Triflic Anhydride Promoted Synthesis of Primary Amides and their Conversion into Nitriles

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Abstract A facile, two-pot conversion of carboxylic acids into the corresponding nitriles has been developed using triflic anhydride as a promoter and aqueous NH₄OH as a source of nitrogen. The methodology involves synthesis of primary amides from carboxylic acids as the key first step using triflic anhydride and aqueous NH₄OH as a source of nitrogen. Triflic anhydride is also found to be an excellent reagent for conversion of primary amides into nitriles, affording high yields with considerable chemoselectivity and functional group tolerance. In spite of the mild reaction conditions and broad substrate scope for the two-step conversions, all attempts for one-pot domino conversion of acids into nitriles exhibited limited success because of poor yields.

Key words primary amides, nitriles, triflic anhydride, ammonium hydroxide

The nitrile functional group constitutes an important structural motif that is present in many organic molecules be they pharmaceutical agents,¹ natural products,² agrochemicals,² fine chemicals or dyes.²c Around 120 natural products containing the nitrile functionality have been isolated from terrestrial and marine sources.² The presence of a nitrile group can provide chemical and metabolic stability and enhanced solubility and biocompatibility compared with primary amides or carboxylic acids.³

There are 30 approved drugs and 20 more in clinical development that contain a nitrile as a key functional group; for example anastrazole, cimetidine, saxagliptin and other gliptin analogues (Figure 1).¹ Apart from this, the nitrile group serves as a valuable precursor in organic synthesis as it can be transformed into a variety of functional groups such as acids, amides, amines, aldehydes, esters, imidates and amidines.⁴ Given their versatility and reactivity, nitriles are often employed as precursors for heterocycles such as thiophenes and fused thiophenes, furans, pyroles, pyridines, quinolones, pyrans, tetrazoles, and isoxazoles.⁵

Synthetic approaches to nitriles are primarily focused around dehydration of amides. While there are methods that do not include dehydration of amides, such as the Rosenmund–von Braun protocol and a one-pot conversion of alcohols and aldehydes into nitriles,⁶ dehydration of amides is still the most common approach for synthesis of nitriles.⁷ Most of the DPP4 inhibitor drugs such as vildagliptin, sexagliptin and analogues, contain nitrile groups that are synthesized from the corresponding amides.⁷ Thus, a simple conversion of acids into primary amides followed by a dehydration to nitriles using a single reagent, preferably in one-pot, would be of significant value compared to existing methods. Along these lines, there is a report of the use of tosyl amide and PCl₅ at 200 °C for the direct conversion of carboxylic acids into nitriles.⁸ Subse-
quently, direct conversion of acids into nitriles was demonstrated using either silica as catalyst at 500 °C or ethyl polyphosphate at 80 °C, with ammonia gas acting as the source of nitrogen. Other reports for the direct synthesis of nitriles include reaction of carboxylic acids with 2,4-dinitrobenzenesulfonamide/oxalyl chloride, bis(2-methoxyethyl)aminosulfur trioxide, sodium azide/triphenyl phosphine, and diphosphorous tetraiodide/ammonium carbonate. Recently Miyagi et al. reported the one-pot conversion of carboxylic acids into nitriles. This method involves formation of the ester and its transformation into the corresponding aldehyde using SDBBA-H. The aldehyde thus formed is converted into an imine, which is eventually transformed into a nitrile by using iodine as catalyst. However, all these reported methods require harsh conditions such as high temperature, strongly acidic reagents, metal azides, rigorously anhydrous conditions, complex addition sequences and expensive catalysts or reagents, which limit their synthetic applicability. Therefore, it is highly desirable to develop a simple, mild, efficient and economical method for conversion of acids into nitriles.

