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Polyphosphate Ester as a Synthetic Agent. XIII.[1) Syntheses of 2-Substituted Benzoxazoles and Benzthiazoles with PPE

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Polyphosphate ester (PPE) was demonstrated to be a good agent in the benzazole synthesis. Benzoxazoles and benzthiazoles were prepared from *o*-substituted anilines and free carboxylic acids under mild conditions. Mechanisms for this reaction were briefly discussed.

Benzazoles, nitrogen heterocycles possessing a general formula **3** of the parent ring system, are often synthesized from bifunctional compounds **1**, *o*-substituted anilines, as shown in Chart 1. The carbon atom C_2 of **3** between two hetero atoms, N and X, is on the oxidation level of carboxylic acid. Thus a number of derivatives of carboxylic acid **2** with appropriate leaving groups, including carboxylic acid itself, have been employed to combine with **1** to form **3**,[3) from which only a recent example with a mixed anhydride[4) may be cited here.

a: X=O b: X=S c: X=NH

Chart 1

When carboxylic acid is used as a starting compound, the carboxyl group must be activated either thermally or by means of some reagent. In Ladenburg's procedure,[5) a prototype of this kind of synthesis (Chart 1), a mixture of components was heated usually around 200° to form **3**a or **3**c. Aqueous hydrochloric acid was later used as acid-catalyst in the preparation of benzimidazoles **3**c, the well-known Phillips' method.[6) However, this modification has been successful neither for the preparation of benzoxazoles **3**a nor benzthiazoles **3**b. The former **3**a is, for example, unstable to hot aqueous acid[7) and the oxazole ring is easily solvolyzed under the conditions. Recently polyphosphoric acid (PPA) was used to prepare **3**a—c although rather high reaction temperature (~200°) is required.[8)

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1) Part XII: Y. Kanaoka, T. Kuga and K. Tanizawa, *Chem. Pharm. Bull.* (Tokyo), **18**, 397 (1970).
2) Location: *Kita-12, Nishi-6, Sapporo.*
3) *a*) T.W. Cornforth, "Heterocyclic Compounds," Vol 5, ed. R.C. Elderfield, John Wiley & Sons, Inc., 1957, p. 420; *b*) J.M. Sprague and A.H. Land, *ibid.*, p. 506; *c*) E.S. Schipper and A.R. Day, *ibid.*, p. 274.
4) H. Quast and E. Schmitt, *Chem. Ber.*, **102**, 568 (1969).
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6) M.A. Phillips, *J. Chem. Soc.*, **1928**, 2393.
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Polyphosphate ester (PPE) has been amply shown to be a good synthetic agent for a variety of dehydrating condensation reactions.[9] In our earlier paper, it was reported that benzimidazoles **3**c are prepared from carboxylic acids **2** and *o*-phenylenediamines **1**c by means of PPE under mild conditions.[10] In extension of this work, the present paper deales with a convenient synthesis of benzazoles **3a**—**b** from carboxylic acids **2** with PPE as a condensing agent.

In a typical experiment, a mixture of *o*-aminophenol (**1a**,) benzoic acid and PPE[11] was heated at 100° (bath-temperature) for 30 min. 2-Phenylbenzoxazole was obtained in 70% yield. Similarly, several aromatic acids with substitutent groups gave corresponding 2-arylbenzoxazoles in moderate yields. Acetic acid formed 2-methylbenzoxazole by heating for only 10 min. Table I summarizes the results obtained by this method. In the presence of PPE, *o*-aminothiophenols (**1b**) undergo the reaction with carboxylic acids even more readily.

TABLE I. Synthesis of 2-Substituted Benzoxazoles 3a

Substrate	Temp. (°C)	Time (min)	Benzoxazole R in **3a**	mp[a] (°C)	Yield (%)	UV λ_{max} mμ(log ε)
Benzoic acid	100	30	phenyl	102—103(E)[b]	70	234(3.86) 292(4.34) 299(4.35)
p-Chlorobenzoic acid	120	20	*p*-chlorophenyl	151—152(E)[c]	57	297(4.49) 304(4.51)
p-Acetoamidobenzoic acid	100	30	*p*-acetamidophenyl	217 (C)[d]	44	316(4.51)
p-Nitrobenzoic acid	120	30	*p*-nitrophenyl	264—265(C)[e]	50	232(4.11) 327(4.32)
Acetic acid	100	10	methyl	bp 115 (30 mmHg)(E)[f]	75	231(3.91) 264(3.43) 270(3.61) 276(3.64)

a) Recrystallized from ethanol(E) or chloroform(C). *b*) lit.,[12] mp 102—103° *c*) lit.,[12] mp 150—151°
d) lit.,[13] mp 212° *e*) lit.,[12] mp 268—269° *f*) lit.,[14] bp 98° (25 mmHg)

