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# One-pot synthesis of amides from carboxylic acids activated using thionyl chloride

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A one-pot synthesis of secondary and tertiary amides from carboxylic acids and amines by using $SOCl_2$ has been developed. Also when sterically hindered amines were used as the starting materials excellent yields of the corresponding amides were obtained. The amidation of *N*-protected α-amino acids with secondary amines proceeds effectively with good yields. The process works well also in the presence of acid sensitive groups and occurs with almost complete retention of stereochemical integrity of chiral substrates. This protocol could be extended to the industrial large-scale production processes.

## Introduction

Amides represent one of the most important and valuable organic functional groups in naturally occurring molecules, pharmaceuticals, agrochemicals, and polymers.[1]
The synthesis of amide is of huge importance in organic, coordination, and medicinal chemistry.[2]
Improved and innovative methods for the synthesis of amides are in great demand both by chemical and pharmaceutical industry.[3-5]
Carboxylic amides are typically obtained from amines and activated carboxylic acid derivatives through a nucleophilic acyl substitution reaction. Acid derivatives most frequently used in the amides synthesis are acyl chlorides.
The amidation of carboxylic acids via acyl chlorides is usually a two-step process,[6] involving first the conversion of the acid into the acyl chloride followed by the coupling itself with the amine.
Chlorination of carboxylic acids is carried out using several chlorinating reagents, such as pivaloyl chloride, phthaloyl dichloride, thionyl chloride and oxalyl chloride.[7-10]
Other chlorinating reagents[11] that can be employed in amide formation are 2,4,6-Trichloro-1,3,5-triazine (CC, cyanuric chloride),[12] 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT)[13] and tetramethyl-α-chloroenamine[14] which gives rise to neutral side-products and bis(trichloromethyl)carbonate (BTC).[15]
Thionyl chloride ($SOCl_2$) is the most popular reagent to activate carboxylic function because it is volatile and the excess can be removed easily by distillation, finally it is non-expensive.
Usually, for the preparation of acid chlorides, thionyl chloride is used, neat or dissolved in a solvent, in the presence of the corresponding acid. The reaction requires heating and can be accelerated by adding pyridine.[16] Improvements of the classical $SOCl_2$-pyridine method was achieved by forming the acid chlorides from dicyclohexylammonium salts of carboxylic acids and thionyl chloride.[17]
Secondary and tertiary amides were also obtained in a one pot reaction by treating carboxylic acids with thionyl chloride and stoichiometric amounts of amines in the absence of base and in the presence of *N*,*N*-disubstituted amides ((*N*,*N*-dimethylacetamide (DMAC), *N*,*N*-dimethylformamide (DMF), *N*-methylpyrrolidone (NMP)).[18-24] The reaction occurs by generating the Vilsmeier complex from *N*,*N*-disubstituted amides (DMAC, DMF, NMP) and thionyl chloride that acts as reagent for chlorination of carboxylic acids. The formation of amides is completed in more than 1 hour and in some cases, to achieve 100 % conversion, it is necessary to heat to 50 °C.[18] In other cases instead, the reaction takes places in longer times and with low yields.[20-21]
In Table 1 is reported a comparison of different one pot thionyl chloride methods for amide synthesis.

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†Electronic Supplementary Informations (ESI) available: $^{1}H$ and $^{13}C$ NMR spectra for compounds **1-17**. $^{13}C$ NMR spectra for elucidation of reaction mechanism, HPLC analyses of compounds **16-17** and of a mixture of **16** and **17**. See DOI: 10.1039/x0xx00000x

**Table 1.** Comparison between different one-pot thionyl chloride methods for amide synthesis.

| Entry | Reaction conditions | $SOCl_2$ (equiv) | Yield (%) | Time | Ref. |
|---|---|---|---|---|---|
| 1 | DMAC[a] 20 to 50 °C | 1.08 | 80-90 | >1h | 18 |
| 2 | DMAC[a] 15 to 20 °C | n.r. | 92 | n.r.[c] | 19 |
| 3 | DMAC[a] -12 to 20 °C | 1.27 | 45 | 9 h | 20 |
| 4 | DMAC[a] - 20 to 20 °C | 1.04 | 51 | 3.5 h | 21 |
| 5 | NMP[a] 0 to 25 °C | 1.04 | 85 | 1.5 h | 22 |
| 6 | DMF[b] $Et_3N$, 45 °C | 1.05 | 69 | 3 h | 23 |
| 7 | Toluene[a] 40-70 °C | 1.20 | n.r. | 2-24 h | 25 |

[a] reaction solvent; [b] 0.05 equiv.; [c] n.r.=not reported

As an alternative, the carboxyl function activation can be performed by using coupling agents[26] that are also widely used for the formation of peptide bond.[27-29] They allow to overcome side reactions such as ketene formation, acyl transfer and to reduce racemization in peptide coupling.

Here we report the use of thionyl chloride as activating agent of carboxylic function for the one-pot synthesis of amides.

The thionyl chloride ($SOCl_2$), used as a chlorinating agent in the formation of acyl chlorides, could also function as coupling agent by activating in situ the carboxylic function of the acid. Then the amine present in the reaction medium could react with the reactive intermediate by generating the amide, and as a result, the reaction would proceed under one-pot conditions.

## Experimental

### Materials and methods

Reagents were commercially available with analytical grade and used as purchased without further purification. All α-amino acids were of the L-series. Solvents were purified according to well-known laboratory methods and freshly distilled prior to use. All reactions were carried out using flame-dried glassware and under an inert atmosphere (dry $N_2$). Reaction mixtures were monitored by thin layer chromatography (TLC) using silica gel 60-F254 pre-coated glass plates. Spots on the TLC plates were visualized with a UV lamp (254 nm) and by spraying with 0.2% ninhidrin in ethanol and charring after elution. $^1H$ and $^{13}C$ NMR spectra were recorded at 300 MHz and 75 MHz, respectively. Spectroscopic analysis was performed at 293 K on diluted solutions of each compound by using $CDCl_3$ as the solvent. Chemical shifts (δ) are reported in ppm and referenced to $CDCl_3$ (singlet at 7.25 ppm for 1H and 77.0 ppm, central line of the triplet, for 13C spectra). Coupling constants (J) are reported in Hertz (Hz).

