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Unmasking Amides: Ruthenium-Catalyzed Protodecarbonylation of N-Substituted Phthalimide Derivatives

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Supporting Information

ABSTRACT: The unprecedented transformation of a wide range of synthetically appealing phthalimides into amides in a single step operation has been achieved in high yields and short reaction times using a ruthenium catalyst. Mechanistic studies revealed a unique, homogeneous pathway involving five-membered ring opening and CO₂ release with water being the source of protons.

The phthalimide motif remains amongst the most widely used functional group in chemical synthesis. It enables the protection of primary amines and also, it behaves as an excellent nucleophile to install primary amines at will after treatment with hydrazine. Phthalimides have also been applied as dyes, porous solids, polymers, organocatalysts, and for different biological applications. In the last decades, phthalimides have also been conceived as key building blocks leading to important chemical skeletons due to their unique molecular structure. They are traditionally reduced employing over-stoichiometric amounts of strong reagents (LiAlH₄ or BH₃), superacids or metal salts derived from Al, Sn and Zn, under harsh reaction conditions. From a sustainable point of view, homogeneous catalysis has been considered to account for the functionalization of phthalimides under milder reaction conditions. As such, pharmaceutically- and agro-chemically-relevant heterocyclic compounds have been obtained starting from phthalimides via (i) transition metal-catalyzed hydrogenations, (ii) fluoride- and zinc-catalyzed reductions with silanes and (iii) ruthenium- and cobalt-catalyzed reductive alkoxylations and aminations. In all the above-stated approaches the bicyclic structure of the phthalimide skeleton remained unreacted after selective hydrogen or nucleophile incorporation.

On the other hand, examples leading to the selective cleavage of the phthalimide skeleton are extremely rare, which highlights the challenges associated with these types of transformations. For instance, in 2007, a ruthenium catalyst was reported to hydrogenate N-protected phthalimides, leading to valuable alcohol-amide products in the presence of 'BuOK as strong base and 30 bar of H₂ (eq 1). One year later, a nickel catalyst enabled the decarboxylative addition of N-arylphthalimides to alkynes, providing isoquinolones (eq 2). Finally, in 2013, a nickel catalyst was reported to hydrogenate phthalimide to benzamide (one example) in 82% selectivity under 50 bar of H₂ after 72 h of reaction time (eq 3). Clearly, the possibilities in terms of molecular diversity arising from breaking the phthalimide backbone in a controlled manner and milder reaction conditions are under-developed, especially, considering that they could lead to new shortcuts in multi-step chemical synthesis. Herein, we present a general and efficient ruthenium-catalyzed protocol enabling the highly chemoselective protodecarbonylation of N-substituted phthalimide derivatives into amides as well as preliminary mechanistic studies that suggest an unexpected decarboxylation pathway (eq 4). It is relevant to highlight that amides are ubiquitous building blocks in the fine and bulk chemical industry, and disclosing new pathways towards their synthesis is always appealing.
Table 1. Optimization of Reaction Conditions

<table>
<thead>
<tr>
<th>entry</th>
<th>deviation from standard conditions</th>
<th>2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>&gt;99 (93)*</td>
</tr>
<tr>
<td>2</td>
<td>with 0.5 mol % of [RuCl₂(η-cymene)]₂</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>130 °C instead of 150 °C</td>
<td>69</td>
</tr>
<tr>
<td>4</td>
<td>110 °C instead of 150 °C</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>no [RuCl₂(η-cymene)]₂</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>no K₂CO₃</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>air instead of Argon</td>
<td>10</td>
</tr>
<tr>
<td>8</td>
<td>undistilled NMP</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>[RuCl₂·xH₂O] instead of [RuCl₂(η-cymene)]₂</td>
<td>35</td>
</tr>
<tr>
<td>10</td>
<td>[Ru₃(CO)₁₂] instead of [RuCl₂(η-cymene)]₂</td>
<td>traces</td>
</tr>
<tr>
<td>11</td>
<td>1 equivalent of K₂CO₃</td>
<td>43</td>
</tr>
<tr>
<td>12</td>
<td>2 equivalents of K₂CO₃</td>
<td>74</td>
</tr>
<tr>
<td>13</td>
<td>no H₂O and 24 h reaction time</td>
<td>56</td>
</tr>
<tr>
<td>14</td>
<td>with overnight-dried K₂CO₃</td>
<td>50</td>
</tr>
<tr>
<td>15</td>
<td>H₂O instead of NMP</td>
<td>traces</td>
</tr>
<tr>
<td>16</td>
<td>with H₂ (1 bar)</td>
<td>8</td>
</tr>
</tbody>
</table>

*a* 1a (0.4 mmol), H₂O (0.6 mmol), K₂CO₃ (1.2 mmol), [RuCl₂(η-cymene)]; (1 mol %) in NMP (2 mL) at 150 °C for 6 h under argon atmosphere. 

