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DIPHOSPHORUS TETRAIODIDE AS A NEW MILD CONDENSING AGENT FOR THE SYNTHESIS OF AMIDES

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In the presence of diphosphorus tetraiodide, a variety of weak carboxylic acids readily react with amines to form the corresponding amides in high yields.

Dehydrative condensation of weak carboxylic acids with amines is too slow to serve as a practical process for amide synthesis.1) Thus the activation of carboxyl function is necessary to facilitate the reaction through the intermediate formation of reactive esters, acid anhydrides, or acyl-onium compounds. The reagents introduced for such purposes include carbodiimide,2) phosphines,3) phosphonates,4) boranes,5) metal or pseudometal halides,6) 2-halopyridinium salts,7) activated acetylenes,8) and azole derivatives.9) However, many of these are not free from some drawbacks such as limited availability, by-product formation, inconvenient handling, high costs, competing side-reactions, or low stability.

Diphosphorus tetraiodide (P_2I_4) is an easily prepared and handled dehydrating agent,10) which can effect the conversion of aldoximes,11) amides,12) and nitroalkanes13) into nitriles under mild conditions. On continuing our research on the reactivity of P_2I_4, we report herein a mild coupling reaction of a variety of weak carboxylic acids with amines in the presence of P_2I_4.

$$\underset{\underline{1}}{\text{R-COOH}} \quad + \quad \underset{\underline{2}}{\text{R'-NH}_2} \quad \xrightarrow[\text{CCl}_4\text{-CH}_2\text{Cl}_2\text{ , }\Delta]{\text{P}_2\text{I}_4} \quad \underset{\underline{3}}{\text{R-CO-NH-R'}}$$

A general procedure is as follows; amine (1.0 mmol) and 2,6-lutidine (1.0 mmol) are added to a suspension of P_2I_4 (1.0 mmol) in dry carbon tetrachloride (10 ml) and the mixture is stirred for several minutes to form a white precipitate. A solution of carboxylic acid (1.0 mmol) in dichloromethane (10 ml) is then added with stirring. The precipitate goes into solution to give a yellow homogeneous mixture, which is heated under gentle reflux for several hours. After cooling, the mixture is quenched with 1M-hydrochloric acid, the organic phase is separated, washed with 5%-sodium

Table 1 Amides Obtained from the P_2I_4-assisted Condensation of Carboxylic Acids with Amines

Carboxylic acid 1	Amine 2	Amide 3	
R	R'	Mp (^oC)	Yield (%)
$4-CH_3O-C_6H_4$	C_6H_5	172-173	~ 100
do	$C_6H_5CH_2$	128-129	90
$3,4-(CH_3O)_2-C_6H_3$	C_6H_5	162-163	~ 100
do	$C_6H_5CH_2$	175-176	98
$4-CH_3-C_6H_4$	C_6H_5	149-150	80
do	$2,4,6-(CH_3)_3-C_6H_2$	197-198	~ 100
$2,4,6-(CH_3)_3-C_6H_2$	C_6H_5	166-167	~ 100
$4-Cl-2,3,5,6-(CH_3)_4-C_6$	do	235-236*	~ 100
$4-CH_3CO-C_6H_4$	do	188-189	81
$4-NO_2-C_6H_4$	do	216-217	~ 100
do	$C_6H_5CH_2$	139-140	80
$C_6H_5CH=CH_2$	C_6H_5	149-150	~ 100
$(CH_3)_3C$	do	133-134	~ 100
do	$C_6H_5CH_2$	83-84	~ 100
do	$2,6-(CH_3)_2-C_6H_3$	205-206*	~ 100
do	$3,5-(CH_3)_2-C_6H_3$	126-127*	~ 100
do	$4-NO_2-C_6H_4$	185-186*	85

* Sublimes.

carbonate solution, dried with sodium sulfate, and evaporated to leave the expected amide as a sole product, which is further recrystallized from methanol. Yields of products range from 85 to 100%. The reaction can be carried out at room temperature, but it usually takes much longer time for completion. As apparent from the Table, the present method is especially attractive for converting weak or hindered amines into amides.

The reagent may also be used for the synthesis of some peptides. Thus N-acetyl- and N-benzyloxycarbonyl-D,L-phenylalanylglycine ethyl esters were obtained in

46% and 53% yields, respectively from the corresponding N-protected D,L-phenylalanine and glycine ethyl esters.

The use of P_2I_4 as a coupling agent for the amide synthesis has some distinct advantages; commercial availability, ease of handling (crystalline solid with no fuming property), simple work-up (oxygen-containing phosphorus by-products are water-soluble), mild reaction conditions (neutral and non-aqueous media; temperature below *ca.* 50°C), compatibility with various functionalities, and high purity of products.

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