Transition metal-free hydration of nitriles to amides mediated by NaOH

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Abstract
A transition metal-free NaOH mediated hydration of organo nitriles to amides under mild reaction conditions has been described. Both aliphatic and aromatic/hetero nitriles were smoothly converted into corresponding amides in moderate to good yields.

Introduction
Amides are an important key intermediate in many organic transformations, as well as they are basic building blocks in biological molecules, agrochemicals, polymers etc.[10] The amide linkage is one of the most important functional group in nature, because they are key connector in peptides and proteins in living organisms.[5] The synthesis of amides were also significant importance in the field of pharmaceutical, medicinal chemistry. Amides are present in around 25% of top-selling in pharmaceuticals industry. Compared to secondary and tertiary amides, the primary amides are important intermediates in organic synthesis and these are raw materials for the synthesis of plastics, detergents and lubricants.[5] Due to the numerous applications of amides,a number of elegant methods have been developed in recent years. Generally, the amide bonds are formed by the condensation of carboxylic acid and esters with amines,[4] or coupling reactions between alcohol/aldehydes with amines[4] and hydroamination of unsaturated hydrocarbons.[4] Apart from these methods, hydration of nitriles is one of the classic transformation as well as simple and straightforward method for the synthesis of variety of amides, in green chemistry point of view, the nitrile hydration methods were also promote as atom efficiency and avoids the generation of environmental waste. Based on these advantages, the hydration of nitriles to amides is a well-established method in the pharmaceutical industry for the synthesis of various amides in large scale production. Recently various groups were reported the hydration of the nitriles to amides using different catalysts such as acids, bases, ionic liquids, and transition metals.[10]

Recently, some green protocols such as, microwave assisted reactions, TBAH catalyst, super basic system DMSO-CsOH, KO’Bu have been recently reported (Scheme 1).[8] In many instances the practicality of the methods have limitations such as harsh reaction conditions, high temperature, strong bases, requirement of precious metal combinations. Therefore, the development of convenient, practical methods for the hydration of nitriles to amides under transition metal-free conditions still holds its relevance.

Results and Discussion
In continuation of our interest on the development of green and sustainable methods for amides,[10] we describe herein hydration of nitriles to the corresponding amides using inexpensive and commercially available NaOH as promoter under metal-free mild conditions.

We initiated our studies with benzonitrile (1a) as a model substrate, using NaOH as a promote at room temperature with isopropyl alcohol (IPA) as solvent, under these conditions the desired product (2a) was obtained in 21% isolated yield after 24 h (Table 1, entry 1).

Based on the initial observation, we raised the reaction temperature (from room temperature) to 55 and 60 °C under the same reaction conditions; the yield of the desired product was significantly increased to 86% and 93% respectively (Table 1, entries 2 & 3). When the amount of base was reduced to 0.5 equivalents, the yield was dropped to 65% (Table 1, entry 4). Under the same conditions, we tested the reaction with other inorganic bases like, K₂CO₃, and Na₂CO₃ no product formation was observed (Table 1, entries 5 & 6). However, lower yield of the product was obtained with LiOH.H₂O and CsOH as base (Table 1, entries 7 & 8). With KOH as a promoter, 85% yield of 2a was obtained.

Scheme 1. Selective hydration of nitriles to amides

Key words: nitriles, base, hydration, amides

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under the same conditions (Table 1, entry 9). Further, keeping with NaOH as promoter, different solvents (EtOH, H₂O, CH₃CN, toluene, DMSO and BuOH) were screened to examine the yield of the product, lower yield to no reaction was observed with these solvents (Table 1, entries 10-15). After screening for various parameters, the optimum conditions identified for the present transformation are as follows: 1.0 equiv. of NaOH as base, and 1.0 mL of IPA at 60 °C, 24 h reaction time.

With the optimized conditions in hand, the substrate scope of the reaction for the hydration of various nitriles were investigated (Table 2). The reactions were found to be very facile with both electron rich and electron deficient groups. In electron donating groups such as -Me, -OMe, -Me (Table 3), the corresponding aliphatic amides are excellent yields. Where as in the case of halogen assisted benzonitriles at the para position such as –F, -Cl, -Br, -I to affords the desired products 2a-2d in good yields (59–63%). Based on experimental observations and literature reports [8d, 9d] an ionic mechanism has been proposed for the present transformation (Scheme 2). Initially, IPA in presence of NaOH forms iso-propoxy anion intermediate, it reacts with nitrile and produces the intermediate 1 which exist as keto - enol form and easily hydrolyzes to form corresponding desired amide.

