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Stereoselective Synthesis of Phosphoryl Derivatives

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The reaction of dialkylphosphonites with N-(bromomethyl)phthalimide furnishes alkyl phenyl hydrogenphosphinates, dialkyl phenylphosphonates, and N-[(bromomethyl)phthalimido)]-phosphinates. The stereoselectivity of the primary product of the reaction appears to increase with the increasing size of the groups attached to the phosphorus atom.

Keywords Alkylphosphinates; dialkylphosphites; mass spectral characterization; Michaelis–Arbuzov reaction; stereoselectivity

INTRODUCTION

In connection with another ongoing project dealing with the synthesis of biologically active chiral phosphorus compounds, the reaction of dialkylphosphonites with N-(bromomethyl)phthalimide was examined and the mass spectral characterization of the compounds formed during the course of the reaction, are presented in this article. In this context, it should be stated that the reaction of N-(bromomethyl)phthalimide with trialkylphosphites has been previously employed in the preparation of novel antibiotics and other synthetically useful reagents.[1]

The classical Michaelis–Arbuzov reaction permits the transformation of tervalent P-compounds into pentavalent compounds containing the P=O (phosphoryl) moiety via the decomposition of the phosphonium salt intermediate formed from the nucleophilic attack by the phosphorus atom.[2,3] The attack by the tervalent P has been described to follow the mechanism of the S_N2 process.[4] The mechanism of the reaction with cyclic tervalent phosphorus compounds, in particular, has attracted a great deal of interest.[4] The transformation of the five- and six-membered cyclic phosphonites into phosphonates has been stated

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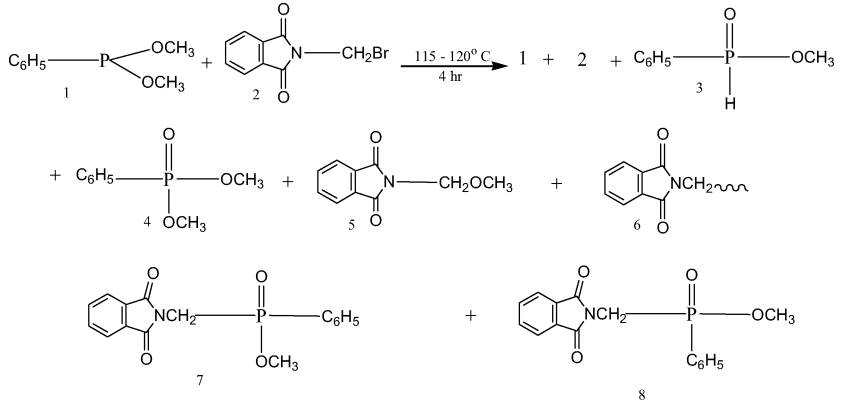
to follow a highly stereospecific course.[5a–5d] This has been found to be true even in the free radical–catalyzed Michaelis–Arbuzov reaction.[5d] Thus, a stereochemical approach has been employed to delineate the reaction pathways.[6,7]

RESULTS AND DISCUSSION

Dimethyl phenylphosphonite (**1**) was subjected to the Michaelis–Arbuzov reaction in the presence of N-(bromomethyl)phthalimide (**2**) at 115–120°C for 4 h. After cooling the reaction mixture to room temperature, the volatile alkyl halide formed during the course of the reaction was removed under house vacuum. The residue solidified after being kept overnight in the refrigerator. The GC-MS analysis of the reaction mixture showed the presence of eight components, two of which were the staring materials, namely **1** and **2** (Scheme 1). There is nothing new about the formation of phenyl hydrogenphosphinate (**3**) and dimethylphenylphosphonate (**4**) from **1**.[2g] Component **5** was identified as N-(methoxymethyl)phthalimide. Its formation apparently involves the displacement of the halogen of N-(bromomethyl)phthalimide (**2**) by the methoxyl group, which itself is formed during the course of the Michaelis–Arbuzov reaction. This inference is supported by previous observations.[8] Compound **6** is present in trace amounts and could not be completely identified, as it undergoes extensive disintegration in the mass spectrometer before its molecular ion peak is registered. As evidenced by the presence of the most prominent peak (m/e = 160) in its mass spectrum, this compound carries the phthalimodomthylene moiety in its structure. Methyl (phthalimidomethyl) phenylphosphinate



