# An Improved Mixed Anhydride Technique for Fatty Amide Synthesis

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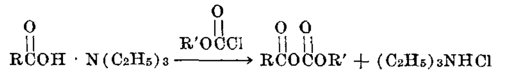
## Abstract

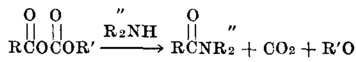
Amides of fatty acids normally prepared in fair-to-good yield and purity by conventional mixed carboxylic-carbonic anhydride techniques can be prepared in higher yield and improved purity by use of a modified method called "inverse addition." By reversal of the classical order of mixing of the reactants and, with the use of excess alkyl chlorocarbonate, side reactions are suppressed and yields are improved.

## Introduction

An earlier study (1) described the application of the classical (2) mixed carboxylic-carbonic anhydride method to the synthesis of a series of amides from the hydroxy fatty acids derivable from castor oil. The method as usually practiced (1,2) involves the addition of an equimolar amount of an alkyl chlorocarbonate to a carboxylic acid salt in a cold inert solvent (Equation 1), followed by the addition of an appropriate amine (Equation 2).

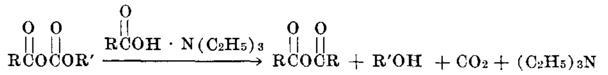


$$\mathrm{R\overset{\overset{O}{\|}}{C}OH \cdot N(C_2H_5)_3 \xrightarrow{R'O\overset{\overset{O}{\|}}{C}Cl} R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}OR' + (C_2H_5)_3NHCl} \qquad [1]$$



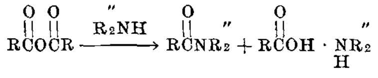
$$\mathrm{R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}OR' \xrightarrow{R''_2NH} R\overset{\overset{O}{\|}}{C}NR''_2 + CO_2 + R'OH} \qquad [2]$$

In this way a series of amides of keto and keto-hydroxy fatty acids were prepared in varying yields (16–83%) by Schipper and Nichols (3). These authors also observed symmetrical anhydrides as by-products and suggested their formation by the reaction shown in Equation 3.



$$\mathrm{R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}OR' \xrightarrow{R\overset{\overset{O}{\|}}{C}OH \cdot N(C_2H_5)_3} R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R + R'OH + CO_2 + (C_2H_5)_3N} \qquad [3]$$

They did not however attempt to avoid the formation of such by-products but utilized reaction 3 to prepare a series of symmetrical anhydrides. The same reaction (Equation 3) was applied during the preparation of a series of hydroxy acid symmetrical anhydrides (4). The facile reactions observed (4) suggested the possibility that reaction 3 was competing with reaction 1 during the formation of the mixed carboxyliccarbonic anhydride. Since the symmetrical anhydrides are only one-half as efficient for amide synthesis (one mole yields one-half mole of product) (Equation 4) as are



$$\mathrm{R\overset{\overset{O}{\|}}{C}O\overset{\overset{O}{\|}}{C}R \xrightarrow{R''_2NH} R\overset{\overset{O}{\|}}{C}NR''_2 + R\overset{\overset{O}{\|}}{C}OH \cdot \underset{H}{NR''_2}} \qquad [4]$$

the mixed carboxylic-carbonic anhydrides (ideal attack exclusively at the carboxylate carbonyl would result in quantitative yields) (Equation 2), the possibility was considered that the rather consistent amide yields (ca. 70–90%) (1) reflected the simultaneous occurrence of reaction followed by reaction 4 in competition with 1 and 2. To test this hypothesis a technique was devised called "inverse addition." Excess amounts of carboxylate anion in the reaction mixture were avoided by slowly adding a solution of amine salt of the carboxylic acid to a cold, stirred solution of the alkyl chlorocarbonate. As the chlorocarbonate ester is depleted and the mixed anhydride concentration increases however, there is a greater probability that the carboxylic acid anion will react as shown in Equation 3. By usng excess alkyl chlorocarbonate (1 to 5 equivalents), reaction 1 is accelerated and reaction 3 suppressed. Addition of amine in sufficient amount to react with both the mixed anhydride and the excess chlorocarbonate leads to considerably improved yields of the product amide mixed with either water-soluble or relatively volatile carbamates.

