Latent Brønsted Base Solvent-Assisted Amide Formation from Amines and Acid Chlorides

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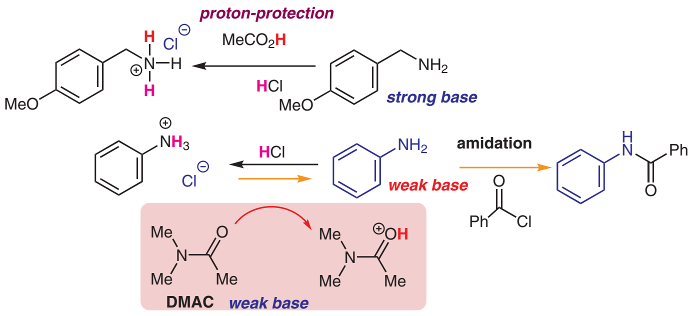

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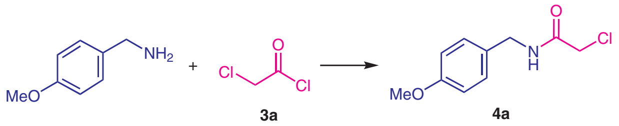
Abstract Weakly basic amines, including even neutral amines such as nitroaniline and aminocarboxylic acids, react with acid chlorides very efficiently in *N*,*N*-dimethylacetamide (DMAC), without addition of a base, to give the corresponding amides in high yields. The role of DMAC and related solvents as latent Brønsted bases was studied in these amidation reactions. Less basic amines, such as aromatic amines, reacted with benzoyl chloride faster than more basic aliphatic amines.

Key words amide, *N*,*N*-dimethylacetamide, urea, Brønsted base, amine, acid chloride

Amide bonds are found in the structures of many active pharmaceutical ingredients (APIs) and related compounds,[1] and amide bond-forming reactions are of continuing interest.[2] Amidation reaction of amines and acid chlorides is an important traditional method in organic synthesis, and many examples of amidation reactions of amines and acid chlorides have been reported (approximately 300 000 hits in the Reaxys® database). In these reactions, *N*,*N*-dimethylformamide (DMF) and *N*,*N*-dimethylacetamide (DMAC) have frequently been utilized as aprotic polar solvents, both on an industrial and laboratory scale (approximately 1800 hits in the database for DMAC as a solvent). Polar solvents can stabilize the charge-polarized transition state of the nucleophilic substitution reaction of acid chloride with amine. In about a half of the examples where DMAC was used as a solvent, a base catalyst such as triethylamine, pyridine and *N*,*N*-diisopropylethylamine (DIPEA, Hünig's base) was added.[3] But, intriguingly, a base catalyst was not used in the remaining half.[4] Thus, although amidation of amines and acid chlorides in DMAC is a common reaction, the full significance of the presence or absence of a base catalyst in this solvent is not still known. If the solvent itself could work as a base, the reaction would be more economic, greener, and more practically useful. Therefore, in this study we examined the effect of DMAC (**1a**) and related solvents as latent bases in the amidation reaction of amines and acid chlorides without addition of a base to neutralize the formed HCl. We show here that DMAC can serve as a latent Brønsted base catalyst;[5] it was effective even in a stoichiometric amount (one equivalent with respect to amine and acyl chloride), and its effect leveled off at two equivalents, indicating that it acts as a reagent rather than as a solvent. In the reactions examined, simple addition of water afforded the amide product either directly as a precipitate, or after in situ recrystallization, and then suction filtration followed by drying in vacuo afford the amide in 70–98% yield with more than 99% purity on a gram scale. Thus, the present methodology is convenient, low-cost, green, and readily applicable for large-scale synthesis, as well as laboratory-scale synthesis.

In DMAC (**1a**), 4-methoxybenzylamine (**2a**) and chloroacetyl chloride (**3a**) gave the corresponding amide **4a** in 78% yield after 2 hours at room temperature in the absence of a base (Table 1, run 1). The yield of the amide **4a** increased to 85%, taking account of additional product extracted from the filtrate with ethyl acetate/*n*-hexane. The reaction yield was unchanged after prolonged reaction (17 h, 79% yield) (run 2). A typical gram-scale experimental procedure was as follows: to a solution of acid chloride in DMAC was added a solution of a slight molar excess of amine in DMAC cooled in an ice-water bath. The mixture was stirred at ambient temperature, and the product was precipitated by adding water. The reverse order of addition, that is, addition of a solution of acid chloride in DMAC to a solution of amine in DMAC gave the same result (82% yield, for details, see the Experimental Section). The reaction was essentially complete within 3 hours. On the other hand, when the reaction of **2a** and **3a** was carried out in a typical acylation solvent,

Table 1 Role of DMAC in Amidation Reaction



Run	Solvent **1**	Additive	Temp (°C)	Time (h)	Yield (%) of amide **4a**
1	DMAC	–	23	2	78[a] (85)[b]
2	DMAC	–	23	17	79[a]
3	CH_2Cl_2	–	23	2	49[c]
4	CH_2Cl_2	–	23	17	45[c]
5	acetone	–	23	17	38[a]
6	EtOAc	–	23	17	38[a] (49)[b]
7	CH_2Cl_2	DMAC (0.5 equiv)	23	17	55[c]
8	CH_2Cl_2	DMAC (1.0 equiv)	23	17	70[c]
9	CH_2Cl_2	DMAC (2.0 equiv)	23	17	82[c]
10	CH_2Cl_2	DMAC (2.0 equiv)	23	2	60[c]
11	acetone	DMAC (2.0 equiv)	23	17	73[a]
12	EtOAc	DMAC (2.0 equiv)	23	17	74[a]
13	CH_2Cl_2	*N*,*N*-dimethylaniline (2.0 equiv)	23	2	87[c]
14	CH_2Cl_2	Et_3N (2.0 equiv)	23	2	53[d]

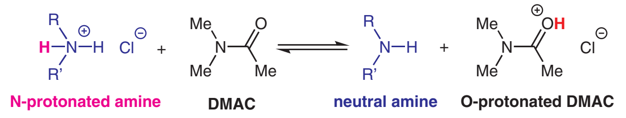
[a] Isolated yield of the precipitate.
[b] Total yield of the product (precipitate plus product extracted from filtrate) is shown in parentheses.
[c] Yield of the product obtained by extraction.
[d] The reaction mixture darkened and the reaction appeared to be complex. Yield of the product obtained by column chromatography.

CH_2Cl_2 (run 3), the reaction stopped at about 50% progress, affording 45% yield of the amide **4a**, even after an extended reaction time of 17 hours (run 4). This is reasonable, because at 50% reaction, the nucleophilicity of the amine is lost due to salt formation with the generated HCl as shown below:

0.5 Amine **2** + 0.5 Acid chloride **3** + 0.5 HCl + 0.5 Amide **4** → 0.5 Amine **2**·HCl + 0.5 Acid chloride **3** + 0.5 Amide **4**

Similar results were obtained with acetone (38% yield) and ethyl acetate (38% yield) (Table 1, runs 5 and 6).

When DMAC was pre-mixed with CH_2Cl_2 solvent (Table 1, runs 7–10), the yield of the corresponding amide **4a** increased with increasing amount of DMAC up to 2 equivalents, at which point the yield of **4a** (run 9, 82%) reached the level obtained in neat DMAC (11 equiv) (run 2, 79%). Similar results were obtained in acetone and ethyl acetate as solvents (runs 11 and 12). When an external base, *N*,*N*-dimethylaniline (2 equiv with respect to amine **2a** or acid chloride **3a**) was added in CH_2Cl_2 solvent (run 13), the yield of the amide **4a** was about the same (87% yield, after extraction) as that obtained by the addition of 2 equivalents of DMAC in CH_2Cl_2 (run 9, 82%). These results suggest that DMAC serves as a weak carbonyl-oxygen Brønsted base ($pK_{BH}{}^+ = -0.19$)[5a–c] to neutralize the HCl, releasing the free amine (see Scheme 1). The amidation of **2a** and **3a** in a mixture of DMAC (2 equiv) and CH_2Cl_2 was rather slow as compared with the reaction in neat DMAC, and when the reaction was quenched after 2 hours, the yield was intermediate (run 10, 60%). On the other hand, the use of triethylamine as an additive in CH_2Cl_2 solvent afforded a dark, complex mixture from which **4a** was isolated in 53% yield by column chromatography (run 14). Triethylamine would induce deprotonation of the α-proton of **3a**, affording a chloroketene intermediate that might generate unidentified polar by-products.[6] Pyridine and DIPEA also produced a colored reaction mixture. Thus, DMAC appears to be advantageous compared with the other bases examined.

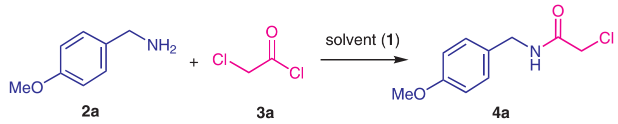


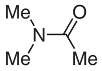
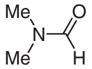
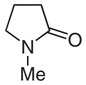
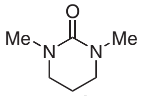
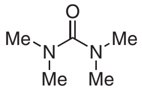
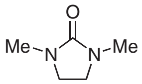
Scheme 1 Protonation equilibrium of amine and DMAC

We also examined the effects of other amide-containing solvents (Tables 2 and 3).

Because ureas are more basic ($pK_{BH}{}^+ = +0.8$) than amides as oxygen bases due to the increased electron density on the oxygen atoms,[5c] we expected that they would also work as latent bases and facilitate the amidation reaction. Indeed, DMF and *N*-methyl-2-pyridone (NMP) worked as well as DMAC (Table 2). The urea-type solvents [*N*,*N*′-dimethylpropyleneurea (DMPU), tetramethylurea (TMU), and 1,3-dimethyl-2-imidazolidinone (DMI)] also facilitated the reaction to similar extent to the amide-type solvents.

Table 2 Solvent Effects of Amidic Solvents



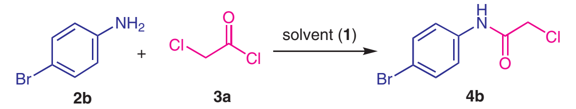
Run	Solvent **1**	Temp (°C)	Time (h)	Yield (%) of amide **4a**
1	 DMAC (**1a**)	23	2	78[a]
2	 DMF (**1b**)	23	2	70[a]
3	 NMP (**1c**)	23	2	75[a]
4	 DMPU (**1d**)	23	2	65[a] (64)[b]
5	 TMU (**1e**)	23	2	18[a] (60)[b]
6	 DMI (**1f**)	23	2	51[a] (55)[b]

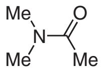
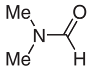
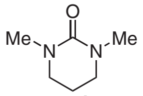
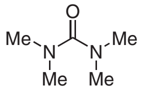
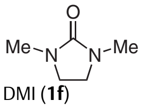
[a] Isolated yield of the precipitate.
[b] Yield of the product obtained by extraction.

However, in the case of the amine **2a** and acid chloride **3a**, the amide product **4a** can be dissolved into a mixture of water and the urea solvent upon aqueous workup; the isolated yield of the precipitate was rather low, particularly in the case of TMU (18% yield, Table 2, run 5). The product **4a** can be obtained by extraction procedure (60% in TMU, see Table 2). DMPU was the best of the urea-type solvents, affording **4a** in 65% yield, as the solid precipitate (run 4).

