[Chem. Pharm. Bull. 16 (2) 280—284 (1968)]

UDC 546.185.04 : 547.551.42

Polyphosphate Ester as a Synthetic Agent. VII.[1] The Beckmann Rearrangement and Formation of Amidines with PPE

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(Received April 24, 1967)

Polyphosphate ester (PPE) was shown to be a good reagent for the Beckmann rearrangement of some ketoximes, whereas dehydration took place in the case of benzaldoximes. When some ketoximes were heated with PPE, N,N′-diphenylamidines (IVa, b) were formed as a result of a sequence of condensation reactions.

In the series of this work it has been shown that polyphosphate ester (PPE) is a good general agent for a variety of dehydrating condensation reactions.[3] Further, PPE was successfully used to effect the Fischer indole synthesis, an acid-catalyzed rearrangement of arylhydrazones.[4a,b] The present paper reports the application of PPE to the Beckmann rearrangement, another example of acid-catalyzed rearrangement reaction. This classic reaction involving rearrangement to an electron-deficient nitrogen atom has been the subject of recent reviews.[5,6]

Acetophenone oxime (Ia), which is known to exist in only one form[7] and to give almost invariably acetanilide as the major product,[8,9] was selected as a substrate of this work. By warming for five minutes in the presence of PPE in chloroform solution, Ia was readily transformed into acetanilide (IIa), though the yield was moderate.

In general, diaryl ketoximes can be rearranged easily with common catalysts.[10] Thus, benzophenone oxime (Ib) was treated similarly with PPE to give benzanilide (IIb) in good yield. The very mild conditions and simple procedure, as described above and shown in Table I and Chart 1 (I→II), indicate that this method may be generally employed for this reaction.

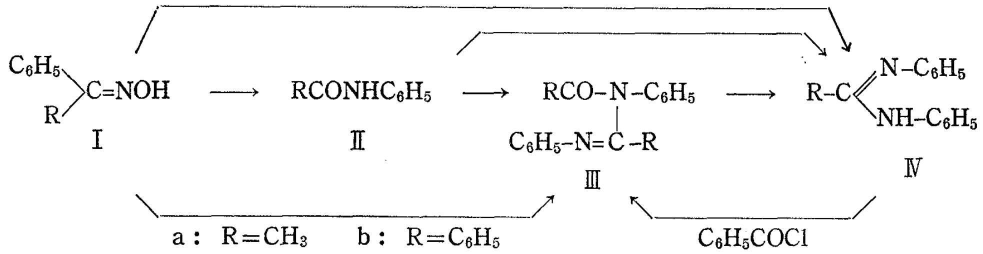

Chart 1

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[1] Part VI: Y. Kanaoka, E. Sato, and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **15**, 101 (1967).
[2] Location: *Kita-12, Nishi-6, Sapporo.*
[3] Y. Kanaoka, papers of this series.
[4] *a*) Y. Kanaoka, Y. Ban, O. Yonemitsu, K. Irie, and K. Miyashita, *Chem. Ind.* (London), 473 (1965). *b*) Y. Kanaoka, Y. Ban, K. Miyashita, K. Irie, and O. Yonemitsu, *Chem. Pharm. Bull.* (Tokyo), **14**, 934 (1966).
[5] L.G. Donaruma and W.Z. Heldt, "Organic Reactions (ed. R. Adams)," **11**, p. 1, 1960, J. Wiley, N.Y.
[6] P.A.S. Smith, "Molecular Rearrangements (ed. P. de Mayo)," part 1, p. 457, 1963, J. Wiley, N.Y.
[7] E.C. Horning and V.L. Stromberg, *J. Am. Chem. Soc.*, **74**, 5151 (1952).
[8] ref. 5, p. 17.
[9] ref. 6, p. 505.
[10] ref. 5, p. 21.

In the course of exploring experimental conditions a reaction mixture was heated at 130° for three hours, from which a crystalline product of mp 169—170° was isolated as a major product. This compound was eventually proven to be N,N′-diphenylbenzamidine (IVb) by direct comparison with the authentic specimen prepared from IIb by reaction with phosphorus pentachloride to give benzanilideimidochloride (V) followed by aminolysis with aniline.

