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Methyl 4-toluenesulfonyloxymethylphosphonate, a new and versatile reagent for the convenient synthesis of phosphonate-containing compounds

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ABSTRACT

A straightforward procedure leading to the new phosphonylating reagent, methyl 4-toluenesulfonyloxymethylphosphonate, requiring no chromatographic purification is described. This stable reagent works with the same efficiency as dimethyl and other dialkyl esters for the introduction of an *O*-phosphonomethyl moiety while, in contrast to dimethyl ester, it does not cause any unwanted methylation of sensitive functionalities. Its utility for the alkylation of protected nucleosides in high yield is exemplified.

The isopolar phosphonate analogs of nucleoside phosphates NMP_c (Fig. 1) were found to be of remarkable biological importance,[1–9] and several drugs based on the acyclic nucleoside phosphonic acids (e.g., Vistide, Hepsera, and Viread) are in clinical use for the treatment of CMV-induced retinitis, hepatitis B, and HIV.[10–14]

Recently, Gilead Sciences, Inc. reported highly promising preclinical studies with the compound GS-9219, a prodrug of PMEG [9-(2-phosphonomethoxyethyl)guanine], against leukemia and non-Hodgkin's lymphoma.[15] In addition, the promising properties of the HIV-RT inhibitor GS-9148 have been reported.[16] The biological activities of phosphonate analogs have stimulated an additional synthetic work[17] which has provided a number of novel and structurally diverse compounds, such as the anti-HIV homologous PMEA derivative **I**,[18] the acyclic 5-azacytosine derivative **II**[19] which is active against DNA viruses, the 2′-deoxy-2′-azidophosphonate nucleoside **III**,[20] the 4′-modified carbocyclic nucleoside phosphonate (HIV-RT inhibitor) **IV**,[21] amongst many others.[22,23] Furthermore, our group has elaborated a method for the introduction of various phosphonate linkages into oligonucleotides.[24–26]

The *O*-methylphosphonate ($O–CH_2–P$) moiety present in nucleotide analogs is important due to its extraordinary chemical and enzymatic stability, and its introduction can be accomplished by etherification of a hydroxy group in a suitably protected nucleoside derivative with dialkyl 4-toluenesulfonyloxymethylphosphonates in the presence of sodium hydride.[1,27,28]

However, in cases when an *O*-methylphosphonate moiety esterified with just one methyl group is required, for example, for the straightforward synthesis of phosphodiester-like derivatives using the advanced phosphotriester method,[29–31] the use of dimethyl 4-tosyloxymethylphosphonate as an alkylating agent is limited because of unwanted extensive methylation of the nucleobase moieties.[31] In addition, an advantage of a methyl group as the phosphorus hydroxy-protecting moiety is its selective and quantitative removal in the presence of any other ester group under mild conditions,[31–33] in contrast to the reported ethyl ester.[34] Therefore, we decided to investigate the synthesis and utility of 4-tosyloxymethylphosphonate monomethyl ester as a new alternative phosphonylating reagent.

The preparation of compounds **1–3** is depicted in Scheme 1 and detailed experimental procedures are described in the Supplementary data (SD). In contrast to the reported methods for the synthesis of α-hydroxyphosphonates,[35,36] the best way to synthesize **1**, in our hands, was via an 'aqueous approach' using aqueous formaldehyde and dimethyl phosphite under triethylamine catalysis.[37–39] The reaction of a slight excess of aqueous formaldehyde with dimethyl phosphite and triethylamine (10–20 mol %) resulted in an exothermic reaction which was complete in a few minutes. NMR spectroscopy revealed about 15% of the mostly negatively-charged side products (see SD) which were easily removable by passing an aqueous solution of crude **1** through a weak anion exchange column (DEAE-Sephadex A25, hydrogen carbonate form). A high yield (84%) of pure **1** was obtained.

On evaluating a number of combinations of solvents and bases, THF (or ethyl acetate) and 1-methylimidazole were chosen for the tosylation of **1** as they provided a very clean reaction without side products. The tosylation was exothermic and pure **2** was isolated

