ISSN 1070-4280, Russian Journal of Organic Chemistry, 2010, Vol. 46, No. 2, pp. 162–165. © Pleiades Publishing, Ltd., 2010.
Original Russian Text © L.I. Minaeva, L.S. Patrikeeva, B.S. Orlinson, I.A. Novikov, M.M. Kabachnik, I.P. Beletskaya, 2009, published in Zhurnal Organicheskoi Khimii, 2010, Vol. 46, No. 2, pp. 172–174.

Synthesis of New Amidophosphates Containing an Adamantyl Fragment under Microwave Irradiation

L. I. Minaeva[a], L. S. Patrikeeva[a], B. S. Orlinson[b], I. A. Novikov[b], M. M. Kabachnik[a], and I. P. Beletskaya[a]

[a]*Lomonosov Moscow State University, Moscow, Russia*
e-mail: mariamk@mail.ru
[b]*Volgograd State Technical University, Volgograd, Rissia*

Received April 9, 2009

Abstract—The reaction of amines containing an adamantly fragment with diethyl phosphite in tetrachloromethane in the presence of triethylamine was studied under the microwave irradiation.

DOI: 10.1134/S1070428010020028

The synthesis of functionally substituted amidophosphates is an urgent task of the modern organophosphorus chemistry, first of all due to the practical application of these compounds in the chemistry, biology, and medicine. The amidophosphates are known to be efficient inhibitors of various enzymes [1–4], they are used in the treatment of virus diseases [5], but the most practically interesting is the AIDS treatment [6] employing this class of organophosphorus compounds. Sometimes the amidophosphates are used as ionic polymerization initiators [7], in other events they are successfully applied as catalysts in asymmetric synthesis [8].

Although versatile amidophosphates are well studied [9], the synthesis of new types of these compounds still remains an urgent task. Organophosphorus compounds with an adamantyl fragment in their structure also are objects of thorough investigation for they exhibit a high biological action against osteoporosis [10], and also antibacterial effect [11].

These compounds are commonly obtained either by the reaction of appropriate amines with phosphoric acid ester chlorides at heating [12–18], or by the Todd–Atherton reaction [19, 20]. In the first case the yields of the reaction products do not exceed 60%; in the second event the reaction proceeds either at the room temperature or at heating (from 2 to 17 h depending on the structure of the initial compounds), and it is complicated by a number of side processes, in particular, by the formation of pyrophosphates and phosphates. The only published example of the use of Todd–Atherton reaction in the synthesis of an amidophosphate with an adamantly fragment was the preparation of diethyl 1-adamantylamidophosphate [20]. The yield of the product was 58%.

The application of microwave irradiation for accelerating some organic processes is widely known [21], in particular, we have successfully used it in the synthesis of α-amino- and α-hydroxyalkylphosphonates [22].

Aiming at the optimization of the synthesis conditions of amidophosphate and at the preparation of previously unknown adamantly-containing organophosphorus compounds we studied the reaction of the corresponding amines with diethyl phosphite in tetrachloromethane in the presence of triethylamine under the microwave irradiation. Previous to our work the Todd–Atherton reaction never was carried out under the microwave irradiation.

The application of the microwave assistance made it possible to obtain fast (in several minutes) and in high yields adamantly-containing amidophosphate and to decrease considerably the formation of the reaction side products.

The reaction of amines **Ia–If** with diethyl phosphite in tetrachloromethane was carried out under the microwave irradiation in the presence of an equimolar quantity of triethylamine. According to the ^{31}P NMR spectra the reaction of amines **Ia–If** with diethyl phosphite under these

conditions proceeded virtually quantitatively.

$$RNH_2 + (EtO)_2P(O)H \xrightarrow[-CHCl_3,\ -Et_3N\cdot HCl]{CCl_4,\ Et_3N,\ MW} RHN\diagdown P(O)(OEt)_2$$

R = $AdCH_2$ (**a**), AdCH(Et) (**b**), AdCH(Ph) (**c**), $Ad(CH_2CH_2)_2$ (**d**), $AdOCH_2CH_2$ (**e**), $AdCH_2CH(CH_3)$ (**f**).

In reaction with amine **Id** containing two equivalent amino groups a double exess was taken of the diethyl phosphite and triethylamine, and this resulted in the formation in a high yield of bis(amidophosphate) **IId**. The structure and composition of compound **IId** were confirmed by the data of ^1H, ^{13}C NMR spectra and elemental analysis. Bringing into this reaction of equimolar amounts of amine **Id**, diethyl phosphite, and triethylamine aso resilted in the formation only of amidophosphate **IId**. No phosphorylation at a single amino group was found.

The process carried out at room temperature is considerably slower. The reaction of amine **Ia** with diethyl phosphite in the presence of triethylamine at room temperature took 1.5 h, and the corresponding amidophosphate **IIa** formed in 62% yield.

Hence we demonstrated that the reaction of the adamantyl-containing amines with diethyl phosphite in tetrachloromethane in the presence of triethylamine under the microwave irradiation provided a possibility to obtain quickly and in high yields previously unknown amidophosphates with adamantyl substituents.

