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THE REACTION OF CYCLIC ANHYDRIDES WITH SODIUM AZIDE IN POLAR APROTIC MEDIA

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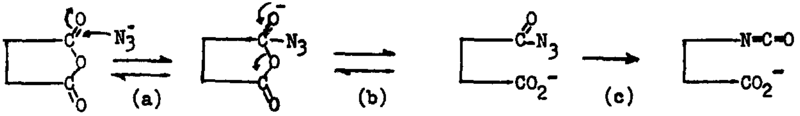
In the course of another investigation it was desired to convert a cyclic anhydride to the amino acid containing one less carbon atom:

Although such a transformation may be effected in several steps involving the Hoffmann, Schmidt, Lossen or related reactions, it was necessary to avoid the hydroxylic or acidic systems usually encountered in such reactions. As a consequence the reaction of sodium azide with such anhydrides in polar aprotic solvents[3] was studied. It was felt that the equilibria (a) and (b) would be established by the anhydride and the azide ion and that step (c) being irreversible due to loss of nitrogen would cause the reaction to proceed to the isocyanato carboxylate (IV) which could then be carefully converted to the desired product.



I II III IV

Since the pKa's of hydrazoic acid and simple carboxylic acids are about the same, azide and carboxylate should be expelled from the tetrahedral intermediate (II) with roughly equal facility and hence a significant amount of azido carboxylate (III) may be reasonably expected in the equilibrium mixture.

The solvents used were dimethyl formamide (DMF), dimethyl sulfoxide (DMSO) and tetraglyme. The solubility of sodium azide in tetraglyme is very small and only a limited number of experiments were run in this solvent. The results were qualitatively similar to those obtained in DMF. The DMF was taken from freshly opened bottles containing 0.08-0.10% water. Usually, an excess of anhydride was added to the reaction mixture in amounts which would stoichiometrically react with the water present. This amount of water does furnish a small number of protons (which are sometimes required for the reaction, vide infra) but does not change the essentially neutral character of the solutions Reactions involving DMF dried over calcium hydride did not lead to significantly different results. The DMSO was dried over calcium hydride and vacuum distilled while the tetraglyme was taken from a freshly opened bottle and not purified.

The general reaction procedure involved stirring the sodium azide and the anhydride in the appropriate solvent and heating to a temperature at which a reasonable rate of nitrogen evolution was detected. Work up was accomplished either by direct filtration of a precipitate or by quenching the solution in water followed by acidification and filtration of a precipitate. The course of the reaction is very largely dependent on the nature of the starting material. Aliphatic anhydrides (succinic, camphoric, hexahydrophthalic) did not give well defined products. Reaction of these anhydrides in the above solvents at several temperatures afforded colored solutions from which it was difficult to isolate starting material. Aromatic anhydrides afforded in addition to the parent diacid: (a) benzimidazolones (b) imides and (c) azido diacids.[4] The results are summarised in Table I.

Table I

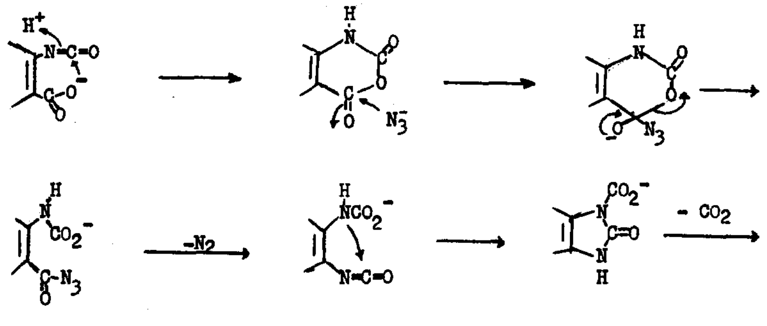
Anhydride	Solvent	Temp.	Product	Yield
Phthalic	DMF	154°	benzimidazolone *	60%
Phthalic	DMSO	189°	benzimidazolone	80% **
Isatoic	DMF	154°	benzimidazolone	76%
3-chlorophthalic	DMF	100°	4-chlorobenzimidazolone	13%
tetrachloro-phthalic	DMSO	27°	tetraazidophthalic acid	95%
3-nitrophthalic	DMF	110°	3-azidophthalic acid	88%
Naphthalic (1,8-naphthalene dicarboxylic acid	DMF	154°	naphthalimide	15%***
Naphthalic	DMSO	189°	naphthalimide	9% ***

* 3% phthalimide can be isolated

** This yield was obtained with "moist" DMSO. Lower yields are obtained with scrupulously dried solvent.

*** The remainder of the starting material is recovered unchanged.

The genesis of benzimidazolone[5] may be explained by considering isatoic anhydride as an intermediate as follows:



This anhydride was indeed converted to benzimidazolone under the reaction conditions. However, when isatoic anhydride was first converted to its sodium salt with sodium hydride, the reaction did not proceed. This suggests that a finite proton concentration is necessary to effect the reaction. A search of the reaction mixture by thin layer chromatography did not reveal any anthranilic acid although it was shown that anthranilic acid survives the conditions of the reaction.

The production of imides must involve reduction of one of the azide nitrogens. This process cannot be readily explained by the authors.[6]

Although 4-nitrophthalic anhydride formed an insoluble complex with azide ion in DMSO, it gave only the 4-nitro diacid on work up. On the other hand 3-nitrophthalic anhydride readily afforded 3-azidophthalic acid. This replacement of the nitro group by an azide, as well as the replacement of the chloro group (vide infra) seems to be one of the first documented cases of an aromatic nucleophilic substitution activated by an anhydride function.[7] Finally while 3-chlorophthalic anhydride yielded

4-chlorobenzimidazolone, the tetrachloro anhydride in DMSO afforded a white crystalline material, m.p. 113° which could be recrystallized from aqueous ethanol and was chlorine free. This material exhibited strong azide and carbonyl absorption in its infrared spectrum. It is a highly explosive compound: a large mortar was shattered when an attempt was made to grind a few milligrams of the dry compound for a spectrum. Although no C-H-N analysis was obtained for this substance, it evolved four equivalents of nitrogen on heating in DMF, and therefore is thought to be the tetraazidophthalic acid.

References

1. Present address: Merck Sharp and Dohme Research Laboratories, Rahway, N.J.
2. National Science Foundation Undergraduate Research Participant.
3. A.J. Parker, Quart. Revs. (London), 16, 163 (1962).
4. All compounds were identified by comparison with authentic materials synthesized according to procedures in the literature.
5. Similar results have been obtained in acetic acid by S. Maffei and G.F. Bettinetti, Ann. chim.,(Rome), 49, 1809 (1959).
6. The reducing ability of DMF has been described by E.C. Taylor and E.E. Garcia, J. Am. Chem. Soc., 86, 4721 (1964); however, DMSO seems to require reagents of high oxidizing potential: see Dimethyl Sulfoxide, Reaction Medium and Reactant, Crown Zellerbach Corporation Publication, p. 13, 1962.
7. The authors are indebted to the referee for calling attention to the report of G. G. Yakobson, V. N. Odinokov, and N. N. Vorozhtsov, Jr., Tetrahedron Letters, 4473 (1965) that tetrachlorophthalic anhydride suffers a nucleophilic replacement by fluoride ion, albeit under very stringent conditions.