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DIRECT SYNTHESIS OF N,N-DISUBSTITUTED FORMAMIDES BY OXIDATION OF IMINES USING HFIP/UHP SYSTEM

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KEYWORDS: Green oxidation, Formamides, Fluorinated alcohol, Imines, Water peroxide

ABSTRACT

The straightforward synthesis of N,N-disubstituted formamides using 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and H₂O₂ combination is described. The unique features of HFIP allowed the utilization of a green oxidant such as H₂O₂ and the products, arising from an oxidation-rearrangement sequence, were obtained in good to high yields under smooth reaction conditions.

INTRODUCTION
Formamides are considered valuable intermediates in organic synthesis which have been extensively utilized in the synthesis of pharmaceutically relevant compounds such as fluoroquinolones, substituted aryl imidazoles or 1,2-dihydroquinolines. Besides, during the last years, formamides have been also used as Lewis bases being employed as catalysts in numerous organic transformations. Further to this, these organic compounds play an important role as reagents in the Vilsmeir formylation reaction.

On the other hand, imines are considered very accessible and versatile compounds. Thus, it is not surprising that oxidation of imines has been addressed in a myriad of articles giving rise to the corresponding oxaziridines or N-substituted amides (Scheme 1, eq. a). However, to the best of our knowledge, there are only a couple of precedents in the literature describing the oxidative rearrangement of imines in order to get access to N,N-disubstituted formamides (Scheme 1, eq. b). In addition, in both routes, the authors use organic peroxyacids, requiring the presence of a strong Lewis or Brønsted acid; hence generating a stoichiometric amount of non-degradable waste in a low atom-economy process. Therefore, the development of a more environmentally benign oxidative route for the synthesis of such formamides from readily available imines, which can overcome such problems, would be highly desirable. In this regard, continuing with an ongoing project about the use of fluorinated alcohols in organic transformations as solvents and reaction mediators, we envisioned the employment of H$_2$O$_2$ or the more stable form UHP (urea-hydrogen peroxide adduct) as a green alternative oxidants to those previously described ones in combination with 1,1,1,3,3,3-hexafluoroispropanol (HFIP) for such purpose (Scheme 1, eq. c). The use of this system would considerably reduce the amount and the environmental impact of the generated waste. The results of this research are herein reported.

Scheme 1. Imines oxidation
RESULTS AND DISCUSSION

The optimization of the reaction conditions was tackled, using N-benzylideneaniline (1a) as model substrate (Table 1). Firstly, different organic polar protic solvents (namely HFIP, H$_2$O, MeOH and TFE) were tested using 2 equiv. of H$_2$O$_2$ (30% v/v) as oxidizing agent at 45 ºC (Table 1, entries 1-4). As depicted in Table 1, only HFIP gave a good conversion towards the formation of 2a (Table 1, entry 1). It is noteworthy that, although in poor conversion, MeOH gave rise to the formation of the regioisomer 3a (Table 1, entry 3). Other commonly employed polar aprotic and apolar organic solvents were also essayed (DMSO, MeCN, EtOAc, THF, acetone, CHCl$_3$, PhMe) remaining the imine unaltered or slightly hydrolysed. Attempts to ameliorate the conversion of 2a were performed by increasing or lowering the amount of H$_2$O$_2$ employed using HFIP as solvent (Table 1, entries 5 and 7). However, whereas the use of 3 equiv. barely changed the result, the employment of 1.5 equiv. resulted in lower conversion. The same experiments were performed with MeOH, trying to favor the formation of 3a (Table 1, entries 6 and 8). Unfortunately, the same trend was observed and no significant improvement was accomplished. It is also noteworthy that, at this point, different solvent mixtures HFIP/MeOH...
and HFIP/H₂O were also tested without further success. Focused on the formation of compound 2a, refining the reaction conditions in order to increase the conversion was next addressed. Thus, the concentration was examined and it was observed that changing the concentration from 1 M to 0.6 M improved the conversion of 2a reaching up to 91% (Table 1, compare entry 9 and 10). The reaction at room temperature was also essayed but the conversion was not as high as at 45 ºC (Table 1, entry 11). Finally, from the presence of benzaldehyde and aniline in the GC-MS analysis, arising from the partial hydrolysis of imine, it was decided to switch to an anhydrous H₂O₂ source in order to minimize such background reaction. In this regard, when UHP was used instead, an excellent conversion towards the formation of 2a was achieved (Table 1, entry 12). Further changes in concentration or temperature did not produce any substantial improvement (Table 1, entries 13-15).