When the aromatic amine such as an aniline derivative **2b** was used, the reaction proceeded also efficiently to give the corresponding amide **4b** as a precipitate in good yields in DMF, DMPU, TMU, and DMI, respectively, similar to the result found in DMAC (up to 90% yield, Table 3). These data shown in Tables 2 and 3 suggested that the urea-type solvents also have latent basicity similar to the amide-type solvents.

Table 3 Solvent Effects of Amidic Solvents



Run	Solvent **1**	Temp (°C)	Time (h)	Yield (%)[a] of amide **4a**
1	 DMAC (**1a**)	23	1.5	90
2	 DMF (**1b**)	23	1.5	88
3	 DMPU (**1d**)	23	1.5	81
4	 TMU (**1e**)	23	1.5	90
5	 DMI (**1f**)	23	1.5	93

[a] Isolated yield of the precipitate.

The generality of the amide synthesis in DMAC was examined next and the results are summarized in Figure 1. Among the combinations of aliphatic/aromatic and amine/acid chloride examined, we found that aliphatic amine-aliphatic acid chlorides **4a** and **4c–f**, aliphatic amine-aromatic acid chlorides **4g–m**, aromatic amine-aliphatic acid chlorides **4b**, **4n**,**o**, and aromatic amine-aromatic acid chlorides **4p–r** provided the amides in good to moderate yields (51–91%) after simple aqueous workup and filtration to collect the precipitated product, except oil products. Interestingly, the combination of aromatic amines and aromatic acid chlorides reacted more quickly than the aliphatic counterparts, for example, **4b** ↔ **4a** and **4o** ↔ **4d**. This is counterintuitive, because aromatic amines are weaker bases than aliphatic amines in general, and therefore are less nucleophilic.

To understand the above results, we studied the amidation reaction of practically neutral amines in DMAC (Figure 2). The amines studied included anilines substituted with a strongly electron-withdrawing group, for example, ester, nitro, and cyano groups (**5a–f**). We found that DMAC af-

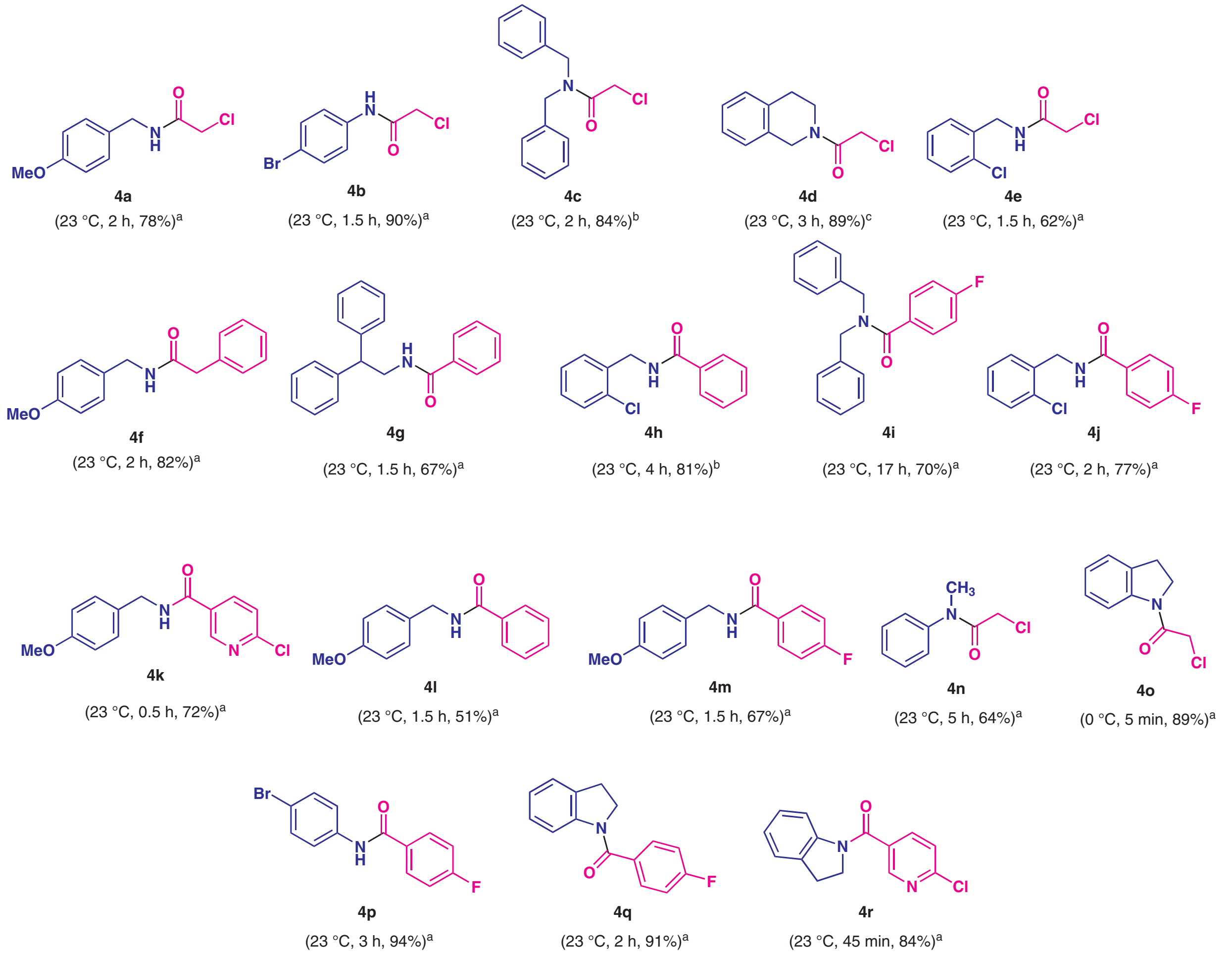
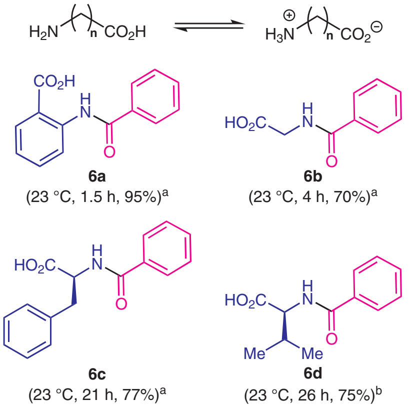


Figure 1 Generality of amidation in DMAC. ^{a} Isolated yield. ^{b} Product obtained as an oil. Isolated yield obtained by column chromatography. ^{c} Product solidified after extraction.

forded a high yield of amide within a short reaction time (up to 98% yield, Figure 2). On the other hand, the $\mathrm{p}K_{\mathrm{BH}}{}^{+}$ values of nitroanilines have been determined to be 2.46 (*meta*, in water) and 1.01 (*para*, in water), respectively,[7] and they are neutral rather than basic.

The reaction is likely to be influenced by the competition for protonation between two weak bases, that is, amine and DMAC, which would increase the concentration of the neutral amine (Scheme 1).

It should be noted that aminocarboxylic acids are zwitterionic (Scheme 2). When the benzoylation of aminocarboxylic acids, such as anthranilic acid (**6a**), and amino acids **6b–d** in DMAC was examined, high yields of the *N*-benzoyl products were obtained (Scheme 2).



Scheme 2 Amidation of aminocarboxylic acids in DMAC. ^{a} Isolated yield of the product. ^{b} Yield of the product obtained by extraction.

Finally, the reactivities of the aliphatic amine **2a** and aromatic amine **2d** were compared toward benzoyl chloride in DMAC in the presence of various acid or base additives (Table 4).

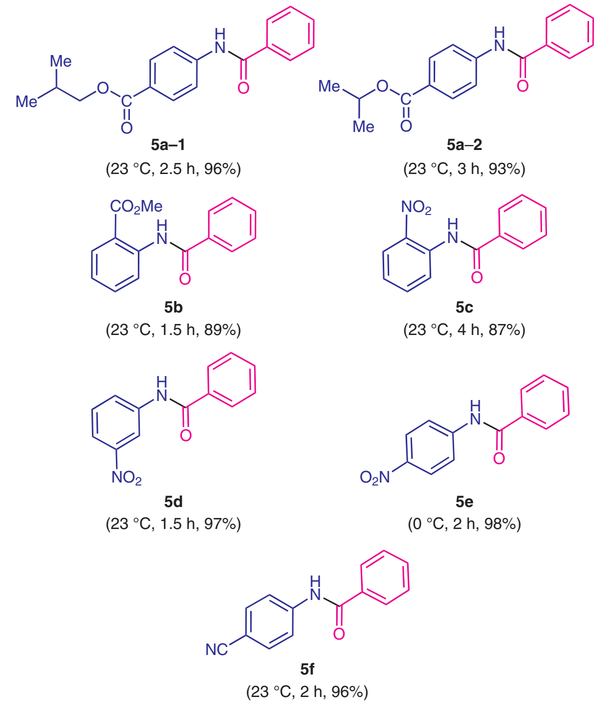
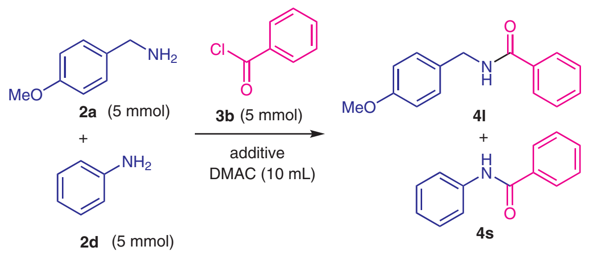


Figure 2 Amidation of neutral amines in DMAC. Isolated yields are shown.

Table 4 Selective Amidation Among Two Amines in DMAC in the Presence of Additives



Run	Additive	Temp (°C)	Time (h)	Yield (%) of amide **4l**/**4s**
1	AcOH (2 equiv)[a]	23	3	8:78[b] [9:91][c]
2	AcOH (5 equiv)[a]	23	3	0:92[b] [0:100][c]
3	Et$_3$N (2 equiv)[a]	23	3	60:28[b] [68:32][c]
4	–	23	3	29:66[b] [31:69][c]

[a] Equivalent amounts with respect to the total amount of amines (10 mmol).
[b] Yields of compounds based on the ^{1}H NMR spectra of the isolated precipitate.
[c] Ratios of amides are shown in square brackets.

As the amount of acetic acid was increased, the yield of amide product **4s** derived from the aromatic amine **2d**, a less basic amine, was increased as compared with the case of amide **4l** derived from the aliphatic amine **2a**, a more basic amine, and selective amidation of the aromatic amide **4s** proceeded in 92% yield without formation of the alternative aliphatic amide **4l** (Table 4, runs 1 and 2) (*proton-protective* effect of **2a**, see also the graphical abstract).[8]

On the other hand, in the presence of triethylamine in DMAC (Table 4, run 3), the aliphatic amide **4l** was formed to a greater extent than the aromatic amide **4s**, probably because the generated HCl was completely neutralized, and the intrinsic difference in nucleophilicity between the aliphatic amine **2a** and the aromatic amine **2d** controlled the product distribution. In the absence of the additive, the reaction in DMAC provided a biased but coexisting distribution of the amides, that is, a 1:2 mixture of **4l** and **4s**, favoring **4s** (run 4). These results are consistent with our hypothesis that less basic aromatic amines react faster than more basic aliphatic amines in DMAC, as implied by the results obtained with various combinations of acid chlorides and amines (Figure 1).

