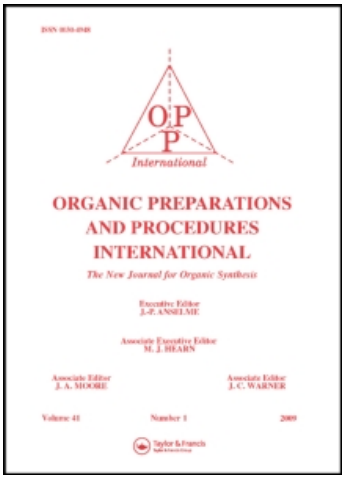

Organic Preparations and Procedures International
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t902189982

A SIMPLE PROCEDURE FOR THE CONVERSION OF CARBOXYLIC ACIDS TO THE CORRESPONDING AMIDES

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To cite this Article Han, Ki-Jong , Tae, Beom Seok and Kim, Misoo(2005) 'A SIMPLE PROCEDURE FOR THE CONVERSION OF CARBOXYLIC ACIDS TO THE CORRESPONDING AMIDES', Organic Preparations and Procedures International, 37: 2, 198 — 203
To link to this Article: DOI: 10.1080/00304940509354888
URL: http://dx.doi.org/10.1080/00304940509354888

A SIMPLE PROCEDURE FOR THE CONVERSION OF CARBOXYLIC ACIDS TO THE CORRESPONDING AMIDES

Submitted by Ki-Jong Han,[†] Beom Seok Tae,[††] and Misoo Kim*,[†††]
(09/20/04)

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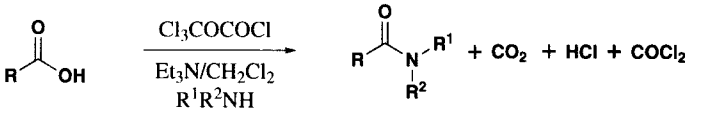
The conversion of carboxylic acids into their corresponding amides is an important functional group transformation in organic synthesis.[1] Most of the preparative methods for amides are based on the reaction of an activated carboxylic acid with an amine. A number of methods for the formation of amide bonds have been reported in the literature.[2-10] However, there have been few applications dealing with the synthesis of tertiary amides from carboxylic acids, and successful results were only obtained under forcing conditions.[11-15] Therefore, an efficient conversion of carboxylic acids into tertiary amides is still in demand to synthesize various organic compounds.

In continuation to our studies on the use of trichloromethyl chloroformate in organic synthesis,[16] we report herein a mild and convenient one-pot procedure for the preparation of amides from carboxylic acids using trichloromethyl chloroformate as an acid activator (*Scheme 1*).

