Reaction of Dicarbonates with Carboxylic Acids Catalyzed by Weak Lewis Acids: General Method for the Synthesis of Anhydrides and Esters

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Abstract: The reaction between carboxylic acids (RCOOH) and di-alkyl dicarbonates [(R’OCO)₂O], in the presence of a weak Lewis acid such as magnesium chloride and the corresponding alcohol (R’OH) as the solvent, leads to the esters RCOOR’ in excellent yields. The mechanism involves a double addition of the acid to the dicarbamate, affording a carboxylic anhydride [(RCO)₂O], R’OH and carbon dioxide. The esters arise from the attack of the alcohols on the anhydrides. Exploiting the lesser reactivity of tert-butyl alcohol in comparison with other alcohols, a clean synthesis of both carboxylic anhydrides and esters has been set up. In the former reaction, an acid/Boc₂O molecular ratio of 2:1 leads to the anhydride in good to excellent yields, depending on the stability of the resulting anhydride to the usual workup conditions. In the latter reaction, stoichiometric mixtures of the acid and Boc₂O are allowed to react with a twofold excess of a primary alcohol, secondary alcohol or phenol (R’OH) to give the corresponding esters (RCOOR’). Purification of the products is particularly easy since all byproducts are volatile or water soluble. A very easy chromatography is required only in the case of nonvolatile alcohols. A broad variety of sensitive functional groups is tolerated on both the acid and the alcohol, in particular a high chemoselectivity is observed. In fact, no transesterification processes occur with the acid-sensitive acetoxy group and methyl esters.

Key words: synthetic methods, anhydrides, esters, Lewis acids, magnesium salts

Dicarbonates have been mainly exploited as useful reagents able to transfer a carbonate moiety to nucleophilic centers, via a reactivity model apparently close to that of carboxylic anhydrides. This kind of reaction has been extensively developed for the formation of carbamates1 and carbonates,2 which find useful applications both in the laboratory and in industry.3,4 In fact, carbamates5 or carbonates6 are frequently used to mask amino and alcoholic groups, respectively, owing to their stability under basic conditions and easy removal with respect to the corresponding amides and esters under acidic conditions.

In addition, dicarbonates show a peculiar reactivity pattern: they can react with carboxylic acids to give esters under both Lewis acidic and basic catalysis. Takeda and co-workers,7 in fact, reported that when a carboxylic acid 1 is treated with an excess of a dicarbonate 2 in the presence of 4-(N,N-dimethylamino)pyridine (DMAP) in substoichiometric amounts, ester 3 is recovered together with alcohol 4 and two equivalents of carbon dioxide from decomposition of the dicarbonate. The authors observed direct experimental evidence of the formation of a carboxylic anhydride 6 as a labile intermediate, while mixed carbonic carboxylic anhydride 5 formation was only supposed. They hypothesized that ester formation might arise from attack of adventitious alcohol to both 5 and 6. In the latter case, a molar equivalent of acid is formed, which restarts the reaction loop (Scheme 1).

Scheme 1 Takeda’s reaction

The reaction is widely applicable, but the reaction conditions must be tuned for the specific case; for example, the 1/2 molecular ratio ranges from 1.2 to 6.2 and DMAP amounts from 10 to 30 mol%. The process generally requires long reaction times (up to 96 h) to go to completion. Moreover, the reaction allows the introduction of alcohol frameworks arising only from easily available or commercial dicarbonates. Finally, DMAP is highly toxic and difficult to remove, since it is an organic amine partially soluble in the organic layer; moreover, it cannot be released into the environment.

To overcome these drawbacks, Gooßen and Döhring8 later reported that the decarboxylative esterification of carboxylic acids with dicarbonates can be successfully
performed in the presence of strong Lewis acids as the catalyst. On the basis of some experimental evidence, they proposed a quite different mechanism. The interaction of carboxylic acid 1 and dicarbonate 2 in the presence of many Lewis acids, in particular magnesium perchlorate, leads to the mixed carbonic carboxylic anhydride 5, as in Takeda’s mechanism assumption, but it spontaneously decomposes to 3 through an intramolecular rearrangement (Scheme 2).

$$\text{CO}_2 + 4 \rightarrow \text{intramolecular rearrangement} \rightarrow 3 + \text{CO}_2$$

