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Chemoselective *N*-tert-butyloxycarbonylation of amines in glycerol

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A catalyst-free, efficient and green protocol has been developed for chemoselective N-Boc protection of amines by using glycerol solvent at room temperature. The varieties of functionalized amines such as aliphatic, aromatic as well as heteroaromatic were protected by using developed protocol. The N-tert-butyloxycarbonylation derivatives were formed without any isocyanate, urea, N,N-di-t-Boc, and oxazolidinone as side products. The operational simplicity, cleaner reaction, rapid reaction convergence, functional group tolerance, excellent yield, high selectivity, catalyst-free and solvent recyclability are the distinct advantages of this protocol. This makes the protocol feasible, economical and environmentally benign.

The amino functional group plays vital role in biological functions as well as in organic synthesis. In most of the active molecules amino functional groups are in active site and it is difficult to stabilize at physiological pH. Protection and deprotection of amino group's plays significant role in organic transformation.[1] There are number of reagents to protect the amino functional groups, moreover an N-tert-butoxycarbonyl (N-Boc) derivatives has becomes widely used strategy in the synthesis of small organic to complex natural products[2]. The N-Boc protection is easy to introduce with simple acid treatment and has distinct stability and efficiency. The N-Boc is quite stable in basic medium and also the carbamates are inert towards the nucleophilic reagents and catalytic hydrogenation[3]. Furthermore, deprotection of the N-Boc group could be easily carried out with acid treatment. Various base catalyzed protocols were available for Boc protection of amines in literature, for example, dimethylaminopyridine (DMAP), NaHMDS, K_2CO_3, NaOH, triethyl amine and also Boc activation of amides has emerged as a major strategy in organic synthesis[4]. However, a base-catalyzed protocol often leads to the formation of side products such as isocyanates, urea and N,N-Di-Boc derivatives[5]. Additionally, high toxicity, unpleasant smell, nonrecyclability and requirement of excess amount catalyst make those protocols objectionable, especially from standpoint of green chemistry.

Alternative protocols used for N-Boc protection of amines involves several Lewis or Brönsted acid catalyst, such as $ZrCl_4$,[6] $Zn(ClO_4)_2 6H_2O$,[7] $LiClO_4$,[8] $FeCl_3$,[9] $Cu(BF_4)_2 H_2O$,[10] $La(NO_3)_3 6H_2O$,[11] $Bi(NO_3)_3 5H_2O$,[12] $InCl_3$, $InBr_3$,[13] CsF,[14] I_2,[15] Me_2SBr_2,[16] $(CF_3)_2CHOH$,[17] thiourea,[18] thioglycoluril,[19] guanidine hydrochloride,[20] sulphamic acid,[21] saccharin sulfonic acid[22] and succinamide sulphonic acid[23] has been reported. The various heterogeneous catalysts, including amberlyst-15, sulfonic acid-functionalized silica, sulfonic acid-functionalized nanoporous titania, sulfonic acid-functionalized ordered nanoporous Na^+-montmorillonite, $H_3PW_{12}O_{40}$, montmorillonite K-10 or KSF, mesoporous silica acid, phenyl sulfonic acid, tungstaophosphoric acid doped mesoporous silica, $HClO_4$-SiO_2, poly(4-vinylpyridinium)perchlorate, nano-TiO_2-$HClO_4$, nano-Fe_2O_3, and indion-190 resin[24]. Acidic ionic liquids, such as [(HMIm)BF_4], [TMG][Ac], [Py][OTf], [H-Suc]HSO_4, an 1-alkyl-3-methylimidazolium based ionic liquids, 1,3-disulfonic acid imidazolium hydrogen sulfate, and imidazolium trifluoroacetate have been used as catalyst for N-tert-butoxycarbonylation of amines[25]. The catalyst-free protocols including the use of β-cyclodextrin,[26] water,[27] ethanol[28] and PEG-400[29] as well as solvent-free conditions with and without microwave irradiation[30] have been used for N-Boc protection of amines. Many of these methods have some synthetic advantages individually, but still suffer from certain limitation, such as maintaining the anhydrous conditions, limited scope of substrate, less yields, toxic catalysts and solvents, slow reaction rate, tedious work-up and less recyclability of the catalysts and solvents. Thus development of safe, environmentally benign, mild, efficient, and high yielding rapid catalyst-free protocol using cost effective and recyclable solvent for N-Boc protection of amines is desirable.