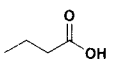
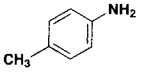
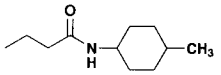
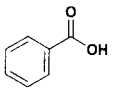
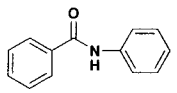
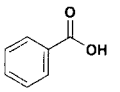
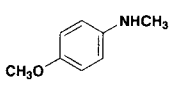
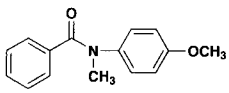
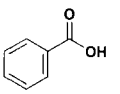
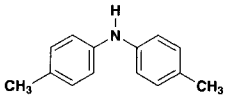
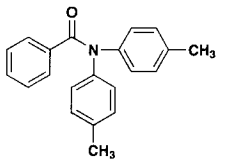
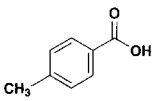
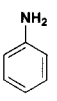
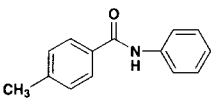
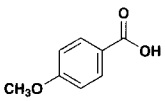
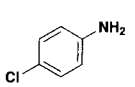
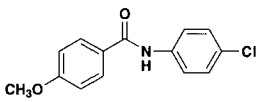
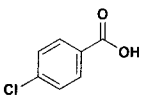
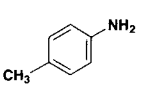
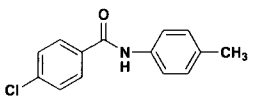
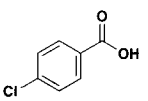
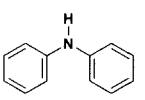
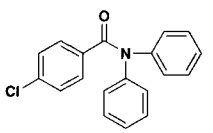
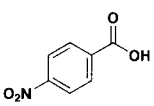
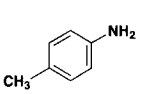
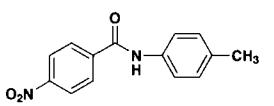
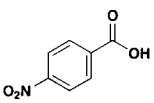
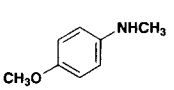
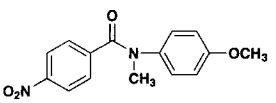
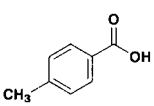
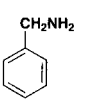
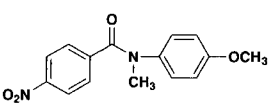
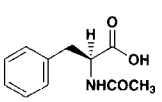
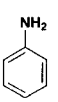
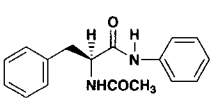


Scheme 1

A variety of amides were conveniently prepared from carboxylic acids and primary or secondary amines at room temperature using trichloromethyl chloroformate in the presence of triethylamine. The carboxylic acids were cleanly converted into the corresponding amides in high yields and the results were summarized in *Table 1*.

In all cases, the amide formation was monitored by disappearance of the starting acid by TLC analysis. The reaction was completed within an hour at room temperature. After completion, the triethylamine hydrochloride was removed by suction filtration, and the filtrate was concentrated under reduced pressure. The crude products were purified by short path silica gel column chromatography.[17] As shown in *Table 1*, this convenient one-pot procedure worked equally well with either secondary or tertiary amide preparation. The products of this amide

Table 1. Preparation of Amides from Carboxylic Acids

Entry	Carboxylic Acid	Amine	Product	Reaction Time	Yield (%)
1				30 min	92
2				30 min	95
3				1 h	87
4				1 h	80
5				30 min	93
6				30 min	84
7				30 min	92
8				1 h	86
9				30 min	91
10				1h	88
11				30 min	93
12				30 min	88

formation were identified by comparison of melting points, IR, and ^{1}H NMR data with that of known compounds.[18] Starting from optically active L-2-acetylamino-3-phenylpropionic acid, the corresponding amide (*Entry 12*) was obtained without racemization.

The reaction is thought to proceed *via* a carbonic anhydride intermediate. The carboxylic acid undergoes reaction with trichloromethyl chloroformate in the presence of triethylamine to give a mixed carbonic anhydride as the activated intermediate. Nucleophilic attack of the amine on the carbonyl carbon of the activated anhydride affords the desired amide, with the concomitant formation of phosgene, carbon dioxide, and hydrogen chloride by a concerted process.

In summary, a mild and efficient one-pot procedure for the conversion of carboxylic acids into their corresponding amides has been described. The present procedure has the advantages of mild reaction conditions, short reaction times, high yields of products and a simple experimental work-up procedure. It can be used as a convenient method for the preparation of both secondary and hindered tertiary amides.