To support our internal drug discovery efforts, we were keen to develop a mild and robust method for conversion of acids into primary amides and primary amides into nitriles to generate structural diversity for lead generation. The focus was to develop a practically simple yet selective transformation at a late stage of the synthesis of lead molecules. In recent years, triflic anhydride mediated amide bond activation has attracted considerable attention. Chemoselective activation of secondary and tertiary amides using trifluoromethanesulfonyl anhydride (Tf₂O) leads to iminium ion intermediates that can be transformed into a variety of functional groups including aldehydes, ketones and ester imidates. However, use of triflic anhydride for activation of acids for the synthesis of primary amides had not been reported and hence we envisaged the formation of primary amides using Tf₂O and ammonia and their subsequent conversion into nitriles. With this aim, we initially focused our efforts on synthesis of primary amides from the corresponding carboxylic acids using Tf₂O. As a model reaction, we investigated the corresponding activation of secondary and tertiary amides using triflic anhydride (Tf₂O) to obtain iminium ion intermediates that can be transformed into a variety of functional groups including aldehydes, ketones and ester imidates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Base</th>
<th>Ammonia source</th>
<th>Yield of 1a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>Et₃N</td>
<td>NH₄Cl</td>
<td>traces</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>Et₃N</td>
<td>NH₄HCO₃</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Cl₂</td>
<td>Et₃N</td>
<td>(NH₄)₂CO₃</td>
<td>35</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>Et₃N</td>
<td>NH₄SCN</td>
<td>&lt;2</td>
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<td>CH₂Cl₂</td>
<td>Et₃N</td>
<td>aq NH₄OH</td>
<td>60</td>
</tr>
<tr>
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<td>7</td>
<td>CH₂Cl₂</td>
<td>DBU</td>
<td>aq NH₄OH</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>CH₂Cl₂</td>
<td>DBU</td>
<td>aq NH₄OH</td>
<td>30</td>
</tr>
<tr>
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<td>CH₂Cl₂</td>
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<td>58</td>
</tr>
<tr>
<td>10</td>
<td>CH₂Cl₂</td>
<td>–</td>
<td>aq NH₄OH</td>
<td>no reaction</td>
</tr>
<tr>
<td>11</td>
<td>DCE</td>
<td>Et₃N</td>
<td>aq NH₄OH</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>MeCN</td>
<td>Et₃N</td>
<td>aq NH₄OH</td>
<td>&lt;2</td>
</tr>
<tr>
<td>13</td>
<td>CH₂Cl₂  (-10 °C)</td>
<td>Et₃N</td>
<td>aq NH₄OH</td>
<td>65</td>
</tr>
<tr>
<td>14</td>
<td>CH₂Cl₂  (-78 °C)</td>
<td>Et₃N</td>
<td>aq NH₄OH</td>
<td>68</td>
</tr>
</tbody>
</table>

* Reaction conditions: benzoic acid (1 equiv) in anhydrous CH₂Cl₂ at 0 °C, Tf₂O (1.1 equiv), base (2.2 equiv) and ammonia source (2.5 equiv).

1a in 60% isolated yield (entry 5). Focusing on this encouraging observation, we tried to optimize yields by evaluating the impact of different bases other than triethylamine (Et₃N). For this study, different organic bases such as NMM, pyridine, DBU and DABCO were used (entries 6–9) and pyridine was found to give the best yield compared to others (entry 9). Although pyridine and Et₃N (entries 5 and 9) gave comparable yields, reaction with Et₃N showed marginally better conversion with a shorter reaction time of 4 h compared to pyridine, which took 12 h for reaction to be complete. It was observed that the presence of a base is critical for acid into amide conversion, since there was no reaction in the absence of base (entry 10). With this understanding, we further studied the effect of solvent on reaction profile and yield. The reaction using solvents such as dichloroethane or acetonitrile afforded poor yields (entries 11 and 12) compared with dichloromethane. We could not use THF as a solvent as it polymerized when exposed to Tf₂O.

After optimization of reaction conditions, we determined the scope of this reaction using different carboxylic acids and tried to generalize the developed protocol (Scheme 1). It was observed that aromatic acids substituted...
with either electron-donating groups (1b, 1c, 1l and 1n) or electron-withdrawing groups (1d, 1g, i, 1j and 1m) afforded good to excellent yields of the corresponding amides. The reaction also worked well and afforded good yields of primary amides with a range of aliphatic acids (1f, 1k, 1q) including racemic amino acids (1t, 1u, 1v, 1w and 1x). Furthermore, the three common amino group protecting groups (Boc, Cbz and Fmoc) were found to be stable under these reaction conditions. The protocol was also found to be suitable for the synthesis of heteroaromatic (1e, 1p and 1s) and α,β-unsaturated (1o) carboxylic amides, as summarized in Scheme 1. In conclusion, triflic anhydride mediated conversion of acids into primary amides without any preactivation of the carboxyl group (e.g., as an acid chloride or mixed anhydride), demonstrated a broader substrate scope with some level of chemoselectivity. Although yields for acid into amide conversions fall short of being quantitative, the experimental simplicity of the process with mild reaction conditions, no need for pre-activation of the carboxylic acid and use of aqueous ammonium hydroxide as source of nitrogen are notable features of this protocol. There has been only one previous report involving direct conversion of carboxylic acids into primary amides at room temperature using aqueous ammonium hydroxide that employed ethyl chloroformate.16

After these promising results for primary amide synthesis, we attempted a Tf₂O mediated one-pot conversion of carboxylic acids through to nitriles via the primary amides. This was based on the fact that Tf₂O had been previously reported to promote conversion of primary amides into nitriles in the presence of an organic base.17 As a model reaction, benzoic acid was treated with 1.1 equivalents of Tf₂O followed by addition of 2.2 equivalents of Et₃N. The reaction mixture was stirred for 30 minutes and then aqueous ammonium hydroxide was introduced. The progress of the reaction was monitored by TLC and, once a maximum conversion into amide 1a was observed, an additional equivalent of Tf₂O and Et₃N was introduced into the reaction mixture.

