was passed through a column packed with 100 g. of alumina as in the previous experiment. Fractionation of the eluent afforded 6.8 g. of bis(α-phenylethyl) ether, b.p. 335–338° (lit.[8] m.p. 335–340°). The infrared spectrum in chloroform showed: 3.2 (w), 3.4 (w), 5.1 (w), 5.2 (w), 5.5 (w), 5.9 (w), 6.2 (s), 6.7 (s), 6.9 (s), 7.3 (s), 7.65 (s), 7.8 (s), 9.2 (s), 9.45 (s), 9.8 (s), 10.5 (s), 10.9 (w), 11.7 (w). Due to the limited information available concerning the assignment of C–O–C bands in aralkyl ethers, we tentatively suggest that 9.2-, 9.5-, 9.8-μ peaks are responsible for such ether linkages.

Methyl Trityl Ether.—Triphenyl carbinol 0.5 g. (m.p. 160°, Matheson Coleman and Bell) dissolved in excess methanol (reagent grade, Baker's) was passed through a column packed with 5 g. of alumina. Evaporation of the eluent led to the isolation of 0.35 g. of pure methyl trityl ether, m.p. 82–83° (lit.[9] m.p. 82°). Mixture melting point with an authentic sample showed no depression.

Ethyl trityl ether was obtained in the same manner in comparable yield, m.p. 81–82° (lit.[10] m.p. and m.m.p. 82–83°).

Attempted Preparation of Dibenzyl Ether.—Benzyl alcohol (5 g.) (Eastman, b.p. 204–206°) dissolved in 50 ml. of benzene was passed through a column packed with 50 g. of alumina as in the previous experiments. Fractionation of the eluent led to the recovery of the starting material in 90% yield, b.p. 205–206°, and no higher boiling fraction was obtained.

Attempted Preparation of Dianisyl Ether.—A solution of 5 g. of anisyl alcohol (Eastman, m.p. 25°) in 50 ml. of benzene was treated with alumina and worked up as in the previous experiment; almost quantitative recovery of anisyl alcohol was obtained. Mixture melting point with the starting material showed no depression.

Attempted Preparation of Trityl Isopropyl Ether.—Triphenyl carbinol, 0.5 g., dissolved in excess of isopropyl alcohol, was treated with 5 g. of alumina and worked up in the same manner as in the case of methyl trityl ether. Triphenyl carbinol (0.45 g.) was recovered, m.p. and m.m.p. 160°.

Attempted Preparation of Methyl Benzhydryl Ether.—A solution of 1 g. of benzhydrol (Eastman, m.p. 68–69°) in excess of methanol was treated with alumina and worked up in the same manner, and the recovery of benzhydrol was almost quantitative.

Acknowledgment.—The author wishes to express his gratitude to Drs. P. L. Levins and H. G. Pars for many helpful discussions during the course of the investigation, and research committee of Arthur D. Little, Inc., for the financial support of the work.

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An Improved Method of Synthesis of Secondary Amides from Carboxylic Esters

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The direct synthesis of amides by the reaction of the appropriate amine and either an acid chloride or anhydride is a well known organic synthetic procedure. However, when it is desired to convert an ester of an organic acid to the corresponding secondary amide, no general direct technique is available. Unsubstituted amides, and some amides from primary aliphatic amines, can be prepared by direct aminolysis. In general, aromatic amines will not undergo this conversion.

The use of a trace of sodium methoxide as a catalyst for the ammonolysis of esters is well known.[1] Catalytic amounts of alkoxides have been used to promote the reaction between aliphatic amines and esters.[2–4] However, no example has been found in the literature in which an aromatic amine and an organic ester can be caused to react under the influence of a metal alkoxide.

The present work reports an improved procedure for the conversion of organic esters and primary aliphatic and aromatic amines to secondary amides by the action of a molar equivalent of sodium methoxide. This conversion may be represented by the following general equation.

$$R{-}\overset{\overset{O}{\|}}{C}{-}OR' + R''NH_2 \xrightleftharpoons{CH_3ONa} R{-}\overset{\overset{O}{\|}}{C}{-}NHR'' + R'OH$$

The results of several experiments dealing with the preparation of N-phenylpropionamide are given in Table I. These help to define some of the variables in this reaction.

