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A New, Efficient, and Catalyst-free Microwave-assisted Approach for Formation of *O-tert*-Butoxy Carbonates

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A new simple, efficient, greener, and catalyst-free chemoselective protocol for the *O-tert*-butoxycarbonylation of various structurally diverse hydroxy compounds was carried out with $(Boc)_2O$ under microwave radiation. The corresponding *O-tert*-butoxy carbonates were obtained in good to excellent yields in a short reaction time without any side reactions.

To tackle serious pollution problems, scientists and chemists have incorporated emerging approaches into the development of new catalysts and energy systems for minimizing the negative impact of chemicals on human health and environment; this progressive development, known as "Green Chemistry" or "sustainable technology," has to take into account several parameters such as the optimization of product yield, minimization of reaction time, avoiding the use of harmful organic solvents, elimination of waste, and reduced use of toxic and/or hazardous substances.[1]

In relation to organic transformations, the development of mild, eco-friendly, and selective protocols for the protection–deprotection of functional groups has received considerable interest in the synthesis of the target molecule in the context of green synthesis.[2]

Protection, one of the most significant methods in organic chemistry, is based on the temporary blocking of one or more functional groups to exploit maximum orthogonality; in other words, the chemo- or/and the regioselectivity.[3] The presence of the hydroxy group in a wide range of biologically active compounds make their protection an important step in synthetic organic and medicinal chemistry, and the carbonates constitute an important class of products having chemical interest.[4]

Among different methods, acylation is a commonly used approach for the protection of the hydroxy group,[5] but its regeneration requires harsh reaction conditions,[6] incompatible with polyfunctional substrates. Furthermore, *O-tert*-butoxycarbonylation is suitable and is the preferred alternative process to protect the hydroxy group. The *tert*-butoxycarbonyl group (abbreviated as Boc or *t*-Boc) continues to attract a great deal of attention due to both their resistance to nucleophilic reagents and ease of regeneration under specific conditions.[2a,2b] Commercially available di-*tert*-butyl pyrocarbonate $(Boc)_2O$ is a better choice for preparing organic carbonates by direct coupling with hydroxy compounds under various conditions.[7]

In general, the different strategies of *O-tert*-butoxycarbonylation of the hydroxy group available in literature were carried out in the presence of a phase-transfer catalyst by using 4-dimethylaminopyridine (DMAP) as catalyst[8] and Lewis acid catalyst such as $Zn(OAc)_2$[9] and $BiCl_3$.[10] Others methods use the organocatalyst such as 1-*tert*-butoxy-2-*tert*-butoxycarbonyl-6,7-dihydroisoquinoline (BBDI),[11] and carbon tetrabromide (CBr_4).[12] The use of $NaLaTiO_4$[13] as a heterogeneous reusable catalyst is also reported.

Recently, Procopio et al.[14] reported a new method for the protection–cleavage of *O-tert*-butoxy carbonates of alcohols and phenols using mesoporous silica-supported (Er^{III}–MCM-41). Gawande et al.[15] also reported an eco-friendly, chemoselective *O-tert*-butoxycarbonylation of alcohols and phenols over $MgO–ZrO_2$ nanoparticles (NPs) under solvent-free conditions. However, these methods have several drawbacks such as long reaction times, formation of side-products during base-catalyzed reactions, and excess reagents in the cases during solid acid-catalyzed reactions.

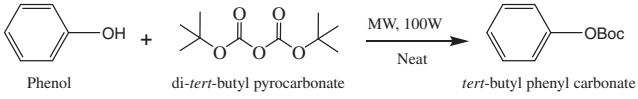
In the last decade, organic synthesis in water under green chemistry conditions has received great attention.[1g,16] In the last few years, our group reported a simple and eco-sustainable method for *O*-Boc and *N*-Boc protection–deprotection under various conditions.[17]

The replacement of conventional energy sources with other alternative laboratory techniques has continued to attract a great deal of attention over the last few years.[18–20] Microwave and ultrasound radiations have been proven to be better in terms of its advantages such as reduced reaction times,[21] enhanced product yields,[21] the elimination of undesirable side products, and the ability to precisely control the temperature and pressure profiles of the reaction.[22] In this context, Dighe et al.[23] and our group[24] are reported a new method for the *N-tert*-butoxycarbonylation of amines using microwave and ultrasound radiation, respectively. It is a green chemistry approach for the synthesis of Boc-protected amines, wherein the use of solvents and catalysts is avoided.