Table 1. Optimization of the reaction conditions

| Entry | H₂O₂ source (x equiv.) | Solvent | Temp (°C) | Conv. (2a/3a ratio)⁷
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂O₂ (2 equiv.)</td>
<td>HFIP</td>
<td>45</td>
<td>85% (98/2)</td>
</tr>
<tr>
<td>2</td>
<td>H₂O₂ (2 equiv.)</td>
<td>H₂O</td>
<td>45</td>
<td>&lt;10%</td>
</tr>
<tr>
<td>3</td>
<td>H₂O₂ (2 equiv.)</td>
<td>MeOH</td>
<td>45</td>
<td>35% (4/96)</td>
</tr>
<tr>
<td>4</td>
<td>H₂O₂ (2 equiv.)</td>
<td>TFE</td>
<td>45</td>
<td>&lt;15%</td>
</tr>
<tr>
<td>5</td>
<td>H₂O₂ (1.5 equiv.)</td>
<td>HFIP</td>
<td>45</td>
<td>77% (95/5)</td>
</tr>
</tbody>
</table>
6 $\text{H}_2\text{O}_2$ (1.5 equiv.) $\text{MeOH}$ 45 $<15\%$
7 $\text{H}_2\text{O}_2$ (3 equiv.) HFIP 45 82% (98/2)
8 $\text{H}_2\text{O}_2$ (3 equiv.) $\text{MeOH}$ 45 39% (4/96)
9 $\text{H}_2\text{O}_2$ (2 equiv.) HFIP\(^c\) 45 91% (>99/1)
10 $\text{H}_2\text{O}_2$ (2 equiv.) HFIP\(^d\) 45 68% (95/5)
11 $\text{H}_2\text{O}_2$ (2 equiv.) HFIP\(^c\) 25 86% (99/1)
12 UHP (2 equiv.) HFIP 45 97% (>99/1)
13 UHP (2 equiv.) HFIP\(^c\) 45 92% (>99/1)
14 UHP (2 equiv.) HFIP\(^d\) 45 87% (>99/1)
15 UHP (2 equiv.) HFIP 25 93% (>99/1)

\(^a\) Reaction conditions: all the reactions were carried out using 0.15 mmol of imine 1\(a\) and the corresponding amount of oxidant in 150 µL of the solvent at the given temperature for 15 h. \(^b\) Conversion and 2\(a\)/3\(a\) ratio, determined by GC-MS. \(^c\) 250 µL of HFIP were used (0.6 M). \(^d\) 50 µL of HFIP were used (3 M).

Once the optimal reaction conditions were selected, the scope of the methodology was performed by using different imines (Table 2). As previously commented, imine 1\(a\) produced the corresponding \(N,N\)-diphenylformamide (2\(a\)) in high yield (Table 2, entry 1). Good yield was also achieved when imine 1\(b\) was tested (Table 2, entry 2). However, imine derived from \textit{para}-anisidine 1\(c\) gave only decomposition and hydrolysis products regardless the reaction conditions employed, probably due to its more basic character, which makes the substrate more prone to be protonated by HFIP and hence more easily hydrolysed (Table 2, entry 3). Aldimine 1\(d\) bearing an electron-withdrawing group in the aniline moiety, produced the desired product in a 62% yield (Table 2, entry 4). Next, aldimes synthesized from different \textit{para}-substituted benzaldehydes were essayed, obtaining high yields in the corresponding disubstituted formamides regardless the electronic nature of such substituent (Table 2, entries 5-8). It is worth mentioning that in the case of imine 1\(h\) bearing an electron-withdrawing group (CF\(_3\)) produced a
substantial 10% of the corresponding isomer 3h arising from the benzylic oxidation (Table 2, entry 8). Imine derived from salicylaldehyde was also explored but unfortunately turned out to be unreactive, probably due to an internal hydrogen bond, and low conversion towards the desired product was detected even when increasing the amount of UHP (Table 2, entry 9). This assumption was further reinforced in view of the good yield achieved for the product 2j when o-anisaldehyde imine derivative 1j was essayed (Table 2, entry 10). Imine 1k bearing para-methyl substituents in both aromatic rings produced formamide 2k in good yield (Table 2, entry 11).