TABLE I

EFFECTS OF VARIABLES IN THE PREPARATION OF N-PHENYLPROPIONAMIDE[a]

$$CH_3CH_2\overset{\overset{O}{\|}}{C}{-}OR + C_6H_5NH_2 \xrightleftharpoons{NaOCH_3} CH_3CH_2\overset{\overset{O}{\|}}{C}{-}NHC_6H_5 + ROH$$

R	Equivalents of $NaOCH_3$ added	% Yield of N-phenylpropionamide
Methyl	1.1	69.4
Butyl	1.1	71.1
Ethyl	1.1	70.0
Ethyl	0	0.0
Ethyl	0.1	5.3
Ethyl	2.2	77.2
Ethyl	1.1	73.3[b]
Ethyl	1.1	82.4[c]

[a] All experiments involved a 7-hr. reflux period except where stated otherwise. [b] A 24-hr. reflux. [c] Methanol removed as benzene azeotrope during reaction.

It can be seen that there was no reaction between aniline and ethyl propionate upon refluxing in benzene for seven hours in the absence of sodium methoxide. The addition of a catalytic amount of sodium methoxide gave only an equivalently small yield of N-phenylpropionamide. However, the use of a slightly greater than molar equivalent of sodium methoxide gave an acceptable yield of the amide. No significant increase in yield was obtained by increasing the sodium methoxide ratio further. An appreciable yield increase was obtained by azeotropically removing the alcohol as it was formed with benzene. In the same way, use of other volatile alcohols (in the form of their esters) and of reaction solvents with which the alcohols form azeotropes, favors the formation of substituted amides. Longer heating times did not appreciably raise the yield with this simple amide.

A brief study has been made to determine some of the limitations of this reaction and the data obtained are summarized in Table II. In each reaction, equivalents of ester, amine, and sodium methoxide were refluxed for seven hours in benzene, and the amides were then isolated in a standard way.

(1) R. L. Betts and L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 1568 (1937).
(2) J. A. Monick, *J. Am. Oil Chemists' Soc.*, **39**, 213 (1962).
(3) M. Meade, U. S. Patent 2,464,094; *Chem. Abstr.*, **43**, 4289 (1949).
(4) J. V. Schurman, U. S. Patent 2,863,888; *Chem. Abstr.*, **53**, 7632 (1959).

TABLE II

STRUCTURAL EFFECTS ON AMINOLYSIS YIELDS

$$R{-}\overset{\overset{O}{\|}}{C}{-}OC_2H_5 + R'NH_2 \xrightleftharpoons{NaOCH_3} R{-}\overset{\overset{O}{\|}}{C}{-}NHR' + C_2H_5OH$$

R	R'	Yield, wt. %	M.p., °C.
C_2H_5	C_6H_5	70	103–105[a]
C_2H_5	2-ClC_6H_4	25	92–93[b]
C_2H_5	3-ClC_6H_4	66	87–89[c]
C_2H_5	4-ClC_6H_4	73	137–139[b]
C_2H_5	4-BrC_6H_4	57	146–148[d]
C_2H_5	4-$CH_3C_6H_4$	70	121–123[e]
C_2H_5	Cyclo-C_6H_{11}	52	86–89[f]
C_2H_5	1-$C_{10}H_7$	92	117–118[g]
C_2H_5	2-$C_{10}H_7$	91	123–124[g]
C_2H_5	4-HOC_6H_4	46[h]	167–168[i]
C_6H_5	C_6H_5	87	162–163[j]
C_6H_5	Cyclo-C_6H_{11}	80	148–149[f]
$CH_2{=}C(CH_3)$	3,4-$(Cl)_2C_6H_3$	78	120–121[k]
$CH_3(CH_3)(OH)C$	C_6H_5	30	133–135[l]
C_2H_5	4-FC_6H_4	65	125–127[m]
C_2H_5	4-$CH_3OC_6H_4$	74	89–91[l]
C_2H_5	2,6-$(CH_3)_2C_6H_4$	0	...
C_2H_5	4-$NO_2C_6H_4$	0	...

