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## ARTICLE

## Aqueous MW eco-friendly protocol for amino group protection.

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In this paper is presented a new catalyst-free and on-water method for protection of amines and amino acids with di-*tert*-butyl dicarbonate, 9-fluorenylmethoxycarbonyl chloride, acetyl chloride and tosyl chloride. The protection can be realized in a few minutes under microwave-assistance. The reaction proved to be chemoselective in presence of ambident nucleophiles and water solution of di- *tert*-butyl carboxylic acid or chloride acid are the only wastes produced.

### Introduction

The need to give serious consideration to the impact that human activities have on the environment, has led the chemical and pharmaceutical industry to adopt the principles of green chemistry in the assessment of the degree of environmental sustainability of each synthetic process.<sup>1</sup>

The essence of 12 Principles of Green Chemistry<sup>2</sup> can be reduced to the useful working definition: *Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste, and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.* Of course, it is not expected that any synthetic process will satisfy all green chemistry principles, but the more it satisfies lower its impact on the environment will be.

It has been estimated that solvents are the major contributor to the E factors of pharmaceutical manufacturing processes, amounting to about 85% of the total mass of chemicals involved in pharmaceutical processes.<sup>3</sup> Consequently, pharmaceutical companies are focusing their effort on minimizing solvent use and in replacement of many traditional organic solvents, such as chlorinated and aromatic hydrocarbons, by more environmentally friendly alternatives including supercritical CO<sub>2</sub>, fluorous biphasic, and ionic liquids alone or in liquid-liquid biphasic combinations. Unfortunately, many of the nonconventional reaction media have prohibitive cost and/or toxicity.<sup>4</sup>

On the contrary, water appears to be a better option having many benefits: it is nontoxic, non-flammable, non-corrosive, abundantly available, and inexpensive. Moreover, the major inconveniences in using aqueous reaction mixture, such as the insolubility of most of organic reactants and the product

isolation,<sup>5</sup> can be successfully tackled by using non-conventional heating systems (microwave, ultrasound, etc...)<sup>6</sup>. Thus, in the last years the role of MW in aqueous systems has had considerable success in many organic synthesis,<sup>7,8</sup> and protective reactions,<sup>9</sup> although the latter are more commonly used in small-scale laboratory work and initial development than in industrial production processes because their use adds additional steps and material costs to the process. Unfortunately, the high reactivity of functional groups such as amines, alcohols and carboxylic acids, etc ... makes the protection of functional groups unavoidable in multi-step organic synthesis. Thus, the protection of the amines and  $\alpha$ -amino functionality of amino acids is one of the most important issues in synthetic organic chemistry and in peptide chemistry.<sup>10</sup>

Because most peptide syntheses, both in solution and on solid phase, are carried out in the C to N direction,  $\alpha$ -amino protecting groups (temporary protecting groups) are used and removed several times during the synthesis, and therefore, the synthetic methods must be mild that do not affect the remaining protecting groups or even the peptidic chain.<sup>11</sup>

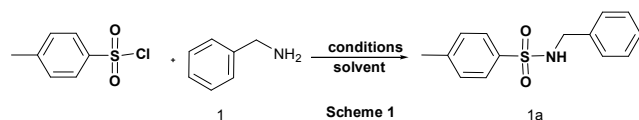
At this regard, sulfonamides and carbamides have become one of the most attractive protecting group for amines.<sup>12</sup> Moreover, these derivatives are extremely useful pharmaceutical compounds for their biological activities such anticancer,<sup>13</sup> anti-inflammatory,<sup>14</sup> and antiviral agents.<sup>15</sup>

In continuation of our interest towards development of useful green synthetic methodologies for the chemical of protecting groups,<sup>16</sup> here we report a simple and ecofriendly method, the use of microwave irradiation<sup>17</sup> for the selective synthesis of different sulfonamide and carbamide derivatives in water without the use of any catalyst.

## Results and discussion

We have recently reported a MW assisted protocol for the rapid and efficient formation/cleavage of *O*-*tert*-butoxy carbonates<sup>17</sup> using erbium(III) salts as catalysts and for the tosylation of a wide set of alcohols in the presence of anhydride derivatives.<sup>18</sup> Now we have decided to test the potential use of MW in the protection of amines and amino acids using sulfonyl and carbonate chlorides as protecting groups.

Thus, in order to investigate product distribution, preliminary experiments were carried out on the model reaction between benzylamine (1 mmol) and tosyl chloride (1.1 mmol) (Scheme 1).



In the first instance, the reaction was performed in dichloromethane using different erbium(III) salts as catalysts. A yield of 96% is obtained only in reflux conditions regardless of the catalyst used (entries 1-5 in Table 1), while poor results were obtained when the reaction was carried out at room temperature.

