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Phospha-Michael Reactions Involving P-Heterocyclic Nucleophiles

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ABSTRACT: *P-heterocyclic γ-ketophosphonates were synthesized by the Michael reaction of methyl vinyl ketone with dibenzo-1,2-oxaphosphorine 2-oxide, 1,3,2-dioxaphosphorine 2-oxide and benzo-1,3,2-dioxaphospholane 2-oxide, respectively. In the first two cases, 50% of 1,8-diazabicyclo[5.4.0]undec-7-ene had to be used that was also required in the addition of dibenzooxaphosphorine oxide to cyclohexenone to result in the formation of the corresponding γ-ketophosphonate. The addition of dibenzooxaphosphorine oxide to less reactive 1,2-dihydrophosphinine oxide was accomplished after activation by an equimolar amount of trimethylaluminum to afford a 3-P(O)<-1,2,3,6-tetrahydrophosphinine oxide, which was subjected to catalytic hydrogenation to provide the corresponding 1,2,3,4,5,6-hexahydrophosphinine oxide.*
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INTRODUCTION

The phospha-Michael reaction is an evergreen method for the synthesis of γ-ketophosphonates, -phosphinates, and -phosphine oxides, as well as, that of related compounds [1–3]. In our laboratory, the possible accomplishments of the phospha-Michael reaction were studied on simple model reactions [4]. The addition of >P(O)H species to α-methyleneglutaric esters was performed to make available potential NAALADase inhibitors useful in the treatment of stroke [5]. The reaction of a series of 1,2-dihydrophosphinine oxides with dialkyl phosphites, diphenylphosphine oxide, and ethyl phenyl-H-phosphinate gave valuable 3-phosphonato-, 3-phosphinoxido-, and 3-phosphinato-1,2,3,6-tetrahydrophosphinine oxides [6–9], whose twist-boat conformation was stabilized by special intramolecular H-bonds. The 3-P(O)Ph_2-1-Ph-tetrahydrophosphinine 1-oxide was a useful bidentate P-ligand after double deoxygenation [10].

In this paper, the Michael addition of heterocyclic >P(O)H species, such as oxaphosphorine-,

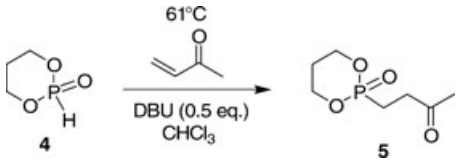
dioxaphosphorine-, and dioxaphospholane derivatives to unsaturated ketones and an unsaturated cyclic phosphine oxide is described.

RESULTS AND DISCUSSION

The first model reaction studied was the addition of dibenzo-1,2-oxaphosphorine oxide (DBOP) **1** to methyl vinyl ketone (MVK). It was found that species **1** was added easily on the double bond of MVK under microwave conditions in the absence of any solvent. This was in accord with the observation of Stockland et al. [3]. An accomplishment in the presence of 50% of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in chloroform at reflux was a suitable alternative (Scheme 1). The addition of DBOP on the electron-poor double bond of cyclohexenone could not, however, be accomplished under microwave, only in the presence of DBU, in boiling chloroform (Scheme 1). The 50% quantity of the DBU was critical from the point of view efficiency of the addition. The use of less DBU led to low conversions, whereas the application of an equimolar amount resulted in complex mixtures. After column chromatography, adduct **3** was obtained in a 54% yield. Owing to the existing and the newly formed stereogenic centers, **3** was formed as a 64:36 mixture of two diastereomers.

The reaction of 1,3,2-dioxaphosphorine oxide **4** with MVK was performed in a similar way to furnish γ-ketophosphonate **5** with a yield of 74% after column chromatography (Scheme 2).

