Organic LETTERS

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4-Toluenesulfonyloxymethyl-(*H*)-phosphinate: A Reagent for the Introduction of *O*- and *S*-Methyl-(*H*)-phosphinate Moieties

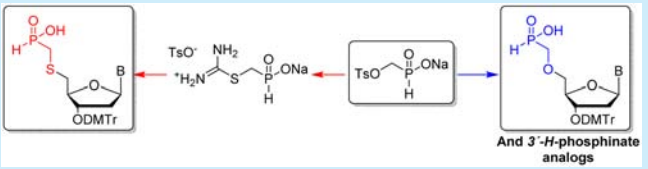
Ondřej Kostov,[†,‡] Ondřej Páv,[*,†] Miloš Buděšínský,[†] Radek Liboska,[†] Ondřej Šimák,[†,‡] Magdalena Petrová,[†] Pavel Novák,[†] and Ivan Rosenberg[*,†]

[†]Institute of Organic Chemistry and Biochemistry AS CR, v.v.i., Flemingovo nám. 2, 166 10 Prague 6, Czech Republic

[‡]Department of Chemistry of Natural Compounds, University of Chemistry and Technology, Prague, Technická 5, 160 00 Prague 6, Czech Republic

Supporting Information

ABSTRACT: The straightforward synthesis of sodium 4-toluenesulfonyloxymethyl-(*H*)-phosphinate and (*H*)-phosphinomethylisothiouronium tosylate as new reagents for the preparation of *O*- and *S*-methyl-(*H*)-phosphinic acid derivatives, respectively, is described. The reactivity of both reagents was demonstrated by the preparation of protected 2′-deoxyribonucleoside-*O*-methyl-(*H*)-phosphinates in the 5′- and 3′-series and 2′,5′-dideoxyribonucleoside-5′-*S*-methyl-(*H*)-phosphinates. These compounds represent a new class of monomers compatible with the solid phase synthesis of oligonucleotides by *H*-phosphonate chemistry, as it was proved with the synthesis of a fully phosphonate heptamer.



The synthesis of structurally diverse phosphonic and phosphinic acids has attracted considerable attention due to their biological activities as, for example, enzyme inhibitors,[1] antibiotics,[2] and peptidomimetics that mimic tightly binding peptidase transition-state inhibitors.[3] Phosphonate derivatives of nucleosides and acyclic nucleosides[4] comprising the phosphonomethyl ether linkage -O-CH_2-P(O)$(OH)_2$ instead of the natural phosphoester -O-P(O)$(OH)_2$ moiety have been found to be of remarkable biological importance. Several drugs based on acyclic nucleoside phosphonic acids (Figure 1) have been approved for the treatment of CMV-induced retinitis, hepatitis B, and HIV.[5]

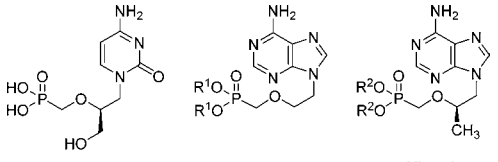


Figure 1. Drugs based on acyclic nucleoside phosphonic acid.

These biologically active compounds are distinguished by the presence of a negatively charged *O*-methylphosphonate moiety, which can be easily introduced by the etherification of a hydroxy group of suitably protected nucleoside derivatives, using dialkyl 4-toluenesulfonyloxymethylphosphonate (**1**) in the presence of sodium hydride.[6] It was recently reported that the *O*-methylphosphonate moiety of acyclic nucleoside phosphonic acids is transformed into *O*-methyl-(*H*)-phosphinate by reduction with $LiAlH_4$−TMSiCl followed by controlled oxidation of the formed −PH_2 compound using hydrogen peroxide.[7] The general usefulness of *H*-phosphinates can be illustrated by their simple conversion to phosphonothioates,[8] boranophosphonates,[9] or C−P−C phosphinates[10] (via Michael addition or Arbuzov reaction). Recently, we published a detailed study on the influence of incorporation of 3′- and 5′-*O*-methylphosphonate units on the hybridization properties of the modified strand and on its ability to activate RNase H.[11] Although the insertion of the bridging -CH_2- group into the phosphoester linkage should increase the total entropy of the system, only the 3′-*O*-methylphosphonate units decreased the stability of heteroduplexes, whereas the 5′-*O*-methylphosphonate units showed a stabilizing effect. Similarly, the 5′-*O*-methyl-phosphonate units alternating with two, three, or four phosphoester units showed superior enhancement of the RNase H cleavage rate. Here we propose the use of nucleoside-*O*-methyl-(*H*)-phosphinates as monomers for the incorporation of -O-CH_2-P(O)-O- phosphonate linkage into oligonucleotides on solid phase using *H*-phosphonate chemistry. We also predict that, similar to classic *H*-phosphonate (3′-O-P(O)(H)-O-5′) bonds, *H*-phosphinate internucleotide linkages (e.g., 3′-O-P(O)(H)-CH_2-O-5′) could be oxidized, sulfurized, borylated, amidated, etc., to create new oligonucleotide analogs. Therefore, the development of a robust method that would allow the introduction of the above-mentioned modifications to the phosphonate internucleotide linkage would be highly useful.