**Table 1.** Optimization of tosylation reaction with aniline as model substrate.<sup>a</sup>

Entry	Lewis acid <sup>b</sup>	Solvent	T °C	Time min	Yield% <sup>c</sup>
1	ErCl <sub>3</sub> x 6H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	r.t	150	4
2	ErCl <sub>3</sub> x 6H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	60	150	96
3	Er(OTf) <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	60	150	96
4	ErCl <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub>	60	150	96
5	ErCl <sub>3</sub> x 6H <sub>2</sub> O	CH <sub>2</sub> Cl <sub>2</sub>	80	150	97
6	ErCl <sub>3</sub> x 6H <sub>2</sub> O	EL	60	150	68
7	Er(OTf) <sub>3</sub>	EL	60	150	68
8	ErCl <sub>3</sub>	EL	60	150	68
9	ErCl <sub>3</sub> x 6H <sub>2</sub> O	2-MeTHF	60	240	98
10	Er(OTf) <sub>3</sub>	2-MeTHF	60	240	98
11	ErCl <sub>3</sub>	2-MeTHF	60	240	98
12	-	2-MeTHF	60	240	97
13	ErCl <sub>3</sub> x 6H <sub>2</sub> O	H <sub>2</sub> O	60	150	94
14	Er(OTf) <sub>3</sub>	H <sub>2</sub> O	60	150	98
15	ErCl <sub>3</sub>	H <sub>2</sub> O	60	150	95
16	-	H <sub>2</sub> O	60	150	0
17 <sup>d</sup>	ErCl <sub>3</sub> x 6H <sub>2</sub> O	H <sub>2</sub> O	MW	15	98
18 <sup>d</sup>	Er(OTf) <sub>3</sub>	H <sub>2</sub> O	MW	15	98
19 <sup>d</sup>	ErCl <sub>3</sub>	H <sub>2</sub> O	MW	15	98
20 <sup>d</sup>	-	H <sub>2</sub> O	MW	15	98
21 <sup>d</sup>	-	H <sub>2</sub> O	MW	10	98
22 <sup>d</sup>	-	H <sub>2</sub> O	MW	5	98
23 <sup>e</sup>	-	-	MW	17	90

<sup>a</sup> General reaction conditions: 2 mmol of aniline and 2.2 mmol of tosyl chloride was dissolved in the solvent (3 mL); <sup>b</sup> 10% mol of Lewis acid; <sup>c</sup> Isolated yield; <sup>d</sup> 60 °C, 80 °C and 110 °C for entries 17, 18 and 19 respectively; <sup>e</sup> 110 °C.

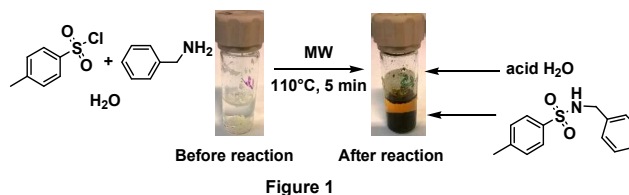
Using green solvent such as ethyl lactate (EL) and 2-MeTHF the reaction yield decreases in the first case (entries 6-8 in Table 1) and increases in the second case (entries 9-11 in Table 1), but no improvement in reaction yields was observed using different catalysts of Er(III) or prolonging the reaction time in both the cases. Noteworthy, still very good result was registered when the reaction was performed in 2-MeTHF in the absence of catalyst (entry 12 in Table 1).

Lastly, the best reaction conditions were found to be using H<sub>2</sub>O as solvent, 10 mol% Er(OTf)<sub>3</sub> as a catalyst at 60 °C for 150 min. (entry 14, Table 1), although no product formation was observed in the absence of catalyst (entry 16 in Table 1).

Anyhow, a marked decrease in reaction times was observed when the same reaction was performed by microwave activation at different temperatures (entries 17-19 in Table 1).

Surprisingly, still excellent results in a short reaction time were registered conducting the same MW-assisted-reaction in the absence of catalyst (entries 20-22 in Table 1). Notably, entry 23 in Table 1 clearly shows that the absence of water retards the reaction time decreasing significantly the reaction yield. This means that the water associated with the system MW plays a fundamental role in the protection reaction.<sup>19</sup>

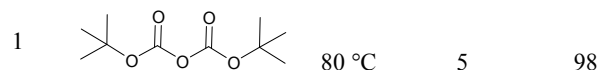
Thus, the catalytic activity Er(III) is brilliantly replaced by the effect of MW in aqueous system and the experimental conditions depicted in Figure 1 (see also entry 22 in Table 1) can be considered the best experimental conditions for this reaction.



To explore the applicability of the above reported method, the same experimental protocol was applied to other protecting groups as *tert*-butyl carbonate (using Boc anhydride as reagent), fluorenylmethoxycarbonyl (using FmocCl as reagent) and acetyl chloride using model substrate benzylamine (Table 2).

