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Thioacids Mediated Selective and Mild N-Acylation of Amines

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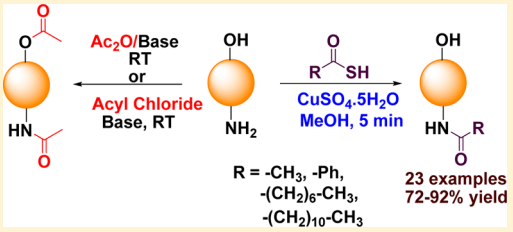
Supporting Information

ABSTRACT: N-Acylated amines are ubiquitous in nature. Selective N-acylation at neutral conditions remains a key area of interest. Here we are reporting the copper sulfate-mediated highly selective, mild, and rapid N-acylation of various aliphatic and aromatic amines using thioacids in methanol at neutral conditions. All N-acylated products of primary and secondary amines were isolated in good to excellent yields. This method is found to be highly selective for the amines and not sensitive to other functional groups such as phenols, alcohols, and thiols. The simple workup, high yields, and high selectivity of this reaction can be an attractive alternative to those of the existing acyl halide- and acid anhydride-mediated N-acylation reactions.



INTRODUCTION

Acylation of amines is a fundamental and the most widely used reaction in organic chemistry.[1,2] In addition, N-acetylation is an important reaction in biology as well as in the pharmaceutical and agricultural industries.[3−6] Typically, acetic anhydride or acetyl chloride in the presence of either basic media or acid catalysts has been used for the N-acetylation reactions.[7−15] In contrast to the organic synthesis, nature selectively uses the N-acylation strategy without affecting the other functional groups such as alcohols, phenols, imidazoles, thiols, etc., in proteins and other biomolecules.[16] In addition, various N-acylated products with alkyl and aryl groups have been found in many biologically active natural products. Acyl chloride- and acid anhydride-mediated N-acylation reactions have been associated with many inherited problems.[17] In addition, many acid chlorides and anhydrides react rapidly with water and alcohols leading to the corresponding acids and esters, respectively. The selective acylation of amines in the presence of other functional groups is rather a difficult process. To circumvent the inherent problems associated with N-acetylation reactions mediated by acetic anhydride and acid chlorides, numerous strategies, including the direct and metal-mediated condensation of unactivated carboxylic acids and amines,[18−20] acylation through *N*-acyl DBN tetraphenyl borate salts,[21] mercury- and ruthenium-catalyzed Beckman rearrangements,[22,23] copper-catalyzed oxidative amidation of benzaldehyde,[24,25] triazole- and imidazole-mediated acyl transfer reactions,[26−28] and acylation through acylbenzotriazoles,[29−31] have been developed. However, most of these reactions require either elevated temperatures or activated carboxylic acids as starting materials. In addition, many of these reactions are not specific to the N-acylation of amines.

In contrast to the carboxylic acids, thioacids have recently gained momentum due to their unique reactivity and selectivity in the amide bond formations.[32−34] Williams et al. reported amide bond formation using thioacids and organic azides.[35] Danishefsky and colleagues effectively demonstrated the reactivity of N-protected amino thioacids in the peptide synthesis as well as in the native chemical ligation.[36] Further, Crich et al. reported the in situ activation of thioacids with dinitrofluorobenzene followed by the peptide bond formation.[37] The reactivity of thioacids with various coupling partners such as isocyanates, thioisocyanate, sulfonamides, and nitroso derivatives has also been explored in the peptide synthesis.[38−40] In addition, Orgel and colleagues demonstrated the thioacetic acid-mediated N-acetylation of α-amino acids in the presence of oxidizing agents.[41] Recently, we reported the copper sulfate-mediated ultrafast peptide synthesis using N-protected thioacids in methanol.[42] In addition, Garner and colleagues reported the copper acetate-mediated peptide synthesis using N-protected amino thioacids as well as peptide thioacids.[43,44] The limitation in the thioacid-mediated peptide coupling reactions is the synthesis of N-protected amino thioacids from the corresponding activated carboxylic acids of N-protected amino acids. Because the activated carboxylic acids of N-protected amino acids can also serve as acylating agents, it requires an additional step in the thioacid-mediated peptide synthesis. However, encouraged by the metal-mediated rapid peptide synthesis in methanol, we sought to investigate whether the N-acetylation can be performed using the commercially available thioacetic acid in methanol solvent. Herein, we are reporting the copper sulfate-mediated rapid and highly selective N-acylation of amines using thioacids in methanol at room temperature. Studies with a wide range of aliphatic and aromatic amines containing various other functional groups such as phenols, thiols, carboxylic acids, and alcohols suggest that the reactions are highly selective for the amines, and the other functional groups are unaffected during the reaction.

