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Unexpected synthesis of hydrogen phosphonate by three component reaction of diphenylphosphite, isocyanates and *N*-methyl imidazole

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Abstract: The 1:1 intermediates generated by addition of *N*-methylimidazole to isocyanates were reacted with diphenylphosphite to produce phosphonates in good to excellent yields under solventless conditions.

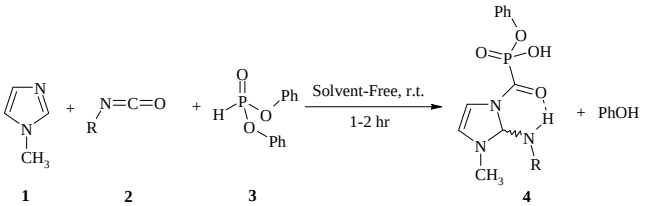
Keywords: Diphenyl phosphite, Phosphonate, *N*-Methyl imidazole, Isocyanates.

Introduction

One of the most challenging task in organic synthesis is the efficient preparation of complex molecules starting from easily available raw materials. Especially attractive are one-pot multi-component coupling reactions (MCRs), which introduce several elements of diversity into a molecule in a single step. MCRs contribute to the requirements of an environmentally friendly process by reducing the number of synthetic steps, energy consumption and waste production [1-8].

In other hand phosphonates exhibit a wide range of notable biological properties, which expand their applications as enzyme inhibitors,metabolic probes [7], peptide mimetics [8], antibiotics, and pharmacologic agents [9] besides to their traditional roles as intermediates in organic synthesis [10]. Extensive efforts have been made to introduce convenient and efficient methods for the synthesis of phosphonates [11-13].

As part of our group current studies on the synthesis of alkyl phosphonates, and α aminophosphonates [15-19] Herein we report the results of our studies involving the reactions of *N*-Methylimidazole (**1**) Isocyanates (**2**) and Diphenylphosphite(**3**) which constitute a synthesis of phenyl hydrogen [(2-anilino-3-methyl-2,3-dihydro-1 *H*-imidazol-1-yl) carbonyl] phosphonate derivatives (**4**) (Scheme **1**). Under similar reaction conditions, we tested diethylphosphite but no reaction was happened.



1 **2** **3** **4**

3, 4	R	Yield % of 4
a	Ph	90
b	4-Cl-C_6H_4	93
c	4-Br-C_6H_4	90
d	4-NO_2-C_6H_4	94
e	Cyclohexyl	89
f	n-Bu	85

Scheme 1: Synthesis of hydrogen phosphonate derivatives.

Results and discussion

The structures of compounds **4a-4f** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C and ^{31}P NMR spectral data. For example, the ^{1}H NMR spectrum of **4a** exhibited methyl protons (δ3.55, s), methine proton (δ 6.83, s), OH proton (δ 8.28, s), and NH proton (δ 9.25, s) along with multiplets for the aromatic protons. The ^{1}H-decoupled ^{13}C NMR spectrum of **3a** showed 13 distinct resonances that

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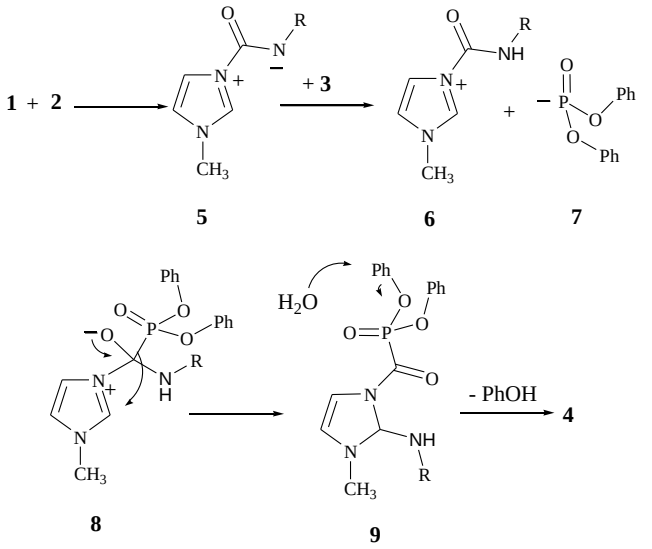
confirms the proposed structure. The ^{1}H-decoupled ^{31}P NMR spectrum of **3a** showed resonance at (δ-8.5 ppm) for the. The IR spectrum of **3a** displayed aliphatic, aromatic and P=O bands (2928, 1663, 1580, 1451, 1377, 1258, 1218 and 1166cm^{-1}). The ^{1}H NMR and ^{13}C NMR spectra of **4b-3f** are similar to those for **4a** except for the amide moieties, which exhibited characteristic resonances in appropriate regions of the spectrum.

