in ppm, CDCl3): \( \delta = 79.28, 124.27, 124.52, 126.43, 131.47, 135.09, 166.50 \). m/z (EI) 269.0 (M\(^+\)).

2-(2,6-dimethylphenyl)isoindoline-1,3-dione 5i

m.p. 202°C; \( \lambda_{\text{max}} \) (methanol)/nm 230 and 291; IR (KBr); \( v_{n\text{max}} \) (in \( \text{cm}^{-1} \)) = 3070, 2933, 2862, 1778, 1706, 1595, 1468, 1375, 1260; \(^1\text{H} \) NMR (in ppm, CDCl3): \( \delta = 2.98, 3.05, 3.95, 4.424 \) (1H, d, \( \text{J} = 7 \)), 4.10 (2H, m, CH\(_2\)), 3.6 (2H, m, \( \text{CH}_{2} \)), 3.3 (9H, s, CH\(_3\)). \(^{13}\text{C} \) NMR (75 MHz, CDCl3), \( \delta = 159.5, 155.1, 150.6, 145.0, 136.85, 166.50 \).

DES (ChCl:urea)

\(^1\text{H} \) NMR (in ppm, CDCl3): \( \delta = 3.187 \) (9H, s, CH\(_3\)), 3.505 (2H, m, CH\(_2\)), 3.95 (2H, m, CH\(_2\)), 4.424 (1H, OH), 6.095 (8H, NH\(_2\)). \(^{13}\text{C} \) NMR (75 MHz, CDCl3), \( \delta = 161.9, 67.8, 55.9, 54.0 \).

DES (ChCl:malonic acid)

\(^1\text{H} \) NMR (in ppm, DMSO): \( \delta = 4.5 \) (1H, OH), 3.9 (2H, m, CH\(_2\)), 3.5 (2H, m, CH\(_2\)), 3.2 (9H, s, CH\(_3\)), 1.9 (2H, s, CH\(_2\)). \(^{13}\text{C} \) NMR (75 MHz, CDCl3), \( \delta = 161.9, 67.8, 55.9, 54.0 \).

DES (ChCl:malonic acid) (30% v/v in Deuterated methanol)

\(^1\text{H} \) NMR (in ppm, Deuterated MeOH): \( \delta = 5.2 \) (2H, s, COOH), 4.6 (1H, OH), 4.0 (2H, m, CH\(_2\)), 3.6 (2H, m, CH\(_2\)), 3.3 (9H, s, CH\(_3\)), 2.0 (2H, s, CH\(_2\)).

Conclusion

This paper offers a prospective alternative to conventional catalysts and solvents in the synthesis of N-arylphthalimide derivatives by use of glycerol and DES of choline chloride with urea/malic acid. These methods showed some important advantages over previously reported procedures like lesser reaction times, easy availability/preparation of catalyst/solvent and their eco-friendly nature, simple work-up method. In addition, the non-tedious recovery, efficient recyclability and cost-effectiveness of glycerol and DES open a wide scope for industrial applicability of these methods.

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Characterization of products

FT-IR spectra

2-phenylisoidoline-1, 3-dione 5a
2-(4-methoxyphenyl) isoindoline-1, 3-dione 5b
2-(3-methoxyphenyl) isoindoline-1, 3-dione 5c
2-p-tolylisoindoline-1, 3-dione 5d
2-m-tolyisoindoline-1, 3-dione 5e
2-o-tolysoidoline-1, 3-dione 5f
2-(4-chlorophenyl)isoindoline-1, 3-dione 5g
2-(2,6-dimethylphenyl)isoindoline-1,3-dione 5i
Mass spectra

2-phenylisoindoline-1,3-dione 5a
2-(4-methoxyphenyl) isoindoline-1,3-dione 5b
2-(3-methoxyphenyl) isoindoline-1,3-dione 5c
2-p-tolylisoindoline-1,3-dione 5d
2-m-tolyisoindoline-1,3-dione 5e
2-o-tolysoindoline-1,3-dione 5f
2-(4-chlorophenyl)isoindoline-1,3-dione 5g
2-(4-nitrophenyl) isoindoline-1,3-dione 5h
2-(2,6- dimethylphenyl)isoindoline-1,3-dione 5i
$^1$H NMR spectra

2-phenylisoindoline-1,3-dione 5a
2-(4-methoxyphenyl) isoindoline-1,3-dione 5b
2-(3-methoxyphenyl) isoindoline-1,3-dione 5c
2-p-tolyisoindoline-1,3-dione 5d
2-m-tolysindoline-1,3-dione 5e
2-λ-tolyisoindoline-1,3-dione 5λ
2-(4-chlorophenyl)isoindoline-1,3-dione 5g
2-(4-nitrophenyl)isoindoline-1,3-dione 5h
2-(2,6- dimethylphenyl)isoindoline-1,3-dione 5i
$^{13}$C NMR spectra

2-phenylisoindoline-1,3-dione 5a
2-(4-methoxyphenyl) isoindoline-1,3-dione 5b
2-(3-methoxyphenyl) isoindoline-1,3-dione 5c
2-p-tolyisoindoline-1,3-dione 5d
2-m-tolyisoindole-1,3-dione 5e
2-o-tolysoidoline-1,3-dione 5f
2-(4-chlorophenyl)isoindoline-1,3-dione 5g
2-(4-nitrophenyl)isoindoline-1,3-dione 5h
2-(2,6- dimethylphenyl)isoindole-1,3-dione 5i
$^1$H-NMR spectra of DES (ChCl:Urea)
\(^{13}\)C-NMR spectra of DES (ChCl:Urea)
$^1$H-NMR spectra of DES (ChCl:Malonic acid)

$^1$H-NMR of Deep eutectic solvent
(ChCl:Malonic acid)
$^1$H-NMR spectra of DES (ChCl:Malonic acid) [(30% v/v) diluted with deuterated methanol]