Highly efficient preparation of amides from aminium carboxylates using *N*-(*p*-toluenesulfonyl) imidazole

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Treatment of aminium carboxylates with *N*-(*p*-toluenesulfonyl)imidazole in the presence of triethylamine in DMF at 100 °C afforded the corresponding amides in good to excellent yields. *N*-(*p*-Toluenesulfonyl)imidazole proved to be a highly efficient coupling reagent for the preparation of numerous structurally diverse primary, secondary and tertiary amides.

Keywords: aminium carboxylate, coupling reagent, *N*-(*p*-toluenesulfonyl)imidazole, amide

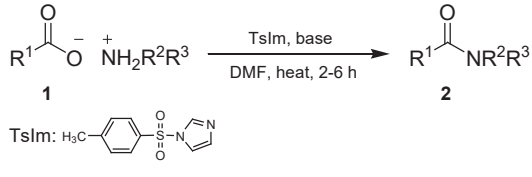
An amide group is an important functional group which plays a vital role in organic and medicinal chemistry.[1–5] Therefore, a wide variety of synthetic approaches have been developed.[6–8] The direct reaction of carboxylic acids with amines is the most extensively used procedure for the synthesis of amides in the laboratory and on the industrial scale. However, harsh reaction conditions like high temperature and long reaction time are essential for the direct conversion of the preformed aminium carboxylate to the corresponding amide.[9] Up to now, numerous coupling reagents including carbodiimides, pyrocarbonates, borates, triazine derivatives, isoxazolium, phosphonium, phosphonic, uronium, immonium, aminium, thiazolium, imidazolium and benzimidazolium salts were employed for the direct condensation of carboxylic acids with amines.[6] Solid-phase synthesis[6] and microwave activation[10] have also been reported. However, most of the coupling reagents used are toxic, expensive, commercially unavailable and moisture sensitive. Thus, there is still a need to develop a practical and robust method for preparing amides directly from carboxylic acids under mild and safe conditions. The use of aminium carboxylates instead of free carboxylic acids and amines for the preparation of amides would be a highly advantageous and attractive strategy due to the enhancement of the carboxylic acid's nucleophilic power towards the coupling reagent and also to prevent the side reaction of amine with the coupling reagent. To the best of our knowledge, there has been no report yet on the direct synthesis of amides from aminium carboxylates using coupling reagents.

N-(*p*-Toluenesulfonyl)imidazole (TsIm) is a cheap, non-toxic, stable, commercially available reagent which has been applied efficiently by us for the preparation of several important classes of organic compounds (see reference[11] and references cited therein). Our successful preparation of esters by the TsIm-catalysed reaction of alcohols R'OH with sodium carboxylates RCO_2Na[12] is particularly relevant, since our plan was to carry out a similar reaction replacing the alcohol with an amine to prepare an amide. We report here a simple procedure for the direct synthesis of amides from aminium carboxylates using TsIm as an efficient coupling reagent.

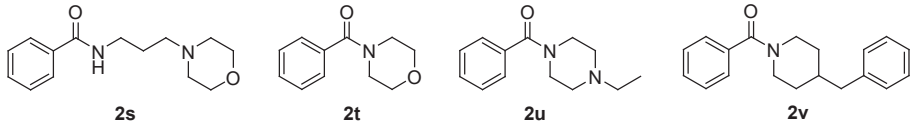
Results and discussion

In view of solubility issues with salts, we chose to use dimethyl formamide (DMF) as solvent for the conversion of aminium carboxylates to amides (Scheme 1). To optimise the reaction conditions, morpholinium benzoate **1t** was selected as the test compound and the influence of various parameters, including temperature, solvent type, base and coupling reagent on its conversion to the corresponding amide **2t** were evaluated. The results obtained are shown in Table 1.

The conversion of morpholinium benzoate **1t** to the corresponding benzamide **2t** was performed using TsIm as the coupling reagent, firstly using trimethylamine as base, at various temperatures. At room temperature, even after heating for 48 h, the desired amide was not formed (entry 1). However, raising the temperature progressively to 60, 75 and 90 °C resulted in increasing yields (entries 2–4). The best result, 96%



2a: R^1= 4-MeO-C_6H_4, R^2= H, R^3= H
2b: R^1= 4-MeO-C_6H_4, R^2= H, R^3= $PhCH_2$
2c: R^1= 3-Me-C_6H_4, R^2= H, R^3= $Et_2NCH_2CH_2$
2d: R^1= 4-NO_2-C_6H_4, R^2= H, R^3= H
2e: R^1= 4-NO_2-C_6H_4, R^2= H, R^3=$CH_3(CH_2)_5$
2f: R^1= 2-Br-C_6H_4, R^2= Me, R^3= Me
2g: R^1= 4-CF_3-C_6H_4, R^2= H, R^3=$PhCH_2$
2h: R^1= 2-pyridinyl, R^2= H, R^3= MeO_2CCH_2
2i: R^1= $PhCH_2$, R^2= H, R^3= $PhCH_2$
2j: R^1= $PhCH_2$, R^2= H, R^3= 3-pyridinylCH_2
2k: R^1= $BocNHCH_2$, R^2= H, R^3= H
2l: R^1= $CbzNHCH_2$, R^2,R^3= $(CH_2)_5$
2m: R^1= CH_3, R^2= H, R^3= $PhCH_2$
2n: R^1= CH_3CH_2, R^2= H, R^3= $CH_3(CH_2)_{15}$
2o: R^1= $CH_3(CH_2)_{14}$, R^2= H, R^3= $CH_3(CH_2)_5$
2p: R^1= phenyl, R^2= H, R^3= H
2q: R^1= phenyl, R^2= H, R^3= $PhCH_2CH_2$
2r: R^1= phenyl, R^2= H, R^3= $Me_2NCH_2CH_2CH_2$



