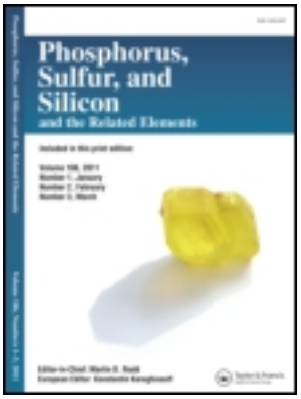


Phosphorus, Sulfur, and Silicon and the Related Elements

Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/gpss20

# A Convenient Procedure for the Synthesis of 6-O-Mono-Phosphate β-Cyclodextrins

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Accepted author version posted online: 26 Jul 2013.Published online: 03 Oct 2013.

To cite this article: Siphamandla Simelane , Brillance Bhekie Mamba & Xavier Yangkou Mbianda (2013) A Convenient Procedure for the Synthesis of 6-O-Mono-Phosphate β-Cyclodextrins, Phosphorus, Sulfur, and Silicon and the Related Elements, 188:12, 1675-1679, DOI: 10.1080/10426507.2013.797419

To link to this article: http://dx.doi.org/10.1080/10426507.2013.797419

*Phosphorus, Sulfur, and Silicon*, 188:1675–1679, 2013

ISSN: 1042-6507 print / 1563-5325 online
DOI: 10.1080/10426507.2013.797419



# A CONVENIENT PROCEDURE FOR THE SYNTHESIS OF 6-*O*-MONO-PHOSPHATE $\beta$-CYCLODEXTRINS

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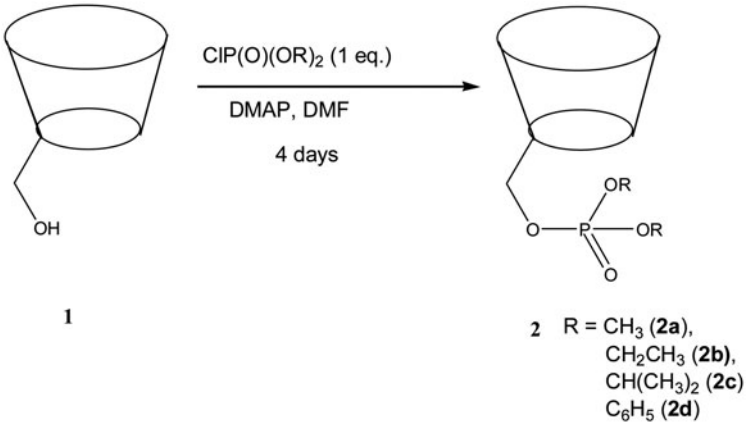
## GRAPHICAL ABSTRACT




**1**

**2** R = $CH_3$ (**2a**), $CH_2CH_3$ (**2b**), $CH(CH_3)_2$ (**2c**) $C_6H_5$ (**2d**)

**Abstract** *The synthesis of $\beta$-cyclodextrin derivatives bearing one phosphate group on the primary rim is reported. These compounds were prepared in good to excellent yields, by reacting $\beta$-cyclodextrin with dialkyl chlorophosphates in the presence of 4-dimethyl amino pyridine (DMAP) catalyst and dimethylformamide (DMF) as solvent. The methodology described is highly selective and the purification of the title compounds is simple, because difficulties due to phosphate regioisomers mixture are avoided.*

**Keywords** $\beta$-Cyclodextrin; 6-*O*-monophosphate $\beta$-cyclodextrin; 4-Dimethyl amino pyridine; Cyclodextrin phosphate

Received 26 February 2013; accepted 16 April 2013.
The authors thank the National Research Foundation (NRF) of South Africa, for financial support.
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## INTRODUCTION

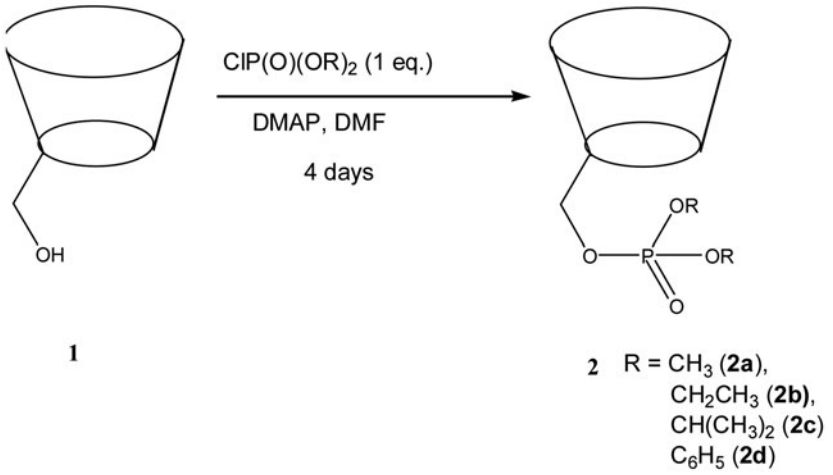
Cyclodextrins (CD) are cyclic oligosaccharides typically containing six ($\alpha$-CD), seven ($\beta$-CD), and eight ($\gamma$-CD) glucopyranose units forming a toroidal shape. This orientation enables cyclodextrins to form inclusion complexes when a guest molecule is partially or fully contained in the interior of the cavity.[1] Due to this characteristic feature, cyclodextrins and cyclodextrin-based polymers have been studied for a number of applications including chromatography, environmental, and pharmaceutical science.[1,2]

