

MILD ARBUZOV REACTIONS OF PHOSPHONOUS ACIDS

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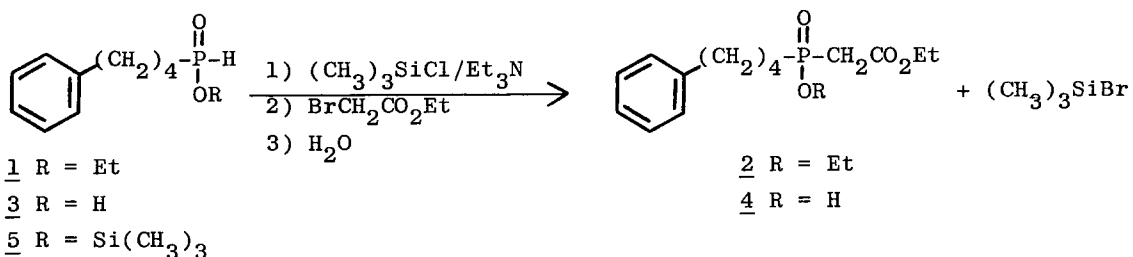
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Abstract: A very mild and simple method for the preparation of phosphinic acids from phosphonous acids through the intermediacy of silylalkyl phosphonites is described.

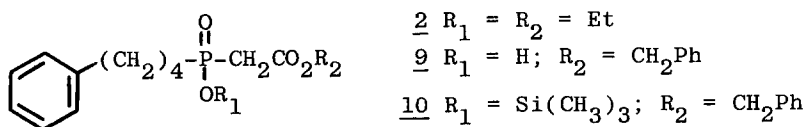
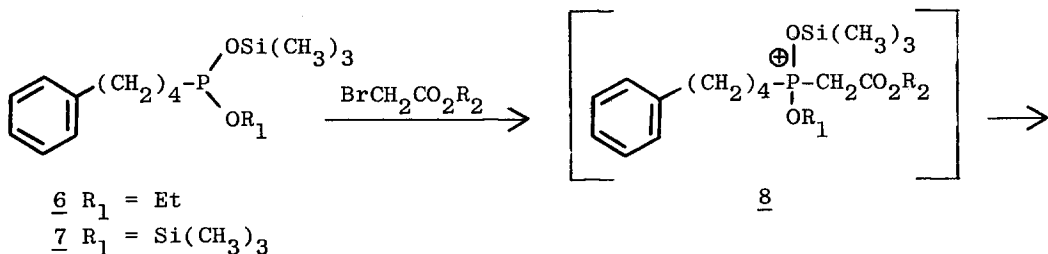
Phosphinic acids have become increasingly important compounds in recent years due to their useful biological properties.¹ The Arbuzov reaction of dialkyl alkylphosphonites with suitable alkylating agents² is a very commonly used method for the preparation of phosphinic acids, but it often requires high temperature, neat reaction mixtures and other harsh conditions. Additionally, complex product mixtures are common due to competitive alkylation by alkyl halide side products generated in the reaction. Preparation of phosphinic acids by base catalyzed alkylation frequently requires strongly alkaline conditions.³ The free radical addition of phosphonous monoesters across olefinic bonds for the preparation of phosphinic acid derivatives usually requires high reaction temperature and pressure while only affording modest to low yields and mixtures of products.⁴

Herein we describe a new, very mild, and convenient method for the preparation of phosphinic acids or esters from phosphonous acids or esters, which are in turn readily accessible by free radical addition of inexpensive sodium hypophosphite or hypophosphorous acid to olefins.^{5,6} Thus, treatment of the easily available phosphonous ester 1 with ethylbromoacetate in chloroform in the presence of trimethylsilyl chloride (TMS-Cl) and triethylamine (TEA) at room temperature effects conversion to phosphinic ester 2 in quantitative yield.

The reaction, though extremely sluggish at -78°C, was complete (by tlc) in 2 hours at 0°C. That the reaction takes place *via* intermediacy of a tervalent silyl phosphonite was confirmed by ³¹P-NMR observations.⁷ The formation of the tervalent phosphonite 6 in CDCl₃ at ambient temperature from 1 was instantaneous; further conversion of 6 to 2 required an additional 0.5 hour at 20°C on a 0.5 g scale.