**Scheme 1**  Triflic anhydride mediated synthesis of primary amides. Reagents and conditions: acid (1 equiv) in anhydrous CH₂Cl₂ at –10 °C, Tf₂O (1.1 equiv), Et₃N (2.2 equiv) and aqueous ammonium hydroxide (2.5 equiv). Substrates 1t–x were used as their racemic mixture.
This led to formation of benzonitrile, albeit in poor isolated yield of 42%, after a reaction time of 5 hours (Table 2, entry 1). We tried to optimize reaction conditions by evaluating the role of the organic base. The use of pyridine, DIPEA and 2-chloropyridine resulted in sluggish reactions and poor yields of 2a (entries 2–5). 1H NMR and TLC monitoring of the reaction mixture revealed that the additional equivalent of Tf₂O was also promoting hydrolysis of the intermediate primary amide 1a back to the carboxylic acid. Unfortunately, all efforts to avoid this by introducing either molecular sieves or anhydrous sodium sulfate proved futile.

### Table 2 Optimization Study for One-Pot Domino Conversion of Benzoic Acid 1 into Benzonitrile 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base for conversion of 1a into 2a</th>
<th>Ammonia source</th>
<th>Temp (°C)</th>
<th>Yield of 2a (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et₃N</td>
<td>aq NH₄OH</td>
<td>–10</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>2-Cl pyridine</td>
<td>aq NH₄OH</td>
<td>–10</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>2-Cl pyridine</td>
<td>aq NH₄OH</td>
<td>40</td>
<td>–</td>
</tr>
<tr>
<td>4</td>
<td>DIPEA</td>
<td>aq NH₄OH</td>
<td>–10</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>pyridine</td>
<td>aq NH₄OH</td>
<td>–10</td>
<td>12</td>
</tr>
<tr>
<td>6</td>
<td>no base</td>
<td>aq NH₄OH</td>
<td>–10</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>no base</td>
<td>aq NH₄OH</td>
<td>0</td>
<td>43</td>
</tr>
</tbody>
</table>

*Reaction conditions: acid (1 equiv) in anhydrous CH₂Cl₂, Tf₂O (1.1 equiv), Et₃N (2.2 equiv) and ammonium hydroxide (2.5 equiv) with addition of Tf₂O (1.1 equiv) and base after amide 1a formation.

Therefore, we planned to overcome this by removal of the remaining water and solvent under reduced pressure before the addition of fresh Tf₂O to induce amide into nitrile conversion. Thus, after solvent and residual water were removed after amide formation, anhydrous CH₂Cl₂ was introduced into the reaction flask followed by addition of Tf₂O at low temperature to facilitate amide 1a into nitrile 2a conversion. However, no improvement in yield was observed. Interestingly, while an additional equivalent of Tf₂O is necessary for amide into nitrile formation, we observed no need for further base addition after amide formation (Table 2, entries 6 and 7). Attempts to perform the reaction with non-aqueous sources of ammonia such as ammonium carbonate, ammonium bicarbonate, ammonium chloride or ammonium thiocyanate were not fruitful due to slow rates of conversion and poor yields of amide. Various carboxylic acids such as acids substituted with electron-donating or electron-withdrawing groups, aliphatic acids and heteroaromatic acids were selected to screen the one-pot conversion of carboxylic acids into nitriles (Scheme 2). In this survey, the carboxylic acid of interest was dissolved in anhydrous CH₂Cl₂. Triflic anhydride was added to this solution at –10 °C followed by addition of Et₃N as base. The reaction was stirred for 30 minutes, aq. NH₄OH was added and the reaction was monitored for formation of the corresponding amide. After maximum conversion of carboxylic acid into the corresponding amide, another equivalent of Tf₂O was added to facilitate the formation of the nitrile.

Aromatic acids substituted with electron-donating groups afforded good yields of the corresponding nitriles (Scheme 2, products 2b and 2c), but reaction with other substrates afforded poor yields of the product. This disappointing result prompted us to investigate Tf₂O promoted amide into nitrile conversion. As a model substrate (Table 3), treatment of a CH₂Cl₂ solution of 1a with one equivalent of Tf₂O afforded a good yield of nitrile 2a with or without the presence of an organic base (entries 1–3).

We found that triethylamine was not required for this conversion, unlike reported previously.¹⁷ We also explored the possibility of using other anhydride analogues of Tf₂O such as mesyl anhydride (Ms₂O) and trifluoroacetic anhydride (TFAA) (Table 3, entries 4–7). This led to the conclusion that Tf₂O is a unique reagent for promoting amide into nitrile conversion in good yield. Even ethyl chloroformate (CICO₂Et), which has been previously found to be a good reagent to promote acid into primary amide conversion,¹⁶ did not work for amide into nitrile conversion under the given conditions (entries 8 and 9). Furthermore, Tf₂O also demonstrated a wide substrate scope along with high level of chemoselectivity for amide into nitrile conversions, as demonstrated in Scheme 3. Reaction proceeded readily, with aromatic amines having an electron-donating group (Scheme 3; products 2b, 2c, 2i, 2s and 2u) affording ex-
protocols, we performed a synthesis of amide reaction conditions. Boc protecting groups were found to be stable under these conditions including ketones (that the conditions are compatible with a range of functional group tolerance and chemoselectivity of the developed protocol, it was observed can facilitate amide into nitrile conversion with high functional groups. However, it is disappointing to see limited success of this methodology for one-pot domino conversion of acids into nitriles due to poor yields.

