Bis(trimethylsilyl) Trimethylsilyloxymethylphosphonite: a Useful Reagent for the Introduction of the Hydroxymethylphosphinate Group

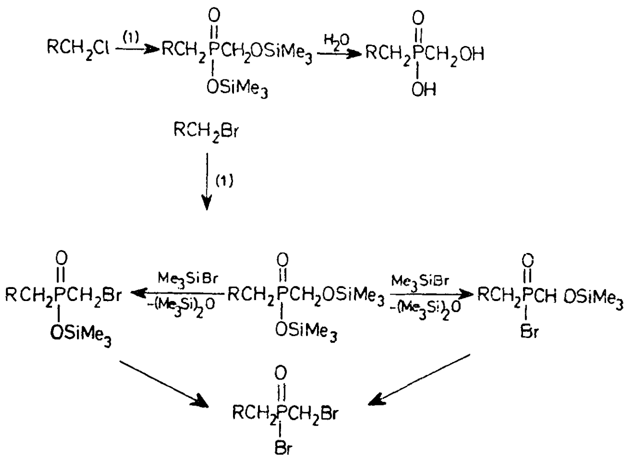
By Arthur F. Rosenthal,* Alex Gringauz, and Luis A. Vargas

(*Biochemical Research Laboratory, Long Island Jewish-Hillside Medical Centre, New Hyde Park, New York* 11040, *and Division of Pharmacotherapeutics, Brooklyn College of Pharmacy, Long Island University, Brooklyn, New York* 11216)

Summary Bis(trimethylsilyl) trimethylsilyloxymethylphosphonite has been synthesized and shown to undergo normal Arbuzov reaction to introduce the hydroxymethylphosphinate group, a phosphate isostere.

The methylenephosphinic acid group has been employed as a nonhydrolysable isosteric analogue of the C–O–P bond of phosphate esters and of the P–O–P bond of phosphoric anhydrides. Synthetic interest in such analogues has extended into areas as diverse as phospholipids[1] and nucleotide polyphosphates.[2] One hindrance to the further extension of such syntheses to new classes of compounds has been the paucity of methods for the introduction of a methylenephosphinate group containing a versatile functional group for further synthetic elaboration. A simple means of preparing unsymmetrical phosphinic acids containing a hydroxymethyl group as one of its two groups containing carbon appeared likely to satisfy this requirement.

We have recently described the synthetic utility of tris(trimethylsilyl) phosphite as an Arbuzov reagent for the



Scheme

preparation of lipid phosphonates.[3] Extension of this approach to the present problem thus required the reagent $Me_3SiOCH_2P(OSiMe_3)_2$ (**1**) as a protected but easily demasked hydroxymethylphosphonite. Treatment of crude, dried hydroxymethylphosphonous acid[4] in acetonitrile with trimethylsilyldiethylamine (3·4 mol) first at 5—10 °C and then at 85 °C (2 h), afforded (**1**), b.p. 51—53 °C at 0·5 mmHg, in 46% yield after two fractionations. The usefulness of this compound as a synthetic reagent is shown in the following example. 3-Chloropropionitrile was heated with 1 equiv. of (**1**) under nitrogen. At 130 °C a vigorous reaction ensued, and Me_3SiCl distilled from the reaction mixture. The reaction appeared complete after *ca.* 5 min, but heating at 135 °C was continued for 1 h. Hydrolysis in aqueous Bu^tOH–tetrahydrofuran (25 °C, 1h) gave a 91% yield of 2-cyanoethyl (hydroxymethyl) phosphinic acid, m.p. 65—67 °C. Preliminary experience suggests that alkyl chlorides are preferable to bromides or iodides in reactions with (**1**), possibly owing to silyl exchange between the reaction products as shown in the Scheme.

The extreme ease with which the phosphinic acid and hydroxymethyl groups can be unmasked after reaction with (**1**) suggests it can be used with more complex chlorides, provided they do not contain functional groups incompatible with Arbuzov reaction conditions.

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