In conclusion, our findings indicate that the present reaction of acid chlorides with amines in amide-type and urea-type solvents in the absence of an added base proceeds in high yield, and is applicable to a broad range of amines. These solvents work as a latent Brønsted base. This methodology is expected to be practically useful for large-scale synthesis, offering a low-cost, green approach that is practically convenient, especially in terms of ease of purification. Further studies of the reaction mechanism are in progress.

Melting points were determined with a Yanaco micro melting point apparatus without correction. ^{1}H NMR (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded on a Bruker Avance 400 spectrometer. Chemical shifts are shown in ppm (δ) values, and the coupling constants are shown in hertz (Hz). Chemical shifts were calibrated with internal TMS or with the solvent peak for the ^{1}H and ^{13}C NMR spectra. Standard abbreviations are used to denote signal multiplicities. Electron spray ionization time-of-flight mass spectra (ESI-TOF MS) were recorded on a Bruker micrOTOF-05 to give high-resolution mass spectra (HRMS). Combustion analysis were carried out in the facility center of this graduate school. All the reagents and solvents were commercially available and used without further purification. In all cases, the yield of the amide product was calculated on the basis of the amount of the acid chloride.

The reaction schemes with numbering of the compounds are illustrated in the Supporting Information.

Amide Formation of 4a (Table 1, run 1)

To a pre-cooled solution of acid chloride **3a** (1.1315 g, 10.02 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2a** (1.4370 g, 10.48 mmol) in DMAC (5 mL) over 3 min and the reaction mixture was stirred at 0 °C for 10 min. A white precipitate was formed. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. The completion of the reaction was confirmed by TLC. H_2O (30 mL) was added to the reaction vessel, and a white precipitate was formed. The whole was stirred for 5 h at 23 °C. The resultant precipitate was collected by suction filtration, and the solid was washed with H_2O (70 mL) and dried in vacuum. Amide **4a** was obtained as a white solid (1.6713 g, 78%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. To check the remaining amount of **4a** in the filtrate, the filtrate was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic fractions were washed with H_2O (3 × 50 mL) and dried ($MgSO_4$). The organic solvent was evaporated to give a colorless liquid (1.0910 g), which was mixture of **4a** and DMAC. The calculated amount of **4a** in the extract was 0.1420 g (6.6%) on the basis of the integration of the ^{1}H NMR signals. Therefore, the total yield of the product **4a** (precipitate plus product extracted from filtrate) is 85%; colorless plates; mp 102 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.220 (2 H, d, *J* = 8.8 Hz), 6.880 (2 H, d, *J* = 8.8 Hz), 6.832 (1 H, br), 4.418 (2 H, d, *J* = 5.6 Hz), 4.075 (2 H, s), 3.800 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.79, 159.35, 129.45, 129.32, 114.30, 55.41, 43.46, 42.71.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{10}H_{12}ClNO_2Na$: 236.0449; found: 236.0451.

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.22; H, 5.66; N, 6.56. Found: C, 55.98; H, 5.63; N, 6.61

Reverse Addition: Addition of Acid Chloride to Amine

To a pre-cooled solution of amine **2a** (1.4423 g, 10.51 mmol) at 0 °C (ice-water bath) was added a solution of **3a** (1.1357 g, 10.06 mmol) in DMAC (5 mL) over 5 min. A white precipitate was formed. The reaction mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. The completion of the reaction was confirmed by TLC. H_2O (40 mL) was added to the reaction vessel to give a white precipitate. The whole was stirred for overnight at 23 °C. The resultant precipitate was collected by suction filtration, and washed with H_2O, and dried in vacuum. Amide **4a** was obtained as a white solid (1.7549 g, 82%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4a (Table 1, run 2)

A solution of acid chloride **3a** (1.1045 g, 9.78 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4012 g, 10.22 mmol) in DMAC (5 mL) was added over 4 min with stirring at 0 °C. A white precipitate was formed and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 17 h. H_2O (30 mL) was added and the mixture was stirred for 23 h at 23 °C. The resultant precipitate was collected by suction filtration, washed with H_2O (100 mL), and dried in vacuum. Amide **4a** was obtained as a white solid (1.6547 g, 79%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product **4a** was identical with the authentic compound in terms of ^{1}H NMR ($CDCl_3$) and combustion analysis.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.227 (2 H, d, *J* = 8.8 Hz), 6.886 (2 H, d, *J* = 8.7 Hz), 6.784 (1 H, br s), 4.429 (2 H, d, *J* = 5.7 Hz), 4.093 (2 H, s), 3.808 (3 H, s).

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.22; H, 5.66; N, 6.56. Found: C, 56.08; H, 5.69; N, 6.63.

Amide Formation of 4a (Table 1, run 3)

A solution of acid chloride **3a** (1.3344 g, 11.82 mmol) in CH_2Cl_2 (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4400 g, 10.50 mmol) in CH_2Cl_2 (5 mL) was added over 5 min with stirring at 0 °C. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. H_2O (30 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic fractions were washed twice with H_2O (80 mL in total) and dried ($MgSO_4$). The solvent was evaporated to give **4a** as a white solid, which was dried in vacuum (1.1042 g, 49%). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR ($CDCl_3$) and the combustion analysis. Solid NaOH (1.35 g) was added to basify the aqueous fraction. The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was evaporated to give the recovered amine **2a** as a colorless oil (0.6280 g, 46% recovery).

Amide Formation of 4a (Table 1, run 4)

A solution of acid chloride **3a** (1.3261 g, 11.74 mmol) in CH_2Cl_2 (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.2448 g, 9.07 mmol) in CH_2Cl_2 (5 mL) was added over 3 min with stirring at 0 °C. A white precipitate was formed and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 17 h. H_2O (30 mL) was added. The mixture was extracted with CH_2Cl_2 (3 × 20 mL), the combined organic fractions were washed thrice with H_2O (150 mL in total), and dried ($MgSO_4$). The solvent was evaporated to give **4a** as a white solid, which was dried in vacuum (0.8788 g, 45%). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR ($CDCl_3$) and the combustion analysis. Solid NaOH (0.96 g) was added to basify the aqueous fraction. The aqueous fraction was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic layers were dried ($MgSO_4$), and the solvent was evaporated to give the recovered amine **2a** as a colorless oil (0.5663 g, 45% recovery).

Amide Formation of 4a (Table 1, run 5)

A solution of acid chloride **3a** (1.1301 g, 10.01 mmol) in acetone (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4388 g, 10.49 mmol) in acetone (5 mL) was added over 3 min with stirring at 0 °C and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the whole was stirred at 23 °C for 17 h. H_2O (30 mL) was added to give a white precipitate and the suspension was stirred for 4 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Absence of product in the filtrate was checked by TLC. Product **4a** was obtained as a white solid (0.8124 g, 38%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4a (Table 1, run 6)

A solution of acid chloride **3a** (1.1336 g, 10.04 mmol) in EtOAc (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). While stirring and cooling at 0 °C, a solution of amine **2a** (1.4433 g, 10.52 mmol) in EtOAc (5 mL) was added over 4 min. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 17 h. H_2O (30 mL) was added and the whole was stirred for 15 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **4a** was obtained as a white solid (0.8124 g, 38%). The filtrate was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic fractions were washed with H_2O (3 × 50 mL), and dried ($MgSO_4$). The solvent was evaporated to give an additional amount of **4a** (0.2302 g) as a white solid, which was dried in vacuum. The combined yield of **4a** was 49% (1.0426 g). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4a (Table 1, run 7)

CH_2Cl_2 was added to DMAC (0.4341 g, 4.98 mmol, 0.5 equiv) to make a total 10 mL solution. A solution of acid chloride **3a** (1.1383 g, 10.08 mmol) in the above CH_2Cl_2/DMAC solvent mixture (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4469 g, 10.547 mmol) in CH_2Cl_2/DMAC (5 mL) was added over 4 min. The mixture was stirred at 0 °C for 12 min. The ice-water bath was replaced with a water bath and the whole was stirred at 23 °C for 17 h. H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic fractions were washed with H_2O (3 × 50 mL), and dried ($MgSO_4$). The solvent was evaporated to give a white solid, which was dried in vacuum to give **4a** (1.1791 g, 55%). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4a (Table 1, run 8)

CH_2Cl_2 was added to DMAC (0.8725 g, 10.02 mmol, 1 equiv) to make a total 10 mL volume of the solvent mixture DMAC/CH_2Cl_2. A solution of acid chloride **3a** (1.1329 g, 10.03 mmol) in DMAC/CH_2Cl_2 (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4385 g, 10.486 mmol) in DMAC/CH_2Cl_2 (5 mL) was added over 4 min. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 17 h. H_2O (30 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic fractions were washed with H_2O (3 × 50 mL), and dried ($MgSO_4$). The solvent was evaporated to give a white solid, which was dried in vacuum to give **4a** (1.5062 g, 70%). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4a (Table 1, run 9)

CH_2Cl_2 was added to DMAC (1.7683 g, 20.30 mmol, 2 equiv) to make a total 10 mL solution of DMAC/CH_2Cl_2 solvent mixture. A solution of acid chloride **3a** (1.1303 g, 10.01 mmol) in DMAC/CH_2Cl_2 (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4384 g, 10.49 mmol) in DMAC/CH_2Cl_2 (5 mL) was added over 3 min with stirring at 0 °C and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 17 h. H_2O (30 mL) was added and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The combined organic fractions were washed with H_2O (3 × 50 mL) and dried ($MgSO_4$). The solvent was evaporated to give **4a** as a white solid, which was dried in vacuum (1.7519 g, 82%). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4a (Table 1, run 10)

CH_2Cl_2 was added to DMAC (1.7376 g, 19.99 mmol, 2 equiv) to make a total 10 mL solution of the DMAC/CH_2Cl_2 solvent mixture. A solution of acid chloride **3a** (1.1336 g, 10.04 mmol) in DMAC/CH_2Cl_2 (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4426 g, 10.52 mmol) in DMAC/CH_2Cl_2 (5 mL) was added over 3 min with stirring at 0 °C and the whole was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. H_2O (30 mL) was added. The mixture was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic fractions were washed with H_2O (3 × 50 mL), and dried ($MgSO_4$). The solvent was evaporated to give **4a** as a white solid, which was dried in vacuum (1.2890 g, 60%). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4a (Table 1, run 11)

Acetone was added to DMAC (1.7431 g, 20.01 mmol, 2 equiv) to make a total 10 mL solution of DMAC/acetone solvent mixture. A solution of acid chloride **3a** (1.1360 g, 10.06 mmol) in DMAC/acetone (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4497 g, 10.57 mmol) in DMAC/acetone (5 mL) was added over 3 min with stirring at 0 °C. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 17 h. H_2O (30 mL) was added to give a white precipitate, which was stirred for 22 h. The solid was filtered by suction, washed with H_2O (70 mL), and dried in vacuum to give **4a** as a white solid (1.5788 g, 73%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4a (Table 1, run 12)

EtOAc was added to DMAC (1.7483 g, 20.07 mmol, 2 equiv) to make a total 10 mL solution of DMAC/EtOAc solvent mixture. A solution of acid chloride **3a** (1.1232 g, 9.95 mmol) in DMAC/EtOAc (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4362 g, 10.47 mmol) in DMAC/EtOAc (5 mL) was added over 3 min with stirring at 0 °C. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 17 h. The completion of the reaction was confirmed by TLC. H_2O (30 mL) was added to give a white precipitate and the mixture was stirred for 2 h. The solid was filtered by suction, washed with H_2O (60 mL), and dried in vacuum to give **4a** as a white solid (1.5788 g, 74%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR (CDCl$_3$) and combustion analysis.