## Experimental Section

Melting points were taken in capillary tubes in an electrically heated block and are uncorrected. Infrared spectra were determined on a Model 137 Infracord by using smears, Nujol mulls, or chloroform solutions.

Commercially available anhydrous amines were used as received or were dried over sodium hydroxide and distilled if necessary. Anhydrous solvents were used, and the usual precautions were observed to exclude moisture. Ethyl chloroformate (Eastman) was used as received. The results obtained were comparable to those with freshly distilled material.

### 12-Hydroxy-cis-9-Octadecenamide

*Direct-addition.* (1) Triethylamine (1.53 ml, 0.011 mole) and 3.3 g (0.011 mole) of 12-hydroxy-*cis*-9-octadecenoic acid (5) in 100 ml of tetrahydrofuran (THF) cooled to −5C were treated dropwise with ethyl chloroformate (1.05 ml, 0.011 mole) maintaining the temperature below 0C. After the mixture had been stirred for 20 min, excess anhydrous ammonia gas was rapidly bubbled in for 10 min, and the system was held one hour at room temperature. The solvent was removed in vacuum and the residue, dissolved in ether, was washed successively with 3 N HCl, 1 M $Na_2CO_3$, and water, dried over magnesium sulfate, and the solvent evaporated, yielding 2.79 g (85%) of a white solid, mp 62–64C; reported (6) 66C. The infrared spectrum was essentially identical to that of an authentic sample, mp 65.5–66.5C, prepared by ester ammonolysis (1).

Acidification of the base wash, extraction with ether, and evaporation of the dried extract gave 280 mg of residue that contained material absorbing in both the amide and carboxylic acid carbonyl regions in the infrared.

An analogous experiment, employing a 10% excess of ethyl chloroformate, resulted in an 86% yield of crude product.

*Inverse Addition.* Ethyl chloroformate (1.05 ml, 0.011 mole) was dissolved in 50 ml of THF and cooled to 0C with vigorous stirring. A solution of 3.3 g (0.011 mole) of 12-hydroxy-*cis*-9-octadecenoic acid and 1.53 ml (0.011 mole) of triethylamine in 50

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[1] ARS, USDA.

TABLE I
Amides from Inverse Addition Mixed Anhydride Synthesis

| Compound | Scale moles | Crude yield % | Estimated[a] purity of crude product % |
|---|---|---|---|
| Ricinoleic acid: | | | |
| N-methylamide | 0.22 | 92 | >95 |
| N-cyclohexylamide | 0.22 | 94 | 92 |
| N-methylenecarboxylic acid amide | 0.22 | 93 | .... |
| Sodium N-methyl-N-methylene sulfonate amide | 0.22 | 93 | .... |
| N,N-di-β-hydroxyethylamide | 0.22 | 93 | .... |
| N,N-di-*sec*-butylamide | 0.011 | 75 | 84 |
| 12-Hydroxystearic acid: | | | |
| N-hexadecylamide | 0.011 | 86 | >95 (mp 98–99C) |
| N-cyclohexylamide | 0.011 | 88 | >98 (mp 108–110C) |
| 9,10-Dihydroxystearic acid: amide | 0.005 | 97 | >95 |
| 9,10,12-Trihydroxystearic acid:amide | 0.010 | 98 | >98 |

[a] Infrared absorption–carbonyl region.

ml of THF was added slowly, maintaining the temperature at 0C. The system was stirred for several minutes, and a stream of anhydrous ammonia gas was rapidly bubbled through for 10 min. After storage overnight the solvent was removed, and the residue was treated as before to yield 2.9 g (89%) of white solid, mp 64–65C. The infrared spectrum was identical to that of a pure sample. The material (120 mg), obtained by acidification of the base wash, contained both acid and amide.

