Preparation of Stable Crystalline Mixed Anhydrides

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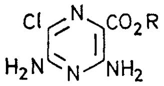
Summary *NN*-Diphenylcarbamoylpyridinium chloride has been used in aqueous solution to synthesize stable crystalline carboxylic carbamic anhydrides.

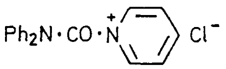
IT has recently been observed that isoxazolium and benzisoxazolium salts, under appropriate conditions, convert carboxylic acids into "active esters".[1] The resulting esters are, in certain cases, crystalline non-hygroscopic materials which can be readily purified and stored.[2] During the course of a recent investigation with esters of this type we reported[3] the preparation, isolation, and purification of (Ib).[4] We now communicate an improved synthesis of (Ib) and the extension of this reaction to a variety of other stable, crystalline mixed anhydrides.



(I)

a; R = H

b; R = CO·NPh$_2$



(II)

3,5-Diamino-6-chloropyrazinecarboxylic *NN*-diphenylcarbamic anhydride (Ib) was originally prepared from (Ia) and *NN*-diphenylcarbamoyl chloride in DMF with triethylamine.[3] This procedure failed with several heterocyclic, aromatic, and aliphatic acids. We have subsequently discovered a relatively general reaction for synthesis of these anhydrides from the aforementioned acids. In fact, (Ib) can be prepared in greater yield (65% *vs.* 44%) with a shorter reaction period, 0·5 rather than 24 h, than previously. The use of *NN*-diphenylcarbamoylpyridinium chloride (II)[5] in aqueous or ethanolic solution has permitted extension of this reaction to a number of carboxylic acids. A solution of the acid and triethylamine in water was added slowly to a solution of (II) in water (0—25°). After *ca.* 0·5 h or less, the precipitated anhydride was filtered off and recrystallized (see Table 1).† The greater efficiency of (II) than diphenylcarbamoyl chloride appears to be based on the differing mechanisms by which each reacts with nucleophiles;[6] S_N1 for diphenylcarbamoyl chloride, S_N2 for (II).

TABLE 1

		M.p. (°C)	Yield (%)
(Ib)		228—230	65
(III)	$PhCO_2\cdot CO\cdot NPh_2$	124—125	89
(IV)	$\overline{O\cdot CH:CH\cdot CH:C}\cdot CO_2\cdot CO\cdot NPh_2$	116—118	89
(V)	$o\text{-}NH_2\cdot C_6H_4\cdot CO_2\cdot CO\cdot NPh_2$	133—135	60
(VI)	$p\text{-}HO\cdot C_6H_4\cdot CO_2\cdot CO\cdot NPh_2$	170—172	23
(VII)	$\text{L-}PhCH_2\cdot CH(N(Phthaloyl))\cdot CO_2\cdot CO\cdot NPh_2$	>51	a

[a] This compound is less stable than the others and was invariably contaminated with diphenylamine even after extensive purification attempts.

TABLE 2

		M.p. (°C)	M.p. (°C) (lit.)
(VIII)	(I; NHPh for OR)	198—202	
(IX)	$PhCO\cdot NH\cdot CH_2\cdot CO_2H$	185—189	187[7]
(X)	$\overline{O\cdot CH:CH\cdot CH:C}\cdot CO\cdot NH\cdot CH_2Ph$	110—112	111—111·5[8]
(XI)	$o\text{-}NH_2\cdot C_6H_4\cdot CO\cdot NH\cdot CH_2Ph$	123—125	124—125[8]
(XII)	$p\text{-}HO\cdot C_6H_4\cdot CO\cdot NH\cdot CH_2Ph$	157—163	
(XIII)	$\text{L-}PhCH_2\cdot CH(N(Phthaloyl))\cdot CO\cdot NH\cdot CH_2\cdot CO_2Et$	159—161	161—162[9]
		$[\alpha]^{23}_D - 150\cdot 16°$	$[\alpha]^{23}_D - 146°$

For further characterization, each anhydride in Table 1 was treated with the appropriate amine in ethanol or water (generally for a few min at 25°) to form the amides listed in Table 2.

Condensation of (II) with several aliphatic acids, including acetic, acetoacetic, and phenylacetic, failed to afford any isolable anhydride even at 0°. Evolution of gas (CO_2) begins as soon as the two solutions are mixed, and diphenylamine was isolated, apparently arising from a generated unstable or extremely reactive mixed anhydride.‡ Similarly attempts to use the *NN*-dimethyl analogue of (II), even with those acids in Table 1, did not lead to isolable products. To date, the only example of a successful reaction with an aliphatic carboxylic acid is the coupling of phthaloyl-L-phenylalanine (VII) (as the mixed anhydride generated *in situ*) with ethyl glycinate in ethanol to give the dipeptide (XIII). A more detailed study would be necessary to define the use of (II) as a reagent for general peptide synthesis, however.

These mixed anhydrides are prepared and *isolated* under normal laboratory conditions with little or no precautions necessary. Except for (VII) all compounds isolated could be stored for at least 1 year. The isolation of the anhydrides from bifunctional acids, (I), (V), and (VI), in addition to the extreme reactivity of the products in Table 1 with amines, indicates that these reagents may be of particular advantage where it is difficult or impossible to prepare the corresponding acid chloride.[10]

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† All compounds in Tables 1 and 2 were consistent with the assigned structures (by spectra and analyses) [exception (VII), Δ^c calc. — found = 0·52]. No effort was made to maximize yields.

‡ The pyridinium salt (II) has been shown to be stable under these conditions; see ref. 7.

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[6] The stability and reactions with nucleophiles of carbamoylpyridinium salts has been studied: S. L. Johnson and K. A. Rumon, *J. Phys. Chem.*, 1964, **68**, 3149; S. L. Johnson and K. A. Rumon, *J. Amer. Chem. Soc.*, 1965, **87**, 4782.

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[10] For example, L. Anshütz and A. Ohnheiser, *Ber.*, 1944, **77B**, 609, failed in an attempt to reproduce B.P. 401,643 claiming the preparation of anthranoyl chloride. Anshütz further stated, "It is doubtful that (I) (anthranoyl chloride) is capable of existance". Similarly attempts to prepare the acid chlorides of various heterocyclic *o*-amino-acids, including (Ia), in our laboratory have failed.