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A Simple Preparation of Amides from Acids and Amines by Heating of their Mixture

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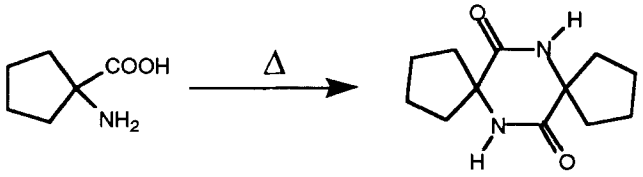
Abstract

Heating a mixture of an amine and an acid is demonstrated as the method of choice for the preparation of many amides. The yields depend on the physical properties and thermal stability of the reactants and range from good to excellent. The ideal reactants should have melting points below 200 °C, should not be highly volatile and should be thermally stable at that temperature for 30 minutes. Some of those disadvantages can be overcome by using acid esters instead of an acid in the reaction. The method stands out among the others by its simplicity, low cost and short reaction time. Also it can be performed in very large scale, does not require solvent and special purification of the reactants.

Although the preparation of an amide by direct combining of an acid and an amine at elevated temperature has been known for a long time,[1] modern methods have chosen to use multi-step, less convenient procedures. It has become conventional to prepare intermediate acid chlorides, esters or other compounds, neglecting the simple direct reaction. It has been stated that this method is less

convenient than the others and is seldom of preparative value.[2] Those methods do not necessarily present simple and certainly not less expensive procedures.

Some of the amides have been prepared in large industrial scale by the pyrolysis of the corresponding salt of an amine and a carboxylic acid. For example the standard procedure for the preparation of acetamide involves vigorous heating of ammonium acetate.[3] In the literature a procedure can be found for the preparation of benzanilide[4], substituted N-β-(phenylethyl)phenylacetamides[5] and N-phenyloleiamide[6]. An interesting adaptation of the method involves formation of piperazinediones by heating of α-amino acids:[7,8]



Variation of this procedure include the use of silica gel, which apparently acts as a catalyst,[9] and of high-boiling hydrocarbon solvents which allows azeotropic removal of water from the reaction mixture.[10] An acidic ion exchange resin has been found to be an excellent catalyst for the preparation of amides[11] in xylene.

A more popular approach for the preparation of amides "directly" from the acid and the amine use catalysts that form very reactive intermediates with either the acid or the amine - intermediate that can often be isolated. For instance, the reaction of amines with carboxylic acids occurs under milder conditions if phosphorus trichloride is added. The reaction proceeds through "phosphoteazo compound" (phosphoramidic imide) which reacts with carboxylic acid to give the amide.[12] A widely used reagent for acylation of amines at room temperature in an inert solvent is 1,1'-carbonyldimidazole.[13] The reagent is suspected to be carcinogenic and it is moisture sensitive. Because of that the reagent should be used with precaution, and the reactants and the solvents must be dried.

Here we would like to present our results on the preparation of a wide variety of amides by heating of a mixture of amines and acids without any catalyst:

$$R_1NH_2 + R_2COOH \xrightarrow{\Delta} R_1NHOCR_2 + H_2O$$

The method is extremely simple and preferable over the more expensive and time consuming contemporary methods for the synthesis of amides. The basic principle of the reaction is that the reaction equilibrium must be shifted in the direction of the product formation by constant elimination of water formed in the reaction. We have found that the optimal conditions for pyrolysis of amide-carboxylic acid mixture is 160-180 °C for 10-30 minutes. Prolonged heating can cause formation of substantial amounts of tar, while heating for a short time gives incoplete reaction. If one of components has a boiling point close to but below 200 °C the reaction should be carried under a condenser with a ~20% excess of the low boiling point component. With higher boiling materials the reaction can be carried in a beaker on a hot plate. Both components should have melting points below 200 °C. If one component does not melt at the reaction temperature the amount of formed amide is negligible even after prolonged heating. For example, heating of 2,4-dimethylaniline (0.1 mol) and terephthalic acid (0.02 mol) at 180 °C for 18 hours afforded only 4% of the mono- and diamide. The isolation of the products includes dissolving the still hot reaction mixture in chloroform and extraction with water, aqueous potassium hydroxide, and/or aqueous hydrochloric acid. The product left after evaporation of the solvent is crystallized from carbon tetrachloride, chloroform-petroleum ether, or petroleum ether.

