

# Short Report

## Appel Reaction of Carboxylic Acids with Tribromoisocyanuric Acid/ Triphenylphosphine: a Mild and Acid-Free Preparation of Esters and Amides

Haryadylla da Cunha Sindra and Marcio C. S. de Mattos\*

Departamento de Química Orgânica, Instituto de Química, Universidade Federal do Rio de Janeiro,  
CP 68545, 21945-970 Rio de Janeiro-RJ, Brazil

A facile and efficient method for esterification and amidation of carboxylic acids under neutral conditions has been developed. Esters and amides can be prepared by reacting a carboxylic acid (1 mmol) with tribromoisocyanuric acid (0.37 mmol) and triphenylphosphine (1 mmol) in dichloromethane at room temperature, followed by addition of an alcohol or an amine, respectively.

**Keywords:** amides, esters, tribromoisocyanuric acid, acylation, triphenylphosphine

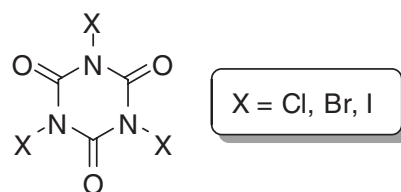
### Introduction

Esters and amides are important intermediates in the chemical and pharmaceutical industries. Besides, some of them are bioactive compounds.<sup>1</sup> In general, their preparations from the corresponding carboxylic acids are well-known transformations and numerous methods have been reported.<sup>2</sup> However, the coupling reactions of carboxylic acids with nucleophiles require activation of the carboxyl group by its conversion into the most reactive acyl halide.<sup>2</sup>

On the other hand, acid halides are traditionally prepared from carboxylic acids and several common reagents such as thionyl halides, oxalyl halides or phosphorus (oxy) halides.<sup>3</sup> However, despite their success, there are still some remaining problems using these reagents as they cannot be applied to acid-sensitive substrates due to the high temperature conditions required and the formation of strong harmful corrosive acids by-produced during the process. Furthermore, if the amount of the reagent used is insufficient, acid anhydrides are obtained instead of acyl halides.<sup>4</sup> Therefore, convenient protocols for the preparation of acid halides under mild conditions is being subject of intensive research.<sup>5</sup> In this context, the Appel reaction<sup>6</sup> of carboxylic acids with carbon tetrachloride,<sup>7</sup> trichloroacetonitrile<sup>8</sup> or trichloroacetamide<sup>9</sup> (among others) in the presence of triphenylphosphine (PPh<sub>3</sub>) have been efficiently used for the preparation of acyl chlorides with high efficiency. Despite being the driving force in Appel-type reactions, the formation of the triphenylphosphine oxide by-product can

result in an inconvenient purification process; therefore the development of new methods that avoid or minimize the triphenylphosphine oxide by-product in Appel reactions is subject of intensive research.<sup>10</sup>

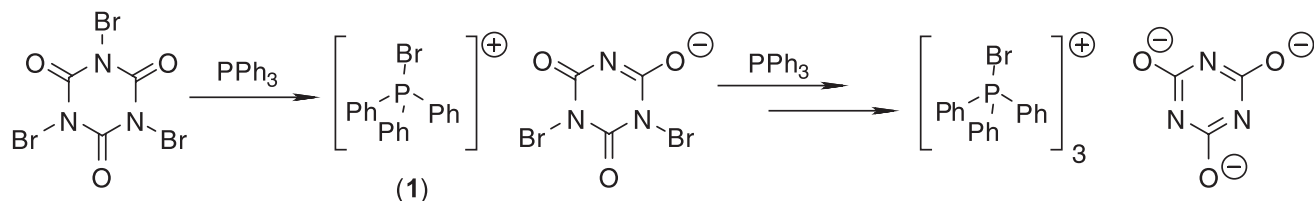
Trihaloisocyanuric acids [1,3,5-trihalo-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-triones] (Figure 1) are safe, stable and easily handled solids used as electrophilic halogenating reagents.<sup>11</sup> Although diverse trihaloisocyanuric acids are known,<sup>12</sup> the most widely used is the inexpensive and commercially available trichloroisocyanuric acid (TCCA; Figure 1, X = Cl). While not yet commercially available, tribromoisocyanuric acid (TBCA; Figure 1, X = Br) can be easily prepared from inexpensive materials (cyanuric acid, KBr and oxone).<sup>13</sup>



**Figure 1.** Trihaloisocyanuric acids.

In a pioneering paper, Hiegel *et al.*<sup>14</sup> reported the conversion of phenylacetic acid into the acyl chloride using trichloroisocyanuric acid along with triphenylphosphine and subsequent addition of dry methanol produced methyl phenylacetate in 95% yield. Later, the trichloroisocyanuric acid/triphenylphosphine system was used to convert several carboxylic acids into amides, esters and acyl azides, by reactions with amines, alcohols<sup>15</sup> and sodium azide,<sup>16</sup> respectively.

\*e-mail: mmattos@iq.ufrj.br



Scheme 1.