The Michael addition of benzo-1,3,2-dioxaphospholane oxide (**6**) on the double bond of MVK could be carried out without the use of any DBU yielding ketophosphonate **7** in a quantitative manner. Sensitivity of a five-membered hetero ring of **7** toward moisture did not allow its purification by column chromatography (Scheme 3). Benzo-1,3,2-dioxaphospholane **6** seemed to be of enhanced reactivity toward MVK than 1,3,2-dioxaphosphorine **4**.



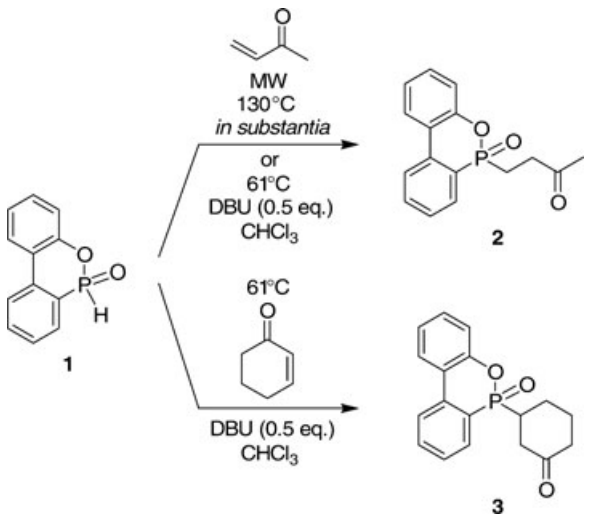
SCHEME 2

Finally, the reaction of DBOP **1** with 1,2-dihydrophosphinine oxide **8** was studied. It was found that neither microwave activation nor DBU catalyst promoted the reaction. The suppressed reactivity of the model under discussion was overcome by the activation of DBOP (**1**) with trimethylaluminum. In this way, the Michael reaction resulting in the 3-P(O)<-tetrahydrophosphinine oxide (**9**) took place and adduct **9** was obtained as a mixture of a major (83%) and a minor (17%) isomer, in a 78% yield after purification by column chromatography (Scheme 4).

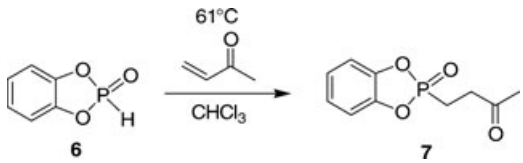
Reduction of tetrahydrophosphinine oxide **9** by catalytically activated hydrogen resulted in hexahydrophosphinine oxide **10** as a 8:2 mixture of a major (82%) diastereomer and two minor (13% and 5%) isomers (Scheme 4). Obviously, hydrogenation of the major diasteromer (83%) of **9** provided the major isomer (82%) of **10**, whereas that of the minor component (17%) of **9** led to the formation of two minor (13% and 5%) isomers of **10**.

All new products (**3, 5, 7, 9**, and **10**) were characterized by ^{31}P, ^{13}C, and ^{1}H NMR, as well as, mass spectral data.

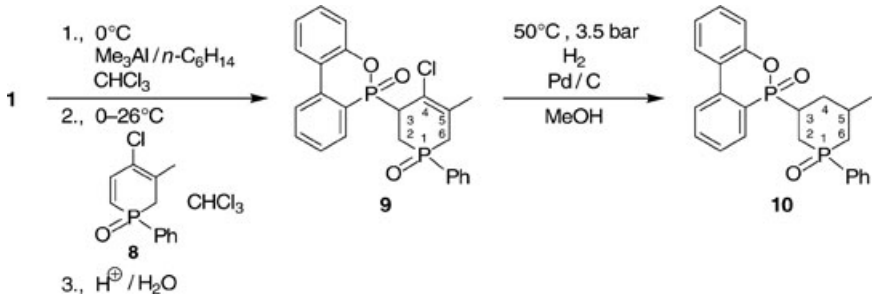
To summarize our results, new phospha-Michael reactions were performed in the sphere of P-heterocyclic >P(O)H species. The reaction conditions had to be tuned to the reactivity of the given model compounds. The γ-ketophosphonates could be well obtained in the presence of 50% of DBU at 61°C, but in one case there was no need for catalyst. The synthesis of a bis(P=O species) required activation by trimethylaluminum.