2s **2t** **2u** **2v**

Scheme 1

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Table 1 Effects of various reaction parameters on the yields of *N*,*N*-disubstituted benzamide **2t** prepared by treatment of morpholinium benzoate (Scheme 1) with TsIm and other coupling agents **3**–**11** (Fig. 1)

Entry	Solvent	Base	Reagent	Temperature/°C	Time/h	Yield[a]/%
1	DMF	Et_3N	TsIm	r.t.	48	NR[b]
2	DMF	Et_3N	TsIm	60	20	18
3	DMF	Et_3N	TsIm	75	15	27
4	DMF	Et_3N	TsIm	90	8	78
5	DMF	Et_3N	TsIm	100	2	96
6	DMF	Et_3N	TsIm	110	2	96
7	DMF	Et_3N	TsIm	130	1.8	94
8	MeCN	Et_3N	TsIm	100	7	80
9	HMPA	Et_3N	TsIm	100	4	84
10	DMSO	Et_3N	TsIm	100	3	78
11	NMP	Et_3N	TsIm	100	3	83
12	Toluene	Et_3N	TsIm	100	15	85
13	Xylene	Et_3N	TsIm	100	18	81
14	DMF	NaH	TsIm	100	20	29
15	DMF	DBU	TsIm	100	3	90
16	DMF	DMAP	TsIm	100	3	87
17	DMF	DABCO	TsIm	100	5	86
18	DMF	MgO	TsIm	100	24	NR
19	DMF	K_2CO_3	TsIm	100	10	58
20	DMF	Cs_2CO_3	TsIm	100	9	62
21	DMF	Basic Al_2O_3	TsIm	100	20	32
22	DMF	Et_3N	**3**	100	5	80
23	DMF	Et_3N	**4**	100	4	84
24	DMF	Et_3N	**5**	100	6	82
25	DMF	Et_3N	**6**	100	10	65
26	DMF	Et_3N	**7**	100	10	68
27	DMF	Et_3N	**8**	100	36	NR
28	DMF	Et_3N	**9**	100	10	41
29	DMF	Et_3N	**10**	100	15	28
30	DMF	Et_3N	**11**	100	15	24
31	DMF	Et_3N	CH_3SO_2Cl	100	8	45
32	DMF	Et_3N	CF_3SO_2Cl	100	8	41
33	DMF	Et_3N	$C_6H_5SO_2Cl$	100	8	52
34	DMF	Et_3N	4-Me–$C_6H_4SO_2Cl$	100	8	56
35	DMF	Et_3N	4-NO_2–$C_6H_4SO_2Cl$	100	8	60

[a]Isolated yield.

[b]No reaction.

was obtained when the reaction was carried out at 100 °C for 2 h (entry 5). Further increases in the reaction temperature did not improve the yield (entries 6 and 7).

Then, we examined the effect of various solvents on the progress of the reaction. As shown in Table 1, DMF proved to be the most efficient solvent and hence it was the solvent of choice for all subsequent reactions (entry 5). The use of MeCN, HMPA, DMSO and NMP (*N*-methyl-2-pyrrolidone) produced **2t** in reasonable yields but in longer reaction times (entries 8–11). Toluene and xylene also provided reasonable yields of **2t**; however, longer times were needed for completion of the reaction (entries 12 and 13).

We also investigated the effect of several organic and inorganic bases on the conversion of morpholinium benzoate to **2t** (Table 1). Among tested bases, Et_3N is the most appropriate base for efficient progress of reaction (entry 5). In general, **2t** was obtained in low to moderate yields using inorganic bases (entries 14 and 18–21). Employing other organic bases such as DBU, DMAP, and DABCO (entries 15–17) afforded satisfactory results, but they were not as effective as Et_3N.

The optimised amount of TsIm was found to be 1.2 equiv. per equivalent of aminium carboxylate. In a series of other experiments, we also studied other TsIm analogues as coupling reagents. The structures of the examined coupling reagents are shown in Fig. 1. As the results in Table 1 indicate, a higher yield of amide and shorter reaction time were obtained using TsIm (entry 5) in comparison with other sulfonyl analogues. Replacing the tolyl group in TsIm with methyl, trifluoromethyl and phenyl (to give **3**,**4** and **5** respectively) produced **2t** in 80–84% yield in longer reaction times (entries 22–24). The use of the other azole analogues of TsIm **6**,**7** and **11** resulted in low to moderate yields of **2t** (entries 25, 26, and 30). The *N*-tosyl imide, *N*-tosylphthalimide was inactive even if the reaction time was prolonged to 36 h (entry 27). In addition, the benzenesulfonyl derivatives of benzimidazole **9** and indole **10** did not give satisfactory results (entries 28 and 29).