Recently, we showed an efficient Appel conversion of alcohols into the corresponding alkyl bromides using tribromoisocyanuric acid/triphenylphosphine system,<sup>17</sup> being a bromophosphonium salt (**1**), formed by reaction of triphenylphosphine with TBCA, the key reactive species for such transformation (Scheme 1).<sup>17,18</sup>

In continuation of our studies on the application of tribromoisocyanuric acid in organic synthesis,<sup>19</sup> herein we report the preparation of esters and amides by reaction of carboxylic acids with alcohols and amines, respectively, in the presence of the tribromoisocyanuric acid/triphenylphosphine system.

## Results and Discussion

The reactions were carried out at room temperature by stirring together the carboxylic acid (1 mmol), tribromoisocyanuric acid (0.37 mmol) and triphenylphosphine (1 mmol) in dichloromethane. The progress of the reaction was followed by gas chromatography with mass spectrometer (GC-MS) and after complete substrate conversion to the acyl bromide (confirmed by MS), an alcohol (1 mmol) or an amine (excess) was added to the reaction media. The reactions gave, respectively, esters and amides (along with triphenylphosphine oxide and cyanuric acid), that were isolated by column chromatography and characterized by their melting points (amides) and spectroscopic techniques. In general, the reactions proceeded smoothly and gave products in moderate to excellent yields, showing that the method is quite general and suitable for the conversion of carboxylic acids into their corresponding esters or amides. Tables 1 and 2 show the results.

Interestingly, although tribromoisocyanuric acid is known to be a powerful alcohol oxidant<sup>20</sup> and electrophilic brominating reagent for alkenes<sup>21</sup> and arenes,<sup>22</sup> no brominated or oxidation products were detected by the analytical techniques employed in the crude reaction, indicating a fast formation of bromotriphenylphosphonium salt from the reaction of TBCA with triphenylphosphine.

Based on the above results, a plausible scheme for this transformation (Scheme 2) proceeds through the bromophosphonium salt (**1**), formed by bromination of

triphenylphosphine by TBCA, that is further converted into the oxyphosphonium intermediate (**2**). Bromide anion attacks on the intermediate **2** gives the acyl bromide and triphenylphosphine oxide. Simple nucleophilic addition of the alcohol or the amine to the acyl bromide led to the ester or amide along with isocyanuric acid.

A comparison between our methodology and similar ones previously published (trichloroacetamide/PPh<sub>3</sub>,<sup>9</sup> trichloroacetonitrile/PPh<sub>3</sub>,<sup>23</sup> ethyl tribromoacetate/PPh<sub>3</sub>,<sup>24</sup> or hexabromoacetone/PPh<sub>3</sub>)<sup>25</sup> for the preparation of *N*-cyclohexylbenzamide indicated similar yields (Table 3). However, the advantages of TBCA compared to other reagents used in such transformations is its stability, easy manipulation and preparation and high atom economy,<sup>26</sup> i.e., percentage of mass transferred to triphenylphosphine to generate the halophosphonium salt (**1**), the reactive species. Besides, the cyanuric acid by-product formed can be reused to produce more TBCA through a green process (Scheme 3).<sup>21</sup>

## Conclusions

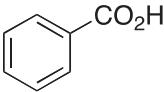

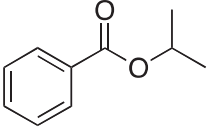
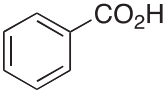
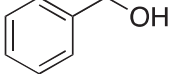
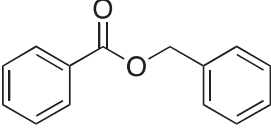
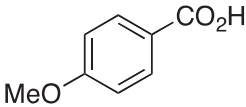

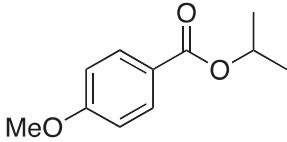
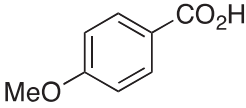
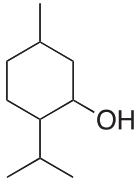
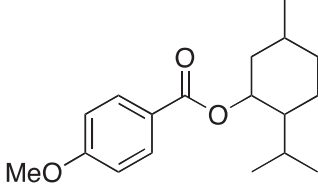
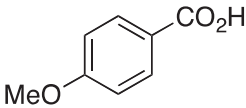
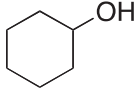
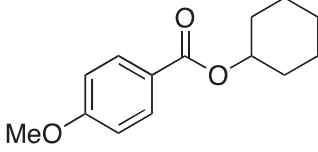
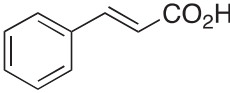

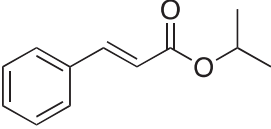
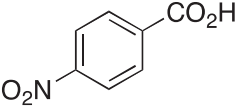
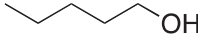
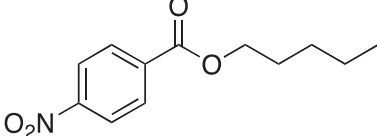
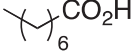
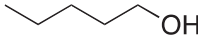
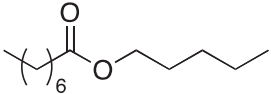
In summary, we have developed a new and convenient route for the preparation of esters and amides from carboxylic acids under neutral conditions. The reaction is easily reproducible, the conditions are mild and the reagents are easily available.

