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Article

A Greener, Efficient and Catalyst-Free Ultrasonic-Assisted Protocol for the *N*-Fmoc Protection of Amines

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A simple, eco-sustainable method for the *N*-(9-fluorenylmethoxycarbonyl) (*N*-Fmoc) protection of various structurally amines under ultrasonic irradiation is reported. The corresponding *N*-Fmoc derivatives were obtained in good to excellent yields within short reaction time. The reaction proceeds without the formation of any side product. Mildness, efficiency and easier work are the main advantages of this new protocol.

Keywords: *N*-Fmoc**,** protection, amines, ultrasound irradiations, green chemistry

Introduction

The development of greener and simple methods for protection of amines and amine derivatives is in great demand in multi-step organic synthesis. Protecting groups are used during organic synthesis to block temporarily certain functional groups and prevent undesired reaction. When the synthesis is complete and protection is no longer necessary, the protective group is removed to restore the functional group to its natural form.

Allyloxycarbonyl (Alloc), *tert*-butyloxycarbonyl (Boc), (trichloroethyl) carbamate (Troc), benzyloxycarbonyl (Cbz) and 9-fluorenylmethoxycarbonyl (Fmoc) are the most useful protecting groups for primary and secondary amines and especially for amino acids.[1] Among them, the Fmoc[2] group is used extensively, as it can be easily introduced by coupling an amine with an activated 9-fluorenymethyl carbonate like Fmoc-chloride (Fmoc-Cl),[3] (9-fluorenylmethoxycarbonyloxy)succinimide (Fmoc-OSu),[4] or Fmoc benzotriazole-1-yl carbonate (Fmoc-OBt).[5] The main advantage of the Fmoc group is its stability towards acidic conditions, which allows the selective removal of other groups like Boc in presence of acids. The Fmoc group is, in general, rapidly removed by primary (i.e., cyclohexylamine, ethanolamine) and secondary (i.e., piperidine, piperazine) and slowly cleaved by tertiary amines.[1]

There are several protocols available for the protection of amino groups as *N*-(9-fluorenylmethoxycarbonyl) (*N*-Fmoc) derivatives, which include polymers,[6] dimethoxytriazinyloxy moiety,[7] triazoles,[8] and water through photochemical acylation.[9] However, some of these procedures, although effective, have several drawback, such as the use of expensive catalysts, long reaction times, formation of the side-product and use of toxic organic solvents.

In the last three years, several eco-sustainable methodologies have been reported. In this context, Gawande and Branco[10] have used water as solvent for the Fmoc protection of amines and lately, Braga and co-workers[11] described a solvent-free Fmoc protection of amines under microwave conditions. More recently, Nardi *et al.*[12] described a new catalyst-free, water mediated method for the protection of amines and amino acids with di-*tert*-butyl dicarbonate, 9-fluorenylmethoxycarbonyl chloride, acetyl chloride and tosyl chloride. The protection is achieved in few minutes under microwave irradiation.

The development of greener and eco-sustainable methodologies for synthetic transformations is in great demand.[13] In this attention, sonochemistry has gained considerable importance in organic chemistry.[14] The implementation of ultrasonic irradiations in organic reactions provides a specific activation based on physical proprieties, such as acoustic cavitation. Sonochemistry offers a more versatile and facile pathway for a large variety of reaction in comparison to conventional methods.

Continuing our interest towards the development of green synthetic methods in chemistry of protecting groups,[15] we report the *N*-Fmoc protection of various structurally amines in the absence of any solvent and catalyst under ultrasonic irradiation.

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Results and Discussion

In our initial attempt, we initiated our study by evaluating the protection reaction of aniline **1** with Fmoc-Cl **2** in dichloromethane (CH_2Cl_2), as solvent, under ultrasonic irradiation. The reaction was completed in three minutes and the *N*-Fmoc product was obtained in 95% yield. We also achieved the reaction in the absence of solvent and got the same yield (Scheme 1). Thus, we concluded that the ultrasonic irradiations plays an essential role and the solvent did not affect the result of the reaction.

After exploiting the scope of various solvents, such as CH_2Cl_2, chloroform ($CHCl_3$), acetonitrile (CH_3CN), ethanol (EtOH), tetrahydrofuran (THF) and water (H_2O) for the reaction, we found no significant difference with solvent free conditions.

Encouraged by these preliminary experimental results and to increase the scope of this reaction, a series of diverse structurally primary and secondary amines were treated with Fmoc-Cl to synthesize a wide range of Fmoc carbamates under ultrasound-assisted solvent-free conditions (Table 1, entries 1-17).

