Heteroatom Chemistry
Volume 16, Number 3, 2005

2-Ethyl-2-phosphabicyclo[2.2.2]oct-7-ene Derivatives: Synthesis and Use in Fragmentation-Related Phosphorylations

Helga Szelke,[1,2] Ágnes Bálint,[1] Erzsébet Király,[1] Krisztina Ludányi,[3] János Kovács,[1] and György Keglevich[1]

[1]*Department of Organic Chemical Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary*

[2]*Research Group of the Hungarian Academy of Sciences at the Department of Organic Chemical Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary*

[3]*Hungarian Academy of Sciences, Chemical Research Center, 1525 Budapest, Hungary*

Received 5 November 2004; revised 7 December 2004

ABSTRACT: *A 2-phosphabicyclo[2.2.2]oct-7-ene oxide (**2**) and a 2-phosphabicyclo[2.2.2]octa-5,7-diene oxide (**3**) with ethyl substituent on the phosphorus atom was synthesized and their fragmentation properties were studied. The phosphabicyclooctadiene oxide (**3**) could be utilized in both the UV light-mediated phosphorylation of simple alcohols and in the thermoinduced phosphorylation of hydroquinone giving an easy access to P-ethylphosphinates (e.g., **4** and **6**). The phosphabicyclooctene oxide (**2**) was, however, not useful in photoinduced phosphorylations; under such conditions the precursor (**2**) underwent dechlorination to afford **5**.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:196–199, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20093

Correspondence to: György Keglevich; e-mail: keglevich@mail.bme.hu.

Contract grant sponsor: National Scientific Research Fund.
Contract grant number: OTKA No. T 042479.

INTRODUCTION

The bridged P-heterocycles, such as the 2-phosphabicyclo[2.2.2]octadiene 2-oxides/sulfides can be regarded as precursors of methylenephosphine oxides/sulfides $YP(X)CH_2$, where X = O, S, Y = phenyl, alkoxy. The latter are novel phosphorylating agents toward a variety of nucleophiles, such as alcohols, phenols, and amines [1,2]. The reaction can be achieved either thermally [3], or under photochemical conditions [4–6]. In the latter instance, a novel addition-elimination mechanism was substantiated to be a competitive pathway [5–7] in addition to the traditional elimination–addition route involving methylenephosphine oxide as the intermediate [4]. The fragmentation-related phosphorylations are of interest, as they require mild reaction conditions, especially those accomplished under photochemical conditions, (26°C and an irradiation of only several hours) and take place efficiently and in a selective way [5,6,8]. During our efforts to find suitable precursors and to evaluate the mechanism of the fragmentations, a series of novel phosphabicyclooctene derivatives were described [9–11]. To extend the sphere of the precursors available, bridged P-heterocycles with ethyl substituent on the phosphorus atom are introduced and their

fragmentation properties are described in the present paper.

RESULTS AND DISCUSSION

Double-bond isomers of the 1-ethyl-1,2-dihydrophosphinine oxide (**1A** and **1B**) [12] were reacted with *N*-phenylmaleimide in boiling toluene to give phosphabicyclo[2.2.2]octene oxide **2** as the mixture of regioisomers (**A** and **B**) (Scheme 1). Similarly, Diels–Alder reaction of the mixture of **1A** and **1B** with dimethyl acetylenedicarboxylate afforded the regioisomers (**A** and **B**) of phosphabicyclo[2.2.2.]octadiene oxide **3**. In this instance, regioisomers **A** and **B** consisted of configurational isomers (Scheme 1).

The crude products **2** and **3** were purified by column chromatography to provide the cycloadducts **2** and **3** in 74% and 54%, yield, respectively. Isomers of the products **2** and **3** were characterized by ^{31}P, ^{13}C, and ^{1}H NMR, as well as mass spectrometry.

Thermal examinations (TG, DTG, and DSC) suggested that phosphabicyclooctene oxide **2** underwent the elimination of the bridging P-moiety in the range of 270–430°C, with a minimum in the DSC at 380°C. This revealed a considerably larger thermostability, as compared to that of phosphabicyclooctadiene oxide **3** eliminating the bridging unit in the range of 190–320°C with a minimum in the DSC at 257°C. Due to their more strained ring, the phosphabicyclooctadiene oxides of type **3** are indeed thermally less stable [13,14].