Amide Formation of 4a (Table 1, run 13)

CH$_2$Cl$_2$ was added to *N*,*N*-dimethylaniline (2.4331 g, 20.08 mmol) to make a total 5 mL solution of *N*,*N*-dimethylaniline/CH$_2$Cl$_2$ solvent mixture. A solution of acid chloride **3a** (1.1316 g, 10.02 mmol) in CH$_2$Cl$_2$ (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4435 g, 10.52 mmol) in *N*,*N*-dimethylaniline/CH$_2$Cl$_2$ (5 mL) was added over 3 min with stirring at 0 °C. The whole was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. H$_2$O (30 mL) was added. The mixture was extracted with CH$_2$Cl$_2$ (4 × 20 mL), the combined organic fractions were washed with 0.01 M aq HCl (3 × 50 mL), and dried (MgSO$_4$). The solvent was evaporated to give **4a** as a white solid, which was washed with H$_2$O (50 mL) and *n*-hexane (50 mL), followed by drying in vacuum (1.8619 g, 87%). The product was pure enough to give a satisfactory combustion analysis without further purification.

Amide Formation of 4a (Table 1, run 14)

CH$_2$Cl$_2$ was added to Et$_3$N (2.0332 g, 20.09 mmol) to make a total 10 mL solution of Et$_3$N/CH$_2$Cl$_2$ solvent mixture. A solution of acid chloride **3a** (1.1313 g, 10.02 mmol) in Et$_3$N/CH$_2$Cl$_2$ (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4373 g, 10.48 mmol) in Et$_3$N/CH$_2$Cl$_2$ (5 mL) was added over 5 min with stirring at 0 °C. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. H$_2$O (30 mL) and aq 2 M HCl (8 mL) were added. The mixture was extracted with CH$_2$Cl$_2$ (4 × 20 mL), the combined organic fractions were washed with H$_2$O (3 × 50 mL), and dried (MgSO$_4$). The solvent was evaporated to give a black solid. The solid was dried in vacuum (1.5088 g). The product was purified by open-chromatography (EtOAc/hexane 1:1) to give **4a** (1.1329 g, 53%). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR (CDCl$_3$) and combustion analysis.

Amide Formation of 4a (Table 2, run 2)

A solution of acid chloride **3a** (1.1353 g, 10.05 mmol) in DMF (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.4460 g, 10.54 mmol) in DMF (5 mL) was added over 3 min with stirring at 0 °C and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 25 °C for 2 h. The completion of the reaction was confirmed by TLC, and H$_2$O (30 mL) was added to give a white precipitate. The mixture was stirred for 21 h. The solid was filtered by suction, washed with H$_2$O (80 mL), and dried in vacuum. Amide **4a** was obtained as a white solid (1.5134 g, 70%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR (CDCl$_3$) and combustion analysis.

Amide Formation of 4a (Table 2, run 3)

To a pre-cooled solution of acid chloride **3a** (1.1283 g, 9.99 mmol) in NMP (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2a** (1.4619 g, 10.66 mmol) in NMP (5 mL) over 2 min and the reaction mixture was stirred at 0 °C for 5 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. H$_2$O (30 mL) was added to the reaction vessel and the resultant precipitate was collected by suction filtration, washed with H$_2$O, and dried in vacuum. Amide **4a** was obtained as a white solid (1.6086 g, 75%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR (CDCl$_3$) and combustion analysis.

Amide Formation of 4a (Table 2, run 4)

Precipitation Method: A solution of acid chloride **3a** (1.1294 g, 10.0 mmol) in DMPU (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). While stirring and cooling at 0 °C, a solution of amine **2a** (1.4351 g, 10.46 mmol) in DMPU (5 mL) was added over 3 min. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. The completion of the reaction was confirmed by TLC, and H$_2$O (30 mL) was added to give a white precipitate. The mixture was stirred for 17 h and the solid obtained was filtered by suction. The filtration residue was washed with H$_2$O (70 mL) and dried in vacuum to give **4a** as a white solid (1.3800 g, 65%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR (CDCl$_3$) and combustion analysis.

Extraction Method: To acid chloride **3a** (1.1324 g, 10.03 mmol) was added DMPU (5 mL) over 4 min at 0 °C (ice-water bath). To this solution was added a solution of amine **2a** (1.3758 g, 10.03 mmol) in DMPU (5 mL) over 5 min at 0 °C with stirring. The mixture was stirred at 0 °C for 5 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. Pale yellow viscous solution was obtained. The completion of the reaction was confirmed by TLC, and H$_2$O (80 mL) was added to give a white precipitate. The mixture was extracted with EtOAc (60 mL). The organic layer was washed with H$_2$O (280 mL in total) repeatedly. The filtration residue was dried (MgSO$_4$) and the solvent was evaporated to give **4a** as a white power (1.3736 g, 64%). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR (CDCl$_3$) and combustion analysis.

Amide Formation of 4a (Table 2, run 5)

Precipitation Method: To a pre-cooled solution of acid chloride **3a** (1.1417 g, 10.11 mmol) in TMU (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2a** (1.4426 g, 10.52 mmol) in TMU (5 mL) over 4 min. The mixture was stirred at 0 °C for 30 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. H$_2$O (60 mL) was added to the reaction vessel and the resultant white precipitate was collected by suction filtration, washed with H$_2$O, and dried in vacuum. Amide **4a** was obtained as a white solid (386.0 mg, 18%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^{1}H NMR (CDCl$_3$) and combustion analysis.

Extraction Method: To a pre-cooled solution of acid chloride **3a** (1.1305 g, 10.01 mmol) in TMU (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2a** (1.3778 g, 10.04 mmol) in TMU (5 mL) over 2 min at 0 °C. A white precipitate was formed and the mixture was stirred at 0 °C for 5 min. The ice-water bath was replaced with a water bath and the whole was stirred at 23 °C for 2 h. H$_2$O (40 mL) was added to the reaction vessel, and the suspension with the white precipitate was extracted with EtOAc (180 mL), and the organic layer was washed with H_2O (200 mL) and dried ($MgSO_4$). Evaporation of the organic solvent gave **4a** as a white solid (1.2852 g, 60%). The product was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4a (Table 2, run 6)

Precipitation Method: To a pre-cooled solution of acid chloride **3a** (1.1263 g, 9.97 mmol) in DMI (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2a** (1.4574 g, 10.47 mmol) in DMI (5 mL) over 2 min. The mixture was stirred at 0 °C for 20 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. H_2O (20 mL) was added to the reaction vessel and the resultant white precipitate was collected by suction filtration, and washed with H_2O, and dried in vacuum. Amide **4a** was obtained as a white solid (1.0840 g, 51%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Extraction Method: To a pre-cooled solution of acid chloride **3a** (1.1275 g, 9.98 mmol) in TMU (5 mL) prepared at 0 °C (ice-water bath) was added a solution of amine **2a** (1.3795 g, 10.06 mmol) in TMU (5 mL) over 3 min at 0 °C. A white precipitate was formed and the mixture was stirred at 0 °C for 5 min. The ice-water bath was replaced with a water bath and the whole was stirred at 23 °C for 2 h. H_2O (50 mL) was added to the reaction vessel, and a white precipitate formed. The whole was extracted with EtOAc (80 mL) and the organic layer was repeatedly washed with H_2O (200 mL in total), and dried ($MgSO_4$). Evaporation of the organic solvent gave **4a** as a white solid (1.1778 g, 55%). The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4b (Table 3, run 1)

A solution of acid chloride **3a** (1.0934 g, 9.68 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2b** (1.8025 g, 10.48 mmol) in DMAC (5 mL) was added over 5 min with stirring at 0 °C and the mixture was stirred at 0 °C for 10 min. The ice bath was replaced with a water bath and the mixture was stirred 23 °C for 1.5 h. Completion of reaction was confirmed by TLC, and H_2O (30 mL) was added to give a white precipitate. After stirring the mixture overnight, the solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **4b** was obtained as a white solid (2.1606 g, 90%). The product was pure enough to give a satisfactory combustion analysis without further purification.

Amide Formation of 4b (Table 3, run 2)

A solution of acid chloride **3a** (1.1276 g, 9.98 mmol) in DMF (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2b** (1.8398 g, 10.69 mmol) in DMF (5 mL) was added over 5 min with stirring at 0 °C and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. A white precipitate was formed and the mixture was stirred for 17 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **4b** was obtained as a white solid (2.1918 g, 88%), which was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4b (Table 3, run 3)

To a pre-cooled solution of acid chloride **3a** (1.1222 g, 9.94 mmol) in DMPU (5 mL) prepared at 0 °C (ice-water bath), was added a solution of amine **2a** (1.7196 g, 10.00 mmol) in DMPU (5 mL) over 2 min. The whole was stirred at 0 °C for 10 min. No precipitate was formed. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. H_2O (80 mL) was added to the reaction vessel, and the resultant white precipitate was collected by suction filtration, washed with H_2O, and dried in vacuum. Amide **4b** was obtained as a white solid (2.0077 g, 81%). The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4b (Table 3, run 4)

A solution of acid chloride **3a** (1.1526 g, 10.21 mmol) in TMU (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 5 °C (ice-water bath). While stirring and cooling at 5 °C, a solution of amine **2b** (1.8148 g, 10.55 mmol) in TMU (5 mL) was added over 5 min. The mixture was stirred at 5 °C for 10 min. The ice bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. The mixture with the white precipitate formed was stirred overnight. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **4b** was obtained (2.2709 g, 90%) as a white solid. The precipitate was pure enough to give a satisfactory combustion analysis without further purification. The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4b (Table 3, run 5)

A solution of acid chloride **3a** (1.1451 g, 10.14 mmol) in DMI (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). While stirring and cooling at 0 °C, a solution of amine **2b** (1.8394 g, 10.69 mmol) in DMI (5 mL) was added over 5 min. The mixture turned yellow and was stirred at 0 °C for 10 min. The ice bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. The mixture became pale yellow and a white precipitate was formed. The mixture was stirred overnight. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **4b** was obtained as a white solid (2.3506 g, 93%). The product was identical with the authentic compound in terms of ^1H NMR ($CDCl_3$) and combustion analysis.