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RESULTS AND DISCUSSION

We began our investigation of N-acetylation with aniline and thioacetic acid in the presence of 30 mol % copper sulfate in methanol. The schematic representation of the copper sulfate-mediated N-acetylation is shown in Scheme 1. The choice of methanol as a solvent in the acylation reactions was mainly due to the high solubility of copper sulfate and the reactants in methanol. Previous studies with N-protected amino thioacids suggested that 30 mol % copper sulfate is sufficient to mediate the fast peptide coupling reactions because its insoluble byproduct CuS also mediates the coupling reactions.[42] In a typical reaction, aniline and thioacetic acid in a 1:1 ratio were dissolved in methanol and the solution was treated with 30 mol % (equivalent to the reacting partners) $CuSO_4 \cdot 5H_2O$. Immediately, the CuS precipitated out as a black material. Completion of the reaction was confirmed by TLC. The reaction mixture was stirred for another 2−3 min and centrifuged to separate the insoluble CuS. A simple aqueous workup of the crude product dissolved in ethyl acetate after the evaporation of the methanol gave a pure sample of *N*-phenylacetamide in 83% yield (Table 1, entry 1). No N-acetylated product of aniline was observed in a control reaction without copper sulfate even after the reaction mixture had been stirred for up to 5 h. The successful strategy of N-acetylation of aniline was then applied to the other aromatic amines, and the results are summarized in Table 1. In order to understand the selectivity and the reactivity of this protocol, we subjected *p*-aminophenol (Table 1, entry 2) to N-acetylation. The reaction proceeded with the same rate as that of aniline. Instructively, analysis of the product suggests the formation of only N-acetylated product, and no O-acylation product was observed in the reaction mixture even after it had been stirred for about 24 h. Selective and rapid N-acetylation of *p*-aminophenol in methanol is also of significant interest for the preparation of antipyretic drug *p*-paracetamol. In contrast, both N- and O-acylation products were isolated in the analogous acetylation reaction of *p*-aminophenol (4-acetamidophenyl acetate, **2a**) using acetic anhydride and pyridine. In order to understand whether or not the amino group can undergo specific N-acetylation in the presence of free thiol (−SH), we subjected *o*-amino thiophenol (Table 1, entry 3) to the acetylation reaction. In contrast to the intramolecular cyclized heterocyclic product, the 2-methyl benzothiazole obtained in the acetic anhydride-mediated acetylation,[45] we isolated the S−S disulfide dimer of *N*-acetyl-*o*-thiophenol in 84% yield, and no other products were observed in the reaction. The mass spectral experiments confirm that the starting thiophenol was a monomer and the oxidative disulfide formation occurred in the process of N-acetylation. We further subjected aromatic amines containing mono- and dicarboxylic acids (Table 1, entries 4 and 5) to investigate whether the free carboxylic acids can play any role in the N-acetylation. Resultant N-acetylation products were isolated in very good yields and confirmed that free carboxylic acids have not played any role in the reaction. Further, to understand the role of electron-withdrawing groups in the reaction, we subjected *m*- and *p*-cyanoanilines (Table 1, entries 6 and 7), *p*-nitro aniline (Table 1, entry 8), and *m*-aminotrifluorotoluene (Table 1, entry 9) to N-acetylation. Except for the *p*-nitroaniline, all other N-acetylated products were isolated in moderate to excellent yields. In comparison with the standard N-acetylation reaction of *p*-nitroanilne with acetic anhydride in pyridine,[46] we obtained almost 9% lower yields, which suggests that strong electron-withdrawing groups may decrease yields in this protocol (Table 1, entry 8).

Further, a similar strategy was adopted for the N-acetylation of aliphatic primary and secondary amines, and their N-acetylated products are summarized in Table 2. Results of N-acetylation of aliphatic amines (Table 2, entries 11 and 12), amino acid (Table 2, entry 13), amino alcohol (Table 2, entry

Scheme 1. Copper Sulfate-Mediated Selective and Rapid N-Acetylation of Amines Using Thioacetic Acid in Methanol

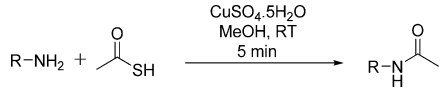
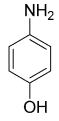
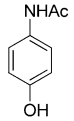
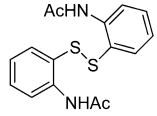
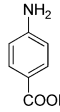
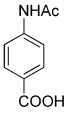
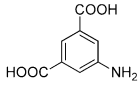
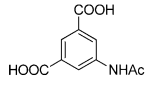
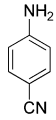
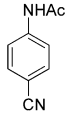
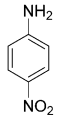
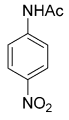
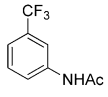
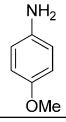
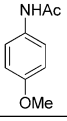


Table 1. Thioacetic Acid-Mediated N-Acetylated Aromatic Amines[a]

Entry	R-NH$_2$	Product	Yield (%)
1			83
2			75
3			84
4			79
5			82
6			76
7			73
8			56
9			88
10			85

[a]Reaction conditions: Thioacetic acid (1 equiv) and aromatic amine (1 equiv) were dissolved in methanol, and the solution was treated with 30 mol % (equivalent to the thioacetic acid or amine) copper sulfate. After completion of the reaction (≈5 min), insoluble CuS was separated through centrifugation, and the solvent was evaporated under reduced pressure to give N-acetylated amine.

