Application of Cl₃CCONH₂/PPh₃ towards the Synthesis of Bioactive Amides

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Cl₃CCONH₂ coupled with PPh₃ was determined to be an effective reagent for the conversion of carboxylic acids to their corresponding acid chlorides. Subsequently, these acid chlorides were successfully trapped with amines in the presence of 4-picoline, yielding amides. This practical and efficient protocol can be utilized for the synthesis of biological amides in excellent yields.

Key Words: Trichloroacetamide, Triphenylphosphine, Chlorinating agent, Amide

Introduction

Currently, synthetic substances are often used to replace natural compounds such as salicylates, vitamins, and xanthines.[1] Certain bioactive compounds are found as simple derivatives of amides, therefore extensive development of synthetic routes for the fabrication of natural compounds from amide derivatives has occurred and is ongoing. Acid chlorides are generally recognized as key intermediates for further conversion into many other functional groups, such as amides, esters, and ketones.[2] They can generally be prepared from various starting materials in a variety of manners by using common reagents such as SOCl₂, COCl₂, PCl₃, PCl₅, POCl₃, PhCCl₃/FeCl₃, cyanuric chloride, C₂Cl₄/(Bu₂N)₂CO or COCl₂/HCON(CHMe₂)₂.[3] However, there are still some remaining problems with using the agents mentioned above. For example, the synthetic procedure requires high temperature; further, the by-products of the reaction are gaseous and are harmful, corrosive chemicals. Also, their use invariably results in acidic conditions when SOCl₂ or COCl₂ is used. Furthermore, if the amount of reagent used is insufficient, acid anhydride is obtained as the product instead of acid chlorides.[4]

Convenient and practical protocols for the preparation of acid chlorides using comparatively non-toxic reagents under mild conditions have been examined, namely, combinations of an organophosphorus compound and a chlorinating agent. The reaction of carboxylic acids with a combination of CCl₄/PPh₃ under mild and neutral conditions was among pioneer works.[5] Therein, the reaction took place to produce the desired product, POPh₃ and CHCl₃. However, this reaction required long reaction times and high temperatures. Later, the utilization of Cl₃CCOCCl₃/PPh₃ and Cl₃CCN/PPh₃ have been cited as other viable routes for the preparation of acid chlorides with high efficiency.[6]

Since acid halides are not very stable, especially in a humid environment, they suddenly convert to more stable and inert organic compound such as amides under the aforementioned conditions.[6,7] Although the methodology for the synthesis of amides has been continuously studied, convenient reaction conditions have not yet been found. For example, carboxylic acid required low temperatures or an excess of a strong base to afford an amide with Cl₃CCOCCl₃/PPh₃ and Cl₃CCN/PPh₃, respectively.[6a,b] Therefore, there is still a great need to pursue the development of methods for synthesizing this important functional group under mild conditions in the absence of a strong base or competing side reactions.

Recently, we have introduced an efficient coupling reagent, Cl₃CCONH₂/PPh₃ for the chlorination of alcohols and carboxylic acids to afford the desired alkyl chlorides and esters in high to excellent yields.[2a,8] Utilizing this facile process, we report herein the use of Cl₃CCONH₂/PPh₃ for the conversion of carboxylic acids into the corresponding acid chlorides. The application of this procedure will further be exploited for synthesizing certain bioactive amides with a 'one pot' reaction.

Results and Discussion

Standard chemical reactions for this work involved the reaction of benzoic acid and a chlorinating agent, which was consequently trapped with cyclohexylamine to obtain the desired product. Various factors including chlorinating agent, base, reaction time and temperature were scrutinized to search for new appropriate chemical reagents and optimal conditions (Table 1).