In all cases, the substrate underwent smooth conversion to the corresponding *N*-Fmoc amines in good to excellent yields. As it can be seen in Table 1, the nature of substituents on the aromatic rings did not affect the yield.

In order to exploit the chemoselectivity of this methodology, we also attempted the *N*-Fmoc protection of β-amino alcohols under the same reaction conditions (Table 2, entries 18-22). The corresponding *N*-Fmoc derivatives were obtained as the only product in excellent yields, without formation of the *O*-fluorenylmethoxycarbonyl (*O*-Fmoc) side produc.

Due to their importance in peptide synthesis, protection of amino acids and their derivatives is of great interest, we decided to extend our study to a series of amino acid esters, *N*-Fmoc amino acid esters (Table 3, entries 23-27). As can be seen in Table 3, the isolated yields of products were in the range of 85-92% after 2 min of reaction.

The structure of all *N*-Fmoc carbamates were unambiguously confirmed by usual spectrometric methods, i.e., proton (^1H) and carbon 13 (^{13}C) nuclear magnetic resonance (NMR), mass spectrometry (MS) and infrared spectroscopy (IR) and comparison with known compounds. The different ^1H NMR spectra showed two characteristic signals between 4 and 5 ppm; a doublet corresponding to the methylene protons (OCH_2) and a triplet corresponding to the methine (CH) group. In the IR spectra, the compounds exhibit characteristic absorption at 1678-1700 cm^{-1} (CO carbamate).

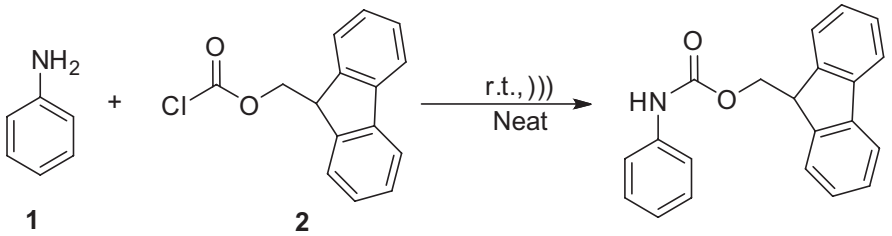
Conclusions

In conclusion, we have developed a new, efficient, simple and catalyst-free chemoselective *N*-Fmoc protection of various amines, using ultrasound irradiation. The protocol is an offering potential and should find many applications in organic synthesis, especially peptides chemistry. The methodology has also several other advantages such as: excellent isolated yields, simple experimental procedure, solvent-less conditions and the absence of any competitive or side reactions. Further work is in progress to explore this process for use in other protecting groups.

Experimental

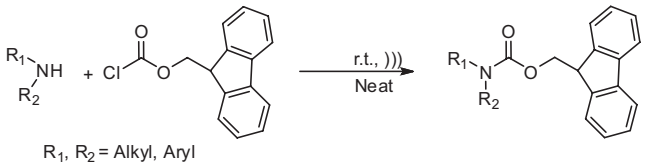
All commercial chemicals were used without further purification. Sonication was performed in a FUNGILAB ultrasonic bath (Spain) with a frequency of 40 kHz and a power of 250 W. All reactions were monitored by thin layer chromatography (TLC) on silica Merck 60 F_{254} percolated aluminum plates (Germany). Melting points were measured in open capillary tubes on an electro-thermal apparatus. ^1H spectra were recorded on a 400 MHz Bruker spectrometer (USA). Chemical shifts are reported in δ units (ppm) with tetramethylsilane (TMS) as a reference. All coupling constants (*J*) are reported on Hz. Multiplicity is indicated as s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet).

^{13}C NMR spectra were recorded on a 100 MHz Bruker spectrometer (USA). Chemical shifts are reported on δ units (ppm) with chloroform ($CDCl_3$) as a reference. Infrared spectra were recorded on a PerkinElmer FT-600 spectrometer (USA). Mass spectra were recorded on a