Green and sustainable chemical processes with reduction or even elimination of the use and production of hazardous

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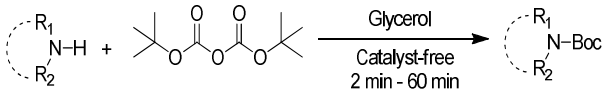
chemicals are high demand. Therefore, the use of non-toxic solvent and catalyst-free protocols has a prime choice. In this context, the development of protocols using recyclable and environmentally friendly solvent has gained much interest recently because of the extensive uses of solvents in almost all of the chemical industries, and of the predicted disappearance of fossil oil.[31] It has also observed that the catalysts employed are not always ecofriendly and because of this, serious environmental pollution often results. In this regard, the use of glycerol as a promoting medium for organic reaction was recently demostrated.[32] Glycerol due to its unique combination of physical and chemical properties such as polarity, low toxicity, no flammability, high boiling point, biodegradability, and easy availability from renewable feed stocks prompted us to extend its use as green solvent in organic synthesis.[33] As a result, we have developed novel, efficient and chemoselective catalyst-free protocol for N-Boc protection of amines using glycerol as recyclable solvent at room temperature. **(Scheme 1)**.

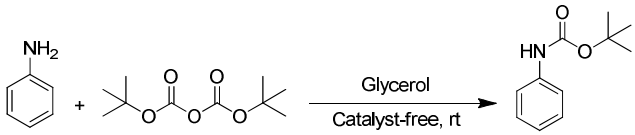


R_1 = alkyl or aryl;
R_2 = H or alkyl

Scheme 1 Catalyst-free N-Boc Protection of amines in glycerol

Results and Discussion

In order to study the scope and limitations of this catalyst-free N-tert-butyloxycarbonylation of amines in glycerol, we began our investigation with a model reaction of aniline **(1a)** with Di-tert-butyl carbonate (1:1mmol) in glycerol (2 mL) under catalyst-free conditions to yield tert-butyl phenylcarbamate **(2a) (Scheme 2).** The reaction was completed in 10 min at room temperature and the corresponding N-Boc protected amine obtained in 98% yield. To understand the role of glycerol on the N-Boc protection of amines, we have tested the reaction of aniline with di-tert-butyl carbonate in solvent-free conditions at room temperature. It should be noted that in solvent-free conditions and after 12h, **2a** was obtained in 25% yield whereas after 24 h it was observed to increase to only 37%. All the attempts to perform the reaction at room temperature (in solvent-and catalyst-free conditions) were fruitless even after 24h.The N-Boc protection of amine in glycerol showed a significant improvement of yield as well as reaction time when compared to the solvent-free reaction.



Scheme 2 N-tert-butyloxycarbonylation of aniline in glycerol.

Also the amount of glycerol is crucial for the elapse of the reaction. When using 0.5 mL of glycerol, **2a** was obtained in 47% after 20 min of reaction. Increasing the amount of glycerol to 1.5 mL the yield slightly increased to 77%. The best result was attained in the presence of 2 mL (98%, Fig. 2). Further increasing the quantity of glycerol had the opposite effect and the yield of product decreased which could be related to the dispersion of the reagents, when large quantity of glycerol is used.

To understand the efficiency of our protocol with respect to others hydroxyl solvents methods like water, methanol, ethanol and PEG-400 for N-tert-butyloxycarbonylation of p-toluidine, the results are collected and depicted in **Table 1**. The results clearly indicates that the catalyst-free N-Boc protection of amines in glycerol media reported here is the most efficient, clean and green process as well as the present protocol offers an advantage in terms of reaction conditions, reaction time and yields.

Table 1 Efficiency of glycerol in comparison with reported methods for the N-tert-butyloxycarbonylation of p-toluidine[a]

Entry	Solvent	Time	Isolated Yield[b]
1	Water[27]	1h	96
2	MeOH[28]	0.5h	93
3	Ethanol[28]	0.5h	96
4	PEG-400[29]	1.5h	96
5	Glycerol	30min	98

[a] Reaction conditions: 1mmol of p-toluidine, 1mmol of Boc_2O, 2ml glycerol.
[b] Isolated yield of pure product.

