Halogenation reactions in biodegradable solvent: Efficient bromination of substituted 1-aminoanthra-9,10-quinone in deep eutectic solvent (choline chloride : urea)†

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Received 10th November 2009, Accepted 7th December 2009
First published as an Advance Article on the web 26th January 2010
DOI: 10.1039/b923589b

A simple ammonium deep eutectic solvent was used as a dual catalyst and environmentally benign reaction medium for the bromination of 1-aminoanthra-9,10-quinone, eliminating the need for volatile organic solvents and concentrated acids like H_2SO_4 as solvents or catalysts. This simple ammonium deep eutectic solvent, easily synthesized from choline chloride and urea, is relatively inexpensive and biodegradable, making it applicable for industrial applications. The deep eutectic solvent was easily separated and reused without loss of activity, and thus provides a good alternative for industrial bromination of 1-aminoanthra-9,10-quinone.

Introduction

Halogenated 1-aminoanthra-9,10-quinones are important intermediates in the dyestuff industry.[1] The halogenation of 1-aminoanthra-9,10-quinone is difficult as anthra-9,10-quinone contains two carbonyl groups that deactivate the ring towards any electrophilic substitution. Several methods can be used to brominate 1-aminoanthra-9,10-quinone, such as bromination of 1-aminoanthra-9,10-quinone in 20% sulfuric acid at 70–80 °C[2] and bromination in 70-95% sulfuric acid at a high temperature to obtain 1-amino-2,4-dibromoanthra-9,10-quinone with or without a catalyst.[3] 1-Amino-2,4-dibromoanthra-9,10-quinone may also be obtained by brominating 1-aminoanthra-9,10-quinone in chloroform.[4] Bromination of 1-methylaminoanthraquinone may be carried out in pyridine solution by treatment with two moles of bromine.[5] These methods, however, all require drastic conditions involving strong acids, high temperature, and chlorinated solvents, all of which are environmentally toxic.

Ionic liquids are attracting increasing interest in the context of green chemistry. Ionic liquids are non-volatile, thermally stable, and their solvation properties can be varied by changing the cation and anion. There are limitations to the use of ionic liquids, however, such as high cost, environmental toxicity, and high purity requirement. Ionic liquids like (BMIM)PF_6 made from 95% pure 1-butyl-3-methylimidazolium chloride are even more expensive than pure acetone or toluene. Ionic liquids were initially introduced as alternative green reaction media because of their unique chemical and physical properties of non-volatility, non-flammability, thermal stability, and controlled miscibility.[6-8] Many ionic liquids, however, are dangerous environmental contaminants, with toxicity similar to or even higher than that of organic solvents.[7] Further, high purity is required for ionic liquids, as even trace impurities affect the physical properties of ionic solvents.[9]

The development of alternative solvents from components that are inexpensive, non-toxic towards the environment, and are biodegradable or obtainable from biodegradable resources is therefore highly desirable to overcome these drawbacks.

Stavber *et al.*[10] reviewed halogenations of organic compounds in ionic liquids. Regioselective aromatic ring bromination of aromatics and heteroaromatics has been performed using *N*-bromosuccinimide as the brominating agent and tetrabutylammonium bromide as a phase transfer catalyst in ionic liquid such as (BMIM)PF_6.[11] α-Halogenation of β-dicarbonyl compounds and cyclic ketones is also possible using *N*-halosuccinimides in [BMIM]PF_6.[12] An ionic liquid such as [BMIM][Br_3] with a tribromide anion functions as both a reagent and solvent. This tribromide-based ionic liquid has been used for the nuclear bromination of activated aromatics.[13] These methods are also limited, however, by their toxicity, and the presence of impurities decreases the activity of the ionic liquids.

We synthesized a deep eutectic solvent composed wholly of biomaterials referred to as "Bio-ILs" or "Deep Eutectic Mixture". Abbott *et al.*[14] published a series of studies on the low melting point of deep eutectic liquid systems based on choline chloride ([Ch] [Cl]). These studies suggest that choline cations can substitute for synthetic cations. Choline is a naturally occurring biocompatible compound that is not hazardous if it is released back to nature as choline or its deep eutectic mixture.[15] Urea is a compound present in all animals. Because choline chloride and urea are both inexpensive, processes that use this deep eutectic solvent are economically viable.