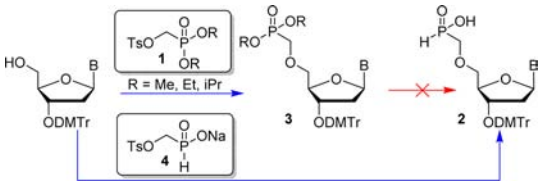
Because the straightforward preparation of protected nucleoside-*O*-methyl-(*H*)-phosphinic acids **2** from readily available dialkyl nucleoside-*O*-methylphosphonates **3** failed when using

Received: April 21, 2016
Published: May 13, 2016

DOI: 10.1021/acs.orglett.6b01167
Org. Lett. 2016, 18, 2704−2707

the reported reduction−oxidation[7d] procedure, we have examined synthetic possibilities to prepare sodium 4-toluenesulfonyloxymethyl-(*H*)-phosphinate (**4**) as a reagent for the direct preparation of protected nucleoside-*O*-methyl-(*H*)-phosphinates **2** (Scheme 1). To the best of our knowledge, a

Scheme 1. General Synthetic Strategy

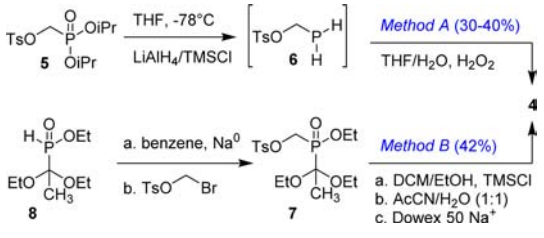


direct introduction of the *H*-phosphinate motif -CH_2-P(H)(O)-(OH) to the hydroxyl of a nucleoside or other hydroxyl-containing compounds in order to provide *O*-methyl-(*H*)-phosphinate derivatives has not been described.

We examined several synthetic routes to prepare the desired tosyloxymethylphosphinic derivative **4**. The method based on the reduction of chloride of tosyloxymethylphosphonic acid[6g,7c,d,12] failed. Direct tosylation of hydroxymethylphosphinic acid, prepared by hydroxymethylation of hypophosphorous acid with paraformaldehyde,[13] failed too. The attempt to use purified benzyloxymethyl phosphinic acid[14] as the precursor of hydroxymethylphosphinic acid was also unsuccessful, since catalytic hydrogenation on Pd led to decomposition, and Birch reduction gave the hydroxy product in poor yield. However, direct tosylation of purified hydroxymethylphosphinic acid also failed.[15]

More positive results were obtained when diisopropyl 4-toluenesulfonyloxymethylphosphonate[16] (**5**) was used as the starting compound. First, the reduction with TMSCl−$LiAlH_4$[7c,d] gave tosyloxymethylphosphine (**6**) which was separated from inorganic salts by filtration through Celite and immediately subjected to a controlled oxidation step with hydrogen peroxide to obtain the desired tosyloxymethylphosphinate **4** in a moderate yield (30−40%). However, the scale-up to multigram quantities significantly reduced the yield of **4** to 20−30% (Scheme 2, Method A).

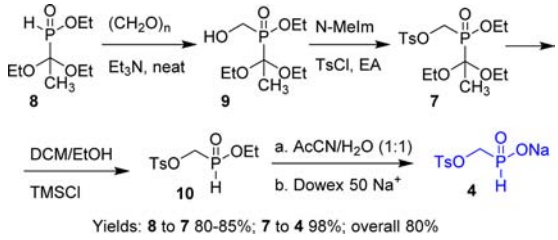
Scheme 2. Synthesis of 4: Methods A and B



Although the Arbuzov reaction of halomethyl 4-toluenesulfonates[17] with bis(trimethylsilyloxy)phosphine did not yield tosyl (*H*)-phosphinate **4**, a moderate yield of its protected precursor, tosyloxymethyl derivative **7**,[18] was obtained by the reaction of bromomethyl tosylate with the sodium salt of ethyl (1,1-diethoxyethyl)-(*H*)-phosphinate (**8**)[19] (Ciba−Geigy reagent, a masked hypophosphorous acid) (Scheme 2, Method B).