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| Entry | Base (equiv.) | Solvent | Temp (°C) | Yield (%) |
|-------|--------------|---------|-----------|-----------|
| 1     | NaOH (1.0)   | IPA     | RT        | 21        |
| 2     | NaOH (1.0)   | IPA     | 50        | 86        |
| 3     | NaOH (0.5)   | IPA     | 60        | 65        |
| 4     | K₂CO₃ (1.0)  | IPA     | 60        | 59        |
| 5     | K₂CO₃ (1.0)  | IPA     | N.R. N.R. |           |
| 6     | NaOH (1.0)   | IPA     | 60        | 26        |
| 7     | LiOH. H₂O    | IPA     | 60        | 85        |
| 8     | KOH (1.0)    | IPA     | 60        | 59        |
| 9     | NaOH (1.0)   | EtOH    | 60        | Trace     |
| 10    | NaOH (1.0)   | H₂O     | 60        | Trace     |
| 11    | NaOH (1.0)   | CH₃CN   | 60        | 67        |
| 12    | NaOH (1.0)   | DMSO    | 60        | 59        |
| 13    | NaOH (1.0)   | BuOH    | 60        | 20        |

*Reaction Conditions: amide (2 mmol), base (2 mmol) and solvent (1.0 mL), isolated yields.

| Entry | Base (equiv.) | Solvent | Temp (°C) | Yield (%) |
|-------|--------------|---------|-----------|-----------|
| 1     | NaOH (1.0)   | IPA     | RT        | 21        |
| 2     | NaOH (1.0)   | IPA     | 50        | 86        |
| 3     | NaOH (0.5)   | IPA     | 60        | 65        |
| 4     | K₂CO₃ (1.0)  | IPA     | 60        | 59        |
| 5     | K₂CO₃ (1.0)  | IPA     | N.R. N.R. |           |
| 6     | NaOH (1.0)   | IPA     | 60        | 26        |
| 7     | LiOH. H₂O    | IPA     | 60        | 85        |
| 8     | KOH (1.0)    | IPA     | 60        | 59        |
| 9     | NaOH (1.0)   | EtOH    | 60        | Trace     |
| 10    | NaOH (1.0)   | H₂O     | 60        | Trace     |
| 11    | NaOH (1.0)   | CH₃CN   | 60        | 67        |
| 12    | NaOH (1.0)   | DMSO    | 60        | 59        |

*Reaction Conditions: Nitrile (2 mmol), NaOH (2 mmol) and IPA (1.0 mL), 60 °C, 24 h, isolated yields.

| Entry | Base (equiv.) | Solvent | Temp (°C) | Yield (%) |
|-------|--------------|---------|-----------|-----------|
| 1     | NaOH (1.0)   | IPA     | RT        | 21        |
| 2     | NaOH (1.0)   | IPA     | 50        | 86        |
| 3     | NaOH (0.5)   | IPA     | 60        | 65        |
| 4     | K₂CO₃ (1.0)  | IPA     | 60        | 59        |
| 5     | K₂CO₃ (1.0)  | IPA     | N.R. N.R. |           |
| 6     | NaOH (1.0)   | IPA     | 60        | 26        |
| 7     | LiOH. H₂O    | IPA     | 60        | 85        |
| 8     | KOH (1.0)    | IPA     | 60        | 59        |
| 9     | NaOH (1.0)   | EtOH    | 60        | Trace     |
| 10    | NaOH (1.0)   | H₂O     | 60        | Trace     |
| 11    | NaOH (1.0)   | CH₃CN   | 60        | 67        |
| 12    | NaOH (1.0)   | DMSO    | 60        | 59        |

*Reaction Conditions: Nitrile (2 mmol), NaOH (2 mmol) and IPA (1.0 mL), 60 °C, 24 h, isolated yields.