SCHEME 1



SCHEME 3



SCHEME 4

EXPERIMENTAL

The ^{31}P, ^{13}C, and ^{1}H NMR spectra were obtained on a Bruker DRX-500 spectrometer operating at 202.4, 125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. FAB measurements were performed on a ZAB-2SEQ instrument using 3-nitrobenzyl alcohol as the matrix.

The >P(O)H reactants were purchased from Aldrich (Schnelldorf, Germany) (**6**), or prepared according to known procedures (**1**) [11] and (**4**) [12]. 1,2-Dihydrophosphinine oxide **8** was synthesized as described earlier [13].

*Synthesis of 6-(butan-3-on-1-yl)-dibenzo[c,e][1,2]oxaphosphorin-6-oxide (**2**) by the reaction of methyl vinyl ketone and dibenzo-1,2-oxaphosphorine oxide (**1**) under microwave irradiation.* The mixture of 38.6 μL (0.46 mmol) of methyl vinyl ketone and 0.10 g (0.46 mmol) of dibenzo-1,2-oxaphosphorine oxide (**1**) was heated at 130°C in a CEM Discovery microwave reactor (applying maximum of 30 W) for 1 h. The product was recrystallized from hexane/ether (6:1) to give 0.10 g (72%) of product **2**; ^{31}P NMR ($CDCl_3$) δ 37.6 (δ_{lit} 37.0) [3].

*General Procedure for the Preparation of Adducts **2, 3**, and **5** by the Reaction of α,β-Unsaturated Ketones and Cyclic >P(O)H in the Presence of DBU*

The mixture of 3.0 mmol of methyl vinyl ketone (0.25 mL) or cyclohexene-2-one (0.29 g), 2.86 mmol of cyclic >P(O)H species **1** or **4** (0.62 and 0.35 g, respectively) and 0.10 mL (1.43 mmol) of DBU in 2 mL of chloroform was kept at reflux for 3 h. Then, the mixture was washed with 5% HCl solution, the organic phase dried, and the crude product was purified by column chromatography (silica gel, 3% methanol in chloroform) to give the corresponding products (**2, 3**, or **5**).

*6-(Butan-3-on-1-yl)-dibenzo[c,e][1,2]*oxaphosphorin *2-Oxide (**2**).* Yield: 0.50 g (52%). ^{31}P NMR ($CDCl_3$) δ 37.4 (δ_{lit} 37.0) [3].

*2-(Cyclohexan-3-on-1-yl)-dibenzo[c,e][1,2]oxaphosphorin 2-Oxide (**3**).* Yield: 0.54 g (54%); $(M + H)^+_{found} = 313.0979$, $C_{18}H_{18}O_3P$ requires 313.0994; ^{1}H NMR ($CDCl_3$) δ 1.56–1.70 (m, 1H, CH), 1.86–2.64 (m, 8H, CH_2), 7.10–8.02 (m, 8H, Ar).

Major: ^{31}P NMR ($CDCl_3$) δ 36.6 (64%); ^{13}C NMR ($CDCl_3$) δ 23.2 ($J = 2.8$, CH_2), 26.1 ($J = 17.5$, CH_2), 37.6 ($J = 97.1$, PCH), 39.2 (CH_2), 41.1 (CH_2), 120.2 ($J = 6.2$, Ar), 122.1 ($J = 10.4$, Ar), 122.5 ($J = 117.4$, PC), 124.1 ($J = 9.4$, Ar), 124.8 (Ar), 125.3 (Ar), 128.6 ($J = 12.8$, Ar), 130.9 ($J = 9.8$, Ar), 131.0 (Ar), 133.8 ($J = 2.2$, Ar), 136.2 ($J = 6.4$, Ar), 149.1 ($J = 8.2$, POC), 208.3 ($J = 14.9$, C=O).