EXPERIMENTAL SECTION

Commercially available reagents and compounds were purchased from Aldrich Chemical Company. Analytical thin layer chromatography was performed on pre-coated Merck silica gel 60 F254 TLC plate. Purification was performed by flash column chromatography by using Merck 230-400 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectral data were obtained on a Jeol JNM-ECP 400 MHz NMR spectrometer. Chemical shifts as given in δ ppm relative to $CDCl_3$ (δ 77.2, ^{13}C) or $CHCl_3$ (δ 7.26, ^{1}H) which is present as an impurity in $CDCl_3$ used. Coupling constants (*J*) are reported in Hertz (Hz). The *J* values are reported directly as given by the spectrometer, hence slight differences in the coupling constants (*J*) may be noticed. Multiplicities are abbreviated as follows: singlet (s), doublet (d), triplet (t), quartet (q), and multiplet (m). The relative areas were determined by electronic integration and reported as number of protons, *e.g.*, ^{1}H. Infrared spectra were recorded using a Jasco FT/IR-410 spectrophotometer with internal calibration. Mass spectra were recorded on a Jeol JMS-700 mass spectrometer. Melting points were taken on a Bibby Sterilin SMP-10 melting point apparatus and are uncorrected. Optical rotations were measured by Jasco P-1010 digital polarimeter. Elemental analyses were performed by Instrumental Analysis Center at Hankyong National University.

CAUTION: Phosgene is highly toxic. This reaction should be carried out in a well-ventilated hood. Rubber gloves should also be used to avoid contact with the toxic reagent. A trap should be used in order to prevent the escape of phosgene. Any excess phosgene should be carefully decomposed in cold aqueous sodium hydroxide or aqueous ammonia.

General Procedure for Preparation of Amides.- To a stirred solution of the carboxylic acid (2 mmol) in CH_2Cl_2 (10 mL) at 0°C were added trichloromethyl chloroformate (2 mmol) and triethylamine (6 mmol). Then amine (2 mmol) was added to the solution. The ice bath was then removed. The reaction mixture was stirred at room temperature until completion of the reaction. The precipated triethylamine hydrochloride was filtered off. Removal of the solvent on rotary

evaporator, followed by short-path silica gel column chromatography purification using 20% ethyl acetate in hexane as the mobile phase afforded the pure product.

***N*-(*p*-Tolyl)butyramide 1**, mp 74-76°C, *lit.*[18a] mp 75°C; IR (KBr): 3301, 2960, 1895, 1642, 1596, 1566, 1403, 1308, 1240, 1196, 1109, 964, 814, 780 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.38 (d, 2H, J = 8.1 Hz), 7.30 (s, 1H), 7.10 (d, 2H, J = 7.7 Hz), 2.36-2.26 (m, 5H), 1.74 (m, 2H), 0.99 (t, 3H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 171.4, 135.5, 133.9, 129.5, 120.1, 39.7, 20.9, 19.2, 13.9; MS (EI) m/z 177 [M^+].

***N*-Phenylbenzamide 2**, mp 162-164°C, *lit.*[18b] mp 162-164°C; IR (KBr): 3344, 1655, 1531, 1438, 1322, 1260, 884, 750, 715 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.87 (d, 2H, J = 8.1 Hz), 7.86 (s, 1H), 7.63 (d, 2H, J = 7.7 Hz), 7.55 (t, 1H, J = 7.3 Hz), 7.48 (t, 2H, J = 7.0 Hz), 7.37 (t, 2H, J = 8.4 Hz), 7.16 (t, 1H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$): δ 165.8, 138.0, 135.1, 131.9, 129.2, 128.9, 127.1, 124.7, 120.3; MS (EI) m/z 197 [M^+].

***N*-(4-Methoxyphenyl)-*N*-methylbenzamide 3**, mp 78-79°C, *lit.*[18c] mp 79°C; IR (KBr): 2934, 1627, 1572, 1506, 1453, 1410, 1375, 1307, 1250, 1174, 1096, 1036, 839, 794, 724 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.29 (d, 2H, J = 7.7 Hz), 7.21 (t, 1H, J = 7.3 Hz), 7.15 (t, 2H, J = 7.3 Hz), 6.95 (d, 2H, J = 8.8 Hz), 6.72 (d, 2H, J = 8.8 Hz), 3.71 (s, 3H), 3.45 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.8, 157.9, 137.8, 136.2, 129.5, 128.7, 128.1, 127.8, 114.3, 55.4, 38.7; MS (EI) m/z 241 [M^+].