Amide Formation of 4c (Figure 1)

To a pre-cooled solution of acid chloride **3-4c** (1.1269 g, 9.98 mmol) in DMAC (5 mL) to 0 °C (ice-water bath) was added a solution of amine **2-4c** (2.0800 g, 10.54 mmol) in DMAC (5 mL) over 4 min. The ice bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. The completion of the reaction was confirmed by TLC, and H_2O (20 mL) was added. The oily product formed was extracted with EtOAc (100 mL in total) and the combined organic fractions were washed with brine (200 mL). The organic fraction was evaporated to give a colorless viscous oil, which was flash-column chromatographed with EtOAc/*n*-hexane (1:4) to give 2.3008 g (84%) of **4c** as a colorless oil. The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.392–7.148 (10 H, m), 4.613 (2 H, s), 4.509 (2 H, s), 4.141 (2 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.28, 136.32, 135.60, 129.08, 128.69, 128.19, 127.94, 127.64, 126.40, 50.23, 48.60, 41.31.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{16}ClNONa^+$: 296.08126; found: 296.08137.

Anal. Calcd for $C_{16}H_{16}ClNO$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.27; H, 6.04; N, 5.10.

Amide Formation of 4d (Figure 1)

To a pre-cooled solution of acid chloride **3-4d** (1.1255 g, 9.97 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2-4d** (1.3964 g, 10.48 mmol) in DMAC (5 mL) over 4 min and the mixture was stirred at 0 °C for 10 min. A yellow precipitate was formed. The ice-water bath was replaced with a water bath and the whole was stirred at 23 °C for 3 h. The completion of the reaction was confirmed by TLC. H_2O (30 mL) and 2 M aq HCl (2 mL) were added to the reaction vessel. The mixture was extracted with EtOAc/*n*-hexane (2:1 v/v, 4 × 25 mL) and the combined organic layers were washed with H_2O (2 × 50 mL). The organic fraction was dried ($MgSO_4$), and the solvent evaporated to give **4d** as a pale yellow solid (1.8638 g, 89%); mp 50–51 °C (colorless plates after recrystallization from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.249 (4 H, m), 4.231 (2 H, s), 3.833 (2 H, t, *J* = 6.7 Hz), 2.744 (2 H, t, *J* = 6.3 Hz), 2.001 (2 H, t, *J* = 6.7 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 138.5, 128.8, 126.7, 126.2, 123.8, 44.0, 42.0, 26.7, 23.9.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{12}ClNONa^+$: 232.0500; found: 232.0505.

Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 62.87; H, 5.84; N, 6.68.

Amide Formation of 4e (Figure 1)

A solution of acid chloride **3-4e** (1.1367 g, 10.07 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2-4e** (1.4868 g, 10.50 mmol) in DMAC (5 mL) was added over 5 min with stirring at 0 °C. The mixture was stirred at 0 °C for 14 min. A white precipitate was formed. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. A white precipitate was formed and the mixture was stirred for 14 h. The solid was filtered by suction, washed with H_2O (100 mL) and dried in vacuum to give **4e** as a white powder (1.3640 g, 62%); mp 76–77 °C; mp 75–77 °C (colorless needles after recrystallization from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.414–7.359 (2 H, m), 7.270 (1 H, dd, *J* = 3.9, 3.5 Hz), 7.247 (1 H, dd, *J* = 3.3, 3.3 Hz), 7.068 (1 H, br s), 4.587 (2 H, d, *J* = 6.1 Hz), 4.086 (2 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.96, 134.89, 133.89, 130.35, 129.81, 129.42, 127.33, 42.75, 41.95.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$) calcd for $C_9H_{10}Cl_2NO^+$: 218.0134; found: 218.0137.

Anal. Calcd for $C_9H_9Cl_2NO$: C, 49.57; H, 4.16; N, 6.42. Found: C, 49.37; H, 4.18; N, 6.43.

Amide Formation of 4f (Figure 1)

A solution of acid chloride **3-4f** (1.5344 g, 9.93 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2-4f** (1.4389 g, 10.49 mmol) in DMAC (5 mL) was added over 4 min with stirring at 0 °C. A white precipitate was formed and the mixture was stirred at 0 °C for 12 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. The completion of the reaction was confirmed by TLC. H_2O (30 mL) was added and the mixture was stirred for 18 h. The mixture was extracted with CH_2Cl_2 (4 × 20 mL) and the combined organic fraction was washed with H_2O (3 × 50 mL). The organic fraction was dried ($MgSO_4$), and the solvent was evaporated to give a white solid, which was dried in vacuum (2.0831 g, 82%). The solid was washed with H_2O (100 mL), filtered, and dried in vacuum to give **4f** (1.5137 g, 60%); colorless needles; mp 139–140 °C (MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.366–7.294 (5 H, m), 7.107 (2 H, ddd, *J* = 8.7, 2.9, 2.1 Hz), 6.824 (2 H, ddd, *J* = 8.7, 2.9, 2.0 Hz), 4.345 (2 H, d, *J* = 5.7 Hz), 3.782 (3 H, s), 3.617 (2 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.72, 158.90, 134.79, 130.17, 129.38, 128.98, 128.84, 127.31, 113.98, 55.23, 43.78, 43.04.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{17}NO_2Na^+$: 278.11515; found: 278.11732.

Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.27; H, 6.71; N, 5.49. Found: C, 75.21; H, 6.77; N, 5.47.

Amide Formation of 4g (Figure 1)

A solution of acid chloride **3-4g** (1.4247 g, 10.14 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). While stirring and cooling at 0 °C, a solution of amine **2-4g** (2.2351 g, 11.33 mmol) in DMAC (5 mL) was added over 8 min at 0 °C. The mixture was stirred at 0 °C for 10 min. The ice bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. The completion of the reaction was confirmed by TLC, and H_2O (20 mL) was added. A white precipitate was formed and the mixture was stirred overnight. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. The precipitated amide **4g** was obtained as a white powder (2.0365 g, 67%); mp 144–145 °C; mp 145–146 °C (colorless needles after recrystallized from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.571 (2 H, d, *J* = 7.2 Hz), 7.44 (1 H, tt, *J* = 7.4, 1.2 Hz), 7.372–7.213 (12 H, m), 4.325 (1 H, t, *J* = 8.0 Hz), 4.089 (2 H, dd, *J* = 8.0 Hz, 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.60, 141.95, 134.70, 131.53, 128.93, 128.65, 128.21, 127.05, 126.90, 50.65, 44.38.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$) calcd for $C_{21}H_{19}NONa$: 324.1359; found: 324.1363.

Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H,6.35; N, 4.65. Found: C, 83.40; H, 6.50; N, 4.66.

Amide Formation of 4h (Figure 1)

To a pre-cooled solution of acid chloride **3-4h** (1.4000 g, 9.96 mmol) in DMAC (5 mL) (prepared at 0 °C in an ice-water bath) was added a solution of amine **2-4h** (1.4838 g, 10.48 mmol) in DMAC (5 mL) over 3 min at 0 °C and stirred at 0 °C for 10 min. A white precipitate was formed. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 4 h. The completion of the reaction was confirmed by TLC. H_2O (40 mL) was added to the reaction vessel to give a white precipitate and the mixture was stirred for 14 h at 23 °C. The resultant precipitate was collected by suction filtration, the solid was washed with H_2O (70 mL), and dried in vacuum. Amide **4h** was obtained as a white solid (1.9768 g, 81%); mp 119–121 °C (colorless plates after frecrystallization from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.786 (2 H, d, *J* = 7.0 Hz), 7.525–7.739 (5 H, m), 7.255–7.237 (2 H, m), 6.621 (1 H, br s), 4.732 (2 H, d, *J* = 6.0 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.5, 135.7, 134.4, 133.9, 131.8, 130.6, 129.7, 129.2, 128.8, 127.3, 127.1, 42.2.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$) calcd for $C_{14}H_{12}ClNONa^+$: 268.0500; found: 268.0513.

Anal. Calcd for $C_{14}H_{12}ClNO$: C, 68.44; H, 4.92; N, 5.70. Found: C, 68.23; H, 5.15; N, 5.73.

Amide Formation of 4i (Figure 1)

To a pre-cooled solution of acid chloride **3-4i** (1.5871 g, 10.02 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2-4i** (2.0790 g, 10.54 mmol) in DMAC (5 mL) over 3 min and the mixture was stirred at 0 °C for 3 min. A white precipitate was formed. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 18 h. The completion of the reaction was confirmed by TLC. H_2O (30 mL) was added to the reaction vessel, the resultant white precipitate was collected by suction filtration, washed with H_2O, and dried in vacuum. The product was contaminated with 4-fluorobenzoic acid. Therefore, the solid was dissolved in CH_2Cl_2 (100 mL), and the organic layer was washed with sat. aq $NaHCO_3$ (50 mL) and brine (40 mL), and dried ($MgSO_4$). Evaporation of the solvent gave **4i** as a white power (2.2358 g, 70%); mp 93–95 °C. The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.497 (2 H, dd, *J* = 8.8, 5.2 Hz), 7.377–7.137 (10 H, m), 7.051 (2 H, t, *J* = 8.8 Hz), 4.697 (2 H, s), 4.406 (2 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.29, 163.3 (d, $^1J_{C,F}$ = 248 Hz), 136.72, 136.24, 132.13, 132.09, 129.02, 128.94, 128.80, 128.39, 127.62, 126.83, 115.6 ($^2J_{C,F}$ = 22 Hz), 51.57, 47.15.

Anal. Calcd for $C_{21}H_{18}FNO$: C, 78.98; H, 5.68; N, 4.39. Found: C, 78.73; H, 5.92; N, 4.39.

Amide Formation of 4j (Figure 1)

A solution of acid chloride **3-4j** (1.5893 g, 10.02 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2-4j** (1.4865 g, 10.50 mmol) in DMAC (5 mL) was added over 5 min with stirring at 0 °C. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. A white precipitate was formed and the mixture was stirred for 13 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **4j** was obtained as a white powder (2.0227 g, 77%); mp 107–108 °C; mp 107–109 °C (colorless prisms after recrystallization from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.791 (2 H, dddd, *J* = 8.9, 5.3, 3.0, 2.2 Hz), 7.446 (1 H, dd, *J* = 5.8, 3.4 Hz), 7.385 (1 H, dd, *J* = 5.6, 3.6 Hz), 7.266–7.223 (2 H, m), 7.094 (2 H, dd, *J* = 8.6, 8.6 Hz), 6.660 (1 H, s), 4.700 (2 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.1, 165.1 (d, $^1J_{C,F}$ = 285 Hz), 135.6, 133.8, 130.5 (d, $^4J_{C,F}$ = 3.0 Hz), 130.5, 129.7, 129.5 (d, $^3J_{C,F}$ = 9.3 Hz), 129.2, 127.3, 115.7 (d, $^2J_{C,F}$ = 22 Hz), 42.2.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{11}ClFNONa^+$: 286.0405; found: 286.0415.

Anal. Calcd for $C_{14}H_{11}ClFNO$: C, 63.77; H, 4.20; N, 5.31. Found: C, 63.63; H, 4.40; N, 5.31.