Reagents and starting materials were obtained from commercial sources and used as received. The solvents were purified and dried by standard procedures prior to use. All reactions were performed under an inert atmosphere. Flash chromatography was carried out using silica gel (100–200 mesh). Thin-layer chromatography was performed on silica gel plates (Merck) and plates were visualized by staining with KMnO₄. ¹H and ¹³C NMR spectra were recorded either with a Bruker Avance DPX 400 (400 MHz for ¹H and 100 MHz for ¹³C) or Bruker Avance 300 (300 MHz for ¹H and 75 MHz for ¹³C) spectrometer in CDCl₃, DMSO-d₆ or acetone-d₆ using TMS as internal standard. Chemical shifts (δ) for ¹H and ¹³C are given in ppm and coupling constants are given in Hz. The following abbreviations are used to indicate peak multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br. s, broad signal. Mass spectra were recorded with an Advion Mass Express CMS instrument. HRMS spectra were recorded with an Orbitrap Fusion mass spectrometer (Thermo) in positive ion mode through direct infusion by syringe. Evaporation of solvents was performed under reduced pressure with a Büchi rotary evaporator.

General Procedure for Screening of Conditions (Table 1)
To a solution of carboxylic acid (1 mmol) in CH₂Cl₂ (10 mL) at 0 °C was added Tf₂O (1.1 mmol) followed by addition of base (0.31 mL, 2.2 mmol). The reaction mixture was stirred for an additional 30 minutes at the same temperature before the addition of the ammonium source (2.5 mmol). Progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was diluted with CH₂Cl₂ (20 mL) and washed with 1 M aq HCl (10 mL) followed by aq. NaHCO₃ (10 mL) and then brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. If required, further purification was carried out using flash column chromatography, eluting with EtOAc–hexane.

General Procedure for Synthesis of Amides from Carboxylic Acids (Scheme 1)
To a solution of the carboxylic acid (1 mmol) in CH₂Cl₂ (10 mL) at −10 °C was added Tf₂O (0.19 mL, 1.1 mmol) followed by Et₃N (0.31 mL, 2.2 mmol). The reaction mixture was stirred for an additional 30 minutes at the same temperature before the addition of aqueous ammonium hydroxide (2.5 mmol; 28% in water). Progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was diluted with CH₂Cl₂ (20 mL) and washed with 1 M aq HCl (10 mL) followed by aq. NaHCO₃ (10 mL) and then brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to furnish the desired product. If required, further purification was carried out using flash column chromatography, eluting with EtOAc–hexane.

Procedure for Scale-up Synthesis of 1b from Benzonic Acid
To a solution of benzoic acid (1 g, 6.57 mmol) in CH₂Cl₂ (25 mL) at −10 °C was added Tf₂O (1.21 mL, 7.23 mmol) followed by Et₃N (2.03 mL, 14.4 mmol). The reaction mixture was stirred for an additional 30 minutes at the same temperature before the addition of aqueous ammonium hydroxide (2.5 mmol; 28% in water). Progress of the reaction was monitored by TLC. After 4 h, reaction mixture was diluted with CH₂Cl₂ (90 mL) and washed with 1 M aq HCl (20 mL), followed by aq washed with 1 M aq HCl (10 mL), followed by aq. NaHCO₃ (10 mL) and then brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to furnish the desired product. If required, further purification was carried out using flash column chromatography, eluting with EtOAc–hexane.

Table 3  Screening of Reagents for Conversion of Benzamide 1a into Benzonitrile 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Reagent</th>
<th>Base</th>
<th>Temp (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tf₂O</td>
<td>Et₃N</td>
<td>−10</td>
<td>82</td>
</tr>
<tr>
<td>2</td>
<td>Tf₂O</td>
<td>–</td>
<td>−10</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Tf₂O</td>
<td>–</td>
<td>0</td>
<td>85</td>
</tr>
<tr>
<td>4</td>
<td>Ms₂O</td>
<td>–</td>
<td>−10</td>
<td>–</td>
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<td>Ms₂O</td>
<td>Et₃N</td>
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<tr>
<td>9</td>
<td>CICOOEt</td>
<td>Et₃N</td>
<td>−10</td>
<td>–</td>
</tr>
</tbody>
</table>

*Reaction conditions: amide (1 equiv) in anhydrous CH₂Cl₂, reagent (1.1 equiv) and Et₃N (2.2 equiv, if required).
NaHCO₃ (20 mL) and then brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to obtain 1a, which was used further without any purification (730 mg, 74%).