In the absence of a chlorinating agent, the desired product was obtained only in trace amounts, indicating that a chlorinating agent was crucial for this reaction (entry 1). Cl₃CCO₂H (entry 2) did not give a good yield of the desired product, probably because of its acidity, which may, in turn, cause the reaction mixture to become acidic. The type of the substituent on chlorinating agents also had a profound effect on the yield of the reaction. For example, Cl₃CCO₂H (entry 2) gave a moderate amide product yield compared with the higher yields of Cl₃CCO₂Et or Cl₃CCN (entries 3 and 4). The latter reagent contained a stronger electron-withdrawing group, thus providing the desired product in higher yield. Other electron-withdrawing group containing reagents such as Cl₃CCONH₂, Cl₃CCONHPh and Cl₃CCONEt₂ (entries 7-9) furnished the target product in comparable yields. Based on the results obtained, Cl₃CCONH₂ was considered as the best chlorinating agent of those studied for further investigation in terms of commercial availability, cost-effectiveness,

Table 1. Effect of chlorinating agents on the preparation of amide by using various chlorinating agents and PPh₃
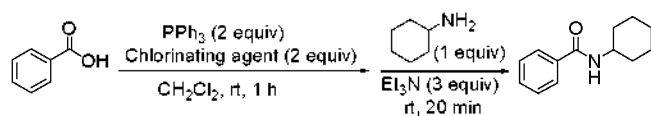
Entry	Chlorinating agent	Isolated yield (%)
1	none	trace
2	Cl₃CCO₂H	40
3	Cl₃CCO₂Et	62
4	Cl₃CCN	64
5	(Cl₃CCO)₂O	12
6	Cl₃CCO₂ⁱPr	55
7	Cl₃CCONH₂	62
8	Cl₃CCONHPh	69
9	Cl₃CCONEt₂	60

Table 2. Effect of bases on the preparation of amide preparation by using Cl₃CCONH₂ and PPh₃
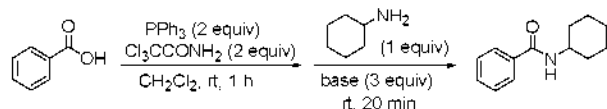
Entry	Base	pKₐ	Isolated yield (%)
1	none	-	75
2	Et₃N	10.72	62
3	DMAP	9.70	57
4	imidazole	6.95	63
5	pyridine-*N*-oxide	6.90	65
6	4-picoline	6.02	90
7	quinaldine	5.87	82
8	pyridine	5.25	86
9	quinoline	4.94	90
10	3-cyanopyridine	3.71	55

and ease of work-up procedure.

According to a literature review, similar reactions reported to produce acid chlorides normally used Et₃N as a base. Nonetheless, not many studies focused on the effect of bases.[6] Table 2 shows that the quantity of the desired amide was significantly increased when weak bases were used, for example, 4-picoline, quinaldine, pyridine and quinoline (entries 6-9). As shown, the reaction could be performed without using any extra base (entry 1) to yield the desired product. The work-up procedure is easily performed with 4-picoline, and the amide product was achieved in excellent yield: this, coupled with the fact that it is relatively inexpensive, makes 4-picoline a good choice for this synthetic strategy.

Common solvents such as CH₂Cl₂, CHCl₃, CH₃CN, EtOAc and THF were selected for examination. CH₂Cl₂ was found to be a good choice of solvent. When the reaction was performed at low temperature (0 ~ 5 °C) in step I, the reaction did not proceed efficiently, affording the desired product. *N*-cyclohexylbenzamide, in 32% yield. However, the reaction in boiling CH₂Cl₂ provided the product in 90% yield within 30 minutes. An addi-
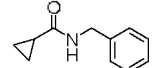
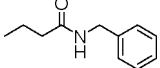**Table 3.** Effect of amines on the synthesis of amides
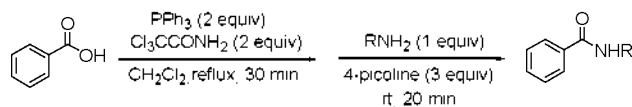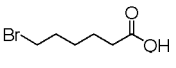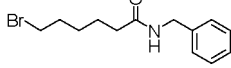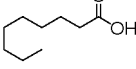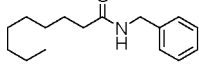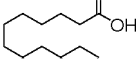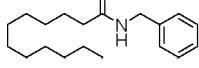
Entry	Amine	Amide	Isolated yield (%)
1			93
2			97
3			84
4			62
5			99
6			99
7			63

tional advantage of carrying out the reaction at elevated temperature is improved solubility for some carboxylic acids: in some cases all products were dissolved at room temperature. It should be mentioned at this point that this new methodology utilized a combination of inexpensive reagents, Cl₃CCONH₂/PPh₃ and 4-picoline.