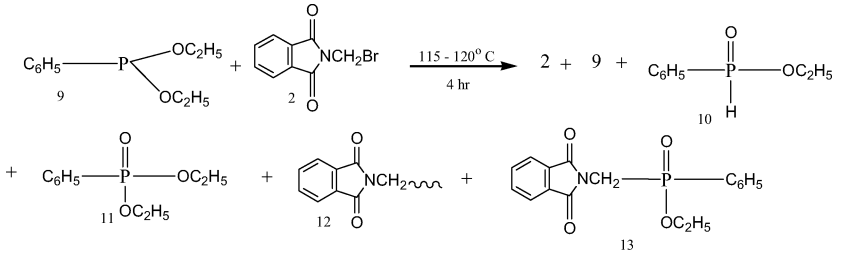
SCHEME 1 Reaction of dimethyl phenylphosphonite.

TABLE I Mass Spectral Fragmentation of Compounds Cited in Scheme 1

1. Hydrogen methyl phenylphosphinate (**3**): $M^+ = 156$ (r.t. = 7.22 min, 2.1%) 155 (M-H, 99%); 141 (M-CH_3); 126 (M-OCH_3); 91 (C_7H_7); 79 (M-C_6H_5, 100%); 77 (C_6H_5); 65 (PH_2O_3) and 51 (C_4H_3).
2. Dimethyl phenyphosphinate (**1**): $M^+ = 170$ (r.t. = 7.54 min, 12.8%); 169 (M-H); 155 (M-CH_3,100%); 140 (M-OCH_2); 125 [$C_6H_5P(O)H$]; 77 (C_6H_5); 63 (PO_3) and 51 (C_4H_3).
3. Dimethyl phenyphosphonate (**4**): $M^+ = 186$ (r.t. = 7.60 min, 2.0%); 185 (M-H, 97%); 169 (185-2H-CH_3); 155 (M-OCH_3); 141 (M OCH_2-CH_3); 125 [$C_6H_5P(O)H$]; 109 (M-C_6H_5); 91 (C_7H_7, 98%); 77(C_6H_5, 100%); 63 (PO_3) and 51 (C_4H_3).
4. N-Methoxymethyl)phthalimide (**5**): $M^+ = 191$ (not seen, r.t. = 9.48.min, 1.0%); 190 (M-H); 176(191-CH_3); 160 (M-OCH_3); 148 (M-OC_2H_3); 133 (148-NH); 117 (133-O); 104 (C_6H_4CO); 77(C_6H_5, 100%); and 51 (C4H3).
5. Unknowm (**6**): M^+ = (not seen recorded); (r.t. = 9.97.min, 02%). This is a phthalimide derivative.The wavy line represents the unknown part of the molecule.
6. N-(Bromomthyl)phthalimide (**2**): $M^+ = 279$ (r.t. = 10..46.min,2.5%); 160 (M-HBr, 100%); 133[C6H4(CHO)(CO)]; 104 (C_6H_4CO); 76 (C_6H_4); 56 ($CONCH_3$) and 44 ($CONH_2$).
7. Methyl (phthalimidomethyl) phenylphosphinate (**7**): $M^+ = 315$ (r.t. = 16.09.min,76.09%); 300 (M-CH_3); 237 (M-C_6H_5-2H); 219 (237-H_2O); 189 (219-OCH_2); 160 (M-$C_6H_4(CO)_2NCH_2$, 100%);133 [C_6H_4(CHO)(CO)]; 104 [C_6H_4(CO)]; 91 (C_7H); 77 (C_6H_5); 65 (PH_2O_3) and 51 (C_4H_3).
8. Methyl (phthalimidomethyl) phenylphosphinate (**8**): $M^+ = 315$ (r.t. = 16..38.min,2.5%); 300 (M-CH_3); 237 (M-C_6H_5-2H); 219 (237-H_2O); 189 (219-OCH_2); 160 (M-C_6H_4(CO)2NCH_2, 100%);133 [C_6H_4(CHO)(CO)]; 104 [C_6H_4(CO)]; 91 (C_7H); 77 (C_6H_5); 65 (PH_2O_3) and 51 (C_4H_3).