EXPERIMENTAL

^1H, ^{13}C, and ^{31}P NMR spectra were registered on a spectrometer Bruker Avance-400 (operating frequencies 400, 100.6, and 161.9 MHz respectively). As internal reference served the chloroform signals (δ_H 7.28, δ_C 77.10 ppm). the melting points were measured on an Electrothermal 9100 instrument. The reaction progress was monitored and the purity of the chemical compounds was checked by TLC (Silufol UV-254). For preparative column chromatography silica gel Merck (40/60) was used.

Synthesis of amidophosphates containing an adamantane fragment under microwave assistance. *General procedure.* Into an open flat-bottom flask of 25 ml capacity was charged 0.01 mol of amine **Ia–If**, 10 ml of tetrachloromethane, then 0.01 mol of O,O'-diethyl phosphite, and 0.01 mol of triethylamine. The reaction was carried out under the microwave irradiation (102 W, 115°C) for 7–20 min. The separated precipitate of triethylamine hydrochloride was filtered off, the amidophosphates were isolated by column chromatography on silica gel (eluent chloroform–hexane, 1 : 1).

Diethyl *N*-[(1-adamantyl)methyl]amidophosphate (IIa). Reaction time 14 min. Yield 2.8 g (93%). Yellow oily substance. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 0.88 d (6H, CCH_2CH, ^3J 6.9 Hz), 1.33 t (3H, OCH_2CH_3, ^3J 7.1 Hz), 1.42 t (3H, OCH_2CH_3, ^3J 7.1 Hz), 1.64 m (6H, $CHCH_2CH$), 1.99 m (3H, CH_2CHCH_2), 3.12 s (2H, CCH_2NH), 4.06 m (4H, OCH_2CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.25 d (OCH_2CH_3), 28.22 s (CH_2CHCH_2), 36.98 s ($CHCH_2CH$), 39.96 s (CCH_2CH), 53.51 s (CCH_2NH), 62.23 s (OCH_2CH_3). ^{31}P NMR spectrum: δ 10.1 ppm. Found, %: C 59.93; H 9.41; N 4.25. $C_{15}H_{38}NO_3P$. Calculated, %: C 59.78; H 9.36; N 4.65.

Diethyl *N*-[1-(1-adamantyl)propyl]amidophosphate (IIb). Reaction time 18 min. Yield 2.8 g (85%), mp 97–99°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.02 t (3H, $NHCHCH_2CH_3$, ^3J 6.9 Hz), 1.10 d (6H, CCH_2CH, ^3J 6.9 Hz), 1.32 t (6H, OCH_2CH_3, ^3J 7.1 Hz), 1.63 m (6H, $CHCH_2CH$), 1.99 m (3H, CH_2CHCH_2), 2.09 m (2H, $NHCHCH_2CH_3$), 2.58 s (1H, CCHNH), 4.09 m (4H, OCH_2CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 11.95 s ($CCHCH_2CH_3$), 16.27 d (OCH_2CH_3), 23.67 s ($CCHCH_2CH_3$), 28.47 s (CH_2CHCH_2), 37.16 s ($CHCH_2CH$), 38.69 s (CCH_2CH), 62.39 s (OCH_2CH_3), 63.32 s ($CCHCH_2CH_3$). ^{31}P NMR spectrum: δ 9.1 ppm. Found, %: C 61.89; H 9.77; N 4.03. $C_{17}H_{32}NO_3P$. Calculated, %: C 61.98; H 9.79; N 4.25.

Diethyl *N*-[α-(1-adamantyl)benzyl]amidophosphate (IIc). Reaction time 10 min. Yield 3.2 g (84%), mp 108–110°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.29 t (6H, OCH_2CH_3, ^3J 7.0 Hz), 1.38 m (6H, CCH_2CH), 1.67 m (6H, $CHCH_2CH$), 1.98 m (3H, CH_2CHCH_2), 2.34 s (1H, CCHNH), 4.00 m (4H, OCH_2CH_3), 7.15–7.31 (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.18 d (OCH_2CH_3), 28.30 s (CH_2CHCH_2), 36.80 s ($CHCH_2CH$), 38.79 s (CCH_2CH), 62.26 s (OCH_2CH_3), 65.60 s [CCH(Ph)NH], 126.78 s, 127.41 s, 128.35 s (C_6H_5). ^{31}P NMR spectrum: δ 8.5 ppm. Found, %: C 66.53; H 8.75; N 3.91. $C_{21}H_{32}NO_3P$. Calculated, %:

C 66.82; H 8.55; N 3.71.