Minor: ^{31}P NMR ($CDCl_3$) δ 36.8 (36%); ^{13}C NMR ($CDCl_3$) δ 23.3 ($J = 4.3$, CH_2), 26.0 ($J = 17.0$, CH_2), 38.1 ($J = 97.2$, PCH), 39.2 (CH_2), 41.1 (CH_2), 120.1 ($J = 6.2$, Ar), 122.4 ($J = 117.0$, PC), 124.0 (Ar), 124.8 (Ar), 125.3 (Ar), 128.6 ($J = 12.7$, Ar), 131.0 (Ar), 131.0 ($J = \sim 9.8$, Ar), 133.8 ($J = 2.2$, Ar), 149.3 ($J = 8.2$, POC), 208.2 ($J = 14.8$, C=O).

*2-(Butan-3-on-1-yl)-1,3,2-dioxaphosphorin 2-Oxide (**5**).* Yield: 0.35 g (74%), ^{31}P NMR ($CDCl_3$) δ 27.9; ^{13}C NMR ($CDCl_3$) δ 17.6 ($J = 144.2$, PCH_2), 26.3 ($J = 7.6$, CH_2), 29.4 (CH_3), 35.6 ($J = 3.8$, CH_2), 66.2 ($J = 6.4$, OCH_2), 205.6 ($J = 13.6$, C=O); ^{1}H NMR ($CDCl_3$) δ 2.00–2.05 (m, 2H, CH_2), 2.05–2.14 (m, 2H, PCH_2), 2.18 (s, 3H, CH_3), 2.76–2.84 (m, 2H, $C(O)CH_2$), 4.21–4.29 (m, 2H, OCH_2), 4.45–4.54 (m, 2H, OCH_2); $(M + H)^+_{found} = 193.0621$, $C_7H_{14}O_4P$ requires 193.0630.

*2-(Butan-3-on-1-yl)-benzo-1,3,2-dioxaphospholane 2-Oxide (**7**).* 7 was prepared measuring in 0.44 g (2.86 mmol) of **6** and 0.35 mL (4.29 mmol) of methyl vinyl ketone as described above, but without the use of any DBU. Owing to the sensitivity of **7**, the crude

product was not purified by chromatography. Evaporation of the volatile components afforded 0.66 g (98%) of product **7** in a purity of 95%. ^{31}P NMR ($CDCl_3$) δ 51.8; ^{13}C NMR ($CDCl_3$) δ 20.2 ($J = 134.3$, PCH_2), 29.1 (CH_3), 35.5 ($J = 4.5$, $C(O)CH_2$), 112.5 ($^3J = 10.2$, CH), 123.7 (CH), 144.4 (CO), 204.4 ($J = 13.4$, C(O)); ^{1}H NMR ($CDCl_3$) δ 2.20 (s, 3H, CH_3), 2.40–2.54 (m, 2H, PCH_2), 2.80–2.94 (m, 2H, CH_2), 6.90–7.20 (m, 4H, Ar); $(M + H)^+_{found} = 227.0461$, $C_{10}H_{12}O_4P$ requires 227.0473.

*Synthesis of 3-(Dibenzo[c,e][1,2]oxaphosphorinoxido)-4-chloro-5-methyl-1-phenyl-1,2,3,6-Tetrahydrophosphinine 1-Oxide (**9**)*

To 0.20 g (1.01 mmol) of the dibenzooxaphosphorine oxide **1** in 10 mL of dry chloroform, 0.50 mL (1.01 mmol) of 2 M trimethylaluminum in hexane at 0°C was added. After a period of 20 min, 0.24 g (1.06 mmol) of the dihydrophosphinine oxide (**8**) in 5 mL of chloroform was added dropwise. After complete addition, the cooling bath was removed and the contents of the flask were stirred for 20 h. Then, the mixture was hydrolyzed by the addition of 0.5 mL of conc. hydrochloric acid in 4.5 mL of water. After filtration, the organic phase was separated and dried (Na_2SO_4). The crude product was purified by column chromatography (silica gel, 3% methanol in chloroform) to afford compound **9**.