Stephen reported that amidines occur as by-products of the rearrangement of diaryl ketoximes in up to 20% yield.[11] Several reagents having chloride, such as acetyl chloride or hydrogen chloride were shown to effect this transformation, among which thionyl chloride in ether was a reagent of choice. This process was discussed in terms of the sequence of intermediate reactions involving successive formation of imidochloride (V), amidodichloride (VI) and their condensation product (VII) as illustrated in Chart 2.[11]

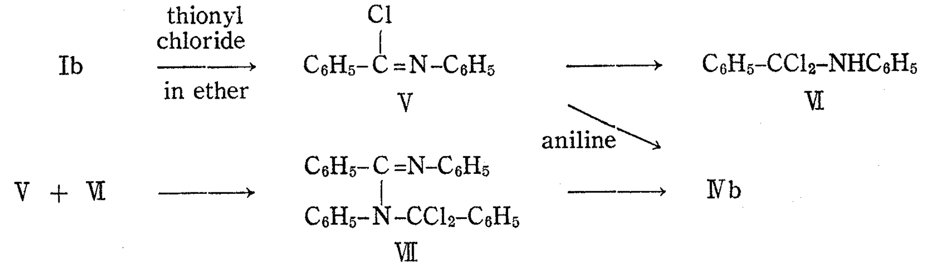

Chart 2

Since the amidine (IVb) contains two nitrogen atoms, the formation of IVb from Ib by means of PPE must involve combination of two molecules of element of oxime. Therefore, benzanilide (IIb), the most probable initial intermediate, was subjected to treatment with PPE in order to clarify the course of the transformation (I→IV). When IIb was heated in the presence of PPE under the same conditions as above, IVb was obtained in 84% yield. Additionally, the treatment of IIb under milder conditions resulted in successful trapping of the second intermediate, IIIb, the structure of which was confirmed by independent synthesis from IVb. IIIb was earlier considered to be a key intermediate in the conversion of Ib to IVb with thionyl chloride by Stephen, but had not been obtained by attempted hydrolysis of VII.[11] Apparently the mild dehydrating medium of PPE made the isolation of IIIb possible. Under similar mild reaction conditions Ib was also converted to IIIb. The formation of IVb from Ib is thus reasonably explained by the sequence of reactions as shown in Chart 1. N,N′-Diphenylacetamidine (IVa) was also obtained from acetanilide (IIa) in a similar manner. Table I summarizes experimental data of the related reactions.

Table I. The Sequence of Reactions forming Amidines from Oximes[a]

Starting material	Product	Temp. (°C)	Time (hr)	Yield (%)
Ia	IIa	water-bath	5 min	77
Ib	IIb	water-bath	5 min	91
Ib	IIIb	water-bath	0.5	52
Ib	IVb	130	3	46
IIa	IVa	130	3	62
IIb	IIIb	water-bath	0.5	60
IIb	IVb	130	3	84
IIIb	IVb	130	3	59

a) *cf.* Chart 1.

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11) H. Stephen and W. Bleloch, *J. Chem. Soc.*, **1931**, 886.

From these results it may be concluded that the formation of amidines from certain oximes or corresponding amides is a general dehydration reaction not limited to ones effected by chlorine-containing reagents. Another interesting implication of the observation may be that certain amide compounds can undergo intermolecular condensation reaction by activation with PPE, a special non-aqueous medium with dehydrating capacity. Parallel studies are being undertaken in our laboratory on the possible dehydration reaction of some peptide chain in the medium of PPE,[12] in connection with our basic studies on chemical modification of proteins.[13]

The Beckmann rearrangement of aldoximes usually leads to formation of unsubstituted amides. Only rarely has the isolation of substituted formamides been reported.[14a] It was also recognized early that aldoximes can be dehydrated readily under conditions of the rearrangement to form nitriles, a process known as an example of Beckmann fragmentation.[14a,b]

Horning, *et al.* found that polyphosphoric acid (PPA), a closely related substance to PPE in the nature, is an effective reagent for the Beckmann rearrangement.[7,15a,b,16] For example, when heated with PPA at 130°, *anti*-benzaldoxime (IX) was converted to benzamide (XII), whereas *syn*-benzaldoxime (VIII) yielded a mixture of XII and formanilide (X). This results were interpreted by partial isomerization of the *syn*-oxime (VIII) to the *anti*-isomer (IX) in contact with PPA as shown in Chart 3.[7]