(**7**) turned out to be the major product of the reaction (76.9%). It is interesting to note the characterization of its diastereomer, **8**, which is present in small amounts (2.5%). This may be due to the steric influence of the phenyl moiety. The mass spectral fragmentation data of the above-mentioned compounds are given in Table I.

This reaction was repeated but with one difference: the substrate **1** was substituted with diethyl phenylphosphite (**9**) in the reaction. In this case, the reaction product, a viscous, oily material, was found to contain six components, namely diethyl phenylphosphite (**9**), ethyl phenyl hydrogenphosphinate (**10**), diethyl phenylphosphonate (**11**), an unknown compound (**12**), N-(bromomethyl)phthalimide (**2**), and ethyl (phthalimidomethyl) phenylphosphinate (**13**) (Scheme 2). Here again, the unknown compound contains the (phthalimidomethyl) moiety. This compound degrades extensively before its molecular ion peak is recorded. Compound **13** was the desired product, which formed about 88.2% of the reaction mixture. Table II furnishes the details of the characterization of the compounds using their GC-MS breakdown

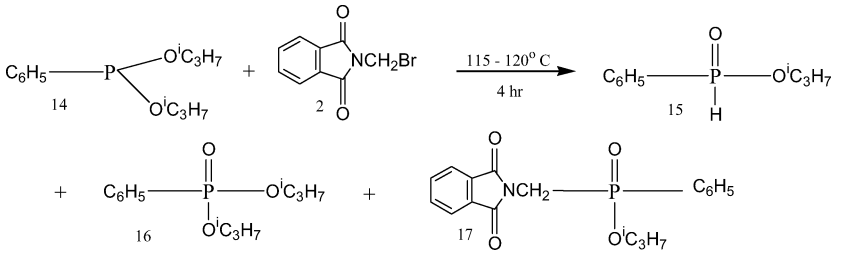


SCHEME 2 Reaction of diethyl phenylphosphonite.

behavior. Next, di-isopropyl phenyl-phosphonite (**14**) was used as the substrate. This reaction was found to be the cleanest of the three reactions, for only trace amounts of two impurities accompanied the expected compound, namely isopropyl (phthalimidomethyl)phenylphosphinate (**17**), and its yield was almost quantitative (98.9%). The two compounds in question are: (i) isopropyl phenyl hydrogenphosphinate (**15**) and (ii) di-isopropyl phenylphosphonate (**16**) (cf. Scheme 3). Table II furnishes the details regarding the mass spectral fragmentation behavior of the compounds cited above.

In the three reactions described above, the presence of the alkyl phenyl hydrogenphosphinates, namely **3**, **10**, and **15**, was detected. This observation suggests that during the course of the reaction, OCH_2-, OC_2H_4-, and OC_3H_6- fragments are expelled from their precursor moieties. There are precedents for this inference.[8a,9]

Also, characterized were the respective phosphonates **4**, **11**, and **16**, which obviously arise from the oxidation reactions. Again, there are precedents for this suggestion.[8,10,11] It is interesting to note the increasing yields of the expected Michaelis–Arbuzov reaction products with the increasing size of the groups attached to the phosphorus atom of the substrates. The third reaction appears to be highly stereoselective, in that it furnishes 98.9% of the desired product. Only in the case



SCHEME 3 Reaction of diiisopropyl phenylphosphonite.

