Facile Direct Synthesis of Amides from Trichloroethyl Esters Using Catalytic DBU

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Abstract: A practical method for the direct synthesis of amide compounds is described. Using small quantities of DBU as a catalyst, the direct conversion of 2,2,2-trichloroethyl esters to their corresponding amides was readily achieved. Based on this protocol, various amide compounds were successfully synthesized in high yield, suggesting a promising approach for the practical one-pot aminolysis from 2,2,2-trichloroethyl protected esters.

Keywords: Amide, DBU, Trichloroethyl ester, Organocatalyst.

Introduction

Amides are one of the most common functional groups and play a crucial role in living systems as amino acid linkage sites in protein.[1,2] Amide bond formation via the acylation of amines is one of the most important organic reactions, and is frequently employed in the synthesis of bioactive molecules. Exemplary amide-containing pharmaceuticals include antibiotics, anticancer agents, local anesthetics, and angiotensin-converting enzyme inhibitors.[3-7] Additionally, many biologically active compounds contain amide bonds within their structures.[8-12]

Strategies for the synthesis of amides have been developed for many years, yielding a variety of synthetic protocols for the formation of amide bonds.[13-15] Coupling reactions or two-step processes including the activation of a carboxylic acid and the reaction of an amine are commonly used methods to synthesize amides.[16,17] The acylation of amines using acid chlorides is a popular method to synthesize amides; however, formation of ketenes via reaction of an acyl chloride containing a proton at an α-stereocenter will erode the stereochemistry of the substrate.[18-21] Acyl azides and anhydrides have also been used to generate amide bonds.[22] However, these methods have not been universally applicable across various multi-step synthesis reactions. The development of a simple, safe, and widely applicable amidation protocol is thus important to organic synthesis.

Carboxylic acids are commonly employed in their protected form as esters during many chemical syntheses. Methyl esters are generally employed to synthesis amide with various catalysts.[23-25] Nevertheless, these reactions require high temperatures and long reaction times to obtain the products. Among several protecting groups, the 2,2,2-trichloroethyl group is known to be an efficient carboxylic acid protecting group and is also easily deprotected via reductive

methods.[26-28] Usually, two separate steps are required to prepare amides from 2,2,2-trichloroethyl esters: removal of the ester group and production of new amides via treatment with amines.

An alternative approach is the direct aminolysis of 2,2,2-trichloroethyl esters with primary and secondary amines as it could lead to a reduction in cost, time, and waste. However, the direct synthesis of amides using 2,2,2-trihaloethyl esters is rarely reported. Burke et al. employed phosphorus(III) compounds to achieve the conversion of a 2,2,2-trihaloethyl ester to an amide (Scheme 1).[29] However, the drawback of producing halogenic acids may affect compounds bearing acid-sensitive functional groups; the method also did not use a catalytic amount of reagent.

The development of a new synthetic methodology employing a small quantity of catalyst is useful for organic synthesis by offering a new synthetic approach within the chemist's toolbox. The direct aminolysis of 2,2,2-trichloroethyl esters in the presence of a catalytic amount of base is an attractive approach to the synthesis of amides. To the best of our knowledge, this route to amides has not been reported. Herein, we describe the synthesis of amides from 2,2,2-trichloroethyl esters by aminolysis using primary and secondary amines and a catalytic amount of DBU.

Scheme 1

Results and discussion

2,2,2-Trichloroethyl benzoate and *n*-butylamine were employed as model substrates to determine the organic catalytic reagents needed for the amidation reaction. Reactions were performed using 1.0 equiv. of 2,2,2-trichloroethyl benzoate and 1.4 equiv. of *n*-butylamine in the presence of a catalytic amount of base. Also, the control reaction without any catalysts was

carried out. First, we screened a series of commercially available organic reagents including 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), pyridine, triethylamine (Et_3N), *N,N*-diisopropylethylamine (DIPEA), 4-dimethylaminopyridine (DMAP), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,4-diazabicyclo[2.2.2]octane (DABCO) as well as inorganic bases ($NaHCO_3$, K_2CO_3) to determine the best catalyst. 0.2 equiv. of each catalyst was tested to determine the best reagent for conversion of the desired amide after reacting for 12 h. As can be seen in Table 1, the yields were affected by the different catalysts. Without any catalyst, low yield of product was observed. The inorganic catalyst bases ($NaHCO_3$, K_2CO_3) displayed a moderate activity, while the organic reagents exhibited various levels of activity. The catalytic activities of pyridine, DIPEA, DABCO, DMAP, and Et_3N were considered moderate, while DBN and DBU exhibited high activity over a reaction period of 12 h. In particular, when DBU was employed for the amidation reaction, the yield increased to 95%. There was also no significant difference in yield (>90%, Table 1, entry 7-8) when 0.2 equiv. or 0.5 equiv. of DBU was used for the reaction after a period of 12 h. Based on the yields, DBU was chosen as the catalyst for further studies.

Figure 1

Table 1

Different solvents were subsequently tested in this reaction to find optimized condition. Reactions performed in toluene resulted in a moderate amide yield, whereas THF, 1,4-dioxane, $PhCF_3$, and CH_3CN were shown to be effective solvents with regard to producing the desired amide (Table 2 entries 1,3,4, and 5: 82% for THF, 87% for 1,4-dioxane, 83% for $PhCF_3$, and 95% for CH_3CN). Based on these results, CH_3CN was determined to be the best solvent among others for the amidation reaction.

We next investigated the effects of temperature on the synthesis of amides. Using 20 mol% of DBU and CH_3CN solvent, reactions were performed at various temperatures (room temperature, 40 °C, 60 °C, and 80 °C). The reaction temperature significantly affected the conversion yield of the corresponding amide. Not surprisingly, the yield of the reaction after 12 h increases with increasing temperature (Table 2, entries 5-8).