Yield: 0.87 g (78%); $(M + H)^+_{found} = 455.0712$, $C_{24}H_{22}ClO_3P_2$ requires 455.0733 for the ^{35}Cl isotope.

Major: ^{31}P NMR ($CDCl_3$) δ 31.6 (P_2) and 32.8 (P_1), $^3J_{PP} = 17.0$ (83%); ^{13}C NMR ($CDCl_3$) δ 23.8 ($^1J = 6.9$, $^2J = 2.6$, C_5—H_3), 24.4 ($^1J = 70.9$, $^2J = 3.7$, C_2), 34.6 ($^1J = 61.9$,$^2J = 2.1$, C_6), 43.8 ($^1J = 4.9$, $^2J = 90.8$, C_3), 120.3 ($^2J = 6.4$, Ar), 121.9 ($^1J = 7.2$, $^2J = 16.5$, C_5), 122.5 ($^2J = 10.5$, Ar), 123.0 ($^1J = 120.5$, PC), 124.0 ($^2J = 10.2$, Ar), 125.3 ($^1J = 16.1$, $C_{3'}$)*, 128.6 ($^2J = 12.8$, Ar), 128.8 ($^1J = 11.5$, $C_{2'}$)*, 129.8 (Ar), 129.9 (Ar), 131.0 (Ar), 131.5 ($^1J = 9.1$, $^2J = 7.7$ C_4), 132.0 ($^2J = 12.5$, Ar), 132.0 ($C_{4'}$), 133.5 ($^1J = 99.6$, $C_{1'}$), 134.2 ($^2J = 2.2$, Ar), 136.4 ($^2J = 7.3$, Ar), 149.0 ($^2J = 8.3$, POC), *may be reversed; ^{1}H NMR ($CDCl_3$) δ 1.77 (d, $J = 5.4$, 3H, C_5—CH_3), 2.52–3.00 (m, 3H, C(3)H and PCH_2), 3.30–3.65 (m, 2H, PCH_2), 7.20–8.10 (m, 13H, Ar).

Minor: ^{31}P NMR ($CDCl_3$) δ 31.9 (P_2) and 34.6 (P_1), $^3J_{PP} = 16.9$ (17%).

*Synthesis of 3-(Dibenzo[c,e][1,2]oxaphosphorinoxido)-5-methyl-1-phenyl-1,2,3,4,5,6-hexahydrophosphinine 1-oxide (**10**)*

A mixture of 0.10 g (0.22 mmol) of 3-dibenzooxaphosphorino-tetrahydrophosphinine oxide (**9**) and 0.08 g of 10% Pd/C in 30 mL of methanol was hydrogenated in an autoclave at 50°C and 3.5 bar for 48 h on stirring. The suspension was filtered, and the solvent was evaporated. Purification of the crude product so obtained by column chromatography (silica gel, 3% methanol in chloroform) afforded hexahydrophosphinine oxide **10** as an 82%–13%–5% mixture of three diastereomers.

Yield: 0.09 g (90%); $(M + H)^+_{found} = 423.1263$, $C_{24}H_{25}O_3P_2$ requires 423.1279.