Scheme 2  Gooßen’s reaction

In contrast to DMAP, the catalyst can be easily separated from the reaction mixture by aqueous workup. Esterification occurs in high yields and many functional groups are compatible; however, as in Takeda’s reaction, only commercially available dicarbonates can be used. Moreover, di-tert-butyl dicarbonate (Boc₂O) is not stable and decomposes to carbon dioxide, tert-butyl alcohol and isobutene in the presence of such strong Lewis acids as perchlorate and triflate salts. As a consequence, a large excess of this expensive reagent is necessary in the synthesis of tert-butyl esters to counterbalance the loss of Boc₂O due to its self-decomposition. Finally, the reaction with Boc₂O does not work in the case of amino acids.

The same authors proposed a modification of the Takeda protocol in order to overcome such drawbacks. Thus, allowing reaction of Boc₂O and carboxylic acids in the presence of equimolecular amounts of an alcohol in nitromethane under DMAP catalysis, they were able to synthesize a large variety of esters, including those with alcoholic frameworks not arising from commercially available dicarbonates. In addition, there was no mention of the formation of carboxylic anhydrides. However, once more, environmentally unfriendly solvent and amine are used.

Recently, during our studies on the mechanism of the reaction between Boc₂O and alcohols, we found that the reaction pathway is influenced by the Lewis acid power: strong Lewis acids afford mainly tert-butyl ethers, while weak Lewis acids address it toward the formation of Boc alcohols. On this basis, we have investigated how to develop a new methodology which could unify all the previous reports and, at the same time, be able to overcome all the drawbacks. This methodology ought to be based on acid catalysis with weak Lewis acids from environmentally benign metals, which are unable to decompose dicarbonates, especially Boc₂O, thus avoiding the use of organic amines.

We tested different weak Lewis acids and the best choice was anhydrous as well as hydrated magnesium chloride, since both reagents give clean reactions and they also have very low costs and toxicity so their waste does not cause environmental problems.

When 3-phenylpropionic acid (1a) and diethyl dicarbonate (Eoc₂O, 2a) were allowed to react in dichloromethane at room temperature in the presence of anhydrous magnesium chloride (10 mol%), ethyl 3-phenylpropanoate (3aa) was obtained in 89% yield in 24 hours. The carboxylic acid did not function as a Brønsted acid catalyst, as already found by both Gooßen and Takeda. In fact, the reaction without magnesium chloride was complete only after several days. Moreover, when dissolved in dichloromethane or acetonitrile in the presence of 10 mol% of magnesium chloride, 2a was demonstrated to survive substantially unaffected for 93 hours at room temperature.

Monitoring the progress of the reaction by TLC showed the presence of a spot which disappeared as time elapsed. Then, only formation of the ester was detected. We followed the reaction by NMR spectroscopy and observed a product with signals very similar to those of the starting acid, which was recognized to be 3-phenylpropionic anhydride (6a) by CI-mass spectrometric analysis of the mixture. The anhydride amount never exceeded 20% conversion and its maximum was reached in the initial times of the process. However, in the presence of magnesium chloride hexahydrate, anhydride 6a was detected in 82% yield after two hours, together with ester 3aa (12%) and starting acid 1a (5%). As the reaction time elapsed, the amount of 6a decreased until only the ester was detected after 36 hours.

The formation of a high yield of anhydride 6a (82%) under magnesium chloride hexahydrate catalysis, relative to the anhydrous salt, is very likely due to the known depressed activity of hydrated Lewis acids, which slows down the attack rate of the alcohol 4a to 6a.

These results strongly support the hypothesis that, in the present reaction, a mechanism much closer to Takeda’s than to Gooßen’s is operative (Scheme 3).

The key step of the reaction mechanism involves an intermolecular attack of the released alcohol 4 onto the carbonyl moiety of activated anhydride 9, and this attack ought to be slow if such high amounts of anhydride are detected. Also, as a consequence, nucleophilic attack of the carboxylic carbonyl of mixed anhydride 8 must therefore be very much slower than the attack of a second molecule of acid, since it is as sterically demanding as attack of the carbonyl of 9. Therefore, ester 3 cannot arise from attack of alcohol 4 to the activated mixed anhydride 8, but only from decomposition of carboxylic anhydride 9.