Table 2

With optimized experimental conditions, the scope of the methodology was examined using various 2,2,2-trichloroethyl esters and primary and secondary amines (Table 3, Chart 1). First, aromatic compounds were investigated as substrates. 2,2,2-Trichloroethyl benzoate. Aryl esters were converted to the corresponding amides in high yield (entries 1-10, table 3). The effect of electron-donating and electron-withdrawing groups on the rate of conversion to aryl esters to product was determined. As expected, an electron withdrawing p-NO_2 group on the ester increased the rate of conversion to product (Figure 2a) as almost complete conversion to product was achieved within one hour. In contrast, an electron donating p-Me group on the ester decreased the rate (Figure 2c) as 12 h was required to achieve 80 % conversion to product with this ester. Again, DBU was the most effective catalyst for both of these reactions (Figures 2a and c).

Figure 2

We also extended the synthetic method for the utilization of secondary amines. The reaction proceeds well with both primary and secondary amines (entries 4, 5, 7, 9, 10, Table 3). Aliphatic esters were also effective substrates (entries 11-22, Table 3). Even 2,2,2-trichloroethyldiphenylacetate, which contains a bulky diphenylmethyl moiety, was converted to the corresponding amide in high yield (Table 3, entries 21 and 22). In additions, the reaction of

the TCE ester of *N*-Boc-D-phenylalanine (1k), a substrate with stereocenter adjacent to the ester group, with benzyl amine produced the corresponding amide **3w** with considerable epimerization at the *α*-stereocentre. The product **3w** was isolated in only 23% enantiomeric excess at the end of the reaction.

Table 3

Next, a scale-up amidation reaction from 2,2,2-trichloroethyl esters was performed (Scheme 2). The reaction to prepare amide was proven to be scalable and practical because the gram-scale reaction was also efficiently carried out. The reaction of 2,2,2-trichloroethyl benzoate **1a** (20.0 mmol, 1.0 equiv., 5.04 g) and *n*-butylamine **2a** (30.0 mmol, 1.5 equiv.) produced the corresponding amide **3a** in 92% yield under optimized reaction conditions.

Scheme 2

We propose a reaction pathway based on a previous report[31] that used DBU as a nucleophilic catalyst for preparing amides from acyl imidazoles. As shown in Figure 3, DBU attacks the carbonyl group of the ester to form intermediate **B**. Intermediate **B** then reacts with the amine to generate the amide.

Figure 3

Chart 1

Conclusion

In summary, we described a practical one-pot method for the preparation of various amide compounds. DBU was shown to be an efficient catalyst for the synthesis of a variety of target amide structures. Our results suggest that the direct one-pot synthesis of amide compounds from 2,2,2-trichloroethyl esters in the presence of DBU catalyst in MeCN is a highly effective method.

Experimental section

General

Solvents used as reaction media were dried over pre-dried molecular sieves (4 Å) in a microwave oven. Solvents for extraction and chromatography were reagent grade and used as received. Reagents were purified prior to use unless otherwise stated following the guidelines of Perrin and Armarego.[30] Column chromatography was performed with silica gel 60 (70−230 mesh) using a mixture of ethylacetate/hexane as eluent. ^{1}H and ^{13}C NMR spectra were, respectively, recorded on a 600 MHz or 400 MHz (^{1}H NMR), 150 MHz or 100 MHz (^{13}C NMR) spectrometer in deuterated chloroform ($CDCl_3$) with tetramethylsilane(TMS) as an internal reference. Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constant(s) in Hz, integration). High-resolution mass spectroscopy was performed using 6200 series TOF/6500 series Q-TOF B.08.00 (B8058.0). The identity of the known compounds was established by the comparison of their ^{1}H and ^{13}C NMR peaks with the authentic values.

*General procedure for the preparation of amide compounds (**3a-3v**)*

To a stirred solution of 2,2,2-trichloroethyl benzoate (**1a**, 0.260 g, 1.03 mmol) in MeCN (2 mL) at room temperature was added *n*-butylamine (0.105 g, 1.44 mmol) and DBU (0.31 g, 0.20 mmol). The mixture was stirred for 12 h at 80 °C, allowed to cool to room temperature and extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was dried over sodium sulfate and concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography on silica gel with hexane-EtOAc as eluent to afford the desired product **3a** (0.173 g, 95%).

_N_-butylbenzamide (3a)

Light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 6.6 Hz, 2H), 7.45 (t, J = 7.8 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 6.30 (s, 1H), 3.41 (q, J = 7.2 Hz, 2H), 1.57 (quint, J = 7.2 Hz, 2H), 1.38 (sextet, J = 7.8 Hz, 2H), 0.92 (t, J = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.7, 134.9, 131.4, 128.6 (2C), 127.0 (2C), 39.9, 31.8, 20.2, 13.9; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{16}NO$ = 178.1232; found 178.1226.

_N_-benzylbenzamide (3b)

White solid. m.p. 107-109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (dd, J = 8.4, 1.6 Hz, 2H), 7.51 (tt, J = 7.2, 2.0 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.39-7.29 (m, 5H), 6.71 (s, 1H), 4.64 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 138.3, 134.3, 131.5, 128.7 (2C), 128.6 (2C), 127.9 (2C), 127.6, 127.0 (2C), 40.1; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{14}H_{14}NO$ = 212.1075; found 212.1070.