Benzamide (1a)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as a white solid (85 mg, 70%).

\[ \text{H NMR (300 MHz, CDCl₃): } \delta = 7.81 (d, J = 7.2 Hz, 2 H), 7.55–7.41 (m, 3 H), 6.22 \ (\text{br s, 2 H}) \]

The analytical data were found to be consistent with the literature.\(^\text{18}\)

4-Methoxybenzamide (1b)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as a white solid (124 mg, 82%).

\[ \text{H NMR (400 MHz, DMSO-d₆): } \delta = 7.84 (d, J = 8.8 Hz, 3 H), 7.19 (br s, 1 H), 6.98 (d, J = 8.8 Hz, 2 H), 3.75 (s, 3 H) \]

The analytical data were found to be consistent with the literature.\(^\text{18}\)

4-(Dimethylamino)benzamide (1c)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as an off white solid (110 mg, 67%).

\[ \text{H NMR (400 MHz, DMSO-d₆): } \delta = 7.72 (d, J = 8.8 Hz, 2 H), 7.62 (br s, 1 H), 6.91 (br s, 1 H), 6.67 (d, J = 9.2 Hz, 2 H), 2.95 (s, 6 H) \]

\[ \text{185} \]
The analytical data were found to be consistent with the literature.\textsuperscript{19}

4-Nitrobenzamide (1d)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as an off white solid (89 mg, 45%).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta = 7.82 \) (d, \( J = 7.5 \) Hz, 2 H), 7.47 (d, \( J = 7.8 \) Hz, 2 H), 6.24 (br s, 1 H), 5.72 (br s, 1 H), 3.12 (s, 3 H), 2.95 (s, 3 H).

\textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}): \( \delta = 168.7, 170.67 \).

HRMS (APCI): \( m/z [M + H]^+ \) calcd for C\textsubscript{7}H\textsubscript{7}N\textsubscript{2}O\textsubscript{2}: 193.0975; found: 193.0972.

3-Indolylbutyramide (1k)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as an off white solid (117 mg, 71%).

\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): \( \delta = 7.79 \) (d, \( J = 8.0 \) Hz, 2 H), 7.49 (br s, 1 H), 7.45 (d, \( J = 7.2 \) Hz, 2 H), 7.40 (d, \( J = 7.7 \) Hz, 2 H), 6.13 (s, 1 H), 5.90 (s, 1 H), 3.02 (s, 6 H).

The analytical data were found to be consistent with the literature.\textsuperscript{25}

4-Cyanobenzamide (1m)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as an off white solid (115 mg, 78%).

\textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}): \( \delta = 8.21 \) (br s, 1 H), 8.02 (d, \( J = 8.4 \) Hz, 2 H), 7.95 (d, \( J = 8.4 \) Hz, 2 H), 7.68 (br s, 1 H).

The analytical data were found to be consistent with the literature.\textsuperscript{25}

4-Trifluoromethoxy Benzamide (1n)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as a white solid (154 mg, 75%).

\textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): \( \delta = 8.07 \) (1 H, s), 7.99 (d, \( J = 8.8 \) Hz, 2 H), 7.49 (br s, 1 H), 7.45 (d, \( J = 8.0 \) Hz, 2 H).

The analytical data were found to be consistent with the literature.\textsuperscript{26}

Cinnamamide (1o)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as a white solid (89 mg, 60%).

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta = 7.64 \) (d, \( J = 15.9 \) Hz, 1 H), 7.50 (br s, 2 H), 7.36 (br s, 3 H), 6.65 (d, \( J = 15.6 \) Hz, 1 H), 5.74 (br s, 2 H).

The analytical data were found to be consistent with the literature.\textsuperscript{25}

2-Furoamide (1p)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as a white solid (81 mg, 73%).

\textsuperscript{1}H NMR (300 MHz, DMSO-d\textsubscript{6}): \( \delta = 7.79 \) (d, \( J = 7.8 \) Hz, 1 H), 7.76 (br s, 1 H), 7.36 (br s, 1 H), 7.08 (d, \( J = 7.8 \) Hz, 1 H), 6.59 (m, 1 H).

The analytical data were found to be consistent with the literature.\textsuperscript{18}
Cyclohexanecarboxamide (1q)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as a white solid (91 mg, 71%).

\(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta = 5.48 \text{ (br s, 2 H)}, 2.15 \text{ (m, 1 H)}, 1.67–1.91 \text{ (m, 5 H)}, 1.17–1.47 \text{ (m, 5 H)}.\)

The analytical data were found to be consistent with the literature.\(^{27}\)

4-Quinolinecarboxamide (1r)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as a white solid (98 mg, 74%).

\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 10.79 \text{ (s, 1 H)}, 7.61 \text{ (d, } J = 7.8 \text{ Hz, 1 H)}, 7.30–7.36 \text{ (m, 2 H)}, 6.94–7.11 \text{ (m, 4 H)}, 6.66 \text{ (d, } J = 8.1 \text{ Hz, 1 H)}, 4.01–4.12 \text{ (m, 1 H)}, 3.09 \text{ (d, } J = 3.3 \text{ Hz, 1 H)}, 2.92 \text{ (m, 1 H)}, 1.31 \text{ (s, 9 H)}.\)

The analytical data were found to be consistent with the literature.\(^{33}\)

Benzyl (1-Amino-1-oxo-3-phenylpropan-2-yl)carbamate (1t)
The title compound was prepared following the general procedure for synthesis of amides from carboxylic acids. It was isolated as a white solid (192 mg, 72%).