The $^1H$, $^{13}C$ spectra of compounds **18**, **19** and **20** were recorded at 298 k on a Bruker Avance 500 MHz instrument ($^1H$: 500.13 MHz, $^{13}C$: 125.77 MHz).

GC-MS analyses were performed using a 30 m × 0.25 mm, PhMesiloxane capillary column. The mass detector was operated in the electron impact ionization mode (EIMS) with an electron energy of 70 eV. The injection port was heated to 250 °C. The oven temperature program was initially set at 100 °C with a hold of 2 min and ramped to 280 °C at 14 °C/min with a hold of 10 min.

Chiral GC-MS analyses of enantiomeric compounds **18** and **19** were performed by using a 25 m × 0.25 mm, Diethyl tertbutyldimethylisilyl-β-cyclodextrine chiral capillary column. The injection port was heated to 250 °C. The oven temperature program was initially set at 50 °C ramped to 200 °C at 0.5 °C/min with a hold of 20 min.

ESI-QTOF mass spectra were recorded on a Quadrupole Time of Flight (QTOF) mass spectrometer fitted with an electrospray ionization source (ESI) operating in positive ion mode.

Analytical RP-HPLC analyses were carried out using a C18 RP analytical column (Tecnocroma Tracer Excel 120, ODSA, 15 x 0.4 cm, 5 µm) with an elution gradient from 20% to 40 % of B over 10 minutes, from 40% to 50% of B in 20 minutes, followed by 50% - 60% of B in 10 minutes, A being $H_2O$ and B $CH_3CN$ and detection at 254 nm. Flow rate was 1 mL/min.

### General procedure for one pot synthesis of amides 1-19

1 mmol of carboxylic acid is added to 1 mmol of amine and 3 mmol of triethylamine ($Et_3N$) in dichloromethane, then 1 mmol of $SOCl_2$ is added at room temperature. The mixture is stirred for 5-20 minutes at room temperature. The recovery of the reaction product is performed by evaporating the solvent under reduced pressure. The resulting residue is taken up in dichloromethane and washed first with 1N HCl* and then with 1N NaOH. The organic phase was dried ($Na_2SO_4$), and evaporated to dryness to afford the corresponding carboxylic amide.

*For the synthesis of *N*,*N*-diethylamides of *N*-Boc-protected amino acids (**15**, **18** and **19**) the acidic work up was performed by using 5% aqueous $NaHSO_4$.

***N,N* diethylbenzamide (1)** Viscous red oil, 86%, $R_f$ = 0.77, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.43-7.34 (m, 5H, ArH), 3.63-3.43 (m, 2H, $NCH_2$), 3.38-3.18 (m, 2H, $NCH_2$), 1.32-1.18 (m, 3H, $CH_2C\underline{H}_3$) 1.17-1.02 (m, 3H, $CH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 171.3, 137.2, 129.1, 128.4, 126.2, 43.3, 39.2, 14.2, 12.9. MS (EI, 70 eV) m/z (% rel.): 177 [$M^{+\cdot}$] (20), 176 (49), 162 (8), 148 (16), 105 (100), 77 (48), 51 (21). Anal. Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.65; H, 8.51; N, 7.88.

***N,N*-diethylpyrazine-2-carboxamide (2)** Viscous colorless oil, 88%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $R_f$ = 0.39; $^1H$ NMR (300 MHz, $CDCl_3$) δ: 8.83-8.78 (m, 1H, ArH), 8.56-8.50 (m,

1H, ArH), 8.49-8.43 (m, 1H, ArH), 3.49 (q, J = 6.5 Hz, 2H, $NCH_2$), 3.31 (q, J = 6.5 Hz, 2H, $NCH_2$), 1.19 (t, J = 6.5 Hz, 3H, $CH_2C\underline{H}_3$), 1.08 (t, J = 6.5 Hz, 3H, $CH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 166.1, 150.2, 144.9, 144.7, 142.5, 43.2, 40.4, 14.2, 12.6. GC/MS: m/z 179[$M^{+\cdot}$](5), 107(30), 79(35), 72(100). Anal. Calcd for $C_9H_{13}N_3O$: C, 60.32; H, 7.31; N, 23.45. Found: C, 60.40; H, 7.29; N, 23.51.

***N,N*-diethyl-3-phenylbenzamide (3)** Viscous colorless oil, 91%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $R_f$ = 0.75; $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.50-7.23 (m, 9H, ArH), 3.85-3.70 (m, 1H, $NCH_2$), 3.10-2.89 (m, 2H, $NCH_2$), 2.71-2.52 (m, 1H, $NCH_2$), 0.89 (t, J = 6.8 Hz, 3H, $CH_2C\underline{H}_3$), 0.74 (t, J = 6.8 Hz, 3H, $CH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 170.7, 139.7, 138.4, 136.1, 128.9, 128.6, 128.5, 128.3, 127.5, 126.8, 42.3, 38.4, 13.3, 11.9; MS (EI, 70 eV) m/z (% rel.): 253 [$M^{+\cdot}$] (37), 252 (75), 181 (100), 152 (51), 77 (38). Anal. Calcd for $C_{17}H_{19}NO$: C, 80.60; H, 7.56; N, 5.53. Found: C, 80.72; H, 7.58; N, 5.54.

***N,N*-diethylcinnamamide (4)** Viscous colorless oil, 86%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $R_f$ = 0.55; $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.73 (d, J = 15.3 Hz, 1H, CH vinyl), 7.61-7.50 (m, 2H, ArH), 7.40-7.34 (m. 3H, ArH), 6.84 (d, J = 15.3 Hz, 1H, CH vinyl), 3.60-3.40 (m, 4H, $NCH_2$), 1.33-1.15 (m, 6H, $CH_2C\underline{H}_3$) ppm; $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 165.7, 142.3, 135.5, 129.4, 128.7, 127.7, 117.7, 42.3, 41.1, 15.1, 13.2 ppm; MS (EI, 70 eV) m/z (% rel.): 203 [$M^{+\cdot}$] (31), 188 (20), 131 (100), 103 (40), 77 (23). Anal. Calcd for $C_{13}H_{17}NO$: C, 76.81; H, 8.43; N, 6.89. Found: C, 76.76; H, 8.41; N, 6.90.