We also investigated the effect of several sulfonyl chlorides instead of TsIm for conversion of morpholinium benzoate to **2t**. However, low to moderate yields were obtained when sulfonyl chlorides were employed as the coupling reagents (entries 31–35), despite being more reactive than TsIm. We rationalised this observation by considering the role of the leaving group in TsIm, which is an imidazolyl residue, with respect to the chloride ion in sulfonyl chlorides. While the former is a base that can help to

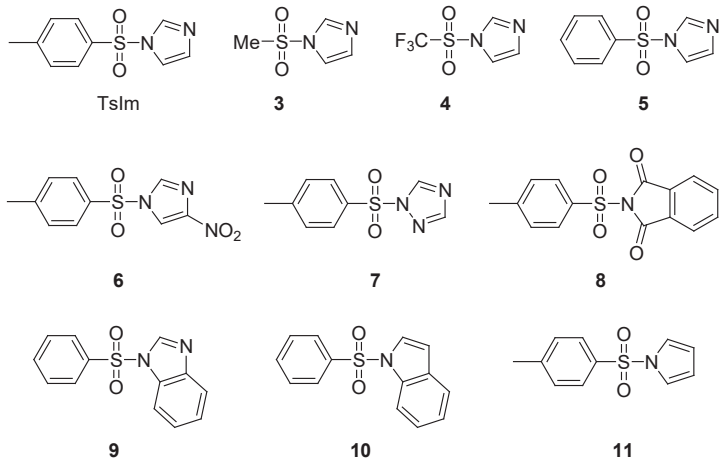


Fig. 1 The structures of TsIm analogues used as the coupling reagents.

Table 2 Yields and duration of reaction for the preparation of amides **2a–v** from aminium carboxylates **1a–v** using TsIm in DMF (Scheme 1)

Entry[ref.]	Product[a]	Time/h	Yield[b]/%
1[13]	**2a**	3.5	85
2[14]	**2b**	3	88
3[15]	**2c**	4	90
4[13]	**2d**	2	91
5[15]	**2e**	3	90
6[16]	**2f**	4	85
7[14]	**2g**	2.5	90
8[14]	**2h**	4	87
9[17]	**2i**	4.5	92
10[18]	**2j**	5	90
11[13]	**2k**	5	87
12[17]	**2l**	5	91
13	**2m**	5	93
14[9]	**2n**	6	89
15[18]	**2o**	6	90
16[13]	**2p**	2.5	87
17[19]	**2q**	3	90
18	**2r**	2	90
19	**2s**	2	92
20[15]	**2t**	2	96
21	**2u**	2	94
22	**2v**	3	93

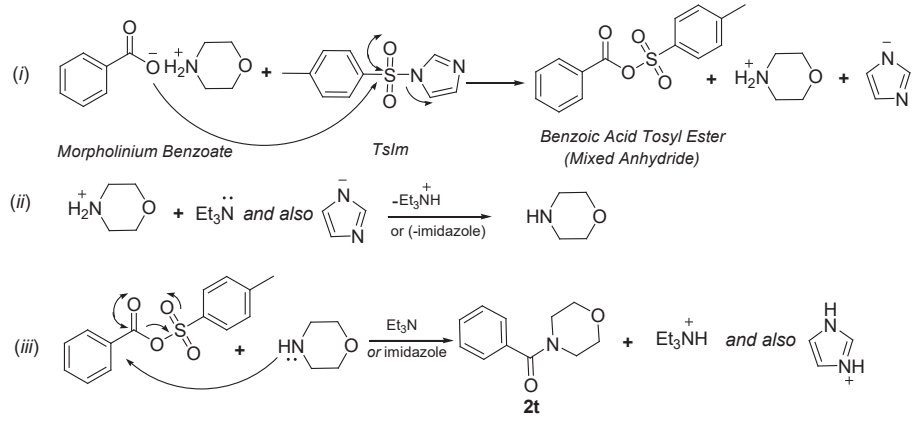
[a]Reaction Conditions: A mixture of aminium carboxylate **1** (0.01 mol) and TsIm (0.012 mol) in DMF (15 mL) was heated at 100 °C for 1 h and then Et_3N (0.012 mol) was added and heating of the reaction mixture was continued at 100 °C for 2–6 h.
[b]Isolated yield.

progress the reaction, the latter is a non-basic anion. However, imidazole is not a strong enough base to progress the reaction alone. Hence the presence of an efficient base is mandatory.

Having obtained the optimised reaction conditions, we then applied them to a variety of structurally diverse aminium carboxylates (Table 2). As can be seen in Table 2, TsIm proved to be an efficient coupling reagent for the production of a wide range of primary, secondary and tertiary amides. The chemistry works well and tolerates many labile functionalities present in both carboxylate and aminium residues.

Aminium carboxylates in which the carboxylate residues are aliphatic, heteroaromatic or aromatic carboxylic acids bearing electron-donating or electron-withdrawing functional groups were efficiently converted to the corresponding amides. Moreover, aminium carboxylates having various structurally diverse aminium residues like benzylic, alicyclic, primary and secondary aliphatic amine derivatives were efficiently acylated using TsIm under the optimised condition, whereas aromatic amines were unreactive. In addition, amidation of *N*-protected (as Boc and Cbz derivatives) and/or *O*-protected (as methyl ester) amino acids afforded satisfactory results using the current protocol (entries 8, 11 and 12). Furthermore, this method is also applicable for fatty acids and amines to provide the corresponding amides in excellent yields (entries 14 and 15). All the synthesised compounds were characterised by ^{1}H NMR and ^{13}C NMR, mass spectroscopy and IR spectroscopy methods and by their elemental analysis.

