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N,N-Di-isopropyl-O,O-Di-*p*-methoxybenzylphosphoramidite --A New Phosphorylating Reagent

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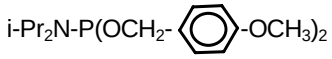
Abstract: A new phosphorylating reagent, N,N-di-isopropyl-O,O-di-*p*-methoxybenzylphosphor-amidite was synthesized from diisopropylamino dichlorophosphine and p-methoxybenzyl alcohol for preparing phosphatydyl inositol polyphosphate particularly with unsaturated components.

Keywords: N,N-Di-isopropyl-O,O-di-*p*-methoxybenzylphosphoramidite, phophorylating reagent, unsaturated component.

The dibenzyl diisopropylphosphoramidite[1,2], which could be cleaved by reduction (hydrogenolysis), is a very useful reagent for the phosphorylation of hydroxy group especially vicinal hydroxy group. It is used very often for the synthesis of nucleotide and myo-inositol polyphosphates. However, it cannot be used for the phosphorylation of the compounds having an olefinic group which would also be reduced to paraffin in the reduction cleaving of the benzyl group. Now, We report the synthesis of a new phosphorylating reagent N,N-di-isopropyl-O,O-di-*p*-methoxybenzylphosphoramidite **1**. Since *p*-methoxybenzyl group as a very useful reagent for the protection of alcohol could be cleaved not only by reduction (hydrogenolysis) but also by oxidation with ammonium ceric nitrate[3] or dicyano dichloro-benzoquinone (DDQ)[4] in the presence of water, **1** can be used for the synthesis of the compounds with unsaturated groups.



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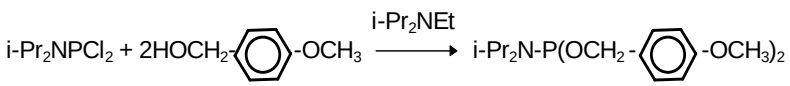
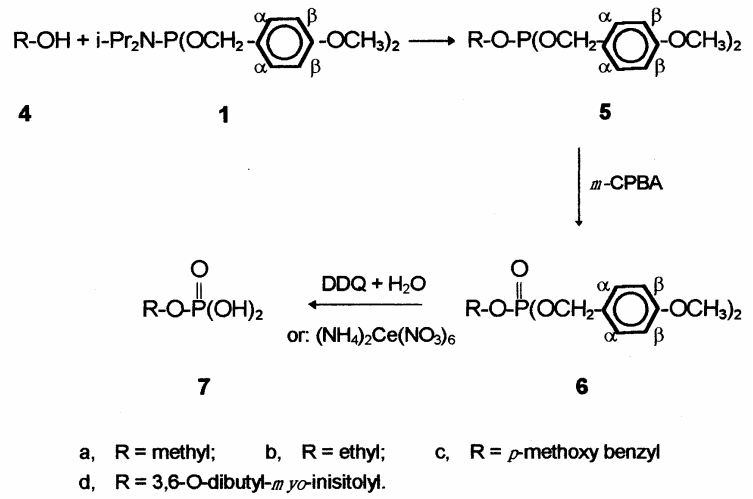
The compound **1** was obtained from diisopropylamino dichlorophosphine **2**[5] and *p*-methoxybenzyl alcohol **3** in the presence of diisopropyl ethylamine.



2 **3** **1**

Amidite **1** reacts with any alcohols **4** to give di-(*p*-methoxylbenzyl)-alkyl (or aryl)-phospite **5** in the presence of tetrazole. Phosphate **5** can be oxidized with *m*-chloro-perbenzoic acid to give di-(*p*-methoxybenzyl)-alkyl (or aryl)-phosphate **6**. Phosphate **6** can be converted to alkyl (or aryl) phosphate **7** by reaction with ammonium ceric nitrate $(NH_4)_2Ce(NO_3)_6$ or with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in the presence of water.



a, R = methyl; b, R = ethyl; c, R = *p*-methoxy benzyl
d, R = 3,6-O-dibutyl-*myo*-inisitolyl.

p-Methoxybenzyl group can be oxidatively cleaved without affecting benzyl group. This new phosphorylating reagent **1** can be used for the synthesis of many phosphates especially phosphatidyl inositol having unsaturated fatty acid component.

Experimental

N,N–di–isopropyl–O,O–di–*p*–methoxybenzylphosphoramidite 1. Diisopropylamino-di-chloro-phosphine **2** (4.0 g, 0.02 mol) was added to an ice cold solution of *p*-methoxy-benzyl alcohol (5.3 g, 0.04 mol), and diisopropyl ethylamine (5.8 g, 0.044 mol) in dry tetrahydrofuran (18 ml) with stirring. Stirring at 0°C was continued for 10 min and at room temperature for 1 h. The precipitate was filtered and the filtrate was evaporated. The residue was passed through silica gel short column (hexane 10, triethylamine 1) to get **1** (3.4 g, 42%). Rf= 0.7 (hexane 2, ethyl acetate 1). ^{1}H-NMR (solvent, $CDCl_3$), δ_H: 1.21 (d, 12H, $-CH_3$ of i-Pr-), 3.60 (q, 2H, -CH- of i-Pr-), 3.80 (s, 6H, $-OCH_3$), 4.68 (d, 4H, $-CH_2-$ of *p*-methoxybenzyl), 6.90 (d, 4H, α-H of benzene ring), 7.32 (d, 4H, β-H of benzene ring).