***N,N*-diethylpalmitamide (5)** Viscous colorless oil, 90%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $R_f$ = 0.68; $^1H$ NMR (300 MHz, $CDCl_3$) δ: 3.42-3.20 (m, 4H, $NCH_2$), 2.35 (t, J = 7.2 Hz, 2H, $CH_2CO$), 1.67-1.50 (m, 2H, $C\underline{H}_2CH_2CO$), 1.34-1.10 (m, 30H, $CH_3(C\underline{H}_2)_{12}CH_2CH_2CO$ and $(C\underline{H}_3CH_2)_2N$), 0.81 (t, J = 6.6 Hz, 3H, $(CH_2)_{14}C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 173.8, 34.2, 32.5, 31.8, 29.6, 29.4, 29.3, 29.2, 25.7, 24.8, 22.6, 14.0; MS (EI, 70 eV) m/z (% rel.): 311 [$M^{+\cdot}$] (12), 128 (25), 115 (100), 100 (28), 72 (16). Anal. Calcd for $C_{20}H_{41}NO$: C, 77.10; H, 13.26; N, 4.50. Found: C, 77.18; H, 13.29; N, 4.48.

***N,N*-diethylmyristamide (6)** Viscous colorless oil, 88%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $R_f$ = 0.67, $^1H$ NMR (300 MHz, $CDCl_3$) δ: 3.38 (q, J = 7.2 Hz, 2H, $NCH_2$), 3.31 (q, J = 7.2 Hz, 2H, $NCH_2$), 2,29 (t, J=7.2 Hz, 2H, $CH_2CO$), 1.70-1.59 (m, 4H, $(C\underline{H}_2)_2CH_2CO$), 1.38-1.23 (m, 18H, $CH_3(C\underline{H}_2)_9(CH_2)_2CH_2CO$), 1.18 (t, J = 7.2 Hz, 3H, $CH_2C\underline{H}_3$), 1.12 (t, J = 7.2 Hz, 3H, $NCH_2C\underline{H}_3$), 0.89 (t, J = 6.6 Hz, 3H, $C\underline{H}_3(CH_2)_{12}CO$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 172.2, 41.9, 39.9, 33.1, 31.9, 29.6, 29.5, 29.4, 29.3, 25.5, 22.6, 14.4, 14.1, 13.1; MS (EI, 70 eV) m/z (% rel.): 283 [$M^{+\cdot}$] (12), 128 (25), 115 (100), 100 (28), 72 (16). Anal. Calcd for $C_{18}H_{37}NO$: C, 76.26; H, 13.16; N, 4.94. Found: C, 76.37; H, 13.27; N, 4.95.

***N*-ethyl-*N*-isopropylbenzamide (7)** Viscous colorless oil, 86%, TLC (eluent: diethyl ether/P.E. 70/30 v/v): $R_f$ = 0.71; $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.50-7.20 (m, 5H, ArH), 4.10-3.80 (m, 1H, NCH), 3.52-3.25 (m, 2H, $NCH_2$), 1.39-0.95 (m, 9H, $CH(C\underline{H}_3)_2$ and $CH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 171.1, 129.9, 128.9, 128.4, 125.9, 50.2, 35.2, 21.1, 14.8; m/z (% rel.): [$M^{+\cdot}$] 191 (22), 190 (25), 176 (5), 162 (10), 148 (5), 105 (100), 77 (35). Anal. Calcd for $C_{12}H_{17}NO$: C, 75.35; H, 8.96; N, 7.32. Found: C, 75.48; H, 8.94; N, 7.31.

***N*-benzoylpiperidine (8)** Viscous colorless oil, 88%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $R_f$ = 0.50; $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.29-7.15 (m, 5H, ArH), 3.65-3.45 (m, 2H, $NCH_2$), 3.28-3.10 (m, 2H, $NCH_2$), 1.58-1.27 (m, 6H, $NCH_2(C\underline{H}_2)_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 170.1, 136,3, 129.2, 128.2, 126.6, 48.5, 42.9, 26.3, 25.5, 24.4; MS (EI, 70 eV) m/z (% rel.): 189 [$M^{+\cdot}$] (35), 188 (100), 105 (75), 77 (41). Anal. Calcd for $C_{12}H_{15}NO$: C, 76.16; H, 7.99; N, 7.40. Found: C, 76.29; H, 8.01; N, 7.41.

***N*-benzyl-*N*-ethylbenzamide (9)** Viscous colorless oil, 85%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $R_f$ =0.59; $^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.60-6.90 (m, 10H, ArH), 4.90-4.42 (m, 2H, $NCH_2Ph$), 3.78-3.05 (m, 2H, $NCH_2$), 1.38-1.02 (m, 3H, $CH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ:170.8, 133.4, 130.1, 129.8, 128.9, 128.5, 128.3, 127.6, 126.6, 53.9, 42.9, 13.9; MS (EI, 70 eV) m/z (% rel.): 239 [$M^{+\cdot}$] (55), 238 (40), 210 (10), 148 (5), 134 (6), 105 (100), 91 (20), 77 (35). Anal. Calcd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.41; H, 7.17 ; N, 5.86.

***N*-propylbenzamide (10)** Viscous colorless oil, 92%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $R_f$ = 0.38 ,$^1H$ NMR (300 MHz, $CDCl_3$) δ: 7.95-7.70 (m, 2H, ArH), 7.51-7.28 (m, 3H, ArH), 3.36 (t, J=7.2 Hz, 2H, $NHC\underline{H}_2$), 1.72-1.54 (m, 2H, $NHCH_2C\underline{H}_2$), 0.90 (t, J=7.2, Hz, 3H, $C\underline{H}_3CH_2$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 168.9, 131.9, 129.9, 128.5, 127.4, 42.3, 22.5, 11.3; MS (EI, 70 eV) m/z (% rel.): 163 [$M^{+\cdot}$] (40), 148 (5), 134 (10), 105 (100), 77 (40). Anal. Calcd for $C_{10}H_{13}NO$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.69; H, 8.04; N, 8.59.

