

AN EFFICIENT PHOSPHORYLATION METHOD
BY THE ACTIVATION OF ALCOHOL

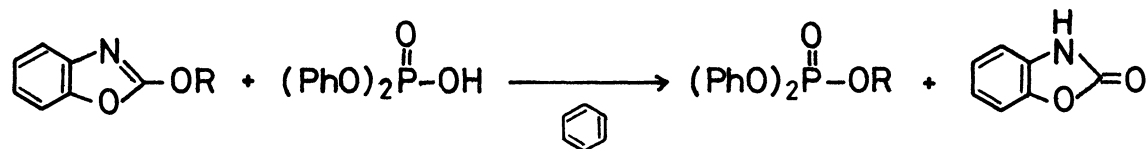
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The reaction of 2-alkyloxybenzoxazoles with diphenyl hydrogen phosphate proceeds smoothly to give the corresponding alkyl diphenyl phosphates in good yields. 2-Alkyloxybenzoxazoles can be readily prepared by treating the parent alcohols with 2-fluorobenzoxazole derived from 2-chlorobenzoxazole by the action of potassium fluoride.

Over the years, a number of methods for phosphorylation of alcohols have been described in literatures.¹⁾ Most of them are based upon the activation of phosphoryl group, and the methods using the activation of alcohol have been scarcely reported.^{2), 3)} Nevertheless, the latter type of phosphorylation possesses following advantages: (1) It is free from formation of pyrophosphate; (2) one enantiomer of optically active alcohol may be converted directly to the phosphoric ester of the other.

During our synthetic investigation utilizing the onium salts of azaaromatics, 2-chloro-3-ethylbenzoxazolium tetrafluoroborate was proved to react rapidly with alcohols to form the corresponding 2-alkyloxybenzoxazolium salts, which in turn reacted with chloride ion to afford alkyl chlorides and 3-ethyl-2-benzoxazolinone with ease.⁴⁾

These facts prompted us to investigate a phosphorylation method by the activation of alcohol with the consideration that protonation on the nitrogen atom of 2-alkyloxybenzoxazole by certain phosphoric acid derivatives would result in the formation of an active intermediate similar to 2-alkyloxy-3-ethylbenzoxazolium salts described above and it would be attacked by the phosphate anion formed at the same time.



The present communication is concerned with the preparation of alkyl diphenyl phosphates by the reaction between 2-alkyloxybenzoxazoles and diphenyl hydrogen phosphate without any additives. The following is a typical procedure for the triester synthesis by the present method.

Table 1. Synthesis of alkyl diphenyl phosphates

R	Time (h)	Temp.	Yield of ester (%) ^{a)}
Ph(CH ₂) ₂	69	r.t.	74
	4	refl.	89
CH ₃ (CH ₂) ₇	48	r.t.	71
	6	refl.	93
(CH ₃) ₂ CHCH ₂ ^{b)}	8	refl.	64
HC≡CCH ₂	68	r.t.	67
CH ₃ O(CH ₂) ₂ ^{b)}	7	refl.	74
PhS(CH ₂) ₂ CO ₂ (CH ₂) ₂	5	refl.	68
CH ₃ (CH ₂) ₁₆ CO ₂ (CH ₂) ₂	6.5	refl.	68

a) All compounds exhibited ir and nmr spectroscopic data in accordance with assigned structures.

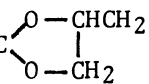
b) Prepared by the reaction between sodium salt of the corresponding alcohol and 2-chlorobenzoxazole according to Elwood and Gates's method.⁷⁾

A benzene (2.5 ml) solution of diphenyl hydrogen phosphate (225 mg, 0.9 mmol)⁵⁾ and 2-octyloxybenzoxazole (173 mg, 0.7 mmol) was gently refluxed for 6 hours under an argon atmosphere. After cooling and addition of benzene, the resulting benzene solution was washed successively with saturated aqueous NaHCO₃ solution, 2N-NaOH solution (2 times), water (2 times), and then with saturated brine, and dried over anhydrous magnesium sulfate. The solution was condensed under reduced pressure to give almost pure octyl diphenyl phosphate (240 mg), which was purified by preparative thin layer chromatography on silica gel eluting with hexane-ethyl acetate (6.5 : 1), and 235 mg (93% yield) of the ester was obtained.

In a similar procedure under the conditions shown in Table 1, various 2-alkyloxybenzoxazoles were smoothly converted into the corresponding alkyl diphenyl phosphates in good yields by the action of 1-1.3 molar amounts of diphenyl hydrogen phosphate. The triesters obtained by the present method can be isolated very easily because 2-benzoxazolinone formed during the reaction is soluble in alkaline solution. Moreover, the method would be superior in terms of reaction time and yield to Cramer's method²⁾ employing alkyl trichloroacetimidates.