To investigate the limitation and scope of the reaction, a variety of amines were employed to react with a model substrate, benzoic acid (Table 3). The yields of the target molecules were generally moderate to excellent regardless of the type of amine. For example, aromatic amines such as benzylamine, 2,6-dimethylaniline, 4-phenoxyaniline and α-naphthylamine provided the desired products in excellent yields (entries 1-4). Aliphatic amines such as cyclohexylamine and diethylamine gave the desired amides in superb yields (entries 5 and 6). Interestingly, a longer aliphatic amine, octadecylamine, yielded *N*-octadecyl-benzamide in moderate yield, perhaps because of steric hindrance caused by folding of aliphatic long chain (entry 7). Considering the extent of reaction obtained, this method has the advantage of being effective for many different amines.

To further examine the scope of these reactions, various types of carboxylic acids were utilized (Table 4). The desired amides formed using short chain aliphatic carboxylic acids could be achieved in higher yields than those stemming from long chain aliphatic carboxylic acids. For example, *N*-benzylcyclopropane-carboxamide, *N*-benzylbutanamide, *N*-benzyl-6-bromohexanamide, *N*-benzylnonanamide and *N*-benzyldodecanamide could be gained in high yields (entries 1-5). The reaction carried out with cyclopropanecarboxylic acid and benzylamine was a discrete reaction that provided a mechanistic clue.
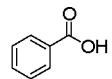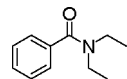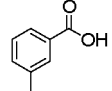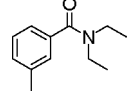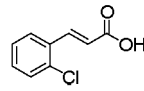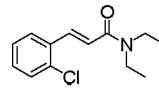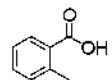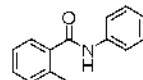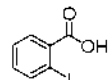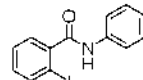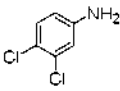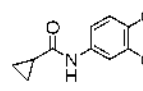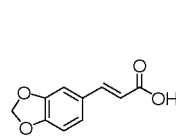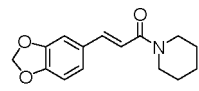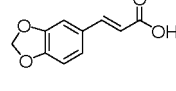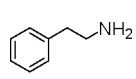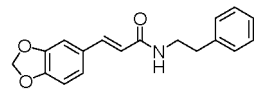
Table 4. Effect of carboxylic acids on the synthesis of amides

PPh₃ (2 equiv)
Cl₃CCONH₂ (2 equiv)
CH₂Cl₂, reflux, 30 min
(1 equiv)
4-picoline (3 equiv)
rt, 20 min

Entry	Carboxylic acid	Amide	Isolated yield (%)
1			97
2			94
3			67
4			89
5			83

Certain amides are useful in biological. pharmaceutical or agricultural applications. The developed acid chloride protocol was therefore attempted for application to the synthesis of those biological amides (Table 5). Eight biologically active amides were synthesized without difficulty in high to excellent yields. N,N-Diethyl-3-methylbenzamide, for example. was obtained with the present protocol in 99% (entry 2). Similarly, the synthesis of 2-methylbenzanilide and 2-iodobenzamide were successfully performed by the reaction of o-MeC₆H₄COCl or o-IC₆H₄COCl with PhNH₂ in benzene in 91% and 88% yields. respectively (entries 4 and 5).