A plausible mechanism for the TsIm-catalysed preparation of amides from aminium carboxylates, exemplified by morpholinium benzoate, is shown in Scheme 2. In the first step,



Scheme 2

the benzoate anion in morpholinium benzoate undertakes a nucleophilic attack on TsIm which affords benzoic acid tosyl ester as a reactive mixed anhydride.[20] The *in situ* generation of benzoic acid tosyl ester was detected at an early stage of the reaction using TLC monitoring and also by comparing to an authentic sample. In the second step, the *in situ* activated amine (liberated from its aminium salt by triethylamine or imidazole) reacts with the mixed anhydride to give **2t**.

In summary, we have described the application of TsIm as a highly efficient and useful coupling reagent for the preparation of amides from aminium carboxylates in the presence of Et_3N in DMF at 100 °C. The mild reaction conditions, simple experimental procedure and high yields which afforded a variety of structurally diverse primary, secondary and tertiary amides are the advantages of the method. Furthermore, the use of aminium carboxylates as substrates overcomes the problems usually associated with handling toxic, odorous and corrosive amines and carboxylic acids or their corresponding acid halide derivatives.

Experimental

All chemical reagents were purchased from either Fluka or Merck. Solvents were purified by standard procedures and stored over 3 Å molecular sieves. Reactions were followed by TLC using SILG/UV 254 silica-gel plates. Column chromatography was performed on silica gel 60 (0.063–0.200 mm, 70–230 mesh; ASTM). Melting points were determined using an Electrothermal IA 9000 melting point apparatus in open capillary tubes and are uncorrected. IR spectra were obtained using a Shimadzu FTIR-8300 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Brüker Avance-DPX-250 spectrometer operating at 250 and 62.5 MHz respectively. Chemical shifts are given in δ relative to tetramethylsilane (TMS) as an internal standard and coupling constants *J* are given in Hz. Abbreviations used for ^{1}H NMR signals are: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. GC/MS was performed on a Shimadzu GC/MS-QP 1000-EX apparatus (*m/z*; rel.%). Elemental analyses were performed on a PerkinElmer 240-B micro-analyser.

Synthesis of aminium carboxylates; general procedure

The carboxylic acid (1 equiv.) was added to a solution of the amine (1 equiv.) in a minimum amount of H_2O–MeOH (70:30). The reaction mixture was stirred at room temperature and the reaction was complete when pH paper indicated that the solution was neutral. The solution was then evaporated under vacuum and the crude product was dried in a vacuum oven for 24 h at 50 °C. The aminium carboxylates were then stored in a desiccator.

Synthesis of TsIm analogues **3**–**11***; general procedure*[21]

The appropriate *N*-heterocycle (0.01 mol) and KOH (0.01 mol) was added in DMSO (15 mL) to a round bottom flask (50 mL) and the mixture was cooled to 0 °C. Then, the appropriate sulfonyl chloride (0.012 mol) was added portionwise and the reaction mixture was stirred at 0 °C for 1–2 h (TLC control). After completion of the reaction, the mixture was poured into water (100 mL) and extracted with $CHCl_3$ or EtOAC (100 mL). The organic layer was then washed with water (4 × 100 mL), dried over anhydrous sodium sulfate and evaporated. The crude product was purified by short column chromatography on silica gel eluting with *n*-hexane:EtOAc.

Synthesis of amides from aminium carboxylates using TsIm; general procedure

A mixture of the appropriate aminium carboxylate (0.01 mol) and TsIm (0.012 mol) was added in DMF (15 mL) to a round bottom flask (50 mL) and the reaction mixture was heated at 100 °C for 1 h. Then, Et_3N (0.012 mol) was added and the heating of the reaction mixture was continued at 100 °C until TLC monitoring indicated no further progress in the conversion (2–6 h, see Table 2). After completion of the reaction, the solvent was evaporated *in vacuo* (*Note*). The remaining foam was then dissolved in $CHCl_3$ (100 mL) and subsequently washed with water (2 × 100 mL). Then, the organic layer was dried over anhydrous sodium sulfate and evaporated. The crude product was purified by column chromatography on silica gel eluting with *n*-hexane:EtOAc.

(*Note*: DMF (b.p. 153 °C) can be evaporated in a rotary evaporator if the vacuum system is capable of sufficiently low pressure. For instance, DMF can be boiled below 80 °C if the vacuum is reduced to 5 torr or less. However, if an efficient vacuum pump is not available, then an alternative procedure can be employed in which the reaction mixture is diluted in water (100 mL). Then, $CHCl_3$ (100 mL) is added and the organic phase is separated. The separated $CHCl_3$ is washed subsequently with water (4 × 100 mL). The $CHCl_3$ is evaporated to obtain the crude product.)

1-Methylsulfonylimidazole (**3**): CAS Number: 40736-26-3; m.p. 85–86 °C (lit.[21] 86 °C).

*1-(Trifluoromethylsulfonyl)-1*H*-imidazole* (**4**): CAS Number: 29540-81-6; m.p. 19–20 °C (lit.[22] 19 °C).

*1-(Phenylsulfonyl)-1*H*-imidazole* (**5**): CAS Number: 46248-01-5; m.p. 81–82 °C (lit.[21] 83 °C).

*4-Nitro-1-tosyl-1*H*-imidazole* (**6**): CAS Number: 71100-56-6; foam.[23]

*1-Tosyl-1*H*-1,2,4-triazole* (**7**): CAS Number: 13578-51-3; foam.[24]

2-Tosylisoindoline-1,3-dione (**8**): CAS Number: 27722-45-8; m.p. 239–240 °C (lit.[25] 239 °C).