Formation of diethyl carbonate was never observed among the reaction products, either in the present reaction or in those previously reported by Takeda or Gooßen. As a consequence, the addition of alcohol 4 to the carbonic carbonyl moiety of both 7 and 8 (or 2 and 5, Scheme 1) is much slower than the attack of the acid 1, under these experimental conditions.
Finally, nucleophilic attack of the carboxylic carbonyl moiety of $2$, which leads to the formation of mixed anhydride $5$, experiences minor steric hindrance than the attack of the carboxylic carbonyl framework of $6$, owing to the greater closeness of the alkyl group $R$ than $R'$ to the reactive center.

Therefore, we reasonably assumed that the formation of anhydrides in high yields can be performed using half a mole of dicarbonate per mole of acid, to stop the ester synthesis loop, and using Boc$_2$O ($2b$) as promoting dicarbonate, since the reactivity of the liberated tert-butyl alcohol to anhydride $6$ should be drastically decreased by its steric bulk.

Actually, when 0.5 equivalent of Boc$_2$O ($2b$) were added to acids $1a$–$i$, in the presence of 10 mol% of magnesium chloride hexahydrate in tetrahydrofuran, we were able to completely convert the acids into the corresponding anhydrides $6$ (Table 1). Tetrahydrofuran was chosen as the solvent, since the reaction of benzoic acid ($1b$) was complete in 1.5 hours (Table 1, entry 2), whereas the same reaction went to completion in five hours in dichloromethane, or significant amounts of ester were present upon reaction in other solvents. Under these conditions, strict control of the reaction time was not necessary, since alcoholysis of the anhydride was a very slow process.

All attempted reactions gave the anhydride as the most abundant product. The most efficient reactions gave the anhydride in good purity after a quick aqueous workup (Table 1, entries 2–8). In two experimental cases, the anhydride was recovered in lower yield and purity (Table 1, entries 1, 9), because we were unable to separate it from the reaction mixture without avoiding decomposition to the starting acid. Finally, in some other cases, we had analytical evidence of the formation of the anhydrides but they decomposed during workup.

It must be outlined that this protocol does not follow stock methods, and in the reaction mixture, the weak Lewis acid magnesium chloride and the starting acid are always present together with the anhydride and only a byproduct, the scarcely reactive tert-butyl alcohol. Therefore, the anhydride should be used in situ for synthetic purposes, without isolation, thus avoiding its decomposition.

**Table 1** Synthesis of Acid Anhydrides $6$ by the Reaction of Carboxylic Acids $1a$–$i$ with Boc$_2$O ($2b$), Catalyzed by MgCl$_2$·6H$_2$O

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Time (h)</th>
<th>Yield$^b$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(CH$_2$)$_3$COOH ($1a$)</td>
<td>23</td>
<td>76$^c$</td>
</tr>
<tr>
<td>2</td>
<td>PhCOOH ($1b$)</td>
<td>1.5</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>PhCH=CHCOOH ($1c$)</td>
<td>23</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>4-MeC$_6$H$_4$COOH ($1d$)</td>
<td>48</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>4-CIC$_6$H$_4$COOH ($1e$)</td>
<td>23</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>$t$-BuCOOH ($1f$)</td>
<td>6</td>
<td>92</td>
</tr>
<tr>
<td>7</td>
<td>Me(CH$_2$)$_3$COOH ($1g$)</td>
<td>23</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>Br(CH$_2$)$_3$COOH ($1h$)</td>
<td>48</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>$t$-PrCOOH ($1i$)</td>
<td>6</td>
<td>88$^c$</td>
</tr>
</tbody>
</table>

$^a$ Reagents and conditions: carboxylic acids $1a$–$i$ (1 equiv), Boc$_2$O ($2b$, 0.5 equiv), MgCl$_2$·6H$_2$O (10 mol%), THF, r.t.

$^b$ Yields calculated on the crude mixture.

$^c$ Decomposed after attempts at purification by chromatography.

Encouraged by the observation that the liberated alcohol does not interfere in the formation of the anhydride, the alcoholysis of $6$ was accelerated by adding larger amounts of alcohol.