These deep eutectic mixtures have been used as solvents in biologic transformation such as hydrolase catalyzed biotransformation[16] and extraction of glycerol from biodiesel into a eutectic-based solvent.[17] Deep eutectic solvents are used as electrolytes for dye-sensitized solar cells.[18] The ability of deep

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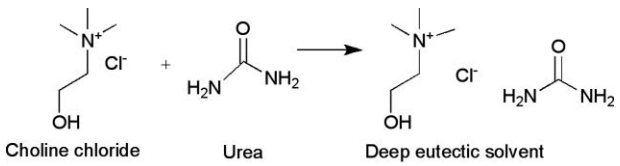
† Electronic supplementary information (ESI) available: Characterisation of products. See DOI: 10.1039/b923589b

eutectic mixtures to serve as solvents, however, has not been adequately explored in the field of synthetic organic chemistry field. Deep eutectic mixtures of urea and a range of quaternary ammonium salts are liquid at ambient temperatures and have interesting solvent properties. These mixtures were initially used for biologic conversion because of their biodegradable properties.[17] Deep eutectic solvents composed solely of biomaterials, in particular choline cations combined with propionate, hydrogen succinate, and hydrogen maleate, are ionic liquids with strong hydrogen bonding characteristics at room temperature.[19]

Here, we evaluated the effectiveness of a mixture of choline chloride and urea (1 : 2) as an environmentally benign solvent for use in the electrophilic substitution of 1-aminoanthra-9,10-quinone. The ability to recover and recycle the solvent used in a reaction is an important aspect to green chemistry.[20] Therefore, in the present study, we also evaluated the recyclability and reusability of this deep eutectic solvent.

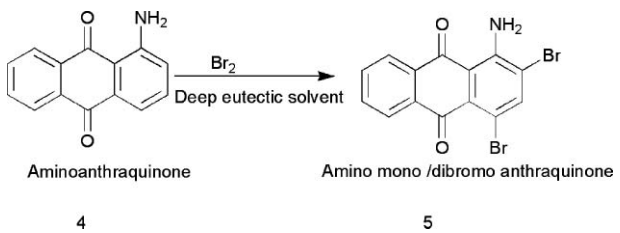
Results and discussion

A deep eutectic solvent was prepared by a previously reported simple method[14a] with 100% atom economy (Scheme 1). Choline chloride (1 mole) was reacted with urea (2 moles) at 80 °C. The resulting molten salt was used directly in reactions without purification. This method produced no byproducts; therefore there was no loss during isolation of the solvent.



Scheme 1 Preparation of deep eutectic solvent.

Bromination of an 1-aminoanthra-9,10-quinone derivative was performed at 50–60 °C using molecular bromine (Scheme 2 and Table 1). Monobrominated products **5e**, **5f**, and **5g** were obtained using 1.5 molar equivalents of bromine. Dibrominated products **5a**, **5b**, and **5d** were obtained by using 2.5 molar equivalents of bromine. Tetrabrominated product **5c** was obtained by using 4.5 molar equivalents. During the reaction, unreacted bromine was neutralized with 2 N aqueous Na_2CO_3 solution. Deep eutectic solvents are miscible with many other solvents such as water, methanol, chloroform, and tetrahydrofuran. The solvent was separated from the product by adding water to the reaction mixture and filtering the product. The deep eutectic solvent was separated from the reaction mixture by phase separation between the product and the aqueous phase. The solvent was recovered easily from the filtrate by evaporating the water under vacuum. This method used no hazardous chemicals, *e.g.*, acetic acid, sulfuric acid, or chloroform.



Scheme 2 Bromination of 1-aminoanthra-9,10-quinone using Choline chloride : urea (ChCl : urea).

To compare the results obtained using the deep eutectic solvent and an organic solvent, bromination of 1-aminoanthra-9,10-quinone was performed using two different solvents (Table 2). Compared to the reaction using the organic solvent, the reaction using the deep eutectic solvent was much faster, requiring only 2 to 3 h for completion. Both yield and purity of the brominated product were greater in the reaction using the deep eutectic solvent than the organic solvents such as methanol and chloroform. Results are summarized in Table 2.

All products were confirmed by melting point assay, FTIR spectroscopy, ^{1}HNMR spectroscopy, and mass spectrometry. The purity of the product was checked by HPLC.

The reaction was effectively scaled-up to 5 g based on a representative reaction of bromination of 1-aminoanthra-9,10-quinone. Therefore, it is easy to scale-up the reaction on an industrial scale.