Herein, we have reported a microwave-assisted effective, simple, mild, rapid, and catalyst-free method for the chemoselective *O-tert*-butoxycarbonylation of hydroxy groups.

In our initial study, we reacted 1 mmol of phenol with 1.1 mmol of $(Boc)_2O$ in the absence of any catalyst with minimum acetone as solvent under microwave irradiation; the reaction was completed in just 30 min. We could also carry out the reaction in the absence of solvent with similar yield. (Scheme 1). Thus, we observed that microwave radiation played an essential role, and the solvent did not affect the result of the reaction.

In order to optimize the reaction conditions, we conducted the *O*-Boc protection of phenol (1 mmol) with $(Boc)_2O$ (1.1 mmol) under various irradiations without solvent. The best



Scheme 1. *O-tert*-Butoxycarbonylation of phenol.

results were obtained at 300 W (Table 1). An excellent yield of the corresponding product was registered within a very short reaction time, and no side-product formation was observed.

Encouraged by these experimental results and to increase the scope of this reaction, a series of structurally diverse aliphatic and cyclic hydroxy compounds were treated in a microwave at 300 W (Scheme 2 and Table 2, Entries 1–20).

Various hydroxy compounds, primary and secondary, aliphatic and aromatic were converted to the *O*-*tert*-Boc derivatives in good to excellent yields.

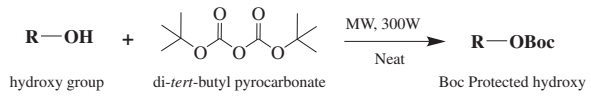
The protection of phenol and naphthol resulted in their corresponding *O*-Boc derivatives within 3–4 min in 80–97% yield, respectively. Phenol or naphthol possessing electron-donating or -withdrawing groups such as OMe, NHAc, NHBoc, NO_2, Br, Cl, COOH, and CHO gave the *O*-Boc products in good yield (Table 2, Entries 1–14). The reaction of benzyl alcohol and cyclohexanol with $(Boc)_2O$ provided a good yield of the desired product within 5 min (Table 2, Entries 15 and 16).

In order to exploit the generality of the methodology, we also reported the protection of aliphatic alcohols under the

Table 1. Influence of irradiations[a]

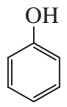
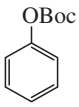
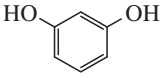
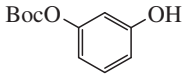
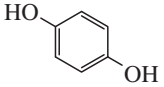
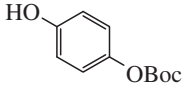
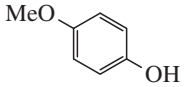
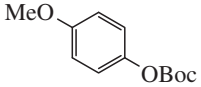
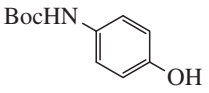
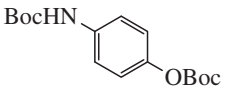
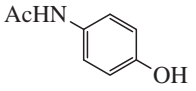
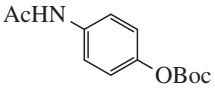
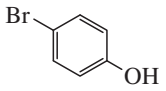
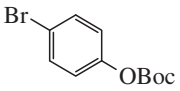
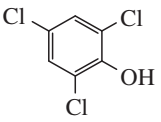
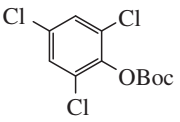
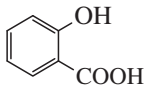
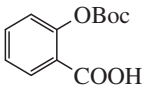
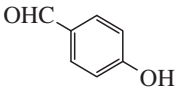
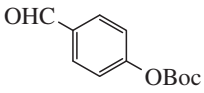
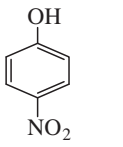
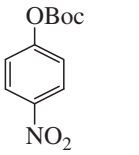
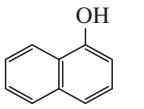
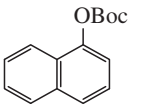
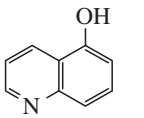
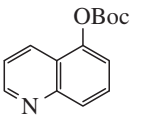
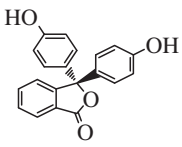
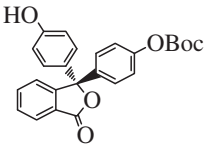
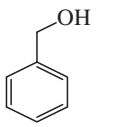
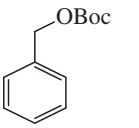
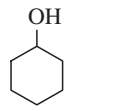
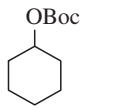
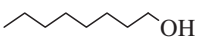
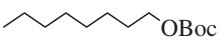
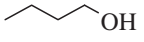
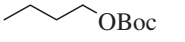
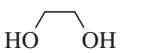
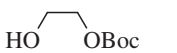
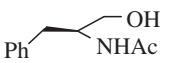
Entry	Irradiation/W	Time/min
1	100	30
2	200	20
3	300	5
4	450	—
5	600	—