Reactions of acids $1$ and commercial Eoc$_2$O, Boc$_2$O, or dimethyl dicarbonate (Moc$_2$O) ($2a$–$c$) were carried out in the minimum amount of the corresponding alcohols $4a$–$c$, respectively. A molecular ratio alcohol/acid of 2:1 is enough to ensure a good homogeneity of the mixture, a low wastage of reagents, and a high yield of the obtained esters (Table 2). The sterically demanding tert-butylation group is more resistant to the reaction, so the temperature must be increased to 40 °C and the equivalents of Boc$_2$O slightly raised to 1.3, since some self-decomposition occurs at this temperature (Table 2, entries 14–22).

The reaction tolerates a broad variety of functional groups, such as ketones (Table 2, entries 5, 6, 15, 24), multiple carbon–carbon bonds (Table 2, entries 7, 8, 16, 17), halogens (Table 2, entries 11, 19) and amides (Table 2, entry 12). When a larger excess of alcohol is used, even remote free hydroxy groups survive unchanged (Table 2, entry 13). On the other hand, 4-hydroxybenzoic acid gave a complex reaction mixture; however, acetoxycarbonyl protection allowed the reaction to easily occur (Table 2, entry 9). The reaction of aromatic acids is slower and the reaction temperature must be increased to 40 °C in order to obtain a good conversion into the esters. However, even
under these conditions, only activated acids gave high yields of esters (Table 2, entry 9); with both benzoic acid (1b) and 4-chlorobenzoic acid (1e), large amounts of the corresponding anhydrides remained unreacted (Table 2, entries 2, 4). The same behavior was observed with the closely related cinnamic acid (1c) (Table 2, entry 3).

It is worth noting that a N-protected α-amino acid is easily converted into its tert-butyl ester (Table 2, entry 21), in contrast to the magnesium perchlorate catalyzed reaction.\(^8\)

Finally, the chemoselectivity of the reaction must be outlined. In fact, notwithstanding its ideal atom efficiency, the classical Fischer reaction is not suitable for starting materials bearing other ester groups, since transesterification always occurs to some extent, even when Lewis acid catalysis is employed.\(^11\) The reaction of carboxylic acids in the presence of coupling reagents is the method of choice for sensitive molecules;\(^1\) however, the separation of esters from byproducts derived from coupling reagents is often the main practical drawback of this approach.

Under the present conditions, the esterification overcomes these synthetic problems. The reaction produces volatile (CO\(_2\)) or easily separable side products (alcohol 4). Moreover, the Lewis acid employed is not able to activate transesterification,\(^19\) and both the acetoxy group and methyl esters are unaffected under the present reaction conditions (Table 2, entries 9, 10, 18). Finally, protected amino groups survive the reaction conditions, both in the ω- and the α-position with respect to the carboxylic moiety (Table 2, entries 12, 21).

If the mechanism depicted in Scheme 3 is operative, the synthesis of esters is not restricted to frameworks arising from commercially available dicarboxonates.