Methyl di–*p*–methoxybenzyl phosphate 6a. The solution of methanol (34.2 mg, 1.07 mmol), **1** (410.1 mg, 1.07 mmol), tetrazole (141 mg, 2.01 mmol) in CH_2Cl_2 (2 ml) was stirred at room temperature for 30 min and then cooled to -40°C. *m*-Chloroperbenzoic acid (265.9 mg, 1.53 mmol) was added to this reaction mixture in one minute and stirred at this temperature for 10 min and then 1 h at room temperature.

The reaction mixture was diluted with ethyl ether and washed with 10% Na_2SO_3, water, 10% $NaHCO_3$ and water, dried over anhydrous Na_2SO_4, evaporated, and then the residue was chromatographed on silica gel (hexane 1.5, ethyl acetate 1) to give **6a** (181 mg, 37%). ^{1}H-NMR (solvent, $CDCl_3$), δ_H: 3.8 (s, 6H, -OCH_3 of *p*-methoxybenzyl), 4.4 (m, 4H, -CH_2- of *p*-methoxybenzyl), 5.2 (m, 3H, CH_3O-P), 6.8-7.0 (m, 4H, α-H of benzene ring), 7.2-7.4 (m, 4H, β-H of benzene ring).

Ethyl di–*p*–methoxybenzyl phosphate 6b. The solution of ethanol (48.5 mg, 1.05 mmol), **1** (417.1 mg, 1.04 mmol), tetrazole (140.1 mg, 2.0 mmol) in 2 ml CH_2Cl_2 was stirred at room temperature for 30 min and then cooled to -40°C. *m*-Chloroperbenzoic acid (273.2 mg, 1.58 mmol) was added to this reaction mixture in one minute and stirred at this temperature for 10 min and then 1 h at room temperature. The reaction mixture was treated as above and **6b** (184.4 mg, 35%) was obtained. ^{1}H-NMR (solvent, $CDCl_3$), δ_H: 1.2 (t, 3H, -CH_3 of ethyl), 3.5 (q, 2H, -CH_2- of ethyl), 3.8 (s, 6H, -OCH_3), 4.4-4.5 (m, 4H, -CH_2- of *p*-methoxybenzyl), 6.8-6.9 (m, 4H, α-H of benzene ring),7.2-7.4 (m, 4H, β-H of benzene ring).

Tri–*p*–methoxybenzyl phosphate 6c. The solution of *p*-methoxy benzyl alcohol (138.0 mg, 1 mmol), **1** (616.9 mg, 1.5 mmol), tetrazole (108.8 mg, 1.55 mmol) in 1ml CH_2Cl_2 was stirred at room temperature for 30 min and then cooled to -40°C. *m*-Chloro-perbenzoic acid (270.2 mg, 1.56 mmol) was added to this reaction mixture in 10 min and stired at this temperature for 10 min and then 1 h at room temperature. The reaction mixture was treated as above and **6c** (114.5 mg, 25%) was obtained. ^{1}H-NMR (solvent, $CDCl_3$), δ_H: 3.68 (s, 9H, -OCH_3), 4.48 (s, 6H, -CH_2- of *p*-methoxybenzyl), 6.93(d, 6H, α-H of benzene ring), 7.35 (d, 6H, β-H of benzene ring).

3,6–O,O–dibutyl–1,2,4,5–tetrakis–(*p*–methoxybenzylphosphoryl)–*myo*–inositol 6d. A mixture of 3,6-O,O-dibutyl-*myo*-inisitol (99 mg, 0.3 mmol), di-O,O-*p*-methoxybenzyl-N,N-di-isopropylphosphoramidite (780 mg, 1.8 mmol), tetrazole (210 mg, 3 mmol) in 4 ml dichloromethane, was stirred at room temperature for 30 min and then cooled to -40°C. *m*-Chloroperbenzoic acid (309.2 mg, 1.8 mmol) was added to this reaction mixture in 10 min and stirred at this temperature for 10 min and then 1 h at room temperature. The **6d** was obtained in the yield of 13.2% (54.6 mg)**.** Rf=0.7 (hexane 1, ethyl acetate 1). ^{1}H-NMR (solvent, $CDCl_3$), δ_H: 0.85 (t, 6H, -CH_3 of butyl), 1.22 (m, 8H, C-CH_2-CH_2-C of butyl), 2.1 (m, 4H, -CH_2-O- of butyl), 3.8-4.0 (m, 24H, -OCH_3), 4.4 (m, 16H, -CH_2- of *p*-methoxybenzyl), 4.4-5.3 (m, 6H, the H of *myo*-inositol), 6.8-7.4 (m, 32H, the H of benzene ring).

3,6–O,O–dibutyl–*myo*–inositol–1,2,4,5–tetrakis–phosphate 7d. A mixture of **6d** (41 mg, 0.03 mmol), DDQ (61.2 mg, 0.27 mmol), water (18 mg, 1 mmol) in CH_2Cl_2 (2 ml) was stirred at room tempeperature for 15 h. The reaction mixture was diluted with 20 ml of CH_2Cl_2, extracted with water. Aqueous layer was dried under vacuum, and the residue was triturated with methanol (2 ml) and dried under vacuum again to give **7d** (6.1 mg, 32%)**.** ^{1}H-NMR (solvent, D_2O), δ_H: 0.8 (t, 6H, -CH_3 of butyl), 1.2 (m, 8H, C-CH_2-CH_2-C of butyl), 2.2 (m, 4H, -CH_2-O- of butyl) , 4.0-5.2 (m, 6H, the H of *myo*-inositol).

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