**Table 2.** Reaction of benzylamine with different protecting group under MW-activation.<sup>a</sup>

Entry	Protecting Group	condit.	Time [min]	Yield [%] <sup>b</sup>
1		80 °C	5	98
	1b (PG: Fmoc)			
	1c (PG: Boc)			
	1d (PG: Ac)			



2		80 °C	5	70
3		80 °C	10	82
4		110 °C	5	99
5		80 °C	5	98

<sup>a</sup>General reaction conditions: 2 mmol of benzylamine and 2,2 mmol of of Boc anhydride (entry 1) or Fmoc chloride (entries 2-4) or acetyl chloride (entry 5) was dissolved in H<sub>2</sub>O (3 mL). The reactions were conducted in a Syntos 3000 Microwave oven (Anton-Paar) at different temperature. <sup>b</sup> Isolated yield.

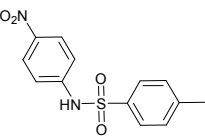
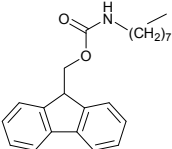
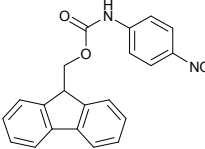
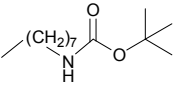
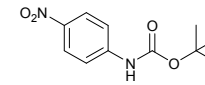
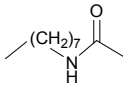
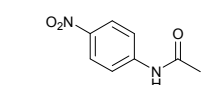
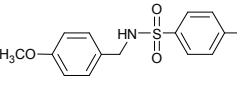
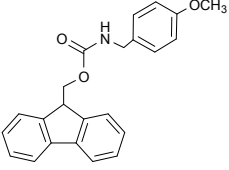
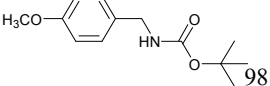
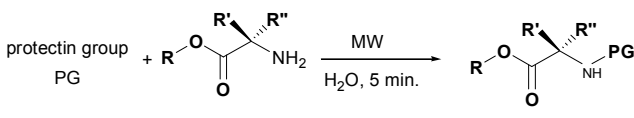
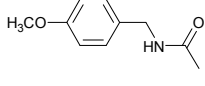
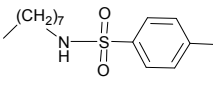
Quantitative yields of protected substrate were obtained for all of the three reagents in only 5 minutes (Table 2) and the need of a higher reaction temperature for the Fmoc derivative can be attributed to its high steric hindrance (entry 2 in Table 2). However, increasing the reaction times up to 10 min, 82% yield of product was obtained (entry 3 in Table 2), and quantitative yield of protected substrate was collected performing the reaction at 110 °C for 10 minutes (entry 4, Table 2).

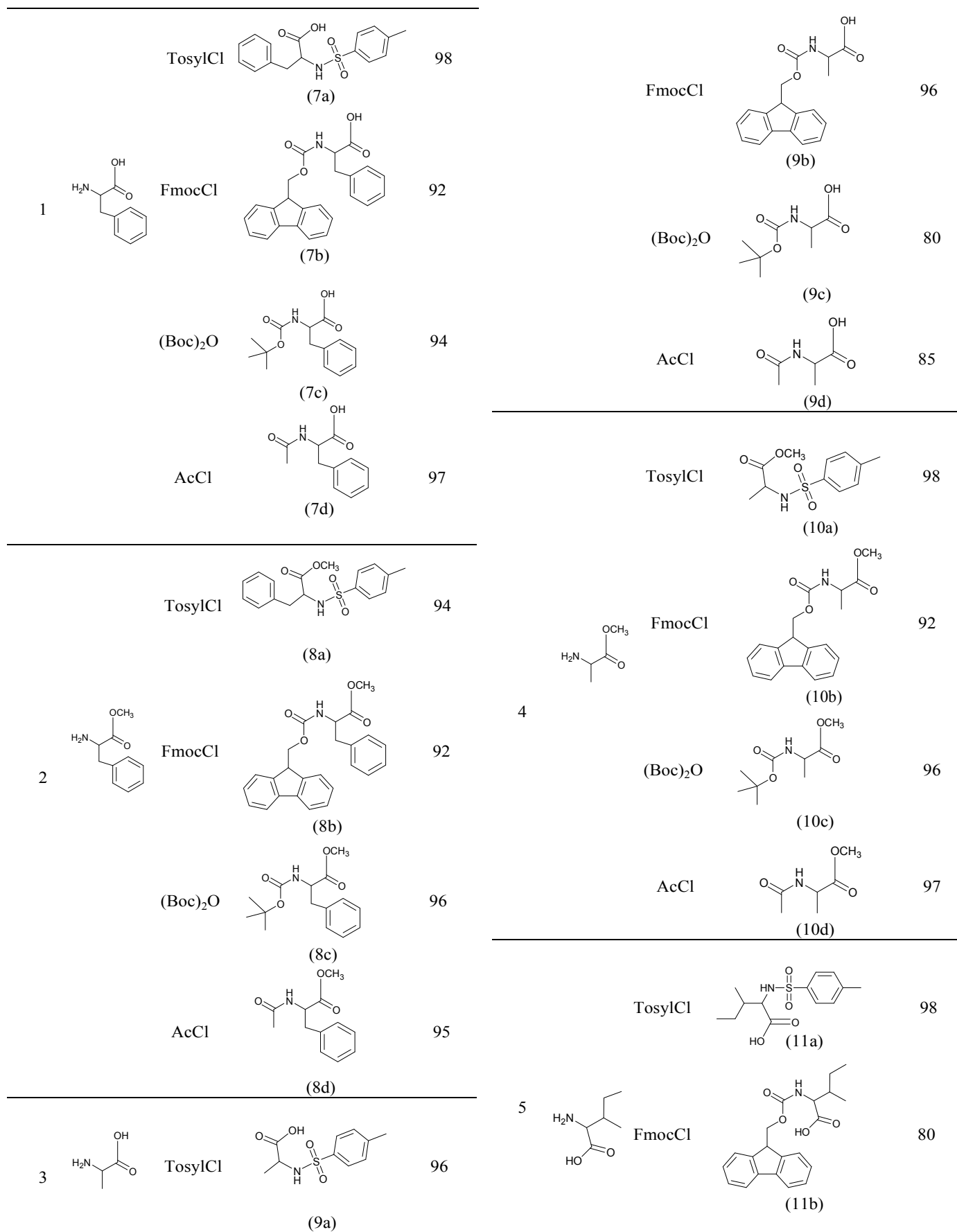
At this point, to explore the applicability/scope of the settled method employed, we have applied the same reaction condition to different aromatic and aliphatic amines (Table 3).