## Experimental

### General information

All chemicals and solvents were used as received. Tribromoisocyanuric acid was prepared as previously described.<sup>13</sup> Nuclear magnetic resonance (NMR) spectra were recorded on a Bruker AC-200 or AC-300 spectrometers (Bruker, Billerica, MA, USA) at 200 or 300 MHz (<sup>1</sup>H) and 50 or 75 (<sup>13</sup>C) using tetramethylsilane (TMS) as internal standard. Gas chromatography were performed on a HP 5890 Series II gas chromatograph (Hewlett-Packard, Palo Alto, CA, USA) with flame ionization detector (FID) using a 30 m (length), 0.25 mm (inner diameter), and 25 μm (phase thickness) RTX-5 capillary column (Restek Corporation, Bellefonte, PA, USA) and H<sub>2</sub> (flow rate 50 cm s<sup>-1</sup>) as carrier

**Table 1.** Esterification of carboxylic acids promoted by tribromoisocyanuric acid (TBCA)/triphenylphosphine

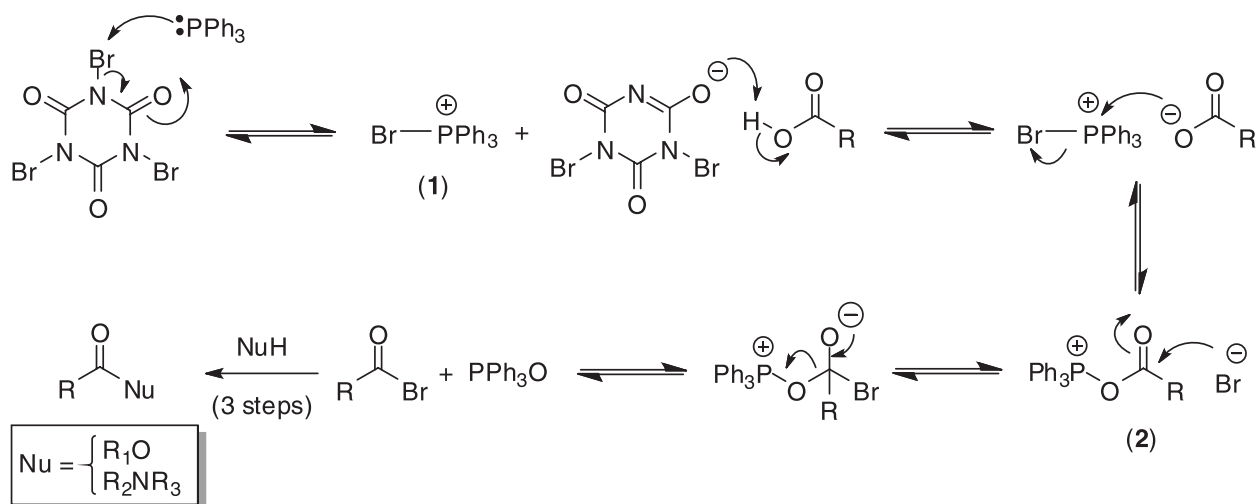
$  \begin{array}{c}  \text{R}-\text{COOH} + \begin{array}{c} \text{Br} \\   \\ \text{O}=\text{N} \\   \\ \text{O} \\   \\ \text{O} \\   \\ \text{Br} \end{array} + \text{PPh}_3 \xrightarrow[2) \text{R}_1\text{OH (1 mmol) / } t_2]{1) \text{CH}_2\text{Cl}_2 / \text{r.t. / } t_1} \text{R}-\text{COOR}_1 \\  (1 \text{ mmol}) \qquad (0.37 \text{ mmol}) \quad (1 \text{ mmol})  \end{array}  $					
Carboxylic acid	time <sub>1</sub> / h	Alcohol	time <sub>2</sub> / h	Product	Yield <sup>a</sup> / %
	1.5		0.25		85
	1.5		0.25		66
	2		0.5		77
	1		1		71
	1.5		1.5		68
	1.5		0.25		65
	3		1.25		75
	4		1		61

<sup>a</sup>Yield of pure product based on carboxylic acid.

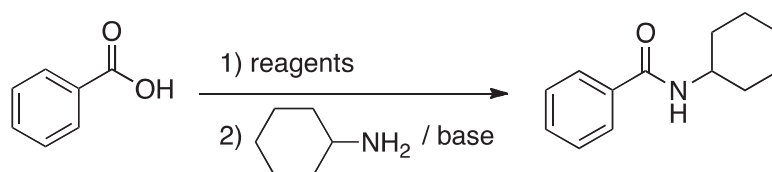
**Table 2.** Amidation of carboxylic acids promoted by tribromoisocyanuric acid (TBCA)/triphenylphosphine

Carboxylic acid	time <sub>1</sub> / h	Amine	time <sub>2</sub> / h	Product	Yield <sup>a</sup> / %
 (1 mmol)                      (0.37 mmol)                      (1 mmol)					
	1		0.5		77
	1		0.5		95
	1		0.5		67
	1.5		0.5		80
	2		1.25		40
	2		2		48
	2		1		76
	2.5		1		53
	2.5		1		67

<sup>a</sup>Yield of pure product based on carboxylic acid.