TABLE II Mass Spectral Fragmentation of Compounds Cited in Schemes 2 and 3

1. Diethyl phenylphosphonite (9): $M^+ = 198$(r. t. = 8.24 min, 2.3%); 170 (M-C_2H_4); 141 ($C_6H_5P(O)OH$,100%);125 [$C_6H_5PH(O)$]; 93[$P(O)OC_2H_5$]; 77 (C_6H_5); 51 (C_4H_3) and 43 (OC_2H_3).
2. Hydrogen ethyl phenylphosphinate (10): $M^+ = 170$ (r. t. = 7.42 min, 4.2%); 169 (M-H); 142 (M-C_2H_4); 125(142-OH, 100%); 91 (C_7H_7 or $P(OH)(OC_2H_5)$; 78 ([$P(O)(OCH_3$]. 77 (C_6H_5); 65 (PH_2O_2); 51 (C_4H_3) and 43(OC_2H_3).
3. Diethyl phenylphosphonate (11): $M^+ = 214$ (r. t. = 8.12 min, 3.1%); 186 (M-C_2H_4); 158 [$C_6H_5P(O)(OH)_2$,100%]; 141 (158-OH, 98%); 124 [$C_6H_5P(O)$]); 94 [$P(O)H_2(OC_2H_5)$; 77 (C_6H_5); 65 (PH_2O_2); 51 (C_4H_3) and 43(OC_2H_3).
4. Unknown (12): M^+ = not known (r. t. = 9.61 min, 3.5%); has a phthalimido moiey.
5. Ethyl (phthalimidomethyl)phenylphosphonate (13): $M^+ = 329$ (r. t. = 15.84 min, 88.2%); 284 (M-OC_2H_5); 237(M-C_6H_5-CH_3); 219 (238-H2O); 189(219-OCH_2); 160 (M-$P(O)(OC_2H_5)$); 141 [$C_6H_5P(O)(OH)$, 100%[;104 (C_6H_5CO); 91 ($P(OH)(OC_2H_5)$; 77 (C_6H_5) and 51 (C_4H_3).
6. Hydrogen isopropyl phenylphosphinate (15): $M^+ = 184$ (r. t. = 8.53min, 1.1%); 183 (M-H); 169 (M-CH_3);143 (M-$C_3H_5$100%); 125 [$C_6H_5P(O)OH$]; 78 ([$P(O)(OCH_3$]. 77 (C_6H_5) and 65 (PH_2O_2).
7. Diisopropyl phenylphosphonate (16): M+ = 242 (r. t. = 9.23min, 0.9%); 227 (M-CH_3); 201 (M-C_3H_5); 183 (201 -H_2O); 159 (201-C_3H_6,: 100%);, 141 [$C_6H_5P(O)(OH)$], 119 [$CH_3P(O)$ (OC_3H_7)]; 84 (201-OC_3H_5); 77 (C_6H_5) and 59(OC_3H_7).
8. Isopropyl (phthalimidomethyl)phenylphosphinate (17): $M^+ = 343$ (r. t. = 19..01 min,98.9%); 301 (M-C_3H_6);284(301-OH); 237 [$C_7H_5N(COP(O)(OC_3H_7)$]; 219 (237-H_2O); 183 (C_6H_5 $P(O)(OC_3H_7)$; 160 (M-$P(O)(OC_3H_7)$;141 [$C_6H_5P(O)(OH)$, 100%); 104 (C_6H_5CO); 91 ($P(OH)(OC_2H_5)$; 77 (C_6H_5) and 65 (PH_2O_2).

of dimethyl phenylphosphonite (**1**) was the presence of the diastereomer (**8**) of the expected product (**7**) detected. Attempts are underway to transform these compounds, namely phthalimidophosphinates (**7**, **13**, and **17**), into bioactive phosphorus-containing compounds.

In summary, the yields of the products of the reaction of N-(bromomethyl)phthalimide (**2**) with dimethyl phenylphosphonite (**1**), diethyl phenylphosphonite (**9**), and diisopropyl phenylphosphonite (**14**) are 76.8%, 88.2%, and 98.9% respectively (cf. Figure 1). This clearly implies the importance of the steric bulk of the alkoxy group attached to the phosphorus atom.

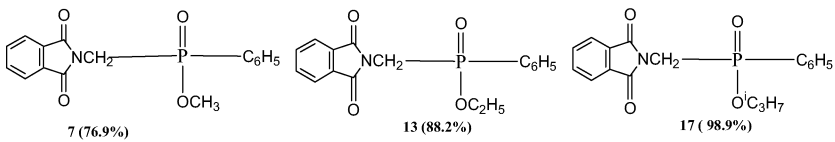


FIGURE 1 Percentage of yields of the products.