Although the mechanistic details of the reaction are not known, a plausible rationalization may be advanced to explain the product formation. Presumably, the intermediate **5** that formed from **1** and **2**, protonated by **3** to produce **6** and **7**, reaction between this intermediateslead to **8**, by intermolecular rearrangement it converted to intermediate **9**, then **9** could undergone eliminationof phenol in the presence of water to product **4** (Scheme **2**).



Scheme 2: Proposed mechanism for the formation of products.

Conclusion

In summary, we report a green synthesis phenyl hydrogen [(2-anilino-3-methyl-2, 3-dihydro-1 *H*-imidazol-1-yl) carbonyl] phosphonate derivatives in good yields under solventless conditions. The present procedure has the advantage that, not only is the reaction performed under solvent free conditions, but also the reactants can be mixed without any prior activation or modification. The simplicity of the present procedure makes it an interesting alternative to other approaches.

Experimental

General procedure:

Compounds 1, 2 and 3 were obtained from Fluka and were used without further purification. M.p. Electrothermal-9100 apparatus. IR Spectra: Shimadzu IR-460 spectrometer. ^{1}H-, ^{13}C-, ^{31}P- NMR spectra: Bruker DRX-500 AVANCE instrument; in $CDCl_3$ at 500, 125 and 200.8 MHz, respectively; δ in ppm. Elemental analyses (C, H, N) were performed with a Heraeus CHN-O-Rapid analyser.

Typical procedure for preparation of (3):

To a stirred mixture of 0.47 g of diphenylphosphite (2 mmol) and Isocyante 2 (2 mmol) was added 0.164 g of *N*-Methylimidazole (2 mmol) at rt. After completion of the reaction (1-2 h), the precipitate was washed with cold ether (4 mL) to afford pure title compounds.

Data:

Phenyl hydrogen [(2-anilino-3-methyl-2,3-dihydro-1 *H*-imidazol-1-yl)carbonyl]phosphonate (**4a**) With powders, mp 135-173 °C, 0.32 g, yield 90%. IR (KBr) (νmax/cm^{-1}): 2928, 1663, 1580, 1451, 1377, 1258, 1218 and 1166. CS (EI, 70 eV): m/z (%) = 283 (7), 267 (5), 158 (12), 94 (100), 82 (49), 76 (12), 56 (68). Anal. Calcd for $C_{17}H_{18}N_3O_4P$ (359.32): C, 56.83; H, 5.05; N, 11.69; found: C, 56.90; H, 5.12; N, 11.79%. ^{1}H NMR: 3.55 (3 H, s, CH_3), 7.13-20 (5 H, m, 5 CH), 7.29-7.37 (4 H, m, 4CH), 7.53 (1 H, d, $^{3}J_{HH}$ =5.0, CH), 7.50 (1 H, $^{3}J_{HH}$ =5.0, CH), 7.64 (2 H, d, $^{3}J_{HH}$ =10.0, 2 CH), 8.28 (1 H, s, OH), 9.25 (1 H, s, NH). ^{13}C NMR: 35.2 (N-CH_3), 115.2 (CH), 120.6 (2 CH),120.9 (2 CH), 122.0 (CH), 123.1 (CH), 127.4 (CH), 128.3 (2 CH), 128.6 (2 CH), 137.4 (CH), 139.0(C), 153.2 (C, d, $^{2}J_{CP}$ = 7.4), 172.1 (C, d, $^{1}J_{CP}$ = 216.2). ^{31}P NMR: -9.3.