[a] See ref. 5; [b] F. D. Chattaway, *J. Chem. Soc.*, **81**, 637 (1902). [c] O. C. M. Davis, *ibid.*, **95**, 1398 (1909). [d] F. D. Chattaway, *ibid.*, **81**, 817 (1902). [e] C. A. Bischoff, *Ann.*, **279**, 172 (1894). [f] W. Scharvin, *Ber.*, **30**, 2862 (1897). [g] G. Tsatsas, R. Delaby, A. Quevaullier, R. Damiens, and O. Blaupin, *Ann. Pharm. Franc.*, **14**, 607 (1956); *Chem. Abstr.*, **51**, 8669 (1957). [h] $NaOCH_3$ (2.2 equiv.) added. [i] C. Rohmann and K. Friedrich, *Arch. Pharm.*, **278**, 456 (1940); *Chem. Abstr.*, **36**, 3494 (1942). [j] O. Wallach and M. Hoffmann, *Ann.*, **184**, 80 (1877). [k] J. M. Horn, C. D. Applewhite, and E. P. Broadus, *Proc. Southern Weed Conf.*, **13**, 235 (1960); *Chem. Abstr.*, **55**, 8740 (1961). [l] E. E. Blaise and M. Montagne, *Compt. rend.*, **174**, 1553 (1922). [m] *Anal.* Calcd. for $C_9H_{10}FNO$: C, 64.64; H, 6.04; N, 8.39. Found: C, 64.68; H, 6.10; N, 8.56. [n] *Anal.* Calcd. for $C_{10}H_{13}NO_2$: C, 67.04; H, 7.32; N, 7.81. Found: C, 66.95; H, 7.50; N, 7.91.

In general, any simple aliphatic or aromatic ester may be used. As shown in Table I, the methyl, ethyl, and butyl esters of propionic acid all gave acceptable and nearly equivalent yields. Esters which are highly branched in the α position have been found to require longer reaction times to reach equilibrium. As shown in Table II, an α-hydroxy-α-methylpropionic ester gave a low yield; unsaturated esters, *e.g.*, methyl methacrylate, gave acceptable yields.

Only primary aliphatic and aromatic amines undergo this reaction. Various ring-substituted anilines and cyclohexylamine gave satisfactory yields with ethyl propionate and ethyl benzoate. N-Methylaniline and diphenylamine gave no product, while 4-nitroaniline yielded only an intractable tar under these reaction conditions. Substitution in the ortho position on the phenyl ring gave a decreased yield as exemplified by 2-chloroaniline, while di-*ortho* substitution allowed no apparent reaction, as illustrated with 2,6-dimethylaniline. A hydroxyl group on the ring did not interfere if a second equivalent of sodium methoxide was added. Halogen, alkyl, and alkoxyl groups did not appear to interfere.

The amides were obtained by hydrolysis of the reaction mixture in dilute mineral acid, followed by standard isolation techniques. They were obtained in nearly pure form directly from the reaction work-up.

The authors have postulated a possible mechanism for this reaction. The reaction of an alkoxide ion with an amine is assumed to be similar to the analogous reaction of ammonia.[1,5] This is followed by the attack of the generated anion I on the carbonyl of the ester to yield an intermediate II.

$$CH_3O^- + RNH_2 \rightleftharpoons \underset{I}{\bar{R}NH} + CH_3OH$$

$$I + R'\overset{\overset{O}{\|}}{C}{-}OR'' \rightleftharpoons R'{-}\overset{\overset{O}{|}}{\underset{\underset{H\text{-}N\text{-}R}{|}}{C}}{-}OR''$$

II

$$II \rightleftharpoons \underset{III}{R'{-}\overset{\overset{O}{\|}}{\underset{\underset{H}{|}}{C}}{-}N{-}R} + \underset{IV}{R''O^-}$$

This intermediate II loses an alkoxide ion to form the final amide III. However, if this were the complete reaction, a small quantity of alkoxide ion would be sufficient to catalyze the reaction as more alkoxide ion IV is continuously formed. If, however, the tautomeric forms of III are attacked by the alkoxide ion, a resonance hybrid V is formed in solution until the mixture is hydrolyzed. This anion is resistant to further attack by the nucleophile $R''O^-$ and the reverse reaction, III → II, is inhibited.