Even though all target amides could be prepared in excellent yields by the cited methods, the experimental conditions required were not very practical. For instance. SOCl₂ or acid chloride. which makes the reaction conditions acidic and requires high temperature. was unavoidably utilized. Consequently. by-products such as SO₂ and HCl. harmfully corrosive gases. were derived directly from the reaction. Moreover, in some cases, low temperatures below 10 °C may be essential. The present method can be carried out under mild conditions, for example. the reaction temperature in Step I at refluxing CH₂Cl₂ and Step II at room temperature.

Table 5. Synthesis of biological active amides using Cl₃CCONH₂ and PPh₃

PPh₃ (2 equiv)
Cl₃CCONH₂ (2 equiv)
CH₂Cl₂, reflux, 30 min
R'NH₂ (1 equiv)
4-picoline (3 equiv)
rt, 20 min

Entry	Carboxylic acid	Amine	Amide	Isolated yield (%)	Usage
1				99	Insect Repellent[9]
2				99	Insect Repellent[9]
3				79	Herbicide[22]
4				91	Fungicide[23]
5				88	Fungicide[10,23]
6				80	Herbicide[24]
7				99[a]	Antiepilepsirnium[25]
8				79	Precursor of Antioxidant[26]

[a]3 Equiv of Cl₃CCONH₂ and PPh₃ were used.

Application of Cl₃CCONH₂/PPh₃

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Conclusions

Since the developed method is carried out under acid free conditions, it can produce amides from a starting material containing acid sensitive functional groups. Moreover, the complicated process of the classical procedure, for instance, the need to re-distilled $SOCl_2$ is no longer an issue.

An effective and efficient protocol using Cl_3CCONH_2/PPh_3 was implemented for transforming carboxylic acids to their analogous acid chlorides under refluxing CH_2Cl_2 within 30 minutes. Upon treatment with amines in the presence of 4-picoline, the corresponding amides were achieved in good to excellent yields. This developed method was employed to prepare eight bioactive amides with higher or comparable yields to those cited in literature.

Experimental Section

All reagent-grade chemicals and solvents were obtained from commercial suppliers (Fluka, Merck and Aldrich). Melting points were determined with a Fisher-Johns melting point apparatus and were uncorrected. The IR spectra were recorded on Nicolet model Impact 410 FT/IR spectrophotometer. The ¹H- and ¹³C-NMR spectra were performed in deuterated $CDCl_3$ or DMSO-d_6 with TMS as an internal reference on a model Mercury plus 400 NMR spectrometer which operated at 399.84 MHz for ¹H and 100.54 MHz for ¹³C nuclei. The chemical shifts (δ) were assigned by comparison with residue solvent protons.

General procedure for the synthesis of amides.

Step I: PPh₃ (1.6 g, 6.0 mmol) in CH_2Cl_2 (3 mL) was added to a mixture of carboxylic acid (3 mmol) and a selected chlorinating agent (6 mmol) in CH_2Cl_2 (3 mL) at room temperature. The mixture was stirred at reflux for 1 h.

Step II: A mixture of amine (3 mmol) and base (9 mmol) was added to the above mixture. The reaction mixture was stirred at room temperature for 20 minutes. When the reaction was completed, the organic layer was washed with 10% HCl and saturated aqueous $NaHCO_3$, and consequently dried over Na_2SO_4 and evaporated *in vacuo*. The mixture was separated with a silica gel column chromatograph eluting with hexane/EtOAc (4:1).

N-Cyclohexylbenzamide. Mp 147 ~ 148 °C (lit.[11] 147 ~ 148 °C). IR (KBr) v_{max}/cm⁻¹: 3242, 2924, 2852, 1629, 1562, 1493, 1444, 1332; ¹H NMR (CDCl₃) δ 1.12-2.03 (10 H, m, alkyl group), 3.88-4.02 (1H, m, NCH), 6.03 (1H, br, NH), 7.24-7.75 (5H, m, Ph).