All the aromatic amines gave high yield of protected substrates (entries 1-4 in Table 3) and only for the *p*-nitroaniline lower yield of tosyl and Fmoc derivatives were observed (4a and 4b entry 3 in Table 3); probably due to the presence of electron-withdrawing group on the aromatic ring.

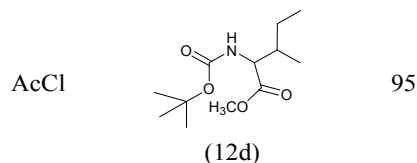
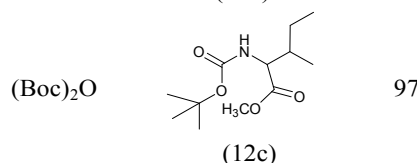
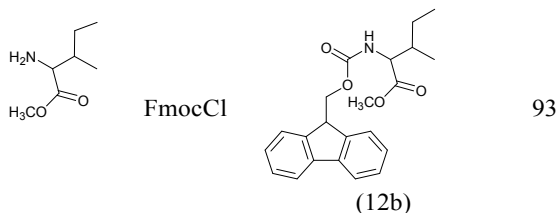
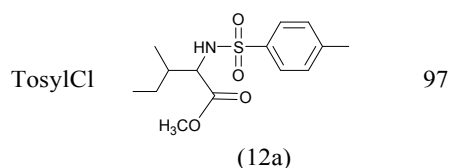
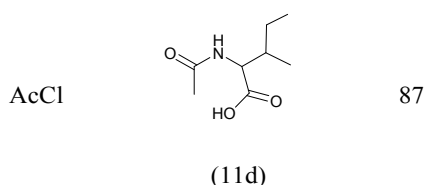
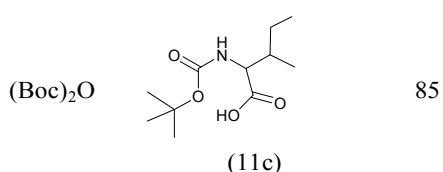
**Table 3.** Protection reaction of different amines with TosylCl, FmocCl, (Boc)<sub>2</sub>O and AcCl in MW/ H<sub>2</sub>O at 110 °C for Tosyl and Fmoc derivatives and 80 °C for Boc derivatives.<sup>a</sup>

Entry	Substrate	Protecting Group	Product	Yield (%)
1		TosylCl		98
		FmocCl		92 <sup>b</sup>
		(Boc) <sub>2</sub> O		94 <sup>b</sup>
		AcCl		98
2		TosylCl		98
		FmocCl		90 <sup>b</sup>
		(Boc) <sub>2</sub> O		98 <sup>b</sup>
		AcCl		97