The reactions were found to be very facile with both electron rich and electron deficient groups. In electron donating groups such as -Me, -OMe, -Ph at para position of benzonitriles (2a-2d) to gives corresponding amides are excellent yields. Where as in the case of halogen assisted benzonitriles at the para position such as –F, -Cl, -Br, -I to affords the desired products 2e-2h were obtained in good to excellent yields (69–97%). The p-tolyl benzonitrile also underwent to the same conditions and provided the desired amide product 2i in 71% yield. Further, in the presence of meta substituted benzonitriles like -OMe, -Me (2j-2k) in this case also reaction underwent smoothly and affords to excellent yields. For halogen substituted either at meta or ortho position of benzonitriles gave the corresponding amides 2l-2p in good to moderate yields (61-73%). And 2-methoxy benzonitriles subjected under standard conditions to affords corresponding amide 2q is 89%. The hydration of α-cyano naphthalene under the present conditions afford the naphthalamide 2r in 69% yield. To validate the present protocol, the product 2a was obtained at gram scale in 92% yield using 10.0 mmol (1.03 g) of 1a.

We then evaluated the hydration of heteroaromatic and aliphatic nitriles under the above optimized conditions (Table 3). Particularly, the heteroaromatic amides are the key intermediates in the preparation of 2-pyridyl urea derivatives which are potent inhibitors of gastric acid secretion. [12] Such amides have been prepared through oxidative coupling of corresponding aldehydes and terminal alkynes using Cu(OTf)₂/I₂ system. [13] Notably, heteroaromatic amides such as thiophene-
In conclusion, we have developed an efficient protocol for the hydration of various benzonitriles to corresponding benzamides using inexpensive and commercially available base (NaOH) under very mild conditions (60°C). The conditions also applicable to heteroaromatic nitriles and aliphatic nitriles and afford the good to excellent yields. The present method represents a significant development for the hydration of nitriles under transition metal-free conditions.

Experimental Section

General information

All commercially available chemicals and reagents were used without any further purification unless otherwise indicated. 1H and 13C NMR spectra were recorded at 500, 600 and 125, 150 MHz, respectively. The spectra were recorded in CDCl₃ and DMSO-d₆ as a solvent. Multiplicity was indicated as follows: s (singlet); d (doublet); t (triplet); m (multiplet); dd (doublet of doublets), etc. Coupling constants (J) were given in Hz. Chemical shifts are reported in δ relative to TMS as an internal standard. The peaks around δ values of 7.26 (1H NMR), 77.0 (13C NMR) correspond to CDCl₃. The peaks around δ values of 2.50 (1H NMR), 39.9 (13C NMR) are corresponding to DMSO. The peak around δ values of 3.35 (1H NMR) is corresponding to the H₂O present in DMSO solvent. Progress of the reactions was monitored by thin layer chromatography (TLC). Silica gel 100-200 mesh size was used for column chromatography using a hexane/ethyl acetate eluent unless otherwise indicated.

General experimental procedure for the synthesis of benzamide from benzonitrile (3a)

A 20 mL round bottomed flask was charged with benzonitrile (2 mmol), sodium hydroxide (2 mmol) dissolved in isopropyl alcohol (1.0 mL). Then the reaction mixture was placed at indicated temperature and time, and the progress of the reaction was monitored by TLC. After completion of the reaction, the crude mixture was dissolved with dichloromethane and filtered the mixture and evaporated to dryness. The residue was then purified by column chromatography (hexane/ EtOAc) to get the pure product. All amide products were characterized by NMR.

Characterization data

Benzamide (2a)

(Eluent: 40% EtOAc/hexane); 93% yield (225.1 mg); white solid; 1H NMR (500 MHz, CDCl₃) δ 7.82 (s, 1H), 7.81 (d, J = 2.0 Hz, 1H), 7.53 (t, J = 6.5 Hz, 1H), 7.44 (t, J = 7.0 Hz, 2H), 6.17 (br, NH, 2H). 13C NMR (125 MHz, CDCl₃) δ 169.5, 133.3, 131.9, 128.5, 127.3.

4-Methylbenzamide (2b)

(Eluent: 40% EtOAc/hexane); 86% yield (232.2 mg); white solid; 1H NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.10 (br, NH, 2H). 13C NMR (125 MHz, CDCl₃) δ 169.5, 142.5, 130.5, 129.2, 127.3.