Next, heteroaromatic aldehyde imine derivatives were employed and different behaviors were observed depending on the electronic properties of the aromatic ring. Thus, whereas imine 1l containing an electron-rich heteroaromatic ring such as furan, gave rise to decomposition and hydrolysis products, imine 1m bearing a pyridine ring, considered as electron poor aromatic ring, produced compound 3m in good yield as main product (Table 2, entries 12 and 13). Imines derived from aliphatic amines were next evaluated. When imine 1n was the substrate of choice, the formation of a mixture of both N-butylbenzamide (3n) and the corresponding formamide 2n was observed in moderate yield (Table 2, entry 14). However, the reaction with imine 1o bearing a cyclohexane ring resulted in the formation of the oxaziridine 4o (Table 2, entry 15). Unexpectedly, N,N-diphenylformamide 2a was obtained in high yield when benzylamine imine derivative 1p was employed (Table 2, entry 16). Next, imines derived from cyclohexanecarbaldehyde were examined. Good results were obtained with imine 1q (Table 2, entry 17). Contrariwise, oxaziridine 4r was obtained in excellent yields from imine 1r (Table 2, entry 18). Finally, cinnamaldehyde derivative imine 1s was also tested and to our surprise a complex mixture of products was obtained (Table 2, entry 19). We were able to distinguish (by GC-MS) among them benzaldehyde and formamide 2a as major products (together with lower
amounts of \( N \)-phenylformamide). At this point we speculate about a possible hydrolysis and retroaldol reaction, which would form benzaldehyde and aniline, hence the \textit{in situ} formation of imine \( 1a \) (see Scheme 2) which would lead to the formation of \( 2a \). Finally, a few ketimines were also tested. Firstly, imine derived from acetophenone (\( 1t \)) was assayed, but unfortunately only 20\% conversion towards the formation of the corresponding \( N,N \)-diphenylacetamide \( 2t \) (Table 2, entry 20) was observed. Imine derived from cyclohexyl methyl ketone \( 1u \) underwent hydrolysis under the reaction conditions (Table 2, entry 21). Finally, all alkylic ketimine \( 1v \) produced the corresponding oxaziridine \( 4v \) in excellent yields (Table 2, entry 22).

\textbf{Table 2. Scope of the reaction\textsuperscript{a}}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Imine</th>
<th>Product</th>
<th>Yield\textsuperscript{b} (2/3 ratio)\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{Ph-N-Ph} ) (1a)</td>
<td>( \text{H-N-Ph} ) (2a)</td>
<td>89 (&gt;99/1)</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Ph-N-C}<em>{6} \text{H}</em>{4} ) (1b)</td>
<td>( \text{H-N-C}<em>{6} \text{H}</em>{4} ) (2b)</td>
<td>82 (&gt;99/1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>3</td>
<td><img src="image1.png" alt="Structure 1c" /></td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>4</td>
<td><img src="image2.png" alt="Structure 1d" /></td>
<td><img src="image3.png" alt="Structure 2d" /></td>
<td>62 (&gt;99/1)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image4.png" alt="Structure 1e" /></td>
<td><img src="image5.png" alt="Structure 2e" /></td>
<td>87 (&gt;99/1)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image6.png" alt="Structure 1f" /></td>
<td><img src="image7.png" alt="Structure 2b" /></td>
<td>80 (&gt;99/1)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image8.png" alt="Structure 1g" /></td>
<td><img src="image9.png" alt="Structure 2g" /></td>
<td>88 (96/4)</td>
</tr>
<tr>
<td>8</td>
<td><img src="image10.png" alt="Structure 1h" /></td>
<td><img src="image11.png" alt="Structure 2h" /></td>
<td>91 (90/10)</td>
</tr>
<tr>
<td>9</td>
<td><img src="image12.png" alt="Structure 1i" /></td>
<td><img src="image13.png" alt="Structure 2i" /></td>
<td>&lt;20% conv. d</td>
</tr>
<tr>
<td>10</td>
<td><img src="image14.png" alt="Structure 1j" /></td>
<td><img src="image15.png" alt="Structure 2j" /></td>
<td>90 (98/2)</td>
</tr>
<tr>
<td></td>
<td><img src="image1.png" alt="Chemical Structure 1k" /></td>
<td><img src="image2.png" alt="Chemical Structure 2k" /></td>
<td>79 (&gt;99/1)</td>
</tr>
<tr>
<td>----</td>
<td>----------------------------------</td>
<td>----------------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>11</td>
<td><img src="image3.png" alt="Chemical Structure 1l" /></td>
<td><img src="image4.png" alt="Chemical Structure 3m" /></td>
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<tr>
<td>12</td>
<td><img src="image5.png" alt="Chemical Structure 1m" /></td>
<td><img src="image6.png" alt="Chemical Structure 3n" /></td>
<td>72 (15/85)</td>
</tr>
<tr>
<td>13</td>
<td><img src="image7.png" alt="Chemical Structure 1n" /></td>
<td><img src="image8.png" alt="Chemical Structure 4o" /></td>
<td>57 (35/65)</td>
</tr>
<tr>
<td>14</td>
<td><img src="image9.png" alt="Chemical Structure 1o" /></td>
<td><img src="image10.png" alt="Chemical Structure 2a" /></td>
<td>98</td>
</tr>
<tr>
<td>15</td>
<td><img src="image11.png" alt="Chemical Structure 1p" /></td>
<td><img src="image12.png" alt="Chemical Structure 2q" /></td>
<td>83 (&gt;99/1)</td>
</tr>
<tr>
<td>16</td>
<td><img src="image13.png" alt="Chemical Structure 1q" /></td>
<td><img src="image14.png" alt="Chemical Structure 4r" /></td>
<td>84 (&gt;99/1)</td>
</tr>
<tr>
<td>17</td>
<td><img src="image15.png" alt="Chemical Structure 1r" /></td>
<td><img src="image16.png" alt="Chemical Structure 4r" /></td>
<td>95</td>
</tr>
</tbody>
</table>