As Gooßen previously reasoned,\(^11\) in fact, the low reactivity of released tert-butyl alcohol and the incapacity of alcohol to attack the carbonate carbonyl should allow the addition of every primary alcohol, secondary alcohol and phenol. Indeed, the reaction of 3-phenylpropionic acid (1a) and Boc\(_2\)O (2b) with n-butanol (4d) in the molecular ratio of 1:1:1 in the presence of magnesium chloride (10 mol%) led to the expected ester butyl 3-phenylpropanoate (3ad) in excellent yield. However, less than 5% of tert-butyl 3-phenylpropanoate (3ab) was detected, very likely from a competitive addition of tert-butyl alcohol. Since with less reactive alcohols this competition could increase, we tested different alcohol/acid 1 molecular ratios and found that a ratio of 2 is enough to completely suppress the side process (Table 3, entry 1), even with phenols (Table 3, entries 5–7, 10, 14, 15) and secondary alcohols (Table 3, entry 9). Moreover, the slight excess of alcohol often ensures better homogeneity of the reaction mixture, and a solvent must be added only with some phenols (Table 3, entries 6, 7, 10, 15). Separation of the excess alcohol from the ester can be very easily performed, and the alcohol can be recycled. Moreover, this reaction does not present the problem of DMAP toxicity and separation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(CH(_2))(_2))COOH (1a)</td>
<td>r.t.</td>
<td>18</td>
<td>89</td>
</tr>
<tr>
<td>2</td>
<td>PhCOOH (1b)</td>
<td>40</td>
<td>36</td>
<td>85(^c)</td>
</tr>
<tr>
<td>3</td>
<td>PhCH=CHCOOH (1c)</td>
<td>40</td>
<td>24</td>
<td>68(^d)</td>
</tr>
<tr>
<td>4</td>
<td>4-CIC(_6)(_2))COOH (1e)</td>
<td>40</td>
<td>24</td>
<td>20(^f)</td>
</tr>
<tr>
<td>5</td>
<td>CH(_2)CO(CH(_2))(_2))COOH (1j)</td>
<td>r.t.</td>
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<td>97</td>
</tr>
<tr>
<td>6</td>
<td>CH(_2)CO(CH(_2))(_3))COOH (1k)</td>
<td>r.t.</td>
<td>18</td>
<td>90</td>
</tr>
<tr>
<td>7</td>
<td>CH(_2)CH=CHCH(_2))COOH (1l)</td>
<td>r.t.</td>
<td>18</td>
<td>81</td>
</tr>
<tr>
<td>8</td>
<td>HC(_2)N(CH(_2))(_3))COOH (1m)</td>
<td>r.t.</td>
<td>18</td>
<td>92</td>
</tr>
<tr>
<td>9</td>
<td>4-AcOC(_6)(_2))COOH (1n)</td>
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<td>95</td>
</tr>
<tr>
<td>10</td>
<td>MeO(_2)C(CH(_2))(_3))COOH (1o)</td>
<td>r.t.</td>
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<td>93</td>
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<tr>
<td>11</td>
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<td>r.t.</td>
<td>18</td>
<td>91</td>
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<td>12</td>
<td>AcNH(CH(_2))(_3))COOH (1q)</td>
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<td>13</td>
<td>HO(CH(_2))(_3))COOH (1r)</td>
<td>r.t.</td>
<td>18</td>
<td>89(^f)</td>
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<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
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<tr>
<td>14</td>
<td>Ph(CH(_2))(_3))COOH (1a)</td>
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<td>15</td>
<td>CH(_2)CO(CH(_2))(_3))COOH (1k)</td>
<td>40</td>
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<tr>
<td>16</td>
<td>C(_6)(_2))CH=CHCH(_2))COOH (1l)</td>
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<td>HC(_2)N(CH(_2))(_3))COOH (1m)</td>
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<td>48</td>
<td>97</td>
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<td>18</td>
<td>MeO(_2)C(CH(_2))(_3))COOH (1o)</td>
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<td>65</td>
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<td>19</td>
<td>Br(CH(_2))(_2))COOH (1p)</td>
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<td>Me(CH(_2))(_2))COOH (1g)</td>
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<td>21</td>
<td>PhCONHCH(_2))COOH (1s)</td>
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<td>Cy(CH(_2))(_2))COOH (1t)</td>
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<td>72</td>
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<th>Temp (°C)</th>
<th>Time (h)</th>
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<tr>
<td>23</td>
<td>Ph(CH(_2))(_3))COOH (1a)</td>
<td>r.t.</td>
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<td>98</td>
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<tr>
<td>24</td>
<td>MeCO(CH(_2))(_3))COOH (1j)</td>
<td>r.t.</td>
<td>18</td>
<td>80</td>
</tr>
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</table>

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\(^{a}\) Reagents and conditions: carboxylic acids (1 equiv), MgCl\(_2\) (10 mol%); Eoc\(_2\)O (2a, 1 equiv)/EtOH (4a, 2 equiv) (for ethyl ester), Boc\(_2\)O (2b, 1.3 equiv) / t-BuOH (4b, 2 equiv) (for tert-butyl ester), or Moc\(_2\)O (2c, 1 equiv)/MeOH (4c, 2 equiv) (for methyl ester).

\(^{b}\) Yields calculated on pure isolated product. When the yields are less than 80% the remaining material is essentially starting acid, if not otherwise noted.

\(^{c}\) Anhydride 6b (13%) was also detected in the crude mixture.

\(^{d}\) Anhydride 6c (28%) was also detected in the crude mixture.

\(^{e}\) Anhydride 6e (78%) was also detected in the crude mixture.