4-Methoxybenzamide (2c)

(Eluent: 30% EtOAc/hexane); 92% yield (278 mg); white solid; 1H NMR (600 MHz, CDCl₃) δ 7.79 (d, J = 7.0 Hz, 2H), 6.94 (d, J = 7.5 Hz, 2H), 5.99 (br, NH, 2H), 3.86 (s, 3H). 13C NMR (150 MHz, DMSO-d₆) δ 167.9, 162.0, 129.8, 127.0, 113.8, 55.8.

3-Methoxybenzamide (2d)

(Eluent: 35% EtOAc/hexane); 89% yield (270.1 mg); white solid; 1H NMR (600 MHz, CDCl₃) δ 7.40 (s, 1H), 7.35 (m, 2H), 7.08 (d, J = 7.5 Hz, 1H), 6.10 (br, NH, 2H), 3.85 (s, 3H). 13C NMR (150 MHz, CDCl₃) δ 169.2, 159.9, 134.8, 129.7, 119.2, 118.3, 112.6, 55.5.

3-Methylbenzamide (2e)

(Eluent: 40% EtOAc/hexane); 82% yield (221.5 mg); white solid; 1H NMR (500 MHz, CDCl₃) δ 7.65 (s, 1H), 7.59 (d, J = 5.5 Hz, 1H), 7.30 (t, J = 6.0 Hz, 2H), 6.49 (br, NH, 2H), 2.37 (s, 3H). 13C NMR (150 MHz, CDCl₃) δ 170.1, 138.4, 133.4, 132.6, 128.4, 128.1, 124.3, 21.3.

2-Methoxybenzamide (2f)

(Eluent: 40% EtOAc/hexane); 86% yield (232.2 mg); white solid; 1H NMR (500 MHz, CDCl₃) δ 7.72 (d, J = 8.0 Hz, 2H), 7.25 (d, J = 8.0 Hz, 2H), 6.10 (br, NH, 2H). 13C NMR (125 MHz, CDCl₃) δ 169.5, 142.5, 130.5, 129.2, 127.3, 21.4.

4-Methoxybenzamide (2c)

(Eluent: 30% EtOAc/hexane); 92% yield (278 mg); white solid; 1H NMR (600 MHz, CDCl₃) δ 7.79 (d, J = 7.0 Hz, 2H), 6.94 (d, J = 7.5 Hz, 2H), 5.99 (br, NH, 2H), 3.86 (s, 3H). 13C NMR (150 MHz, DMSO-d₆) δ 167.9, 162.0, 129.8, 127.0, 113.8, 55.8.

3-Methoxybenzamide (2d)

(Eluent: 35% EtOAc/hexane); 89% yield (270.1 mg); white solid; 1H NMR (600 MHz, CDCl₃) δ 7.40 (s, 1H), 7.35 (m, 2H), 7.08 (d, J = 7.5 Hz, 1H), 6.10 (br, NH, 2H), 3.85 (s, 3H). 13C NMR (150 MHz, CDCl₃) δ 169.2, 159.9, 134.8, 129.7, 119.2, 118.3, 112.6, 55.5.

3-Methylbenzamide (2e)

(Eluent: 40% EtOAc/hexane); 82% yield (221.5 mg); white solid; 1H NMR (500 MHz, CDCl₃) δ 7.65 (s, 1H), 7.59 (d, J = 5.5 Hz, 1H), 7.30 (t, J = 6.0 Hz, 2H), 6.49 (br, NH, 2H), 2.37 (s, 3H). 13C NMR (150 MHz, CDCl₃) δ 170.1, 138.4, 133.4, 132.6, 128.4, 128.1, 124.3, 21.3.

2-Methoxybenzamide (2f)
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Eluent: 30% EtOAc/hexane; 84% yield (255.1 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.22, 7.49 (m, 1H), 7.08 (t, J = 6.0 Hz, 1H), 7.00 (d, J = 6.5 Hz, 1H), 6.06 (br, NH, 2H), 3.97 (s, 3H). 13C NMR (150 MHz, CDCl3) δ 167.1, 157.8, 133.4, 132.6, 121.3, 120.8, 111.4, 56.0.

4'-Methyl-[1, 1'-biphenyl]-4-carboxamide (2g)

Eluent: 40% EtOAc/hexane; 71% yield (301.6 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.86, 7.64 (d, J = 7.0 Hz, 2H), 7.50 (d, J = 6.5 Hz, 2H), 6.08 (br, NH, 2H), 2.39 (s, 3H). 13C NMR (150 MHz, DMSO-d6) δ 168.0, 143.1, 137.9, 136.8, 133.3, 130.1, 128.6, 127.2, 126.6, 21.2.

