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Sustainable and chemoselective N-Boc protection of amines in biodegradable deep eutectic solvent

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Abstract A green and practical approach for the chemoselective N-*tert*-butyloxycarbonylation of structurally diverse amines with di-*tert*-butyl dicarbonate (Boc_2O) is described. Selective N-Boc protection was achieved in excellent yields in urea-choline chloride deep eutectic solvent (DES) as the most promising environmentally benign and cost-effective solvent under mild reaction condition. DES can protect various aromatic and aliphatic amines using Boc_2O in good to excellent yields in short reaction times without any side products.

Graphical abstract

Keywords Green chemistry · Deep eutectic solvent · *tert*-Butyloxycarbonylation · Amines · Boc_2O

Introduction

Protecting groups play a pivotal role in organic synthesis, particularly in the multi-step synthesis of multifunctional targets and structurally complicated natural products [1]. One of the most common methods of protecting amines as well as amino acids in peptide chemistry involves the formation of N-Boc functionality due to their ease of formation and cleavage [2]. The stability of the *tert*-butyl carbamates towards basic and nucleophilic attacks make them the most frequently protective groups used in complex structure where the selectivity is a prime issue [3–5]. Furthermore, several mild methods are available for the removal of the Boc protecting group which mostly utilizes acidic condition at room temperature [6–8]. A vast array of catalyst and promoter have been used for N-tert-butoxycarbonylation of amines in the literature that some of them using di-*tert*-butyl dicarbonate Boc_2O a more eco-sustainable reagent [9–19].

Green Chemistry has emerged as a research area with the aim of providing sustainable materials and environmentally preferable products to achieve an upstanding sustainable environment maintaining the health and safety of animal and people [20]. The most common pollutants in the academic and industrial process are volatile organic solvents, especially halogenated solvents that used in large quantities due to a wide range of application from analysis to synthesis [21]. In this context, four main alternatives to organic solvents have been developed [22]: (1) water is really green solvent regarding the aforementioned considerations and unconventional properties, yet the negligible solubility of carbon compounds in water and the reaction of some organometallic compounds with water limits its applications [23–25], (2) use of ‘‘bio-solvents’’, i.e., solvents produced with renewable resources or solvent-free processes [26], (3) supercritical fluids and fluorous biphasic systems have been reported as recyclable, environmentally benign reaction media [27], (4) ionic liquids (ILs) are molten salts with a melting point below 100 °C, came into the spotlight during the last decade, is an excellent green

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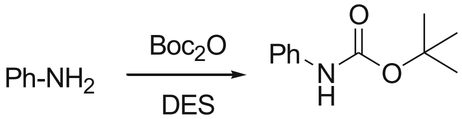
solvent due to their unique properties, such as low vapor pressure, high thermal stability, recyclability, non-flammability, and wide liquid range [28–32]. Furthermore, the IL characteristics can be controlled by many combinations of cations and anions and allow the design of ionic liquids with unique properties and special application [33]. In addition, by incorporating a functional group it was possible to make task-specific ionic liquids that have dual properties [34–36]. The main disadvantages of ionic liquids such as non-biodegradable, toxic, and commercially expensive enforced the scientists to discover environmentally friendly reaction media. Alternative sustainable to traditional solvents and ionic liquids is deep eutectic solvents (DESs), that they are usually obtained by the complexation of a quaternary ammonium salt such as choline chloride with a metal salt or hydrogen bond donor like urea, carboxylic acid, sugar and amide [30, 37–39]. DESs as an alternative to ILs, not only have similar characteristics to traditional imidazolium based ILs, but also have several advantages such as ease of preparation, and available from bulk renewable resources [40–44]. Preparation of DESs involves the simple mixing of their components under gently heating or freeze drying method without any further modification [45]. Furthermore, choline chloride (ChCl) and urea are both a naturally occurring biocompatible sustainable building block of DESs that are not hazardous if they release back into the nature [46]. Besides, they are cheap and the processes which use these DESs are economically viable and green [47].

Results and discussion

In the past few years, our research group has explored applicability of an abundant and nontoxic urea-choline chloride based DES as new alternative renewable solvents for various organic transformations while adopting a more eco-sustainable approach [48–50]. For the first time, we here report a convenient protocol for the *N*-Boc protection of amines using DES as a solvent under catalyst-free conditions.