EXPERIMENTAL

All solvents were dry and freshly distilled prior to use. Mass spectra were obtained using a Finnigan TSQ-7000 GC/MS/MS equipped with a 30 m × 0.25 mm, i.d. DB-5 capillary column (J and W Scientific, Folsom, CA) or a Finnigan 5100 GC/MS equipped with a 15 m × 0.25 mm, i.d. Rtx-5 capillary column (Restek, Bellefonte, PA). The conditions on the 5100 were oven temperature 60–270°C at 10°C/min, injection temperature was 210°C, interface temperature 230°C, electron energy 70 eV, emission current 500 μA, and scan time 1 sec. The conditions on the TSQ-7000 were oven temperature 60–270°C at 15°C/min, injection temperature 220°C, interface temperature 250°C, source temperature 150°C, electron energy 70 eV (EI) or 200 eV (CI), emission current 400 μA (EI) or 300 μA (CI), and scan time 0.7 sec. Data were obtained in both the electron ionization mode (range 45–450 da) and chemical ionization mode (mass range 60–450 da). Ultrahigh purity methane was used as the CI agent gas with a source pressure of 0.5 Torr (5100) or 4 Torr (TSQ-7100). Routine GC analyses were accomplished with a Hewlett-Packard 5890A gas chromatograph equipped with a J and W Scientific 30 m × 0.53 mm, i.d. DB-5 column (J and W Scientific, Folsom, CA).

General Procedure

Reaction of Dimethyl Phenylphosphonite (1) with N-(Bromomethyl)phthalimide (2)

A mixture containing dimethyl phenylphosphonite (**1**, 5 mmol) and N-(bromomethyl)-hthalimide (**2**, 5 mmol) was heated with stirring and under nitrogen for 4 h at 115–120°C. The reaction mixture was cooled to ambient temperature, and the volatile material was distilled off in vacuo. The residue was first analyzed by gas chromatography. Then, it was heated again under house vacuum and reanalyzed using GC. When no additional peaks appeared in the chromatogram, the reaction product was then subjected to GC-MS analysis (using both the EI and CI modes). The following compounds were thus identified: (i) hydrogen methyl phenylphosphinate (**3**), (ii) dimethyl phenylphosphinite (**1**); (iii) dimethyl phenylphosphonate (**4**), (iv) N-(methoxymethyl)phthalimide (**5**), (v) unknown (**6**), (vi) N-bromomethylphthalimide (**2**), (vii) methyl (phthalimidomethyl) phenylphosphinate (**7**), and (viii) methyl (phthalimidomethyl) phenylphosphinate (**8**, isomer of **7**), and their mass spectral data are given in Table I.

Reaction of Diethyl Phenylphosphonite (9) with N-(Bromomethyl)phthalimide (2)

The reaction was carried out in an analogous manner as described above, except **1** was replaced with diethyl phenylphosphonite (**9**). The GC-MS analysis permitted the characterization of (i) diethyl phenylphosphite (**9**), (ii) hydrogen ethyl phenyl-phosphinate (**10**), (iii) diethyl phenylphosphonate (**11**), (iv) unknown (**12**), (v) N-bromomethyl(phthalimide (**2**), and (vi) ethyl (phthalimidomethyl) phenylphosphinate (**13**) (cf. Scheme 2). Here again, the unknown compound possesses the phthalimido moiety, and its molecular ion peak could not be ascertained due to its premature extensive degradation. The desired product, namely ethyl (phthalimidomethyl) phenylphosphinate (**13**), was formed in 88.2% yields. Table II provides the mass spectral information.

Reaction of Diisopropyl Phenylphosphonite (14) with N-(Bromomethyl)phthalimide (2)

The reaction was conducted in a similar manner as described above, except **1** was replaced with diisopropyl phenylphosphonite (**14**). The GC-MS analysis enabled the identification of the three components, namely (i) hydrogen isopropylphenylphosphinate (**15**), (ii) diisopropyl phenylphosphonate (**16**), and (iii) isopropyl (phthalimidomethyl) phenylphosphinate (**17**). The last compound was obtained in 98.9% yields. The mass spectral breakdown of the three compounds is given in Table II.

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