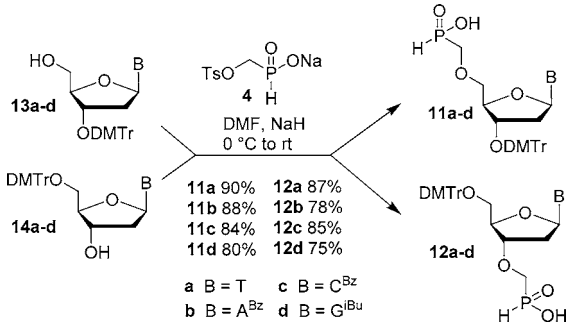
When the Ciba−Geigy reagent **8** was first hydroxymethylated with paraformaldehyde in the presence of triethylamine, the subsequent tosylation of the obtained derivative **9**[20] gave tosyloxymethyl compound **7** with an excellent yield of 80−85% over the two steps. Since the protected tosyl derivative **7** is not suitable for nucleophilic substitution with an alkoxide anion due to *O*-ethylation as a side reaction, the step-by-step removal of the phosphorus protecting groups[21] had to be performed. First, the 1,1-diethoxyethyl moiety was removed using HCl generated *in situ* from TMSCl in a mixture of DCM−ethanol, followed by the hydrolysis of the remaining ester group of **10** in 50% aqueous acetonitrile. The shelf-stable sodium tosyloxymethylphosphinate **4** was obtained with an 80% overall yield (Scheme 3, Method C).

Scheme 3. Synthesis of 4: Method C



To demonstrate the usefulness of sodium tosyloxymethyl-(*H*)-phosphinate **4** in reactions with alkoxides, we synthesized nucleoside-*O*-methyl-(*H*)-phosphinic acids **11a−d** and **12a−d** from 3′-*O*-dimethoxytrityl-2′-deoxynucleotides **13a−d** and 5′-*O*-dimethoxytrityl-2′-deoxynucleotides **14a−d**,[22] respectively, with excellent isolated yields (Scheme 4).[23]

Scheme 4. Preparation of Monomers 11a−d and 12a−d

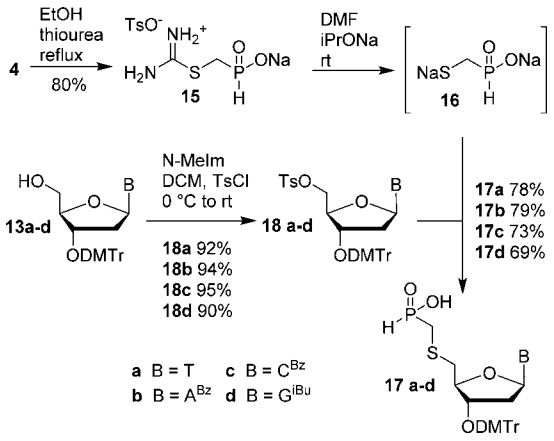


Recently, we reported[24] phosphonomethylisothiouronium tosylate as a precursor of mercaptomethylphosphonic acid. Here, we present a new reagent, (*H*)-phosphinomethylisothiouronium tosylate (**15**), as a synthetic equivalent of the unknown mercaptomethyl-(*H*)-phosphinic acid. This reagent is suitable for the introduction of the *S*-methyl-(*H*)-phosphinate moiety into compounds containing halo or alkyl/arylsulfonyloxy groups. Thus, sodium tosyloxymethyl-(*H*)-phosphinate **4** reacted effectively with thiourea to afford a crystalline, shelf-stable isothiouronium derivative **15**. 5′-Deoxynucleoside 5′-*S*-methyl-(*H*)-phosphinates **17a−d** were then readily prepared, starting from 2′-deoxy-3′-*O*-dimethoxytrityl-5′-*O*-tosylnucleosides **18a−d** and sodium mercaptomethyl-(*H*)-phosphinate (**16**), which was generated *in situ* from **15** and sodium isopropoxide in DMF (Scheme 5).[25]

Nucleoside (*H*)-phosphinates **11**, **12**, and **17** represent a new class of monomers for the solid phase synthesis of phosphonate oligonucleotides using *H*-phosphonate chemistry.[26] To illustrate their synthetic potential, we used monomers **11a−d** for the preparation of a fully phosphonate heptamer, 5′-d(TCGTCGA)-

DOI: 10.1021/acs.orglett.6b01167
Org. Lett. 2016, 18, 2704−2707

Scheme 5. Preparation of Monomers 17a−d



3′, comprising the 3′-O-P(O) (OH)-CH_2-O-5′ internucleotide linkages (Figure 2).