To gain further insights into the reaction mechanism, the gas phase of the reaction mixture was qualitatively analyzed by GC. It indicated the presence of H₂ and CO₂ as the major components (Figures S2-S4). The detection of H₂ together with the deuterium experiments might indicate the formation of ruthenium-hydride species during the catalytic cycle. However, the similar amounts of H₂ detected in a blank experiment and the fact that the catalytic reaction was almost unproductive under 1 bar of H₂ (Table 1, entry 16) preclude the involvement of H₂ in the catalytic cycle and ruled out a standard ruthenium-catalyzed hydrogenation mechanism.16a Regarding the formation of CO₂, control experiments indicated that CO₂ was formed during the decarbonylation of the phthalimide ring since without the substrate almost no CO₂ was detected. To verify whether the reaction is initiated via hydrolysis of the phthalimide ring, 2-(phenylcarbamoyl)benzoic acid was submitted to the standard reaction conditions. Benzoic acid and aniline were the only products formed (Figure 1b), thereby excluding any hydrolysis of the phthalimide backbone previous to the decarboxylation process. In order to trap some potential intermediates, the catalysis was performed in the presence of 1 equivalent of TEMPO (Table 1, entry 15).
tetramethylpipеридин-1-ил)оксил]. Although the conversion of 1a decreased to ~30%, the formation of ring-opened intermediates containing two fragments of TEMPO (m/z = 474) were detected by GC-MS analysis (Figure 1c). In addition, performing the catalytic reaction with a phthalimide build-up on a six-membered ring did not proceed (Figure 1d), indicating that the ring strain release in 1a is probably the driving force for the initial step of the catalytic cycle. Mercury tests indicated the homogeneous regime of the catalysis and attempts to identify ruthenium intermediates by different spectroscopic analysis failed so far.

Considering the above findings and previous contributions,[18,21] a mechanism is tentatively postulated in Figure 1e. First, ruthenium chloride-free species were formed after reaction of [RuCl2(p-cymene)], with K2CO3. N-Coordination (or O-coordination) of ruthenium species to 1a should lead to A1 (or A2)[21] that after ring opening could form B. Hydroxylation followed by release of protons or dihydrogen would lead to C, which after decarboxylation would form ruthenacycle D.[22] Protonolysis might lead to E that is in equilibria with 2a; and the ruthenium catalyst is regenerated.

Different N-substituted phthalimide derivatives (1) conveniently provided the corresponding amides (2-3, Scheme 1). Aliphatic chains in the N-side are well tolerated although their bulkiness has a direct impact in the conversion. Butyl-substituted phthalimide 2b was obtained in 50% yield, and the bulkier propyl-substituted phthalimide 2c in 24% yield. These yields were improved by increasing the reaction time to 24 h (88% yield of 2b) and the catalyst loading to 2.5 mol % too (87% yield of 2c). The sterically-congested adamantyl-substituted phthalimide 2d was not formed. Aliphatic chains appended with a cyano group provided 2e in a good yield (63%), which was increased to 91% after 24 h of reaction time. Aliphatic chains containing other C–O bonds such as ethers, ketones and esters were compatible under the catalytic conditions, enabling the formation of the corresponding amides 2f, 2g and 2h in 98%, 73% and 26% isolated yields, respectively. In the former case (2h), a higher yield of 50% was obtained when performing the catalysis during 24 h and 2.5 mol % catalyst loading. Notably, the ruthenium catalyst is site-selective by performing the protodecarbonylation in the phthalimide skeleton without interfering with other C–O and N–C=O bonds. When the N-substituent of the phthalimide contains aromatic moieties with different functional groups at the para-position (methyl, methoxy, fluoro, ketone, ester and nitro), isolated yields of 80%-98% of the corresponding amides 2i-2o were obtained. Bromide- and iodide-containing phthalimides were converted into amides 2p and 2q, although the dehalogenated product (2i) was observed in 26% and 76% yields, respectively. meta-Substituted phenyl groups with a methoxy moiety were also compatible, leading to 2r in 97% yield. N-Substituted phenyl groups containing ortho substituents gave good conversions. The chloro-derivative 2s was isolated in 63% yield (no dechlorination was observed) and the methyl derivative 2t in 89% yield. A methoxy group incorporated at the ortho position of the N-substituted phenyl moiety yielded 2u in a poor 34%, likely due to inhibition by chelation to the catalyst. Nevertheless, the yield was increased to 78% by performing the catalysis during 48 h using 5 mol % of [RuCl2(p-cymene)]. A naphthalene group was also compatible (2v, 92% yield). The very coordinating quinoline-containing amide 2w was obtained in 33% yield after 48 h reaction time using 5 mol % of [RuCl2(p-cymene)], indicating that relevant heterocyclic motifs are compatible under the studied reaction conditions. Benzyl fragments bearing different functional groups (methyl, cyano and trifluoromethyl) were also tolerated, leading to 2x-3a in 90%-99% yields. The structure of 2x was further confirmed by X-ray crystallographic analysis (see SI). The benzylpyridine-containing amide derivative 3b was isolated in 88% yield, and the thiophenec containing amide 3c in 60% yield after 48 h reaction time and 5 mol % of catalyst. The efficiency of the catalytic reaction enabled a double protodecarbonylation (3d) in 93% yield. Hydroxyl-containing phthalimides led to unknown mixtures of products, and a substrate containing a C=C double bond afforded the hydrogenated starting material in low yield due to the formation of H2 during the catalysis. The steric effects and the coordinating properties of the substituents may account for those few very cases where the yields were low. Interestingly, by simply increasing the reaction time and the catalyst loading, high yields were obtained even for these reluctant substrates.