TABLE II. Synthesis of 2-Substituted Benzthiazoles 3b

Substrate	Temp.	Time (min)	Benzthiazole R in **3b**	mp[a] (°C)	Yield (%)	UV λ_{max} mμ (log ε)
Benzoic acid	refl. in $CHCl_3$	30	phenyl	112—113 (E)[b]	77	297 (4.29)
p-Nitrobenzoic acid	100°	30	*p*-nitrophenyl	229 (C)[c]	50	334 (4.35)
Furan-2-carboxylic acid	refl. in $CHCl_3$	60	2′-furyl	102—104 (E)[d]	64	317 (4.39)
Nicotinic acid	refl. in $CHCl_3$	60	3′-pyridyl	127—128[e]	68	300 (4.25)
Acetic acid	refl. in $CHCl_3$	30	methyl	bp 105 (7 mmHg)[f]	73	283 (3.24) 293 (3.15)

a) Recrystallized from ethanol (E) or chloroform(C). *b*) lit.,[8] mp 113—114° *c*) lit.,[15] mp 227°
d) lit.,[16] mp 105° *e*) lit.,[17] mp 127° *f*) lit.,[14] bp 118° (30 mmHg)

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9) For a review see: Y. Kanaoka, *Kagaku*, **24**, 234 (1969) (in Japanese).
10) Y. Kanaoka, O. Yonemitsu, K. Tanizawa and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **12**, 773 (1964).
11) Y. Kanaoka, M. Machida, O. Yonemitsu and Y. Ban, *Chem. Pharm. Bull.* (Tokyo), **13**, 1065 (1965).
12) K. Nakagawa, H. Onoue, and J. Sugita, *Chem. Pharm. Bull.* (Tokyo), **12**, 1135 (1964).
13) F.F. Stepens and J.D. Bower, *J. Chem. Soc.*, **1949**, 2971.
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17) K. Wallenfels, M. Gellrich and F. Kubowitz, *Ann.*, **621**, 137 (1959).

As shown in Table II, the formation of benzthiazoles **3b** did occur by refluxing in chloroform solution for 30—60 min. This enhanced reactivity of **1b** may be ascribed to higher nucleophilicity of the mercapto group of **1b** than that of the hydroxyl group of **1a**. Thus 2-substituted benzthiazoles **3b**, including those carrying heterocyclic substitutents, such as furan and pyridine, were very easily prepared by this procedure.

A number of mechanisms can be considered for this reaction as outlined in Chart 2[3,10,18,19]. Addition of amino group to the carboxylic acid may give an adduct **4**, which can eliminate water leaving the N-monoacyl derivative **5**. Subsequent intramolecular nucleophilic attack by XH group can then lead to the cyclic carbinolamine **6** which, by elimination of water, gives benzazoles **3**. Initial adduct **4** could also cyclize directly to **6**. Alternatively, further acylation of **5** leads to the diacyl compound **7** which might, by cyclization and a facile hydrolysis, give the final product **3**. Of course it is also possible that initial reaction takes place at XH group instead of amino group leading to the parallel reaction sequence involving adduct **8** and monoacyl derivative **9**. Cyclization or further acylation gives rise to the same intermediate **6** or **7**.

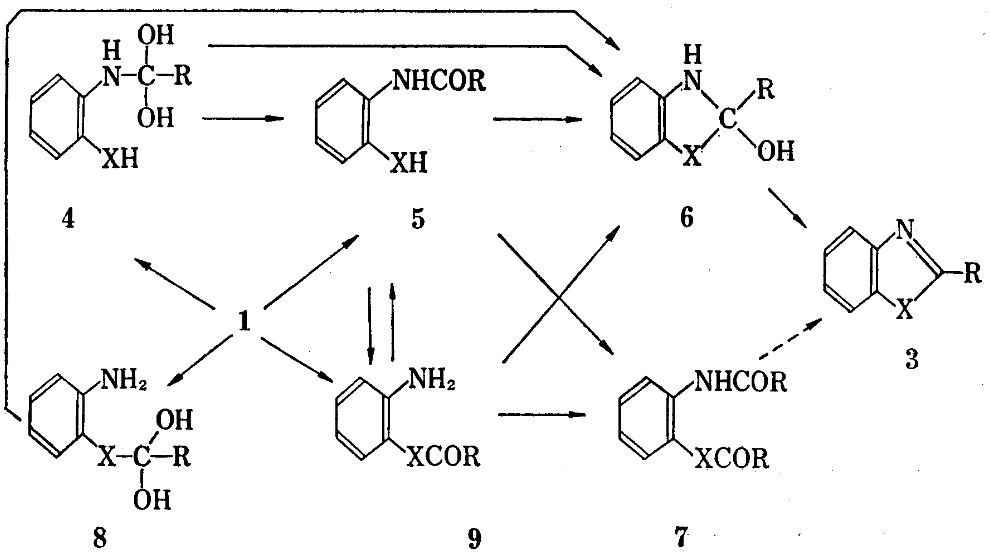

Chart 2

To examine the route from **7** to **3**, diacyl derivatives **7** (X=O; R=Me or Ph) were prepared and treated with PPE. Under the reaction conditions as above, diacetyl derivative was transformed into 2-methylbenzoxazole very slowly, while dibenzoyl derivative resisted to cyclization. These results indicate that the route involving diacyl compound **7** is not important. In fact, small amount of dibenzoylaminophenol was isolated as by-product in the preparation