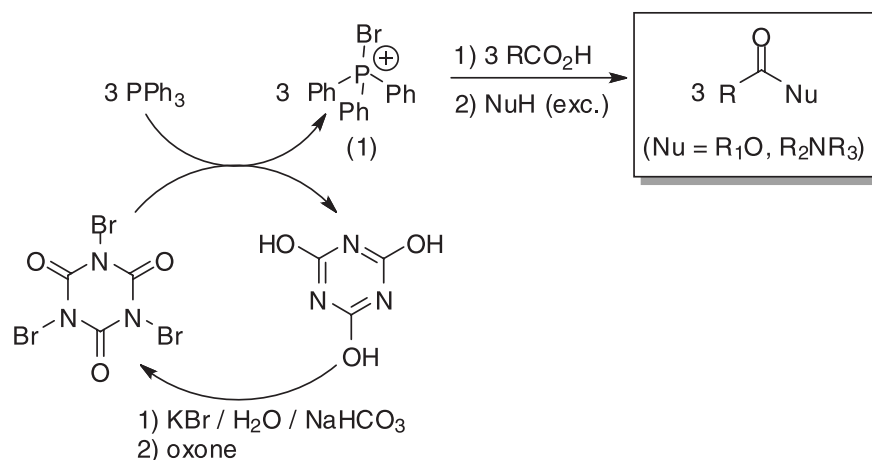


Scheme 2.

Table 3. Preparation of *N*-cyclohexylbenzamide

Reagent <sup>a</sup>	Base	Yield / %	Reference
CCl <sub>3</sub> CONH <sub>2</sub> (2 equiv.), PPh <sub>3</sub> (2 equiv.)	4-picoline (3 equiv.)	99	9
CCl <sub>3</sub> CN (2 equiv.), PPh <sub>3</sub> (2 equiv.)	NEt <sub>3</sub> (3 equiv.)	97	23
CBr <sub>3</sub> CO <sub>2</sub> Et (2 equiv.), PPh <sub>3</sub> (2 equiv.)	NEt <sub>3</sub> (3 equiv.)	92	24
(CBr <sub>3</sub> ) <sub>2</sub> CO (0.3 equiv.), PPh <sub>3</sub> (1.5 equiv.)	NEt <sub>3</sub> (3 equiv.)	75	25
TBCA (0.37 equiv.), PPh <sub>3</sub> (1 equiv.)	–	95	this work

<sup>a</sup>All reactions performed in CH<sub>2</sub>Cl<sub>2</sub>. PPh<sub>3</sub>: Triphenylphosphine; TBCA: tribromoisocyanuric acid; NEt<sub>3</sub>: triethylamine.



Scheme 3.

gas (split 1:10). GC-MS analyses were performed on a Shimadzu GCMS-QP2010S gas chromatograph (Shimadzu, Kyoto, Japan) with electron impact (70 eV) by using a 30 m DB-5 silica capillary column with 0.25 mm inner diameter and 0.25 mm phase thickness. Melting points were determined on a Laboratory Device Mel-Temp II (Laboratory Devices, USA) and are corrected.

General procedure for esterification of carboxylic acids promoted by TBCA/triphenylphosphine

To a stirred solution of TBCA (0.37 mmol) and triphenylphosphine (1 mmol) in  $\text{CH}_2\text{Cl}_2$  (6  $\text{cm}^3$ ) was added the carboxylic acid (1 mmol) at room temperature. The progress of the reaction was monitored by GC-MS (time<sub>1</sub> in Table 1) and, then, alcohol (1 mmol) was added. After time<sub>2</sub> (Table 1), cyanuric acid was filtered off and the liquid was evaporated on a rotatory evaporator under reduced pressure. The products were purified by column chromatography (silica gel 70-230 mesh) using diethyl ether/pentane as eluent.

#### Isopropyl benzoate<sup>27</sup>

Colorless liquid; <sup>1</sup>H NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.35 (d, 6H, *J* 6.3), 5.16-5.36 (hept, 1H, *J* 6.2), 7.38-7.52 (m, 3H), 8.05 (m, 2H); <sup>13</sup>C NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  22.0, 68.4, 128.3, 129.6, 131.0, 132.8, 166.2; MS (70 eV) *m/z* 164 ( $\text{M}^+$ ), 123, 105 (100%), 77, 59, 51, 43.

#### Benzyl benzoate<sup>28</sup>

Colorless liquid; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  5.40 (s, 2H), 7.37-7.50 (m, 7H), 7.56-7.61 (m, 1H), 8.10-8.14 (m, 2H); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  66.9, 128.3, 128.4, 128.6, 128.8, 129.9, 130.3, 133.2, 136.2, 166.6; MS (70 eV) *m/z* 212 ( $\text{M}^+$ ), 194, 105 (100%), 91, 77, 65, 51.