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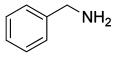
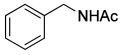
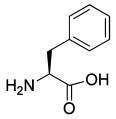
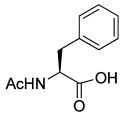
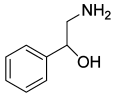
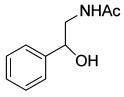
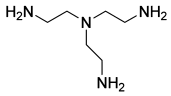
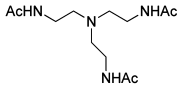
Table 2. N-Acetylation of Aliphatic Amine Using Thioacetic Acid[a]

Entry	R-NH_2	Product	Yield (%)
11			81
12			76
13			90
14			81
15			84

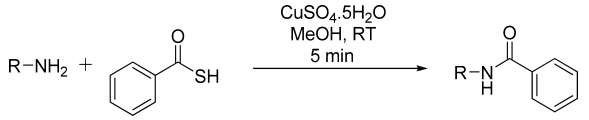
[a]Reaction conditions: Thioacetic acid (1 equiv) and aliphatic amine (1 equiv) were dissolved in methanol, and the solution was treated with 30 mol % (equivalent to the thioacetic acid or amine) copper sulfate. After completion of the reaction (≈5 min), insoluble CuS was separated through centrifugation, and the solvent was evaporated under reduced pressure to give N-acetylated amine.

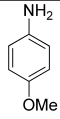
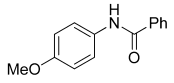
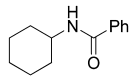
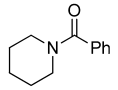
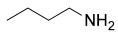
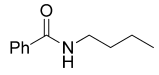
14), and trisamine (Table 2, entry 15) suggest that the reaction was specific to primary and secondary amines, and all N-acetylated products of aliphatic amines were isolated in good to excellent yields.

Similar to the N-acetylation, N-benzoylation is also a very important reaction in the protection of amino groups in organic synthesis. Typically, N-benzoylation is performed under Schotten–Baumann conditions using benzoyl chloride in the presence of a base.[7] The intriguing results of N-acetylation from thioacetic acid encouraged us to carry out N-benzoylation under similar reaction conditions. In order to perform the N-benzoylation, pure thiobenzoic acid was subjected to the N-benzoylation with amines in the presence of 30 mol % $CuSO_4{\cdot}5H_2O$ in methanol. The list of amines and resultant N-benzoylated products is given in Table 3. Except for the secondary amine (Table 3, entry 18), all the other aromatic and aliphatic amines (Table 3, entry 16, 17, and 19) gave excellent yields of N-benzoylated products. All N-benzoylation reactions proceeded smoothly and were completed within 5 min.

We then investigated the utility of this protocol for the synthesis of biologically important N-acylation of fatty acids. *N*-Acyl fatty acids play a significant role in the antimicrobial activities of lipopeptides.[47,48] We randomly selected octanoic and dodecanoic acids for the N-acylation reactions with aliphatic and aromatic amines. Thiooctanoic and thiododecanoic acids were synthesized from the corresponding fatty acid *N*-hydroxysuccinimide esters and NaSH.[42] N-Acylation of thiofatty acids with various amines also proceeded with complete conversion within 5 min, similar to that of thioacetic acid. Results are listed in Table 4. As a proof of concept, we used both aromatic (Table 4, entries 21 and 22) and aliphatic amines (Table 4, entries 20 and 23) for the N-acylation with thiofatty acids. All four N-acylated products were isolated in good to excellent yields (78–92%).

Table 3. N-Benzoylation of Amine Using Thiobenzoic Acid in Methanol[a]



Entry	Amine	Product	Yield (%)
16			82
17			88
18			72
19			89

[a]Reaction conditions: Thiobenzoic acid (1 equiv) and amine (1 equiv) were dissolved in methanol, and the solution was treated with 30 mol % (equivalent to the thioacetic acid or amine) copper sulfate. After completion of the reaction (≈5 min), insoluble CuS was separated through centrifugation, and the solvent was evaporated under reduced pressure to give N-benzoylated amine.

■ CONCLUSION

In conclusion, we have developed a mild, fast, efficient, and highly selective method for the N-acylation of amines using thioacids in methanol at room temperature. The reactions were mediated by 30 mol % copper sulfate. Compatibility of the reaction was studied with a wide range of aliphatic and aromatic amines containing various other functional groups. All N-acylation products were isolated in moderate to high yields. This method was found to be highly selective to amines, and other functional groups such as phenols, alcohols, and thiols were unaffected in the reaction. The simple workup, mild reaction conditions, high yields, and high selectivity of this reaction may serve as an attractive alternative to those of the existing methods.