Amide Formation of 4k (Figure 1)

A solution of acid chloride **3-4k** (1.0476 g, 5.95 mmol) in DMAC (3 mL) was prepared at r.t. The solution was transferred into a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). While stirring and cooling at 0 °C, a solution of amine **2-4k** (0.8560 g, 6.24 mmol) in DMAC (3 mL) was added over 3 min. The mixture was stirred at 0 °C for 4 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 0.5 h. The completion of the reaction was confirmed by TLC, and H_2O (20 mL) was added. An increase in the white precipitate was noted and the mixture was stirred for 19 h. The solid was filtered by suction, washed with H2O (100 mL), and dried in vacuum. Amide **4k** was obtained as a white solid (1.1792 g, 72%); mp 139 °C; colorless powder after recrystallized from MeOH. The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.731 (1 H, dd, *J* = 2.5, 0.7 Hz), 8.084 (1 H, dd, *J* = 8.3, 2.5 Hz), 7.390 (1 H, dd, *J* = 8.3, 0.7 Hz), 7.257 (2 H, ddd, *J* = 8.3, 3.2, 1.9 Hz), 6.871 (2 H, ddd, *J* = 8.8, 2.9, 2.0 Hz), 6.631 (1 H, br), 4.557 (2 H, d, *J* = 5.4 Hz), 3.796 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.49, 159.42, 154.36, 148.05, 140.16, 138.18, 129.55, 129.12, 124.52, 114.372, 55.45, 43.97.

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}ClN_2O_2^+$: 277.0738; found: 277.0731.

Anal. Calcd for $C_{14}H_{13}ClN_2O_2$: C, 60.77; H, 4.74; N, 10.12. Found: C, 60.68; H, 4.87; N, 10.10.

Amide Formation of 4l (Figure 1)

A solution of acid chloride **3-4l** (1.4187 g, 10.09 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2-4l** (1.4443 g, 10.53 mmol) in DMAC (5 mL) was added over 4 min with stirring at 0 °C. A white precipitate was formed and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. The white precipitate formed was dissolved and was formed again. The mixture was stirred for 17 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **4l** was obtained as a white solid (1.2393 g, 51%); mp 96–98 °C (precipitate, colorless fine needles); mp 101 °C (colorless needles, recrystallized from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.127 (1 H, dd, *J* = 9.0, 5.4 Hz), 7.790 (2 H, dd, *J* = 8.9, 5.3 Hz), 7.285 (2 H, ddd, *J* = 8.7, 3.0, 2.1 Hz), 7.177–7.072 (3 H, m), 6.891 (2 H, ddd, *J* = 8.7, 3.0, 2.1 Hz), 4.573 (2 H, d, *J* = 5.4 Hz), 3.808 (3 H, s).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 167.25, 159.04, 134.38, 131.43, 130.23, 129.24, 128.50, 126.91, 114.08, 55.26, 43.56.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{15}NO_2Na^+$: 264.09950; found: 264.09937.

Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found (precipitate): C, 74.66; H, 6.38; N, 5.70. Found (crystal): C, 74.46; H, 6.38; N, 5.83.

Amide Formation of 4m (Figure 1)

A solution of acid chloride **3-4m** (1.5893 g, 10.02 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2-4m** (1.4391 g, 10.49 mmol) in DMAC (5 mL) was added over 4 min with stirring at 0 °C. A white precipitate was formed and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. The white precipitate formed was dissolved and was formed again. The mixture was stirred for 18 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **4m** was obtained as a white solid (1.7441 g, 67%)mp 117–118 °C (colorless plates after recrystallized from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.778 (2 H, d, *J* = 7.0 Hz), 7.497 (1 H, t, *J* = 7.3 Hz), 7.420 (2 H, d, d, *J* = 7.8, 5.4 Hz), 7.290 (2 H, d, *J* = 8.8 Hz), 6.889 (2 H, d, *J* = 8.7 Hz), 4.580 (2 H, d, *J* = 5.6 Hz), 3.806 (3 H, s).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.18, 165.92, 163.42, 159.12, 130.58, 130.55, 130.08, 129.28, 129.20, 115.65, 115.43, 114.13, 55.28, 43.66.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{14F}NO_2Na^+$: 282.09008; found: 282.08946.

Anal. Calcd for $C_{15}H_{14}FNO_2$: C, 69.49; H, 5.44; N, 5.40. Found (crystal): C, 69.37; H, 5.63; N, 5.44.

Amide Formation of 4n (Figure 1)

To a pre-cooled solution of acid chloride **3-4n** (1.1219 g, 9.93 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2-4n** (1.1122 g, 10.38 mmol) in DMAC (5 mL) over 3 minand the mixture was stirred at 0 °C for 10 min. A white precipitate was formed. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 5 h. H_2O (30 mL) was added to the reaction vessel, and a white precipitate appeared. The whole was stirred for 1 h at 23 °C. The resultant precipitate was collected by suction filtration, and the solid was washed with H_2O (60 mL), and dried in vacuum. Amide **4n** was obtained as a white solid (1.1619 g, 64%); mp 67–68 °C (colorless plates after recrystallization from toluene). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.459 (2 H, dd, *J* = 7.7, 7.0 Hz), 7.270–7.255 (1 H, m), 7.260–7.240 (2 H, m), 3.851 (2 H, s), 3.322 (3 H, s).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 166.4, 142.8, 130.2, 128.7, 127.2, 41.7, 38.1.

HRMS (ESI-TOF): *m*/*z* [N + Na]$^+$ calcd for $C_9H_{10}ClNONa^+$: 206.0343; found: 206.0345.

Anal. Calcd for $C_9H_{10}ClNO$: C, 58.87; H, 5.49; N, 7.63. Found (precipitate): C, 58.78; H, 5.56; N, 7.60.

Amide Formation of 4o (Figure 1)

To a pre-cooled solution of acid chloride **3-4o** (1.1235 g, 9.95 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2-4o** (1.2549 g, 10.53 mmol) in DMAC (5 mL) over 5 min at 0 °C. A large amount of white precipitate was immediately formed. The resultant precipitate was collected by suction filtration, and the solid was dried in vacuum to give **4o** as colorless needles (1.7290 g, 89%); mp 135–136 °C. The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, CDCl$_3$): δ = 8.202 (1 H, d, *J* = 8.0 Hz), 7.213 (2 H, dd, *J* = 8.8, 8.0 Hz), 7.060 (1 H, dd, *J* = 7.6, 7.2 Hz), 4.153–4.111 (4 H, m), 3.225 (2 H, t, *J* = 8.4 Hz).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 163.89, 142.40, 131.13, 127.61, 124.60, 124.43, 117.23, 47.77, 43.09, 28.11.

HRMS (ESI-TOF): *m*/*z* [N + Na]$^+$ calcd for $C_{10}H_{10}ClNONa^+$: 218.03431; found: 218.03411.

Anal. Calcd for $C_{10}H_{10}ClNO$: C, 61.39; H, 5.15; N, 7.16. Found: C, 61.13; H, 5.26; N, 7.15.

Amide Formation of 4p (Figure 1)

A solution of acid chloride **3-4p** (1.5672 g, 9.88 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). While stirring and cooling at 0 °C, a solution of amine **2-4p** (1.7920 g, 10.42 mmol) in DMAC (5 mL) was added over 4 min. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 3 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. A white precipitate was formed and the mixture was stirred for 15 h. The solid was filtered by suction, washed with H_2O (100 mL) and dried in vacuum. Amide **4p** was obtained as a white solid (2.7391 g, 94%); mp 168–176 °C (colorless needles after recrystallization from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification

^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.878 (2 H, dd, *J* = 8.9, 5.2 Hz), 7.741 (1 H, br s), 7.511 (4 H, dddd, *J* = 10.4, 9.1, 2.4, 2.4 Hz), 7.177 (2 H, dd, *J* = 8.8, 8.4 Hz).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 164.52, 164.13 ($^1J_{C,F}$ = 248 Hz), 138.47, 131.44, 131.12, 131.09, 130.48, 130.39, 122.23, 115.40, 115.4 ($^2J_{C,F}$ = 22 Hz).

HRMS (ESI-TOF): *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{10}BrFNO^+$: 293.9924; found: 293.9920.

Anal. Calcd for $C_{13}H_9BrFNO$: C, 53.09; H, 3.08; N, 4.76. Found: C, 53.08; H, 3.34; N, 4.73.

Amide Formation of 4q (Figure 1)

A solution of acid chloride **3-4q** (1.6248 g, 10.25 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2-4q** (1.2728 g, 10.68 mmol) in DMAC (5 mL) was added over 5 min with stirring at 0 °C. A white precipitate was formed immediately and the mixture was stirred at 0 °C for 10 min. The ice bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. The completion of the reaction was confirmed by TLC, and H_2O (20 mL) was added. The preformed precipitate was dissolved once and another white precipitate was formed. The mixture was stirred overnight. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum to give **4q** (2.2605 g, 91%) as a white solid; mp 104–105 °C (pale red powder); mp 101–102 °C (colorless rods after recrystallization from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.850–7.600 (1 H, br), 7.500 (2 H, dd, *J* = 8.4, 5.6 Hz), 7.154 (2 H, dd, *J* = 11.6, 7.6 Hz), 7.057 (2 H, dd, *J* = 8.6, 8.6 Hz), 6.958 (1 H, d, *J* = 6.4 Hz), 4.010 (2 H, br), 3.050 (2 H, t, *J* = 8.4 Hz).

^{13}C NMR (400 MHz, $CDCl_3$): δ = 168.0, 163.9 (d, $^1J_{C,F}$= 249 Hz), 142.6, 133.1, 132.5, 129.7, 129.6, 127.3, 125.1, 124.1, 115.7 (d, $^2J_{C,F}$= 22 Hz), 50.8, 28.2.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{12}FNONa^+$: 264.0795; found: 264.0791.

Anal. Calcd for $C_{15}H_{12}FNO$: C, 74.68; H, 5.01; N, 5.81. Found: C, 74.47; H, 5.03; N, 5.88.

Amide Formation of 4r (Figure 1)

A solution of acid chloride **3-4r** (1.0557 g, 6.00 mmol) in DMAC (3 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2-4r** (0.7543 g, 6.33 mmol) in DMAC (3 mL) was added over 3 min with stirring at 0 °C. The mixture was stirred at 0 °C for 4 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 45 min. The completion of the reaction was confirmed by TLC, and H_2O (20 mL) was added. A white precipitate was formed and the mixture was stirred for 17 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **4r** was obtained as a white solid (1.3105 g, 84%); mp 132–134 °C (colorless prisms, after recrystallization from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.613 (1 H, d, *J* = 2.0 Hz), 8.188 (1 H, br s), 7.873 (1 H, dd, *J* = 8.2, 2.4 Hz), 7.442 (1 H, dd, *J* = 8.2, 0.7 Hz), 7.245 (2 H, d, *J* = 7.8 Hz), 7.079 (1 H, br s), 4.087 (2 H, br s), 3.167 (2 H, t, *J* = 8.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.2, 153.3, 148.5, 142.3, 137.9, 131.8, 127.6, 125.2, 124.8, 124.5, 50.8, 28.3.

HRMS (ESI-TOF): *m*/*z* $[N + H]^+$ calcd for $C_{14}H_{12}ClN_2O^+$: 259.0633; found: 259.0647.

Anal. Calcd for $C_{14}H_{11}ClN_2O$: C, 65.00; H, 4.29; N, 10.83. Found: C, 64.62; H, 4.50; N, 10.85.