***N*-phenylbenzamide (11)** Viscous colorless oil, 89%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): $R_f$ =0.58 , $^1H$ NMR (300 MHz, $CDCl_3$) δ: 8.35-7.05 (m, 11H, ArH and NH), $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 165.9, 137.9, 133.2, 130.1, 129.0, 128.7, 127.1, 124.3, 120.3 MS (EI, 70 eV) m/z (% rel.): 197 [$M^{+\cdot}$] (60), 105 (100), 77 (50). Anal. Calcd for $C_{13}H_{11}NO$: C, 79.16; H, 5.62; N, 7.10. Found: C, 79.27; H, 5.63; N, 7.11.

***N,N*-diethyl-(S)-2-(4-nitrophenylsulfonamido)-3-phenylpropanamide (12)** Pale yellow oil, 81%, TLC (eluent: chloroform/methanol 90:10 v/v): $R_f$ = 0.62; $^1H$ NMR (300 MHz, $CDCl_3$) δ: 8.22 (d, J = 9.0 Hz, 2H,), 7.88 (d, J = 9.0 Hz, 2H, ArH), 7.25-7.15 (m, 3H, ArH), 7.14-7.04 (m, 2H, ArH), 6.24 (d, J =8.1 Hz, 1H, NH), 4.48-4.32 (m, 1H, CHCO), 3.39-3.23 (m, 1H, $C\underline{H}_2CH_3$), 3.09-2.83 (m, 5H, $CH_2Ph$ and $NCH_2$), 0.99-0.80 (m, 6H, $CH_2C\underline{H}_3$); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ: 169.3, 149.8, 146.3, 135.4, 129.5, 128.6, 128.2, 127.3, 123.9, 54.5, 41.5, 40.7, 13.9, 12.5; MS (EI, 70 eV) m/z (% rel.): 405 [$M^{+\cdot}$] (2), 314 (51), 305 (100), 203 (44), 100 (55), 72 (61). Anal. Calcd for $C_{19}H_{23}N_3O_5S$: C, 56.28; H, 5.72; N, 10.36; S, 7.91. Found: C, 56.43; H, 5.74; N, 10.33; S, 7.88.

***N,N*-diethyl-(S)-2-(4-nitrophenylsulfonamido)-propanamide (13)** Pale yellow oil, 83%, TLC (eluent: chloroform/methanol 90:10 v/v): $R_f$ = 0.72; $^1$H NMR (300 MHz, $CDCl_3$) δ: 8.32 (d, J = 8.1 Hz, 2H, ArH), 8.04 (d, J = 8.1 Hz, 2H, ArH), 6.24 (d, J = 8.7 Hz, 1H, NH), 4.32-4.18 (m, 1H, CHCO), 3.30-3.05 (m, 4H, $NCH_2$), 1.33 (d, J = 6.9 Hz, 3H, $CHCH_3$), 1.09 (t, J = Hz, 3H, $CH_2CH_3$), 0.92 (t, J = Hz, 3H, $CH_2CH_3$); $^{13}$C NMR (75 MHz, $CDCl_3$) δ: 170.1, 149.9, 146.3, 128.4, 124.1, 49.2, 41.6, 40.6, 20.5, 14.3, 12.6; MS (EI, 70 eV) m/z (% rel.): 229 (69), 186 (15), 122 (10), 100 (95), 72 (100). Anal. Calcd for $C_{13}H_{19}N_3O_5S$: C, 47.41; H, 5.81; N, 12.76; S, 9.74. Found: C, 47.55; H, 5.82; N, 12.80; S, 9.76.

**4-acetamidophenylacetate (14)** Viscous colorless oil, 48%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): Rf= 0.88; $^1$H NMR (300 MHz, $CDCl_3$) δ: 7.91 (s, 1H, NH), 7.55 (d, J = 9.0 Hz, 2H, ArH), 7.01 (d, J = 9.0 Hz, 2H, ArH), 2.29 (s, 3H, $CH_3CO$), 2.17 (s, 3H, $CH_3CO$), $^{13}$C NMR (75 MHz, $CDCl_3$) δ 169.8, 168.6, 147.0, 135.9, 121.8, 120.8, 24.4, 21.1; MS (EI, 70 eV) m/z (% rel.): 193 [$M^{+\cdot}$] (10), 151(55), 109 (100), 80 (10). Anal. Calcd for $C_{10}H_{11}NO_3$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.26; H, 5.75; N, 7.26.

***N,N*-diethyl-(S)-2-(*tert*-butoxycarbonyl)-amino-3-phenylpropanamide (15)** Pale yellow oil, 78%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): Rf= 0.81; $^1$H NMR (300 MHz, $CDCl_3$) *δ*: 7.26-7.10 (m, 5H, ArH), 5.39 (d, J=9 Hz, 1H, NH), 4.74-4.64 (m, 1H, CHCO), 3.53-3.41 (m, 1H $CH_2CH_3$); 3.11-2.80 (m, 5H $CH_2Ph$, $CH_2CH_3$), 1.37 (s, 9H, tBu), 0.99 (t, J=7.2 Hz, 3H, $CH_3CH_2N$), 0.92 (t, J=7.2 Hz, 3H, $CH_3CH_2N$), $^{13}$C NMR (75 MHz, $CDCl_3$) *δ* 170.8, 154.9, 136.5, 129.5, 128.3, 126.7, 79.5, 51.3, 41.5, 40.4, 28.2, 14.0; MS (EI, 70 eV) *m/z* (% rel.): 320 [$M^{+\cdot}$] (2), 229(6), 220(20), 164(45), 129(40), 120(100), 100(35), 91(20), 72(40), 57(70). Anal. Calcd for $C_{18}H_{28}N_2O_3$: C, 67.47; H, 8.81; N, 8.74. Found: C, 67.51; H, 8.87; N, 8.75.

***N*-((R)-1-phenylethyl)-2-(S)-(4-nitrophenylsulfonamido)-propanamide (16)** Pale yellow oil, 75%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): Rf= 0.88; $^1$H NMR (300 MHz, $CDCl_3$) *δ*: 8.17 (d, J=8.7 Hz, 2H, ArH), 7.93 (d, J=8.7 Hz, 2H, ArH), 7.34-7.23 (m, 5H, ArH), 5.94 (d, J=8.2, 1H, NH), 5.55 (d, J=8.1, 1H, NH), 4.97-4.86 (m, 1H, CHPh), 3.90-3.79 (m, 1H, CHCO), 1.44 (d, J=6.9 Hz, 3H, $CH_3CHPh$), 1.39 (d, J=6.9 Hz, 3H, $CH_3CHCO$); $^{13}$C NMR (75 MHz, $CDCl_3$) *δ* 168.1, 152.1, 142.1, 137.9, 128.8, 128.2, 127.8, 125.9, 124.3, 55.1, 49.7, 21.8, 20.1; Anal. Calcd for $C_{17}H_{19}N_3O_5S$: C, 54.10; H, 5.07; N, 11.13; S, 8.50. Found: C, 54.18; H, 5.15; N, 11.28; S, 8.61. ESI-QTOF-MS: 378.1063 $(M+H)^+$, 400.0944 $(M+Na)^+$.