[a]Reaction conditions: phenol, 1 mmol; $(Boc)_2O$, 1.1 mmol; catalyst, no use of catalyst; solvent, no use of solvent; yield, 98%.



Scheme 2. *O*-*tert*-Butoxycarbonylation of hydroxy group.

Table 2. Microwave-assisted *O*-*tert*-butoxycarbonylation of hydroxy compounds at 300 W[a]

Entry	Substrates	Products	Time/min and Isolated yield/%
1			3/80
2			3/85
3			3/84
4			3/82
5			4/79
6			4/79
7			4/78
8			4/77
9			4/76
10			4/76
11			4/75
12			4/78
13			4/77
14			3/79
15			5/72
16			5/68
17			5/75
18			5/75
19			5/67
20			5/74

[a]Reaction conditions: 1 mmol of substrate was treated with 1.1 mmol of $(Boc)_2O$ at 300 W in microwave irradiation in the absence of any catalysts and any solvents.

same reaction conditions (Table 2, Entries 17 and 18). These compounds were well tolerated, affording their corresponding *O*-Boc derivatives in moderate yield.

The scope of this process was further extended by investigating the possible regioselectivity of this reaction by carrying out competitive reactions between two alcoholic functional groups (Table 2, Entries 2, 3, and 19). The *O*-*tert*-butoxycarbonylation of Entries 2, 3, and 19 under the same conditions affords a mixture of mono-*O*-*tert*-Boc and di-*O*-*t*-Boc. Mono-*O*-*t*-Boc was obtained as the major product in good yield.

The presence of substituents at the *ortho*, *para*, or *meta* positions of phenol did not have a significant effect on the reaction (Table 2, Entries 2 and 3).

In order to exploit the regioselectivity of this method, we also reported the protection of *N*-acylamino alcohol under the same reaction conditions (Table 2, Entry 20). The corresponding *O*-Boc carbonate is obtained in good yield, and the reaction preserves stereochemical integrity of the *O*-Boc amino alcohol.

Microwave energy when applied to the reaction without any base or acid catalyst generates a mechanical effect and facilitates the nucleophilic attack of the alcohol functional group on the carbonyl group leading to the formation of *O*-Boc-protected hydroxy groups. The structures of the compounds were confirmed by ^{1}H NMR; the Boc group is characterized by the appearance of a signal at 1.5 ppm corresponding to the *tert*-butyl protons. The structures of the compounds were also characterized by IR spectroscopy, where the presence of a band at 1720 cm^{-1} was characteristic of the carbonyl group.

To summarize, we developed a new, effective, simple, mild, rapid, and catalyst-free microwave-assisted method for the chemoselective *O*-*tert*-butoxycarbonylation of a wide range of alcohols. The protocol shows potential in different applications in organic synthesis. The methodology also has several other advantages such as high reaction rates, excellent isolated yields, simple experimental procedure, solvent-free conditions, and the absence of competitive side reactions.[25]

Further work to explore this process for use in other organic transformations is in progress.

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References and Notes

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