Urea-choline chloride DES was synthesized by mixing urea with choline chloride at 60 °C for 2 h until the clear, transparent, homogeneous DES appears. First, aniline (0.5 mmol) and di-*tert*-butyl dicarbonate (0.5 mmol) was chosen as model compound using different amounts of DES at room temperature (Table 1). It was found the use of 0.5 cm^3 of DES gave the optimum yield (84%), at room temperature within 1 h, whereas 0.1 cm^3 and 0.3 cm^3 resulted in 67 and 74% yields, respectively. The results are shown in Table 1. Prolonged reaction times (4 h) or excess of DES (3 cm^3) could not improve the yields. Next, we attempted to improve the yields by increasing the reaction temperature. It was found that the temperature plays key factor and the reaction completed within 20 min at 50 °C leading to excellent yields of the protected aniline. The protection reaction was quantitative, and no product other than Boc-protected aniline was present in the reaction mixture. Importantly, the isolation and purification steps are very simple and easy that involves the addition of a

Table 1 Optimization of the model reaction



Entry	DES/cm^3	Time/min	Temp./°C	Yield/%[a,b]
1	0.1	60	rt	67
2	0.2	60	rt	67
3	0.3	60	rt	74
4	0.4	60	rt	82
5	0.5	60	rt	84
6	1.0	60	rt	84
7	3.0	240	rt	88
8	0.5	10	40	90
9	0.5	10	50	97
10	0.5	10	60	97
11	0.5	10	80	97

[a] Isolated yields

[b] Reaction conditions: aniline (0.5 mmol), Boc_2O (0.5 mmol), and DES

water and filtration of products and recrystallization from EtOH.

Next, we examined the protection of a wide variety of amines using this methodology, and the results are summarized in Table 2. A range of commercially available amines (aliphatic, aromatic, and heteroaromatic) underwent the conversion efficiently. Under optimized conditions aniline with both electron donating and electron withdrawing substituents at various positions reacted instantaneously and almost a white precipitate of *tert*-butyl-*N*-aryl carbamates are formed after addition of water to the reaction mixture. Anilines bearing electron-donating groups had slightly higher yields than those with electron-neutral and electron-withdrawing moieties. Good to excellent yields were obtained when primary and secondary aliphatic amines, such as benzylamine, 4-methoxybenzylamine, 4-chlorobenzylamine, 1-naphthylmethylamine, and dihexylamine with Boc_2O even at room temperature. Importantly, the reaction also works with sterically hindered amines like 2,6-dimethylaniline under the same mild conditions. Benzo[*d*]thiazol-2-amine as heteroaromatic amines gives moderated yields of product. However, deactivated aromatic amines such as pyridin-2-amine and 4-nitroaniline give only starting materials.

The chemoselectivity of the DES was also investigated by the substrates with an OH/NH_2 group. Reaction with 4-aminophenol (Table 2, entry 20) resulted in chemoselective formation of the *N*-Boc-aniline without O-tertbutoxycarbonylation. Furthermore, chemoselective mono-N-Boc protection of *o*-phenylenediamine was also possible in DES.

Although the details of the reaction mechanism are not clear at present, a possible mechanism for the N-Boc protection of amines in deep eutectic solvent was shown in Scheme 1. This reaction presumably occurs via activation of the carbonyl group of Boc_2O with the hydrogen bonding ability of deep eutectic solvent to form a zwitterionic species, making the carbonyl group susceptible to nucleophilic attack by the amine. Successive elimination of CO_2 and *t*-BuOH in the presence of DES to form the corresponding N-Boc derivatives.

The recovery and reuse of DES was important which helps address both economic and environmental viewpoints in industrial and chemical process. The investigation of the reusability of the DES using a model reaction of aniline (5 mmol) and Boc_2O (5 mmol) in 3 cm^3 DES for the formation of **2a** was shown in Fig. 1. After completion, 10 cm^3 water was added to the reaction mixture, shaken vigorously and filter off the solid product, the deep eutectic solvent was recovered from filtrate by evaporating the water phase at 80 °C in vacuum and reused with minimal loss of activity (Fig. 1).

Conclusion

In summary, efficient and recyclable DES was successfully applied as a green solvent for N-*tert*-butyloxycarbonylation of amines that is one of the most important functional group protections in organic synthesis. A range of aromatic and aliphatic amines with different functional groups were successful protected in good to excellent yields under short reaction times.