*1-(Phenylsulfonyl)-1*H*-benzo[*d*]imidazole* (**9**): CAS Number: 15728-43-5; m.p. 105–106 °C (lit.[26] 104 °C).

*1-(Phenylsulfonyl)-1*H*-indole* (**10**): CAS Number: 40899-71-6; m.p. 78–79 °C (lit.[27] 78 °C).

*1-Tosyl-1*H*-pyrrole* (**11**): CAS Number: 17639-64-4; m.p. 99–100 °C (lit.[28] 98 °C).

4-Methoxybenzamide (**2a**): Off-white prism crystals; yield 85%; m.p. 115–116 °C (lit.[13] 114–116 °C); IR (ν_{max}): 3300, 3176, 3069, 2981, 1650, 1611, 1449, 1235 cm^{-1}; ^{1}H NMR: δ 3.80 (s, 3H, OCH_3), 7.15 (d, *J* = 8.0 Hz, 2H, aryl), 7.79 (d, *J* = 8.0 Hz, 2H, aryl), 7.95 (s, 2H, NH_2, exchangeable with D_2O); ^{13}C NMR: δ 57.8, 116.4, 127.0, 128.6, 163.5, 169.8; MS (EI) *m/z* (%): 151 (10.5) (M^+). Anal. calcd for $C_8H_9NO_2$: C, 63.56; H, 6.00; N, 9.27; found: C, 63.69; H, 6.14; N, 9.35%.

N-*Benzyl-4-methoxybenzamide* (**2b**): Yellow prism crystals; yield 88%; m.p. 130–131 °C (lit.[14] 129–130 °C); IR (ν_{max}): 3367, 3040, 2968, 1655, 1600, 1449, 1218 cm^{-1}; ^{1}H NMR: δ 3.72 (s, 3H, OCH_3), 4.64 (d, *J* = 5.9, 2H, NHCH_2), 6.37 (s, 1H, NH, exchangeable with D_2O), 6.93–6.98 (m, 3H), 7.35–7.41 (m, 2H), 7.64–7.70 (m, 4H, aryl); ^{13}C NMR: δ 44.9, 54.0, 114.3, 126.1, 127.9, 128.5, 128.9, 129.4, 137.0, 163.8, 169.5; MS (EI) *m/z* (%): 241 (14.7) (M^+). Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81; found: C, 74.53; H, 6.16; N, 5.89%.

N-*[2-(Diethylamino)ethyl]-3-methylbenzamide* (**2c**): Yellow liquid; yield 90%; IR (ν_{max}): 3280, 3067, 2934, 1679, 1612, 1476 cm^{-1}; ^{1}H NMR: δ 1.18 (t, *J* = 7.3 Hz, 6H, $2CH_3$), 2.42 (s, 3H, Ph–CH_3), 2.59 (q, *J* = 7.3 Hz, 4H, $2CH_2CH_3$), 2.74 (t, *J* = 6.1 Hz, 2H, NCH_2), 3.60 (q, *J* = 6.1 Hz, 2H, NHCH_2), 6.78 (br s, 1H, NH, exchangeable with D_2O), 7.39–7.50 (m, 3H, aryl), 7.65 (s, 1H, aryl); ^{13}C NMR: δ 13.8, 22.7, 45.7, 52.0, 56.8, 121.9, 126.1, 128.0, 133.0, 134.0, 138.6, 169.1; MS (EI) *m/z* (%): 234 (16.7) (M^+). Anal. calcd for $C_{14}H_{22}N_2O$: C, 71.76; H, 9.46; N, 11.95; found: C, 71.70; H, 9.49; N, 11.87%.

4-Nitrobenzamide (**2d**): Off-white prism crystals; yield 91%; m.p. 128–129 °C (lit.[13] 128–130 °C); IR (ν_{max}): 3347, 3168, 3072, 1683, 1621, 1549, 1442, 1340 cm^{-1}; ^{1}H NMR: δ 7.89 (d, *J* = 7.9 Hz, 2H, aryl), 8.10 (d, *J* = 7.9 Hz, 2H, aryl), 8.26 (s, 2H, NH_2, exchangeable with D_2O); ^{13}C NMR: δ 125.9, 129.4, 141.7, 153.0, 170.2; MS (EI) *m/z* (%): 166 (9.1) (M^+). Anal. calcd for $C_7H_6N_2O_3$: C, 50.61; H, 3.64; N, 16.86; found: C, 50.74; H, 3.71; N, 16.75%.

N-*Hexyl-4-nitrobenzamide* (**2e**): White needle crystals; yield 90%; m.p. 79–80 °C (lit.[15] 80–81 °C); IR (ν_{max}): 3268, 3100, 2983, 1678, 1615, 1528, 1475, 1335 cm^{-1}; ^{1}H NMR: δ 0.91 (t, *J* = 7.1 Hz, 3H, CH_3), 1.26–1.31 (m, 6H, $3CH_2$), 1.67 (quint, *J* = 7.1 Hz, 2H, NCH_2CH_2), 3.38 (q, *J* = 7.1 Hz, 2H, NHCH_2), 7.42–7.49 (m, 4H, aryl), 8.51 (s, 1H, NH,

exchangeable with D_2O); ^{13}C NMR: δ 14.5, 21.9, 25.7, 29.3, 32.4, 42.0, 124.1, 129.0, 143.2, 150.9, 168.0; MS (EI) *m/z* (%): 250 (12.9) (M^+). Anal. calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.25; N, 11.19; found: C, 62.31; H, 7.29; N, 11.26%.