In the next stage of our work, we tested the new precursors **2** and **3** in fragmentation-related phosphorylations. Irradiation of the acetonitrile solution of phosphabicyclooctadiene oxide **3** at 254 nm in the presence of methanol or ethanol at 26°C yielded the corresponding *P*-ethyl phosphinates **4a** and **4b**, respectively in ca. 71% yield and in a purity of ca. 95% after flash column chromatography (Scheme 2).

Photolysis of phosphabicyclooctene oxide **2** under similar conditions using methanol did not give, however, the expected phosphinate **4a**. Only traces of the desired product **4a** could be detected. Instead, precursor **2** underwent dechlorination to furnish phosphabicyclooctene oxide **5** (Scheme 3).

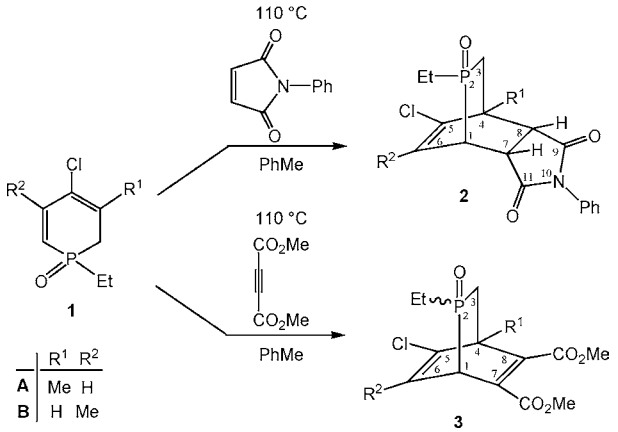
Like cycloadduct **2**, compound **5** formed also did not eliminate the bridging P-unit. The unreactivity of phosphabicyclooctene oxides **2** and **5** is surprising, as on the basis of the UV absorption they should be suitable precursors. The UV spectrum of cycloadduct **2** showed an intensive absorption in the range of ~220–270 nm with a maximum at 252 nm that is similar to the spectrum of the *P*-phenyl analogue revealing a maximum at 254 nm.

Phosphabicyclooctadiene oxide **3** was also useful in the thermo-induced phosphorylation of hydroquinone. Heating the mixture of **3** and the hydroxycompound at 240°C for 10 min led to phosphinate **6** in 64% yield and in a purity of 94% after flash column chromatography (Scheme 4). Carrying out the fragmentation-related phosphorylation under microwave conditions, the reaction was more efficient (72% yield), and the product (**6**) was cleaner (98%). Phosphinates **4a**, **4b**, and **6** were characterized by ^{31}P NMR and mass spectrometrical data. Mass spectral data were obtained by GC-MS.

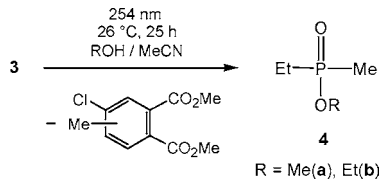
To summarize the results, two new phosphabicyclo[2.2.2]octene derivatives with ethyl substituent at the phosphorus atom were introduced and tested in thermoinduced and UV light-mediated fragmentation-related phosphorylations. Hence, our methodology has now been extended to **P**-ethyl model compounds.

EXPERIMENTAL

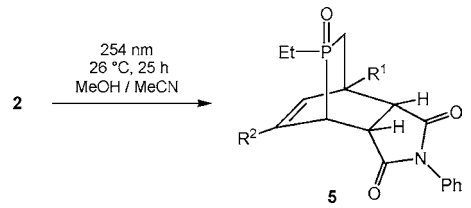
The ^{31}P, ^{13}C, and ^{1}H NMR spectra were recorded on a Bruker DRX-500 spectrometer operating at 202.4, 125.7, and 500 MHz, respectively. Chemical shifts are downfield relative to 85% H_3PO_4 or TMS. The couplings are given in Hz. GC-MS was



SCHEME 1



SCHEME 2



SCHEME 3

performed on a Fisons GC 8000/MD 800 apparatus connecting a PE SCIEX API 2000 type triple quadrupol mass spectrometer. FAB mass spectrometry was performed on a ZAB-2SEQ instrument. The ethyl-dihydrophosphinine oxides (**1A** and **1B**) were prepared as described earlier [12].