#### Isopropyl 4-methoxybenzoate<sup>29</sup>

Yellowish liquid; <sup>1</sup>H RMN (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.35 (d, 6H, *J* 6.2), 3.83 (s, 3H), 5.16-5.28 (hept, 1H, *J* 6.2), 6.90 (d, 2H, *J* 8.9), 7.98 (d, 2H, *J* 9.0); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  22.2, 55.6, 68.1, 113.7, 123.6, 131.7, 163.4, 166.1; MS (70 eV) *m/z* 194 ( $\text{M}^+$ ), 179, 152, 135 (100%), 92, 77, 64, 43.

#### Menthyl 4-methoxybenzoate<sup>30</sup>

Yellowish oil; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  0.80 (d, 3H, *J* 6.9), 0.91-0.94 (m, 7H), 1.03-1.16 (m, 2H), 1.49-1.59 (m, 2H), 1.70-1.75 (m, 2H), 1.94-2.01 (m, 1H), 2.10-2.14 (m, 1H), 3.86 (s, 3H), 4.86-4.95 (m, 1 H), 6.92 (d, 2H, *J* 9.0), 8.01 (d, 2H, *J* 8.8); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  16.8, 21.0, 22.2, 23.9, 26.7, 31.6, 34.6, 41.3, 47.5, 55.6, 74.7, 113.7, 123.5, 131.74, 163.4, 166.1; MS (70 eV) *m/z* 290 ( $\text{M}^+$ ), 152, 135 (100%), 123, 95, 81, 55, 41.

#### Cyclohexyl 4-methoxybenzoate<sup>31</sup>

Yellowish oil; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.31-1.63 (m, 6H), 1.76-1.83 (m, 2H), 1.91-1.95 (m, 2H), 3.87 (s, 3H), 4.96-5.04 (m, 1H), 6.91 (d, 2H, *J* 9.0), 7.99 (d, 2H, *J* 9.0); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  23.9, 25.7, 31.9, 55.6, 72.9, 113.7, 123.7, 131.7, 163.4, 166.0; MS (70 eV) *m/z* 234 ( $\text{M}^+$ ), 152, 135 (100%), 107, 92, 77, 67, 55, 41.

#### Isopropyl cinnamate<sup>32</sup>

Yellowish liquid; <sup>1</sup>H NMR (300 MHz,  $\text{CDCl}_3$ )  $\delta$  1.32 (d, 6H, *J* 6.7), 5.09-5.22 (hept, 1H, *J* 6.2), 6.43 (d, 1H, *J* 16.0), 7.35-7.39 (m, 3H), 7.49-7.54 (m, 2H), 7.68 (d, 1H, *J* 16.0); <sup>13</sup>C NMR (75 MHz,  $\text{CDCl}_3$ )  $\delta$  22.1, 67.9, 119.0, 128.1, 129.0, 130.3, 134.7, 144.4, 166.6; MS (70 eV) *m/z* 190 ( $\text{M}^+$ ), 147, 131 (100%), 103, 77, 51, 43.

#### Pentyl 4-nitrobenzoate<sup>33</sup>

Colorless liquid; <sup>1</sup>H NMR (300 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  0.92-0.97 (m, 3H), 1.37-1.48 (m, 4H), 1.74-1.83 (m, 2H), 4.35 (t, 2H, *J* 6.6), 8.19 (d, 2H, *J* 9.0), 8.29 (d, 2H, *J* 9.0); <sup>13</sup>C NMR (75 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  12.8, 21.6, 27.4, 27.5, 65.3, 123.1, 130.0, 136.5, 150.1, 164.2; MS (70 eV) *m/z* 238 ( $\text{M}^+$ ), 168, 150, 120, 104, 70 (100%), 55, 42.

#### Pentyl octanoate<sup>34</sup>

Colorless liquid; <sup>1</sup>H NMR (300 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  0.88-0.95 (m, 6H), 1.31-1.37 (m, 12H), 1.57-1.64 ppm (m, 4H), 2.28 (t, 2H, *J* 7.3), 4.04 (t, 2H, *J* 6.6 Hz); <sup>13</sup>C NMR (75 MHz,  $\text{CD}_3\text{CN}$ )  $\delta$  14.4, 14.5, 23.2, 23.5, 26.0, 29.0, 29.3, 29.9, 29.9, 32.6, 35.0, 65.0, 174.5; MS (70 eV) *m/z* 214 ( $\text{M}^+$ ), 145, 127, 70 (100%), 57, 55, 43.

General procedure for amidation of carboxylic acids promoted by TBCA/triphenylphosphine

To a stirred solution of TBCA (0.37 mmol) and triphenylphosphine (1 mmol) in  $\text{CH}_2\text{Cl}_2$  (6  $\text{cm}^3$ ) was added the carboxylic acid (1 mmol) at room temperature. The progress of the reaction was monitored by GC-MS (time<sub>1</sub> in Table 2) and, then, the amine (25-75 mmol) was added. After the time<sub>2</sub> (Table 2), cyanuric acid was filtered off, and the liquid was evaporated on a rotatory evaporator under reduced pressure. The products were purified by column chromatography (silica gel 70-230 mesh) using diethyl ether/pentane as eluent.