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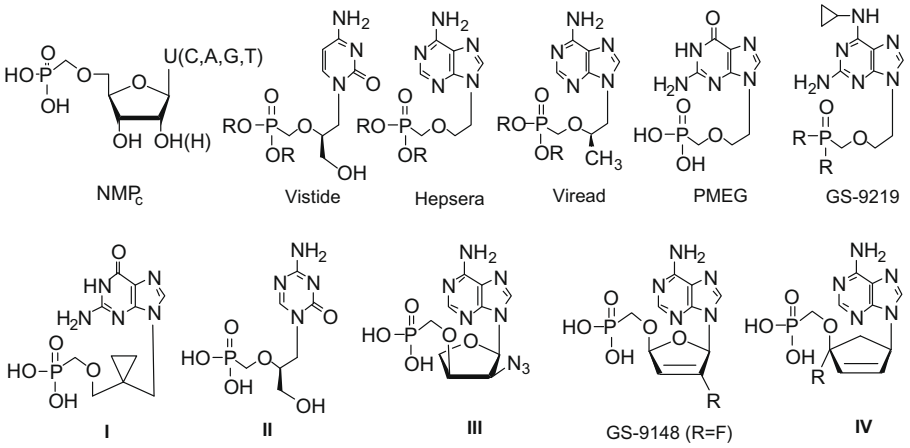
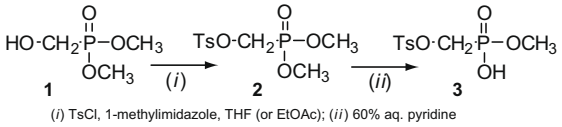


Figure 1. Structures of biologically significant and novel nucleoside phosphonic acids.



Scheme 1. Synthesis of methyl 4-toluenesulfonyloxymethylphosphonate. Reagents: (i) TsCl, 1-methylimidazole, THF (or EtOAc); (ii) 60% aq pyridine.

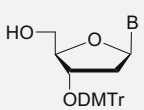
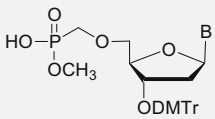
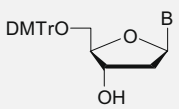
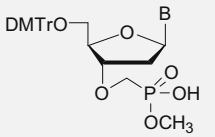
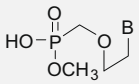
by extraction with ethyl acetate followed by crystallization from the same solvent. We examined two routes, **A** and **B** (see SD), which differed in the amount of 1-methylimidazole used (1.5 or 1.05 equiv) and in the temperature. The formation of compound **3** as the second reaction product can be suppressed by a low reaction temperature, as is reflected in the 'classical' approach **B**. Using route **A**, we allowed the exothermic tosylation reaction to proceed in order to demonstrate that the formed methyl ester **3** could be easily separated, even from a large quantity of salts, after acidification with a mineral acid and extraction with ethyl acetate followed by crystallization.

Selective hydrolysis of one of the methyl groups in **2** by treatment with 60% aqueous pyridine either at rt or at elevated temperature afforded **3**. Removal of the formed *N*-methylpyridinium cation was accomplished by filtration through a Dowex 50 (H^+) column or by acidification of the reaction mixture with hydrochloric acid and extraction of **3** from the solution with ethyl acetate (for large-scale reactions). Final purification was achieved by crystallization from ethyl acetate. Yields of ca. 80% were obtained in both cases.

In order to confirm the utility of the novel phosphonylating reagent for introducing a methyl phosphonomethyl moiety, we carried out the reactions of **3** (Table 1) with 3′-protected deoxynucleosides **5a–d** using sodium hydride in DMF. The respective products **6a–d** were obtained in yields of over 90% after silica gel purification. Likewise, the 2′-deoxypyrimidine phosphonates **6e** and **6f** were obtained from compounds **5e** and **5f** in 77% and 73% yields, respectively. The NMR data of the prepared compounds **6a–d**,**f** were in accordance with those published.[24] Finally, the reaction of **3** with unprotected 9-(2-hydroxyethyl)adenine[40] (**7**) as a precursor for the preparation of Hepsera (a potent antiviral based on PMEA) provided the desired PMEA monomethyl ester **8** in crystalline form in an isolated yield of 87%. The reaction conditions for the preparation of compounds **5e**,**f** and **7** were not optimized.

In conclusion, a straightforward and scalable synthesis of methyl 4-toluenesulfonyloxymethylphosphonate as a novel alkylating reagent for the introduction of a methyl group-esterified *O*-methylphosphonate moiety has been described. The efficiency of the alkylation was demonstrated by the preparation of several 2′-deoxyribonucleoside-*O*-methylphosphonate derivatives as well as the synthesis of a Hepsera precursor. No methylation of the nucleobases was observed. The monomethyl esters, as products of alkylations, can be used in phosphotriester chemistry to prepare phosphodiester-like compounds, or, upon saponification of the

Table 1
Reaction of **3** with nucleoside derivatives (for Experimental procedures, see SD)

Starting compound	B	Product	Yield (%)
 **5a** **5b** **5c** **5d**	Thymin-1-yl N^6-Benzoyladenosin-9-yl N^4-Benzoylcytosin-1-yl N^2-Isobutyrylguanosin-9-yl	 **6a** **6b** **6c** **6d**	90 99 93 97
 **5e**	Uracil-1-yl	 **6e**	77
5f	Thymin-1-yl	**6f**	73
 **7**	Adenin-9-yl	 **8**	87

remaining methyl ester group, provide free nucleoside phosphonic acids.

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Supplementary data

Supplementary data (experimental details for the synthesis of reported compounds including their characterization) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.09.062.

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