■ EXPERIMENTAL SECTION

General Methods. Thioacetic acid, thiobenzoic acid, octanoic acid, dodecanoic acid, acetic anhydride, N-hydroxysuccinimide, and all aromatic and aliphatic amines were used as commercially available. Column chromatography was performed on silica gel (100–200 mesh). ^1H and ^{13}C NMR spectra were recorded on a 400 MHz instrument (100 MHz for ^{13}C) using the residual solvent signals as an internal reference. The chemical shifts (δ) were reported in parts per million and coupling constants (J) were given in hertz. IR spectra were recorded on an FT-IR spectrophotometer using KBr pellets. High resolution mass spectra were obtained from an ESI-TOF MS spectrometer.

General Procedure for N-Acylation of Amines Using Thioacid and Copper Sulfate. Thioacid (3 mmol) and free amine (3 mmol) were dissolved in distilled methanol (5 mL) either in a Falcon tube or in an RB flask. The reaction mixture was then treated with 30 mol % $CuSO_4{\cdot}5H_2O$. After 5 min, the clear reaction mixture had turned into a dark brown turbid solution, indicating the completion of the reaction (also by TLC). The reaction mixture was

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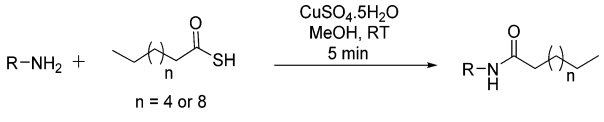
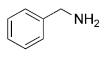
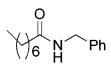
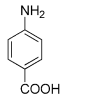
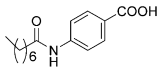
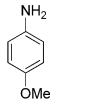
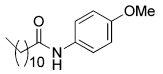
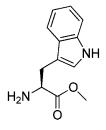
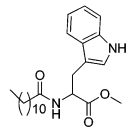
Table 4. N-Acylations of Amine Using Thiofatty Acids in Methanol[a]



Entry	Amine	Thioacid	Product	Yield (%)
20				92
21				89
22				78
23				83

[a]Reaction conditions: Thiofatty acid (1 equiv) and amine (1 equiv) were dissolved in methanol, and the solution was treated with 30 mol % (equivalent to the thiofatty acid or amine) copper sulfate. After completion of the reaction (≈5 min), insoluble CuS was separated through centrifugation, and the solvent was evaporated under reduced pressure to give N-acylated amine.

then centrifuged, and the residue was further washed with methanol. The combined methanol solution was evaporated under reduced pressure. The residue was then dissolved in ethyl acetate (75 mL) and washed with 10% aq Na_2CO_3, 5% aq HCl, and brine and dried over anhydrous Na_2SO_4. The organic layer was concentrated under reduced pressure to get the *N*-acyl derivatives of amines. The pure N-acylated amines were obtained after the column purification using EtOAc and petroleum ether.

*N-Phenylacetamide (**1**)*[21]*:* white powder (0.336 g, 83%); mp = 112−115 °C; UV (λ_{max}) = 241 nm; IR ν (cm^{-1}) 3293, 1661, 1603, 1550, 1493, 1468, 1435, 1319, 1260, 755, 696; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.70 (br, 1H), 7.5 (d, 2H, J = 8.2 Hz), 7.31 (t, 2H, J = 7.3 Hz), 7.11 (t, 1H, J = 7.36 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.6, 137.8, 128.9, 124.2, 119.9, 24.4; HRMS (ESI) m/z calcd for $C_8H_{10}NO$ $[M + H]^+$ = 136.0762, observed $[M + H]^+$ = 136.0766.

*N-(4-Hydroxyphenyl)acetamide (**2**)*[45]*:* white powder (0.339 g, 75%); mp = 168−171 °C; UV (λ_{max}) = 248 nm; IR ν (cm^{-1}) 3326, 3161, 1655, 1610, 1565, 1506, 1442, 1372, 1259, 1243, 1226, 837, 808, 713, 518; ^{1}H NMR (400 MHz; DMSO-d_6) δ 9.64 (br, 1H), 9.13 (s, 1H), 7.33 (d, 2H, J = 8.68 Hz), 6.66 (d, 2H, J = 8.72 Hz) 1.97 (s, 3H); ^{13}C NMR (100 MHz; DMSO-d_6) δ 167.5, 153.1, 131.0, 120.8, 115.6, 23.7; HRMS (ESI) m/z calcd for $C_8H_{10}NO_2$ $[M + H]^+$ = 152.0712, observed $[M + H]$ = 152.0713.

*4-Acetamidophenyl Acetate (**2a**).* Obtained from the reaction between acetic anhydride and 4-aminophenol in pyridine. Briefly, 4-aminophenol (0.327 g, 3 mmol) was dissolved in pyridine (3 mL). This solution was treated with acetic anhydride (0.918 g, 9 mmol) and stirred for another 30 min after the completion of reaction (indicated by TLC); the solvent pyridine was evaporated, and the residue was diluted with 100 mL of ethyl acetate. The organic layer was washed with 5% aq HCl and brine and dried over anhydrous Na_2SO_4. The product **2a** was isolated as an 85% (0.492 g) yield after evaporating the organic layer under reduced pressure: brown solid (0.492 g, 85%); mp = 152−154 °C; UV (λ_{max}) = 244 nm; IR ν (cm^{-1}) 3743, 3294, 3265, 3204, 3142, 3075, 2363, 1753, 1665, 1614, 1507, 1406, 1365, 1319, 1237, 1202, 1100, 1042, 1015, 914, 850, 741; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.96 (br, 1H), 7.45 (d, 2H, J = 12 Hz), 6.98 (d, 2H, J = 12 Hz), 2.29 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.9, 168.7, 146.6, 135.8, 121.8, 120.9, 24.2, 21.1; HRMS (ESI) m/z calcd for $C_{10}H_{12}NO_3$ $[M + H]^+$ = 194.0817, observed = 194.0814.