Although the method is very general, not all amides can be prepared in this way. Termally sensitive compounds will decompose. The amides and acids that have low boiling point will evaporate and diminish the yield of the reaction. Compounds that can sublime, as for example, *tert*-butylbenzoic acid must be added

to the melted reaction mixture in small portions over a prolonged period (20 portions over a period of an hour for the preparation of the amide between 4-*tetrt*-butylbenzoic acid and dodecylamine) and must be used in excess (~50%). If the acid readily decarboxylates at the elevated temperature, as for example, C-alkyl derivatives of malonic acid, derivatives of acetamide are the major products from pyrolysis with the amines. Furthermore where the acid has a high melting point or can decarboxylate the ethyl or methyl esters can be used successfully for the preparation of the corresponding amides. It is interesting to note that the time necessary to complete the reaction with an ester is about ten times longer than that required with acids. This is in contradiction with the broadly accepted reactivates of the acid derivatives.[14]

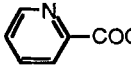
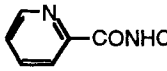
Our attempts to prepare diacylated amines by pyrolysis of carboxylic acids with an amine failed. Even in experiments when as large as 5 molar excess of the acids were used, we were not able to detect any amount of the diacylated product (imides). In all reactions it is necessary to assure that the evaporated water will not condense on the wall of the reaction vessel and return to the reaction mixture. When this happens the yield of the reaction is be drastically reduced.

One might expect that the high temperature of the reaction would cause the racemization of either optically pure amine or acid. However, all cases listed in Table I when chiral starting materials were used, no racemization was detected by our own ^1H NMR technique.[15]

Conclusion

As a conclusion we can state that the pyrolitic preparation of amides should be considered as a primary method for their synthesis. The advantages are: (a) the procedure is extremely simple, (b) the reaction time is short (c) does not required special equipment, (d) does not require any catalyst, (e) the starting materials do not

Table I. List of the reactants, the obtained amides and their yields.

Starting Materials		Product	%
Acid	Amine	Amide	
$CH_3(CH_2)_7COOH$	$CH_3(CH_2)_7NH_2$	$CH_3(CH_2)_7CONH(CH_2)_7CH_3$	98
$CH_3(CH_2)_8COOH$	$CH_3(CH_2)_8NH_2$	$CH_3(CH_2)_8CONH(CH_2)_8CH_3$	95
$CH_3(CH_2)_{10}COOH$	$CH_3(CH_2)_{10}NH_2$	$CH_3(CH_2)_{10}CONH(CH_2)_{10}CH_3$	96
$CH_3(CH_2)_{16}COOH$	$CH_3(CH_2)_{16}NH_2$	$CH_3(CH_2)_{16}CONH(CH_2)_{16}CH_3$	86
$CH_3CONHCH_2COOH$	$CH_3(CH_2)_{11}NH_2$	$CH_3CONHCH_2CONH(CH_2)_{11}CH_3$	93
4-$(CH_3)_3PhCOOH$	$CH_3(CH_2)_{11}NH_2$	4-$(CH_3)_3PhCONH(CH_2)_{11}CH_3$	78
$HOCH_2COOH$	$CH_3(CH_2)_{11}NH_2$	$CH_3CONHCH_2CONH(CH_2)_{11}CH_3$	87
(*R*)-PhCH(OH)COOH	$CH_3(CH_2)_{11}NH_2$	(*R*)-PhCH(OH)CONH$(CH_2)_{11}CH_3$	92
(*S*)-PhCH(OH)COOH	$CH_3(CH_2)_{11}NH_2$	(*S*)-PhCH(OH)CONH$(CH_2)_{11}CH_3$	89
$HOCH_2COOH$	(*S*)-PhCH$(CH_3)NH_2$	(*S*)-PhCH$(CH_3)NHOCCH_2OH$	88
$HOCH_2COOH$	(*R*)-PhCH$(CH_3)NH_2$	(*R*)-PhCH$(CH_3)NHOCCH_2OH$	94
$HOCH_2COOH$	(*R,S*)-PhCH$(CH_3)NH_2$	(*R,S*)-PhCH$(CH_3)NHOCCH_2OH$	88
	(*S*)-PhCH$(CH_3)NH_2$		93
(*R,S*)-PhCH(OH)COOH	$PhNH_2$	(*R,S*)-PhCH(OH)CONHPh	86

have to be dried and specially purified before use, (f) does not required solvent, (g) it is highly possible that racemization will not occur in the course of the reaction, and (h) diacylation products (imines) will not form. The disadvantages are (a) the amines, the acids, and the products should survive heating at 160-180 °C for 30 minutes, (b) both the amines and the acid should melt in that temperature range, (c) volatile, low boiling, and sublimable compounds cannot be used because they will be lost from the reaction mixture at that temperature, and (d) 1,3-dicaboxylic acids will decarboxylate. An alternative for the preparation of amides from both high melting point acids and acids that decarboxylate is the use of their esters as starting materials. For volatile and sublimable compounds, slow addition of an excess is suggested.

