## Communications to the Editor

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# CATALYTIC EFFECT OF CESIUM FLUORIDE FOR ALKYLATION OF PHOSPHORIC ACIDS

Hiroshi Takaku,*,[a] Kazuo Kamaike,[a] Hisashi Mori,[a]
and Yoshiharu Ishido[b]
Laboratory of Organic Chemistry, Chiba Institute of Technology,[a] Narashino-shi, Chiba 275 and Department of Chemistry, Tokyo Institute of Technology,[b]
Ookayama, Meguro-ku, Tokyo 152, Japan

The phosphoric acids were smoothly alkylated with alkyl halides in the presence of cesium fluoride.

KEYWORDS——phosphorylation; phosphotriester; cesium fluoride; alkylation

Most general methods for the preparation of phosphoric esters are based on the phosphorylation of alcohols, phenols, and amines with activated phosphoric acid.1-6) On the other hand, Mitsunobu et al.7) reported the phosphorylation by activating the alcohol moiety. In this method, there is no possibility of pyrophosphate formation as a side reaction. Further, there has been reported a phosphorylation by alkyl halides of phosphoric acids in the form of their quaternary ammonium salts,8) but this method, employing ammonium salts of phosphoric acid, was not satisfactory.

Recently, fluoride ion has been reported as the most suitable catalyst to promote various types of base-catalyzed reactions in organic synthesis.9)

In the course of our investigations on phosphotriester synthesis, we have found that cesium fluoride is a hydrogen bond-forming catalytic reagent for alkylation of phosphoric acids.

First, the alkylation of dialkyl phosphates (I) in the presence of cesium fluoride was performed as follows: When a dry acetonitrile solution of methyl iodide was momentarily added to a dry acetonitrile solution of dibutyl phosphate and cesium fluoride, the corresponding dibutyl methyl phosphate was obtained in poor yield (36%). In order to improve the yield of phosphotriesters (III), we examined the best conditions for this reaction, and finally found that when alkyl halides were added dropwise to a dry acetonitrile solution of I and cesium fluoride during 1 h, the phosphotriesters (III) were obtained in good yields. A typical procedure is as follows: A dry acetonitrile solution (1 ml) of alkyl halide (II: $R^2=CH_3$, X=I) (0.28 ml, 4.5 mmol) was added dropwise to a dry acetonitrile solution (5 ml) of dibutyl phosphate [I: $R^1$=n-$CH_3(CH_2)_3$] (631 mg, 3 mmol) and cesium fluoride (1.36 g, 9 mmol) at room temperature during 1 h. After further stirring for 5 h, the solution was evaporated *in vacuo* and the resulting residue was purified by silica gel column chromatography (eluent: $CH_2Cl_2$-MeOH, 9:1, v/v). The solvent was then evaporated *in vacuo* and the residue distilled. Dibutyl methyl phosphate was obtained in 88% (589 mg) yield.

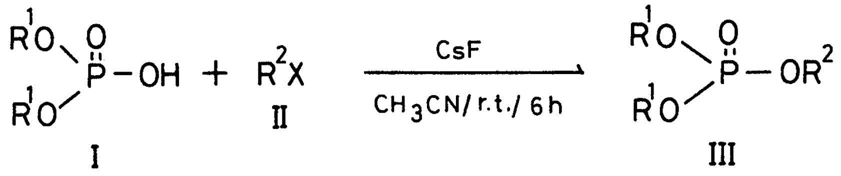

Table I. Alkylation of Dibutyl Phosphate

| Alkyl halide II $R^2$ | X | Yield(%) | bp °C/mmHg | Molecular formula[a)] or lit. bp |
|---|---|---|---|---|
| $CH_3$ | I | 88 | 85-87/2 | $C_9H_{21}O_4P$ (224.3) |
| $C_2H_5$ | I | 89 | 135/14 | 95-96/3[10)] |
| iso-$C_3H_7$ | I | 96 | 124/4 | $C_{11}H_{25}O_4P$ (252.3) |
| n-$C_4H_9$ | I | 86 | 135/5 | 154/10[11)] |
| n-$C_4H_9$ | Br | 81 | | |
| n-$C_7H_{15}$ | I | 79 | 148/2 | $C_{17}H_{33}O_4P$ (332.4) |
| n-$C_9H_{19}$ | Br | 75 | 145/1 | $C_{19}H_{37}O_4P$ (360.5) |
| $CH_2=CHCH_2$ | Br | 76 | 118/2 | $C_{11}H_{23}O_4P$ (250.3) |

a) Satisfactory microanalyses obtained: C± 0.4, H± 0.3, P± 0.2.

Table II. Alkylation of Dimethyl Phosphate

| Alkyl halide II $R^2$ | X | Yield(%) | bp °C/mmHg | Molecular formula[a)] or lit. bp |
|---|---|---|---|---|
| $C_2H_5$ | I | 81 | 67/5 | 87/15[12)] |
| iso-$C_3H_7$ | I | 88 | 71/6 | 83/12[13)] |
| n-$C_4H_9$ | I | 84 | 73/4 | 107/15[12)] |
| n-$C_4H_9$ | Br | 80 | | |
| n-$C_6H_{13}$ | I | 84 | 99/2 | 110/1.7[14)] |
| $C_6H_5CH_2$ | Br | 75 | 133/3 | 100/0.05[13)]<br>$C_8H_{11}O_4P$ (202.1) |

a) Satisfactory microanalyses obtained: C± 0.4, H± 0.2, P± 0.2.

Similarly, several phosphoric acid triesters (III) were obtained in good yields as shown in Tables I and II. As can be seen from Tables I and II, alkyl iodides and bromides were found to be effective reagents for alkylation of dialkyl phosphates. Further, the use of acetonitrile afforded the phosphotriesters (III) in better yields than the use of THF, dioxane, or $CH_2Cl_2$. Furthermore, when freeze-dried potassium fluoride[10)] was used in place of cesium fluoride in the above reaction, the yield of dibutyl methyl phosphate decreased (67%).

In conclusion, it was found that the phosphoric acids were smoothly alkylated with alkyl halides in the presence of cesium fluoride under mild conditions.

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