\(^1\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta = 7.29–7.89 \text{ (m, 9 H)}, 6.95 \text{ (s, 1 H)}, 4.20–4.30 \text{ (m, 3 H)}, 3.95 \text{ (m, 1 H)}, 1.48–1.39 \text{ (m, 3 H)}, 0.85 \text{ (m, 6 H)}.\)

MS (APCI+): \(m/z = 353.22 \text{ [M + H]}^+.\)

The analytical data were found to be consistent with the literature.\(^{32}\)

General Procedure for Synthesis of Nitriles from Carboxylic Acids (Scheme 2)
To a solution of carboxylic acid (1 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at –10 °C was added Tf\(_2\)O (0.19 mL, 1.1 mmol) followed by base (2.2 mmol). The reaction mixture was stirred for an additional 30 minutes at the same temperature before the addition of ammonium hydroxide (2.5 mmol). Progress of the reaction was monitored by TLC for amide formation. After 4 h, one more equivalent of triflic anhydride (0.19 mL, 1.1 mmol) was introduced. After 4 h, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (20 mL) and washed with 1 M aq HCl (10 mL), followed by aq NaHCO\(_3\) (10 mL) and then brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the desired product. The product was purified by flash column chromatography eluting with EtOAc–hexane.

Benzonitrile (2a)
To a solution of carboxylic acid (1 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at –10 °C was added Tf\(_2\)O (0.19 mL, 1.1 mmol) followed by Et\(_3\)N (0.31 mL, 2.2 mmol). The reaction mixture was stirred for an additional 30 minutes at the same temperature before the addition of ammonium hydroxide (2.5 mmol). Progress of the reaction was monitored by TLC for amide formation. After 4 h, one more equivalent of triflic anhydride (0.19 mL, 1.1 mmol) was introduced. After 4 h, reaction mixture was diluted with CH\(_2\)Cl\(_2\) (20 mL) and washed with 1 M aq HCl (10 mL), followed by aq NaHCO\(_3\) (10 mL) and then brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography eluting with EtOAc–hexane.
4-Methoxybenzonitrile (2b)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxylic acids. It was isolated as an off white solid (104 mg, 78%).
\[ \text{H NMR (400 MHz, CDCl}_3\text{):} \delta = 7.60 (d, J = 8.8 Hz, 2 H), 6.96 (d, J = 9.24 Hz, 2 H), 3.87 (s, 3 H). \]
The analytical data were found to be consistent with the literature.\(^{38}\)

4-Dimethylamino-benzonitrile (2c)
The title compound was prepared following the general procedure for synthesis of nitrile from carboxylic acid. It was isolated as a yellow solid (114 mg, 78%).
\[ \text{H NMR (300 MHz, CDCl}_3\text{):} \delta = 7.95 (s, 1 H), 7.43 (s, 1 H), 7.30 (s, 1 H). \]
The analytical data were found to be consistent with the literature.\(^{35}\)

4-Nitrobenzonitrile (2d)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxylic acids. It was isolated as an off white solid (92 mg, 30%).
\[ \text{H NMR (300 MHz, CDCl}_3\text{):} \delta = 8.35 (d, J = 8.8 Hz, 2 H), 7.88 (d, J = 8.8 Hz, 2 H). \]
The analytical data were found to be consistent with the literature.\(^{35}\)

Thiophene-3-carbonitrile (2e)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxylic acids. It was isolated as pale-yellow solid (36 mg, 24%).
\[ \text{H NMR (400 MHz, CDCl}_3\text{):} \delta = 7.95 (s, 1 H), 7.43 (s, 1 H), 7.30 (s, 1 H). \]
The analytical data were found to be consistent with the literature.\(^{35}\)

2-Phenylacetonitrile (2f)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxylic acids. It was isolated as colorless oil (22 mg, 18%).
\[ \text{H NMR (300 MHz, CDCl}_3\text{):} \delta = 7.41–7.30 (m, 5 H), 3.76 (s, 2 H). \]
The analytical data were found to be consistent with the literature.\(^{37}\)

4-Acetylbenezonitrile (2g)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxylic acids. It was isolated as an off white solid (41 mg, 28%).
\[ \text{H NMR (300 MHz, CDCl}_3\text{):} \delta = 8.02 (d, J = 8.1 Hz, 2 H), 7.74 (d, J = 8.1 Hz, 2 H), 2.62 (s, 3 H). \]
The analytical data were found to be consistent with the literature.\(^{38}\)

tert-Butyl (4-Cyanophenyl)carbamate (2h)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxylic acids. It was isolated as a yellow solid (48 mg, 22%).
\[ \text{H NMR (300 MHz, CDCl}_3\text{):} \delta = 7.80 (br s, 1 H), 7.57 (d, J = 8.4 Hz, 2 H), 7.47 (d, J = 8.4 Hz, 2 H), 6.75 (br s, 1 H), 5.24 (s, 9 H). \]
The analytical data were found to be consistent with the literature.\(^{39}\)