ACS Paragon Plus Environment
<table>
<thead>
<tr>
<th></th>
<th>Structure</th>
<th>Description</th>
<th>Yield/Conversion</th>
</tr>
</thead>
<tbody>
<tr>
<td>19</td>
<td><img src="image1" alt="Image of 1s" /></td>
<td>Complex Mixture</td>
<td>&gt;95% conv.&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>20</td>
<td><img src="image2" alt="Image of 1t" /></td>
<td></td>
<td>~20% conv.&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>21</td>
<td><img src="image3" alt="Image of 1u" /></td>
<td></td>
<td>—</td>
</tr>
</tbody>
</table>
| 22 | ![Image of 1v](image4) | | 95%

<sup>a</sup> Reaction conditions: all the reactions were carried out using 0.15 mmol of imine 1 and 2 equiv. of UHP in 150 µL of HFIP (1 M) at 45 °C for 15 h. <sup>b</sup> Isolated yield of 2 or the 2/3 mixture after preparative TLC or chromatography column. <sup>c</sup> 2/3 ratio determined by GC-MS from the crude mixture. <sup>d</sup> Determined by GC-MS. <sup>e</sup> Not purely isolated; yield determined by <sup>1</sup>H NMR from the crude.

After the scope of the reaction was tested, we decided to explore the one-pot imine formation-oxidative rearrangement sequence (Scheme 2). Thus, onto in situ formed benzylideneaniline 1a, synthesised by mixing benzaldehyde and aniline for 20 minutes in the absence of solvent, UHP (2 equiv.) and HFIP was added in one portion. After 15 hours and subsequent purification the formamide 2a was obtained in 81% yield. It is also worth mentioning that when this one-pot was implemented in a larger scale reaction (5 mmol), the corresponding formamide 2a was obtained in a notable 73% yield. In addition, since benzylidene amine it is not a very stable compound, we decided to perform the same one-pot sequence reaction but using ammonium hydroxide. Using a slightly modified procedure (longer reaction time to form the imine and 5 equiv. of both
ammonium hydroxide and UHP) we were able to isolate benzamide 3w in a good 59% yield, being in addition, the only regioisomer observed.

**Scheme 2. One-pot imine formation-oxidation sequence.**

Finally, based on experimental evidences, a possible reaction mechanism was proposed as depicted in Scheme 3. Firstly, the corresponding oxaziridine B would be formed thanks to the electrophilic activation of hydrogen peroxide by HFIP\(^{13}\) which allows the nucleophilic attack of the iminic nitrogen and subsequent oxaziridine formation from the oxime derivative A. The formation of intermediate B is seemingly plausible from the fact that this kind of products have been isolated, for example in compound 4o, 4r and 4v. From this intermediate, a Meinwald-type rearrangement mediated by HFIP could occur rendering the expected amide. Although less probable, a Beckmann-type rearrangement from intermediate A cannot be ruled out.

**Scheme 3. Proposed reaction mechanism.**

CONCLUSIONS
In summary, we have developed an efficient and environmentally benign methodology for the synthesis of formamides by means of the oxidation of aldimines using UHP as green oxidant. The use of this safe and non-toxic oxidant in absence of any Lewis acid has been possible because the presence of HFIP as solvent and reaction mediator. The peculiar properties of such fluorinated alcohols allow the electrophilic activation of hydrogen peroxide which is crucial for the reaction to proceed. The corresponding formamides 2 were obtained generally in good yields under smooth reaction conditions. However, the formation of the corresponding aryl amides 3 or oxaziridines 4 was also observed for imines derived from electron-poor aldehydes or cyclohexanamine, respectively. The one-pot imine formation-oxidative rearrangement sequence has been also described obtaining good results even when a big-scale reaction was performed. In this regard this one-pot sequence allowed the synthesis of benzamide in good yields using benzaldehyde and aqueous ammonia which to the best of our knowledge represents the first example of this transformation in absence of metal or Lewis acid catalysts. Finally, the mechanism was proposed to proceed via formation of the corresponding oxaziridine and subsequent rearrangement.