4-Fluorobenzamide (2h)

Eluent: 40% EtOAc/hexane; 69% yield (193.1 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.83, 7.12 (t, J = 9.0 Hz, 2H), 6.06 (br, NH, 2H). 13C NMR (125 MHz, CDCl3) δ 168.3, 166.0, 164.0, 129.8 (d, J = 8.75 Hz), 129.7, 115.8 (d, J = 0.17 Hz), 115.6.

3-Fluorobenzamide (2i)

Eluent: 35% EtOAc/hexane; 78% yield (235.3 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.80 (s, 1H), 7.67 (d, J = 6.5 Hz, 1H), 7.50 (d, J = 7.0 Hz, 1H), 7.38 (t, J = 6.0Hz, 1H), 6.09 (br, NH, 2H). 13C NMR (150 MHz, CDCl3) δ 167.9, 135.0, 134.8, 132.0, 129.9, 127.7, 125.3.

4-Bromobenzamide (2j)

Eluent: 40% EtOAc/hexane; 84% yield (218.2 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.85, 7.67 (d, J = 6.5 Hz, 1H), 7.50 (d, J = 7.0 Hz, 1H), 7.38 (t, J = 6.0 Hz, 1H), 6.09 (br, NH, 2H). 13C NMR (150 MHz, CDCl3) δ 167.9, 135.0, 134.8, 132.0, 129.9, 127.7, 125.3.

3-Bromobenzamide (2k)

Eluent: 30% EtOAc/hexane; 87% yield (235.3 mg); white solid; 1H NMR (500 MHz, CDCl3): δ 7.80, 7.67 (d, J = 6.5 Hz, 1H), 7.50 (d, J = 7.0 Hz, 1H), 7.38 (t, J = 6.0 Hz, 1H), 6.09 (br, NH, 2H). 13C NMR (150 MHz, CDCl3) δ 167.9, 135.0, 134.8, 132.0, 129.9, 127.7, 125.3.

4-Chlorobenzamide (2l)

Eluent: 30% EtOAc/hexane; 97% yield (271.3 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.70 (d, J = 6.5 Hz, 1H), 7.50 (d, J = 7.0 Hz, 1H), 6.08 (br, NH, 2H). 13C NMR (150 MHz, CDCl3) δ 167.9, 135.0, 134.8, 132.0, 129.9, 127.7, 119.2.

4-Fluorobenzamide (2m)

Eluent: 40% EtOAc/hexane; 90% yield (358.0 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.62, 7.38 (d, J = 6.5 Hz, 2H), 6.11 (br, NH, 2H). 13C NMR (150 MHz, CDCl3) δ 168.2, 132.1, 131.9, 128.9, 126.8.
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(Eluent: 40% EtOAc/hexane); 95% yield (469.6 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.82 (d, J = 7.5 Hz, 2H), 7.54 (d, J = 7.5 Hz, 2H), 6.02 (br, NH, 2H). 13C NMR (150 MHz, DMSO-d6) δ 167.7, 137.6, 132.0, 129.9, 118.5, 99.4.

[1, 1’-Biphenyl]-4-carboxamide (2q)

(Eluent: 40% EtOAc/hexane); 77% yield (304.9 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.90 (d, J = 7.0 Hz, 2H), 7.67 (d, J = 7.0 Hz, 2H), 7.61 (d, J = 6.5 Hz, 2H), 7.47 (t, J = 6.5 Hz, 2H), 7.40 (t, J = 6.0 Hz, 1H), 6.11 (br, NH, 2H). 13C NMR (150 MHz, DMSO-d6) δ 168.0, 143.2, 139.7, 133.6, 129.5, 128.6, 128.5, 127.4, 126.9.

1-Naphthamide (2r)

(Eluent: 40% EtOAc/hexane); 69% yield (235.9 mg); white solid; 1H NMR (500 MHz, CDCl3): δ 8.44 (d, J = 7.0 Hz, 1H), 7.95 (d, J = 6.5 Hz, 1H), 7.72 (t, J = 6.5 Hz, 1H), 7.47 (t, J = 6.5 Hz, 1H), 7.40 (t, J = 6.0 Hz, 1H), 6.12 (br, NH, 2H). 13C NMR (125 MHz, CDCl3) δ 171.5, 133.7, 133.0, 131.2, 130.0, 128.3, 127.3, 126.5, 125.4, 124.6.