***N*-((S)-1-phenylethyl)-2-(S)-(4-nitrophenylsulfonamido)-propanamide (17)** Pale yellow oil, 68%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): Rf= 0.88; $^1$H NMR (300 MHz, $CDCl_3$) *δ*: 8.35 (d, J=9 Hz, 2H, ArH), 8.05 (d, J=9 Hz, 2H, ArH), 7.38-7.21 (m, 5H, ArH), 5.97 (d, J=7.2 Hz 1H, NH), 5.60 ($s_{broad}$, 1H, NH), 4.98-4.88 (m, 1H, CHPh), 3.91-3.82 (m, 1H, CHCO), 1.40 (d, J=6.9 Hz, 3H, $CH_3CHPh$), 1.35 (d, J=6.9 Hz, 3H, $CH_3CHCO$); $^{13}$C NMR (75 MHz, $CDCl_3$) *δ* 168.1, 151.8, 141.2, 136.9, 128.8, 128.4, 127.8, 125.9, 124.3, 52.5, 49.1, 22.8, 21.1; Anal. Calcd for $C_{17}H_{19}N_3O_5S$: C, 54.10; H, 5.07; N, 11.13; S, 8.50. Found: C, 54.15; H, 5.09; N, 11.23; S, 8.59. ESI-QTOF-MS: 378.1092 $(M+H)^+$, 400.0939 $(M+Na)^+$.

***1-(tert*-butoxycarbonyl)-2-(S)-(*N,N*-diethylaminocarbonyl)-pyrrolidine (18)** Pale yellow oil, 75%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): Rf= 0.78; $^1$H NMR (500 MHz, $CDCl_3$) two conformers (60*:40) δ: 4.55 (dd, J=7.8 Hz, J=2.9 Hz, 1H, CHCO), 4.41* (dd, J=8.4, J=3.8 Hz, 1H, CHCO), 3.63-3.15 (m, 6H, $CH_2CH_2NCO$, $CH_2CH_3$), 2.21-1.91 (m, 2H, $CH_2CH_2CHCO$), 1.87-1.71 (m, 2H, $CH_2CH_2CHCO$), 1.41 and 1.47* (2s, 9H, tBu), 1.24-1.15 (m, 3H, $CH_3CH_2N$), 1.13-1.03 (m, 3H, $CH_3CH_2N$); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.06, 154.62, 154.07*, 79.63*, 79.33, 56.57*, 56.32, 47.08, 46.94*, 41.84, 41.05*, 40.84, 31.35*, 30.37, 28.62, 28.57*, 24.29, 23.53*, 14.85, 13.26*, 13.04; MS (EI, 70 eV) *m/z* (% rel.): 270 [$M^{+\cdot}$] (1), 197(18), 170(37), 114(88), 100(29), 70(100), 57(43). Anal. Calcd for $C_{14}H_{26}N_2O_3$: C, 62.19; H, 9.69; N, 10.36. Found: C, 62.25; H, 9.65; N, 10.30.

***1-(tert*-butoxycarbonyl)-2-(R)-(*N,N*-diethylaminocarbonyl)-pyrrolidine (19)** Pale yellow oil, 73%, TLC (eluent: diethyl ether/P.E. 70:30 v/v): Rf= 0.78; $^1$H NMR (500 MHz, $CDCl_3$) two conformers (59*:41) δ: 4.53 (dd, J=7.8 Hz, J= 3.0 Hz, 1H, CHCO), 4.38* (dd, J=8.4 Hz, J=3.8 Hz, 1H, CHCO), 3.60-3.11 (m, 6H, $CH_2CH_2NCO$, $CH_2CH_3$), 2.19-1.90 (m, 2H, $CH_2CH_2CHCO$), 1.86-1.68 (m, 2H, $CH_2CH_2CHCO$), 1.38 and 1.34*(2s, 9H, tBu), 1.22-1.13 (m, 3H, $CH_3CH_2N$), 1.10-1.01 (m, 3H, $CH_3CH_2N$); $^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.10, 154.60, 154.03*, 79.53*, 79.28, 56.62*, 56.35, 46.95, 41.78, 40.96, 31.34*, 30.31, 28.58, 24.27, 23.44*, 14.76, 13.14; MS (EI, 70 eV) *m/z* (% rel.): 270 [$M^{+\cdot}$] (1), 197(19), 170(40), 114(94), 100(30), 70(100), 57(45). Anal. Calcd for $C_{14}H_{26}N_2O_3$: C, 62.19; H, 9.69; N, 10.36. Found: C, 62.23; H, 9.63; N, 10.31.

**Synthesis of dipeptide methyl 3-methyl-2-(S)-(2-(R)-(4-nitrophenylsulfonamido)-propanamido)butanoate (20)**

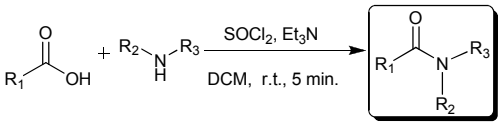
1 mmol of 2-(S)-(4-nitrophenylsulfonamido)propanoic acid is added to 1 mmol of (S)-methyl 2-amino-3-methylbutanoate hydrochloride and 5 mmol of triethylamine ($Et_3N$) in dichloromethane, then 1 mmol of $SOCl_2$ is added at room temperature. The mixture is stirred for 40 minutes at room temperature. The recovery of the reaction product is performed by evaporating the solvent under reduced pressure. The resulting residue is taken up in dichloromethane and washed first with 1N HCl and then with 1N NaOH. The organic phase was dried ($Na_2SO_4$), and evaporated to dryness to afford the corresponding dipeptide **20**.