#### *N*-Isopropyl-benzamide

Yellowish solid; m.p. 94-96 °C (lit. 95 °C);<sup>35</sup> <sup>1</sup>H NMR (200 MHz,  $\text{CDCl}_3$ )  $\delta$  1.24 (d, 6H, *J* 6.5), 4.18-4.35 (sext, 1H, *J* 6.6), 6.27 (s, 1 H), 7.37-7.45 (m, 3 H), 7.74-7.77 (m, 2 H); <sup>13</sup>C NMR (50 MHz,  $\text{CDCl}_3$ )  $\delta$  22.9, 42.0, 127.0,

128.6, 131.3, 135.1, 166.9; MS (70 eV)  $m/z$  163 ( $M^+$ ), 148, 105 (100%), 77, 51.

#### *N*-Cyclohexyl-benzamide

White solid; m.p. 138-140 °C (lit. 139-141 °C);<sup>36</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.18-2.05 (m, 10H), 3.92-4.04 (m, 1H), 6.06 (s, 1H), 7.38-7.49 (m, 3H), 7.74-7.78 (m, 2H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 25.1, 25.8, 33.4, 48.9, 127.0, 128.7, 131.4, 135.3, 166.8; MS (70 eV)  $m/z$  203 ( $M^+$ ), 123, 122, 105 (100%), 77, 51.

#### *N*-Cyclohexyl-4-methoxybenzamide

White solid; m.p. 153-155 °C (lit. 153-154 °C);<sup>37</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.16-1.29 (m, 3H), 1.35-1.50 (m, 2H), 1.62-1.79 (m, 3H), 2.02-2.06 (m, 2H), 3.84 (s, 1H), 3.91-4.03 (m, 1H), 5.93 (s, 1H), 6.91 (d, 2H, *J* 8.9), 7.72 (d, 2H, *J* 8.8); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 25.1, 25.8, 33.5, 48.8, 55.6, 113.9, 127.6, 128.8, 162.2, 166.3; MS (70 eV)  $m/z$  233 ( $M^+$ ), 232 (2,49), 152, 151, 135 (100%), 107, 92, 79, 77.

#### *N*-Isopropyl-4-methoxybenzamide

White solid; m.p. 112-114 °C (lit. 123°C);<sup>35</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.25 (d, 6H, *J* 6.3), 3.83 (s, 3H), 4.21-4.33 (m, 1H), 6.00 (s, 1H), 6.89 (d, 2H, *J* 8.9), 7.73 (d, 2H, *J* 8.9); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 23.0, 41.9, 55.5, 113.8, 127.3, 128.8, 162.1, 166.4; MS (70 eV)  $m/z$  193 ( $M^+$ ), 135 (100%), 107, 104, 92, 77.

#### *N*-Benzyl-4-methoxybenzamide

White solid; m.p. 120-122 °C (lit. 124-126 °C);<sup>38</sup> <sup>1</sup>H NMR (300 MHz, CD<sub>3</sub>CN) δ 2.42 (s, 1H), 3.83 (s, 3H), 4.53 (d, 2H, *J* 6.1), 6.97 (d, 2H, *J* 8.9), 7.23-7.35 (m, 5H), 7.49 (s, 1H), 7.81 (d, 2H, *J* 8.9); <sup>13</sup>C NMR (75 MHz, CD<sub>3</sub>CN) δ 44.3, 56.5, 115.0, 128.3, 128.7, 129.8, 130.3, 141.2, 163.6, 167.9; MS (70 eV)  $m/z$  241 ( $M^+$ ), 135 (100%), 107, 92, 77, 64, 51.

#### *N*-Isopropyl-cinnamamide

Yellowish solid; m.p. 94-96 °C (lit. 101-103 °C);<sup>39</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.22 (d, 6H, *J* 6.6), 4.24 (sext, 1H, *J* 6.5), 5.94 (s, 1H), 6.43 (d, 1H, *J* 15.6), 7.31-7.33 (m, 3H), 7.46-7.49 (m, 2H), 7.62 (d, 1H, *J* 15.3); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 23.0, 41.8, 121.4, 128.0, 129.0, 129.7, 135.2, 140.9, 165.4; MS (70 eV)  $m/z$  189 ( $M^+$ ), 174, 161, 146, 131 (100%), 118, 112, 103, 91, 87, 77, 63, 58, 51, 43.

#### *N*-(Cyclohexylcarbonyl)-morpholine<sup>40</sup>

Yellowish oil; <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 1.21-1.82 (m, 10H), 2.37-2.47 (m, 1H), 3.55-3.68 (m, 8H); <sup>13</sup>C NMR

(75 MHz, CDCl<sub>3</sub>) δ 26.0, 29.5, 40.4, 42.1, 46.1, 67.1, 174.9; MS (70 eV)  $m/z$  197 ( $M^+$ ), 142, 129, 83 (100%), 70, 55, 41.