The deep eutectic solvent was recycled based on the representative reaction of bromination of 1-aminoanthra-9,10-quinone. We recycled the deep eutectic solvent five times without purification. The reactions using recycled deep eutectic solvent continued to produce excellent results without and a decrease in the yield or purity as shown in the Table 3.

Experimental

Materials and equipment

All melting points are uncorrected and are presented in degrees Celsius. FT-IR spectra were recorded on a Bomem Hartmann and Braun MB-Series FT-IR spectrometer. ^{1}H NMR spectra were recorded on Varian 400 MHz mercury plus spectrometer, and chemical shifts are expressed in δ ppm using TMS as an internal standard. Mass spectral data were obtained with a micromass - Q - TOF (YA105) spectrometer. Common reagent grade chemicals were procured from SD Fine Chemical Ltd. (Mumbai, India) and were used without further purification.

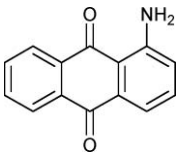
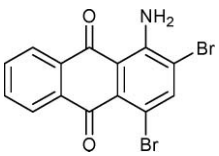
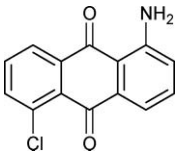
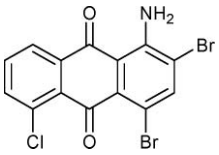
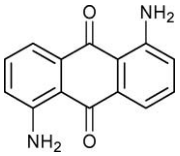
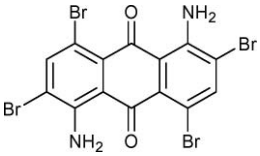
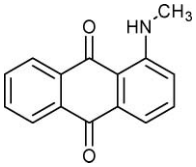
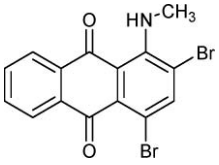
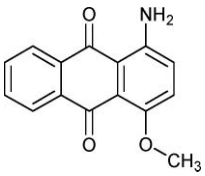
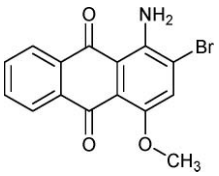
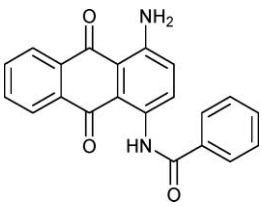
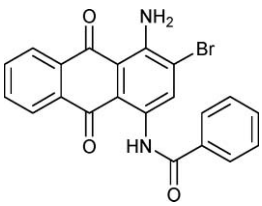
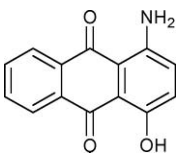
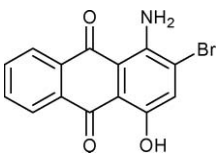
Preparation of deep eutectic solvent (choline chloride : urea) 3.[10a]

Choline chloride (100 g, 71 mmol) and urea (86 g, 140 mmol) were placed in a round bottom flask and heated to 70 to 80 °C, until liquid began to form. After 15 to 20 min, a homogenous colorless liquid (186 g, 100%) formed, which was used directly for the reactions without purification.

Bromination of 1-aminoanthra-9,10-quinone using an organic solvent.

1-Aminoanthra-9,10-quinone (1 g, 4.48 mmol) was added to the solvent (dichloromethane or methanol; 7 ml). Bromine (0.6 ml; 11.2 mmol) was slowly added to the reaction mixture. The reaction mixture was stirred at 50–60 °C for 12 h. The reaction was monitored by TLC. After completion of the reaction, water was added, and the mixture filtered and dried in an oven to isolate the product.

Table 1 Bromination of 1-aminoanthra-9,10-quinone derivative using deep eutectic solvent (ChCl : Urea)

Entry	Amino-anthra-9,10-quinone derivative	Brominated Product	Yield (%)[a]	HPLC Purity (%)	Melting Point
5a			95	97.01	222 °C[21]
5b			87	99.8	249 °C
5c			94	97.8	Decomposes >250 °C
5d			88	99.3	154 °C
5e			84	99.6	176 °C
5f			91	98.8	247 °C
5g			92	98.9	198 °C

[a] Isolated by filtration. †In Reaction **5a**, **5b** and **5d**, 2.5 equivalent bromine was used. In reaction **5e**, **5f**, **5g** and 7, 1.2 equivalent bromine while in reaction **5c**, 4.5 equivalent of bromine was used. †Reaction time is same for all the reactions *i.e.* 2-3 h. [b] In Reaction **5a**, **5b** and **5d**, 2.5 equivalent bromine was used. In reaction **5e**, **5f**, **5g** and 7, 1.2 equivalent bromine while in reaction **5c**, 4.5 equivalent of bromine was used. [c] Reaction time is same for all the reactions *i.e.* 2-3 h.