TABLE III. Benzoxazoles from Acyl-Derivatives of *o*-Aminophenol **1a**

o-Aminophenols	Temp. (°C)	Time (min)	Benzoxazole R in 3a	Yield (%)
N-Benzoyl-[21]	refl. in $CHCl_3$	40	C_6H_5	20
O,N-Dibenzoyl-[21]	refl. in $CHCl_3$	240	C_6H_5	—
N-Acetyl-[22]	refl. in $CHCl_3$	40	CH_3	70
O,N-Diacetyl-[23]	refl. in $CHCl_3$	40	CH_3	15
O,N-Diacetyl-[23]	refl. in $CHCl_3$	180	CH_3	58

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18) J.B. Wright, *Chem. Rev.*, **48**, 307 (1951).

19) K.J. Morgan and A.M. Turner, *Tetrahedron*, **25**, 915 (1969).

of 2-phenylbenzoxazole. When treated with benzoic acid in the presence of PPE under milder conditions, *o*-aminophenol gave N-benzoyl derivative **5a** in 13% yield, which was, on further treatment with PPE, transformed into 2-phenylbenzoxazole in support of the mechanism by way of **5** (or **9**). N-Acetyl-*o*-aminophenol also gave 2-methylbenzoxazole similarly. Apparantly preparation of *o*-aminophenyl ester **9** is desirable to examine the alternative path *via* **9**. However, attempt to prepare **9** was not made since it is well known that **9** is generally very unstable and rearranges rapidly to N-acyl-*o*-aminophenol **5** by the O to N migration.[20)]

In conclusion, these results demonstrate that PPE can be conveniently employed for the preparation of benzoxazoles and benzthiazoles as well as benzimidazoles from *o*-substituted anilines and free carboxylic acids under mild conditions. Further application of this method to synthesis of various benzazoles and to peptide chemistry will be reported in separate papers.

Experimental[24)]

General Procedure for the Preparation of Benzoxazoles (*cf.* Table I)——To a heated mixture of 1a (10 mmoles) and PPE (10 g) at 100°, was added carboxylic acid (15 mmoles). After heating at 100° (bath-temp.) for 30 min, the reaction mixture was cooled, decomposed by adding ice water (*ca.* 50 ml) and neutralized with excess of $NaHCO_3$. The precipitate was collected, washed, dried and extracted with hot solvent (hexane for R=phenyl, *p*-chlorophenyl: benzene for R=*p*-acetamidophenyl; ether for R=methyl) to separate from impure material, or simply recrystallized. Products are obtained on evaporation of the solvent *in vacuo* and purified in the usual manner.

General Procedure for the Preparation of Benzthiazoles (*cf.* Table II)——To a solution of 1b (5 mmoles) and PPE (6 g) in $CHCl_3$ (10 ml) was added carboxylic acid (7.5 mmoles) and the whole was refluxed for 30 min. After evaporation of the solvent *in vacuo*, the residue was treated with ice-water, neutralized with $NaHCO_3$, extracted (hexane for R=phenyl, furyl; ether for R=methyl) or recrystallized as above.

Isolation of Acyl Derivatives of 1a——N-Benzoyl-*o*-aminophenol: A solution of 1a (1.09 g; 10 mmoles) and PPE (10 g) in $CHCl_3$ (20 ml) and benzoic acid (1.22 g; 10 mmoles) were mixed and the mixture was refluxed for 30 min, treated as in the general procedure to give 2-phenylbenzoxazole in 17% yield. The residue, left after the extraction with hexane, was recrystallized from benzene to give N-benzoyl-*o*-aminophenol as colorless needles of mp 167—168° (lit.[21)], mp 169—171°); 279 mg or 13%.

N,O-Dibenzoyl-*o*-aminophenol——Benzoic acid and 1a were reacted as in the general procedure to give 2-phenylbenzoxazole in 70% yield. Subsequent to the extraction with hexane, the residue was recrystallized from EtOH to give the dibenzoyl compound as colorless needles of mp 178—180° (lit,[18)] mp 179°); 430 mg or 14%.

Reaction of Acyl Derivatives of 1a——Forty to fifty mg of mono- and diacyl derivative of 1a was dissolved in 2 ml of chloroform containing 500 mg of PPE, and the solution was heated under reflux. The yield of benzoxazole determined by OD in UV spectrum is shown in Table III.

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20) L.H. Amundsen and C. Ambrosio, *J. Org. Chem.*, **31**, 731 (1966).
21) M. Bergmann, R. Ulpts, and F. Eamacho, *Chem. Ber.*, **55**, 2796 (1922).
22) F. Bell and J. Kenyon, *J. Chem. Soc.*, **1926**, 1963.
23) E. Bamberger, *Chem. Ber.*, **36**, 2050 (1903).
24) All mps were uncorrected.