White solid, 65%; Mp 144–148 °C; TLC (eluent: chloroform/methanol 90:10 v/v): Rf= 0,53; $^1$H NMR (500 MHz, $CDCl_3$) δ: δ 8.27 (d, J=8.8 Hz, 2H, ArH), 8.00 (d, J=8.8 Hz, 2H, ArH), 6.47 (d, J=8.7 Hz, 1H, $NHSO_2ArH$), 5.93 (d, J=8.5 Hz, 1H, $NHCHCOOCH_3$), 4.31 (dd, J=8.5 Hz, J=4.8 Hz, 1H, $CHCOOCH_3$), 4.02–3.91 (m, 1H, $NHCH(CH_3)CO$), 3.69 (s, 3H, $OCH_3$), 2.12-2.04 (m, 1H, $CH(CH_3)_2$), 1.33 (d, J=7.1 Hz, 3H, $CH_3CH$), 0.84 (d, J=6.9 Hz, 3H, $CH(CH_3)_2$), 0.80 (t, J=6.9 Hz, 3H, $CH(CH_3)_2$).$^{13}$C NMR (126 MHz, $CDCl_3$) δ 172.31, 171.13, 150.35, 145.75, 128.68, 124.60, 57.22, 52.88, 52.61, 31.47, 20.40, 19.07, 17.70; MS (EI, 70 eV) *m/z* (% rel.): 328 [$M^{+\cdot}$-COOMe] (28), 274(8), 229(100),

186(27), 130(27), 122(21), 72(14). Anal. Calcd for $C_{15}H_{21}N_3O_7S$: C, 46.50; H, 5.46; N, 10.85; S, 8.28.Found: C, 46.38; H, 5.48; N, 10.90; S, 8.26.

## Results and discussion

In order to verify the one-pot formation of the amide by using thionyl chloride as activating agent, we designed an experiment in which benzoic acid, the carboxylic acid chosen as model system, is treated, in the presence of triethylamine, with thionyl chloride and the amine (Scheme 1).




**Scheme 1.** One pot synthesis of amides from carboxylic acids using $SOCl_2$ and $Et_3N$.

1 mmol of benzoic acid was added to 1 mmol of diethylamine ($Et_2NH$) and 3 mmol of triethylamine ($Et_3N$) in dichloromethane, then 1 mmol of $SOCl_2$ was added.

After 5 minutes stirring at room temperature, TLC analysis of the reaction mixture showed the complete conversion of benzoic acid.

The recovery of the reaction product was performed by evaporating the solvent under reduced pressure to remove traces of unreacted thionyl chloride. The resulting residue, after work up, provided the corresponding *N,N*-diethylbenzamide (**1**) in 86% overall yield (Table 2).

The molecular structure of **1** was assigned by $^1H$ and $^{13}C$ NMR spectroscopy and GC/MS analysis.

An additional experiment was performed to investigate the reaction progress in absence of the tertiary amine $Et_3N$. To this aim 1 mmol of $SOCl_2$ was added to 1 mmol of benzoic acid and 1 mmol of diethylamine ($Et_2NH$) in dichloromethane at room temperature. After 20 minutes the reaction was not yet complete and a mixture of benzoic acid (65% yield) and *N,N*-diethylbenzamide (31% yield) was recovered.

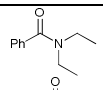
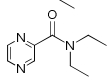
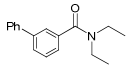
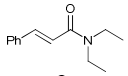
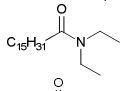
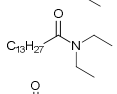
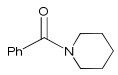
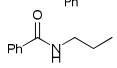
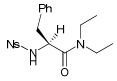
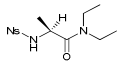
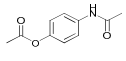
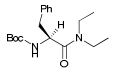
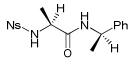
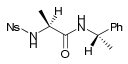
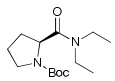
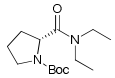
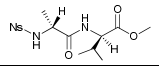
The use of stoichiometric amounts of diethylamine, in absence of $Et_3N$, leads to a lower conversion to amides since the diethylamine works also as a base to neutralize the hydrochloric acid that is generated during the reaction. This result demonstrated that the presence of the tertiary amine is essential to obtain the amide in high yields.

We also experienced that the outcome of the reaction is strongly dependent on the order of reagent addition. In fact, if benzoic acid is preliminarily added to thionyl chloride and $Et_2NH$ and $Et_3N$ are added subsequently, the reaction yield is lowered and after 5 minutes, the reaction is not yet complete. The obtained reaction product contained also the benzoyl chloride with a percentage of 35% as detected by GC/MS analysis.

Furthermore, it was verified that $SOCl_2$ does not react with the amine. In fact, the *N*-benzyl-*N*-ethylamine was recovered unchanged after it was treated with $SOCl_2$ at room temperature for 1 hour.

With the aim of investigating the reaction mechanism, we designed $^{13}C$ NMR experiments by performing and monitoring the reactions directly into the NMR tube using $CDCl_3$ as solvent and observing the chemical shifts of the carbonyl groups of the products present in the reaction mixture.

**Table 2.** Results of one pot synthesis of amides under the reaction conditions reported in Scheme 1.

| | Product | Reaction Time (min.) | Yield[a] (%) |
|---|---|---|---|
| 1 |  | 5 | 86 |
| 2 |  | 5 | 88 |
| 3 |  | 5 | 91 |
| 4 |  | 5 | 86 |
| 5 |  | 5 | 90 |
| 6 |  | 5 | 88 |
| 7 |  | 5 | 86 |
| 8 |  | 5 | 88 |
| 9 |  | 5 | 85 |
| 10 |  | 5 | 92 |
| 11 |  | 5 | 89 |
| 12 |  | 20 | 81 |
| 13 |  | 20 | 83 |
| 14 |  | 5 | 48 |
| 15 |  | 15 | 78 |
| 16 |  | 20 | 75 |
| 17 |  | 20 | 68 |
| 18 |  | 16 | 75 |
| 19 |  | 15 | 73 |
| 20 |  | 40 | 65 |

[a]Yields based on starting amount of carboxylic acid

The purpose of these experiments was to identify the reactive intermediate generated during the one pot amide formation reaction. Therefore, we recorded preliminarily the $^{13}C$ NMR spectra of benzoic acid and benzoyl chloride that exhibit carbonyl resonance signals respectively at 172.51 ppm and 168.38 ppm.