$$III + IV \rightleftharpoons \underset{V}{[R'{-}\overset{\overset{O^-}{|}}{C}{=}N{-}R} \longleftrightarrow R'{-}\overset{\overset{O}{\|}}{C}{-}\bar{N}R] + R\ddot{O}H$$

These last assumptions are given credence by two observations made in this study. First, when methanol was azeotropically removed with benzene during the reaction of methyl propionate with aniline, almost two equivalents were obtained, presumably one formed from the original methoxide, and one from the ester. This allows for shifting the equilibrium to the resonance hybrid V, and thence to the amide by removal of the alcohol during reaction. Secondly, infrared spectra of solutions of reaction mixtures before hydrolysis, and after alcohol removal, showed only a trace of amide carbonyl absorption in the 6.05–6.15-μ region. The absence of carbonyl absorption lends favor to the imino form as the predominant contributing structure to the resonance hybrid V in solution at that point.

The lack of reactivity of secondary amines in this reaction may be explained by the steric inhibition of the formation of anion II. Tertiary amides, if formed, cannot in turn form the hybrid anion V and be stabilized against reversal of the reaction.

Regardless of the mechanism of the reaction, this procedure represents a convenient improvement in the preparation of secondary amides directly from carboxylic esters, and particularly in the preparation of N-aryl amides. It is especially suited for use in instances where the ester is more readily obtainable than the free acid.

Experimental

The substituted anilines employed were Eastman reagent grade materials. Matheson Coleman and Bell powdered sodium methoxide was used in all experiments in this study. The

(5) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 296.

Matheson Coleman and Bell ethyl propionate and the Eastman ethyl benzoate were practical grade chemicals.

All melting points are uncorrected and were taken on a Mel-Temp melting point apparatus. Analytical data were obtained at this laboratory. The following procedure is illustrative of the general technique employed.

N-Phenylpropionamide.—A mixture of 20.4 g. (0.2 mole) of ethyl propionate, 18.6 g. (0.2 mole) of aniline, 12.0 g. (0.22 mole) of sodium methoxide powder, and 200 ml. of dry benzene was stirred and refluxed for 7 hr., cooled, and poured carefully into 200 ml. of 10% hydrochloric acid. This mixture was stirred and cooled in an ice bath while 200 ml. of hexane was added. The resulting slurry was filtered on a Büchner funnel, and the filter cake was washed with 100 ml. of cold water, followed by 50 ml. of cold hexane. The resulting crystalline material was air-dried to yield 21 g. (70%) of nearly pure amide which melted between 103 and 105° (lit.[6] m.p. 103–105°).

(6) A. W. Crossley and W. H. Perkin, Jr., *J. Chem. Soc.*, **73**, 33 (1898).

Cyclization of Propynylureas to 2-Imidazolones

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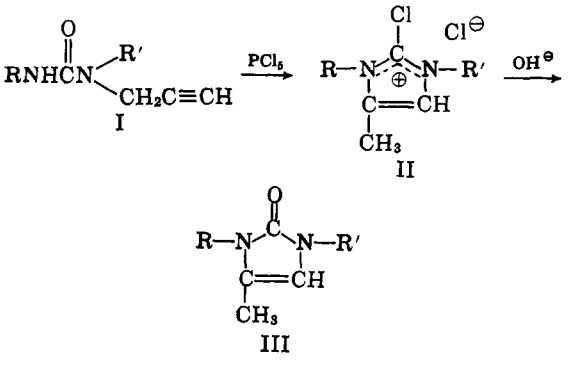
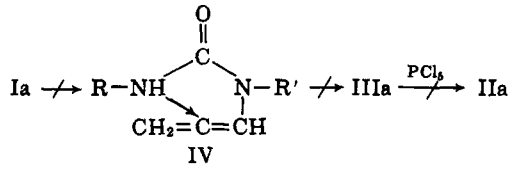
We have reported[1,2] that propynylureas I undergo intramolecular cyclization on treatment with phosphorus pentachloride to give stable isolable imidazolium chlorides II which were converted by aqueous sodium hydroxide to the imidazolones III.