Experimental

Choline chloride, urea, and all substrates for the protection of amine derivatives are commercially available and were purchased and used without further purification. Solvents were purchased from commercial sources and distilled from the relevant agents prior to use. All products were confirmed by melting point or boiling point, FT-IR spectroscopy, and ^1H NMR spectroscopy. All the reactions are monitored by thin layer chromatography (TLC) carried out on 0.25 mm silica gel with relevant detecting agents. Melting points and boiling points were recorded in Buchi 535 melting point apparatus. The FT-IR spectra of the samples were obtained on a BrukerVector-22 infrared spectrometer using KBr disks.^1H NMR spectra were recorded at r.t. on a FT-NMR Bruker UltraShield^{TM} (500 MHz) instrument as $CDCl_3$ as a solvent, chemical shifts have been expressed in ppm downfield from TMS.

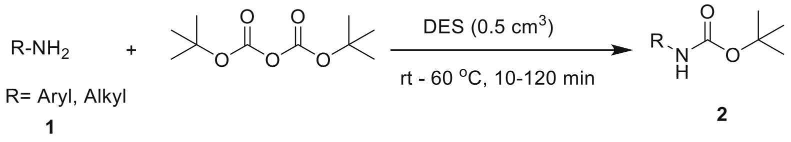
Deep eutectic solvent preparation

Choline chloride-urea based DES was prepared by mixing of urea (200 mmol) and choline chloride (100 mmol) under 60 °C until a clear liquid was appeared [42]. The obtained DES was used without any further purification.

General procedure

A dried test tube, equipped with a magnetic stir bar, was charged with 0.5 cm^3 DES, amine derivatives (0.5 mmol), and Boc_2O (0.5 mmol) and the mixture was heated at 50 °C until the reaction was complete (monitored by TLC and IR). After this time, 5 cm^3 water was added and in the most cases a white solid was obtained. The solid product was collected by filtration and washed successively with water and recrystallized from ethanol to get the pure final product [51–60]. The viscous products extracted with ethyl acetate and were purified by column chromatography, using ethyl acetate–petroleum ether.

Table 2 *N*-Boc protection of various amines in deep eutectic solvent



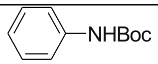
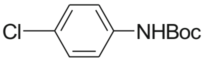
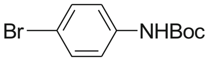
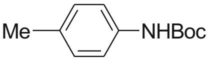
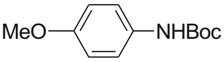
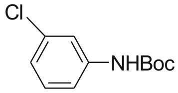
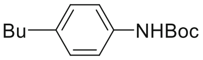
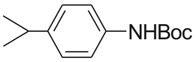
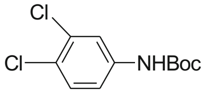
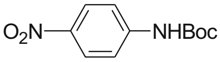
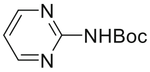
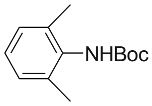
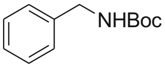
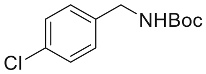
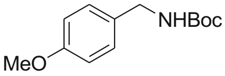
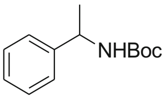
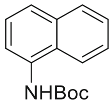
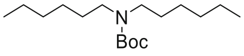
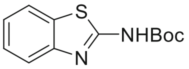
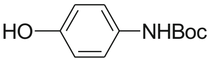
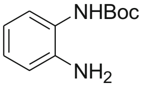
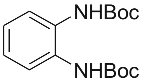
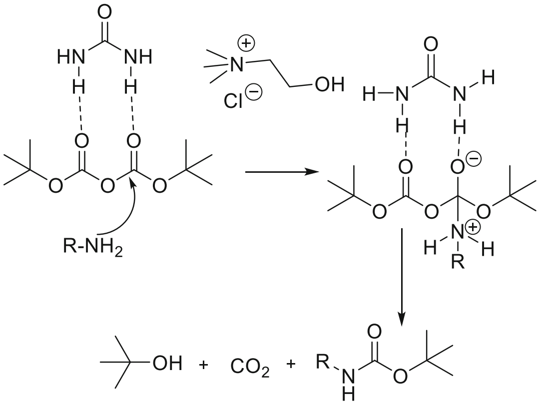
Entry	Products **2**	Yield / %[a]	M.p. / °C	
			Found	Reported
1	 **2a**	97	134-136	133-137 [52]
2	 **2b**	90	104-106	101-102 [53]
3	 **2c**	92	98-100	100-102 [53]
4	 **2d**	97	86-88	84-86 [53]
5	 **2e**	97	92-93	92-93 [53]
6	 **2f**	92	60-62	63-64 [53]
7	 **2g**	90	56-58	57-59 [54]
8	 **2h**	95	98-100	104-105 [55]
9	 **2i**	85	107-109	114-115 [56]
10	 **2k**	0	-	-
11	 **2l**	0	-	-
12	 **2m**	90	88-89	86-87 [57]
13[b]	 **2n**	95	54-56	55-57 [52]
14	 **2o**	90	74-75	75-76 [58]
15	 **2p**	95	52-54	50-50.5 [59]
16	 **2q**	97	84-86	80-82 [18]
17	 **2r**	74	96-98	98-99 [57]