*N,N′-(Disulfanediylbis(2,1-phenylene))diacetamide (**3**):* colorless oil (0.420 g, 84%); UV (λ_{max}) = 266 nm; IR ν (cm^{-1}) 3063, 2924, 2853, 1698, 1568, 1433, 1306, 1241, 760, 729, 643; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.93 (d, 2H, J = 8.24 Hz), 7.77 (d, 2H, J = 7.32 Hz), 7.43−7.38 (m, 2H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.7, 153.1, 135.4, 125.7, 124.5, 122.1, 121.1, 19.8; HRMS (ESI) m/z calcd for $C_{16}H_{17}N_2O_2S_2$ $[M + H]^+$ = 333.0731, observed $[M + H]^+$ = 333.0737.

*4-Acetamidobenzoic acid (**4**)*[7,49]*:* white powder (0.424 g, 79%); mp > 320 °C; UV (λ_{max}) = 266 nm; IR ν (cm^{-1}) 3305, 2924, 1671, 1522, 1426, 1314, 1296, 1264, 768, 701, 546; ^{1}H NMR (400 MHz; DMSO-d_6) δ 12.66 (br, 1H), 10.23 (br, 1H), 7.87 (d, 2H, J = 8.72 Hz), 7.68 (d, 2H, J = 8.72 Hz), 2.07 (s, 3H); ^{13}C NMR (100 MHz; DMSO-d_6) δ 168.8, 166.9, 143.3, 130.3, 124.8, 18.1, 24.1; HRMS (ESI) m/z calcd for $C_9H_{10}NO_3$ $[M + H]^+$ = 180.0661, observed $[M + H]^+$ = 180.0663.

*5-Acetamidoisophthalic acid (**5**)*[50]*:* white powder (0.548 g, 82%); mp = 230−232 °C; UV (λ_{max}) = 218 nm; IR ν (cm^{-1}) 3741, 3589, 2929, 2315, 1794, 1677, 1547, 1215, 749, 669; ^{1}H NMR (400 MHz; DMSO-d_6) δ 13.99 (br, 2H), 10.31 (s, 1H), 8.41 (d, 2H, J = 1.36 Hz), 8.14 (t, 1H, J = 1.6 Hz), 2.07 (s, 3H); ^{13}C NMR (100 MHz; DMSO-d_6) δ 168.8, 166.5, 139.9, 131.6, 124.3, 123.3, 24.0; HRMS (ESI) m/z calcd for $C_{10}H_{10}NO_5$ $[M + H]^+$ = 224.0559, observed = 224.0555.

*N-(3-Cyanophenyl)acetamide (**6**)*[51]*:* white powder (0.364 g, 76%); mp = 130−132 °C; UV (λ_{max}) = 221 and 248 nm; IR ν (cm^{-1}) 3269, 2226, 1667, 1605, 1586, 1557, 1326, 1294, 1262, 1021, 895, 794, 680, 531; ^{1}H NMR (400 MHz; DMSO-d_6) δ 10.27 (br, 1H), 8.07 (br, 1H), 7.77−7.74 (m, 1H), 7.53−7.47 (m, 2H), 2.07 (s, 3H); ^{13}C NMR (100 MHz; DMSO-d_6) δ 168.9, 140.0, 130.2, 126.5, 123.4, 121.5, 118.7, 111.4, 24.0; HRMS (ESI) m/z calcd for $C_9H_9N_2O$ $[M + H]^+$ = 161.0715, observed $[M + H]^+$ = 161.0720.

*N-(4-Cyanophenyl)acetamide (**7**)*[52]*:* white powder (0.350 g, 73%); mp = 201−204 °C; UV (λ_{max}) = 217 and 251 nm; IR ν (cm^{-1}) 3259, 3303, 2221, 1665, 1594, 1541, 1507, 1404, 1361, 1322, 1265, 1175, 836, 546; ^{1}H NMR (400 MHz; DMSO-d_6) δ 10.36 (br, 1H), 7.74 (br, 4H), 2.08 (s, 3H); ^{13}C NMR (100 MHz; DMSO-d_6) δ 169.1, 143.4, 133.2, 119.0, 118.8, 104.6, 24.1; HRMS (ESI) m/z calcd for $C_9H_9N_2O$ $[M + H]^+$ = 161.0715, observed $[M+H]^+$ = 161.0722.