Thiophene-2-carboxamide (3a)

(Eluent: 30% EtOAc/hexane); 89% yield (226.8 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.54 (t, J = 5.0 Hz, 2H), 7.10 (t, J = 3.5 Hz, 1H), 5.80 (br, NH, 2H). 13C NMR (150 MHz, CDCl3) δ 163.3, 137.6, 131.0, 129.3, 127.8.

Thiophene-3-carboxamide (3b)

(Eluent: 30% EtOAc/hexane); 87% yield (221.0 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 7.91 (s, 1H), 7.40 (d, J = 4.0 Hz, 1H), 7.36(t, J = 4.0 Hz, 1H), 5.84 (br, NH, 2H). 13C NMR (150 MHz, CDCl3) δ 164.5, 136.4, 129.3, 126.7, 126.3.

Picolinamide (3c)

(Eluent: 45% EtOAc/hexane); 60% yield (146.3 mg); white solid; 1H NMR (500 MHz, CDCl3): δ 8.58 (d, J = 4.5 Hz, 1H), 8.20 (d, J = 7.5 Hz, 1H), 7.86 (m, 1H), 7.45 (m, 1H), 6.10 (br, NH, 2H). 13C NMR (125 MHz, CDCl3) δ 166.9, 149.5, 148.3, 137.2, 126.4, 122.4.

Nicotinamide (3d)

(Eluent: 45% EtOAc/hexane); 51% yield (124.2 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 9.03 (s, 1H), 8.76 (d, J = 3.5 Hz, 1H), 8.17 (d, J = 6.5 Hz, 1H), 7.42 (t, J = 4.5 Hz, 1H), 6.28 (br, NH, 2H). 13C NMR (150 MHz, CDCl3) δ 167.3, 152.7, 148.2, 135.5, 129.1, 123.6.

Isonicotinamide (3e)

(Eluent: 50% EtOAc/hexane); 68% yield (158.4 mg); white solid; 1H NMR (600 MHz, CDCl3): δ 9.43 (s, 1H), 8.78 (d, J = 2.5 Hz, 1H), 8.56 (d, J = 1.5 Hz, 1H), 5.98 (br, NH, 2H). 13C NMR (125 MHz, CDCl3) δ 165.3, 147.5, 144.1, 142.7.

Pyrazine-2-carboxamide (3f)

(Eluent: 70% EtOAc/hexane); 57% yield (270.1 mg); white solid; 1H NMR (600 MHz, DMSO-d6): δ 8.56 (d, J = 4.5 Hz, 1H), 8.52 (s, 1H), 8.04 (t, J = 5.5 Hz, 3H), 7.97 (d, J = 5.5 Hz, 2H), 7.63 (d, J = 7.0 Hz, 1H), 7.38 (s, 1H), 7.31 (t, J = 5.0 Hz, 1H), 6.95 (s, 1H). 13C NMR (150 MHz, CDCl3) δ 168.1, 145.2, 143.5, 136.7, 133.8, 128.5, 127.6, 126.2, 125.7, 117.0, 113.2, 110.7.

Acetamide (3h)
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(Eluent: 40% EtOAc/hexane); 58% yield (68.9 mg); white solid; 1H NMR (600 MHz, CDCl3): 5.82 (br, NH, 2H), 1.98 (s, 3H), 13C NMR (125 MHz, CDCl3) δ 172.9, 22.7.

Pentanamide (3i)

\[ \text{NH}_2 \]

(Eluent: 40% EtOAc/hexane); 59% yield (119.4 mg); white solid; 1H NMR (600 MHz, DMSO-d6): δ 7.23 (br, NH, 2H), 2.02 (t, J = 6.5 Hz, 2H), 1.45 (t, J = 6.0 Hz, 2H), 1.26 (q, J = 6.0 Hz), 0.86 (t, J = 5.5 Hz, 3H), 13C NMR (150 MHz, DMSO-d6) δ 174.9, 27.7, 22.3, 14.2.

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