N-Benzylbenzamide. Mp 103 ~ 105 °C (lit.[12] 104 ~ 105 °C). IR (KBr) v_{max}/cm⁻¹: 3292, 3062, 1641, 1548, 1450, 1419, 1317, 1256; ¹H NMR (CDCl₃) δ 4.66 (2H, d, J = 6.5 Hz, CH_2Ph), 6.39 (1H, br, NH), 7.26-7.51 (8H, m, Ph), 7.79 (2H, d, J = 7.6 Hz, Ph).

N-(2,6-Dimethylphenyl)benzamide. Mp 155 ~ 157 °C (lit.[13] 159 ~ 161 °C). IR (KBr) v_{max}/cm⁻¹: 3280, 3050, 2953, 2914, 1642, 1579, 1520, 1474, 1302, 1213; ¹H NMR (CDCl₃) δ 2.33 (6H, s, PhCH_3), 7.17 (3H, s, Ph), 7.44 (1H, br, NH), 7.54 (2H, t, J = 7.1 Hz, Ph), 7.61 (1H, t, J = 7.3 Hz, Ph), 7.96 (2H, d, J = 7.1 Hz, Ph).

N-(4-Phenoxyphenyl)benzamide.[14] Mp 157 ~ 160 °C. IR (KBr) v_{max}/cm⁻¹: 3316, 1645, 1593, 1516, 1491, 1409, 1317, 1224;

¹H NMR (CDCl₃) δ 7.07-7.15 (6 H, m, Ph), 7.37 (2H, t, J = 7.0 Hz, Ph), 7.54 (2H, t, J = 7.0 Hz, Ph), 7.64 (2H, d, J = 8.8 Hz, Ph), 7.83 (1H, br, NH), 7.91 (2H, d, J = 7.0 Hz, Ph).

N-(1-Naphthyl)benzamide. Mp 164 ~ 166 °C (lit.[15] 159 ~ 161 °C). IR (KBr) v_{max}/cm⁻¹: 3237, 3047, 1649, 1593, 1526, 1501, 1429, 1393, 1342, 1285; ¹H NMR (CDCl₃) δ 7.58-7.67 (5H, m, Ph), 7.80 (1H, d, J = 7.8 Hz, Ph), 7.96-7.97 (3H, m, Ph), 8.04 (2H, d, J = 7.0 Hz, Ph), 8.11 (1H, d, J = 7.0 Hz, Ph), 8.24 (1H, br, NH).

N,N-Diethylbenzamide.[16] Yield: 99% (yellow liquid). IR (neat) v_{max}/cm⁻¹: 2970, 1629, 1524, 1450, 1372, 1291, 1096. ¹H-NMR (CDCl₃) δ 1.10 (3H, br s, CH₂CH_3), 1.25 (3H, br s, CH₂CH_3), 3.26 (2H, br s, CH_2CH₃), 3.55 (2H, br s, CH_2CH₃), 7.38 (5H, br s, Ph).

N-Octadecylbenzamide. Mp 88 ~ 89 °C (lit.[17] 82 °C). IR (KBr) v_{max}/cm⁻¹: 3334, 2919, 2843, 1634, 1532, 1465, 1296; ¹H NMR (CDCl₃) δ 0.92 (3H, t, J = 7.0 Hz, CH₂CH_3), 1.29 (30H, m, (CH_2)₁₅), 1.64 (2H, qui, J = 7.0 Hz, CH_2CH₂NH), 3.49 (2H, q, J = 7.0 Hz, CH_2NH), 6.11 (1H, br, NH), 7.45-7.55 (3H, m, Ph), 7.79 (2H, d, J = 7.0 Hz, Ph).