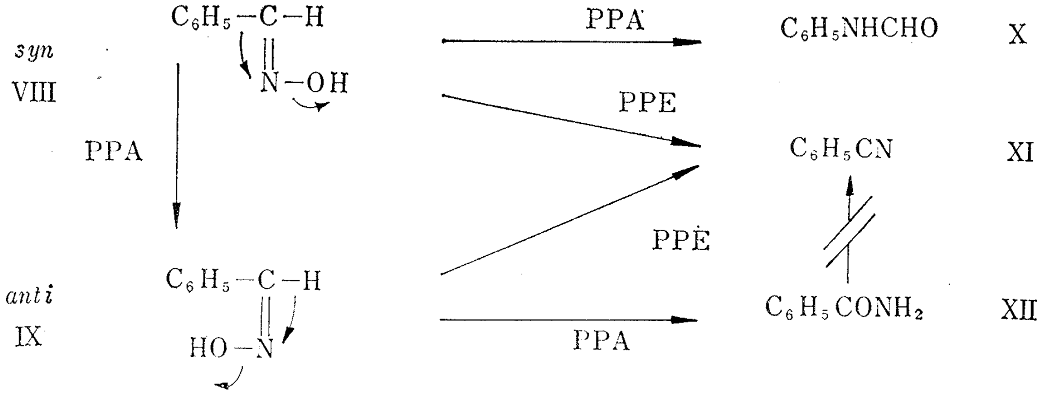

Chart 3

Since PPE is considered to be aprotic medium unlike PPA,[17] it seemed conceivable that isomerization of aldoximes in a medium of PPE occurs at least in less extent than in that of PPA. Benzaldoximes were, therefore, treated with PPE in the hope of conducting the rearrangement stereospecifically without isomerization during reaction. *syn*-Benzaldoxime (VIII) was prepared from *syn*-benzaldoxime hydrochloride by neutralization. Nuclear magnetic resonance spectrum of VIII was consistent with the data reported recently.[18] *anti*-Benzaldoxime hydrochloride was prepared from VIII by careful treatment with the acid, whereas free *anti*-benzaldoxime (IX), obtained by neutralization of the corresponding hydrochloride, showed contamination of the isomeric oxime (VIII) as detected by NMR determination, although the sample prepared immediately before measurement had mp 102—105°,

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[12] Y. Kanaoka, T. Hamada, and O. Yonemitsu, in preparation.
[13] Y. Kanaoka and O. Yonemitsu, to be published in a series of papers.
[14a] ref. 5, p. 42, 43. *b*) ref. 6, p. 504.
[15a] E.C. Horning and V.L. Stromberg, *J. Am. Chem. Soc.*, 74, 2680 (1952). *b*) E.C. Horning, V.L. Stromberg, and H.A. Lloyd, *J. Am. Chem. Soc.*, 74, 5153 (1952).
[16] F.D. Popp and W.E. McEwen, *Chem. Rev.*, 58, 370 (1958).
[17] Y. Kanaoka, M. Machida, O. Yonemitsu, and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), 13, 1065 (1965).
[18] E. Buehler, *J. Org. Chem.*, 32, 261 (1967).

close to that in lit.[19] (103—105°). Therefore, hydrochloride of IX was directly used as a substrate in the experiment.

Attempted rearrangement of benzaldoximes (VIII and IX) with PPE yielded solely benzonitrile (XI) as a result of dehydration even under mild conditions. From *syn*-benzaldoxime (VIII), by refluxing in chloroform solution for five minutes in the presence of PPE, XI was obtained in 80% yield. Hydrochloride of *anti*-benzaldoxime (IX), also gave only XI in 80% yield. To test the possibility that XI was produced from IX by way of XII, XII was allowed to react under similar conditions. Nearly quantitative amount of XII was recovered unchanged to exclude the pathway *via* XII.

According to the well-accepted *trans*-migration mechanism of the Beckmann rearrangement,[20a,b] X and XII were expected as the product from the reaction of VIII and IX, respectively. However, competing dehydration reaction took place very readily before rearrangement, and neither X nor XII was detected in the reaction product as summarized in Chart 3. No information was thus available on the equilibrium between oxime isomers in the medium of PPE. The good dehydrating ability of PPE, in accord with the work by Mukaiyama, *et al.* with mixtures of phosphorus pentoxide and alcohols,[21] obviously favored the competing dehydration of benzaldoximes to give XI as the major product in the reaction.