*N-(4-Nitrophenyl)acetamide (**8**)*[7]*:* yellowish solid (0.307 g, 57%); mp = 145−147 °C; UV (λ_{max}) = 370 nm; IR ν (cm^{-1}) 3481, 3362, 3222, 2363, 1676, 1631, 1595, 1547, 1473, 1446, 1301, 1185, 1111, 1025, 839, 801, 751; ^{1}H NMR (400 MHz; $CDCl_3$) δ 10.56 (br, 1H), 8.21 (d, 2H, J = 8 Hz), 7.82 (d, 2H, J = 8 Hz), 2.08 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.4, 145.5, 142.0, 125.0, 118.5, 24.3; HRMS (ESI) m/z calcd for $C_8H_9N_2O_3$ $[M + H]^+$ = 181.0613, observed = 181.0614.

*N-(3-(Trifluoromethyl)phenyl)acetamide (**9**)*[53]*:* white powder (0.535 g, 88%); mp = 109−111 °C; UV (λ_{max}) = 220 nm; IR ν (cm^{-1}) 3306, 3282, 1661, 1607, 1554, 1446, 1327, 1284, 1212, 1175, 1114, 1068, 1019, 895, 792, 696, 667; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.79 (br, 1H), 7.73 (d, 1H, J = 7.8 Hz), 7.67 (br, 1H), 7.44−7.34 (m, 2H), 2.20 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.6, 138.3, 129.5, 125.1, 122.8, 120.8, 118.8, 116.4, 24.5; HRMS (ESI) m/z calcd for $C_9H_9F_3NO$ $[M + H]^+$ = 204.0636, observed = 204.0642.

*N-Acyl anisidine (**10**)*[20]*:* white powder (0.420 g, 85%); mp = 128−130 °C; UV (λ_{max}) = 248 nm; IR ν (cm^{-1}) 3243, 1647, 1606, 1560, 1512, 1465, 1455, 1410, 1368, 1303, 1285, 1246, 1031, 838; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.38 (d, 3H, J = 9.16 Hz), 6.84 (d, 2H, J = 9.16 Hz), 3.78 (s, 3H), 2.14 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 168.3, 156.3, 130.9, 121.9, 114.0, 55.4, 24.2; HRMS (ESI) m/z calcd for $C_9H_{12}NO_2$ $[M + H]^+$ = 166.0868, observed $[M + H]^+$ = 166.0872.

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*N-Benzylacetamide (**11**)*[21]*:* white powder (0.362 g, 81%); mp = 62−64 °C; UV (λ_{max}) = 213 nm; IR ν (cm^{-1}) 3294, 1647, 1545, 1499, 1374, 1357, 1282, 1067, 1032, 751, 741, 696, 606, 503; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.33−7.24 (m, 5H), 6.21 (br, 1H), 4.37 (d, 2H, J = 5.5 Hz), 1.97 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.0, 138.1, 128.5, 127.7, 127.3, 43.5, 23.0; HRMS (ESI) m/z calcd for $C_9H_{12}NO$ $[M + H]^+$ = 150.0919, observed $[M + H]^+$ = 150.0910.

*N-Cyclohexylacetamide (**12**)*[54]*:* white powder (0.321 g, 76%); mp = 109−111 °C; IR ν (cm^{-1}) 3290, 2932, 2851, 1639, 1557, 1443, 1373, 1314, 1154, 1116, 980, 892, 736, 606, 550; ^{1}H NMR (400 MHz; $CDCl_3$) δ 5.68 (br, 1H), 3.76−3.66 (m, 1H), 1.92 (s, 3H), 1.88 (dd, 2H, J = 9.16 Hz), 1.70−1.55 (m, 3H), 1.37−1.28 (m, 2H), 1.17−1.04 (m, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 169.1, 48.1, 33.0, 25.4, 24.8, 23.0; HRMS (ESI) m/z calcd for $C_8H_{16}NO$ $[M + H]^+$ = 142.1232, observed $[M + H]^+$ = 142.1232.

*2-Acetamido-3-phenylpropanoic acid (**13**)*[44]*:* white powder (0.558 g, 90%); mp = 170−174 °C; UV (λ_{max}) = 206 nm; IR ν (cm^{-1}) 3329, 1697, 1624, 1555, 1438, 1276, 1243, 1117, 707; ^{1}H NMR (400 MHz; DMSO-d_6) δ 12.66 (br, 1H), 8.18 (d, 1H, J = 8.24 Hz), 7.29−7.18 (m, 5H), 4.42−4.36 (m, 1H, CH), 3.03 and 2.82 (dd and dd, 2H, J = 9.16 Hz and J = 4.12 Hz), 1.77 (s, 3H); ^{13}C NMR (100 MHz; DMSO-d_6) δ 173.1, 169.2, 137.7, 129.0, 128.1, 126.3, 53.4, 36.7, 22.3; HRMS (ESI) m/z calcd for $C_{11}H_{14}NO_3$ $[M + H]^+$ = 208.0974, observed $[M + H]^+$ = 208.0969.

