A Modified Curtius Reaction[1]

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The Curtius rearrangement, which involves heating an acid azide to cause loss of nitrogen and formation of an isocyanate, is a valuable method for the conversion of acids to amines.[2] The usual procedure of obtaining acid azides, which consists of treating an acid chloride with sodium azide, suffers from the disadvantage that it is often difficult to obtain pure acid chlorides in good yield from acids which either decompose or undergo isomerization in the presence of mineral acids. The much less convenient alternative sequence of ester to hydrazide to azide has been used to circumvent this difficulty.

Recently the use of mixed carboxylic-carbonic anhydrides in peptide synthesis and in the place of acid chlorides for the preparation of amides and esters of sensitive acids has been developed.[3] We have found that mixed anhydrides react with sodium azide under very mild conditions to form acid azides in excellent yield. These can be rearranged to the isocyanate and hydrolyzed to the amine without isolation of intermediates. For example, *cis*-2-phenylcyclopropylamine[4] was prepared in 77% yield from *cis*-2-phenylcyclopropanecarboxylic acid. In the original preparation of this amine it was found necessary to avoid preparation of the acid chloride to prevent isomerization to the *trans* acid chloride. This new procedure has been applied extensively in our laboratories and elsewhere with excellent results.[5]

EXPERIMENTAL

cis-2-Phenylcyclopropylamine. *cis*-2-Phenylcyclopropanecarboxylic acid (14.0 g., 0.086 mole) was suspended in 15 ml. of water and sufficient acetone was added to complete the solution. The solution was cooled to 0° (ice-salt bath) and 10.2 g. (0.1 mole) of triethylamine in 175 ml. of acetone was added. While maintaining the temperature at 0°, a solution 12.5 g. (0.11 mole) of ethyl chloroformate in 45 ml. of acetone was added slowly. The mixture was stirred for 30 min. at 0° and then a solution of 8.6 g. (0.13 mole) of sodium azide in 30 ml. of water was added dropwise. The mixture was stirred (0°) for 1 hr.; then it was poured into an excess of ice water. The oil which separated was extracted into ether and the combined ether extracts were dried with magnesium sulfate. Solvent was removed *in vacuo* at room temperature to leave a dark red oil (azide), which was dissolved in 50 ml. of anhydrous toluene. The toluene solution was heated on a steam bath until no more nitrogen was evolved. Removal of toluene *in vacuo* afforded a mobile red liquid which was shown to be almost pure isocyanate by its infrared spectra (4.4 μ). The isocyanate was suspended in 90 ml. of 20% aqueous hydrochloric acid and the mixture was heated under reflux for 9 hr. Evaporation of the resulting solution *in vacuo* gave a dark semi-solid residue. This was dissolved in 100 ml. of water and the solution was made strongly alkaline by the addition of a 40% sodium hydroxide solution. The oil which separated was extracted into ether and the combined extracts were dried with anhydrous magnesium sulfate. Removal of the solvent under reduced pressure gave a clear pale brown oil. This was distilled *in vacuo* (using a bath at a temperature of 70° or below) and gave 8.9 g. (77%) of colorless free base; b.p., (0.3–0.4 mm.) 50–52°.

A hydrochloride was prepared in the usual manner (isopropyl alcohol-ether); it melted at 169–170° and did not depress the melting point of an authentic sample of *cis*-2-phenylcyclopropylamine hydrochloride.

In a variation of the above procedure used in subsequent work the acid azide was extracted directly into toluene rather than into ether. The toluene solution was then dried over magnesium sulfate and added dropwise to a flask equipped with a stirrer which was heated on a steam bath. This helped to control the vigorous evolution of nitrogen which takes place during the rearrangement.

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[1] This work was presented at the Third Delaware Valley Regional Meeting, American Chemical Society, Philadelphia, Pa., February 25, 1960.

[2] For a brief review of the Curtius rearrangement see P. A. S. Smith, *Org. Reactions,* III, 337 (1946).

[3] R. L. Barnden, R. M. Evans, J. C. Hamlet, B. A. Hems, A. B. A. Jansen, M. E. Trevett, and G. B. Webb, *J. Chem. Soc.* (1953), 3733. R. M. Evans and A. B. A. Jansen, *J. Chem. Soc.* (1954), 4037. D. A. Johnson, *J. Am. Chem. Soc.,* **75**, 3636 (1953). J. R. Vaughan, Jr., *J. Am. Chem. Soc.,* **73**, 3547 (1951); **74**, 676 (1952).

[4] A. Burger and W. L. Yost, *J. Am. Chem. Soc.,* **70**, 2198 (1948).

[5] Unpublished work of Dr. Carl Kaiser, Smith, Kline & French Laboratories and Dr. A. Burger, University of Virginia.

A New Intermolecular Hydrogen-Transfer Reaction[1]

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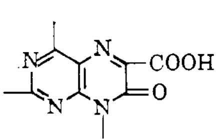
The reactions of mesoxalic acid derivatives with 1,2-diamines which have previously been reported appear to be uncomplicated. Thus, the condensation of sodium mesoxalate with 4,5-diaminopyrimidines yields derivatives of 7(8*H*)-pteridinone-6-carboxylic acid (I)[2,3] and is completely analogous to the condensation of diethyl mesoxalate with 1,2-



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[2] W. Pfleiderer and E. C. Taylor, *J. Am. Chem. Soc.,* **82**, 3765 (1960).

[3] E. C. Taylor and H. M. Loux, *J. Am. Chem. Soc.,* **81**, 2474 (1959).