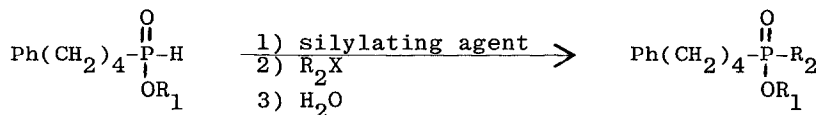



Similarly phosphonous acid 3, on treatment with two equivalents each of trimethylsilyl chloride and triethylamine and one equivalent of ethyl bromoacetate, produced phosphinic acid 4 in quantitative yield. ^{31}P -NMR experiments indicated that silyl ester 5 was the initially formed species which in turn was converted to disilylalkylphosphonite 7. Conversion of 7 to 10 was qualitatively faster than conversion of 6 to 2. The predicted signal corresponding to hypothetical intermediate 8 was not detected in either case.



As expected it was necessary to use an additional equivalent of silylating agent to achieve complete conversion when α -halo acids (instead of ester) were used as alkylating agents. Reaction of 1 with bromoacetic acid proceeds in 97% yield in the presence of two equivalents of TMS-Cl and TEA (run #7, Table 1) yet in the presence of one equivalent of each, no reaction takes place. Presumably, in the absence of excess silylating agent fast silyl transfer from phosphonous oxygen to carboxylic oxygen is the cause for the above observation.

Table 1



Run	R ₁	Silylating Agent	R ₂ X	Yield ^a
<u>1</u>	Et	(CH ₃) ₃ SiCl ^b	BrCH ₂ CO ₂ Et	99%
<u>2</u>	H	(CH ₃) ₃ SiCl ^c	BrCH ₂ CO ₂ Et	99%
<u>3</u>	H	(CH ₃) ₃ SiCl ^c	BrCH ₂ CO ₂ Bz	71%
<u>4</u>	C(CH ₃) ₃	(CH ₃) ₃ SiCl ^b	BrCH ₂ CO ₂ Bz	88%
<u>5</u>	Et	(CH ₃) ₃ SiCl ^b	BrCH ₂ CH ₂ CO ₂ Et	96%
<u>6</u>	Et	(CH ₃) ₃ SiCl ^b	CH ₃ CH(Br)CO ₂ Et	74%
<u>7</u>	Et	(CH ₃) ₃ SiCl ^c	BrCH ₂ CO ₂ H	97%
<u>8</u>	H	(CH ₃) ₃ SiCl ^d	BrCH ₂ CO ₂ H	28% ^f
<u>9</u>	Et	(CH ₃) ₃ SiCl ^c	BrCH ₂ CON-  -CO ₂ H	57%
<u>10</u>	Et	(CH ₃) ₃ SiCl ^b	Ph(CH ₂) ₄ Cl	N.R.
<u>11</u>	Et	(CH ₃) ₃ SiCl ^b	Ph(CH ₂) ₄ I	91% ^g
<u>12</u>	H	(CH ₃) ₃ SiCl ^c	Ph(CH ₂) ₄ I	48% ^g
<u>13</u>	Et	MSA ^e	BrCH ₂ CO ₂ Et	92%

^aCrystallized or chromatographed; ^b1 equivalent of silylating agent;

^c2 equivalents of silylating agent; ^d3 equivalents of silylating

agent; ^emonotrimethylsilylacetamide, 1 equivalent; ^fThe low yield

is due to isolation difficulties of the product, which is very

water soluble; ^gcrude yield.

A typical experimental procedure (run #3) is as follows: a mixture of phosphonous acid 3 (2.0 g, 0.01 mole) and triethylamine (3.2 ml, 0.022 moles) in chloroform (40 ml) was cooled in an ice bath. Trimethylsilyl chloride (2.8 ml, 0.02 moles) was added to the solution followed by benzyl bromoacetate (1.6 ml, 0.011 moles). After 5 hr, standard extractive aqueous work-up followed by crystallization from ether-hexane gave 2.48 g (71%) of phosphinic acid 9, m.p. 68-70°C.

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7. ³¹P Chemical shifts (ppm) and coupling constants (Hz) are as follows: 1, 39.13 (m.d.); 2, 48.36 (m); 3, 37.75 (b.d, 542.0); 5, 28.0 (m.d.); 6, 173.0 (s); 7, 163.0 (s); 9, 49.46 (m); 10, 37.93 (b.s).
8. Satisfactory IR, NMR (¹H and ¹³C), MS and/or elemental analysis were obtained for all new compounds.

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