Amide Formation of 5a-1 (Figure 2)

To a pre-cooled solution of acid chloride **3-5a1** (1.4072 g, 10.01 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2-5a1** (1.9390 g, 10.03 mmol) in DMAC (5 mL) was added over 3 min and the mixture was stirred at 0 °C (ice-water bath) for 20 min. A white precipitate was formed. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2.5 h. The completion of the reaction was confirmed by TLC. H_2O (40 mL) was added to the reaction vessel, and the resultant precipitate was collected by suction filtration, and washed with H_2O, and dried in vacuum. Amide **5a-1** was obtained as a white solid (2.8470 g, 96%); mp 128.5–129.0 °C (colorless needles after recrystallization from water-DMAC). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.064 (3 H, d, *J* = 6.8 Hz), 7.882 (2 H, d, *J* = 6.8 Hz), 7.750 (2 H, d, *J* = 8.8 Hz), 7.573 (1 H, dd, *J* = 7.6, 7.2 Hz), 7.495 (2 H, dd, *J* = 8.4, 8.0 Hz), 4.097 (2 H, d, *J* = 6.4 Hz), 2.088 (1 H, sept, *J* = 6.8 Hz), 1.023 (6 H, d, *J* = 6.8 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.12, 165.80, 142.04, 134.53, 132.20, 130.83, 128.88, 127.07, 126.20, 119.18, 70.96, 27.89, 19.20.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{19}NO_3Na^+$: 320.12571; found: 320.12618.

Anal. Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.42; H, 6.57; N, 4.77.

Amide Formation of 5a-2 (Figure 2)

A solution of acid chloride **3-5a2** (1.3828 g, 9.87 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2a** (1.8565 g, 10.36 mmol) in DMAC (5 mL) was added over 3 min with stirring at 0 °C and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 3 h. After the addition of H_2O (30 mL), the mixture was extracted with CH_2Cl_2 (4 × 20 mL), the combined organic fractions were washed with H_2O (3 × 50 mL), and dried ($MgSO_4$). The solvent was evaporated to give the amide **5a-2** as a white solid, which was dried in vacuum (2.6013 g, 93%); mp 97–99 °C (colorless needles, after recrystallization from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.210 (1 H, s), 8.028 (2 H, d, *J* = 8.6 Hz), 7.872 (2 H, d, *J* = 7.4 Hz), 7.745 (2 H, d, *J* = 8.6 Hz), 7.552 (1 H, dd, *J* = 7.2, 7.1 Hz), 7.467 (2 H, dd, *J* = 7.8, 7.7 Hz), 5.232 (1 H, sept, *J* = 6.2 Hz), 1.365 (6 H, d, *J* = 6.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.05, 165.79, 142.16, 134.68, 132.29, 130.90, 128.97, 127.24, 126.70, 119.31, 68.46, 22.10.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{17}H_{17}NO_3Na^+$: 306.1101; found: 306.1115.

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.89; H, 6.16; N, 4.98.

Amide Formation of 5b (Figure 2)

To a pre-cooled solution of acid chloride **3-5b** (1.4040 g, 9.99 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2-5b** (1.5264 g, 10.10 mmol) in DMAC (5 mL) over 2 min and the mixture was stirred at 0 °C for 10 min. A white precipitate was formed. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. The completion of the reaction was confirmed by TLC. H_2O (50 mL) was added to the reaction vessel, and the resultant precipitate was collected by suction filtration, washed with H_2O, and dried in vacuum. Amide **5b** was obtained as a white solid (2.2723 g, 89%); mp 99–100 °C (white powder after recrystallization from water-DMAC). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 12.044 (1 H, s), 8.931 (1 H, s), 8.068 (3 H, dd, *J* = 10.0, 8.8 Hz), 7.068 (1 H, ddd, *J* = 8.8, 7.2, 1.6 Hz), 7.563–7.511 (3 H, m), 7.123 (1 H, dd, *J* = 8.0, 7.6 Hz), 3.962 (3 H, s).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 169.04, 165.69, 141.85, 134.81, 131.92, 130.92, 128.78, 127.35, 122.58, 120.43, 115.12, 52.45.

HRMS (ESI-TOF): *m*/*z* $[M + Na]^+$ calcd for $C_{15}H_{13}NO_3Na^+$: 278.07876; found: 278.07938.

Anal. Calcd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49. Found: C, 70.41; H, 5.24; N, 5.51.

Amide Formation of 5c (Figure 2)

A solution of acid chloride **3-5c** (1.4035 g, 9.99 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). While stirring and cooling at 0 °C, a solution of amine **2-5c** (1.4482 g, 10.49 mmol) in DMAC (5 mL) was added over 3 min, and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 4 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. A yellow precipitate was formed and the mixture was stirred for 21 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. Amide **5c** was obtained as a white solid (2.1020 g, 87%); mp 94 °C (yellow needles after recrystallization from water-DMAC). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.015 (1 H, dd, *J* = 8.5, 1.3 Hz), 8.288 (1 H, dd, *J* = 8.5, 1.5 Hz), 8.005 (2 H, d, *J* = 6.9 Hz), 7.725 (1 H, td, *J* = 7.9, 1.5 Hz), 7.617 (1 H, dd, *J* = 7.4, 7.2 Hz), 7.548 (2 H, dd, *J* = 7.6, 7.0 Hz), 7.231 (1 H, ddd, *J* = 7.9, 7.8, 1.3 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.92, 136.61, 136.37, 135.51, 134.19, 132.81, 129.21, 127.52, 126.08, 123.47, 122.29.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{10}N_2O_3Na^+$: 265.0584; found: 265.0587.

Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.22; H, 4.38; N, 11.51.

Amide Formation of 5d (Figure 2)

To a pre-cooled solution of acid chloride **3-5d** (1.4071 g, 10.01 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2a-5d** (1.3863 g, 10.04 mmol) in DMAC (5 mL) over 1 min and the mixture was stirred at 0 °C for 20 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. H_2O (20 mL) was added to the reaction vessel, and the resultant white precipitate was collected by suction filtration, and washed with H_2O, and dried in vacuum. Amide **5d** was obtained as a white solid (2.3405 g, 97%); mp 158–159 °C (colorless fine needles after recrystallization from water-DMAC). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 10.717 (1 H, s), 8.835 (1 H, dd, *J* = 2.0, 2.0 Hz), 8.220 (1 H, ddd, *J* = 8.0, 2.4, 0.8 Hz), 8.020 (2 H, d, *J* = 8.0 Hz), 8.969 (1 H, ddd, *J* = 8.0, 2.4, 0.8 Hz), 7.645 (2 H, dd, *J* = 7.2, 6.8 Hz), 7.578 (2 H, dd, *J* = 7.2, 6.8 Hz).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 166.04, 147.89, 140.39, 134.24, 132.03, 130.02, 128.50, 127.78, 126.13, 118.09, 114.32.

HRMS (ESI-TOF): *m*/*z* [N + Na]$^+$ calcd for $C_{13}H_{10}N_2O_3Na^+$: 265.05836; found: 265.05828.

Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.66; H, 4.38; N, 11.65.

Amide Formation of 5e (Figure 2)

To a pre-cooled solution of acid chloride **3-5e** (1.4028 g, 9.98 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added a solution of amine **2a-5e** (1.4101 g, 10.20 mmol) in DMAC (5 mL) over 3 min and the mixture was stirred at 0 °C for 2 h. H_2O (50 mL) was added to the reaction vessel, and the white precipitate formed was collected by suction filtration, and washed with H_2O, and dried in vacuum. Amide **5e** was obtained as a white solid (2.3573 g, 98%); mp 201–202 °C (pale green powder after recrystallization from water-DMAC). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 10.820 (1 H, br s), 8.279 (2 H, d, *J* = 9.2 Hz), 8.079 (2 H, d, *J* = 9.2 Hz), 8.079 (2 H, d, *J* = 9.6 Hz), 7.990 (2 H, d, *J* = 7.6 Hz), 7.654 (2 H, dd, *J* = 7.2, 7.2 Hz), 7.572 (2 H, dd, *J* = 8.0, 8.0 Hz).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 166.29, 145.51, 142.46, 134.23, 132.18, 128.52, 127.92, 124.80, 119.83.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{10}N_2O_3Na^+$: 265.05836; found: 265.05815.

Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.26; H, 4.29; N, 11.60.

Amide Formation of 5f (Figure 2)

A solution of acid chloride **3-5f** (1.4051 g, 10.00 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). While stirring and cooling at 0 °C, a solution of amine **2-5f** (1.2370 g, 10.47 mmol) in DMAC (5 mL) was added over 4 min. The mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. A white precipitate was formed and the mixture was stirred for 15 h. The solid was filtered by suction, washed with water (100 mL), and dried in vacuum. Amide **5f** was obtained as a white solid was obtained (2.1417 g, 96%); mp 165–167 °C (colorless powder after recrystallized from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.027 (1 H, br s), 7.876 (2 H, d, *J* = 7.0 Hz), 7.801 (2 H, d, *J* = 8.9 Hz), 7.662 (2 H, d, *J* = 8.8 Hz), 7.601 (1 H, dd, *J* = 7.6, 7.3 Hz), 7.518 (2 H, dd, *J* = 7.7, 7.2 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.2, 143.5, 134.4, 133.1, 132.1, 128.5, 127.9, 120.2, 119.1, 105.3.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{14}H_{10}N_2ONa^+$: 245.0685; found: 245.0688.

Anal. Calcd for $C_{14}H_{10}N_2O$: C, 75.66; H, 4.54; N, 12.60. Found: C, 75.63; H, 4.69; N, 12.62.

Amide Formation of 6a (Scheme 2)

To a pre-cooled solution of acid chloride **3-6a** (1.4057 g, 10.00 mmol) in DMAC (5 mL), a solution of amine **2-6a** (1.3716 g, 10.00 mmol) in DMAC (5 mL) was added over 5 min at 0 °C (ice-water bath) and the mixture was stirred at 0 °C for 5 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 1.5 h. H_2O (40 mL) was added to the reaction vessel, and the white precipitate was collected by suction filtration, washed with H_2O, and dried in vacuum. Amide **6a** was obtained as a white solid (2.2910 g, 95%); mp 182.2–183 °C (coloress fine needles after recrystallization from water-DMAC). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, DMSO-*d*$_6$): δ = 13.817 (1 H, br s), 12.204 (1 H, s), 8.742 (1 H, dd, *J* = 8.6, 1.2 Hz), 8.082 (1 H, dd, *J* = 7.8, 2.0 Hz), 7.981 (2 H, dd, *J* = 7.8, 1.2 Hz), 7.683 (1 H, td, *J* = 8.0, 1.6 Hz), 7.647 (1 H, td, *J* = 7.2, 1.6 Hz), 7.608 (2 H, td, *J* = 6.8, 1.6 Hz), 7.227 (1 H, t, d, *J* = 7.4, 1.2Hz).

^{13}C NMR (100 MHz, DMSO-*d*$_6$): δ = 170.04, 164.70, 141.14, 134.54, 134.35, 132.20, 131.30, 129.00, 127.03, 122.95, 119.89, 116.51.

HRMS (ESI-TOF): [M – H]$^-$ calcd for $C_{14}H_{10}NO_3^-$: 240.06662; found: 240.06760.