Over the past five decades, modified cyclodextrins have received increasing interest due to their applications in various fields, ranging from supramolecular chemistry to drug delivery, biosensors, and water purification.[3] The selective modification of cyclodextrins is a challenge because of the presence of three different types of hydroxyl groups in their structure as well as due to the hydrophobic nature of their cavity. The various hydroxyl groups compete for the modifying reagent making the extent of the functionalization (mono, di, tri, etc.) difficult to control. Alternatively, the hydrophobic cavity is capable of complexing the reagent and directing substitution to the formation of unexpected products.[4–6] The size of the cyclodextrin cavity and the solvent used are the other factors that can also affect the reaction product. Few methods are known for the preparation of monosubstituted cyclodextrins bearing organophosphate groups.[7,8] However, these methods have drawbacks, such as the use of pyridine which is a toxic solvent, tedious work-up procedures, and poor yield. For example, Breslow's research group[7] reports the preparation of 6-*O*-monophosphorylated $\beta$-cyclodextrins using a method containing a series of protection–deprotection and recrystallization steps leading to poor yields. Pyridine was selected as solvent in these methods, because of its ability to orient the substitution reactions to the primary hydroxyl groups of the cyclodextrin moiety. However, it also forms a pyridinium complex, with the cavity of CDs, which complicates the work-up procedure[6] and leads to poor yield. Our current interest in the application of modified cyclodextrins polymers for water purification[9–11] led our quest for convenient ways of obtaining these compounds with high yield and purity.

In this letter, we wish to report a convenient and better yielding method for the monophosphorylation of $\beta$-cyclodextrin **1** using dialkyl or diaryl chlorophosphates in the presence of 4-dimethylamino pyridine (DMAP) as a catalyst and dimethylformamide (DMF) as a solvent (Scheme 1) to produce the corresponding 6-*O*-monophosphate $\beta$-cyclodextrin compound **2** in good to excellent yields.

## RESULTS AND DISCUSSION

In this study, DMF as solvent with DMAP as catalyst is proposed as an attractive alternative to pyridine (non–user-friendly solvent) used in most of the approaches reported for the monosubstitution of cyclodextrins in the literature. DMAP is known to catalyze a wide variety of reactions like acylation, carbamylation, silylation, sulphonylation, and phosphorylation of amino and hydroxyl groups.[12] According to Loannou and colleagues[13], DMAP also activates acylation toward primary hydroxyl groups over secondary hydroxyl. In addition, it functions as an acid (HCl) scavenger to prevent the hydrolysis of the phosphate esters. Another advantage of using DMAP is that it is a non-hygroscopic solid, easy to handle when compared with liquid tertiary amines that are commonly used. In this procedure, the cyclodextrin and the phosphorylating agent were reacted at room temperature (25°C) and in diluted solution to avoid highly substituted derivatives. In addition, the phosphorylating agent was added slowly to ensure that the cyclodextrin remained in excess in the reaction




**Scheme 1** Preparation of compound 2.



flask.[14] This reaction was highly regioselective, because only a single signal was observed in the $^{31}$P NMR spectra of the crude products (Table 1). At higher temperatures or with more concentrated solution of phosphorochloridate, the reaction selectivity was lost and multiple signals were observed in the $^{31}$P NMR spectra of the crude products.

The proposed mechanism for phosphorylation by DMAP-catalyzed reaction is illustrated in Scheme 2.