\(^{f}\) EtOH (0.5 mL) was used. Lesser amounts gave oligomerization of the starting acid.
The reaction maintains a wide tolerability of functionality on the acid, as above, and also further tolerates a broad variety of functional groups on the alcohol, such as multiple carbon–carbon bonds (Table 3, entries 3, 4, 13), halogens (Table 3, entries 6, 8, 15) and aldehydes (Table 3, entry 7).

In conclusion, alternative and efficient protocols for the preparation of anhydrides and for the esterification of carboxylic acids with primary, aromatic and secondary alcohols in the presence of Boc₂O under weak Lewis acid catalysis have been developed. A wide range of functionalities on the alcohol, such as multiple carbon–carbon bonds (Table 3, entries 3, 4, 13), halogens (Table 3, entries 6, 8, 15) and aldehydes (Table 3, entry 7).

Table 3  Synthesis of Esters 3 by the Reaction of Carboxylic Acids and Boc₂O (2b) with Alcohols 4d–l, Catalyzed by MgCl₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid</th>
<th>Alcohol</th>
<th>Yieldb (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph(CH₂)₃COOH (1a)</td>
<td>n-BuOH (4d)</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>Ph(CH₂)₃COOH (1a)</td>
<td>PhCH₂OH (4e)</td>
<td>94</td>
</tr>
<tr>
<td>3</td>
<td>Ph(CH₂)₃COOH (1a)</td>
<td>CH₃CBCH₂OH (4f)</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>Ph(CH₂)₃COOH (1a)</td>
<td>Me₂C=CHCH₂OH (4g)</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>Ph(CH₂)₃COOH (1a)</td>
<td>PhOH (4h)</td>
<td>79</td>
</tr>
<tr>
<td>6</td>
<td>Ph(CH₂)₃COOH (1a)</td>
<td>4-CIC₃H₆OH (4i)</td>
<td>85c</td>
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<tr>
<td>7</td>
<td>Ph(CH₂)₃COOH (1a)</td>
<td>4-CHOC₆H₄OH (4j)</td>
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<td>8</td>
<td>Ph(CH₂)₃COOH (1a)</td>
<td>Br(CH₂)₃OH (4k)</td>
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<tr>
<td>9</td>
<td>Ph(CH₂)₃COOH (1a)</td>
<td>t-PrOH (4l)</td>
<td>91</td>
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<td>10</td>
<td>PhCOOH (1b)</td>
<td>PhOH (4m)</td>
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<tr>
<td>11</td>
<td>MeCO(CH₂)₃COOH (1j)</td>
<td>n-BuOH (4d)</td>
<td>70</td>
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<tr>
<td>12</td>
<td>MeCO(CH₂)₃COOH (1j)</td>
<td>PhCH₂OH (4e)</td>
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<tr>
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<td>MeCO(CH₂)₃COOH (1j)</td>
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<td>87</td>
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<td>15</td>
<td>EtCH=CHCH₂COOH (1l)</td>
<td>4-CIC₃H₆OH (4i)</td>
<td>98c</td>
</tr>
</tbody>
</table>

* Reagents and conditions: carboxylic acids (1 equiv), alcohols 4d–l (2 equiv), Boc₂O (2b, 1 equiv), MgCl₂ (10 mol%), r.t., overnight.

1H NMR spectra were recorded on Varian Mercury or Inova spectrometers at 400 or 600 MHz, respectively, while 13C NMR spectra were recorded on a Varian Mercury spectrometer at 100 MHz. Mass spectra were recorded on an HP 5973 workstation spectrometer at 70 eV. Purification of reaction products was carried out by flash chromatography on silica gel (230–400 mesh), when necessary. Commercial grade reagents and solvents were used without further purification. All starting alcohols, acids, magnesium chloride and dicarboxylic esters were purchased and used as received.

Carboxylic Anhydrides [(RCO)₂O] 6; General Procedure:
In a two-necked flask equipped with a magnetic stirring bar, MgCl₂·6H₂O (0.10 mmol), Boc₂O (2b) (0.5 mmol) and an acid 1a–i (1.0 mmol) were dissolved in THF (1 mL). The mixture was stirred at r.t. for the times reported in Table 1. The crude reaction mixture was diluted with H₂O (10 mL) and quickly extracted with THF (3 × 10 mL). The organic layer was washed with brine, dried (MgSO₄) and filtered, and the solvent was removed by rotary evaporation. The crude mixture was then submitted to full characterization. When the NMR spectrum of the crude product revealed a purity lower than 90%, chromatographic separation with light petroleum ether–Et₂O (9:1) was attempted, but only starting acid was always recovered. On the other hand, when the product accounted for more than 90% of the spectrum, the anhydride was considered pure enough for further applications. For yields, see Table 1.