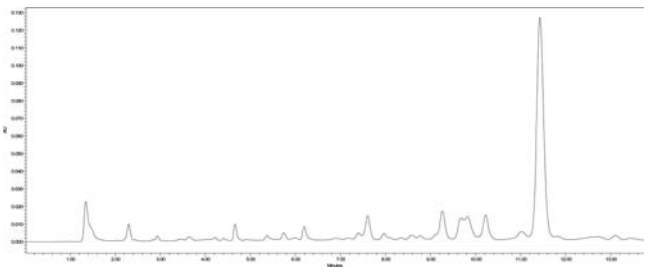


Figure 2. Example of IEC HPLC profile of crude fully phosphonate heptamer 5′-d(TCGTCGA)-3′.

During the search for the best condensation conditions, we have encountered the different reactivity of *H*-phosphinate monomers compared to standard *H*-phosphonate ones. The two mostly used condensation agents, adamantanecarbonyl chloride and pivaloyl chloride, affording only a low condensation yield.[27] Therefore, we selected 2-chloro-5,5-dimethyl-1,3,2-dioxaphosphorinane-2-oxide[28] as a condensation agent for the *H*-phosphinate coupling step, which is applicable also to classic *H*-phosphonates. Since the *H*-phosphinate linkage is very sensitive toward conventional water-containing oxidizers, suitable anhydrous oxidation conditions had to be found. The final oxidation of the synthesized oligonucleotide was successfully performed with an anhydrous mixture of CCl_4−methanol−Et_3N−MeIm (70:20:5:5; v/v), giving a fully $P^{(V)}$ oligonucleotide chain (Table 1).

We present here the scalable, straightforward synthesis of sodium tosyloxymethyl-(*H*)-phosphinate **4** and (*H*)-phosphinomethylisothiouronium tosylate **15** as new shelf-stable, crystalline reagents for the introduction of *O*- and *S*-methyl-(*H*)-phosphinate moieties, respectively, into nucleosides. Isothiouronium derivative **15** is a synthetic equivalent of the so far unknown mercaptomethyl-(*H*)-phosphinic acid. The excellent reactivity of both reagents **4** and **15** was demonstrated by the preparation of 2′-deoxyribonucleoside-*O*-methyl-(*H*)-phosphinates **11a−d** and **12a−d** in the 5′- and 3′-series, respectively, and 2′,5′-dideoxyribonucleoside-5′-*S*-methyl-(*H*)-phosphinates **17a−d**. Nucleoside-(*H*)-phosphinates represent a new class of monomers compatible with *H*-phosphonate chemistry, as was exemplified by the synthesis of a fully phosphonat heptamer using monomers **11a−d**. The synthesis of oligonucleotides with a mixed sequence using *H*-phosphinates and classic *H*-phosphonates under the described coupling and oxidation conditions will be the subject of a separate publication. The preparation of deoxyribooligonucleotides modified with phosphonoamide or thiophosphonate linkages as well as the synthesis of *ribo* nucleoside-(*H*)-phosphinate monomers is currently in progress. Last but not least, the great synthetic potential of **4** and **15** opens an easy access to structurally diverse, potentially biologically active compounds featuring the *O*- and *S*-methyl-(*H*)-phosphinate motif, respectively.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01167.

Full experimental details; ^1H, ^{13}C, and ^{31}P NMR spectra of all new compounds; HPLC; and MALDI-TOF-MS spectra of new oligonucleotide (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: pav@uochb.cas.cz.
*E-mail: rosenberg@uochb.cas.cz.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Czech Science Foundation (13-26526S to O.K., O.P., R.L., O.Š., M.P., and I.R.), Ministry of Health of the Czech Republic, Grant No. 15-31604A (all rights reserved), the Technology Agency of the Czech Republic (TA03010598 to M.P., O.P., Š.R., R.L., O.Š., and I.R.), and the Ministry of Education of the Czech Republic (programme "NPU I") Project LO1304 under the IOCB research project RVO: 61388963.

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Table 1. Solid Phase Synthesis Protocol

		H-phosphinate/*H*-phosphonate condensation method	
1	detritylation	3% DCA in DCM	180 s
2	coupling	0.1 M *H*-phosphonate/*H*-phosphonate monomers in pyridine−acetonitrile (50:50, v/v); 0.3 M NEP in pyridine−acetonitrile (5:95, v/v)	180 s
3	oxidation	CCl_4−methanol−Et_3N−MeIm (70:20:5:5; v/v)	600 s

DOI: 10.1021/acs.orglett.6b01167
Org. Lett. 2016, 18, 2704−2707

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DOI: 10.1021/acs.orglett.6b01167
Org. Lett. 2016, 18, 2704−2707