2-Bromo-N,N-*dimethylbenzamide* (**2f**): Yellow oil; yield 85%; IR (ν_{max}): 3087, 2934, 1631, 1602, 1427, 650 cm^{-1}; ^1H NMR: δ 2.98 (s, 3H, CH_3), 3.10 (s, 3H, CH_3), 7.19–7.25 (m, 2H, aryl), 7.35 (d, *J* = 7.8 Hz, 1H, aryl), 7.59 (d, *J* = 7.8 Hz, 1H, aryl); ^{13}C NMR: δ 34.0, 37.3, 123.8, 124.9, 131.7, 132.0, 133.4, 140.6, 169.2; MS (EI) *m/z* (%): 228 (7.8) (M^+). Anal. calcd for $C_9H_{10}BrNO$: C, 47.39; H, 4.42; N, 6.14; found: C, 47.47; H, 4.51; N, 6.08%.

N-*Benzyl-4-(trifluoromethyl)benzamide* (**2g**): Yellow needle crystals; yield 90%; m.p. 168–169 °C (lit.[14] 168–170 °C); IR (ν_{max}): 3285, 3050, 2944, 1674, 1609, 1427, 1126 cm^{-1}; ^1H NMR: δ 4.58 (d, *J* = 5.6 Hz, 2H, NHCH_2), 6.68 (br s, 1H, NH, exchangeable with D_2O), 7.34–7.42 (m, 5H, aryl), 7.53 (d, *J* = 8.0 Hz, 2H, aryl), 7.80 (d, *J* = 8.0 Hz, 2H, aryl); ^{13}C NMR: δ 43.9, 124.3, 126.1, 127.4, 128.0, 128.7, 130.5, 134.2, 136.0, 138.9, 168.0; MS (EI) *m/z* (%): 279 (18.3) (M^+). Anal. calcd for $C_{15}H_{12}F_3NO$: C, 64.51; H, 4.33; N, 5.02; found: C, 64.66; H, 4.41; N, 5.12%.

Methyl 2-(picolinamido)acetate (**2h**): White prism crystals; yield 87%; m.p. 83–84 °C (lit.[14] 82–84 °C); IR (ν_{max}): 3354, 3063, 2924, 1735, 1673, 1600, 1446, 1240 cm^{-1}; ^1H NMR: δ 3.70 (s, 3H, CH_3), 4.36 (d, *J* = 6.1 Hz, 2H, NHCH_2), 7.95–8.07 (m, 3H, aryl), 8.17 (d, *J* = 7.9 Hz, 1H, aryl), 8.40 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR: δ 42.0, 53.1, 123.0, 127.1, 136.9, 147.6, 150.9, 165.4, 171.0; MS (EI) *m/z* (%): 194 (11.7) (M^+). Anal. calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43; found: C, 55.73; H, 5.14; N, 14.49%.

N-*Benzyl-2-phenylacetamide* (**2i**): White prism crystals; yield 92%; m.p. 77–78 °C (lit.[17] 76–78 °C); IR (ν_{max}): 3290, 3038, 2979, 1650, 1598, 1433 cm^{-1}; ^1H NMR: δ 3.71 (s, 2H, CH_2CO), 4.52 (d, *J* = 6.4 Hz, 2H, NHCH_2), 5.89 (br s, 1H, NH, exchangeable with D_2O), 7.21–7.32 (m, 6H, aryl), 7.42–7.54 (m, 4H, aryl); ^{13}C NMR: δ 42.9, 43.5, 126.7, 127.0, 127.4, 128.9, 129.5, 130.1, 134.8, 139.0, 170.8; MS (EI) *m/z* (%): 225 (15.9) (M^+). Anal. calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22; found: C, 79.83; H, 6.82; N, 6.28%.

2-Phenyl-N-*(pyridin-3-ylmethyl)acetamide* (**2j**): White needle crystals; yield 90%; m.p. 102–103 °C (lit.[18] 100–102 °C); IR (ν_{max}): 3297, 3069, 2948, 1667, 1602, 1472 cm^{-1}; ^1H NMR: δ 3.75 (s, 2H, CH_2CO), 4.69 (d, *J* = 5.5 Hz, 2H, NHCH_2), 6.62 (s, 1H, NH, exchangeable with D_2O), 7.14–7.17 (m, 1H, aryl), 7.22 (d, *J* = 8.0 Hz, 1H, aryl), 7.31–7.40 (m, 5H, aryl), 7.98 (d, *J* = 8.0 Hz, 1H, aryl), 8.37 (s, 1H, aryl); ^{13}C NMR: δ 44.1, 45.3, 120.8, 121.9, 126.4, 128.5, 129.3, 135.0, 137.1, 150.9, 157.0, 170.8; MS (EI) *m/z* (%): 226 (13.4) (M^+). Anal. calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38; found: C, 74.23; H, 6.29; N, 12.34%.

tert-*Butyl 2-amino-2-oxoethylcarbamate* (**2k**): Off-white cube crystals; yield 87%; m.p. 86–87 °C (lit.[13] 85–87 °C); IR (ν_{max}): 3312, 3184, 2925, 1715, 1674, 1613 cm^{-1}; ^1H NMR: δ 1.48 (s, 9H, $3CH_3$), 3.65 (d, *J* = 6.7 Hz, 2H, NHCH_2), 7.16 (br s, 2H, NH_2, exchangeable with D_2O), 8.04 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR: δ 29.1, 48.6, 78.9, 157.0, 170.5; MS (EI) *m/z* (%): 174 (9.1) (M^+). Anal. calcd for $C_7H_{14}N_2O_3$: C, 48.26; H, 8.10; N, 16.08; found: C, 48.40; H, 8.21; N, 16.19%.