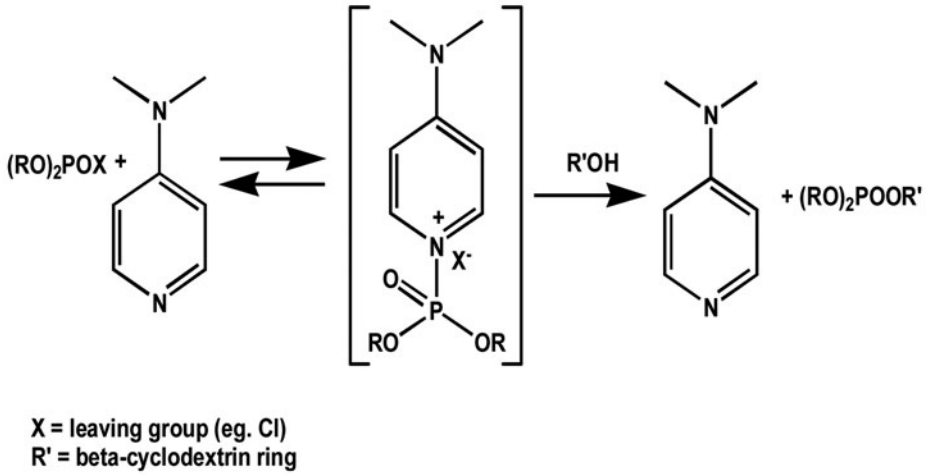
It begins with a nucleophilic attack of DMAP on the phosphoryl halide to generate a phosphorylpyridinium-anion-pair intermediate, which reacts selectively with the primary hydroxyl groups of the cyclodextrin to yield the phosphate ester product while regenerating the DMAP.

The work-up procedure for obtaining the final products involved: precipitation with diethyl ether, and washing several times with isopropanol to remove DMAP and its hydrochloride salt.[15] This protocol afforded the production of the title compounds in yields ranging from 60% to 85% as shown in Table 1. To the best of our knowledge, the synthesis

**Table 1** Percentage yields and spectroscopic data for cyclodextrin phosphorylated derivatives

| Compound R | % Yield | $^{31}$P NMR $\delta$(PPM) | FT-IR ($\nu$, cm$^{-1}$) |
|---|---|---|---|
| (**2a**) | 69% | 1.1 | 1 251 cm$^{-1}$ (P=O) |
| $CH_3$- | | | 1 025 cm$^{-1}$ (P-OCH$_3$) |
| (**2b**) | 85% | −0.9 | 1 252.2 cm$^{-1}$ (P=O) |
| $CH_3CH_2$- | | | 1 026 cm$^{-1}$ (P-OCH$_2$CH$_3$) |
| (**2c**) | 70% | 1.0 | 1 241 cm$^{-1}$ (P=O) |
| $(CH_3)_2CH$- | | | 1 027 cm$^{-1}$ (P-OCH(CH$_3$)$_2$) |
| (**2d**) | 60%[a] | −11.5 | 1 247 cm$^{-1}$ (P=O) |
| $C_6H_5$- | | | 1 194 cm$^{-1}$ (P-OC$_6$H$_5$) |

[a]Yield = 32% and 49% in ref.7 and ref.8 respectively.




**Scheme 2** Proposed mechanism of catalysis of phosphorylation by DMAP.

of these compounds have never been reported in the literature, except for the mono(6-*O*-diphenoxyphosphoryl)-$\beta$-cyclodextrin (**2d**) that have been synthesized by Breslow and colleagues[7] and Liu and colleagues[8] with 32% and 49% yield respectively.

## CONCLUSION

We have developed a convenient and efficient method for the synthesis of 6-*O*-monophosphorylated $\beta$-cyclodextrin derivatives in good yields. The monophosphorylation of cyclodextrins is selectively obtained in DMF by controlled addition of the phosphorylating agent, with DMAP being a catalyst and base. The work-up and purification procedures of the title compounds are simple, because the production of phosphate regioisomer mixtures that leads to purification difficulties, as described in other procedures in the literature, is avoided.