#### *N*-Butyl-4-nitrobenzamide

Yellowish solid; m.p. 102-104 °C (lit. 104-104.5 °C);<sup>41</sup> <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.92-0.97 (t, 3H, *J* 7.3), 1.40 (sext, 2H, *J* 7.2), 1.61 (quint, 2H, *J* 7.5), 3.45 (q, 2H, *J* 7.2), 6.60 (s, 1H), 7.92 (d, 2H, *J* 9.0), 8.24 (d, 2H, *J* 9.0); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 13.2, 19.6, 31.1, 39.7, 123.2, 127.6, 140.0, 149.0, 165.1; MS (70 eV)  $m/z$  222 ( $M^+$ ), 193, 180, 150 (100%), 120, 104, 92, 76, 50, 41.

#### *N*-Butyl-octanamide<sup>42</sup>

<sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 0.83-0.92 (m, 6H), 1.26-1.36 (m, 10H), 1.41-1.49 (m, 2H), 1.57-1.62 (m, 2H), 2.14 (t, 2H, *J* 7.4), 3.22 (q, 2H, *J* 7.2), 5.72 (s, 1H); <sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>) δ 13.2, 13.5, 19.6, 22.1, 25.4, 28.5, 28.8, 31.2, 36.4, 38.7, 172.9; MS (70 eV)  $m/z$  199 ( $M^+$ ), 170, 156, 142, 128, 115 (100%), 100, 86, 73, 57, 44, 41.

## Supplementary Information

<sup>1</sup>H NMR, <sup>13</sup>C NMR and MS spectra of synthesized compounds are available free of charge at <http://jbcs.sbq.org.br>.

## Acknowledgments

We thank CNPq and FAPERJ for the financial support.

## References

- Otera, J.; Nishikido, J.; *Esterification: Methods, Reactions, and Applications*; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2003; Negwer, M.; Scharnow, H.-G.; *Organic-Chemical Drugs and Their Synonyms*, 8<sup>th</sup> ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2001; Pattabiraman, V. R.; Bode, J. W.; *Nature (London, U. K.)* **2011**, *480*, 471.
- Larock, R. C.; *Comprehensive Organic Transformations, a Guide to Functional Group Preparation*, 2<sup>nd</sup> ed.; John Wiley & Sons: New York, 1999; Trost, B. M.; *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Synthesis*, vol. 6; Pergamon Press: Oxford, 1991.
- Ansell, M. F. In *The Chemistry of Acyl Halides*; Patai, S.; ed.; Interscience: London, 1972, ch. 2; McMaster, L.; Ahmann, F. F.; *J. Am. Chem. Soc.* **1928**, *50*, 145; Chen, H.; Xu, X.; Liu, L.; Tang, G.; Zhao, Y.; *RSC Adv.* **2013**, *3*, 16247.
- Adams, R.; Ulich, L. H.; *J. Am. Chem. Soc.* **1920**, *42*, 599.
- Bahrami, K.; Khodaei, M. M.; Targhan, H.; Arabi, M. S.; *Tetrahedron Lett.* **2013**, *54*, 5064.