Benzyl 2-oxo-2-(piperidin-1-yl)ethylcarbamate (**2l**): White cube crystals; yield 91%; m.p. 114–115 °C (lit.[17] 113–116 °C); IR (ν_{max}): 3290, 3100, 2962, 1712, 1653, 1593, 1426 cm^{-1}; ^1H NMR: δ 1.60–1.68 (m, 6H, $3CH_2$), 3.41 (t, *J* = 6.5 Hz, 4H, $2NCH_2$), 4.01 (d, *J* = 5.8 Hz, NHCH_2), 5.12 (s, 2H, OCH_2), 6.08 (s, 1H, exchangeable with D_2O), 7.26–7.39 (m, 5H, aryl); ^{13}C NMR: δ 24.8, 25.6, 42.9, 44.7, 46.9, 66.1, 127.4, 128.0, 129.2, 135.8, 158.7, 168.6; MS (EI) *m/z* (%): 276 (17.3) (M^+). Anal. calcd for $C_{15}H_{20}N_2O_3$: C, 65.20; H, 7.30; N, 10.14; found: C, 65.26; H, 7.38; N, 10.21%.

N-*Benzylacetamide* (**2m**): White prism crystals; yield 93%; m.p. 56–57 °C; IR (ν_{max}): 3280, 3068, 2983, 1661, 1602, 1449 cm^{-1}; ^1H NMR: δ 1.95 (s, 3H, CH_3), 4.65 (d, *J* = 6.2 Hz, 2H, NHCH_2), 6.97 (s, 1H, NH, exchangeable with D_2O), 7.36–7.42 (m, 5H, aryl); ^{13}C NMR: δ 25.7, 44.9, 127.6, 128.0, 129.8, 139.0, 170.0; MS (EI) *m/z* (%): 149 (11.5) (M^+). Anal. calcd for $C_9H_{11}NO$: C, 72.46; H, 7.43; N, 9.39; found: C, 72.34; H, 7.51; N, 9.45%.

N-*Hexadecylpropanamide* (**2n**): White prism crystals; yield 89%; m.p. 67–68 °C (lit.[9] 68–69 °C); IR (ν_{max}): 3294, 2960, 1627, 1591 cm^{-1}; ^1H NMR: δ 0.91 (t, *J* = 7.1 Hz, 3H, CH_3), 1.19 (t, *J* = 7.5 Hz, 3H, CH_3), 1.38–1.47 (m, 28H, $14CH_2$), 2.28 (q, *J* = 7.5 Hz, 2H, CH_2CO), 3.41 (q, *J* = 7.1 Hz, 2H, NHCH_2), 5.82 (br s, 1H, NH, exchangeable with D_2O); ^{13}C NMR: δ 10.3, 14.5, 23.0, 27.6, 28.0, 28.8, 29.1, 29.3, 29.5, 29.7, 29.9, 30.1, 30.4, 32.5, 42.7, 171.6; MS (EI) *m/z* (%): 297 (18.6) (M^+). Anal. calcd for $C_{19}H_{39}NO$: C, 76.70; H, 13.21; N, 4.71; found: C, 76.79; H, 13.32; N, 4.75%.

N-*Hexylhexadecanamide* (**2o**): White needle crystals; yield 90%; m.p. 63–64 °C (lit.[18] 62–64 °C); IR (ν_{max}): 3297, 2961, 1668, 1596 cm^{-1}; ^1H NMR: δ 0.89–0.94 (m, 6H, $2CH_3$), 1.41–1.57 (m, 34H, $17CH_2$), 2.33 (t, *J* = 7.5 Hz, 2H, CH_2CO), 3.49 (q, *J* = 6.8 Hz, 2H, NHCH_2), 5.98 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR: δ 13.1, 21.5, 22.9, 23.4, 24.9, 27.0, 28.7, 29.0, 29.2, 29.3, 29.4, 29.6, 29.8, 30.2, 30.5, 31.8, 32.4, 35.9, 38.7, 171.8; MS (EI) *m/z* (%): 339 (20.7) (M^+). Anal. calcd for $C_{22}H_{45}NO$: C, 77.81; H, 13.36; N, 4.12; found: C, 77.72; H, 13.30; N, 4.05%.

Benzamide (**2p**): Off-white prism crystals; yield 87%; m.p. 127–128 °C (lit.[13] 127–129 °C); IR (ν_{max}): 3300, 3194, 3082, 1671, 1615, 1457 cm^{-1}; ^1H NMR: δ 6.07 (br s, 2H, NH_2, exchangeable with D_2O), 7.38–7.46 (m, 3H, aryl), 7.65–7.74 (m, 2H, aryl); ^{13}C NMR: δ 126.8, 128.5, 132.9, 134.7, 170.1; MS (EI) *m/z* (%): 121 (8.1) (M^+). Anal. calcd for C_7H_7NO: C, 69.41; H, 5.82; N, 11.56; found: C, 69.49; H, 5.95; N, 11.62%.