**Scheme 1. Substrate Scope**

The selectivity of the catalysis with N-phenyl phthalimides containing substituents at 3' and 4' position was studied since two possible isomers could form (Scheme 1). Phthalimides containing fluoro, chloro and nitro groups at the 3' position led exclusively to the meta isomers 3e-g, respectively, with no evidence by TLC, 1H NMR spectroscopy and GC-MS analysis.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>1H NMR spectroscopy analysis.</th>
<th>48 h reaction time.</th>
<th>5 mol % of [RuCl2(p-cymene)].</th>
<th>25.2 mol % of [RuCl2(p-cymene)].</th>
<th>&quot;Isolated yields. 24 h reaction time.</th>
<th>Product not isolated, yield estimated by 1H NMR spectroscopy analysis.</th>
<th>48 h reaction time.</th>
<th>5 mol % of [RuCl2(p-cymene)].</th>
<th>25.2 mol % of [RuCl2(p-cymene)].</th>
<th>&quot;Isolated yields. 24 h reaction time.</th>
</tr>
</thead>
<tbody>
<tr>
<td>3e</td>
<td>64% (m.p = 50.41)</td>
<td>3f</td>
<td>65%</td>
<td>3g</td>
<td>38%</td>
<td>3h</td>
<td>50% (m.p = 56.62)</td>
<td>3i</td>
<td>62% (m.p = 57.41)</td>
<td>3j</td>
</tr>
<tr>
<td>3k</td>
<td>30% (m.p = 28.28)</td>
<td>3l</td>
<td>62%</td>
<td>3m</td>
<td>38%</td>
<td>3n</td>
<td>78% (m.p = 75.45)</td>
<td>3o</td>
<td>51%</td>
<td>3p</td>
</tr>
<tr>
<td>3q</td>
<td>30% (m.p = 28.28)</td>
<td>3r</td>
<td>62%</td>
<td>3s</td>
<td>38%</td>
<td>3t</td>
<td>78% (m.p = 75.45)</td>
<td>3u</td>
<td>51%</td>
<td>3v</td>
</tr>
</tbody>
</table>
for the formation of other isomers. The halide-containing amides 3e and 3f were obtained in ca. 65% yield and the nitro-containing amide 3g in 87% yield. By increasing the reaction time to 24 hours, 3e was obtained in 93% yield. A phthalimide substituted at the 3’ position with a methyl group (3h) provided a mixture of ortho and meta isomers in 38:62 ratio with an overall yield of 92%. This indicates that electron-withdrawing groups such as nitro at 3’ position enhance the cleavage of the carbonyl group at the ortho position (with respect to 3’ position). On the other hand, substituents at the 4’ position (with respect to 3’ position) have little impact on the selectivity, and mixture of isomers of phthalimides were obtained in ca. 60:40 ratio. The electron-donating capabilities of the substituents (Me > F > I) were observed. The conversions of the phthalimides were found to depend on the electronic properties of the substituents at the 4’ position. By decreasing the electron-donating capabilities of the substituents (Me > F > NO2), the yield of the corresponding amides (3i-k) decreased from 98% to 82% to 49%, respectively. Phthalimide and phthalic anhydride afforded benzamide and benzoic acid in 17% and 51%, respectively; and substrates I-IV that are structurally related to I did not follow protodecarboxylation.

In summary, a general, chemoselective ruthenium-catalyzed reaction enabling the conversion of phthalimides into amides has been developed. The mechanism, which does not follow a standard hydrogenation pathway, involves a key decarboxylation step, with water serving as the source of protons. Since the reaction is operationally simple and proceeds without any pressure of H2, it can be carried out in conventional laboratories with minimal risks. This work represents a new entry for the activation and further functionalization of challenging C–C(O) and C–N(R2) bonds. Because the synthesis of amides and phthalimides is appealing in many scenarios relevant to chemistry and biology, we anticipate that the presented method will inspire new synthetic shortcuts.

ASSOCIATED CONTENT

Supporting Information.
The Supporting Information is available free of charge on the ACS Publications website at DOI: XXX.
Experimental data and characterizations of compounds (PDF)
Crystallographic data for 2x (CIF)

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Notes
The authors declare no competing financial interest.

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REFERENCES


38 examples
up to 99% yield
usually 6 hours
no need of autoclave reactors
mechanistic investigations