Table 2 Bromination of 1-aminoanthra-9,10-quinone derivative using organic solvents using 2.5 equivalent of bromine at 20-30 °C

Entry	Solvent	Reaction time (hr.)	Yield (%)[a]	HPLC Purity (%)
1	Methanol	10-12	75	95
2	Chloroform	10-12	70	92
3	Deep eutectic solvent	2-3	95	97

[a] Isolated by filtration.

Table 3 Recycling of deep eutectic solvent in bromination of 1-aminoanthra-9,10-quinone at room temperature

Recycle of IL	Yield (%)[a]
Fresh, Non- Recycled	84.3%
First	97.5%
Second	92.7%
Third	93.4%
Forth	94.1%
Fifth	82.0%

[a] Isolated by filtration.

Typical procedure for the bromination of 1-aminoanthra-9,10-quinone (5a, 5b, 5c, 5d, 5e, 5f, 5g).

1-Aminoanthra-9,10-quinone (1 g, 4.48 mmol) was added to the deep eutectic solvent (5 ml) with stirring for 15 min, and bromine (0.6 ml, 11.2 mmol) was slowly added to the reaction mixture. In the case of **5c**, a 4.5-molar equivalent of Br_2 was used and in the cases of **5e**, **5f**, **5g**, 1.1 molar equivalents of Br_2 were used. The reaction mixture was stirred at 50–60 °C for 2 to 3 h. During the reaction, unreacted bromine that was expelled was neutralized in a trap containing aqueous Na_2CO_3 solution. The reaction was monitored by TLC. After completion of the reaction, water was added, the mixture filtered, and residual product dried in an oven under vacuum.

1-Amino-2,4-dibromoanthracene-9,10-dione 5a. (1.6 g, 93.2%) An orange colored solid. Melting point (measured) 222 °C (from water) (lit, 221 °C[17]); λmax (methanol)/nm 381; ν_{max}/cm^{-1} 3396(NH), 1670 and 1577 (CO), and 715 (CBr); δ_H (400 MHz; DMSO; Me_4 Si) 3.4 (2H, s, NH), 7.6-8.4(5H, m, aromatic); *m/z* (EI) 380 (M-1) for ^{80}Br. $C_{14}H_7Br_2NO_2$ calculated *m/z*: 380.9

1-Amino-2,4-dibromo-5-chloroanthracene-9,10-dione 5b. Orange colored solid. Melting point (measured) 249 °C from water; λmax (methanol)/nm 415; ν_{max}/cm^{-1} 3452 and 3307 (NH), 167 and 1635 (CO) and 759 (CBr); δ_H (400 MHz; DMSO; Me_4 Si) 3.4 (1H, s, NH), 7.6-8.4(5H, m, aromatic); *m/z* (EI) 414 (M-1) for ^{80}Br. $C_{14}H_6Br_2ClNO_2$ calculated *m/z*: 414.9.

1,5-Diamino-4,8-dibromoanthracene-9,10-dione 5c. Brown colored solid. Decomposes >250 °C (from water); λmax (methanol)/nm 554; ν_{max}/cm^{-1} 3446 and 3319(NH), 1577 and 1560 (CO) and 759 (CBr); δ_H (400 MHz; $CDCl_3$; Me_4 Si) 2.1 (4H, s, NH) 7.5-7.8 (2H, m, C–H); *m/z* (EI) 553 (M-1) for ^{80}Br; $C_{14}H_6Br_4N_2O_2$ calculated *m/z*: 553.7.

2,4-Dibromo-1-(methylamino) anthracene-9,10-dione 5d. Brown colored solid. Melting point (measured) 154 °C (from water); λmax (Methanol)/nm 395; ν_{max}/cm^{-1} 3458 and 3099(NH), 1672 and 1625 (CO) and 737 (CBr); δ_H(400 MHz; $CDCl_3$; Me_4 Si) 3.5 (3H, s, $NHCH_3$), 7.4-8.0(5H, m, C–H aromatic) and 9.9 (1H, s weak, NH); *m/z* (EI) 396 (M+1) for ^{80}Br; $C_{15}H_9Br_2NO_2$ calculated *m/z*: 394.9.