Benzonic (6b), hexanoic (6g) and isobutyric (6i) anhydrides are commercial products and the synthetic materials were compared with authentic samples. Cinnamic (6e), 4-methoxybenzonic (6d), 4-chlorobenzoic (6e), pivalic (6f) and 6-bromohexanoic (6h) anhydrides are known compounds and the spectra of the synthetic materials were superimposable with reported spectra.

3-Phenylpropionic Anhydride (6a)
Bp 164–167 °C/0.3 mmHg (Lit. 26 165–167 °C/0.3 mmHg).

The reaction maintains a wide tolerability of functionality on the acid, as above, and also further tolerates a broad variety of functional groups on the alcohol, such as multiple carbon–carbon bonds (Table 3, entries 3, 4, 13), halogens (Table 3, entries 6, 8, 15) and aldehydes (Table 3, entry 7).

In conclusion, alternative and efficient protocols for the preparation of anhydrides and for the esterification of carboxylic acids with primary, aromatic and secondary alcohols in the presence of Boc₂O under weak Lewis acid catalysis have been developed. A wide range of functionalities is tolerated, especially esters and amides that are cleaved under classic standard esterification conditions. Multiple carbon–carbon bonds are also tolerated, since decomposition of Boc₂O, which leads to carbonium ions, is avoided. The release of water-soluble and volatile byproducts renders the reaction very attractive for synthetic chemistry. Moreover, the reaction has a very low environmental impact, since it generally works under solvent-free conditions and a very low-toxic catalyst is used. This method gathers the advantages of Gooßen’s and Takeda’s previously reported procedures, while overcoming their restrictions. In fact, it bypasses their main drawbacks; thus, we have obtained a substantial reagent saving, by using almost stoichiometric amounts of reagents, and DMAP use is avoided, thereby overcoming its separation and toxicity problems.
cholorbenzoate (3ea),

1H NMR (600 MHz, CDCl3); δ = 1.26 (t, J = 7.2 Hz, 2 H). 1.35 (app quin, J = 7.7 Hz, 2 H), 1.52 (app quin, J = 7.7 Hz, 2 H), 1.64 (app quin, J = 7.7 Hz, 2 H). 1.97 (s, 3 H), 2.30 (s, J = 7.5 Hz, 2 H). 3.28 (m, 2 H), 4.13 (q, J = 7.2 Hz, 2 H). 6.01 (br s, 1 H, NH).

13C NMR (100 MHz, CDCl3); δ = 14.14 (CH2), 23.09 (CH2), 24.33 (CH2), 26.20 (CH2). 29.03 (CH3), 33.92 (CH3). 39.21 (CH3). 60.16 (CH2). 170.14 (C). 173.60 (C).

MS (EI); m/z (%); 64 100, 71 15, 86 (29), 112 (14), 137 (100), 164 (14), 191 (6), 217 (18). Anal. Calcd for C10H18O2: C, 73.59; H, 11.35. Found: C, 73.60; H, 11.07.

tert-Butyl 7-Oxooctanoate (3kb)

Oil.

1H NMR (400 MHz, CDCl3); δ = 1.27–1.38 (m, 2 H), 1.44 (s, 9 H). 1.39 (app quin, J = 7.5 Hz, 4 H), 2.13 (t, J = 7.3 Hz, 2 H). 2.18 (s, 3 H), 2.43 (t, J = 7.5 Hz, 2 H).

13C NMR (100 MHz, CDCl3); δ = 23.28 (CH2), 24.66 (CH2), 27.95 (3 × CH2), 28.39 (CH2), 29.70 (CH2). 35.18 (CH2), 43.31 (CH2). 79.90 (C), 172.98 (C), 208.90 (C).

MS (EI); m/z (%); 123 100, 124 19, 137 37, 149 100, 150 28, 151 100. Anal. Calcd for C11H22O2; C, 75.78; H, 12.00. Found: C, 75.81; H, 12.07.

tert-Butyl 5-Hexynoate (3mb)

Oil.