4-methyl-_N_-phenethylbenzamide (3c)

White solid; m.p. 83-85°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.58 (d, J = 8.4 Hz, 2H), 7.31 (t, J = 7.8 Hz, 2H), 7.21-7.21 (m, 3H), 7.18 (d, J = 7.2 Hz, 2H), 6.19 (s, 1H), 3.69 (q, J = 6.6 Hz, 2H), 2.91 (t, J = 7.2 Hz, 2H), 2.37 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.5, 141.9, 139.1, 131.8, 129.3 (2C), 128.9 (2C), 128.8 (2C), 126.9 (2C), 126.6, 41.2, 35.8, 21.5; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{16}H_{18}NO$ = 240.1388; found 240.1383.

Pyrrolidin-1-yl(p-tolyl)methanone (3d)

White solid; m.p. 81-83°C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 8.4 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 3.70-3.30 (m, 4H), 2.35 (s, 3H), 1.89 (br s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ

169.8, 139.8, 134.3, 128.8 (2C), 127.2 (2C), 49.6, 46.2, 26.4, 24.5, 21.4; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{16}NO$ = 190.1232; found 190.1226.

(4-methoxyphenyl)(pyrrolidin-1-yl)methanone (3e)

White solid; m.p. 78-80 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.48 (d, J = 9.0 Hz, 2H), 6.87 (d, J = 9.0 Hz, 2H), 3.80 (s, 3H), 3.53 (br s, 4H), 1.88 (br s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.4, 160.7, 129.4, 129.1 (2C), 113.4 (2C), 55.3, 49.8, 46.3, 26.5, 24.4; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{16}NO_2$ = 206.1181; found 206.1176.

***N*-butyl-4-chlorobenzamide (3f)**

White solid; m.p. 79-81 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (d, J = 7.8 Hz, 2H), 7.36 (d, J = 8.4 Hz, 2H), 6.29 (s, 1H), 3.41 (q, J = 7.8 Hz, 2H), 1.56 (quint, J = 6.6 Hz, 2H), 1.38 (sextet, J = 7.8 Hz, 2H), 0.92 (t, J = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.6, 137.6, 133.2, 128.8 (2C), 128.4 (2C), 40.0, 31.8, 20.2, 13.9; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{15}ClNO$ = 212.0842; found 212.0837.

(4-chlorophenyl)(pyrrolidin-1-yl)methanone (3g)

White solid; m.p. 73-75 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 8.4 Hz, 2H), 3.70-3.30 (m, 4H), 1.90 (br s, 4H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.5, 135.8, 135.5, 128.7 (2C), 128.5 (2C), 49.6, 46.3, 26.4, 24.4; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{13}ClNO$ = 210.0686; found 210.0680.

***N*-butyl-4-nitrobenzamide (3h)**

White solid; m.p. 102-104 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.25 (d, J = 9.0 Hz, 2H), 7.90 (d, J = 9.0 Hz, 2H), 6.33 (s, 1H), 3.46 (q, J = 6.6 Hz, 2H), 1.60 (quint, J = 6.6 Hz, 2H), 1.40 (sextet, J

= 7.2 Hz, 2H), 0.94 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 165.6, 149.5, 140.5, 128.1 (2C), 123.9 (2C), 40.2, 31.6, 20.2, 13.8; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{15}N_2O_3$ = 223.1083; found 223.1077.

(4-nitrophenyl)(pyrrolidin-1-yl)methanone (3i)

White solid; m.p. 92-94 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 2H), 7.65 (d, *J* = 9.0 Hz, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 3.35 (t, *J* = 6.6 Hz, 2H), 1.98 (quint, *J* = 6.6 Hz, 2H), 1.89 (quint, *J* = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.4, 148.4, 143.2, 128.2 (2C), 123.8 (2C), 49.5, 46.4, 26.5, 24.4; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{13}N_2O_3$ = 221.0926; found 221.0921.

Morpholino(4-nitrophenyl)methanone (3j)

White solid; m.p. 104-106 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.4 Hz, 2H), 7.55 (d, *J* = 9.0 Hz, 2H), 3.77 (s, 4H), 3.60 (s, 2H), 3.58 (s, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.1, 148.5, 141.5, 128.2 (2C), 124.0 (2C), 66.8 (2C), 48.1, 42.6; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{11}H_{13}N_2O_3$ = 237.0875; found 237.0870.

***N*-(4-methylbenzyl)butyramide (3k)**

White solid; m.p. 75-77 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.77 (s, 1H), 4.37 (d, *J* = 6.0 Hz, 2H), 2.32 (s, 3H), 2.16 (t, *J* = 7.2 Hz, 2H), 1.67 (sextet, *J* = 7.8 Hz, 2H), 0.93 (t, *J* = 7.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.9, 137.3, 135.5, 129.4 (2C), 127.9 (2C), 43.4, 38.8, 21.2, 19.3, 13.9; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{18}NO$ = 192.1388; found 192.1383.

***N*-phenethylbutyramide (3l)**

White solid; m.p. 49-51 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, J = 7.2 Hz, 2H), 7.21 (t, J = 7.2 Hz, 1H), 7.17 (d, J = 6.6 Hz, 2H), 5.59 (s, 1H), 3.50 (q, J = 7.2 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H), 2.08 (t, J = 7.8 Hz, 2H), 1.61 (sextet, J = 7.8 Hz, 2H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.1, 139.0, 128.8 (2C), 128.7 (2C), 126.6, 40.6, 38.8, 35.8, 19.2, 13.9; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{12}H_{18}NO$ = 192.1388; found 192.1383.

