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Polyphosphate Ester as a Synthetic Agent. XII.[1] A Convenient Synthesis of Nitriles by the Dehydration of Amides with PPE

Yuichi Kanaoka, Takeshi Kuga and Kazutaka Tanizawa

Faculty of Pharmaceutical Sciences, Hôkkaido University[2]

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Two of the most familiar methods of introducing a cyanide group functionally into a given molecule are the conversion of halide or amide by substitution or elimination reaction, respectively.[3a–c] The latter, the dehydration of amides, is probably the best known of the elimination reaction for the preparation of nitriles.[3] For example, the dehydration with phosphorus pentoxide has been used for many years and good yields have often been reported. However, the method involves a dry distillation process and is sometimes encountered practically by "messy"[3c] results.

In the course of our studies on proteolytic enzymes, we have prepared a series of amidine derivatives as synthetic substrates and inhibitors of trypsin.[4] Various nitriles were required as intermediates for the synthesis of these amidines. In an effort to improve these yields of nitriles, a study of the dehydration of amides was undertaken. Many dehydrating agents have been suggested for the reaction,[3a–c] *i.e.*; phosphorus pentoxide, phosphorus oxychloride, phosphorus pentachloride, boron trifluoride, silica gel with heating, phosphorus pentachloride with *p*-toluenesulfonamide,[3a] and *p*-toluenesulfonyl chloride in pyridine.[5] Since polyphosphate ester (PPE) has been shown to be a good dehydrating agent for a variety of condensation reactions in this laboratory,[6] the reagent is now applied to the synthesis of nitriles from amides.[7]

A chloroform solution of benzamide, a simple primary amide, was refluxed with PPE of five parts in weight. In a period of 2 hr, the amide disappeared as monitored by thin-layer chromatography, and benzonitrile was isolated from the reaction mixture after purification through column chromatography with silical gel in 87% yield. In a like manner, benzamide derivatives with various substituents as well as β-naphthamide were converted into nitriles usually in good yields. Aliphatic amides, such as amides of cyclopentane- or cyclohexanecarboxylic acid and phenyl acetic acid, were also readily dehydrated in the presence of PPE to give corresponding nitriles. As examples of amides possessing heterocycles, nicotinamide and isonicotinamide were subjected to the reaction. Nitriles were obtained though the yields

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6) Papers in this series. For a review see: Y. Kanaoka, *Kagaku*, **24**, 234 (1969).
7) Mukaiyama, *et al.* prepared mixtures of alcohol and P_4O_{10}, which were employed as a dehydrating agent, for example, for aldoxime to give nitrile.[8] However, this mixture failed to dehydrate benzamide to nitrile.[8]
8) T. Mukaiyama and T. Hata, *Bull. Chem. Soc. Japan*, **34**, 99 (1962).

were rather moderate. Furancarboxamide-2, however, resisted to dehydration. When treated with PPE, the amide was recovered even after prolonged heating.

o- and *m*-Hydroxybenzonitriles were required as intermediates to amidines. Conventional dry distillation of *p*-hydroxybenzamide with phosphorus pentoxide gave the product in only 10% yield. By the PPE method, however, the nitrile was obtained ultimately in 67% yield although long reaction time was necessary due to low solubility of the substrate in chloroform.

In conclusion, the PPE method presents a convenient procedure for the synthesis of nitriles. Table I summarizes the results obtained. It must be noted that PPE, prepared

Table I. Preparation of Nitriles by the Dehydration of Amides[a]

Substrate	Product	Reaction time (hr)[b]	Yield (%)	mp (°C)	IR (CN) (cm^{-1})[t]
Benzamide	benzonitrile	2	87	bp 105 (115 mmHg)	2280[u]
m-Nitrobenzamide	*m*-nitrobenzonitrile	2	82	116—117 (118)[e]	2270
p-Nitrobenzamide	*p*-nitrobenzonitrile	2	90	148—149 (149)[f]	2280
o-Chlorobenzamide	*o*-chlorobenzonitrile	2	95	42 — 43 (42—43)[g]	2260
m-Hydroxybenzamide	*m*-hydroxybenzonitrile[c]	4	64	84.5— 86 (87)[h]	2280
p-Hydroxybenzamide	*p*-hydroxybenzonitrile[c]	2	35	110 —111 (113)[i]	2280
		5	65		
m-Methoxybenzamide	*m*-methoxybenzonitrile	2	88	bp 160 —168 (120 mmHg) (111 —112 (12—13 mmHg))[j]	2270[u]
p-Methoxybenzamide	*p*-methoxybenzonitrile	2	91	56 — 57 (59)[k]	2280
2,3-Dimethoxybenzamide	2,3-dimethoxybenzonitrile	2	41	44 — 45 (47)[l]	2260
		4	70		
β-Naphthamide	*β*-naphthonitrile	2	90	64 — 65 (66)[m]	2270
Cyclopentanecarboxamide	cyclopentanecarbonitrile	2.5	83	bp 95 —100 (100 mmHg) (170 —171 (760 mmHg))[m]	2270[u]
Cyclohexanecarboxamide	cyclohexanecarbonitrile	2	84	bp 102 —109 (95 mmHg) (187 —187.5(728 mmHg))[o]	2270[u]
Phenylacetoamide	phenylacetonitrile	2	95	bp 105 —107 (10—15 mmHg) (233 —234 (760 mmHg))[p]	2290[u]
2-Furamide	2-furonitrile	12	10	bp 95 —102 (100 mmHg) (146 —148 (760 mmHg))[q]	2280[u]
Nicotinamide	nicotinonitrile[d]	3	53	47 — 48 (48)[r]	2270
Isonicotinamide	isonicotinonitrile[c]	7	43	75.5— 77 (79)[s]	2280