Experimental[22]

The Beckmann Rearrangement of Acetophenone Oxime——To a solution of acetophenone oxime (Ia) (1.35 g; 10 mmoles) in chloroform (6 ml) was added PPE[17] (6 g) and the mixture was refluxed for 5 min. Exothermic reaction was observed when heating was started. The reaction mixture was cooled, cold water (2 ml) was added and most of chloroform was evaporated *in vacuo* at room temp. Cold water (30 ml) was added followed by stirring for 3 hr to decompose excess of PPE, and the whole was made alkaline with powdered $NaHCO_3$, extracted with benzene, the extract being washed with satd. aq. NaCl, dried with Na_2SO_4 and evaporated *in vacuo*. Recrystallization of the residue from water gave acetanilide (IIa) as colorless needles of mp 112—114°; 1.05 g.

The Beckmann Rearrangement of Benzophenone Oxime——To a solution of benzophenone oxime (Ib) (493 mg) in chloroform (5 ml) was added PPE (0.7 g) and the mixture was refluxed for 5 min. After cooling the solvent was evaporated *in vacuo* below 30°, and the residue was mixed with ice-water followed by stirring for 1 hr. The precipitate was collected by suction, washed with water and dried to give fairly pure benzanilide (IIb) (mp 155—157.5°); 448 mg.

N-Benzoyl-N,N′-diphenylbenzamidine (IIIb)——i) From IVb[23]: Authentic sample of IIIb was prepared by benzoylation of IVb with benzoyl chloride in pyridine solution as described.[23] Recrystallization from EtOH gave IIIb as colorless needles of mp 169—170° (lit.,[23] mp 171°).

ii) From Ib with PPE: A mixture of Ib (493 mg) and PPE (5g) was warmed in water-bath under stirring for 30 min. After cooling ice-water was added followed by stirring for 1 hr and the precipitate was collected, dried and recrystallized from EtOH to give IIIb forming colorless needles of mp 168—169.5°; 243 mg. One more recrystallization gave analytical sample of mp 169.5—171°. *Anal.* Calcd. for $C_{26}H_{20}ON_2$ (IIIb): C, 82.95; H, 5.36; N, 7.44. Found: C, 82.88; N, 5.59; N, 7.31. This compound was shown to be identical with the sample obtained above (i) by mixed mp and IR comparison.

iii) From IIb with PPE: IIb (493 mg) was reacted as above to yield IIIb (282 mg); mp 169—170.5°.

N,N′-Diphenylbenzamidine (IVb)——i) From benzanilide (IIb): Authentic specimen of IVb was synthesized from IIb *via* V as described.[24] Colorless needles of mp 144—145° from 80% EtOH.

ii) From benzophenone oxime (Ib) with PPE: A mixture of Ib (985 mg) and PPE (10 g) was heated at 130° for 3 hr. After cooling ice-water was added to decompose excess of PPE and the whole was stirred for 30 min, extracted with EtOAc, the extract being washed with aq. $NaHCO_3$, water, dried with Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from aq. EtOH to give IVb as colorless needles of mp 144.5—145°; 314 mg. *Anal.* Calcd. for $C_{19}H_{16}N_2$ (IVb): N, 10.29. Found: N, 10.27. This compound was shown to be identical with the sample obtained above (i) by mixed mp and IR comparison.

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[19] C.M. Luxmoore, *J. Chem. Soc.*, **69**, 177 (1896).

[20*a*] ref. 5, p. 5. *b*) ref. 6, p. 486.

[21] T. Mukaiyama and T. Hata, *Bull. Chem. Soc. Japan*, **34**, 99 (1961).

[22] Melting points are uncorrected.

[23] H.L. Wheeler and T.B. Johnson, *Am. Chem. J.*, **30**, 36 (1903).

[24] Org. Syn., Coll. vol. 4, 383 (1963).

iii) From IIb with PPE: IIb (493 mg) was heated with PPE (5 g) as in the case of ii). The EtOAc layer was extracted with 10% HCl three times and the combined aq. extracts was made alkaline with excess of $NaHCO_3$. The precipitate was collected by suction, washed with water and recrystallized from aq. EtOH to give IVb; 284 mg.

iv) From IIIb with PPE: IIIb (104 mg) was reacted as in the case of iii) to give IVb; 45 mg.