N-*Phenethylbenzamide* (**2q**): Colourless oil; yield 90%; IR (ν_{max}): 3310, 3048, 2973, 1682, 1619, 1470 cm^{-1}; ^1H NMR: δ 2.90 (t, *J* = 5.9 Hz, 2H, Ph–CH_2), 3.79 (q, *J* = 5.9 Hz, 2H, NHCH_2), 6.31 (s, 1H, NH, exchangeable with D_2O), 7.30–7.48 (m, 8H, aryl), 7.75–7.82 (m, 2H, aryl); ^{13}C NMR: δ 34.0, 40.6, 125.9, 127.1, 128.2, 128.7, 129.4, 132.1, 133.8, 137.6, 168.8; MS (EI) *m/z* (%): 225 (14.5) (M^+). Anal. calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22; found: C, 79.85; H, 6.80; N, 6.31%.

N-*(3-(Dimethylamino)propyl)benzamide* (**2r**): Creamy foam; yield 90%; IR (ν_{max}): 3343, 3065, 2968, 1674, 1612, 1469 cm^{-1}; ^1H NMR: δ 1.62 (quint, *J* = 6.0 Hz, 2H, CH_2), 2.19 (s, 6H, $2CH_3$), 2.37 (t, *J* = 6.0 Hz, 2H, Me_2NCH_2), 3.42 (q, *J* = 6.0 Hz, 2H, NHCH_2), 7.28–7.40 (m, 3H, aryl), 7.68–7.72 (m, 2H, aryl), 8.39 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR: δ 27.1, 38.7, 46.5, 58.4, 126.9, 128.0, 133.6, 135.8, 169.2; MS (EI) *m/z* (%): 206 (12.8) (M^+). Anal. calcd for $C_{12}H_{18}N_2O$: C, 69.87; H, 8.80; N, 13.58; found: C, 69.80; H, 8.94; N, 13.63%.

N-*(3-Morpholinopropyl)benzamide* (**2s**): White prism crystals; yield 92%; m.p. 274–275 °C; IR (ν_{max}): 3300, 3037, 2950, 1680, 1602, 1437, 1210 cm^{-1}; ^1H NMR: δ 1.77 (quint, *J* = 6.3 Hz, 2H, CH_2), 2.53–2.61 (m, 6H, $3NCH_2$), 3.53 (q, *J* = 6.3 Hz, 2H, NHCH_2), 3.70–3.73 (m, 4H, $2OCH_2$), 7.38–7.52 (m, 3H, aryl), 7.80–7.84 (m, 2H, aryl), 8.20 (s, 1H, NH, exchangeable with D_2O); ^{13}C NMR: δ 28.5, 39.2, 50.9, 53.7, 68.2, 127.8, 129.0, 133.2, 135.4, 168.6; MS (EI) *m/z* (%): 248 (16.1) (M^+). Anal. calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28; found: C, 67.86; H, 8.25; N, 11.20%.

(Morpholin-4-yl)(phenyl)methanone (**2t**): Yellow liquid; yield 96%; IR (ν_{max}): 3067, 2968, 1676, 1610, 1476, 1229 cm^{-1}; ^1H NMR: δ 3.53–3.70 (m, 8H, $4CH_2$), 7.28–7.37 (m, 5H, aryl); ^{13}C NMR: δ 41.9, 46.4, 67.3, 127.9, 129.2, 131.5, 134.8, 170.0; MS (EI) *m/z* (%): 191 (12.4) (M^+). Anal. calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.32; found: C, 69.20; H, 6.98; N, 7.41%.

(4-Ethylpiperazin-1-yl)(phenyl)methanone (**2u**): Bright brown oil; yield 94%; IR (ν_{max}): 3051, 2940, 1662, 1607, 1463 cm^{-1}; ^1H NMR: δ 1.38 (t, *J* = 6.9 Hz, 3H, CH_3), 2.49 (q, *J* = 6.9 Hz, 2H, CH_2CH_3), 2.83 (t, *J* = 5.8 Hz, 4H, $2CH_2$), 3.57 (t, *J* = 5.8 Hz, 4H, $2CH_2$), 7.19–7.24 (m, 3H, aryl), 7.32–7.37 (m, 2H, aryl); ^{13}C NMR: δ 14.8, 47.1, 50.2, 53.1, 56.8, 126.9, 128.5, 130.0, 134.8, 170.6; MS (EI) *m/z* (%): 218 (15.6) (M^+). Anal. calcd for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83; found: C, 71.41; H, 8.39; N, 12.94%.

(4-Benzylpiperidin-1-yl)(phenyl)methanone (**2v**): Pale-yellow foam; yield 93%; IR (ν_{max}): 3060, 2935, 1657, 1605, 1428 cm^{-1}; ^1H NMR: δ

1.48–1.54 (m, 4H, $2CH_2$), 1.91–1.94 (m, 1H, CH), 2.65 (s, 2H, PhCH_2), 3.32–3.37 (m, 4H, $2NCH_2$), 7.15–7.21 (m, 5H, aryl), 7.60–7.66 (m, 3H, aryl), 7.85–7.89 (m, 2H, aryl); ^{13}C NMR: δ 24.1, 30.5, 40.7, 43.9, 47.1, 126.0, 127.2, 128.0, 128.5, 129.0, 129.7, 134.6, 139.5, 173.0; MS (EI) *m/z* (%): 279 (17.3) (M^+). Anal. calcd for $C_{19}H_{21}NO$: C, 81.68; H, 7.58; N, 5.01; found: C, 81.79; H, 7.71; N, 5.15%.

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