a) Elution solv. was benzene unless otherwise stated. *b*) reflux in chloroform
c) elution solv.; benzene:AcOEt=2:1 *d*) elution solv.; ether
e) A.Claus, *J. Prakt. Chem.*, (2), **51**, 400 (1912) *f*) W.Borsche, *Ber.*, **42**, 3597 (1909)
g) L.Henry, *Ber.*, **2**, 492 (1868). *h*) H.J. Smith, *J. Prakt.Chem.*, (2), **16**, 221 (1877)
i) O. Hartmann, *J. Prakt. Chem.*, (2), **16**, 55 (1877)
j) W.H. Carothers, C.F. Bickford and G.J. Hurwitz, *J. Am. Chem. Soc.*, **49**, 2912 (1927)
k) E. Bamberger and W. Pemsel, *Ber.*, **36**, 370 (1904) *l*) W. Baker and F.M. Fastwood, *J. Chem. Soc.*, **1929**, 2907
m) K. Gasiorowski and V. Merzi, *Ber.*, **18**, 1008 (1884) *n*) C. Gärtner, *Ann.*, **275**, 335 (1893)
o) N. Demjanow, *Chemishes Zentralblatt*, **1904**, I 1214 *p*) S. Cannizzaro, *Ann.*, **96**, 247 (1855)
q) O. Wallach, *Ann.*, **214**, 227 (1882) *r*) H. Meyer, *Monatshefte für Chemie.*, **23**, 901 (1905)
s) H. Meyer, *Monatshefte für Chemie.*, **23**, 903 (1905) *t*) nujol *u*) direct

from phosphorus pentoxide and ether,[9] is a good dehydrating agent for amides, whereas a mixture of phosphorus pentoxide and alcohol behaved differently.[7,8] While the former is regarded to be aprotic medium, the latter is apparently protic. The marked difference observed above may be interpreted as being due to the nature of this dehydration, which would be very sensitive to such a variation of the reaction media.

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Experimental

Synthesis of Primary Amides——Primary amides were prepared from carboxylic acids by way of acid chloride followed by ammonolysis as usual. Acid chlorides were prepared by conventional method using thionyl chloride or phosphorus pentachloride. Since isonicotinic acid resisted to chlorination by heating with thionyl chloride even for 49 hr, adaptation of Bosshard's method was made, in which dimethylformamide was used as a catalyst.[10]

p- and *m*-Hydroxybenzamide were prepared by heating respective ethyl esters with conc. NH_3 in an autoclave.

General Procedure for the Preparation of Nitriles (*cf.* Table I)——A solution of amide (1 part) and PPE[9] (5 parts in wt.) in chloroform was refluxed until the substrate disappeared (usually within 2 hr). The solvent was evaporated *in vacuo* and the residues was treated with 30% Na_2CO_3 solution (10 parts) with stirring and cooling for 1 hr to decompose excess of PPE. The reaction mixture was extracted with ether and extract was washed with water, dried with Na_2SO_4 and evaporated *in vacuo* to leave crude product. To separate phosphorylated impurities the above residue was purified through a column chromatography (silica gel of 10—15 parts of the product in wt.—benzene). On evaporation of the solvent *in vacuo* nitrile was obtained in practically pure state. When a product is solid of relatively high mp, such as *p*-nitrobenzonitrile, one recrystallization of the precipitate from the reaction mixture may usually be enough to give nearly pure nitrile.

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Reactivities of Radiation-Protective Aminoalkylisothiuronium Salts. VI.[1] Estimation of the Stability of N-Substituted Derivatives of 2-Aminoethylisothiuronium Salt from the Potentiometric Titration Curve

Akira Hanaki

National Institute of Radiological Sciences[2]

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The potentiometric titration curve of 2-aminoethylisothiuronium (AET) salt, a prototype of the radiation-protective aminoalkylisothiuronium salt,[3] displays different patterns depending on the rate of alkali addition.[4] This phenomenon was explained as a result of the transformation reactions of this compound, which include both the transguanylation to yield 2-mercaptoethylguanidine (MEG) and the cyclization to 2-amino-2-thiazoline (2-AT).[5] Both the ionized AET, *i.e.*, the acid-dissociated form, and the cyclization product are able to associate with free hydrogen ion to form corresponding conjugate bases, while the transguanylation product has not an ability to associate with hydrogen ion. Therefore, when the AET solution which had been titrated with alkali was neutralized with equimolar hydrochloric acid to the alkali added, a portion of the acid corresponding to the amounts of the transguanylation product becomes surplus and was titrated as free acid.[5] The amount of free hydrogen ion thus determined is in parallel with the instability of the isothiuronium salt. The present paper concerned with the stabilities of N-substituted derivatives of AET estimated from the potentiometric titration curve.

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