***N*,*N*-Di-(*p*-tolyl)benzamide 4**, mp 122-124°C, *lit.*[18d] mp 123-124°C; IR (KBr): 3024, 1656, 1577, 1508, 1446, 1342, 1301, 1179, 1105, 1022, 812, 790, 772, 725 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.45 (d, 2H, J = 7.3 Hz), 7.24 (t, 1H, J = 7.7 Hz), 7.17 (t, 2H, J = 7.3 Hz), 7.10-6.97 (m, 8H), 2.26 (s, 6H); ^{13}C NMR ($CDCl_3$): δ 170.7, 141.6, 136.5, 136.1, 130.1, 129.8, 129.2, 127.9, 127.3, 21.1; MS (EI) m/z 301 [M^+].

4-Methyl-*N*-phenylbenzamide 5, mp 150-151°C, *lit.*[18e] mp 149-150°C; IR (KBr): 3351, 1650, 1612, 1597, 1524, 1508, 1439, 1320, 1260, 1188, 1107, 1019, 910, 885, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.05 (s, 1H), 7.74 (d, 2H, J = 8.4 Hz), 7.63 (d, 2H, J = 8.4 Hz), 7.32 (t, 2H, J = 8.4 Hz), 7.21 (d, 2H, J = 8.1 Hz), 7.12 (t, 1H, J = 8.4 Hz), 2.39 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 166.0, 142.4, 138.2, 132.2, 129.4, 129.1, 127.2, 124.5, 120.4, 21.6; MS (EI) m/z 211 [M^+].

***N*-(4-Chlorophenyl)-4-methoxybenzamide 6**, mp 206-208°C, *lit.*[18f] mp 207-209°C; IR (KBr): 3356, 1655, 1594, 1505, 1397, 1306, 1179, 1092, 1024, 823, 762 cm^{-1}; ^1H NMR ($CDCl_3$): δ 10.2 (s, 1H), 7.95 (d, 2H, J = 8.8 Hz), 7.80 (d, 2H, J = 8.8 Hz), 7.38 (d, 2H, J = 9.2 Hz), 7.05 (d, 2H, J = 8.8 Hz), 3.83 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 165.1, 162.1, 138.3, 130.0, 128.5, 127.1, 126.7, 121.9, 113.7, 55.5; MS (EI) m/z 261 [M^+].

4-Chloro-*N*-(*p*-tolyl)benzamide 7, mp 215-217°C, *lit.*[18g] mp 215-217°C; IR (KBr): 3349, 1652, 1599, 1530, 1406, 1323, 1092, 1088, 816, 754 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.79 (d, 2H, J = 8.4 Hz), 7.71 (s, 1H), 7.48 (d, 2H, J = 8.4 Hz), 7.44 (d, 2H, J = 8.4 Hz), 7.17 (d, 2H, J = 8.0 Hz), 2.34 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 164.5, 138.0, 135.1, 134.5, 133.4, 129.6, 129.0, 128.4, 120.3, 20.9; MS (EI) m/z 245 [M^+].

4-Chloro-*N,N*-diphenylbenzamide 8, mp 135-136°C, *lit.*[18h] mp 135.5-136°C; IR (KBr): 3037, 1651, 1589, 1489, 1447, 1400, 1344, 1307, 1109, 1088, 1015, 957, 835, 758 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.40 (d, 2H, *J* = 8.4 Hz), 7.30 (t, 4H, *J* = 7.7 Hz), 7.24-7.10 (m, 8H); ^{13}C NMR ($CDCl_3$): δ 169.4, 143.6, 136.2, 134.4, 130.6, 129.1, 128.1, 127.3, 126.5; MS (EI) m/z 307 [M^+].