Table 2 continued

18		**2s**	90	Colorless liquid	[59]
19		**2t**	62	99-101	98-100 [60]
20		**2u**	82	145-147	146 [18]
23[c]		**2x**	90	112-112	110-113 [61]
24		**2y**	85	104-106	105-106 [61]

[a] Isolated yields. [b]Aliphatic amines were carried out at room temperature. [c] 3 eq. Boc_2O was used.

Scheme 1



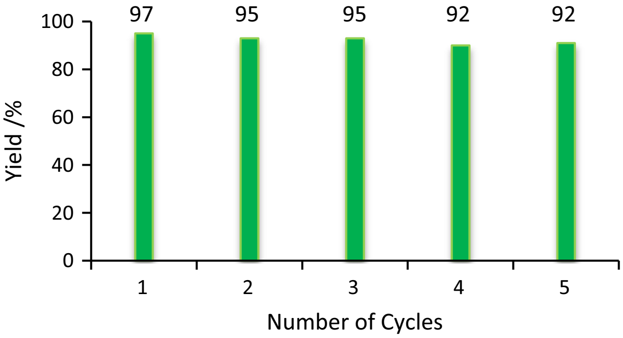


Fig. 1 The reusability of the DES using a model reaction (**2a**)

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References

1. Greene TW, Wuts PGM (1999) Protecting group in organic synthesis. Wiley, New York
2. Konnert L, Gauliard A, Lamaty F, Martinez J, Colacino E (2013) ACS Sustain Chem Eng 1:1186
3. Shirini F, Goli Jolodar O, Seddighi M, Takbiri Borujeni H (2015) RSC Adv 5:19790
4. Chakraborti AK, Chankeshwara SV (2006) Org Biomol Chem 4:2769
5. Sartori G, Ballini R, Bosica G, Maggi R, Righi P (2004) Chem Rev 104
6. Bogdan AR, Charaschanya M, Dombrowski AW, Wang Y, Djuric SW (2016) Org Lett 18:1732
7. Chakraborti AK, Roy SR (2009) J Am Chem Soc 131:6902
8. Varala R, Nuvula S, Adapa SR (2006) J Org Chem 71:8283
9. Lebel H, Leogane O (2005) Org Lett 7:4107
10. Mirmashhori B, Azizi N, Saidi MR (2006) J Mol Catal A Chem 247:159
11. Sarkar A, Roy SR, Parikh N, Chakraborti AK (2011) J Org Chem 76:7132
12. Sunitha S, Kanjilal S, Reddy SP, Prasad BN (2008) Tetrahedron Lett 49:2527
13. Suryakiran N, Prabhakar P, Srikanth Reddy T, Rajesh K, Venkateswarlu Y (2006) Tetrahedron Lett 47:8039
14. Sharma GVM, Reddy JJ, Lakshmi PS, Krishna PR (2004) Tetrahedron Lett 45:6963
15. Chankeshwara SV, Chakraborti AK (2006) Synthesis 2784
16. Upadhyaya DJ, Barge A, Stefania R, Cravotto G (2007) Tetrahedron Lett 48:8318
17. Reddy MS, Narender M, Nageswar YVD, Rao KR (2006) Synlett 1110–1112