Preparation of Compounds

All starting materials for the preparation of the amides were purchased from Aldrich and used without further purification. Melting points (uncorrected) were determined on an Electrothermal IA 9000 Digital Melting Point Apparatus. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Gemini 300 instrument at 300 MHz and 75 MHz, respectively. The deuterium signal of the solvent ($CDCl_3$ or DMSO-d_6) was used as the lock, and the hydrogen or carbon signal of the solvent as the reference signal. IR spectra were recorded on a Nicolet 550 FT-IR at 2 cm^{-1} resolution as KBr plates. GS and MS were recorded on a Hewlett Packard 5890 series II gas chromatograph with a Hewlett Packard 5971 series mass selective detector.

(*R,S*)-*N*-(2',4'-dimethylphenyl-2-hydroxy-2-phenylacetamide.

Racemic 2-hydroxy-2-phenylacetic acid (3.8 g; 0.025 mol) and 2,4-dimethylaniline (3.6 g; 0.03 mol) were heated without solvent at 160-180 ^{o}C for 30 minutes. The mixture was cooled down at approximately 50 ^{o}C and chloroform (200 mL) was added. The chloroform solution was extracted with 10% sodium hydroxide (2x100 mL) and water (100 mL). The chloroform layer was dried over anhydrous magnesium sulfate and evaporated. The oily residue was dissolved in ~5 mL of chloroform and petroleum-ether (~300 mL) was added. The crystallization of the product was observed after a couple of minutes. The white crystals were separated by filtration and washed with petroleum ether. The yield was 91% (6.2 g). IR (KBr) 3375, 3355, 3267, 1663, 1653, 1543, 1453, 1064, and 730 cm^{-1}; ^{1}H NMR(DMSO-d_6) δ 2.13(s, 3H, CH_3), 2.24 (s, CH_3, 3H), 5.14 (s, 1H, OH), 6.55 (s, 1H, CHOH), 6.97 (s + t 2H, aromatic protons), 7.35 (d +t +d, 4H, aromatic protons), 7.52 (d, 2H, aromatic protons), 9.33 (s, 1H, NH).; ^{13}C NMR(DMSO-d_6) δ 15.9 (*p*-CH_3), 19.01 (*m*-CH_3), 72.32 (CHOH), 122.27, 124.92, 125.02, 125.97, 126.45, 129.16, 129.21, 131.56, 132.47, and 139.44,

(ten aromatic carbon signals), 169.10 (CO).; MS m/e 51, 65, 77, 79 (100%), 106, 107, 108, 120, 121, 149, 255 (M^+), 256 ($M+1^+$), and 257 ($M+2^+$).

***N*-Dodecyl-3,4-dimethoxybenzamide.** A mixture of 3,4-dimethoxybenzoic acid (1.82 g; 0.01 mol) and dodecylamine (1.85 g; 0.01 mol) were heated without solvent at 160-180 °C for about 20 minutes. The cooled reaction mixture were dissolved in chloroform (100 mL) and the chloroform solution was extracted with 10% sodium hydroxide (50 mL), 10% hydrochloric acid (50 mL), and water (50 mL). The organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated. The oily residue was dissolved in petroleum-ether (500 mL) and left for about 30 minutes at room temperature. The resulting suspension was kept overnight at -5 °C. The crystals were separated by filtration. The yield was 97% (3.56 g). IR (KBr) 3421, 3331, 3050, 2920, 2849, 1629, 1584, 1516, 1465, 1274, 1033, 1024 cm^{-1}.; ^1H NMR($CDCl_3$) δ 0.88 (t, J=6.8 Hz, 3H, CH_3), 1.25 (m, 18H, n-alkyl chain), 1.57 (seq, J=6.8Hz, 2H, CH_2CH_2N), 3.40 (q, J=6.8Hz, CH_2N), 3.88 (s, 3H, OCH_3), 3.89 (s, 3H, OCH_3), 6.59 (t, J=5.3Hz, NH), 6.82 (d, J=8.4Hz, 1H, hydrogen in 5 position of aromatic ring), 7.32 (d of d, J_1=8.4Hz, J_2=1.8Hz, 1H, hydrogen in 6 position of aromatic ring), 7.44 (d, J=1.8 Hz, 1H, hydrogen in 1 position of aromatic ring); ^{13}C NMR($CDCl_3$) δ 14. 06, 22.62, 26.99, 29.28, 29.30, 29.42, 29.52, 29.54, 29.57, 29.59, 29.67, 31.83, 40.09, and 55.77 (fourteen aliphatic carbons), 110.00, 110.41, 119.13, 127.30, 148.61, and 151.24 six aromatic carbons), and 166.82 (CO).; MS m/e 55, 79, 85, 122, 137 165 (100%), 181, 195, 348, 349 (M^+), 350 ($M+1^+$), and 351 ($M+2^+$).