N,N′-Diphenylacetamidine (IVa)——A mixture of acetanilide (IIa; 1.35 g) and PPE (6 g) was heated at 130° for 3 hr. After cooling ice-water was added and the whole was stirred for 30 min, extracted with benzene and the aq. layer was made alkaline by adding excess of powdered $NaHCO_3$, extracted with benzene, the extract being washed with water, dried with Na_2SO_4 and evaporated *in vacuo*. The residue was recrystallized from aq. EtOH forming colorless needles of mp 128—130° (lit.,[25] mp 131—132°); 654 mg. *Anal.* Calcd. for $C_{14}H_{14}N_2$ (IVa): C, 79.96; H, 6.71; N, 13.32. Found: C, 79.74; H, 6.43; N, 13.12.

***syn*-Benzaldoxime (VIII)**——Asolution of hydroxylamine hydrochloride (10.5 g; 0.15 mole) in water (30 ml) was mixed with c. HCl (30 ml) and to this mixture was added benzaldehyde (10.6 g; 0.1 mole) portionwise under shaking. Shaking was continued for 30 min, while oily aldehyde gradually solidified, and the precipitate was collected after cooling. Recrystallization from chloroform–petroleum ether gave *syn*-benzaldoxime hydrochloride forming colorless needles of mp 64—65° (lit.,[26] mp 66°; lit.,[19] mp 66—67°); 12.3 g. The hydrochloride was suspended in water and the mixture was extracted with ether. The extract was washed with satd. aq. NaCl, dried with Na_2SO_4 and evaporated. The residual oil was purified by distillation to give VIII as colorless solid of bp 95—98°(5 mmHg) and mp 33—34° (lit.,[19] bp 118—119° (10 mmHg); mp 34°); 8.5 g or 80%. The NMR spectrum of VIII showed absorption at 2.35 (2H: aromatic *o*-H), 1.83 (1H, singlet: oxime CH), 2.55 τ (3H: aromatic *m*-, *p*-H), obtained in DMSO-d_6 with a Hitachi Model H-60 NMR spectrometer with tetramethylsilane as an internal standard (lit.,[18] 2.28 (2H), 1.70 (1H), and 2.52 τ (3H), with the same assignment).

***anti*-Benzaldoxime (IX)**——The above *syn*-oxime (2.5 g) was mixed with c. H_2SO_4 (13 ml) and water (1.3 ml) and the mixture was stirred for 10 min. Cold water (80 ml) was added and the whole was extracted with ether, the extract was washed with satd. aq. NaCl, dried with Na_2SO_4 and evaporated. The oily residue was dissolved in abs. ether (20 ml) through which dry HCl was introduced under cooling. The white precipitate was collected, washed with abs. ether, and dried to give *anti*-benzaldoxime hydrochloride as colorless needles of mp 102—105°; 2.85 g or 89% (lit.,[19] mp 103—105°).

The Attempted Rearrangement of VIII and IX; Dehydration to form XI:——i) From VIII: A solution of VIII (2.420 g) in chloroform (10 ml) was treated with PPE (13 g) as in the case of Ia. After decomposing excess of PPE with cold water, the whole was extracted with benzene, the extract being washed with 10% NaOH, and satd. aq. NaCl, dried with Na_2SO_4 and evaporated *in vacuo*. The residual oil was purified by distillation to give benzonitrile (XI) (bp 92—94° (39 mmHg)); 1.654 g or 80%. IR cm^{-1} (liquid): ν_{max} 2340 (C≡N). The crude oil before distillation contained no appreciable amount of amide compound as measured by IR.

ii) From the hydrochloride of IX: The hydrochloride of IX (2.450 g) was dissolved in chloroform (10 ml) and treated with PPE (10 g) as above. Benzonitrile was obtained as colorless oil of bp 103—106° (44 mmHg); 1.262 g or 80%.

Treatment of Benzamide with PPE——Benzamide (602 mg) was dissolved in chloroform (10 ml) and treated with PPE and worked up as above to recover the starting material (520 mg). The crude product contained no appreciable amount of nitrile as measured by IR.

Acknowledgement We are indebted to Mrs. T. Toma and Miss A. Maeda for elemental analyses. This work was supported by a grant from the Ministry of Education, Japan, and a grant (MH 08187-04) from the United States Public Health Service, which are gratefully acknowledged.

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[25] E. Bamberger and J. Lorenzen, *Ann.*, **273**, 300 (1893).

[26] A. Lapworth, *J. Chem. Soc.*, **91**, 1137 (1907).