N-Benzylcyclopropanecarboxamide. Mp 132 ~ 135 °C (lit.[18] 139 ~ 141 °C). IR (KBr) v_{max}/cm⁻¹: 3288, 3069, 2999, 1634, 1544, 1459, 1396, 1353, 1241; ¹H NMR (CDCl₃) δ 0.76 (2H, q, J = 2.9 Hz, alkyl group), 1.09 (2H, q, J = 2.9 Hz, alkyl group), 1.36 (1H, m, CHCO), 4.56 (2H, d, J = 5.9 Hz, CH_2Ph), 5.91 (1H, br, NH), 7.29-7.37 (5H, m, Ph).

N-Benzylbutanamide.[19] IR (neat) v_{max}/cm⁻¹: 3293, 3073, 2955, 2818, 1634, 1547, 1455, 1383, 1214; ¹H NMR (CDCl₃) δ 0.96 (3H, t, J = 7.4 Hz, CH₂CH_3), 1.68 (2H, sextet, J = 7.4 Hz, CH_2CH₂CO), 2.20 (2H, t, J = 7.4 Hz, CH_2CO), 4.42 (2H, d, J = 5.7 Hz, CH_2Ph), 6.58 (1H, br, NH), 7.26-7.35 (5H, m, Ph).

N-Benzyl-6-bromohexanamide.[20] IR (neat) v_{max}/cm⁻¹: 3293, 2934, 2858, 1639, 1547, 1455, 1373, 1235; ¹H NMR (CDCl₃) δ 1.50 (2H, qui, J = 7.8 Hz, BrCH₂CH₂CH_2), 1.71 (2H, qui, J = 7.8 Hz, BrCH₂CH₂CH_2CH₂), 1.89 (2H, qui, J = 7.8 Hz, BrCH₂CH_2), 2.25 (2H, t, J = 7.0 Hz, CH₂CO), 3.42 (2H, t, J = 7.0 Hz, BrCH_2), 4.44 (2H, d, J = 6.2 Hz, CH_2Ph), 6.00 (1H, br, NH), 7.29-7.38 (5H, m, Ph).

N-Benzylnonanamide. Mp 69 ~ 70 °C (lit.[19] 66 ~ 69 °C). IR (KBr) v_{max}/cm⁻¹: 3295, 3081, 2921, 2848, 1637, 1548, 1454, 1330, 1232; ¹H NMR (CDCl₃) δ 0.91 (3H, t, J = 7.4 Hz, CH₂CH_3), 1.29-1.33 (10H, m, (CH_2)₅), 1.69 (2H, sextet, J = 7.8 Hz, CH_2CH₂CO), 2.25 (2H, t, J = 7.8 Hz, CH_2CO), 4.48 (2H, d, J = 5.4 Hz, CH_2Ph), 5.78 (1H, br, NH), 7.29-7.39 (5H, m, Ph).

N-Benzyldodecanamide. Mp 74 ~ 76 °C (lit.[21] 82 ~ 83 °C). IR (KBr) v_{max}/cm⁻¹: 3295, 3069, 2915, 2851, 1630, 1552, 1431, 1330, 1201; ¹H NMR (CDCl₃) δ 0.91 (3H, t, J = 6.9 Hz, CH₂CH_3), 1.28 (16H, m, (CH_2)₈), 1.69 (2H, sextet, J = 7.6 Hz, CH_2CH₂CO), 2.25 (2H, t, J = 7.6 Hz, CH_2CO), 4.48 (2H, d, J = 5.4 Hz, CH_2Ph), 5.73 (1H, br, NH), 7.29-7.37 (5H, m, Ph).

N,N-Diethyl-3-methylbenzamide (N,N-diethyl-m-toluamide).[9] IR (neat) v_{max}/cm⁻¹: 2970, 1619, 1564, 1460, 1367, 1219, 1091; ¹H NMR (CDCl₃) δ 1.10 (3H, br, CH₂CH_3), 1.28 (3H, br, CH₂CH_3), 2.40 (3H, s, PhCH_3), 3.25 (2H, br, CH_2CH₃), 3.58 (2H, br, CH_2CH₃), 7.15-7.28 (4H, m, Ph).