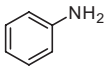
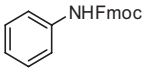
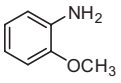
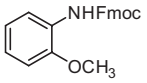
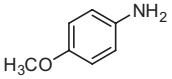
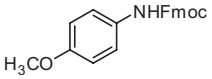
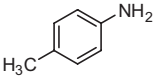
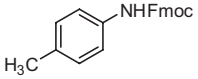
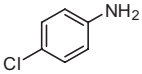
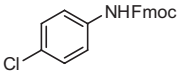
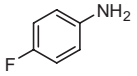
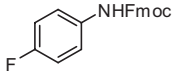
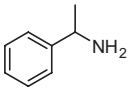
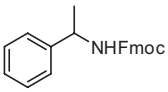
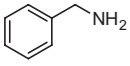
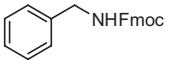
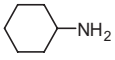
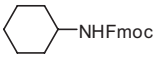
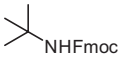
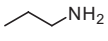
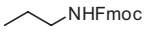
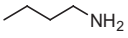
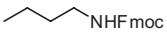
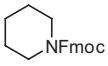
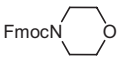
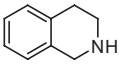
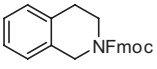
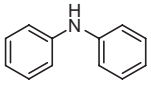
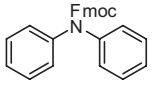
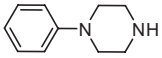
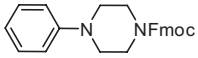


Scheme 1. *N*-(9-Fluorenylmethoxycarbonyl) protection of aniline.

Table 1. *N*-(9-Fluorenylmethoxycarbonyl) derivatives of primary and secondary amines under ultrasound irradiation

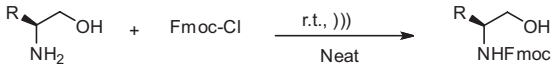


R_1, R_2 = Alkyl, Aryl

entry	Substrate	Product	Yield / %	time / min	m.p.[a] / °C
1			95	5	191 191-192[11]
2			93	4	189
3			91	5	184 192-193[11]
4			94	5	192-193 195-197[11]
5			90	4	162 163-165[10]
6			91	4	176 172-174[10]
7			92	3	191
8			92	3	192
9			88	3	175-179
10			85	3	137
11			83	2	103-105
12			84	2	102
13			77	5	121
14			72	5	112 113-115[11]
15			75	5	Oil
16			87	5	120 119-120[11]
17			79	5	117

[a]Melting point.

Table 2. *N*-(9-Fluorenylmethoxycarbonyl) of β-amino alcohols under ultrasound irradiation



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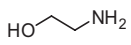
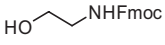
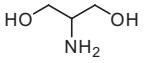
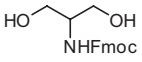
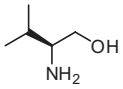
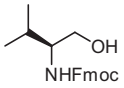
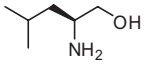
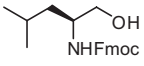
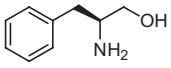
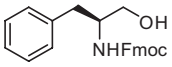
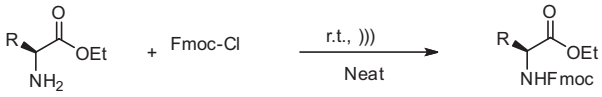
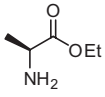
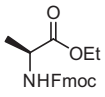
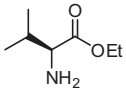
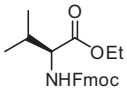
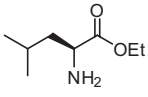
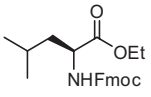
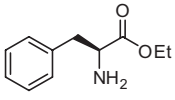
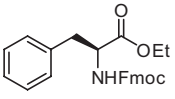
18			87	2	146
19			85	2	138
20			86	2	120-123
21			87	2	117-119
22			89	2	112

[a]Melting point.

Table 3. *N*-(9-Fluorenylmethoxycarbonyl) of α-amino acid esters under ultrasound irradiation.



entry	Substrate	Product	Yield / %	time / min	m.p.[a] / °C
23			90	2	108
24			85	2	98-90
25			91	2	87
26			88	2	85-87
27			92	2	107

[a]Melting point.

Shimadzu QP 1100 Ex mass spectrometer (USA) operating at an ionization potential of 70 eV.

General procedure of *N*-Fmoc protection on amines derivatives promoted by ultrasound irradiations

Amine (1 mmol) and Fmoc-Cl (1.1 mmol) were placed in a glass tube under neat conditions and were sonicated for a suitable time (as indicated in Tables 1, 2 and 3). All reactions were performed in a water bath at room temperature. After completion of the reaction (as indicated by TLC), 5 cm^3 of diethyl ether was added to the mixture. The *N*-Fmoc derivatives were crystallized and were obtained in good to excellent yields.

Purification of the product was accomplished by recrystallization from diethyl ether.

Supplementary Information

Supplementary data (^{1}H and ^{13}C NMR spectra of coupling products) are available free of charge at http://jbcs.sbq.org.br as PDF file.

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