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 C₂ 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 anhydride⁴⁾ may be cited here.

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 **3a** or **3c**. Aqueous hydrochloric acid was later used as acid-catalyst in the preparation of benzimidazoles **3c**, the well-known Phillips' method.⁶⁾ However, this modification has been successful neither for the preparation of benzoxazoles **3a** nor benzthiazoles **3b**. The former **3a** is, for example, unstable to hot aqueous acid⁷⁾ and the oxazole ring is easily solvolyzed under the conditions. Recently polyphosphoric acid (PPA) was used to prepare **3a**—**c** although rather high reaction temperature (~200°) is required.⁸⁾

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- 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.
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- 7) Y. Kanaoka and T. Hamada, unpublished data.
- 8) D.W. Hein, R.J. Alheim and J.J. Leavitt, *J. Am. Chem. Soc.*, **79**, 427 (1957).

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 **3c** are prepared from carboxylic acids **2** and *o*-phenylenediamines **1c** by means of PPE under mild conditions.¹⁰⁾ In extension of this work, the present paper deals 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 PPE¹¹⁾ was heated at 100° (bath-temperature) for 30 min. 2-Phenylbenzoxazole was obtained in 70% yield. Similarly, several aromatic acids with substituent 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 $\lambda_{\max}$ $m\mu(\log \epsilon)$
Benzoic acid	100	30	phenyl	102—103(E) ^{b)}	70	234(3.86) 292(4.34) 299(4.35)
<i>p</i> -Chlorobenzoic acid	120	20	<i>p</i> -chlorophenyl	151—152(E) ^{c)}	57	297(4.49) 304(4.51)
<i>p</i> -Acetoamidobenzoic acid	100	30	<i>p</i> -acetamidophenyl	217 (C) ^{d)}	44	316(4.51)
<i>p</i> -Nitrobenzoic acid	120	30	<i>p</i> -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.,¹³⁾ mp 150—151°d) lit.,¹³⁾ mp 212°e) lit.,¹³⁾ 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 $\lambda_{\max}$ $m\mu(\log \epsilon)$
Benzoic acid	refl. in CHCl ₃	30	phenyl	112—113 (E) ^{b)}	77	297 (4.29)
<i>p</i> -Nitrobenzoic acid	100°	30	<i>p</i> -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.,⁹⁾ 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)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. Stephens and J.D. Bower, *J. Chem. Soc.*, **1949**, 2971.14) W. Ried and E. Schmidt, *Ann.*, **676**, 114 (1964).15) F. Kröhnke and H. Leister, *Chem. Ber.*, **91**, 1479 (1958).16) M.T. Bogert and A. Stull, *J. Am. Chem. Soc.*, **48**, 248 (1926).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 substituents, 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^{23,10,18,19}). 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**

<i>o</i> -Aminophenols	Temp. (°C)	Time (min)	Benzoxazole R in 3a	Yield (%)
N-Benzoyl- ²¹⁾	refl. in CHCl ₃	40	C ₆ H ₅	20
O,N-Dibenzoyl- ²¹⁾	refl. in CHCl ₃	240	C ₆ H ₅	—
N-Acetyl- ²³⁾	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

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. Apparently 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.

Experimental²⁴⁾

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 NaHCO₃. 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 CHCl₃ (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 NaHCO₃, 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 CHCl₃ (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.¹⁹⁾ 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.

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.