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Bis(hydroxymethyl)phosphine Oxides and Hydroxymethyl Phosphinic Acids as Phosphonic Acid Analogs

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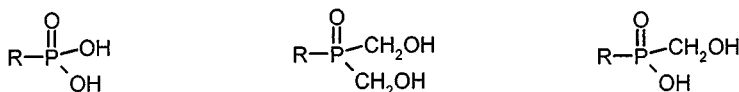
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BIS(HYDROXYMETHYL)PHOSPHINE OXIDES AND HYDROXYMETHYL PHOSPHINIC ACIDS AS PHOSPHONIC ACID ANALOGS

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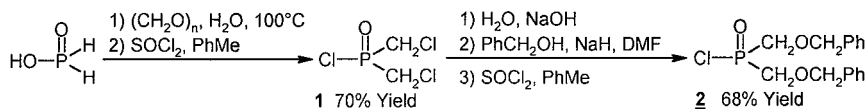
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Very active phosphonate or phosphinate compounds have been recently synthesized. However, their high ionic character can sometimes slow down their transport through cell membranes. New phosphorus pharmacophores constituted by bis(hydroxymethyl) phosphine oxide and hydroxymethylphosphinic acid groups were introduced in biologically active phosphorus compounds to evaluate their potential activity.



SCHEME 1

The construction of such compounds requires the synthesis of new building blocks bearing these two groups. One of them, bis(benzyloxymethyl)phosphinic chloride **2**, was obtained in five steps from hypophosphorous acid in a good overall yield. Its reactivity toward C-nucleophiles was also studied.

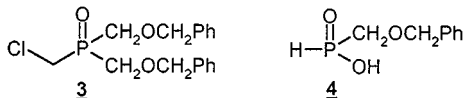


SCHEME 2

Bis(benzyloxymethyl)chloromethylphosphine oxide **3** was obtained from tetrakis(hydroxymethyl)phosphonium chloride by double

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protection of two hydroxy groups and was used further in reaction with heteroatomic nucleophiles. Benzyloxymethylphosphinate was synthesized from hypophosphorous acid and its reactivity is still under investigation.



SCHEME 3

Using these reagents, we were able to synthesize some biologically active phosphonic acids analogs of aminophosphonates and geminal bisphosphonates.¹

REFERENCE

- [1] H.-J. Cristau, C. Brahic, and J.-L. Pirat, *Tetrahedron*, **57**, 9149–9156 (2001).