6. de Andrade, V. S. C.; de Mattos, M. C. S.; *Curr. Org. Synth.* **2015**, *12*, 309.
7. Lee, J. B.; *J. Am. Chem. Soc.* **1966**, *88*, 3340; Tömösközi, I.; Gruber, L.; Radics, L.; *Tetrahedron Lett.* **1975**, *16*, 2473.
8. Jang, D. O.; Park, D. J.; Kim, J.; *Tetrahedron Lett.* **1999**, *40*, 5323.
9. Chaysripongkul, S.; Pluempanupat, W.; Jang, D. O.; Chavasiri, W.; *Bull. Korean Chem. Soc.* **2009**, *30*, 2066.
10. For selected examples, see: Tang, X.; An, J.; Denton, R. M.; *Tetrahedron Lett.* **2014**, *55*, 799; Kosal, A. D.; van Kalker, H. A.; Blom, A. L.; Rutjes, F. P. J. T.; Huijbregts, M. A.; *Green Chem.* **2013**, *15*, 1255; Byren, P. A.; Rajendran, K. V.; Muldoon, J.; Guilheany, D. G.; *Org. Biomol. Chem.* **2012**, *10*, 3531; Wilson, E. E.; Ashfeld, B. L.; *Angew. Chem., Int. Ed.* **2012**, *51*, 12036; Rao, A. N.; Ganesan, K.; Shinde, C. K.; *Synth. Commun.* **2012**, *42*, 2299; O'Brien, C. J.; Tellez, J. L.; Nixon, Z. S.; Kang, L. J.; Carter, A. L.; Kunkle, S. R.; Przeworski, K. C.; Chass, G. A.; *Angew. Chem., Int. Ed.* **2009**, *48*, 6863.
11. Mendonça, G. F.; de Mattos, M. C. S.; *Curr. Org. Synth.* **2013**, *10*, 820.
12. Gottardi, W.; *Monatsh. Chem.* **1967**, *98*, 507; Gottardi, W.; *Monatsh. Chem.* **1970**, *101*, 655; Ribeiro, R. S.; Esteves, P. M.; de Mattos, M. C. S.; *Tetrahedron Lett.* **2007**, *48*, 8747; de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S.; *Synlett* **2007**, *11*, 1687; Ribeiro, R. S.; Esteves, P. M.; de Mattos, M. C. S.; *J. Braz. Chem. Soc.* **2012**, *23*, 228.
13. de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S.; *Synlett* **2006**, *10*, 1515.
14. Hiegel, G. A.; Ramírez, J.; Barr, R. K.; *Synth. Commun.* **1999**, *29*, 1415.
15. Rodrigues, R. C.; Barros, I. M. A.; Lima, E. L. S.; *Tetrahedron Lett.* **2005**, *46*, 5945.
16. Akhlaginia, B.; Rouhi-Saadabad, H.; *Can. J. Chem.* **2013**, *91*, 181.
17. de Andrade, V. S. C.; de Mattos, M. C. S.; *J. Braz. Chem. Soc.* **2014**, *25*, 975.
18. Appel, R.; *Angew. Chem., Int. Ed.* **1975**, *14*, 801.
19. de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S.; *Curr. Green Chem.* **2014**, *1*, 94.
20. Crespo, L. T. C.; de Mattos, M. C. S.; Esteves, P. M.; *Quim. Nova* **2013**, *36*, 320.
21. Tozetti, S. D. F.; de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S.; *J. Braz. Chem. Soc.* **2007**, *18*, 675; Crespo, L. T. C.; Ribeiro, R. S.; de Mattos, M. C. S.; Esteves, P. M.; *Synthesis* **2010**, *14*, 2379.
22. de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S.; *Synthesis* **2006**, *13*, 221; de Almeida, L. S.; Esteves, P. M.; de Mattos, M. C. S.; *Tetrahedron Lett.* **2009**, *50*, 3001; de Almeida, L. S.; de Mattos, M. C. S.; Esteves, P. M.; *Synlett* **2013**, *24*, 603.
23. Jang, D. O.; Park, D. J.; Kim, J.; *Tetrahedron Lett.* **1999**, *40*, 5323.
24. Kang, D. H.; Joo, T. Y.; Lee, E. H.; Chaysripongkul, S.; Chavasiri, W.; Jang, D. O.; *Tetrahedron Lett.* **2006**, *47*, 5693.
25. Menezes, F. G.; Kolling, R.; Bertoluzzi, A. J.; Gallardo, H.; Zucco, C.; *Tetrahedron Lett.* **2009**, *50*, 2559.
26. Trost, B. M.; *Science (Washington, DC, U. S.)* **1991**, *254*, 1471.
27. Kim, B. R.; Sung, G. H.; Lee, S.-G.; Yoon, Y. J.; *Tetrahedron* **2013**, *69*, 3234.
28. Li, L.; Sheng, H.; Xu, F.; Shen, Q.; *Chin. J. Chem.* **2009**, *27*, 1127.
29. Wu, X.-F.; Darcel, C.; *Eur. J. Org. Chem.* **2009**, *8*, 1144.
30. Akiyama, F.; Tokura, N.; *Bull. Chem. Soc. Jpn.* **1966**, *39*, 131.
31. Kleinpeter, E.; Bölke, U.; Frank, A.; *Tetrahedron* **2008**, *64*, 10014.
32. Jia, X.-S.; Wang, H.-L.; Huang, Q.; Kong, L.-L.; Zhang, W.-H.; *J. Chem. Res.* **2006**, *2*, 135.
33. Xie, F.; Yan, F.; Chen, M.; Zhang, M.; *RSC Adv.* **2014**, *4*, 29502.
34. Giang, L.; Xinzong, L.; Eli, W.; *New J. Chem.* **2007**, *31*, 348.
35. Rahman, O.; Kihlberg, T.; Lngstroem, B.; *J. Org. Chem.* **2003**, *68*, 3558.
36. Jo, Y.; Ju, J.; Choe, J.; Song, K. H.; Lee, S.; *J. Org. Chem.* **2009**, *74*, 6358.
37. Pelletier, G.; Bechara, W. S.; Charette, A. B.; *J. Am. Chem. Soc.* **2010**, *132*, 12817.
38. Fairfull-Smith, K. E.; Jenkins, I. D.; Loughlin, W. A.; *Org. Biomol. Chem.* **2004**, *2*, 1979.
39. Huang, Z.; Wen, L.; Huang, X.; *Synth. Commun.* **1990**, *20*, 2579.
40. Glynn, D.; Bernier, D.; Woodward, S.; *Tetrahedron Lett.* **2008**, *49*, 5687.
41. Connors, K. A.; Bender, M. L.; *J. Org. Chem.* **1961**, *26*, 2498.
42. Kunishima, M.; Kikuchi, K.; Kawai, Y.; Hioki, K.; *Angew. Chem., Int. Ed.* **2012**, *51*, 2080.

Submitted: October 21, 2015

Published online: January 15, 2016