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14. *Synthesis of 6-O-mono-phosphate β-Cyclodextrin Materials*: DMF was dried by distilling over calcium hydride under reduced pressure. β-cyclodextrin was dried by heating at 65°C for 24 h under vacuum. Other reagents were obtained from Sigma Aldrich and they were used without further purification. All the reactions were carried out under argon. *General procedure:* To a solution of β-cyclodextrin (5 g, 4.41 mmol) and DMAP (0.298 g, 2.44 mmol) in DMF (100 mL), dialkyl (or diaryl) chlorophosphate (0.761 g, 4.41 mmol) in DMF (50 mL) was added drop-wise under argon. The reaction was stirred at room temperature for 4 d under argon. The solvent was removed from the reaction mixture under reduced pressure, and the residue was triturated with diethyl ether (100 mL) and stirred for 2 d. The obtained suspension was filtrated and washed 5 times with isopropanol (80 mL). The product was dried at room temperature under vacuum to give the title compound. *Instruments*: $^{1}$H, $^{13}$C, and $^{31}$P NMR spectra were recorded at 300 MHz on a Varian Gemini-300 Spectrometer or at 400 MHz on a Bruker Avance Spectromer in dimethyl sulfoxide (DMSO-$d_6$) or dimethyl formamide (DMF-$d_7$). FT-IR spectra were obtained on a Perkin Elmer Spectrum 100 spectrometer. (**2a**) (2.34 g, 69%). FT-IR $\nu$ (cm$^{-1}$) 3291, 2896, 1651, 1565, 1409, 1327, 1294, 1251, 1223, 1153, 1102, 1079, 1025, 999, 938, 854, 755, 7036. $^{1}$H NMR (DMSO-$d_6$) $\delta$ 5.70 broad (m, 14H, OH-2, OH-3), 4.81 (s, 7H, H-1), 4.20–3.42 (m, 41H, $OCH_3$, H-6, H-5, H-3, $H_2O$), 3.36–2.71 (m, 23H, H-4, H-2, OH-6).$^{13}$C NMR (DMF-$d_7$) $\delta$ 103.2 (C-1), 82.8 (C-4), 74.1 (C-3), 73.7 (C-5), 73.1 (C-2), 63.2 ($OCH_3$), 61.2 (C-6).$^{31}$P NMR (DMSO-$d_6$) $\delta$ 1.1. Found: C, 39.92; H, 6.27. Calc. For $C_{44}H_{75}O_{38}P.5H_2O$: C, 39.63; H, 6.38%. (**2b**) (4.90 g, 85%). FT-IR: $\nu$ (cm$^{-1}$) 3286, 2924, 1703, 1658, 1404, 1364, 1328, 1294, 1253, 1223, 1153, 1079, 1026, 1000, 938, 846, 795, 753, 703. $^{1}$H NMR (DMSO-$d_6$) $\delta$ 5.76–5.71 (m, 14H, OH-2, OH-3,), 4.81 (s, 7H, H-1), 4.47 (m, 4H, $OCH_2$-), 3.64–3.53 (m, 34H, H-6, H-5, H-3, $H_2O$), 3.35–3.28 (m, 21H, H-4, H-2, OH-6), 1.18–1.10 (m, 6H, $CH_3$). $^{13}$C NMR (DMF-$d_7$): $\delta$ 103.2 (C-1), 82.9 (C-4), 74.2 (C-3), 73.80 (C-5), 73.2 (C-2), 61.3–61.0 ($OCH_2$,C-6, C-6'), 16.8–16.7 ($CH_3$).$^{31}$P NMR (DMSO-$d_6$) $\delta$ -0.9. Found: C, 40.49; H, 6.47. Calc. For $C_{46}H_{79}O_{38}P.5H_2O$: C, 40.58; H, 6.54%. (**2c**) (4.10 g, 70%). FT-IR $\nu$ (cm$^{-1}$) 3301, 2926, 1659, 1411, 1362, 1328, 1296, 1241, 1154, 1080, 1027, 1000, 937, 890, 846, 795, 754, 706. $^{1}$H NMR (DMSO-$d_6$) $\delta$ 5.18 broad (m, 20H, OH-2, OH-3, OH-6), 4.81–4.08 (m, 7H, H-1), 3.79–3.04 (m, 52H, $OCH(CH_3)_2$, H-6, H-5, H-3, H-4, H-2, $H_2O$), 1.18–1.11 (m, 12H $OCH(CH_3)_2$).$^{13}$C NMR (DMF-$d_7$) $\delta$ 103.2 (C-1), 82.8 (C-4), 74.2 (C-3), 73.7 (C-5), 73.2 (C-2), 61.3 (C-6), 24.3–24.2 ($CH_3$). $^{31}$P NMR (DMSO-$d_6$) $\delta$ 1.0.. Found: C, 40.77; H, 6.25. Calc. For $C_{52}H_{83}O_{38}P.10H_2O$: C, 40.89; H, 6.01%. (**2d**)[8] (2.42 g, 60%). FT-IR $\nu$ (cm$^{-1}$) 3284, 2914, 1649, 1592, 1490, 1413, 1368, 1330, 1300, 1247, 1195, 1154, 1098, 1079, 1024, 1000, 937, 862, 753, 702, 686; $^{1}$H NMR (DMSO-$d_6$) $\delta$ 7.26 – 6.94 (m, 10H, Ar), 5.69 broad (m, 20H, OH-2, OH-3, OH-6), 4.80 (s, 7H, H-1), 3.65–3.16 (m, 62H, H-6, H-5, H-3, H-4, H-2, $H_2O$); $^{13}$C NMR (DMF-$d_7$) $\delta$ 129.7, 123.3, 120.7–120.6 (phenyl), 103.2 (C-1), 82.8 (C-4), 74.1 (C-3), 73.7 (C-5), 73.1 (C-2), 61.2 (C-6); $^{31}$P NMR (DMSO-$d_6$) $\delta$ -11.5 .Found: C, 41.75; H, 6.60. Calc. For $C_{54}H_{79}O_{38}P.10H_2O$: C, 41.91; H, 6.40%.
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