2-Chloro-N,N-diethylcinnamamide.[22] IR (neat) v_{max}/cm⁻¹: 2947, 1643, 1601, 1564, 1465, 1367, 1046; ¹H NMR (CDCl₃) δ 1.26 (6H, br, CH₂CH_3), 3.55 (4H, q, J = 7.0 Hz, CH_2CH₃),

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6.84 (1H, d, J = 15.2 Hz, CH = CHCO), 7.30 (2H, d, J = 4.7 Hz, Ph), 7.43 (1H, d, J = 4.7 Hz, Ph), 7.61 (1H, d, J = 4.7 Hz, Ph), 8.04 (1H, d, J = 15.2 Hz, CH=CHCO).

2-Methylbenzanilide (mebenil). Mp 124 ~ 126 °C (lit.[23] 126 °C). IR (KBr) v_{max}/cm^{-1}: 3227, 3119, 1645, 1594, 1439, 1326, 1265; ^{1}H NMR (CDCl$_3$) δ 2.55 (3H, s, CH_3), 7.18-7.67 (9H, m, Ph).

2-Iodobenzamide (benodanil). Mp 147 ~ 148 °C (lit.[23] 143 ~ 144 °C). IR (KBr) v_{max}/cm^{-1}: 3307, 3032, 1660, 1598, 1524, 1439, 1322; ^{1}H NMR (CDCl$_3$) δ 7.20 (2H, q, J = 7.6 Hz, Ph), 7.40-7.59 (4H, m, Ph), 7.68 (2H, d, J = 7.6 Hz, Ph), 7.97 (1H, d, J = 7.6 Hz, Ph).

3',4'-Dichlorocyclopropanecarboxanilide (cypromid). Mp 130 ~ 132 °C (lit.[24] 130 ~ 131 °C). IR (KBr) v_{max}/cm^{-1}: 3283, 3098, 1665, 1588, 1470, 1398, 1265; ^{1}H NMR (CDCl$_3$) δ 0.88 (2H, q, J = 4.0 Hz, alkyl group), 1.09 (2H, q, J = 4.0 Hz, alkyl group), 1.50 (1H, m, CHCO), 7.34 (2H, s, Ph), 7.57 (1H, br, NH), 7.77 (1H, s, Ph).

N-(3,4-Methylenedioxycinnamoyl)piperidide. Mp 80 ~ 82 °C (lit.[25] 83 °C). IR (neat) v_{max}/cm^{-1}: 3001, 2934, 2858, 1645, 1593, 1495, 1439, 1352, 1245; ^{1}H NMR (CDCl$_3$) δ 1.63 (6H, br, alkyl group), 3.68 (4H, br, alkyl group), 6.02 (2H, s, OCH_2O), 6.76 (1H, d, J = 15.6 Hz, CH = CHCO), 6.82 (1H, d, J = 7.6 Hz, Ph), 7.02 (1H, d, J = 7.6 Hz, Ph), 7.07 (1H, s, Ph), 7.59 (1H, d, J = 15.6 Hz, CH = CHCO).

N-(3,4-Methylenedioxycinnamoyl)phenethylamide. Mp 120 ~ 123 °C (lit.[26] 117 °C). IR (KBr) v_{max}/cm^{-1}: 3073, 2904, 1645, 1547, 1495, 1439, 1321, 1250; ^{1}H NMR (CDCl$_3$) δ 2.92 (2H, t, J = 7.0 Hz, CH_2Ph), 3.69 (2H, q, J = 7.0, CH_2CH$_2$Ph), 5.60 (1H, br, NH), 6.02 (2 H, s, OCH_2O), 6.17 (1H, d, J = 15.2 Hz, CH = CHCO), 6.82 (1H, d, J = 7.6 Hz, Ph), 7.00 (2H, d, J = 7.6 Hz, Ph), 7.27 (3H, q, J = 7.0 Hz, Ph), 7.37 (2H, t, J = 7.0 Hz, Ph), 7.57 (1H, d, J = 15.2 Hz, CH = CHCO).

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