With the established optimal conditions, the scope of the reaction was probed. As highlighted in **Table 2** and **3** the N-Boc protection of various amines (aromatic, aliphatic, cyclic and heterocyclic), amino alcohols, amino phenols, chiral amines and amino ester were carried out in excellent yields and reduced time, between 2 min to 60 min. Generally, aniline and aromatic amines bearing electron donating groups undergoes the N-tert-butyloxycarbonylation in shorter reaction time with excellent yields **(Table 2, entries 1-9)**. However, the reaction is somewhat sluggish at room temperature for the aromatic amines bearing electron withdrawing groups but at 90°C the amines reacted with Boc_2O to furnish corresponding N-Boc product in much improved yield **(Table 2, entries 10-14).** Other aromatic amines such as 1-amino naphthalene, 2-amino naphthalene, 2-amino pyridine, 2-amino thiazole, 2-amino benzothiazole and 2-amino benzimidazole all are converted to the corresponding N-Boc derivatives in excellent yield in shorter reaction time **(Table 2, entries 15-20)**. This protocol was highly efficient for aliphatic primary, secondary or cyclic amines which afforded corresponding N-Boc protected derivatives at room temperature in excellent yield **(Table 3, entries 1-14).** The aliphatic amine reacted faster than aromatic amines and gave selectively monoprotected derivatives in good to excellent yields. It is important to note that no side reactions were observed in case of primary aliphatic amines, such as formation of isocyanates or ureas, there was not any bis-Boc derivatives observed.

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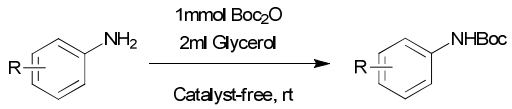
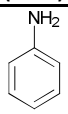
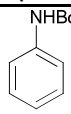
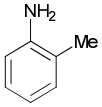
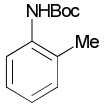
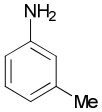
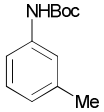
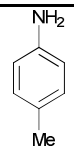
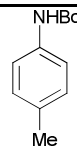
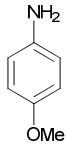
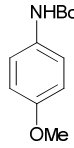
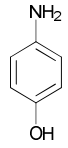
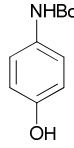
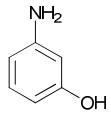
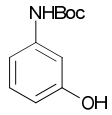
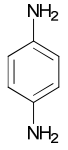
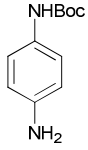
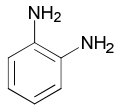
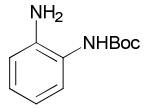
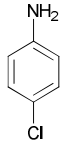
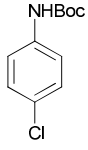
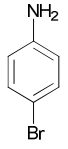
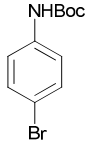
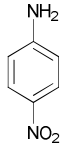
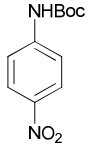
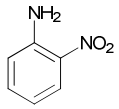
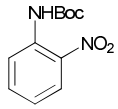
Excellent chemoselectivity was observed in case of amino alcohol, amino phenol and aromatic as well as aliphatic diamines, no bis-Boc derivatives or mixture of O/N Boc-derivatives was observed. The amine group was exclusively protected in comparatively good yields in the presence of phenolic or alcoholic hydroxy group **(Table 2, entries 6-7 and Table 3, entry 2, 14).** Aliphatic and aromatic diamines were converted to exclusively mono-Boc protected derivatives in shorter reaction time with excellent yields **(Table 2, entries 8-9 and Table 3, entries 3-4).** It is 100% mono-selective we did not observe di-protection of aliphatic amines and diamines. No comparative side reactions leading to formation of isocyanate, urea of *N,N*-di-Boc derivatives were detected by thin layer chromatography, ^{1}H NMR and ^{13}C NMR analyses of the crude products. Chiral amines, esters of amino acids and amino alcohol were efficiently protected to give optically pure N-Boc derivatives without racemization in good to excellent yield **(Table 3, entry 11-14).**

The solvent recycling and its reusability is an important feature of this protocol. We also investigate the recycling efficiency of the glycerol under catalyst-free conditions at room temperature. After the completion of reactions, the reaction mixture was diluted and extracted with mixture of pet ether/ethyl aceate (9:1). The upper phase was dried and the solvent evaporated. The glycerol phase was dried under vacuum and directly reused. Glycerol maintained its good level of efficiency even after being reused three times. The product **2a** was obtained in 98%, 97% and 96% yields after the successive cycles.