Treatment of 2-(3 β -cholestanyloxy)benzoxazole with 1.3 molar amounts of diphenyl hydrogen phosphate at room temperature for 19 hours gave 32% of 3 α -cholestanyl diphenyl phosphate along with 37% of 2-cholestene (and/or 3-cholestene), while no 3 β -cholestanyl ester could be detected chromatographically.

Table 2. 2-Alkyloxybenzoxazoles obtained by the reaction between alcohols and 2-fluorobenzoxazole

Ra)	Reaction time (h) ^{b)}	Yield (%)	Bp ^{c)} [or Mp]
Ph(CH ₂) ₂	14	75 ^{d)}	160-170 °C/2.0 mmHg
CH ₃ (CH ₂) ₇	20	66	145-150 °C/1.3 mmHg
HC ≡ CCH ₂	30	81	95-110 °C/1.8 mmHg
PhS(CH ₂) ₂ CO ₂ (CH ₂) ₂	13.5	88	—
CH ₃ (CH ₂) ₁₆ CO ₂ (CH ₂) ₂	20	90	45.5-47.0 °C from MeOH
(CH ₃) ₂ C 	13	89	140-145 °C/0.9 mmHg

a) Each product gave satisfactory spectral data.

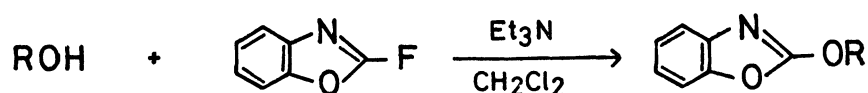
b) Reaction at room temperature.

c) Bath temperature.

d) When the reaction was carried out in boiling 1,2-dichloroethane for 6.5 hours, 93 % of 2-phenethyloxybenzoxazole was obtained.

This result supports that the present phosphorylation reaction proceeds through an S_N2 type process which includes attack of diphenyl phosphate ion on protonated 2-alkyloxybenzoxazole.

Although methoxy-⁶⁾ or allyloxybenzoxazole⁷⁾ was so far prepared by treating sodium salt of methyl or allyl alcohol with 2-chlorobenzoxazole, it was found that 2-fluorobenzoxazole, prepared from 2-chlorobenzoxazole and potassium fluoride, reacted readily with various primary alcohols in the presence of triethylamine to give the corresponding 2-alkyloxybenzoxazoles in good yields. This reaction provides a convenient method for the preparation of 2-alkyloxybenzoxazoles under mild conditions. The results are shown in Table 2.



Preparation of 2-fluorobenzoxazole has been accomplished by the following procedure: Prior to the reaction, 4-5 molar amounts of potassium fluoride was dried by utilizing a benzene azeotrope (2 times). To the anhydrous potassium fluoride thus obtained was added catalytic amounts of 1,4,7,10,13,16-hexaoxacyclooctadecane and azeotropic removal of the moisture was repeated once. After benzene was completely expelled under reduced pressure, freshly distilled 2-chlorobenzoxazole was added at one portion and the resulting mixture was heated at 110-120°C with stirring under an argon atmosphere. The reaction was monitored by gas chromatography. Stirring was continued for 15-25 hours and 2-fluorobenzoxazole (45-65% yields) was isolated by direct distillation from the reaction mixture, bp 81-82°C/54-55 mmHg.⁸⁾ Since

2-fluorobenzoxazole is highly reactive, it must be stocked in a refrigerator at about -10°C as a petroleum ether solution standardized.

The next is a typical procedure for the synthesis of 2-alkyloxybenzoxazoles by the use of 2-fluorobenzoxazole: To 1-octanol (75 mg, 0.50 mmol) and triethylamine (66 mg, 0.65 mmol) in dichloromethane (1.5 ml) cooled in an ice-bath was added a petroleum ether solution (0.65 ml) containing about 0.65 mmol of 2-fluorobenzoxazole under an argon atmosphere. The reaction mixture was stirred at room temperature for 20 hours and then quenched by adding petroleum ether and water. The organic layer was washed 2 times with water and dried over anhydrous sodium sulfate. The residue obtained by evaporation of volatile materials under reduced pressure was chromatographed on silica gel eluting with hexane-ethyl acetate (8:1) to yield 81 mg (66 %) of 2-octyloxybenzoxazole. It has bp $145-150^{\circ}\text{C}$ (bath temperature)/1.3 mmHg.

Similarly, various 2-alkyloxybenzoxazoles were prepared in good yields as shown in Table 2.

It should be noted that the present method provides a simple and rapid procedure for the preparation of phosphoric triesters starting from alcohols and diphenyl hydrogen phosphate via 2-alkyloxybenzoxazoles.

Further work on the scope and utility of the method is now in progress.

REFERENCES AND NOTES

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NMR(CDCl_3): δ 7.16-7.73 (m), MS: m/e 137 (M^+).

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