18. Amira A, Ktir H, Berredjem M, Aou NE (2014) Monatsh Chem 145:509
19. Niedermeyer H, Hallett JP, Villar-Garcia IJ, Hunt PA, Welton T (2012) Chem Soc Rev 41:7780
20. Monte F, Carriazo D, Serrano MC, Gutiérrez MC, Ferrer ML (2014) Chemsuschem 7:999
21. Gawande MB, Bonifácio VDB, Luque R, Branco PS, Varma RS (2013) Chem Soc Rev 42:5522
22. Li CJ, Chen L (2006) Chem Soc Rev 35:68
23. Gawande MB, Bonifcio VBD, Luque R, Branco PS, Varma RS (2014) Chemsuschem 7:24
24. Pirrung MC, Sarma KD (2004) J Am Chem Soc 126:444
25. Lee CH, Chong MF, Robinson J, Binner EA (2014) Ind Eng Chem Res 53:18357
26. Hobbs HR, Thomas NR (2007) Chem Rev 107:2786
27. Jordan A, Gathergood N (2015) Chem Soc Rev 44:8200
28. Paiva A, Craveiro R, Aroso I, Martins M, Reis RL, Duarte ARC (2014) ACS Sustain Chem Eng 2:1063
29. Rogers RD, Seddon KR (2003) Science 302:792
30. Khandelwal S, Kumar Tailor Y, Kumar M (2016) J Mol Liq 215:345
31. Craveiro R, Aroso I, Flammia V, Carvalho T, Viciosa MT, Dionísio M, Barreiros S, Reis RL, Duarte ARC, Pai A (2016) J Mol Liq 215:534
32. Chaturvedi D (2011) Cur Org Chem 15:1236
33. Yue C, Fang D, Liud L, Yi TF (2011) J Mol Liq 163:99
34. Rajawat A, Khandelwal S, Kumar M (2014) RSC Adv 4:5105
35. Zhang Q, Vigier KD, Royer S, Jerome F (2012) Chem Soc Rev 41:7108
36. Carriazo D, Concepción Serrano M, Concepción Gutiérrez M, Luisa Ferrer M, del Monte F (2012) Chem Soc Rev 41:4996
37. Tang BK, Row KH (2013) Monatsh Chem 144:1427
38. Xu P, Cheng J, Lou WW, Zong MH (2015) RSC Adv 5:6357
39. Li XT, Liu YH, Liu X, Zhang ZH (2015) RSC Adv 5:25625
40. Hu HC, Liu YH, Li BL, Cui ZS, Zhang ZH (2015) RSC Adv 5:7720
41. Alonso DA, Baeza A, Chinchilla R, Guillena G, Pastor IM, Ramón DJ (2016) Eur J Org Chem 612
42. Abbott AP, Capper G, Davies DL, Rasheed RK Tambyrajah V (2003) Chem Commun 70–71
43. Liu P, Hao JW, Mo LP, Zhang ZH (2015) RSC Adv 5:48675–48704
44. Zhang ZH, Zhang XN, Mo LP, Li XY, Ma FP (2012) Green Chem 14:1502
45. Smith EL, Abbott AP, Ryder K (2014) Chem Rev 114:11060
46. Crawford DE, Wright LA, James SL, Abbott AP (2016) Chem Commun 52:4215
47. Singh BS, Lobo HR, Pinjari DV, Jarag KJ, Pandit AB, Shankarling GS (2013) Ultrason Sonochem 20:633
48. Azizi N, Batebi E (2012) Catal Sci Technol 2:2445
49. Azizi N, Batebi E, Bagherpour S, Ghafuri H (2012) RSC Adv 2:2289
50. Azizi N, Gholibeglo E (2012) RSC Adv 2:7413
51. Nardi M, Herrera Cano N, Costanzo P, Oliverio M, Sindonaa G, Procopioc A (2015) RSC Adv 5:18751
52. Chengliang F, Ningning Ch, Shuguang Zh, Jin C, Junqing Ch, Huayou H, Min J (2013) J Chem Res 37:757
53. Amaoka Y, Kamijo S, Hoshikawa T, Inoue M (2012) J Org Chem 77:9959
54. Cervantes A, Contreras CA, Guzman A, Vale EE, Velarde E, Berthiaume SL, Muchowski JM (1995) Can J Chem 73:336
55. Beaver DJ, Roman DP, Stoffel PJ (1963) J Med Chem 6:501
56. Vilaivan T (2006) Tetrahedron Lett 47:6739
57. Tanaka KI, Yoshifuji Sh, Nitta Y (1988) Chem Pharm Bull 36:3125
58. Afonso CAM (1998) Synth Commun 28:261
59. Shirini F, Khaligh NG, Jolodar OG (2013) J Iran Chem Soc 10:181
60. Tanwar B, Purohit P, Raju BN, Kumar D, Kommi DN, Chakraborti AK (2015) RSC Adv 5:11873