4-Nitro-*N*-(*p*-tolyl)benzamide 9, mp 201-203°C, *lit.*[18i] mp 203°C; IR (KBr): 3323, 1651, 1598, 1528, 1406, 1344, 1320, 1297, 1263, 1104, 903, 871, 724 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.33 (d, 2H, *J* = 8.8 Hz), 8.03 (d, 2H, *J* = 8.4 Hz), 7.84 (s, 1H), 7.51 (d, 2H, *J* = 8.1 Hz), 7.20 (d, 2H, *J* = 8.0 Hz), 2.36 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 163.5, 149.8, 140.7, 135.2, 134.7, 129.8, 128.3, 124.1, 120.5, 21.0; MS (EI) m/z 256 [M^+].

***N*-(4-Methoxyphenyl)-*N*-methyl-4-nitrobenzamide 10**, mp 98-100°C, *lit.*[18j] mp 98-101°C; IR (KBr): 3103, 1939, 1651, 1604, 1506, 1351, 1301, 1251, 1181, 1099, 1030, 847, 794, 771 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.02 (d, 2H, *J* = 8.1 Hz), 7.45 (d, 2H, *J* = 8.4 Hz), 6.97 (d, 2H, *J* = 8.4 Hz), 6.75 (d, 2H, *J* = 8.4 Hz), 3.73 (s, 3H), 3.48 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 168.5, 158.5, 147.8, 142.5, 136.6, 129.5, 128.2, 123.0, 114.7, 55.4, 38.4; MS (EI) m/z 286 [M^+].

***N*-Benzyl-4-methylbenzamide 11**, mp 133-135°C, *lit.*[18k] mp 133-134.5°C; IR (KBr): 3311, 3058, 3026, 2917, 1639, 1548, 1507, 1450, 1420, 1361, 1323, 1309, 1258, 1057, 992, 842 cm^{-1}; ^1H NMR ($CDCl_3$): δ 7.68 (d, 2H, *J* = 8.0 Hz), 7.34-7.23 (m, 5H), 7.19 (d, 2H, *J* = 7.7 Hz), 6.58 (s, 1H), 4.60 (d, 2H, *J* = 5.5 Hz), 2.37 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 167.3, 141.8, 138.3, 131.5, 129.1, 128.7, 127.8, 127.4, 126.9, 44.0, 21.4; MS (EI) m/z 225 [M^+].

2-Acetylamino-3,*N*-diphenylpropionamide 12, mp 208-209°C; IR (KBr): 3425, 3286, 3070, 2931, 1651, 1543, 1450,1311, 1018, 756, 694 cm^{-1}; ^1H NMR ($CDCl_3$): δ 8.06 (s, 1H), 7.30-7.42 (m, 10H), 6.40 (d, 1H, *J* = 7.7 Hz), 4.84 (t, 1H, *J* = 7.4 Hz), 3.12 (d, 2H, *J* = 8.1 Hz), 2.00 (s, 3H); ^{13}C NMR ($CDCl_3$): δ 170.4, 169.1, 137.3, 136.5, 129.3, 128.9, 128.8, 127.1, 124.6, 120.0, 55.4, 38.4, 23.2; $[\alpha]_D^{25}$ = +1.5° (c = 1, CH_3COCH_3); HRMS (EI) m/z: Calcd for ($C_{17}H_{18}N_2O_2$): 282.1368. Found: 282.1371 [M^+].

Anal. Calcd for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92. Found: C, 72.24; H, 6.51; N, 10.00

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17. The crude products were dissolved in a minimum volume of dichloromethane and absorbed onto a 5 cm deep pad of silica gel pad contained within a 2.5 cm wide flash chromatography column. The silica pad was eluted with 20% of ethyl acetate in hexane and 10 mL fractions were collected. Ten grams of silica gel was used to purify 1.0 g of the crude product.

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