(*R*)-*N*-(1'-Phenyl-1'-ethyl)-2-hydroxybenzamide. Salicylic acid (2.74 g; 0.02 mol) and (*R*)-α-methylbenzylamine (2.9 g; 0.024 mol; 20% excess) were

heated without solvent at 160-180 °C for about 15 minutes. The warm liquid reaction mixture was dissolved in chloroform (200 mL). The chloroform solution was washed with water (200 mL) dried over anhydrous magnesium sulfate and evaporated. The oily residue was dissolved in hot carbon tetrachloride and left at room temperature. The precipitated white crystals were separated by filtration an washed with petroleum-ether. Yield was 87% (4.17 g). IR (KBr) ~3000 (broad signal), 1635, 1592, 1555, 1481, 1451, 1386, 1250, 753, and 702 cm^{-1}.; ^1H NMR($CDCl_3$) d 1.50 (d, J=6.8 Hz, 3H, CH_3), 4.22 (q, J=6.8Hz, $CHCH_3$), 6.67 (d of d of d J_1=7.1Hz, J_2=7.1Hz, J_3=1.8Hz, 1H, hydrogen in 4 position of the benzamide ring), 6.89 (d of d, J_1=8.0Hz, J_2=1.8Hz, 1H, hydrogen in 3 position of the benzamide ring), 7.19 (m, 7H, Ph+NH+OH), 7.31 (d of d of d, J_1=8.0 Hz, J_2=7.1Hz, J_3=1.8Hz, 1H, hydrogen in 5-position of the benzamide ring), 7.49 (d of d, J=8.0 Hz, J_2=1.8Hz, 1H, hydrogen atom in 6-position of the benzamide ring).; ^{13}C NMR ($CDCl_3$) d 20.52, 51.37 (two aliphatic carbons), 116.64, 117.34, 118.11, 126.13, 128.63, 128.83, 130.30, 133.62, 137.24, 161.24 (ten aromatic carbons), and 175.40 (CO).; MS m/e 51, 65, 77, 92, 104, 105(1005), 106, 120, 121, 241 (M^+), 242 ($M+1^+$), 243 ($M+2^+$).

***N,N'*-Di(1-phenyl-1-ethyl)malonamide.** Racemic α-Methylbenzylamine (2.42 g; 0.02 mol) and diethyl malonate (1.6 g; 0.01 mol) were heated without solvent at 140 °C for twelve hours (overnight). The mixture was cooled down and dissolved in chloroform (500 mL). The chloroform solution was extracted with 10% hydrochloric acid (3x100 mL), water (3x100 mL), 10% sodium hydroxide (3x100 mL), water (3x 100 mL), and dried over anhydrous magnesium sulfate. The solvent was evaporated and the white crystal residue was crystallized from chloroform-petroleum ether. The yield was 93% (2.76 g). IR (KBr) 3450, 3593, 3062, 2977, 1640, 1531, 1495, 1446, 1290, 1207, 1334, 757, 700, and 585 cm-

1. ^{1}H NMR($CDCl_3$) δ 1.41 (d, *J*=7Hz, 6H), 3.04 (s, 2H), 4.99 (quintet, *J*=7Hz, 2H), 7.20 (m, 10H), 7.90 (d, *J*=7.30Hz, 2H).; ^{13}C NMR ($CDCl_3$) d 23, 43, 49, 125.127, 129, 144, and 165, MS *m/e* 51, 77, 91, 195, 120 (100%), 146, 163, 191, 205, 281, 295, 310 (M^+), and 311 ($M+1^+$)..

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