**EXPERIMENTAL SECTION**

**General Remarks:**

All reagents and solvents were obtained commercially and used without further purification. Substrates that were not commercially available were synthesized according to known literature procedures.

NMR spectra were performed on a Bruker AV-300 or Bruker AV-400 (Bruker Corporation) using CDCl$_3$ as solvent and TMS as internal standard unless otherwise stated.
Low resolution mass spectra (MS) were recorded in the electron impact mode (EI, 70 eV, He as carrier phase) using an Agilent GC/MS 5973 Network Mass Selective Detector spectrometer apparatus equipped with a HP-5MS column (Agilent technologies, 30 m × 0.25 mm) and giving fragment ions in \( m/z \) with relative intensities (%) in parentheses.

Analytical TLC was performed on Merck silica gel plates and the spots visualized with UV light at 254 nm. Flash chromatography employed Merck silica gel 60 (0.040-0.063 mm). Silica gel 60 \( F_{254} \) containing gypsum was employed for preparative layer chromatography.

**General Procedure for the Oxidation Reaction of Imines**

In a capped tube, onto the corresponding imine (0.15 mmol), HFIP (150 \( \mu \)L) and UHP (2.0 equiv.) were added in one portion. The reaction was then stirred at 45 °C in a sand bath for 15 hours, until the reaction was judged to be completed by GC-MS. After this time, the reaction mixture was filtered over silica/celite plug and then the solvent was evaporated and the crude material was directly purified by flash chromatography or preparative TLC using hexane/ethyl acetate mixtures.

Spectroscopic and analytical data for isolated compounds are given below:

**N,N-Diphenylformamide (2a):** Slightly yellow solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 29.0 mg, 89% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \( \delta_H = 8.69 \) (s, 1H), 7.46 – 7.39 (m, 4H), 7.37 – 7.27 (m, 4H), 7.23 – 7.16 (m, 2H) ppm; \(^{13}\)C{\(H\)} NMR (101 MHz, CDCl\(_3\)): \( \delta_C = 161.8, 141.7, 139.6, 129.7, 129.2, 127.1, 126.9, 126.1, 125.1 \) ppm; MS (EI): \( m/z \) 197 (M\(^+\), 100%), 169 (58), 168 (79), 167 (45), 104 (12), 77 (17), 66 (19), 51 (13).
**N-Phenyl-N-(p-tolyl)formamide (2b):** Dark orange oil; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 25.3 mg, 82% yield, mixture of rotamers; $^1$H NMR (300 MHz, CDCl$_3$): $\delta_{H} = 8.69$ (s, 1H), 8.64 (s, 1H), 7.47 – 7.35 (m, 5H), 7.35 – 7.26 (m, 5H), 7.24 (s, 2H), 7.20 – 7.14 (m, 4H), 7.13 – 7.05 (m, 2H), 2.39 (s, 3H), 2.37 (s, 3H) ppm; $^{13}$C{H} NMR (75 MHz, CDCl$_3$): $\delta_{C} = 161.8, 141.9, 139.8, 139.2, 137.2, 136.9, 130.3, 129.8, 129.6, 129.1, 126.8, 126.6, 126.2, 125.8, 125.3, 124.7, 29.7, 21.1, 20.9$ ppm; MS (EI): $m/z$ 211 (M$^+$, 100%), 183 (68), 182 (75), 180 (14), 168 (11), 167 (38), 108 (13), 91 (18), 80 (13), 77 (17).

**N-(4-Acetylphenyl)-N-phenylformamide (2d):** White solid; purification by preparative TLC (hexane/ethyl acetate 8.5/1.5), 22.2 mg, 62% yield; mixture of rotamers; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_{H} = 8.83$ (s, 1H), 8.66 (s, 1H), 8.17 – 8.09 (m, 2H), 8.06 – 7.94 (m, 7H), 7.95 – 7.86 (m, 2H), 7.80 (d, $J = 8.8$ Hz, 1H), 7.60 (ddd, $J = 8.8, 5.0, 1.6$ Hz, 1H), 7.56 – 7.35 (m, 11H), 7.25 – 7.20 (m, 4H), 2.62 (s, 4H), 2.61 (s, 4H) ppm; $^{13}$C{H} NMR (101 MHz, CDCl$_3$): $\delta_{C} = 161.8, 161.3, 132.3, 130.0, 129.9, 129.8, 129.5, 129.4, 129.3, 128.9, 128.4, 127.9, 127.7, 127.1, 126.8, 126.1, 124.9, 123.4, 123.2, 119.3, 26.8, 26.6$ ppm; MS (EI): $m/z$ 239 (M$^+$, 100%), 196 (72), 167 (58), 121 (23), 77 (12).