*Phenyl hydrogen {[2-(4-chloroanilino)-3-methyl-2,3-dihydro-1H-imidazol-1-yl]carbonyl}phosphonate (**4b**):*

With powders, mp 145-147 °C, 0.37 g, yield 93%. IR (KBr) (νmax/cm^{-1}): 2930, 1643, 1580, 1453, 1379, 1258, 1213 and 1166. MS (EI, 70 eV): m/z (%) = 317 (6), 266 (5), 158 (13), 94 (100), 82 (65), 76 (14), 56 (55). Anal. Calcd for $C_{17}H_{17}ClN_3O_4P$ (393.76): C, 51.86; H, 4.35; N, 10.67; found: C, 51.92; H, 4.43; N, 10.60%. ^{1}H NMR: 3.80 (3 H, s, CH_3), 6.96 (1 H, t, $^{3}J_{HH}$ =7.5, CH), 7.13 (2 H, d, $^{3}J_{HH}$ =8.0, 2 CH), 7.20 (2 H, d, $^{3}J_{HH}$ =8.0, 2 CH), 7.24 (1 H, s, CH), 7.31 (2 H, d, $^{3}J_{HH}$ =9.0, 2 CH), 7.54 (1 H, br s, CH), 7.61 (1 H, br s, CH), 7.73 (2 H, d, $^{3}J_{HH}$ =9.0, 2 CH), 8.91 (1 H, s, OH), 9.88 (1 H, s, NH).^{13}C NMR: 35.3 (N-CH_3), 118.2 (CH), 120.7 (2 CH), 120.8 (2 CH),122.4 (CH), 123.0 (CH), 127.2 (CH), 128.4 (2 CH), 128.7 (2 CH), 137.4

(C), 139.8(C),153.2 (C, d, $^2J_{CP}$ = 7.4),172.1 (C, d, $^1J_{CP}$ = 210.3). ^{31}P NMR: -8.7.

*Phenyl hydrogen {[2-(4-bromoanilino)-3-methyl-2,3-dihydro-1H-imidazol-1-yl]carbonyl}phosphonate (**4c**):*

With powders, mp 146-148° C, 0.37 g, yield 90%. IR (KBr) (νmax/cm^{-1}): 2933, 1644, 1570, 1456, 1379, 1259, 1220 and 1176 cm^{-1}. MS (EI, 70 eV): m/z (%) = 362 (8), 265 (5), 158 (16), 94 (100), 82 (60), 76 (11), 56 (65). Anal. Calcd for $C_{17}H_{17}BrN_3O_4P$ (438.21):C, 46.60; H, 3.91; N, 9.59;found: C, 46.68; H, 3.86; N, 9.70%. ^{1}H NMR: 3.78 (3 H, s, CH_3), 7.06 (1 H, t, $^3J_{HH}$ =7.4, CH), 7.16 (2 H, d, $^3J_{HH}$ =8.1, 2 CH), 7.20 (2 H, d, $^3J_{HH}$ =8.1, 2 CH), 7.27 (1 H, s, CH), 7.31 (2 H, d, $^3J_{HH}$ =8.9, 2 CH), 7.54 (1 H, br s, CH), 7.56 (1 H, br s, CH), 7.71 (2 H, d, $^3J_{HH}$ =8.9, 2 CH), 8.85 (1 H, s, OH), 9.83 (1 H, s, NH). ^{13}C NMR: 35.4 (N-CH_3), 118.1 (CH), 120.6 (2 CH), 120.9 (2 CH), 122.2 (CH), 123.1 (CH), 127.2 (CH), 128.5 (2 CH), 128.7 (2 CH), 137.1 (C), 139.5(C), 153.2 (C, d, $^2J_{CP}$ = 8.0), 172.4 (C, d, $^1J_{CP}$ = 211.4). ^{31}P NMR: -10.1.

*Phenyl hydrogen {[3-methyl-2-(4-nitroanilino)-2,3-dihydro-1H-imidazol-1-yl]carbonyl}phosphonate (**4d**):*

With powders, mp 150-152° C, 0.38 g, yield 94%. IR (KBr) (νmax/cm^{-1}): 2931, 1653, 1571, 1443, 1387, 1261, 1215 and 1165. MS (EI, 70 eV): m/z (%) = 328 (10), 269 (5), 158 (12), 94 (100), 82 (65), 76 (14), 56 (75). Anal. Calcd for $C_{17}H_{17}N_4O_6P$ (404.31): C, 50.50; H, 4.24; N, 13.86;found: C, 50.59; H, 4.34; N, 13.77%. ^{1}H NMR: 3.84 (3 H, s, CH_3), 6.95 (1 H, t, $^3J_{HH}$ =7.2, CH), 7.13-7.20 (4 H, m, 4 CH), 7.22 (1 H, s, CH), 7.60 (1 H,bs, CH), 7.65 (1 H, bs, CH), 8.03 (2 H, d, $^3J_{HH}$ =10.0, 2 CH), 8.16 (2 H, d, $^3J_{HH}$ =10.0, 2 CH), 8.98 (1 H, s, OH), 10.40 (1 H, s, NH).^{13}C NMR: 35.2 (N-CH_3), 118.0 (CH), 119.5 (2 CH),120.6 (2 CH), 122.4 (CH), 122.9 (CH), 124.5 (2 CH), 128.7 (2 CH), 135.7 (CH), 142.3(C), 144.8 (C), 153.2 (C, d, $^2J_{CP}$ = 7.5), 172.0 (C, d, $^1J_{CP}$ = 210.0). ^{31}P NMR: -7.8.