3-methyl-*N*-phenethylbutanamide (3m)

White solid; m.p. 75-77 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, J = 7.8 Hz, 2H), 7.21 (t, J = 7.8 Hz, 1H), 7.17 (d, J =7.2 Hz, 2H), 5.57 (s, 1H), 3.50 (q, J = 7.2 Hz, 2H), 2.80 (t, J = 6.6 Hz, 2H), 2.06 (nonet, J = 6.0 Hz, 1H), 1.96 (d, J = 7.2 Hz, 2H), 0.90 (d, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.6, 139.0, 128.8 (2C), 128.7 (2C), 126.6, 46.2, 40.7, 35.9, 26.2, 22.5 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{13}H_{20}NO$ = 206.1545; found 206.1539.

***N*-(furan-2-ylmethyl)-3-methylbutanamide (3n)**

Light yellow oil; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (s, 1H), 6.28 (dd, J = 2.4, 1.2 Hz, 1H), 6.19 (d, J = 3.6 Hz, 1H), 5.93 (s, 1H), 4.39 (d, J = 6.6 Hz, 2H), 2.10 (nonet, J = 7.2 Hz, 1H), 2.03 (d, J = 6.6 Hz, 2H), 0.91 (d, J = 6.0 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.4, 151.5, 142.2, 110.5, 107.4, 46.0, 36.4, 26.2, 22.5 (2C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{10}H_{16}NO_2$ = 182.1181; found 182.1176.

***N*-benzylcyclohexanecarboxamide (3o)**

White solid; m.p. 112-114 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (t, J = 6.6 Hz, 2H), 7.27-7.22 (m, 3H), 5.85 (s, 1H), 4.40 (d, J = 6.6 Hz, 2H), 2.10 (tt, J = 12.0, 3.0 Hz, 1H), 1.86 (dd, J = 13.8, 1.8 Hz, 2H), 1.81-1.72 (m, 2H), 1.69-1.62 (m, 1H), 1.45 (ddd, J = 24.6, 12.0, 2.4 Hz, 2H), 1.29-

1.17 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.1, 138.6, 128.8 (2C), 127.8 (2C), 127.5, 45.6, 43.4, 29.8 (2C), 25.8 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{14}H_{20}NO$ = 218.1545; found 218.1539.

_N_-phenethylcyclohexanecarboxamide (3p)

White solid; m.p. 95-97 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.29 (t, J = 7.8 Hz, 2H), 7.22 (t, J = 7.8 Hz, 1H), 7.17 (d, J = 7.8 Hz, 2H), 5.49 (s, 1H), 3.49 (q, J = 6.6 Hz, 2H), 2.79 (t, J = 6.6 Hz, 2H), 2.00 (tt, J = 11.4, 3.0 Hz, 1H), 1.85-1.70 (m, 4H), 1.69-1.59 (m, 1H), 1.45-1.31 (m, 2H), 1.27-1.14 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 176.2, 139.1, 128.9 (2C), 128.7 (2C), 126.6, 45.6, 40.4, 35.8, 29.7 (2C), 25.8 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{15}H_{22}NO$ = 232.1701; found 232.1696.

_N_-benzyl-3-phenylpropanamide (3q)

White solid; m.p. 85-87 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30-7.22 (m, 5H), 7.22-7.16 (m, 3H), 7.13 (d, J = 7.2 Hz, 2H), 5.73 (s, 1H), 4.37 (d, J = 6.6 Hz, 2H), 2.91 (t, J = 7.8 Hz, 2H), 2.50 (t, J = 8.4 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 140.8, 138.2, 128.7 (2C), 128.6 (2C), 128.5 (2C), 127.8 (2C), 127.5, 126.3, 43.6, 38.6, 31.8; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{16}H_{18}NO$ = 240.1388; found 240.1383.

_N_-butyl-3-phenylpropanamide (3r)

White solid; m.p. 34-36 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.25 (t, J = 7.8 Hz, 2H), 7.19-7.15 (m, 3H), 5.53 (s, 1H), 3.18 (q, J = 7.2 Hz, 2H), 2.93 (t, J = 7.8 Hz, 2H), 2.44 (t, J = 8.4 Hz, 2H), 1.38 (quint, J = 7.8 Hz, 2H), 1.24 (sextet, J = 7.2 Hz, 2H), 0.86 (t, J = 6.6 Hz, 3H); ^{13}C NMR (150

MHz, $CDCl_3$) δ 172.1, 141.0, 128.6 (2C), 128.4 (2C), 126.3, 39.3, 38.6, 31.9, 31.7, 20.1, 13.8; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{13}H_{20}NO$ = 206.1545; found 206.1539.

_N_-isobutyl-3-phenylpropanamide (3s)

White solid; m.p. 59-61 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.26 (t, J = 7.8 Hz, 2H), 7.21-7.16 (m, 3H), 5.46 (s, 1H), 3.02 (t, J = 6.6 Hz, 2H), 2.95 (t, J = 7.2 Hz, 2H), 2.47 (t, J = 8.4 Hz, 2H), 1.66 (nonet, J = 6.6 Hz, 1H), 0.80 (d, J = 7.2 Hz, 6H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 141.0, 128.6 (2C), 128.4 (2C), 126.3, 46.9, 38.7, 31.9, 28.5, 20.1 (2C); HRMS (ESI) m/z $(M+Na)^+$ calcd for $C_{13}H_{19}NONa$ = 228.1364; found 228.1359.

_N_-(furan-2-ylmethyl)-3-phenylpropanamide (3t)

White solid; m.p. 60-62 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 7.31 (d, J = 2.4 Hz, 1H), 7.25 (t, J = 7.2 Hz, 2H), 7.20-7.14 (m, 3H), 6.28 (dd, J = 3.0, 1.8 Hz, 1H), 6.13 (d, J = 3.0 Hz, 1H), 5.82 (s, 1H), 4.37 (d, J = 5.4 Hz, 2H), 2.95 (d, J = 7.8 Hz, 2H), 2.47 (d, J = 7.8 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.0, 151.3, 142.2, 140.8, 128.6 (2C), 128.4 (2C), 126.3, 110.5, 107.5, 38.4, 36.5, 31.7; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{14}H_{15}NO_2$ = 230.1181; found 230.1176.