*N-(2-Hydroxy-2-phenylethyl)acetamide (**14**)*[54]*:* colorless oil (0.434 g, 81%); UV (λ_{max}) = 202 nm; IR ν (cm^{-1}) 3280, 2929, 1646, 1547, 1373, 1295, 1215, 1073, 1041, 754, 668; ^{1}H NMR (400 MHz; DMSO-d_6) δ 8.23 (d, 1H, J = 8.24 Hz), 7.30−7.19 (m, 5H), 4.86−4.79 (m, 2H), 3.52 (t, 2H, J = 6.18 Hz), 1.86 (s, 3H); ^{13}C NMR (100 MHz; DMSO-d_6) δ 168.8, 141.4, 128.0, 126.9, 126.7, 64.7, 54.9, 22.7; HRMS (ESI) m/z calcd for $C_{10}H_{14}NO_2$ $[M + H]^+$ = 180.1025, observed $[M + H]^+$ = 180.1024.

*N,N′,N″-(Nitrilotris(ethane-2,1-diyl))triacetamide (**15**):* yellowish oil (0.473 g, 84%); IR ν (cm^{-1}) 3282, 1633, 1546, 1435, 1371, 1291, 1169, 749; ^{1}H NMR (400 MHz; DMSO-d_6) δ 7.78 (t, 3H, J = 5.72 Hz), 3.07−3.02 (q, 6H, J = 5.96 Hz), 2.44 (t, 6H, J = 6.4 Hz), 1.80 (s, 9H); ^{13}C NMR (100 MHz; DMSO-d_6) δ 169.7, 53.5, 37.1, 22.7; HRMS (ESI) m/z calcd for $C_{12}H_{25}N_4O_3$ $[M + H]^+$ = 273.1927, observed $[M + H]^+$ = 273.1930.

*N-(4-Methoxyphenyl)benzamide (**16**)*[55]*:* white powder (0.681 g, 82%); mp > 320 °C; UV (λ_{max}) = 223 and 277 nm; IR ν (cm^{-1}) 3330, 1646, 1529, 1514, 1414, 1270, 1249, 1032, 825, 716; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.86 (d, 3H, J = 7.36 Hz), 7.55−7.45 (m, 5H), 6.90 (d, 2H, J = 8.68 Hz), 3.81 (s, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 160.3, 156.5, 134.9, 131.6, 130.9, 128.7, 126.9, 122.1, 114.1, 55.4; HRMS (ESI) m/z calcd for $C_{14}H_{14}NO_2$ $[M + H]^+$ = 228.1025, observed = 228.1048.

*N-Cyclohexylbenzamide (**17**)*[56]*:* white powder (0.535 g, 88%); mp = 151−153 °C; UV (λ_{max}) = 224 nm; IR ν (cm^{-1}) 3238, 2928, 2851, 1638, 1626, 1577, 1560, 1453, 1330,1089, 700; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.76−7.74 (m, 2H), 7.50−7.40 (m, 3H), 6.01 (d, 1H, J = 4.56 Hz), 4.03−3.93 (m, 1H), 2.03 (dd, 2H, J = 8.72 Hz), 1.78−1.63 (m, 4H), 1.48−1.37 (m, 2H), 1.29−1.18 (m, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 166.6, 135.0, 131.2, 128.4, 126.7, 48.6, 33.2, 25.5, 24.8; HRMS (ESI) m/z calcd for $C_{13}H_{18}NO$ $[M + H]^+$ = 204.1388, observed = 204.1393.

*Phenyl(piperidin-1-yl)methanone (**18**)*[57]*:* colorless oil (0.408 g, 72%); UV (λ_{max}) = 224 nm; IR ν (cm^{-1}) 2929, 2856, 1736, 1632, 1442, 1371, 1277, 1237, 1043, 913, 775, 729; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.97 (d, 2H, J = 7.32 Hz), 7.45 (t, 1H, J = 6.2 Hz), 7.32 (t, 2H, J = 7.8 Hz), 3.6 (br, 2H), 3.2 (br, 2H), 1.80 (d, 1H, J = 12 Hz), 1.39 (br, 2H), 1.25−0.97 (m, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 170.4, 136.1, 133.2, 129.9, 129.3, 128.3, 126.7, 49.2, 48.7, 26.4, 25.4, 24.7, 24.4; HRMS (ESI) m/z calcd for $C_{12}H_{16}NO$ $[M + H]^+$ = 190.1232, observed = 190.1229.

*N-Butylbenzamide (**19**)*[58]*:* colorless oil (0.472 g, 89%); UV (λ_{max}) = 224 nm; IR ν (cm^{-1}) 3317, 2959, 2930, 2867, 1639, 1542, 1489, 1460, 1306, 701; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.75 (d, 2H, J = 8.72 Hz), 7.50−7.39 (m, 3H), 6.27 (br, 1H), 3.47−3.42 (q, 2H, J = 5.96 Hz), 1.63−1.55 (q, 2H, J = 7.32 Hz), 1.45−1.36 (q, 2H, J = 7.32 Hz), 0.95 (t, 3H, J = 7.32 Hz); ^{13}C NMR (100 MHz; DMSO-d_6) δ 167.5, 134.7, 131.2, 128.4, 126.7, 39.7, 31.6, 20.1, 13.7; HRMS (ESI) m/z calcd for $C_{11}H_{16}NO$ $[M + H]^+$ = 178.1232, observed $[M + H]^+$ = 178.1236.