General Procedure for the Synthesis of Cycloadducts **2** *and* **3**

The mixture of 1.0 g (5.25 mmol) of ethyl-dihydrophosphinine oxide **1** consisting of 75% of the **A** isomer and 25% of the **B** isomer and 5.78 mmol of the dienophile (1.0 g of *N*-phenylmaleimide or 0.72 mL of dimethylacetylene dicarboxylate) in 25 mL of toluene was stirred at the boiling point for 5 days. Solvent was evaporated, and the residue so obtained was purified by column chromatography (silica gel, 3% methanol in chloroform) to furnish cycloadduct **2** and **3**, respectively, as the mixture of isomers. The data are listed below.

*1- and 11-Methyl-10-chloro-4-phenyl-8-ethyl-4-aza-8-phosphatricyclo[5.2.2.0^{2,6}]undec-10-ene-3,5-dione 8-oxide (***2A** *and* **2B***) [15]*

Yield: 1.4 g (74%) of **2** as a 6:4 mixture of isomers **A** and **B**; mp 257–259°C (acetone); FAB-MS, 364 (M + H); $(M + H)^+_{found}$ = 364.0869, $C_{18}H_{20}ClNO_3P$ requires 364.0806 for the ^{35}Cl isotopomer.

2A: ^{31}P NMR ($CDCl_3$) δ 51.8; ^{13}C NMR ($CDCl_3$) δ 5.1 (^2J = 5.3, CH_2CH_3), 21.4 (^1J = 70.9, CH_2CH_3), 23.3 (^3J = 10.3, C(4)—CH_3), 34.8 (^1J = 70.3, C(3)), 58.7 (^1J = 36.6, C(1)), 38.9 (C(7)), 43.8 (^2J = 6.1, C(4)), 49.2 (^2J = 10.1, C(8)), 121.8 (^2J = 5.0, C(6), 126.3 (C(3′)),* 128.6 (C(4′)), 128.9 (C(2′)),* 131.4 (C(1′)), 139.5 (^3J = 10.8 C(5)), 173.9 (C(9)), 175.9 (^3J = 14.1, C(11)), * may be reversed; ^1H NMR ($CDCl_3$) δ 2.38 (m, CH_2CH_3), 2.85 (s, C(4)—CH_3), 7.27 (dd, $^3J_{PH}$ = $^3J_{HH}$ 7.7, C(6)—H).

2B: ^{31}P NMR ($CDCl_3$) δ 58.7; ^{13}C NMR ($CDCl_3$) δ 5.1 (^2J = 5.3, CH_2CH_3), 18.3 (C(6)—CH_3), 21.3 (^1J = 69.8, CH_2CH_3), 26.4 (^1J = 71.9, C(3)), 39.7 (C(7)), 41.6 (^1J = 58.2, C(1)), 42.5 (^2J = 6.9, C(4)), 45.0 (^2J = 11.9, C(8)), 126.2 (C(3′)),* 139.5 (^3J = 11.0, C(5)), 128.7 (C(4′)), 129.0 (C(2′)),* 129.8 (^2J = 5.0, C(6)), 131.4 (C(1′)), 175.1 (C(9)), 176.1 (^3J = 13.8, C(11)), * may be reversed; ^1H NMR ($CDCl_3$) δ 2.38 (m, CH_2CH_3), 2.99 (s, C(6)—CH_3).

*4- and 7-Methyl-8-chloro-2-ethyl-2-oxo-2-phosphabicyclo[2.2.2]octa-5,7-diene-5,6-dicarboxylic Acid Dimethyl Ester (***3***) [15]*

Yield: 0.94 g (54%) oily product after repeated chromatography (silica gel, 3% methanol in chloroform) as a 32%, 29%, 25%, and 14% mixture of four isomers; FAB-MS, 333 (M + H); $(M + H)^+_{found}$ = 333.0658, $C_{14}H_{19}ClO_5P$ requires 333.0601 for the ^{35}Cl isotopomer.

3A-1: ^{31}P NMR ($CDCl_3$) δ 58.9 (32%); ^{13}C NMR ($CDCl_3$) δ 5.6 (CH_2CH_3)[a], 19.7 (J = 9.4, C(4)—CH_3)[b], 30.8 (J = 89.8, CH_2)[c], 34.0 (J = 109.9, C(3))[d], 41.5 (J = 46.8, C(1))[e], 47.0 (J = 8.3, C(4))[f], 52.4[g], 52.3[g] (MeO), 124.2 (J = 11.5, C(6))[h], 136.4 (J = 5.7, C(7))[i], 138.3 (J = 19.2, C(8))[j], 162.2 (J = 4.6, C(10))[k], 164.3 (C(9))[l].