_N_-hexyl-2,2-diphenylacetamide (3u)

White solid; m.p. 74-76 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.32 (m, 4H), 7.32-7.25 (m, 6H), 5.65 (s, 1H), 4.95 (s, 1H), 3.29 (q, J = 7.2 Hz, 2H), 1.50 (quint, J = 7.2 Hz, 2H), 1.36-1.20 (m, 6H), 0.89 (d, J = 6.8 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 139.5 (2C), 128.9 (4C), 128.8 (4C), 127.2 (2C), 59.3, 39.9, 31.4, 29.4, 26.5, 22.5, 14.0; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{20}H_{26}NO$ = 296.2014; found 296.2009.

_N_-phenethyl-2,2-diphenylacetamide (3v)

White solid; m.p. 111-113 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 (t, J = 7.2 Hz, 4H), 7.27-7.18 (m, 5H), 7.15 (d, J = 7.8 Hz, 4H), 7.02 (d, J = 6.6 Hz, 2H), 5.61 (s, 1H), 4.87 (s, 1H), 3.54 (q, J = 7.2 Hz, 2H), 2.76 (t, J = 6.6 Hz, 2H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 139.4 (2C), 138.7, 129.0 (4C), 128.9 (6C), 128.7 (2C), 127.3 (2C), 126.6, 59.3, 40.9, 35.6; HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{22}H_{22}NO$ = 316.1701; found 316.1696.

(*R*)-*tert*-butyl 1-(benzylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (3w)

White solid; m.p. 147-149 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33-7.24 (m, 6H), 7.23-7.18 (m, 2H), 7.18-7.06 (m, 2H), 6.20 (br s, 1H), 5.13 (br s, 1H), 4.45-4.30 (m, 3H), 3.15-3.03 (m, 2H), 1.40 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 155.4, 137.7, 136.7, 129.3 (2C), 128.7 (2C), 128.6 (2C), 127.6 (2C), 127.4, 126.9, 80.2, 56.0, 43.4, 38.6, 28.2 (3C); HRMS (ESI) m/z $(M+H)^+$ calcd for $C_{21}H_{27}N_2O_3$ = 355.2022; found 355.2016. $[\alpha]^{16}_{D}$ -2.6 (c 1.00, $CHCl_3$); HPLC conditions: DAICEL CHIRALCEL AS-H, eluent: Hexane/2-Propanol = 9.0:1.0, flow: 1.0 mL/min, detection: 220 nm, t_R: 12.74 min (major), 7.93 min (minor).

Acknowledgements

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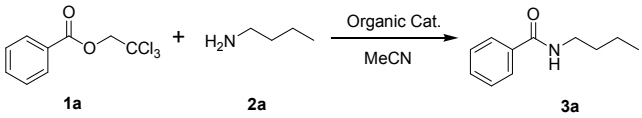
Table 1. Screening of catalytic agents for the synthesis of amide structures



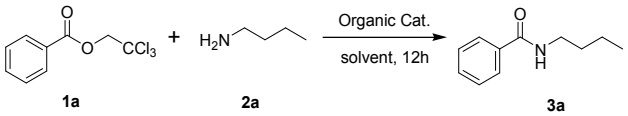
1a 2a 3a

Entry	Catalyst (equiv.)	Time (h)	Yield (%)[b]
1	Pyridine (0.2)	12	71
2	DABCO (0.2)	12	53
3	Et_3N (0.2)	12	69
4	DIPEA (0.2)	12	52
5	DMAP (0.2)	12	65
6	DBN (0.2)	12	78
7	DBU (0.2)	12	95
8	DBU (0.5)	12	95
9	K_2CO_3 (0.2)	12	73
10	$NaHCO_3$ (0.2)	12	64
11	None	12	25

[a] Reaction conditions: 1**a** 2,2,2-trichloroethyl benzoate (1.0 mmol), amine (1.4 mmol), MeCN, 80 ^oC.

[b] Isolated yield after column purification.

Table 2. Screening of reaction conditions for the preparation amide structures [a]



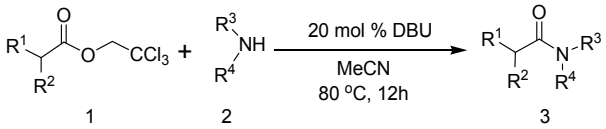
1a 2a 3a

Entry	Solvent	Temp	Yield (%)[b]
1	THF	80 °C	82
2	Toluene	80 °C	56
3	1,4-dioxane	80 °C	87
4	$PhCF_3$	80 °C	83
5	CH_3CN	80 °C	95
6	CH_3CN	r.t.	41
7	CH_3CN	40 °C	53
8	CH_3CN	60 °C	64

[a] Reaction conditions: 1**a** 2,2,2-trichloroethyl benzoate (1.0 mmol), amine (1.4 mmol), 12h.

[b] Isolated yield after column purification.