**N-(4-Methoxyphenyl)-N-phenylformamide (2e):** Dark yellow solid; purification by preparative TLC (hexane/ethyl acetate 8.5/1.5), 36.1 mg, 87% yield, mixture of rotamers; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_{H} = 8.69$ (s, 1H), 8.59 (s, 1H), 7.46 – 7.35 (m, 4H), 7.34 – 7.30 (m, 3H), 7.26 – 7.19 (m, 3H), 7.19 – 7.12 (m, 4H), 6.95 (dd, $J = 8.9, 1.3$ Hz, 4H), 6.79 (d, $J = 1.0$ Hz, 1H), 3.85 (s, 3H), 3.83 (s, 3H) ppm; $^{13}$C{H} NMR (101 MHz, CDCl$_3$): $\delta_{C} = 161.9, 161.9, 129.6, 129.1, 127.7, 127.2, 126.7, 126.5, 125.4, 124.4, 114.9, 114.5, 55.5, 55.4$ ppm; MS (EI): $m/z$ 277 (M$^+$, 100%), 206 (32), 199 (17), 184 (76), 154 (20), 124 (13), 76 (11).
N-(4-Chlorophenyl)-N-phenylformamide (2g): Brown solid; 30.4 mg, 88% yield (without further purification); \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta_H = 8.65 \text{ (d, } J = 2.6 \text{ Hz, 1H)}, 7.49 - 7.36 \text{ (m, 5H)}, 7.30 - 7.24 \text{ (m, 2H)}, 7.19 \text{ (dd, } J = 5.3, 3.3 \text{ Hz, 1H}), 7.13 \text{ (d, } J = 8.7 \text{ Hz, 1H) ppm}; \(^{13}\)C\{H\} NMR (101 MHz, CDCl\(_3\)): \(\delta_C = 161.8, 161.5, 141.2, 140.3, 139.2, 138.1, 132.9, 132.4, 129.9, 129.4, 129.3, 127.5, 127.3, 127.2, 126.1, 126.1, 125.3 \text{ ppm}; \) MS (EI): \(m/z \) 231 (M\(^+\), 100%), 205 (20), 204 (11), 203 (60), 168 (49), 167 (84), 166 (17), 77 (11), 66 (12).

N-Phenyl-N-[4-(trifluoromethyl)phenyl]formamide (2h): white sticky solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 36.1 mg, 91% yield, mixture of rotamers (and regioisomer 3h); only the signals for the major isomer 2h are given: \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta_H = 8.78 \text{ (s, 1H)}, 8.66 \text{ (s, 2H)}, 8.01 \text{ (d, } J = 8.0 \text{ Hz, 1H)}, 7.75 \text{ (d, } J = 8.1 \text{ Hz, 1H)}, 7.27 \text{ (dd, } J = 7.6, 3.9 \text{ Hz, 5H)}, 7.21 \text{ (d, } J = 7.6 \text{ Hz, 5H) ppm}; \(^{13}\)C\{H\} NMR (101 MHz, CDCl\(_3\)): \(\delta_C = 164.4, 161.7, 161.2, 144.9, 142.8, 140.8, 138.7, 138.3, 137.6, 133.6, 130.0, 129.5, 129.1, 128.5, 128.1, 127.9, 127.7, 127.6, 126.9, 126.8, 126.7, 126.2, 126.2, 125.9, 125.8, 125.7, 125.4, 124.9, 124.0, 122.5, 120.4 \text{ ppm}; \) MS (EI): \(m/z \) 265 (M\(^+\), 100%), 237 (73), 236 (34), 216 (17), 168 (16), 167 (42), 77 (11), 66 (13); HRMS (GC/MS-EI/Q-TOF): \(m/z \) calcd. for C\(_{14}\)H\(_{10}\)F\(_3\)NO 265.0714, found 265.0717.