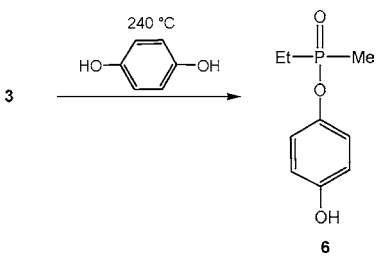
3A-2: ^{31}P NMR ($CDCl_3$) δ 59.6 (29%); ^{13}C NMR ($CDCl_3$) δ 5.5 (CH_2CH_3)[a], 19.6 (J = 8.7, C(4)—CH_3)[b], 30.3 (J = 89.6, CH_2)[c], 33.5 (J = 103.5, C(3))[d], 41.2 (J = 46.9, C(1))[e], 46.5 (J = 8.2, C(4))[f], 51.9[g], 52.0[g] (MeO), 123.9 (J = 6.8, C(6))[h], 134.6 (J = 6.3, C(7))[i], 139.4 (J = 18.6, C(8))[j], 163.9 (C(9))[l], 165.6 (J = 3.2, C(10))[k], [a–l] tentative assignment.

3B-1: ^{31}P NMR ($CDCl_3$) δ 55.3 (25%); ^{13}C NMR ($CDCl_3$) δ 5.7 (CH_2CH_3), 18.1 (C(6)—CH_3), 48.2 (J = 46.1, C(1)), 45.0 (J = 8.9, C(4)), 52.2, 52.4 (MeO), 130.9 (J = 10.9, C(6)), 132.0 (C(7)), 139.7 (J = 16.3, C(8)).

3B-2: ^{31}P NMR ($CDCl_3$) δ 55.5 (14%).

General Procedure for the Photoinduced Fragmentation-Related Phosphorylations

The solution of 0.10 g (0.301 mmol) of precursor **3** as a 32, 29, 25, and 14% mixture of isomers (obtained as shown above) in 45 mL of dry acetonitrile was irradiated in the presence of 4.0 mL of the corresponding alcohol (methanol or ethanol) in a photochemical



SCHEME 4

quartz reactor with a 125 W mercury lamp for 2 h. Volatile components were removed, and the residue so obtained purified by flash column chromatography (silica gel, 3% methanol in chloroform) to give the corresponding phosphinic esters (**4a** and **4b**) as oils in a purity of ca. 95%.

4a was obtained in the presence of methanol; yield: 74%; ^{31}P NMR ($CDCl_3$) δ 59.0; ES-MS, 123 (M + H); HR-FAB $(M+H)^+_{found} = 123.0555$, $C_4H_{11}O_2P$ requires 123.0575; GC-MS, *m/z* (rel. int.) 122 (M^+, 28), 107 (22), 94 (100), 91 (5), 79 (87), 59 (61).

4b was obtained in the presence of ethanol; yield: 69%; ^{31}P NMR ($CDCl_3$) δ 57.4; ES-MS, 137 (M + H); HR-EI $M^+_{found} = 136.0632$, $C_5H_{13}O_2P$ requires 136.0653; GC-MS, *m/z* (rel. int.) 136 (M^+, 70), 135 (100), 107 (17), 92 (14), 77 (30).

Photolysis of phosphabicyclooctene regioisomers **2A** and **2B** under similar conditions in the presence of methanol led to the dechlorinated derivative of precursor **5**. After an irradiation time of 75 min, the conversion was found to be 53%. ^{31}P NMR ($CDCl_3$) δ 55.2; FAB-MS, 330 (M + H).

Thermoinduced Fragmentation-Related Phosphorylation of Hydroquinone Using Phosphabicyclooctadiene **3**

0.20 g (0.60 mmol) of cycloadduct **3** as the mixture of four isomers and 0.20 g (1.8 mmol) of hydroquinone was heated at 240°C in a vial for 10 min. Flash column chromatography (silica gel, 3% methanol in chloroform) afforded 7.7 mg (64%) phosphinate **6** in a purity of ca. 94%. ^{31}P NMR ($CDCl_3$) δ 59.3; FAB-MS, 201 (M + H); HR-FAB $(M+H)^+_{found} = 201.0647$, $C_9H_{13}O_3P$ requires 201.0681; GC-MS, *m/z* (rel. int.) 200 (M^+, 100), 185 (1), 172 (12), 171 (10), 157 (37), 110 (80), 107 (57), 91 (51).