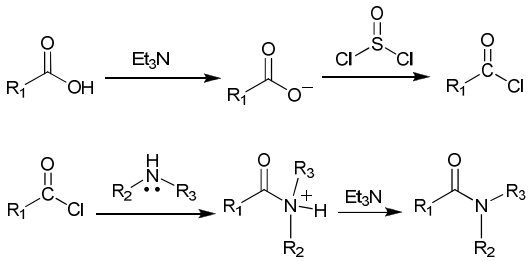
Subsequently in a NMR tube, benzoic acid (1 mmol) was treated with thionyl chloride (1mmol) at room temperature in $CDCl_3$ as solvent. The progress of the reaction was followed by recording the $^{13}C$ NMR spectrum of the reaction mixture. After more than 2 hours $^{13}C$ NMR spectrum showed the presence of the signal at (172.44 ppm) corresponding to the carbonyl group of benzoic acid and a signal of very low intensity, that can be just appreciated, relating to acyl chloride carbonyl group (168.52 ppm) This demonstrated that benzoyl chloride is formed hardly under these reaction conditions.

In an additional experiment, the same reaction was performed at room temperature by adding thionyl chloride (1 mmol) to a mixture of benzoic acid (1 mmol) and triethylamine (3 mmol) dissolved in $CDCl_3$. In this case the reaction proceeds rapidly and in the $^{13}C$ NMR spectrum it was observed immediately the disappearance of the signal relating to the resonance of benzoic acid carbonyl group and the appearance at 168,13 ppm of the signal generated by benzoyl chloride carbonyl group.

Finally, we reproduced, the one pot formation of *N*,*N*-diethylbenzamide (**1**) in a NMR tube, under the described conditions for the synthesis of amides **1-17**, and immediately recorded the $^{13}C$ NMR spectrum. In the obtained $^{13}C$ NMR spectrum at once the presence of two resonances attributable to the carbonyl groups of *N*,*N*-diethylbenzamide at 171.36 ppm and of benzoyl chloride at 168.32 ppm was observed. After about 10 minutes, the re-recorded $^{13}C$ NMR spectrum of the reaction mixture revealed only the presence of the resonance corresponding to the amidic carbonyl group.

These results could be justified by the action of tertiary amine that causes the formation of the carboxylate, which reacts quickly at room temperature with thionyl chloride to form the acid chloride that immediately reacts with the *N*,*N*-diethylamine to give the corresponding amide.

This experimental evidence suggests that benzoyl chloride is the reactive intermediate of the adopted one pot procedure (Scheme 2).




**Scheme 2.** Proposed mechanism of the one pot amide synthesis

The reaction was subsequently extended to other aromatic substrates, in all experimented cases the reaction is complete within 5 minutes and has provided excellent yields (86-91%) (Table 2, **2-4**).

The methodology was then applied to two long chain aliphatic carboxylic acids, palmitic and myristic acid. Also with these systems no changes were observed during the reaction, in fact

the amide formation occurs even in short times and high yields (88-90%) (Table 2, **5-6**).

In order to evaluate the possible effects due to the steric hindrance of the amine, *N*-ethyl-*N*-isopropylamine, piperidine and *N*-benzyl-*N*-ethylamine were treated with benzoic acid under the described reaction conditions.

Significant effects due to steric hindrance of the amines were not detected. Both the reaction kinetics that the reaction yields are similar to those of the reaction with diethylamine (Table 2, **7-9**).

Then, with the purpose to investigate the steric hindrance present on the carboxylic acid, the developed procedure was applied to two *N*-protected α-amino acids, *N*-nosyl-L-phenylalanine and *N*-nosyl-L-alanine.

*N*-nosyl-L-phenylalanine and *N*-nosyl-L-alanine were converted into the corresponding *N*,*N*-diethylamides (Table 2, **12-13**) in 20 minutes and with yields slightly lower.

Based on these results it can be argued that steric hindrance offered by the groups on the nitrogen atom of the amine does not affect the reaction progress while the reaction times are longer and the reaction yields are a little lower when sterically hindered carboxylic acids are used.

The adopted procedure for obtaining *N*,*N*-diethylamides was also applied successfully to *N*-Boc-L-phenylalanine, a substrate bearing the acid labile group *tert*-butoxyxorbonyl (Boc). The corresponding *N*,*N*-diethylamide (**15**) was obtained in 78 % yield keeping unchanged the acid-sensitive Boc group (Table 2). On the contrary the application of the two-step amide synthesis, through the formation of acyl chloride, to *N*-Boc-L-phenylalanine does not work well due to the instability of the corresponding acyl chloride that, when isolated in the absence of the nucleophile, decomposes readily.

The described protocol was also employed to obtain secondary amides by using primary amines as nucleophilic reagents. To this aim, *N*-propylamine and aniline were selected as nucleophiles. The reactions afforded the corresponding amides in short times and high yields (Table 2, **10-11**) by demonstrating that the adopted one-pot procedure is also applicable successfully for obtaining secondary amides.

We also investigated the stereochemical aspects of the reaction by extending the developed procedure to the formation of a couple of diastereoisomeric amides. To this aim *N*-((R)-1-phenylethyl)-2-(S)-(4-nitrophenylsulfonamido)-propanamide (**16**) and *N*-((S)-1-phenylethyl)-2-(S)-(4-nitrophenylsulfonamido)propanamide (**17**) were synthesized by treating *N*-(4-nitrobenzenesulfonyl)-L-alanine with (R)-1-phenylethylamine and (S)-1-phenylethylamine respectively according the adopted conditions. The corresponding amides **16** and **17** were obtained in 68-75 % yields after 20 minutes (Table 2). The $^{1}$H NMR and $^{13}$C NMR spectroscopic data of crude amides **16** and **17** did not show any signals from possible epimers resulting from an inversion of the configuration at the α-carbon atom of the alanine.