A similar experiment, using a 10% excess of chloroformate, led to a 92.5% crude yield of acceptable product. On a ten-fold larger scale the yield of crude product with acceptable properties was 97%.

### N-t-Butyl-12-Hydroxy-cis-9-Octadecenamide

This derivative, prepared in the same fashion as the unsubstituted amide with direct addition (1) and a ten-fold excess of *t*-butylamine, was obtained in 88% yield, showing considerable extraneous carbonyl in the infrared. When inverse addition was employed, the yield was 98.5% with approximately one-half the amount of extraneous absorbance in the carbonyl region of the infrared. This absorbance was eliminated by distilling the *t*-butylamine just before use and protecting the reaction system from carbon dioxide. These precautions permitted the preparation of an 85% yield via inverse addition, showing a single peak at 6.05 μ with a shoulder at 5.9 μ. The base wash contained an additional 6% of amide. Short-path, high-vacuum distillation gave an analytical sample bp 149C/5 μ Hg, $N_D^{25} = 1.4740$; single carbonyl absorbance at 6.05 μ. Calculated for $C_{22}H_{43}NO_2$ C, 74.7; H, 12.3; N, 3.96. Found: C, 74.5; H, 12.1; N, 3.96.

In two twenty-fold larger scale experiments the yields of crude product with acceptable infrared spectra were 82%.

### N-t-Butyl-12-Hydroxyoctadecanamide

Use of excess, freshly distilled *t*-butylamine with the saturated acid as with the unsaturated derivative led to a 77% yield of the *t*-butylamide, mp 107–109C, by direct addition of the chloroformate while inverse addition permitted the preparation in 89% yield, mp 107–109C. Both preparations showed only single carbonyl absorbance in the infrared at 6.05 μ, and repeated crystallizations from ethyl acetate: petroleum ether did not raise their melting points.

### N,N-Diethyl-12-Hydroxyoctadecanamide

Direct addition (1) of ethyl chloroformate to the acid salt in THF as above and use of an equimolar amount of diethylamine resulted in a 58% yield of an oil that slowly changed to a clear jell. With inverse addition under similar conditions an 87% yield of oil that slowly solidified was obtained. The infrared spectra of these preparations indicated some extraneous carbonyl absorbance, and limited attempts at recrystallization were only partially successful because the material melts just above room temperature.

### N,N-Diethyl-9,10,12-Trihydroxystearamide

Direct addition on a 0.011 mole scale led to 78% yield of a crude product which could not be purified to an acceptable level by recrystallization. Inverse addition permitted the preparation of an 81% yield of crude product. On recrystallization from ethyl acetate a white solid, mp 76.5–77.5C, was obtained. Calculated for $C_{22}H_{46}NO_4$: C, 68.2; H, 11.7; N, 3.61. Found: C, 68.3; H, 11.7; N, 3.58.

In addition to these direct comparisons, a considerable number of amides were prepared by using the inverse addition technique. The yields of product and some indications of purity are given in Table I. Typically, additional amide was recoverable by careful extraction of the base washes. Depending on the solubility characteristics of the amides, several per cent of the product were often carried down in the soap.

## Discussion

It is evident from a consideration of the results obtained that addition order and reactant concentration have considerable influence on the product amount and quality in this system. Also to be noted is the effect of scale up. It has been found that dilution and stirring also affect the end results. These results can all be rationalized by considering the competing reactions noted above.

This modified method has been found most useful for both large- and small-scale, castor-based amide preparation. The same modifications would also be applicable to the preparation of other carboxylic acid amides, and their value in the synthesis of peptides has been discussed (7). The addition of soluble amine salts of the acids to the alkyl chlorocarbonate solution presents no special problems and consistently leads to higher purity products in improved yield.

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