N-(2-Methoxyphenyl)-N-phenylformamide (2j): Dark orange oil; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 31.1 mg, 90% yield, mixture of rotamers; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta_H = 8.57 \text{ (s, 1H)}, 8.26 \text{ (s, 1H)}, 7.31 - 7.21 \text{ (m, 4H)}, 7.17 - 7.01 \text{ (m, 6H)}, 6.93 \text{ (d, } J = 8.3 \text{ Hz, 3H)}, 3.69 \text{ (s, 3H)}, 3.69 \text{ (s, 3H) ppm}; \(^{13}\)C\{H\} NMR (101 MHz, CDCl\(_3\)): \(\delta_C = 163.42, 162.41, 155.6, 155.1, 141.6, 140.0, 129.9, 129.8, 129.7, 129.6, 129.5, 129.4, 128.8, 127.5, 126.4, 126.2, 124.8, 123.1, 121.2, 112.5, 112.4, 55.7 \text{ ppm}; \) MS (EI): \(m/z \) 227 (M\(^+\), 53%), 200 (11), 199
(71), 185 (14), 184 (100), 183 (23), 167 (16), 166 (14), 156 (24), 129 (25), 128 (17), 77 (15), 51 (11); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for C_{14}H_{13}NO_{2} 227.0946; found 227.0939.

N,N-Di-p-tolylformamide (2k):\textsuperscript{18} Slightly orange solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 26.8 mg, 79% yield; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta_{H} = 8.63 \) (s, 1H), 7.21 (t, \( J = 5.5 \) Hz, 6H), 7.07 (d, \( J = 8.3 \) Hz, 2H), 2.39 (s, 3H), 2.37 (s, 3H) ppm; \textsuperscript{13}C{\{H} NMR (101 MHz, CDCl\textsubscript{3}): \( \delta_{C} = 161.8, 139.4, 137.2, 136.9, 136.7, 130.2, 129.7, 125.8, 124.9, 21.0, 20.9 \) ppm; MS (EI): m/z 225 (M\(^+\), 100%), 197 (65), 196 (69), 181 (23), 180 (29), 108 (20), 91 (19), 80 (20), 65 (13).

N-Phenyl-3-pyridinecarboxamide (3m):\textsuperscript{19} Dark orange solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 20.5 mg, 72% yield (90:10 isomeric mixture), only the major isomer signals are given; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta_{H} = 9.10 \) (s, 1H), 8.75 (d, \( J = 3.6 \) Hz, 1H), 8.39 (s, 1H), 8.23 (dt, \( J = 7.9, 1.8 \) Hz, 1H), 7.66 (d, \( J = 7.9 \) Hz, 2H), 7.47 – 7.35 (m, 3H), 7.19 (t, \( J = 7.4 \) Hz, 1H) ppm; \textsuperscript{13}C{\{H} NMR (101 MHz, CDCl\textsubscript{3}): \( \delta_{C} = 163.9, 152.2, 147.8, 137.5, 135.6, 130.9, 129.2, 125.1, 123.7, 120.5 \) ppm; MS (EI): m/z 198 (M\(^+\), 61%), 197 (16), 106 (100), 78 (54), 51 (17).

N-Butylbenzamide (3n):\textsuperscript{20} White solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 15.5 mg, 57% yield (not pure isolated); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta_{H} = 7.81 – 7.73 \) (m, 2H), 7.50 (dd, \( J = 5.0, 3.7 \) Hz, 1H), 7.47 – 7.42 (m, 2H), 6.10 (s, 1H), 3.54 – 3.44 (m, 2H), 1.71 – 1.58 (m, 2H), 1.45 (dd, \( J = 15.1, 7.4 \) Hz, 2H), 0.99 (t, \( J = 7.3 \) Hz, 3H) ppm; MS (EI): m/z 177 (M\(^+\), 11%), 135 (20), 134 (19), 105 (100), 77 (33).

2-Cyclohexyl-3-phenyl-1,2-oxaziridine (4o):\textsuperscript{21} White solid; purification by preparative TLC (hexane/ethyl acetate 8.5/1.5), 26.8 mg, 98% yield; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta_{H} = 7.47 – \)
7.43 (m, 1H), 7.42 – 7.38 (m, 1H), 4.55 (s, 1H), 2.16 – 2.05 (m, 1H), 1.90 – 1.80 (m, 1H), 1.78 – 1.72 (m, 1H), 1.70 – 1.56 (m, 1H), 1.47 (ddd, J = 23.0, 12.2, 3.8 Hz, 1H), 1.39 – 1.21 (m, 2H), ppm; \(^{13}\text{C}\{\text{H}\} \text{NMR (101 MHz, CDCl}_3\}: \delta_C = 135.3, 129.9, 128.5, 127.4, 79.8, 70.2, 31.6, 29.2, 25.7, 24.6, 24.1 ppm; MS (EI): m/z 203 (M\(^+\), 40%), 122 (78), 105 (100), 77 (42).