The absence of epimerization was also monitored by HPLC analysis of the crude amides **16** and **17** and of a suitably prepared mixture of the two diastereisomers **16** and **17** (approx. 30 %: 70 %). The two diastereoisomers were readily resolved by HPLC: the presence of two chromatographic peaks with retention times of 15.558 and 16.867 minutes was observed in the HPLC analysis of the mixture (Figure 1 **B**). Chromatograms of the single amide **16** (Figure 1 **A**) and **17** (Figure 1 **C**) showed the presence of a unique peak with retention times of 16.908 and 15.433 minutes respectively.

HPLC analysis in combination with NMR data of the two diastereomeric amides 16 and **17,** demonstrated the absence of epimerization products excluding any detectable epimerization throughout the synthetic process.

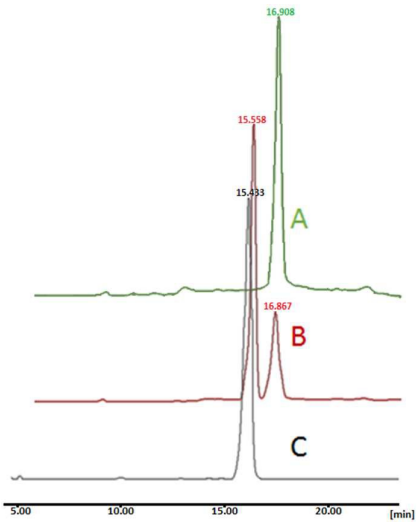



**Figure 1.** HPLC analyses of crude amides **16** and **17: (A)** N-((R)-1-phenylethyl)-2-(S)-(4-nitrophenylsulfonamido)-propanamide (**16**); **(B)** a mixture of **16** and **17** (approx. 30 %: 70 %); **(C)** N-((S)-1-phenylethyl)-2-(S)-(4-nitrophenylsulfonamido)-propanamide (**17**)

Furthermore, in order to evaluate the enantiomeric purity of *N*,*N*-diethylamides of *N*-Boc protected α-amino acids, two *N*,*N*-diethylamides of *N*-Boc-L-proline (**18**) and its enantiomer *N*-Boc-D-proline (**19**) were synthesized using the developed protocol (Table 2) and characterized by chiral GC/MS analysis.

The separation of L-amide **18** and D-amide **19** was achieved by chiral GC/MS analysis of a mixture of the two enantiomers **18** and **19** (approx. 70 %: 30 %): the corresponding chromatogram showed the presence of two peaks with retention times of 114.08 and 114.73 minutes related to **18** and **19** respectively.

The chiral GC/MS analysis of the single amide **18** showed a unique peak at 113.97 min. while that of the single amide **19** showed two peaks at 113.88 and 114.75 minutes which corresponded to identical mass spectra. The estimated enantiomeric excess of D-amide **19** was 99.2 %. The resulting ee was really satisfactory.

For completeness, since the amidation is mainly used in peptide synthesis, the developed protocol was also experimented for the synthesis of a small peptide. For this purpose the dipeptide system methyl 3-methyl-2-(S)-(2-(R)-(4-nitrophenylsulfonamido)-propanamido)butanoate (**20**) was prepared by treating *N*-4-nitrophenylsulfonyl-D-alanine (1mmol) with L-valine methyl ester hydrochloride (1mmol) under the adopted

reaction conditions using 5 equivalents of $Et_3N$. The methodology was successful in giving, after 40 minutes, the desired dipeptide derivative **20**, which was isolated in good yields (65%, Table 2).

A last experiment was performed to verify the preparation of the amides in large scale. 10 grams of benzoic acid were treated with $Et_2NH$ (8.5 ml) and $Et_3N$ (34.5 ml) in dichloromethane, then $SOCl_2$ (8.5 ml) was added to the reaction mixture at room temperature. The reaction, monitored by TLC ($Et_2O$/petroleum ether, 7:3, v/v), was complete after 15 minutes and provided the *N,N*-diethylbenzamide (**1**) in 78 % yield. This experiment showed that our protocol can be also applied successfully to synthesis of amides on a multi-gram scale.

Finally, we evaluated the chemoselectivity of the reaction by using a nucleophile containing both an amino and a phenolic function. According to the developed procedure*, p*-amino phenol was treated with an equimolar amount of acetic acid and thionyl chloride. After 15 minutes, TLC analysis ($Et_2O$/ petroleum ether, 7:3, v/v) showed the complete conversion of the starting material. The reaction workup afforded *p*-acetamidophenyl acetate in 48% yield (Table 2, **14**). Therefore, the acylation reaction takes place both on the amino and phenolic function without any chemoselectivity.

## Conclusions

Thionyl chloride works as coupling reagent and allows obtaining, at room temperature and in short times, secondary and tertiary amides in high yields without need of further purification. Furthermore, the adopted conditions did not cause any significant loss of the optical integrity at the chiral centres of the precursors as confirmed by HPLC and NMR analysis of a couple of synthesized diastereisomeric amides and by the high enantiomeric eccess estimated for *N,N*-diethylamides of *N*-Boc-D-proline.

The reaction progress is affected by steric hindrance only when bulky groups are present on the carboxylic acid molecule. The synthesis of amides is performed in an efficient one-pot procedure under mild reaction conditions; the order of reagent addition is predetermined for obtaining the amides in high yields.

The reaction mechanism was investigated by performing $^{13}C$ NMR experiments, which showed, as the reactive intermediate is the acyl chloride. This is formed easily from the carboxylate generated in situ from the corresponding carboxylic acid in the presence of the tertiary amine.

Our approach was successfully extented to $\alpha$-amino acids bearing acid-sensitive groups and to the synthesis of a dipeptide system; these results prove the applicative validity of the developed procedure also in the peptide synthesis.

Finally, the reaction can be also applied for large-scale synthesis of amides demonstrating its applicability for amide syntheses of preparative and semi-industrial interest.

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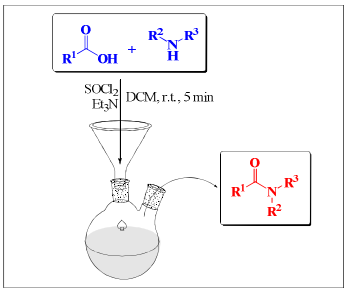


We report on a one-pot synthesis of secondary and tertiary amides from carboxylic acids and amines in the presence of a tertiary amine by using thionyl chloride.