Table 3. Scope of amidation from 2,2,2-trichloroethyl esters[a]



1 2 3

Entry	Trichloroethyl ester	Product	Yield(%)[b]	Entry	Trichloroethyl ester	Product	Yield(%)[b]
1	1a	3a	96	13	1g	3m	93
2	1a	3b	94	14	1g	3n	88
3	1b	3c	88	15	1h	3o	94
4	1b	3d	90	16	1h	3p	94
5	1c	3e	87	17	1i	3q	93
6	1d	3f	93	18	1i	3r	92
7	1d	3g	94	19	1i	3s	92
8	1e	3h	90	20	1i	3t	89
9	1e	3i	87	21	1j	3u	94
10	1e	3j	93	22	1j	3v	91
11	1f	3k	93	23	1k	3w	87
12	1f	3l	94				

[a] Reaction conditions: 2,2,2-trichloroethyl ester (1.0 mmol), amine (1.4 mmol), DBU (0.2 mmol), MeCN, 80 °C for 12 h,

[b] Isolated yields after column purification.

Scheme and Figure Captions

Scheme 1. Synthesis of amide via 2,2,2-trichloroethyl esters

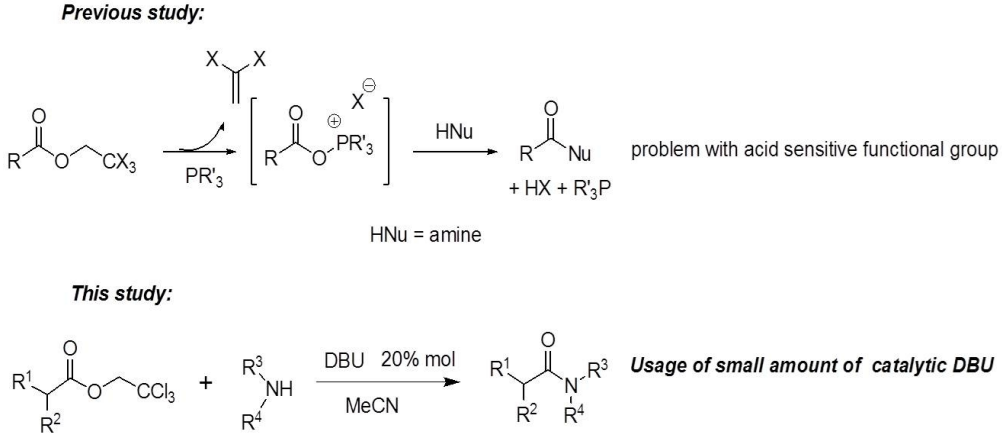
Scheme 2. The gram-scale reaction of 2,2,2-trichloroethyl benzoate **1a** with *n*-butylamine **2a**

Figure 1. Structures of basic organic reagents used for screening

Figure 2. The effects of aromatic substituents on the rate of amidation reaction

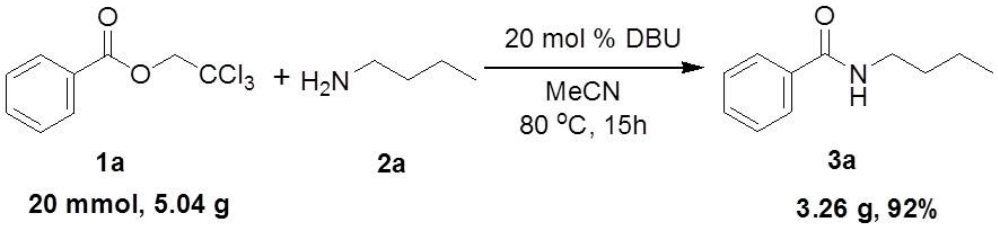
Figure 3. The proposed mechanism of aminolysis reaction

Chart 1. The structures of 2,2,2-trichloroethyl esters and amides



Scheme 1. Synthesis of amide via 2,2,2-trichloroethyl esters

222x97mm (150 x 150 DPI)



1a **2a** **3a**

20 mmol, 5.04 g **3.26 g, 92%**

Scheme 2. The gram-scale reaction of 2,2,2-trichloroethyl benzoate 1a with n-butylamine 2a

150x35mm (150 x 150 DPI)