1H NMR (400 MHz, CDCl3); δ = 1.45 (s, 9 H). 1.81 (app quin, J = 7.2 Hz, 2 H), 1.96 (t, J = 7.2 Hz, 1 H). 2.25 (dt, J = 2.7 Hz, J = 7.1 Hz, 2 H), 2.35 (t, J = 7.2 Hz, 2 H).

13C NMR (100 MHz, CDCl3); δ = 17.72 (CH2), 23.70 (CH2), 27.98 (3 × CH2), 34.12 (CH2), 68.78 (CH2). 80.17 (C). 83.38 (C), 172.29 (C).

MS (EI); m/z (%); 151 100, 152 100, 153 100. Anal. Calcd for C11H20O2; C, 74.43; H, 10.52. Found: C, 74.50; H, 10.50.

tert-Butyl 8-Bromo-octanoate (3pb)

Oil.

1H NMR (600 MHz, CDCl3); δ = 1.30–1.38 (m, 4 H), 1.44 (s, 9 H), 1.40–1.70 (m, 4 H). 1.97 (app quin, J = 7.3 Hz, 2 H). 2.21 (t, J = 7.2 Hz, 2 H), 3.41 (t, J = 6.77 Hz, 2 H).

13C NMR (100 MHz, CDCl3); δ = 24.87 (CH2), 27.90 (CH2), 28.03 (3 × CH2), 28.34 (CH2), 28.77 (CH2). 32.64 (CH2), 33.77 (CH2). 35.42 (CH2), 79.94 (C), 179.20 (C).

MS (EI); m/z (%); 229/225 (11) M+ [M+ – 55], 205/207 (14), 143 (8), 125 (7), 97 (10). 57 (100).

Anal. Calcd for C11H18BrO2; C, 51.62; H, 8.24; Br, 28.67. Found: C, 51.60; H, 8.25; Br, 28.70.
Phenyl Levulinate (3jb)
Mp 31–32 °C (Lit. 47 32 °C).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3): \delta = 2.22 (s, 3 H), 2.79–2.89 (m, 4 H), 7.05–7.16 (m, 2 H), 7.18–7.26 (m, 1 H), 7.32–7.41 (m, 2 H). \]

\[ ^1^3C \text{ NMR (100 MHz, CDCl}_3): \delta = 28.13 (CH), 29.84 (CH), 37.90 (CH), 121.48 (2 × CH), 125.79 (CH), 129.37 (2 × CH), 150.65 (C), 171.42 (C), 206.37 (C). \]

MS (El): m/z (%): 192 (1) [M⁺], 99 (100), 94 (70), 71 (16), 65 (11), 55 (10).

Anal. Calcd for C\textsubscript{12}H\textsubscript{13}ClO\textsubscript{2}: C, 64.11; H, 5.79; Cl, 15.85. Found: C, 64.24; H, 5.73; Cl, 15.81.

4-Chlorophenyl 3-Hexenoate (3li)
Oil.

\[ 6.25. \]

Anal. Calcd for C\textsubscript{11}H\textsubscript{12}O\textsubscript{3}: C, 68.75; H, 6.25. Found: C, 68.70; H, 6.25.

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References


(4) Organic carbonates, for example, find employment as fuel additives, lubricating oils, herbicides, pesticides, plastics and solvents, and for medicinal and biological applications.


(6) Ref. 5, p 281.


(13) By comparison, Goolen obtained methyl 3-phenylpropanoate (3ae) in 95% yield after 16 hours at room temperature by mixing acid 1a, Moc-O (2e), and Mg(ClO\textsubscript{4})\textsubscript{2} in nitromethane (4 mL) in the ratio 1:1.3:0.01, respectively.


(15) In a blank run, ethanol and dicarbonate 2a were allowed to react in the presence of 10 mol% of magnesium chloride at room temperature and, after 48 hours, no appreciable amount of carbonate was detected.


(19) In contrast to magnesium perchlorate, which has a high activity for esterification (see ref. 9), magnesium chloride is unable to catalyze esterification between acid and alcohol 4a in reaction times comparable with those reported in Table 2.


(22) Dhimitraka, I.; Santacuria, J. Jr. Org. Lett. 2006, 8, 47.