4-Fluorobenzonitrile (2i)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (22 mg, 18%).
\[ \text{H NMR (300 MHz, CDCl}_3\text{):} \delta = 7.65–7.70 (m, 2 H), 7.15–7.26 (m, 2 H). \]
The analytical data were found to be consistent with the literature.\(^{40}\)

1-Chloroacetyl-2-pyrrolidinecarbonitrile (3)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxylic acids. It was isolated as off white solid (52 mg, 30%).
\[ \text{H NMR (300 MHz, CDCl}_3\text{):} \delta = 4.88–4.76 (m, 1 H), 4.24–4.01 (m, 2 H), 3.72–3.46 (m, 2 H), 2.41–2.02 (m, 4 H). \]
The analytical data were found to be consistent with the literature.\(^{7}\)

General Procedure for Optimization Studies (Table 3)
To a solution of benzamide (1 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at –10 °C was added Tf\(_2\)O (1.1 mmol), followed by Et\(_3\)N (0.31 mL, 2.2 mmol), if stated. Progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (20 mL) and washed with aq NaHCO\(_3\) (10 mL) and then brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give pure product. Pure product was obtained by flash column chromatography, eluting with EtOAc–hexane.

General Procedure for Synthesis of Nitriles 2 from Carboxamide (Scheme 3)
To a solution of carboxamide (1 mmol) in CH\(_2\)Cl\(_2\) (10 mL) at –10 °C was added Tf\(_2\)O (0.19 mL, 1.1 mmol), followed by addition of Et\(_3\)N (0.31 mL, 2.2 mmol), if stated. Progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (20 mL) and washed with aq NaHCO\(_3\) (10 mL) and then brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give the desired product. Pure product was obtained by flash column chromatography, eluting with EtOAc–hexane.

Procedure for Scale-up Synthesis of 2b from Carboxamide (1b)
To a solution of amide 1a (700 mg, 4.63 mmol) in CH\(_2\)Cl\(_2\) (20 mL) at –10 °C was added Tf\(_2\)O (0.86 mL, 5.09 mmol). Progress of the reaction was monitored by TLC. After 4 h, the reaction mixture was diluted with CH\(_2\)Cl\(_2\) (90 mL) and washed with aq NaHCO\(_3\) (20 mL) and then brine (20 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to give pure desired product (480 mg, 78%).
Note: By using this procedure, compounds 2a–i were obtained in excellent yields (Scheme 3) and their spectroscopic data found to be in accordance with previously synthesized compounds as mentioned in Scheme 2.

4-Cyano-N,N-dimethylbenzamide (2j)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as an off white solid (143 mg, 82%).
\[ \text{H NMR (300 MHz, CDCl}_3\text{):} \delta = 7.71 (d, J = 7.2 Hz, 2 H), 7.52 (d, J = 7.5 Hz, 2 H), 3.13 (s, 3 H), 2.96 (s, 3 H). \]
The analytical data were found to be consistent with the literature.\(^{41}\)
(3-Indoly)butanenitrile (2k)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a brown solid (136 mg, 74%).

1H NMR (300 MHz, CDCl3): δ = 8.09 (br s, 1 H), 7.58 (d, J = 8 Hz, 1 H), 7.37 (d, J = 8.0 Hz, 1 H), 7.23–7.04 (m, 3 H), 7.04 (br s, 1 H), 2.95 (t, J = 7.2 Hz, 2 H), 2.34 (t, J = 6.9 Hz, 2 H), 2.06 (m, 2 H).
The analytical data were found to be consistent with the literature.42

3-[(Dimethylamino)benzonitrile (2l)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a brown solid (117 mg, 80%).

1H NMR (300 MHz, CDCl3): δ = 7.19 (br s, 2 H), 6.90–6.83 (m, 3 H), 2.91 (s, 6 H).
The analytical data were found to be consistent with the literature.41

Terephthalonitrile (2m)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (97 mg, 76%).

1H NMR (300 MHz, CDCl3): δ = 7.8 (s, 4 H).
The analytical data were found to be consistent with the literature.44

4-Cyanoacetanilide (2n)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (105 mg, 80%).

1H NMR (300 MHz, CDCl3): δ = 10.37 (br s, 1 H), 7.75 (s, 4 H), 2.08 (s, 3 H).
The analytical data were found to be consistent with the literature.38

(E)-3-Phenylprop-2-enenitrile (2o)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (86 mg, 67%).

1H NMR (400 MHz, CDCl3): δ = 7.43–7.37 (m, 6 H), 5.87 (d, J = 13.5 Hz, 1 H).
The analytical data were found to be consistent with the literature.45

4-Formylbenzonitrile (2p)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a yellow solid (105 mg, 80%).

1H NMR (300 MHz, CDCl3): δ = 10.10 (s, 1 H), 8.01 (d, J = 7.8 Hz, 2 H), 7.85 (d, J = 7.8 Hz, 2 H).
The analytical data were found to be consistent with the literature.35

4-Methylbenzonitrile (2q)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (99 mg, 83%).