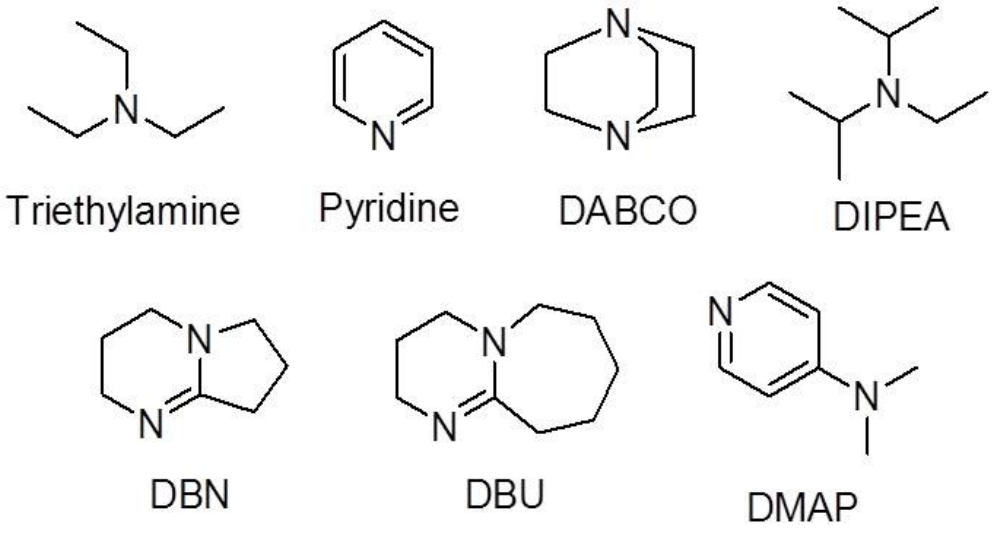
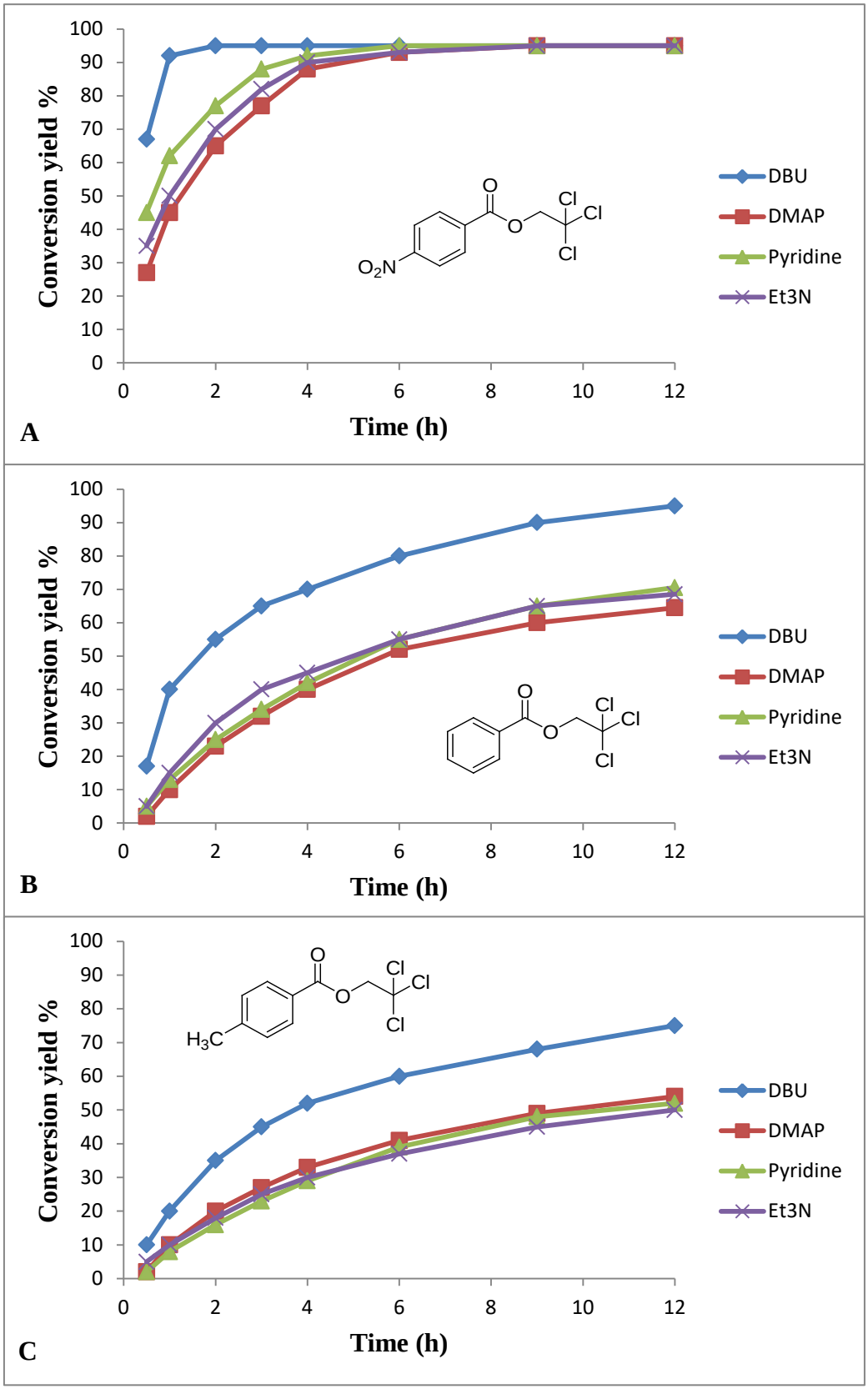


Figure 1. Structures of basic organic reagents used for screening

115x62mm (150 x 150 DPI)