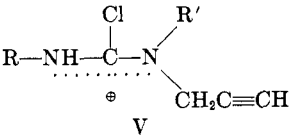
a, R = 3,4-dichlorophenyl; R′ = isopropyl
b, R = butyl; R′ = isopropyl

The possibility of the conversion of I directly to III *via* an allene intermediate IV by isomerization of the propynyl group prior to cyclization was proven to be untenable. Treatment of IIIa with phosphorus pentachloride under the same conditions gave only untractable tars.

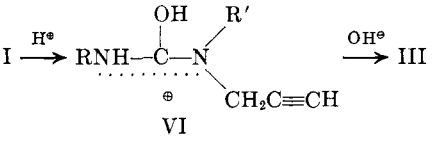


The cyclization of aliphatic propynylureas Ia with phosphorus pentachloride gave extremely hygroscopic intermediate salts, which could not be purified for analysis, but were converted directly with no difficulty to the imidazolones III.

Our proposed mechanism[1] for I → II → III visualized an intermediate carbamido chloride V.



Since amides and ureas reportedly[3a,b] undergo O-protonation in the presence of strong acids, we postulated that cyclization I → III could be effected in a similar manner through VI.



Treatment of Ia with concentrated sulfuric acid or *p*-toluenesulfonic acid in benzene gave a sirupy intermediate which could neither by crystallized nor purified, but gave infrared spectra similar to IIa. These sirups, or the aqueous acidic solution directly, gave III on treatment with aqueous sodium hydroxide. Cyclization of Ia could not be induced by anhydrous hydrogen chloride in benzene but cyclized smoothly using a more polar solvent, dioxane.

The acid cyclization of I undoubtedly occurs *via* the O-protonated urea VI following a mechanistic sequence similar to that proposed for phosphorus pentachloride.

When the urea Ia was heated with dilute sodium hydroxide, the imidazolone IIIa was obtained directly. Alkaline cyclization might well involve the allene intermediate IV discussed previously.

Experimental

3′-(3,4-Dichlorophenyl)-1-isopropyl-4-methyl-2-imidazolone (IIIa) A. Sulfuric Acid.—A solution of urea Ia (28.3 g., 0.1 mole) and concentrated sulfuric acid (10.5 g., 0.12 mole) in 100 ml. of benzene was refluxed for 6 hr. A dark blue acid layer separated from the benzene. The acid layer was stirred into 500 ml. of water and made alkaline with 50% aqueous sodium hydroxide. The product separated and was recrystallized from methanol in colorless prisms, m.p. 112.1–112.8°, 25.0 g., 87.5% yield.

B. *p*-Toluenesulfonic Acid.—The reaction was run exactly as in method A using toluenesulfonic acid (20.0 g., 0.11 mole). The product was obtained as colorless prisms, m.p. 111.5–112.2°, 19.0 g., 66.7% yield.

C. Hydrochloric Acid.—With the same charge as A, and passing in anhydrous hydrogen chloride for 8 hr. at 80°, gave unchanged urea Ia. The same charge using 100 ml. of dioxane at 80° for 8 hr. gave the cyclized urea IIIa by quenching the reaction in 500 ml. of water, adding 50% aqueous sodium hyroxide until alkaline, and extracting IIIa with three 100-ml. portions of ether. Large white prisms were obtained from ethyl acetate, m.p. 111.1–112.1°, 19.7 g., 69.0% yield.

D. Sodium Hydroxide.—A slurry of urea Ia (14.4 g., 0.05 mole) in 20 ml. of 20% aqueous sodium hydroxide and 100 ml. of water was held at 80° for 8 hr. On cooling, a tan oil separated. The remaining liquid was extracted with three 50-ml. portions of ether and combined with the oil. Ether was evaporated, giving the solid product. Small prisms were obtained from ethyl acetate, m.p. 110.8–111.6°, 9.0 g., 62.0% yield.

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(3) (a) W. D. Kumler, *J. Am. Chem. Soc.*, **84**, 4983 (1962); (b) A. R. Katritzky and R. A. Y. Jones, *Chem. Ind.* (London), 722 (1961).