1H NMR (300 MHz, CDCl3): δ = 7.57 (d, J = 7.8 Hz, 2 H), 7.28 (d, J = 7.5 Hz, 2 H), 2.44 (s, 3 H).
The analytical data were found to be consistent with the literature.38

4-Aminobenzonitrile (2r)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as an off white solid (97 mg, 82%).

1H NMR (300 MHz, CDCl3): δ = 7.40 (d, J = 7.8 Hz, 2 H), 6.64 (d, J = 8.1 Hz, 2 H), 4.20 (br s, 2 H).
The analytical data were found to be consistent with the literature.38

4-(Bromomethyl)benzonitrile (2s)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (172 mg, 88%).

1H NMR (300 MHz, CDCl3): δ = 7.64 (d, J = 6.6 Hz, 2 H), 7.50 (d, J = 8.1 Hz, 2 H), 4.48 (s, 2 H).
The analytical data were found to be consistent with the literature.45

4-Hydroxybenzonitrile (2t)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (62 mg, 52%).

1H NMR (300 MHz, DMSO-d6): δ = 10.62 (s, 1 H), 7.63 (d, J = 8.1 Hz, 2 H), 6.89 (d, J = 7.8 Hz, 2 H).
The analytical data were found to be consistent with the literature.35

1,3-Benzodioxole-5-carbonitrile (2v)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as an off white solid (95 mg, 84%).

1H NMR (300 MHz, CDCl3): δ = 7.67 (d, J = 7.8 Hz, 2 H), 7.51 (d, J = 8.1 Hz, 2 H), 4.61 (s, 2 H).
The analytical data were found to be consistent with the literature.46

Benzyl (1-Cyano-2-phenylethyl)carbamate (2w)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (215 mg, 76%).

1H NMR (300 MHz, CDCl3): δ = 7.62–7.41 (m, 10 H), 5.38 (d, J = 13.5 Hz, 1 H).
The analytical data were found to be consistent with the literature.45

1,3-Benzodioxole-5-carbonitrile (2v)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (106 mg, 72%).

1H NMR (300 MHz, CDCl3): δ = 7.22 (dd, J = 8.1, 1.7 Hz, 1 H), 7.04 (d, J = 1.5 Hz, 1 H), 6.87 (d, J = 8.1 Hz, 1 H), 6.07 (s, 2 H).
The analytical data were found to be consistent with the literature.47

Benzyl (1-Cyano-2-phenylethyl)carbamate (2w)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (215 mg, 76%).

1H NMR (300 MHz, CDCl3): δ = 7.26–7.41 (m, 10 H), 5.38 (d, J = 7.2 Hz, 1 H), 5.10 (s, 2 H), 4.86 (m, 1 H), 3.13 (d, J = 5.7 Hz, 2 H).
The analytical data were found to be consistent with the literature.48

4-(Hydroxymethyl)benzonitrile (2u)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as an off white solid (95 mg, 84%).

1H NMR (300 MHz, CDCl3): δ = 7.35 (s, 1 H), 7.06 (d, J = 8.1 Hz, 2 H), 6.80 (d, J = 8.1 Hz, 1 H), 6.12 (d, J = 7.8 Hz, 2 H).
The analytical data were found to be consistent with the literature.47

1,3-Benzodioxole-5-carbonitrile (2v)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as an off white solid (106 mg, 72%).

1H NMR (300 MHz, CDCl3): δ = 7.22 (dd, J = 8.1, 1.7 Hz, 1 H), 7.04 (d, J = 1.5 Hz, 1 H), 6.87 (d, J = 8.1 Hz, 1 H), 6.07 (s, 2 H).
The analytical data were found to be consistent with the literature.47

tert-Butyl (1-Cyano-2-phenylethyl)carbamate (2x)
The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (192 mg, 78%).

1H NMR (300 MHz, CDCl3): δ = 7.26–7.36 (m, 5 H), 4.94 (d, J = 8.1 Hz, 1 H), 4.83 (m, 1 H), 3.13 (m, 2 H), 1.43 (s, 9 H).
The analytical data were found to be consistent with the literature.49
The analytical data were found to be consistent with the literature.\(^5\)

**tert-Butyl (1-Cyano-2-(1H-indol-3-yl)ethyl)carbamate (2z)**

The title compound was prepared following the general procedure for synthesis of nitriles from carboxamides. It was isolated as a white solid (204 mg, 71%).

\(^1\)H NMR (300 MHz, acetone-\(d_6\)): \(\delta = 10.31\) (br s, 1 H), 7.68 (d, \(J = 7.8\) Hz, 1 H), 7.43 (d, \(J = 7.9\) Hz, 1 H), 7.34 (s, 1 H), 7.15–7.02 (m, 2 H), 6.92 (br m, 1 H), 4.87 (q, \(J = 8.1\) Hz, 1 H), 3.34 (m, 2 H), 1.39 (s, 9 H).

The analytical data found to be consistent with the literature.\(^5\)

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**Supporting Information**

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**References**


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