Microwave-Assisted Fragmentation-Related Phosphorylation of Hydroquinone Using Phosphabicyclooctadiene **3**

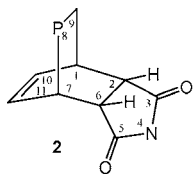
A mixture of cycloadduct **3** (0.10 g, 0.30 mmol) and 0.10 g (0.9 mmol) of hydroquinone in a glass vial was placed into a focused 300 W CEM Discover microwave reactor, and the sample was heated at 240°C for 10 min with a power of 35 W in the stacioner stage. Flash column chromatography (silica gel, 3% methanol in chloroform) afforded 8.6 mg (72%) phosphinate **6** in a purity of ca. 98%.

ACKNOWLEDGMENTS

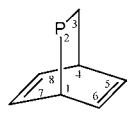
We are grateful to Andrea Márton (Department of Organic Chemical Technology) for carrying out the thermal examinations and to Zoltán Nagy (Gedeon Richter Ltd.) for performing the GC-MS measurements.

REFERENCES

[1] Heydt, H. Methyleneimino, -oxo, -thioxo, and -selenoxo phosphoranes. In Multiple Bonds and Low Coordination in Phosphorus Chemistry; Regitz, M.; Scherer, O. J. (Eds.); G. Thieme Verlag: Stuttgart, 1990; Ch. E2, p. 381.
[2] Keglevich, Gy.; Szelke, H.; Kovács J. Curr Org Synth 2004, 1, 377.
[3] Keglevich, Gy.; Szelke, H.; Dobó, A.; Nagy, Z.; Tőke, L. Synth Commun 2001, 31, 119.
[4] Quin, L. D.; Tang, J-S.; Quin, G. S.; Keglevich, Gy. Heteroatom Chem 1993, 4, 189.
[5] Keglevich, Gy.; Steinhauser, K.; Ludányi, K.; Tőke, L. J Organomet Chem 1998, 570, 49.
[6] Keglevich, Gy.; Szelke, H.; Nagy, Z.; Dobó, A.; Novák, T.; Tőke, L. J Chem Res 1999, 581.
[7] Jankowski, S.; Rudzinski, J.; Szelke, H.; Keglevich, Gy. J Organomet Chem 2000, 595, 109.
[8] Szelke, H.; Ludányi, K.; Imre, T.; Nagy, Z.; Vékey, K; Tőke, L.; Keglevich, Gy. Synth Commun 2004, 34, 4171.
[9] Keglevich, Gy.; Szelke, H.; Tamás, A. M.; Harmat, V.; Ludányi, K.; Vaskó, Á. Gy.; Tőke, L. Heteroatom Chem 2002, 13, 626.
[10] Keglevich, Gy.; Kovács, J.; Parlagh, Gy.; Imre, T.; Ludányi, K.; Hegeűds, L.; Hanusz, M.; Simon, K.; T˝ oke, L. Heteroatom Chem., 2004, 15, 97.
[11] Keglevich, Gy.; Szelke, H.; Bálint, Á.; Imre, T.; Ludányi, K.; Nagy, Z.; Hanusz, M.; Simon, K.; Harmat V.; Tőke, L. Heteroatom Chem 2003, 14, 443.
[12] Keglevich, Gy.; Lovász, C. S.; Újszászy, K.; Szalontai, G.; Heteroatom Chem 1994, 5, 395.
[13] Keglevich, Gy.; Tőke, L.; Böcskei, Zs.; Menyhárd, D.; Quin, L. D. Heteroatom Chem 1995, 6, 593.
[14] Keglevich, Gy.; Steinhauser, K.; Keserű, Gy. M.; Böcskei, Zs.; Újszászy, K.; Marosi, Gy.; Ravadits, I.; K.; Tőke, L. J Organomet Chem 1999, 579, 182.
[15] For naming compounds **2** and **3**, the IUPAC nomenclature was used (see below). At the same time, the traditional numbering was applied during the NMR assignments.



2



3