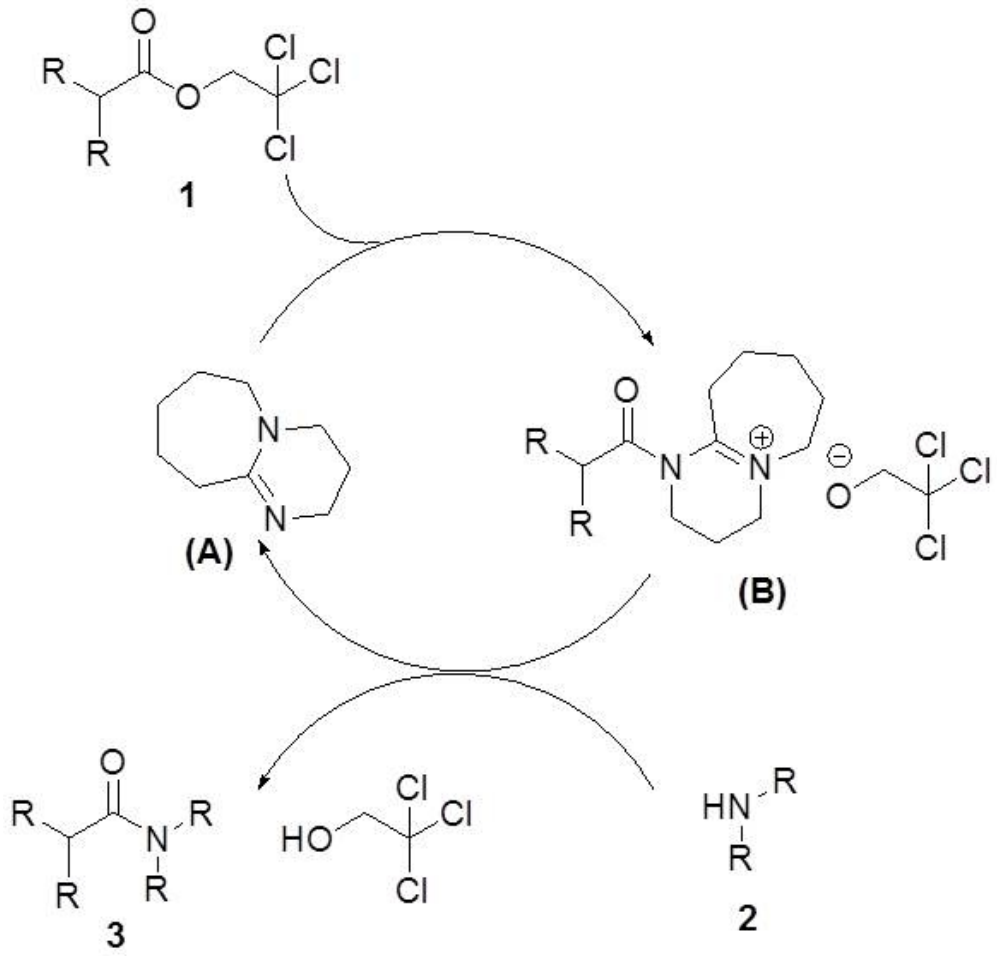


Figure 3. The proposed mechanism of aminolysis reaction

98x95mm (150 x 150 DPI)

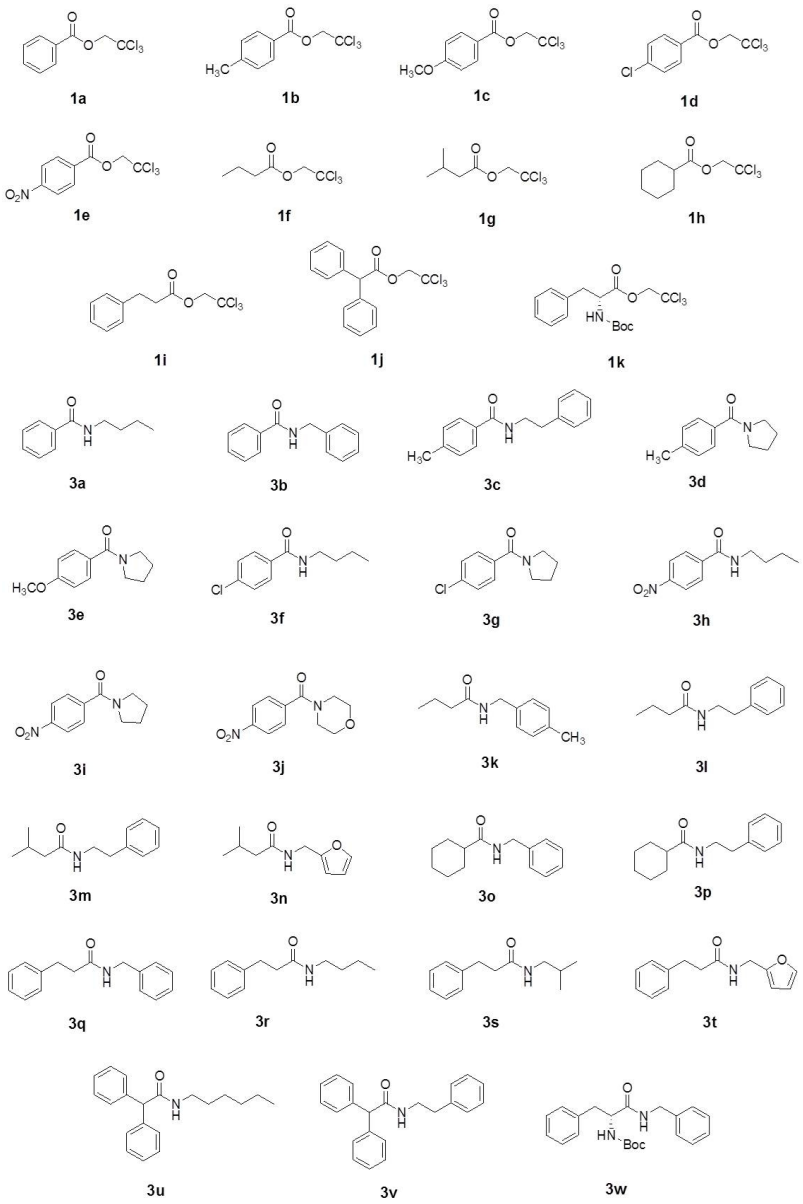
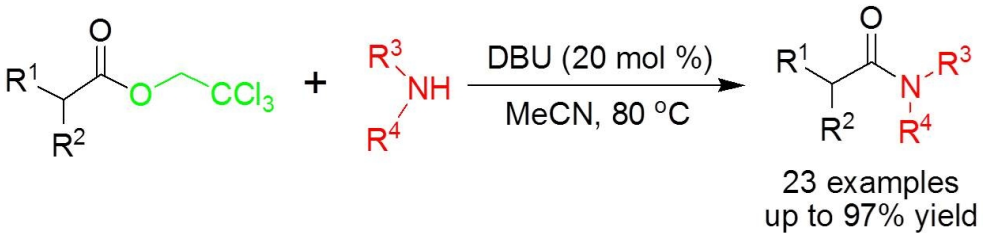


Chart 1. The structures of 2,2,2-trichloroethyl esters and amides

192x287mm (150 x 150 DPI)



Facile direct synthetic method for amides from the 2,2,2-trichloroethyl ester compounds using catalytic DBU is developed.

214x78mm (150 x 150 DPI)