3	TosylCl		85	5	CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub> NH <sub>2</sub>	FmocCl		95										
	FmocCl		80			(Boc) <sub>2</sub> O		91										
	(Boc) <sub>2</sub> O		98			AcCl		97										
	AcCl		96															
4	TosylCl		98	<sup>a</sup> Reaction conditions: amine (2 mmol), protecting reagent (2.2 mmol), water 2 mL in MW for 5 min, <sup>b</sup> for 2b, 3b 2c and 3c the reaction was carried out for 10 min.														
	FmocCl		95	Lastly, the good performances reported in Table 3 for the protection reactions conducted on various amines showed the efficiency of the presented protocol, pushing our interest to explore its applicability as rapid and efficient protection method of amino acids (Scheme 2).														
	(Boc) <sub>2</sub> O		98	 <p style="text-align: center;">R: H, Me <span style="margin-left: 200px;">Scheme 2</span></p>														
	AcCl		97	In Table 4 are described the results of the protection reactions performed on a series of free or <i>O</i> -methylated amino acids. In all the reported examples, the <i>N</i> -protected amino acids were obtained in excellent yields in only 5 minutes, therefore making this method particularly appropriate for the environmentally friendly protection and deprotection of amino acids.														
	TosylCl		83	<b>Table 4:</b> Protection reaction of different amino acids with TosylCl, FmocCl, (Boc) <sub>2</sub> O in H <sub>2</sub> O under MW-activation.														
		(6a)		<table border="1"> <thead> <tr> <th>Entry</th> <th>Substr.</th> <th>Protecting Group</th> <th>Product</th> <th>Yield (%)<sup>b</sup></th> </tr> </thead> <tbody> <tr> <td></td> <td></td> <td></td> <td></td> <td></td> </tr> </tbody> </table>					Entry	Substr.	Protecting Group	Product	Yield (%) <sup>b</sup>					
Entry	Substr.	Protecting Group	Product	Yield (%) <sup>b</sup>														







<sup>a</sup>Reaction conditions: amino acid (2 mmol), protecting group (2.2 mmol), water 2 mL, MW, at 110 °C for 5 min. <sup>b</sup>Isolated yield.

## Experimental section

### General:

All chemicals and solvents were purchased from common commercial sources and were used as received without any further purification. All reactions were monitored by TLC on silica Merck 60 F254 percolated aluminum plates and were developed by spraying with ninhydrin solution when possible or with a GC-MS Shimadzu workstation, constituted by a GC 2010 (provided of a 30 m-QUADREX 007-5MS capillary column, operating in “splitless” mode, 1 ml min<sup>-1</sup> flow of He as carrier gas) and a 2010 quadrupole mass-detector. All reactions were carried out in the a Syntos 3000 Microwave oven (Anton-Paar) with rotor 4×24MG5. Proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectra were recorded on a Brücker spectrometer at 300 MHz. Chemical shifts are reported in δ units (ppm) with TMS as reference (δ 0.00). All coupling constants (*J*) are reported in Hertz. Multiplicity is indicated by

one or more of the following: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Carbon nuclear magnetic resonance (<sup>13</sup>C-NMR) spectra were recorded on a Brücker at 75 MHz. Chemical shifts are reported in δ units (ppm) relative to CDCl<sub>3</sub> (δ 77.0). Melting points were obtained on a Kofler apparatus.

### General Procedure to determine the substrate scope

To a stirred solution of tosyl chloride fmoc chloride, Boc anhydride (2.2 mmol), in H<sub>2</sub>O (3 mL) was added the N-nucleophile (2.0 mmol) and conducted in MW. The reaction mixture until TLC indicated consumption of the starting material. The reaction mixture presents a organic precipitate The same , repeatedly washed with water is subsequently dried.

**N-Benzyl-*p*-toluenesulfonamide (1a):** yellow solid obtained in 90 % yield (mp 115.1-115.9 °C); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.76 (d, 2H, *J* = 8.24, CH<sub>ar</sub>), 7.24 -7.32 (m, 4H, CH<sub>ar</sub>), 7.17 - 7.21, (m, 2H, CH<sub>ar</sub>), 4.76 (t, 1H, NH, *J* = 6.15), 4.11 (d, 2 H, CH<sub>2</sub>, *J* = 6.22), 2.44 (s, 3H, CH<sub>3</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 21.85, 47.59, 114.34, 127.52, 128.20, 129.01, 136.07, 137.26, 136.64, 143.84.

**N-(9-Fluorenylmethoxycarbonyl) benzylamine (1b):** Colorless solid obtained in 98 % yield. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.58-7.79 (m, 4H, CH<sub>ar</sub>), 7.25-7.46 (m, 5H, CH<sub>ar</sub>), 4.51 (dd, 2H, CH<sub>2</sub>), 4.21-4.39 (m, 2 H, CH<sub>2</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 46.20, 47.32, 66.71, 79.74, 125.00, 127.05, 127.39, 127.55, 127.69, 127.27, 128.73, 141.33, 142.42, 143.93, 156.43.

**N-(tert-Butoxycarbonyl) benzylamine (1c):** white solid obtained in 98% yield (mp 55-57 °C); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.25-7.35 (m, 5H, CH<sub>ar</sub>), 4.31 (d, *J* = 5.49, 2H), 1.46 (s, 9H) <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 46.20, 47.32, 66.71, 79.74, 125.00, 127.05, 127.39, 127.55, 127.69, 127.27, 128.73, 141.33, 142.42, 143.93, 156.43.