Anal. Calcd for $C_{14}H_{11}NO_3$: C, 69.70; H, 4.60; N, 5.81. Found: C, 69.93; H, 4.82; N, 5.90.

Amide Formation of 6b (Scheme 2)

To a pre-cooled solution of acid chloride **3-6b** (1.4039 g, 9.99 mmol) in DMAC (5 mL) at 0 °C (ice-water bath) was added the neat amino acid **2-6b** (748.0 mg, 9.96 mmol) over 1 min at 0 °C and the mixture was stirred at 0 °C for 20 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 4 h. The completion of the reaction was confirmed by TLC. H_2O (11 mL) was added to the reaction vessel, and the resultant precipitate was collected by suction filtration, and dried in vacuum. Amide **6b** was obtained as a white solid (1.2561 g, 70%); mp 190.5–190.7 °C (colorless fine needles after recrystallization from water-DMAC). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.611 (1 H, br s), 8.847 (1 H, t, *J* = 5.8 Hz), 7.881 (2 H, d, *J* = 7.2 Hz), 7.551 (1 H, dd, *J* = 7.6, 7.2 Hz), 7.483 (2 H, dd, *J* = 7.6, 6.8 Hz), 3.938 (2 H, d, *J* = 6.0 Hz).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 171.39, 166.51, 133.86, 131.46, 128.39, 127.27, 41.25.

HRMS (ESI-TOF): *m*/*z* [M – H]$^-$ calcd for $C_9H_8NO_3^-$: 178.05097; found: 178.05185.

Anal. Calcd for $C_9H_9NO_3$ + $0.1H_2O$: C, 59.73; H, 5.12; N, 7.74. Found: C, 59.85; H, 5.02; N, 7.87.

Amide Formation of 6c (Scheme 2)

A solution of acid chloride **3-6c** (1.4031 g, 9.98 mmol) in DMAC (10 mL) was prepared at r.t. The solution was transferred to a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). While stirring and cooling at 0 °C, neat valine (**2-6c**; 1.7290 g, 10.47 mmol) was added over 9 min at 0 °C and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 21 h. H_2O (30 mL) was added to give a white precipitate and the mixture was stirred for 7 h. The solid was filtered by suction, washed with H_2O (150 mL), and dried in vacuum. Amide **6c** was obtained as a white solid (2.0819 g, 77%): mp 137–138 °C (white powder after recrystallization from water-DMAC). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.687 (2 H, d, *J* = 7.0 Hz), 7.519 (1 H, t, *J* = 7.4 Hz), 7.421 (2 H, dd, *J* = 7.8, 7.2 Hz), 7.341–7.274 (3 H, m), 7.213 (2 H, d, *J* = 6.3 Hz), 6.546 (1 H, d, *J* = 7.2 Hz), 5.082 (1 H, ddd, *J* = 7.3, 7.3, 7.3 Hz), 3.376 (1 H, dd, *J* = 38.6, 5.6 Hz), 3.280 (1 H, dd, *J* = 38.6, 5.6 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 174.9, 167.9, 135.8, 133.6, 132.2, 129.6, 128.9, 128.8, 127.5, 127.2, 57.8, 37.4.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{15}NO_3Na^+$: 292.0944; found: 292.0959.

Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.36; H, 5.61; N, 5.20. Found: C, 71.04; H, 5.80; N, 5.28.

Amide Formation of 6d (Scheme 2)

To a pre-cooled solution of acid chloride **3-6d** (1.3990 g, 9.95 mmol) in DMAC (10 mL) at 0 °C (ice-water bath) was added the amino acid **2-6d** (1.2298 g, 10.50 mmol) and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 ° C for 26 h. MeOH (5 mL) was added to the reaction vessel and the mixture was stirred for 5 h. Aq 2 M HCl (5 mL) was added and the mixture was extracted with Et_2O (3 × 30 mL). The combined organic fractions were dried ($MgSO_4$) and the solvent was evaporated to afford a colorless liquid (1.8638 g), which was open-chromatographed ($CHCl_3$/MeOH/AcOH 90:10:1) to give the amide **6d** (1.6565 g, 75%); mp 133–136 °C (colorless rods after recrystallization from water-DMAC). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 9.393 (1 H, br s), 7.812 (2 H, d, *J* = 6.9 Hz), 7.535 (1 H, dd, *J* = 7.5, 7.2 Hz), 7.458 (2 H, dd, *J* = 7.6, 7.5 Hz), 6.644 (1 H, d, *J* = 8.4 Hz), 4.810 (1 H, dd, *J* = 8.5, 4.8 Hz), 2.414–2.334 (1 H, m), 1.056 (6 H, dd, J = 10.3, 6.9 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.80, 168.28, 133.88, 132.11, 128.80, 127.28, 57.70, 31.45, 19.16, 17.94.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{15}NO_3Na^+$: 244.0944; found: 244.0947.

Anal. Calcd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83; N, 6.33. Found: C, 64.97; H, 6.93; N, 6.43.

Experiments of Table 4

Formation of Amide 4s

A solution of acid chloride **3b** (1.4129 g, 10.05 mmol) in DMAC (5 mL) was prepared at r.t. The solution was transferred into a 30 mL round-bottomed flask and cooled to 0 °C (ice-water bath). A solution of amine **2d** (0.9779 g, 10.50 mmol) in DMAC (5 mL) was added over 3 min with stirring at 0 °C. The mixture was stirred at 0 °C for 10 min. The ice bath was replaced with a water bath and the mixture was stirred at 23 °C for 2 h. The completion of the reaction was confirmed by TLC, and H_2O (30 mL) was added. A white precipitate was formed and the mixture was stirred for 2 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum to give **4s** (1.8857 g, 95%) as a white solid. mp 164–166 °C (colorless plates after recrystallized from MeOH). The product was pure enough to give a satisfactory combustion analysis without further purification.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.877 (2 H, d, *J* = 6.9 Hz), 7.807 (1 H, br s), 7.647 (2 H, d, *J* = 8.4 Hz), 7.562 (1 H, t, *J* = 7.3 Hz), 7.497 (2 H, dd, *J* = 7.6, 7.0 Hz), 7.384 (2 H, dd, *J* = 8.5, 7.5 Hz), 7.162 (1 H, t, *J* = 7.4 Hz).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.84, 138.05, 135.17, 132.02, 129.28, 128.97, 127.15, 124.74, 120.31.

HRMS (ESI-TOF): *m*/*z* [M + Na]$^+$ calcd for $C_{13}H_{11}NONa^+$: 220.0733; found: 220.0703.

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 78.92; H, 5.85; N, 7.13.

Amide Formation (Table 4, run 1)

A 30 mL round-bottomed flask equipped with a stirring bar was charged with an aromatic amine **2d** (0.4918 g, 5.28 mmol) and an aliphatic amine **2a** (0.7054 g, 5.14 mmol). The flask was immersed into an ice-water bath (0 °C). DMAC (5 mL) and AcOH (1.2331 g, 20.54 mmol) were added with stirring. A solution of acid chloride **3b** (0.7039 g, 5.008 mmol) in DMAC (5 mL) was added over 7 min at 0 °C and the mixture was stirred at 0 °C for 25 min. The ice-water bath was replaced with a water bath and the mixture was stirred at 23 °C for 3 h. H_2O (30 mL) was added to give a white precipitate and the mixture was stirred for 1 h. The solid was filtered by suction, washed with H_2O (60 mL), and dried in vacuum. The mixture of the amide products was separated by column chromatography (EtOAc/*n*-hexane 1:4). The ratio of the amides was determined by the integration of ^{1}H NMR signals in comparison of the authentic amides **4s** (see above) and **4l** (see Table 4). Yields of the products were 0.7727g (78%) for **4s** and 0.0944 g (8%) for **4l**, respectively.

Amide Formation (Table 4, run 2)

A 30 mL round-bottomed flask equipped with a stirring bar was charged with an aromatic amine **2d** (0.4865 g, 5.22 mmol) and aliphatic amine **2a** (0.7059 g, 5.15 mmol). The flask was immersed into an ice-water bath (0 °C). DMAC (5 mL) and AcOH (3.0567 g, 50.90 mmol) were added with stirring. A solution of acid chloride **3b** (0.7048 g, 5.01 mmol) in DMAC (5 mL) was added over 3 min and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the whole was stirred at 23 °C for 3 h. H_2O (40 mL) was added to give a white precipitate and the mixture was stirred for 3 h. The solid was filtered by suction, washed with H_2O (80 mL), and dried in vacuum to give **4s** (0.9090 g, 92%). The product was identical with the authentic compound in terms of ^{1}H NMR ($CDCl_3$) and combustion analysis.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.873 (2 H, d, *J* = 7.0 Hz), 7.832 (1 H, br s), 7.644 (2 H, d, *J* = 8.5 Hz), 7.557 (1 H, t, *J* = 7.3 Hz), 7.491 (2 H, dd, *J* = 7.6, 7.0 Hz), 7.379 (2 H, dd, *J* = 8.5, 7.5 Hz), 7.159 (1 H, t, *J* = 7.4 Hz).

Anal. Calcd for $C_{13}H_{11}NO$: C, 79.17; H, 5.62; N, 7.10. Found: C, 78.96; H, 5.81; N, 7.09.

Amide Formation (Table 4, run 3)

A 30 mL-round-bottomed flask equipped with a stirring bar was charged with an aromatic amine **2d** (0.5023 g, 5.39 mmol) and aliphatic amine **2a** (0.7061 g, 5.15 mmol). The flask was immersed into an ice-water bath (0 °C). DMAC (5 mL) and Et_3N (2.0340 g, 18.63 mmol) were added with stirring. A solution of acid chloride **3b** (0.7098 g, 5.05 mmol) in DMAC (5 mL) was added over 5 min and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the whole was stirred at 23 °C for 3 h. H_2O (30 mL) was added to give a white precipitate and the mixture was stirred for 15 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. The mixture of the amide products was separated by column chromatography (EtOAc/*n*-hexane 1:4). The ratio of the amides was determined by integration of ^{1}H NMR signals. Yields of the products were 0.2794 g (28%) for **4s** and 0.7317 g (60%) for **4l**.

Amide Formation (Table 4, run 4)

A 30 mL round-bottomed flask equipped with a stirring bar was charged with an aromatic amine **2d** (0.4849 g, 5.21 mmol) and an aliphatic amine **2a** (0.6940 g, 5.06 mmol). The flask was immersed into an ice-water bath (0 °C). DMAC (5 mL) was added with stirring. A solution of acid chloride **3b** (0.7000 g, 4.98 mmol) in DMAC (5 mL) was added over 5 min at 0 °C and the mixture was stirred at 0 °C for 10 min. The ice-water bath was replaced with a water bath and the whole was stirred at 23 °C for 3 h. H_2O (40 mL) was added to give a white precipitate and the mixture was stirred for 2 h. The solid was filtered by suction, washed with H_2O (100 mL), and dried in vacuum. The precipitate contained only a mixture of the amide products. The ratio of the amides was determined by integration of ^{1}H NMR signals. The yields of the amide products were 0.6482 g (66%) for **4s** and 0.3298 g (29%) for **4l**, respectively.

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Supporting Information

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