1-Amino-2-bromo-4-methoxyanthracene-9,10-dione 5e. Brown colored solid. Melting point (measured) 176 °C (from water); λmax (methanol)/nm 411; ν_{max}/cm^{-1} 3434 and 3284 Br (NH), 1659 and 1625 (CO) and 798 (CBr); δ_H(400 MHz; CDCl3; Me_4 Si) 3.9 (3H, s, OCH_3), 5.3 (2H, weak s, NH), 7.4-8.4(5H, m C–H aromatic); *m/z* (EI) 332 (M+1) for ^{80}Br; $C_{15}H_{10}BrNO_3$ calculated *m/z*: 330.9.

***N*-(1-Amino-2-bromo-9,10-dihydro-9,10-dioxoanthracen-4-yl) benzamide 5f.** Brown colored solid. Melting point (measured) 247 °C (from water); λmax (MeOH)/nm 486; ν_{max}/cm^{-1} 3460 and 3252 br (NH), 1670,1627 and 1575 (CO) and 736 (CBr); δ_H(400 MHz; CDCl3; Me_4 Si) 1.5(2H, weak s, NH_2),7.4-8.4 (9H, m, C–H aromatic), 9.6 (1H, s, C–H) and 13.5 (1H, s, NH); *m/z* (EI) 421 (M+1) for ^{80}Br; $C_{21}H_{13}BrN_2O_3$ calculated *m/z*: 420.0.

1-Amino-2-bromo-4-hydroxyanthracene-9,10-dione 5g. Brown colored solid. Melting point (measured) 198 °C (from water); λmax (methanol)/nm 397; ν_{max}/cm^{-1} 3453 and 3306 br (NH), 1670 and 1635 (CO) and 759 (CBr); δ_H (400 MHz; CDCl3; Me_4 Si) 3.4 (2H, s, NH), 7.5-8.4 (5H, m, C–H aromatic); *m/z* (EI) 318 (M+1) for ^{80}Br; $C_{14}H_8BrNO_3$ calculated *m/z*: 316.9.

Scale-up of bromination of 1-amino-anthra-9,10-quinone and recycling of choline chloride: urea (deep eutectic solvent).

1-Aminoanthra-9,10-quinone 5 g (22.4 mmol) was added to deep eutectic solvent (50 ml). The reaction mixture was stirred for 15 min, bromine (2.9 ml, 56.0 mmol) was added slowly, and the reaction mixture stirred at 50–60 °C for 2 to 3 h. During the reaction, liberated HBr gas was neutralized using 2 N aqueous Na_2CO_3 solution. The reaction was monitored by TLC. After completion of the reaction, 50 ml of water was slowly added, the mixture was filtered to obtain the product using a Büchner funnel under vacuum and dried in an oven to afford an orange-colored solid of 1-amino-2,4-dibromoanthra-9,10-quinone (8.1 g, 94%). The deep eutectic solvent was recovered from the filtrate by evaporating the water phase at 80 °C under vacuum. The recycled deep eutectic solvent was used for the next batch and recycled again.

Conclusion

The present reaction using a readily available and biodegradable ammonium deep eutectic solvent (choline chloride : urea) provides an efficient and convenient method for the bromination of 1-aminoanthra-9,10-quinones using molecular bromine without the use of any other catalyst or organic solvent. This method offers marked improvements in terms of simplicity, decreased reaction time, simple reaction conditions, general applicability, high isolated product yields, and the use of environmentally benign procedures and solvents. This method also eliminates the use of hazardous organic solvents and toxic catalysts, and thus provided a better and practical alternative to the existing procedures. Most significantly, however, this procedure demonstrates that selectivity and balance among yields are achievable. It is easy to separate the catalyst and substrate after completion of the reaction. The halogenated 1-aminoanthraquinones were easily isolated with high purity. These deep eutectic solvents provide a good alternative for industrial synthesis of mono or di-bromo derivatives of 1-aminoanthra-9,10-quinone, as the reaction is readily scalable.

Acknowledgements

Authors are thankful to SAIF IIT- Bombay for recording ^{1}H NMR spectra.

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