Table 2 Substrate scope for N-Boc protection of aromatic amines in glycerol[a]



1a-1t 2a-2t

Entry	Amine (1a-1t)	Product (2a-2t)	Time (Min)	Yield[b] (%)
1	 1a	 2a	20	98
2	 1b	 2b	60	96
3	 1c	 2c	40	97
4	 1d	 2d	30	98
5	 1e	 2e	25	98
6	 1f	 2f	30	96
7	 1g	 2g	40	95
8	 1h	 2h	20	97
9	 1i	 2i	40	92
10	 1j	 2j	55	89
11	 1k	 2k	720 45[c]	37 87
12	 1l	 2l	720 65[c]	23 84
13	 1m	 2m	720 90[c]	16 81

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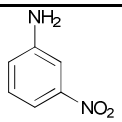
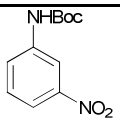
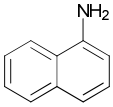
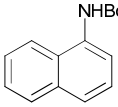
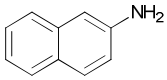
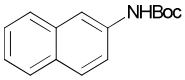
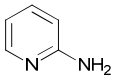
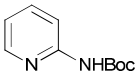
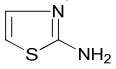
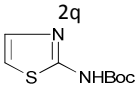
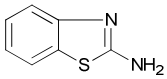
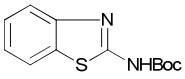
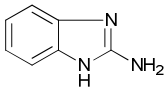
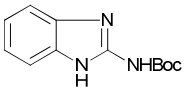
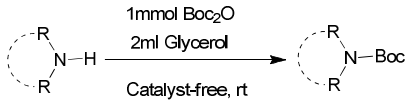
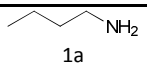
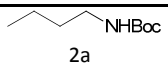
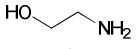
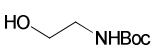
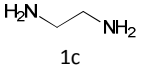
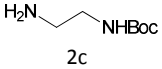
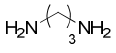
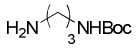
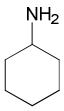
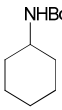
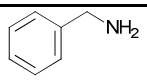
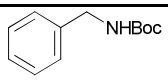
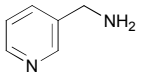
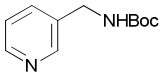
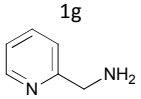
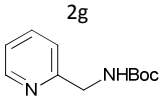
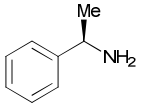
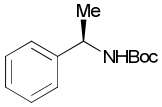
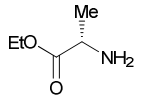
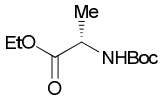
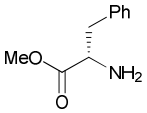
14	 1n	 2n	720 50[c]	47 85
15	 1o	 2o	40	95
16	 1p	 2p	45	94
17	 1q	 2q	30	96
18	 1r	 2r	30	95
19	 1s	 2s	35	93
20	 1t	 2t	40	91

[a]All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR. [b]Isoltaed yield of pure product. [c]Reaction carried at 90^{O}C.

Table 3 Substrate scope for N-Boc protection of aliphatic amines in glycerol[a]



1a-1n **2a-2n**

Entry	Amine (1a-1n)	Product (2a-2n)[b]	Time (Min)	Yield[b] (%)
1	 1a	 2a	2	98
2	 1b	 2b	2	96
3	 1c	 2c	3	97
4	 1d	 2d	3	96
5	 1e	 2e	5	98
6	 1f	 2f	5	98
7	 1g	 2g	5	96
8	 1h	 2h	5	95
9	 1i	 2i	3	94
10	 1j	 2j	3	96
11	 1k	 2k	5	98
12	 1l	 2l	20	93
13	 1m	2m	20	92
14	1n	2n	20	92

[a]All the products were characterized by IR, ^{1}H NMR, ^{13}C NMR. [b]Isoltaed yield of pure product.

The role of glycerol for the N-tert-butyloxycarbonylation of amines is presented in Scheme 3. Hydrogen bond formation between glycerol and the carbonyl oxygen atoms of Boc_2O causes “electrophilic activation" making the carbonyl group more susceptible to nucleophilic attack. Due to hydrogen bonding established by the glycerol the two compounds, the di-tert-butylcarbonate and amines will be in the vicinity of each other and the outcome will be an enhancement of electrophilicity of carbonyl group and increased nucleophilicity of the amines nitrogen. Intramolecular nucleophilic attack by nitrogen atom on the carbonyl carbon followed by elimination of CO_2, ^{t}BuOH, and the product N-Boc protected amine. A similar mechanism for activation carbonyl compounds through the hydrogen bonding has been reported in water[27], alcoholic solvents[28] and in thioglycoluril[19].