*Phenyl hydrogen {[2-(cyclohexylamino)-3-methyl-2,3-dihydro-1H-imidazol-1-yl]carbonyl}phosphonate (**4e**):*

With powders, mp 144-146 °C, 0.38 g, yield 89%. IR (KBr) (νmax/cm^{-1}): 2910, 1730, 1533, 1443, 1261, 1206 and 1067 cm^1. MS (EI, 70 eV): m/z (%) = 326 (10), 250 (10), 158 (9), 94 (100), 82 (50), 76 (16), 56 (85). Anal. Calcd for $C_{17}H_{23}N_3O_4P$ (365.36): C, 55.89; H, 6.62; N, 11.50; found: C, 55.94; H, 6.67; N, 11.60%. ^{1}H NMR: 1.23 (3 H, m, 3 CH), 1.35 (2 H, m, 2 CH), 1.61-1.71 (3 H, m, 3 CH), 1.93 (2 H, m, 2 CH), 3.54 (3 H, s, CH_3), 3.72 (1 H, m, N-CH), 5.53 (1 H, s, CH), 6.85 (1 H, t, $^3J_{HH}$ =8.0, CH), 7.04-7.20 (3 H, m, 3 CH), 7.35 (1 H, br s, CH), 7.45 (1 H, br s, CH), 8.33 (1 H, s, OH), 10.20 (1 H, s, NH). ^{13}C NMR: 24.8 (CH_2), 24.9 (CH_2), 25.6 (CH_2), 33.3 (CH_2), 33.5 (CH_2), 35.2 (N-CH_3), 50.0 (N-CH), 115.0 (CH), 115.2 (2 CH),121.3 (CH),123.7 (CH), 123.5 (CH),129.0 (2 CH),152.0 (C, d, $^2J_{CP}$ = 7.5), 171.0 (C, d, $^1J_{CP}$ = 211.2). ^{31}P NMR: -11.4.

*phenyl hydrogen {[2-(butylamino)-3-methyl-2,3-dihydro-1H-imidazol-1-yl]carbonyl}phosphonate (**4f**):*

With powders, mp 142-145 °C, 0.29 g, yield 85%. IR (KBr) (νmax/cm^{-1}): 2913, 1726, 1536, 1448, 1269, 1215 and 1060. MS (EI, 70 eV): m/z (%) = 300 (8), 224 (8), 158 (15), 94 (100), 82 (580), 56 (80). Anal.Calcd for $C_{15}H_{22}N_3O_4P$ (339.33): C, 53.09; H, 6.53; N, 12.38; found: C, 53.15; H, 6.613; N, 12.48%. ^{1}H NMR: 0.95 (3 H, t, $^3J_{HH}$ =7.0, Me), 1.39 (2 H,m, CH_2), 1.52 (2 H, m, CH_2), 3.32 (2 H, t, $^3J_{HH}$ = 7.1, N-CH_2), 3.50 (3 H, s, N-CH_3), 5.63 (1 H, s, CH), 6.90 (1 H, t, $^3J_{HH}$ =7.6, CH), 7.04-7.20 (4 H, m, 4 CH), 7.39 (1 H, br s, CH), 7.48 (1 H, br s, CH), 8.43 (1 H, s, OH), 9.80 (1 H, s, NH). ^{13}C NMR: 13.7 (Me), 20.1 (CH_2), 32.0 (CH_2), 32.8 (CH_2-N),35.6 (N-CH_3), 114.4 (CH), 115.8 (2 CH), 121.0 (CH), 123.7 (CH), 123.5 (CH), 129.2 (2 CH), 152.2 (C, d, $^2J_{CP}$ = 8.5), 171.0 (C, d, $^1J_{CP}$ = 212.3). ^{31}P NMR: -10.4.

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