**N-benzylacetamide (1d):** yellow flake solid obtained in 98% yield (mp 60-62°C). Spectroscopic data compared to those of the pure product.

**N-phenyl-*p*-toluenesulfonamide (2a):** white solid obtained in 98 % yield (mp 101.5-102.2 °C); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): 7.67 (d, *J* = 7.5 Hz, 2H, CH<sub>ar</sub>), 7.08-7.32 (m, 5H, H-Ar), 7.11 (d, *J* = 7.5 Hz, 2H, CH<sub>ar</sub>), 2.38 (s, 3H, CH<sub>3</sub>), 1.74, (s, 1H, NH). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 21.5, 111.1, 121.1, 125.7, 126.0, 129.5, 136.7, 143.1, 149.6.

**N-(9-fluorenylmethoxycarbonyl) aniline (2b):** Brown solid obtained in 92 % yield; <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.79 (d, 2H, CH<sub>ar</sub>, *J*=7.4 Hz), 7.63 (d, 2H, CH<sub>ar</sub>, *J*=7.0 Hz), 7.43-7.05 (m, 8H, CH<sub>ar</sub>), 6.63 (br s, 1H), 4.56 (d, 2H, *J*=6.4 Hz), 4.28 (t, 1H, *J*=6.4 Hz). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 47.1, 66.8, 118.81, 120.0, 123.6, 124.9, 127.1, 127.8, 129.1, 137.7, 141.4, 143.8, 153.4.

**N-(tert-Butoxycarbonyl) aniline (2c):** White solid obtained in 94 % yield (mp 133-137 °C); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.38-7.25 (m, 4 H), 1.52 (s, 9H), 7.25 (tt, 1H, Ar, *J* = 7.27; *J* = 1.38), 6.49 (s, 1H, NH), <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 28.69, 80.83, 118.89, 123.38, 129.31, 138.69, 153.99.

**N-Acetyl aniline (2d):** White solid obtained in 98 % yield (114–116 °C). Spectroscopic data compared to those of the pure product.

**N-toluidine *p*-toluenesulfonamide (3a):** Colorless oil obtained in 98 % yield. Spectroscopic data compared to those of the pure product.

**N-(9-Fluorenylmethoxycarbonyl)-toluidine (3b):** colorless solid obtained in 90 % yield (mp 195–197 °C). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.79–7.77 (m, 2H, CH<sub>ar</sub>), 7.63–7.61 (m, 2H, CH<sub>ar</sub>), 7.44–7.26 (m, 6H, CH<sub>ar</sub>), 7.11–7.09 (m, 2H, CH<sub>ar</sub>), 7.08–6.90 (m, 4H, CH<sub>ar</sub>), 4.53 (m, 2H), 4.27 (br, 1H, NH), 2.30 (s, 3H), <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ = 20.76, 47.17, 66.74, 120.03, 127.11, 127.16, 129.55, 141.86, 143.8.

**N-(*tert*-Butoxycarbonyl)-toluidine (3c):** brown solid obtained in 98 % yield (mp 34–36 °C); <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.22–7.26 (m, 2H, CH<sub>ar</sub>), 7.08 (d, J = 8.25, 2H, CH<sub>ar</sub>), 6.56 (s, 1H, NH), 2.29 (s, 3H), 1.50 (s, 9H); <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ = 28.69, 80.64, 119.03, 129.78, 132.87, 136.06, 153.23

**N-Acetyl-toluidine (3d):** off white to brown flake solid obtained in 97 % yield (mp 34–36 °C).

**N-(*p*-nitro-aniline) *p*-toluenesulfonamide (4a):** yellow flake solid obtained in 85 % yield (mp 190–191 °C). Spectroscopic data compared to those of the pure product.

**N-(9-fluorenylmethoxycarbonyl) *p*-nitro-aniline (4b):** yellow solid obtained in 80 % yield. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ = 8.14–8.17 (m, 2H, CHar), 7.19–7.79 (m, 10H, CHar), 4.53 – 4.63 (m, 1H, CH), 4.26 (t, 2 H, CH<sub>2</sub>, J = 6.05). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ = 46.20, 47.32, 66.71, 79.74, 125.00, 127.05, 127.39, 127.55, 127.69, 127.27, 128.73, 141.33, 142.42, 143.93, 156.43.

**N-(*tert*-Butoxycarbonyl) *p*-nitro-aniline (4c)** yellow flake oil obtained in 98 % yield. Spectroscopic data compared to those of the pure product. **N-*p*-nitro-aniline acetamide (4d):** Solid, yellow obtained in 96% yield (mp 214–216 °C). Spectroscopic data compared to those of the pure product.