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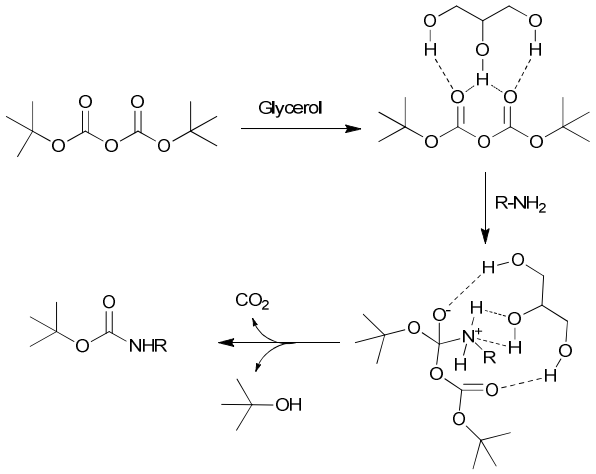

Scheme 3 Plausible mechanism for N-Boc protection of amines

Conclusions

In conclusion, a very efficient and catalyst-free methodology for N-tert-butyloxycarbonylation of amines in glycerol is reported. The method is highly efficient and environmentally benign owing to the mild conditions, high yields, excellent chemoselectivity, easy of product isolation and purification which fulfil the criterion for a green chemistry practice.

Conflicts of interest

"There are no conflicts to declare".

Notes and references

General procedure for N-tert-butoxycarbonylation of amines: A mixture of amine **(**1 mmol) and $(Boc)_2O$ (1mmol) in glycerol (2.0 ml) was vigorously stirred at room temperature for appropriate time (Table 2 and 3) until complete disappearance of amines was observed in the TLC monitoring. After the completion of reactions, the reaction mixture was extracted with mixture of pet ether/ethyl aceate (9:1). The combined organic layer was dried over anhydrous sodium sulfate and concentrated under reduced pressure to give a crude product. The glycerol phase was dried under vacuum and reused without loss of activity. After removal of the solvent, the pure products were obtained and no recrystallization or column chromatography is needed. All the compounds were characterized by comparison with mp and IR, ^{1}H NMR, ^{13}C NMR spectra with literature. Selected spectral data for:

(2R,3R)-ethyl-3-((tert-butoxycarbonyl)amino)-2-hydroxy-3-phenylpropanoate (Table 3, entry 2n):

White solid; mp 115-117°C; Yield 92% , FT-IR (υ, cm^{-1}): 3372, 1716, 1696, ^{1}H NMR (400 MHz, $CDCl_3$, TMS, ppm): δ 7.27-7.26(m, 5H), 5.64-5.62(d, J = 7.6Hz, 1H), 5.11-5.10(d, J = 7.2Hz, 1H), 4.57(bs, 1H), 4.16-4.08 (m, 2H), 2.94-2.93(d, J = 6.4 Hz), 1.42(s, 9H), 1.25-1.22(t, *J* = 7.2Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.84, 154.94, 128.34, 128.07, 127.40, 79.84, 73.15, 61.99, 56.53, 28.29, 14.03, HRMS (ESI): Calculated $[M + H]^+$: 310.16, Found: 310.16.

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Graphical Abstract

Chemoselective *N*-tert-butyloxycarbonylation of amines in glycerol

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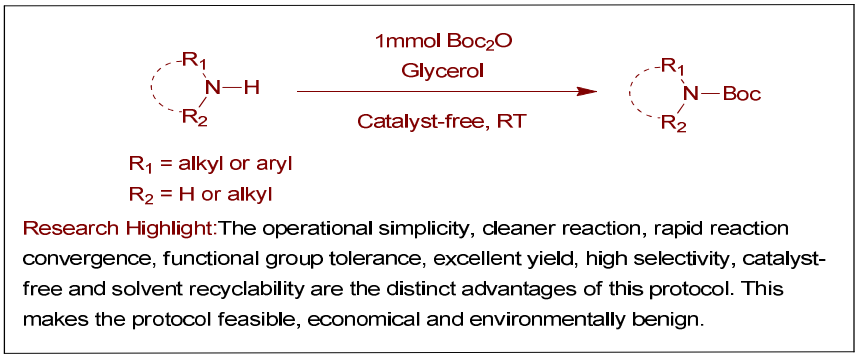

Research Highlight:The operational simplicity, cleaner reaction, rapid reaction convergence, functional group tolerance, excellent yield, high selectivity, catalyst-free and solvent recyclability are the distinct advantages of this protocol. This makes the protocol feasible, economical and environmentally benign.