N-Cyclohexyl-N-phenylformamide (2q): Orange oil; purification by preparative TLC (hexane/ethyl acetate 8.5/1.5), 25.9 mg, 84% yield; \(^1\text{H} \text{NMR (400 MHz, CDCl}_3\}): \delta_H = 8.17 (s, 1H), 7.51 – 7.36 (m, 3H), 7.23 – 7.12 (m, 2H), 4.54 – 4.27 (m, 1H), 1.88 (d, J = 12.2 Hz, 2H), 1.78 (d, J = 13.8 Hz, 2H), 1.66 – 1.57 (m, 1H), 1.47 – 1.25 (m, 5H), 1.01 (qt, J = 12.9, 3.7 Hz, 1H) ppm; \(^{13}\text{C}\{\text{H}\} \text{NMR (101 MHz, CDCl}_3\}: \delta_C = 162.6, 138.6, 129.3, 129.1, 128.2, 53.7, 31.4, 25.7, 25.3 ppm; MS (EI): m/z 203 (M\(^+\), 15%), 160 (16), 132 (17), 122 (13), 121 (100), 93 (34), 77 (15).

2,3-Dicyclohexyl-1,2-oxaziridine (4r): White solid; purification by preparative TLC (hexane/ethyl acetate 8.0/2.0), 28.5 mg, 95% yield; m.p. 48-49 ºC; \(^1\text{H} \text{NMR (400 MHz, CDCl}_3\): \delta_H = 3.48 (d, J = 6.6 Hz, 1H), 1.99 (d, J = 13.4 Hz, 1H), 1.86 – 1.71 (m, 8H), 1.71 – 1.57 (m, 4H), 1.35 – 1.12 (m, 8H) ppm; \(^{13}\text{C}\{\text{H}\} \text{NMR (101 MHz, CDCl}_3\): \delta_C = 85.3, 69.3, 40.2, 31.6, 290, 27.7, 27.5, 26.3, 25.7, 25.2, 24.5, 23.9 ppm; MS (EI): m/z 209 (M\(^+\), 30%), 192 (19), 154 (23), 150 (18), 138 (42), 128 (98), 127 (18), 126 (48), 125 (44), 110 (42), 98 (18), 95 (28), 84 (22), 83 (79), 82 (33), 81 (18), 68 (14), 67 (52), 56 (39), 55 (100), 54 (55); HRMS (GC/MS-EI/Q-TOF): m/z calcd. for C\(_{13}\)H\(_{23}\)NO 209.1780, found 209.1778.

2-Cyclohexyl-1-oxa-2-azaspiro[2.5]octane (4v): Slightly yellow oil; purification by flash chromatography (hexane/ethyl acetate 8.0/2.0), 25.7 mg, 95% estimated yield (not pure isolated); \(^1\text{H} \text{NMR (300 MHz, CDCl}_3\): \delta_H = 2.55 – 2.27 (m, 1H), 1.97 – 1.77 (m, 4H), 1.75 – 1.55 (m, 6H), 1.54 – 1.38 (m, 3H), 1.34 – 1.16 (m, 6H) ppm; \(^{13}\text{C}\{\text{H}\} \text{NMR (75 MHz, CDCl}_3\): \delta_C = 85.1, 60.2,
36.6, 31.9, 29.7, 29.2, 27.8, 25.7, 25.5, 25.4, 24.9, 24.4, 24.2 ppm; MS (EI): m/z 195 (M⁺, 15%),
179 (20), 178 (34), 152 (15), 138 (12), 136 (25), 114 (100), 113 (11), 98 (47), 97 (12), 96 (20),
83 (16), 82 (15), 81 (21), 69 (18), 67 (24), 56 (13), 55 (52), 54 (20); HRMS (GC/MS-EI/Q-TOF):
m/z calcd. for C₁₂H₂₁NO 195.1623, found 195.1625.

Benzamide (3w): White solid; purification by preparative TLC (hexane/ethyl acetate 9.0/1.0),
12.3 mg, 59% yield; ¹H NMR (400 MHz, DMSO-d₆): δ_H = 7.99 (s, 1H), 7.88 (dd, J = 5.3, 3.4 Hz,
2H), 7.51 (ddd, J = 6.3, 3.7, 1.3 Hz, 1H), 7.48 – 7.41 (m, 2H), 7.38 (s, 1H) ppm; ¹³C{H} NMR
(101 MHz, DMSO-d₆): δ_C = 168.4, 134.7, 131.7, 128.6, 127.9 ppm; MS (EI): m/z 121 (M⁺,
84%), 105 (100), 77 (83), 51 (25).

ASSOCIATED CONTENT

Supporting Information.

The following files are available free of charge.

Copies of NMR spectra for all isolated compounds.

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The manuscript was written through contributions of all authors. All authors have given approval
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Notes

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