**N-*p*-nitro-aniline-*p*-toluenesulfonamide (5a)** white solid obtained in 98% yield (mp 181–183°C). Spectroscopic data compared to those reported in the literature.<sup>20</sup>

**N-(9-fluorenylmethoxycarbonyl) *p*-methoxybenzylamine (5b):** yellow solid obtained in 95 % yield (mp). <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ: 7.77 (d, 2H, J=7.0 Hz), 7.59 (d, 2H, J=5.8 Hz), 7.51–7.19 (m, 6H), 6.87 (d, 2H, J=6.9 Hz), 4.45 (d, 2H, J=5.5 Hz), 4.45–4.22 (m, 5 H) 3.80 (s, 3H). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 44.6, 47.3, 55.3, 66.6, 114.1, 120.0, 125.0, 127.0, 127.7, 128.9, 130.5, 141.3, 143.9, 156.3, 159.1

**N-(*tert*-Butoxycarbonyl) *p*-methoxybenzylamine (5c):** colorless oil 98. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.26–7.19 (m, 2H, CHar), 6.87– 6.84 (m, 2H, CHar), 4.25–4.23 (m, 2 H, CH<sub>2</sub>), 3.79 (s, 3H), 1.47 (s, 9H), <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>) δ: 28.76, 44.52, 55.64, 79.74, 114.34, 129.19, 131.36, 156.18, 159.25.

***p*-methoxybenzyl acetamide (5d):** yellow oil obtained in 97 % yield. Spectroscopic data compared to those of the pure product.

**N-Octyl *p*-toluenesulfonamide (6a):** yellow oil obtained in 83 % yield. <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>) δ = 7.73 (d, J = 7.4

Hz, 2H, CHar), 7.31 (d, J = 7.4 Hz, 2H, CHar), 3.17–3.15 (m, 2H, NCH<sub>2</sub>), 2.40 (s, 3H, CH<sub>3</sub>), 1.56–1.53 (m, 2H, CH<sub>2</sub>), 1.37–1.20 (m, 10 H, 5 CH<sub>2</sub>), 0.90– 1.00 (m, 3 H, CH<sub>3</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 14.38, 22.83, 24.53, 43.53, 27.11, 29.48, 29.61, 31.23, 41.50, 127.28, 128.97, 136.37, 141.74.

**N-(9-fluorenylmethoxycarbonyl) Octylamine (6b):** Pale yellow solid obtained in 95% yield (mp 91–93°C). <sup>1</sup>H-NMR (300 MHz, CDCl<sub>3</sub>): δ = 7.80–7.19 (m, 8H, CH<sub>ar</sub>), 4.50–4.32 (m, 2H, CH<sub>2</sub>O), 4.32–4.20 (m, 1 H, CH), 3.19 (dd, 2H, NCH<sub>2</sub>, J = 12.9, J = 6.66), 1.58–1.40 (m, 2H, CH<sub>2</sub>), 1.38–1.05- (m, 10 H, 5 CH<sub>2</sub>), 0.90–0.70 (m, 3 H, CH<sub>3</sub>). <sup>13</sup>C-NMR (75 MHz, CDCl<sub>3</sub>): 14.42, 22.97, 44.52, 27.07, 29.54, 29.57, 32.12, 41.44, 47.65, 66.80, 120.28, 125.36, 127.34, 127.97, 141.66, 144.37, 156.75.

**N-(*tert*-Butoxycarbonyl) Octylamine (6c):** Colourless oil obtained in 91% yield. Spectroscopic data compared to those reported in the literature.<sup>21</sup>

**N-Octyl acetamide (6d):** Colorless oil obtained in 97% yield. Spectroscopic data compared to those of the pure product.

***p*-toluenesulfonamide phenylalanine (7a):** White solid obtained in 98 % yield (mp 165– 166 °C). Spectroscopic data compared to those of the pure product.

**N-(9-fluorenylmethoxycarbonyl)-phenylalanine (7b):** white solid obtained in 92 % yield (mp 180–187 °C). Spectroscopic data compared to those of the pure product.

**N-(*tert*-Butoxycarbonyl)-phenylalanine (7c):** white solid obtained in 94 % yield (mp 85–87 °C). Spectroscopic data compared to those of the pure product.

**N-Acetyl-phenylalanine (7d):** white solid obtained in 97 % yield (mp 171–173 °C). Spectroscopic data compared to those of the pure product.

***p*-toluenesulfonamide phenylalanine methyl ester (8a):** white solid obtained in 94% yield. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.63 (d, J=8.25 Hz, 2H), 7.28–7.20 (M, 5H), 7.05 (dd, J=5.42, 2.02 Hz, 2H), 5.08 (d, 1H, NH, J = 9.06), 4.20 (dt, J= 9.06, J = 5.90, Hz, 2H), 3.48 (s, 3H, CH<sub>3</sub>), 3.02 (d, 2H, J = 5.90), 2.40 (s, 3H, CH<sub>3</sub>); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz) δ = 21.84, 39.70, 52.68, 56.93, 127.50, 127.57, 128.90, 129.72, 129.92, 135.25, 136.94, 143.92, 171.56.