*N-Benzyloctanamide (**20**)*[59]*:* white powder (0.643 g, 92%); mp = 70−72 °C; UV (λ_{max}) = 213 nm; IR ν (cm^{-1}) 3291, 2921, 2854, 1632, 1553, 1444, 732, 692; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.35−7.26 (m, 5H), 5.83 (br, 1H), 4.44 (d, 2H, J = 5.96 Hz), 2.21 (t, 2H, J = 7.8 Hz), 1.69−1.61 (q, 2H), 1.30−1.27 (m, 8H), 0.88 (t, 3H, J = 6.84 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 173.0, 138.3, 128.6, 127.7, 127.4, 43.5, 36.7, 31.6, 29.2, 28.9, 25.7, 22.5, 14.0; HRMS (ESI) m/z calcd for $C_{15}H_{24}NO$ $[M + H]^+$ = 234.1858, observed = 234.1861.

*4-Octanamidobenzoic acid (**21**)*[60]*:* white powder (0.702 g, 89%); mp = 176−178 °C; UV (λ_{max}) = 214 nm; IR ν (cm^{-1}) 3319, 2924, 2855, 1666, 1607, 1591, 1519, 1509, 1427, 1404, 1322, 1300, 1250, 1181, 769; ^{1}H NMR (400 MHz; DMSO-d_6) δ 12.62 (br, 1H), 10.17 (s, 1H), 7.86 (d, 2H, J = 8.68 Hz), 7.70 (d, 2H, J = 9.16 Hz), 2.32 (t, 2H, J = 7.5 Hz), 1.58 (t, 2H, J = 7.12 Hz), 1.27−1.23 (m, 8H), 0.84 (t, 3H, J = 6.88 Hz); ^{13}C NMR (100 MHz; DMSO-d_6) δ 171.8, 166.9, 143.4, 130.3, 124.8, 118.2, 36.5, 31.2, 28.5, 25.0, 22.1, 13.9; HRMS (ESI) m/z calcd for $C_{15}H_{22}NO_3$ $[M + H]^+$ = 264.1600, observed = 264.1604.

*N-(4-Methoxyphenyl)dodecanamide (**22**):* white powder (0.713 g, 78%); mp = 90−92 °C; UV (λ_{max}) = 249 nm; IR ν (cm^{-1}) 3238, 2928, 2851, 1626, 1638, 1577, 1560, 1453, 1330, 1082, 700; ^{1}H NMR (400 MHz; $CDCl_3$) δ 7.41 (d, 2H, J = 9.16 Hz), 6.84 (d, 2H, J = 16 Hz), 3.78 (s, 3H), 2.35−2.30 (m, 2H), 1.74−1.67 (m, 2H), 1.25 (br, 16H), 0.88 (t, 3H, J = 6.88 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 171.4, 156.2, 131.0, 121.7, 114.0, 55.4, 37.6, 33.9, 31.8, 29.5, 29.3, 25.7, 22.6, 14.0; HRMS (ESI) m/z calcd for $C_{19}H_{32}NO_2$ $[M + H]^+$ = 306.2433, observed = 306.2431.

*(S)-Methyl 2-dodecanamido-3-(1H-indol-3-yl)propanoate (**23**)*[61]*:* colorless oil (0.996 g, 83%); UV (λ_{max}) = 221 nm; IR ν (cm^{-1}) 3305, 2924, 2852, 1737, 1652, 1517, 1458, 1370, 1236, 1100, 1044, 912, 733; ^{1}H NMR (400 MHz; $CDCl_3$) δ 8.30 (br, 1H), 7.53 (d, 1H, J = 7.8 Hz), 7.36 (d, 1H, J = 8.2 Hz), 7.19 (t, 1H, J = 7.56 Hz), 7.11 (t, 1H, J = 7.56 Hz), 6.97 (d, 1H, J = 1.8 Hz), 6.01 (d, 1H, J = 7.8 Hz), 6.99−6.95 (m, 1H), 3.69 (s, 3H), 3.33−3.31 (m, 2H), 2.14 (t, 2H, J = 7.8 Hz), 1.56 (t, 2H, J = 7.34 Hz), 1.24 (br, 16H), 0.88 (t, 3H, J = 6.64 Hz); ^{13}C NMR (100 MHz; $CDCl_3$) δ 172.8, 172.5, 122.6, 122.1, 119.8, 118.5, 111.2, 110.0, 52.8, 52.3, 36.5, 31.8, 29.6, 29.5, 29.4, 29.2, 29.1, 27.6, 25.4, 22.6, 14.1; HRMS (ESI) m/z calcd for $C_{24}H_{37}N_2O_3$ $[M + H]^+$ = 401.2804, observed = 401.2795.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra of all N-acylated amines (**1**−**24**). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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