Major: ^{31}P NMR ($CDCl_3$) δ 34.1 (P_2) and 36.5 (P_1), $^3J_{PP} = 56.6$ (82%); ^{13}C NMR ($CDCl_3$) δ 23.9 ($^1J = 15.8$, $^2J = 2.1$, C_5—CH_3), 24.1 ($^1J = 63.0$, $^2J = 4.2$, C_2), 31.2 ($^1J = 3.3$, $^2J = 18.0$, C_5), 32.2 ($^1J = {}^2J = 2.9$, C_4), 34.4 ($^2J = 93.3$, $^1J = 1.5$, C_3), 34.8 ($^1J = 64.0$, C_6), 120.1 ($^2J = 6.2$, Ar), 122.2 ($^2J = 10.3$, Ar), 122.4 ($^1J = 116.6$, $^2J = 2.2$, PC), 124.2 ($^2J = 9.6$, Ar), 124.9 (Ar), 125.5 (Ar), 128.5 ($^2J = 12.6$, Ar), 129.0 ($^1J = 5.6$, $C_{3'}$)*, 129.1 ($^1J = 3.5$, $C_{2'}$)*, 130.6 ($^2J = 9.6$, Ar), 130.9 ($C_{4'}$), 132.0 ($^2J = 2.5$, Ar), 133.8 ($^2J = 2.0$, Ar), 136.2 ($^2J = 6.5$, Ar), 149.0 ($^2J = 8.1$, POC), *may be reversed; ^{1}H NMR ($CDCl_3$) δ 1.03 ($^1J = 6.3$, $^2J = 2.9$, 3H, C_5—CH_3), 1.24–1.44 (m, 2H, CH_2), 1.80–2.06 (m, 3H, C_3H and CH_2), 2.06–2.20 (m, 1H, C_5H), 2.46–2.72 (m, 2H, CH_2), 7.28–7.58 and 7.70–8.00 (m, 13H, Ar).

Minor$_1$: ^{31}P NMR ($CDCl_3$) δ 33.6 (P_2) and 35.9 (P_1), $^3J_{PP} = 58.8$ (13%).

Minor$_2$: ^{31}P NMR ($CDCl_3$) δ 32.5 (P_2) and 37.3 (P_1), $^3J_{PP} = 54.7$ (5%).

REFERENCES

[1] Enders, D.; Saint-Dizier, A.; Lannou, M-I.; Lenzen, A. Eur J Org Chem 2006, 29.

[2] Enders, D.; Tedeschi, L.; Bats, J. W. Angew Chem, Int Ed 2000, 39, 4605.

[3] Stockland, R. A.; Taylor, R. I.; Thompson, L. E.; Patel, P. B. Org Lett 2005, 7, 851.

[4] Keglevich, Gy.; Sipos, M.; Takács, D.; Greiner, I. Heteroatom Chem 2007, 18, 226.

[5] Harsányi, K.; Domány, Gy.; Greiner, I.; Forintos, H.; Keglevich, Gy. Heteroatom Chem 2005, 16, 562.

[6] Keglevich, Gy.; Sipos, M.; Imre, T.; Ludányi, K.; Szieberth, D.; Tőke, L. Tetrahedron Lett 2002, 43, 8515.

[7] Keglevich, Gy.; Sipos, M.; Szieberth, D.; Nyulászi, L.; Imre, T.; Ludányi, K.; Tőke, L. Tetrahedron 2004, 60, 6619.

[8] Keglevich, Gy.; Sipos, M.; Ujj, V.; Körtvélyesi, T. Lett Org Chem 2005, 2, 608.

[9] Sipos, M.; Körtvélyesi, T.; Ujj, V.; Ludányi, K.; Vékey, K.; Tőke, L.; Keglevich, Gy. Heteroatom Chem 2007, 18, 747.

[10] Keglevich, Gy.; Sipos, M.; Szieberth, D.; Petöcz, Gy.; Kollár, L. J. Organomet Chem 2004, 689, 3158.
[11] Chernyshev, E. A.; Aksenov, V. I.; Ponomarev, V. V.; Golubtsov, S. A.; Bugerenko, E. F. Zh Obshch Khim 1972, 42, 93.
[12] Sakirov, I. H.; Safiullin, A. R.; Sagidullin, R. R.; Polozov, A. M. Izv Akad Nauk Ser Khim 1992, 12, 2725.
[13] Keglevich, Gy.; Androsits, B.; Tőke, L. J Org Chem 1988, 53, 4106.