**N-(9-fluorenylmethoxycarbonyl)-phenylalanine methyl ester (8b):** white solid obtained in 92% yield. <sup>1</sup>H-NMR (CDCl<sub>3</sub>, 300 MHz) δ 7.76 (d, J=7.5 Hz, 2H), 7.56 (t, J=6.7 Hz, 2H), 7.40 (td, J=7.5, 0.6 Hz, 2H), 7.33–7.27 (m, 5H), 7.08 (d, J=6.5 Hz, 2H), 5.26 (d, J=8.1 Hz, 1H), 4.67 (m, 1H), 4.44 (dd, J=10.6, 7.1 Hz, 1H), 4.34 (dd, J=10.6, 6.9 Hz, 1H), 4.20 (t, J=7.0 Hz, 1H), 3.73 (s, 3H), 3.11 (m, 2H); <sup>13</sup>C-NMR (CDCl<sub>3</sub>, 75 MHz) δ = 38.4, 47.3, 52.6, 54.9, 67.1, 120.2, 125.3, 127.3, 127.4, 127.9, 128.8, 129.5, 135.9, 141.5, 144.0, 155.7, 172.1.

**N-(*tert*-Butoxycarbonyl)-phenylalanine methyl ester (8c):** white solid obtained in 96% yield. (mp 36–40 °C). Spectroscopic data compared to those of the pure product.

**N-Acetyl-phenylalanine methyl ester (8d):** colorless oil obtained in 95% yield. Spectroscopic data compared to those of the pure product.

***p*-toluenesulfonamide alanine (9a):** white solid obtained in 96% (mp 132–137 °C). Spectroscopic data compared to those of the pure product.



**N-(9-fluorenylmethoxycarbonyl)-alanine (9b):** white solid obtained in 96% (mp 147-153 °C). Spectroscopic data compared to those of the pure product.

**N-(tert-Butoxycarbonyl)- alanine (9c):** white solid obtained in 96% (mp 79-83 °C). Spectroscopic data compared to those of the pure product.

**N-Acetyl-alanine (9d):** white solid obtained in 96 % yield. (mp 126-128 °C). Spectroscopic data compared to those of the pure product.

**p-toluenesulfonamide alanine methyl ester (10a):** white solid obtained in 98% yield (mp 101-103 °C). Spectroscopic data compared to those reported in the literature.<sup>22</sup>

**N-(9-fluorenylmethoxycarbonyl)-alanine methyl ester (10b):** white solid obtained in 92% yield (mp 110–112 °C). Spectroscopic data compared to those of the pure product.

**N-(tert-Butoxycarbonyl)-alanine methyl ester (10c):** colorless oil obtained in 93% yield. Spectroscopic data compared to those reported in the literature.<sup>23</sup>

**N-Acetyl-alanine methyl ester (10 d):** colorless oil obtained in 97% yield. Spectroscopic data compared to those of the pure product.

**p-toluenesulfonamide isoleucine (11a):** white solid obtained in 86% yield (mp 140-145 °C). Spectroscopic data compared to those of the pure product.

**N-(9-fluorenylmethoxycarbonyl)-isoleucine (11b):** white solid obtained in 80% yield (mp 145-147 °C). Spectroscopic data compared to those of the pure product.

**N-(tert-Butoxycarbonyl)-isoleucine (11c)** white solid obtained in 85% yield (mp 66-69 °C). Spectroscopic data compared to those of the pure product.

**N-Acetyl-isoleucine (11d)** white solid obtained in 87% yield (mp 132-147 °C). Spectroscopic data compared to those of the pure product.

**p-toluenesulfonamide isoleucine methyl ester (12a):** white solid obtained in 98% yield (mp 84–86 °C). Spectroscopic data compared to those reported in the literature.<sup>24</sup>

**N-(9-fluorenylmethoxycarbonyl) isoleucine methyl ester (12b):** white solid obtained in 93% yield (mp 140-143 °C). Spectroscopic data compared to those of the pure product.

**N-(tert-Butoxycarbonyl)-isoleucine methyl ester (12c):** white solid obtained in 97% yield (mp 68-72°C). Spectroscopic data compared to those of the pure product.

**N-Acetyl-isoleucine methyl ester (12d):** colorless oil obtained in 95% yield. Spectroscopic data compared to those of the pure product.

## Conclusions

Synthetic organic protocols using greener and more efficient methodologies are crucial for the development of more sustainable processes. This article highlights the importance of water in organic synthesis and exhibits a novel and efficient route for water-mediated *N*-protection of amines with MW. The absence of acid/base and the use of water makes present procedure environmentally friendly. In the light of these premises, further developments of benign by design methodologies are expected in the coming study. The authors

believe that these methods of sustainable protection are stimulus to the development of synthetic methods for peptides that meet the 12 principles of Green Chemistry.<sup>2</sup>

## Notes and references

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