Tetraethyl[adamantane-1,3-diylbis(ethane-2,2'-diyl)]bisamidophosphate (IId). Reaction time 20 min. Yield 4.1 g (82%). Oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 m (4H, CCH_2CH), 1.25 t (4H, CH_2CH_2NH, ^3J 7.2 Hz), 1.30 t(12H, OCH_2CH_3, ^3J 7.3 Hz), 1.42 m (6H, $CHCH_2CH$, 2H, CCH_2C), 1.54 m (6H, CH_2CHCH_2CH), 1.95 m (3H, CH_2CHCH_2), 2.86 t (2H, CCH_2CH_2NH, ^3J 7.2 Hz), 4.03 m (8H, OCH_2CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.22 d (OCH_2CH_3), 28.75 s (CH_2CHCH_2), 32.51 s (CCH_2CHCH_2CH), 36.32 s (CCH_2CH_2NH), 41.76 s (CCH_2CH), 46.07 s (CCH_2CH_2NH), 47.45 s (CCH_2C), 62.10 s (OCH_2CH_3). ^{31}P NMR spectrum: δ 9.2 ppm. Found, %: C 53.10; H 9.12; N 5.56. $C_{22}H_{44}N_2O_6P$. Calculated, %: C 53.43; H 8.97; N 5.66.

Diethyl *N*-[2-(1-adamantyl)oxyethyl]amidophosphate (IIe). Reaction time 12 min. Yield 3.1 g (95%). Oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 m (6H, CCH_2CH), 1.26 t (6H, OCH_2CH_3, ^3J 7.2 Hz), 1.55 m (6H, $CHCH_2CH$), 1.67 m (3H, CH_2CHCH_2), 2.73 t (2H, OCH_2CH_2NH, ^3J 5.9 Hz), 3.42 t (2H, OCH_2CH_2NH, ^3J 5.9 Hz), 4.10 m (4H, OCH_2CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.42 d (OCH_2CH_3), 28.52 s (CH_2CHCH_2), 36.96 s ($CHCH_2CH$), 41.57 s ($OCCH_2CH$), 50.18 s (OCH_2CH_2NH), 61.25 s (OCH_2CH_2NH), 62.75 s (OCH_2CH_3). ^{31}P NMR spectrum: δ 9.2 ppm. Found, %: C 57.31; H 9.21; N 4.12. $C_{16}H_{30}NO_4P$. Calculated, %: C 57.99; H 9.12; N 4.23.

Diethyl *N*-[1-(1-adamantyl)propan-2-yl]amidophosphate (IIf). Reaction time 7 min. Yield 2.9 g (87%). Oily substance. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 d (6H, CCH_2CH, ^3J 6.9 Hz), 1.15 d [3H, $CCH_2CH(CH_3)NH$, ^3J 6.8 Hz], 1.32 t (6H, OCH_2CH_3, ^3J 6.9 Hz), 1.56 m (6H, $CHCH_2CH$), 1.67 m (3H, CH_2CHCH_2), 1.94 m [2H, $CCH_2CH(CH_3)NH$], 3.16 m [1H, $CCH_2CH(CH_3)NH$], 4.06 m (4H, OCH_2CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 16.23 d (OCH_2CH_3), 26.34 s [$CCH_2CH(CH_3)NH$], 28.63 s (CH_2CHCH_2), 32.41 s [$CCH_2CH(CH_3)NH$], 37.00s ($CHCH_2CH$), 42.79 s (CCH_2CH), 43.71 s [$CCH_2CH(CH_3)NH$], 54.45 s [$CCH_2CH(CH_3)NH$], 62.13 (OCH_2CH_3). ^{31}P NMR spectrum: δ 7.7 ppm. Found, %: C 61.26; H 9.88; N 4.64. $C_{17}H_{32}NO_3P$. Calculated, %: C 60.93; H 9.59; N 4.44.

The study was carried out under a financial support of the Russian Foundation for Basic Research (grant no. 08-03-00178).

REFERENCES

1. Gillespie, S.G., Lau, S.L., and Paulson, S.C., *Phosph., Sulfur, Silicon*., 1997, vol. 122, p. 205.
2. Wu, L.Y., Anderson, M.O., Toriyabe, Yo., Maung, J., Campbell, T.Y., Tajon, Ch., Kazak, M., Moser, J., and Berkman, C.E., *Bioorg. Med. Chem*., 2007, vol. 15, p. 7434.
3. Mucha, A., Kunert, A., Grembecka, J., Pawelczak, M., and Kafarski, P., *Eur. J. Med. Chem.,* 2006, vol. 41, p. 768.
4. Whalen, L.J., McEvoy, K.A., and Halcomb, R.L., *Bioorg. Med. Chem. Lett.,* 2003, vol. 13, p. 301.
5. Shen, W., Kim, J.-S., Kish, Ph.E., Zhang, J., Mitchell, S., Gentry, B.G., Breitenbach, E., Drach, J.C., and Hilfinger, J., *Bioorg. Med. Chem. Lett.,* 2009, vol. 19, p. 792.
6. Mehellou, Yu., McGuigan, C., Brancalea, A., and Balzarinib, J., *Bioorg. Med. Chem. Lett*., 2007, vol. 17, p. 3666; Giovannageli, C., Diviacco, S., Labrousse, V., Gryaznov, S., Charneau, P., and Helene, C., *Proc. Natl. Acad. Sci. USA*., 1997, vol. 94, p. 79; Vleighe, P., Clerc, T., Pannecouque, C., Witvrouw, M., De Clerque, E., Salles, J.P., and Kraus, J.L., *J. Med. Chem.,* 2002, vol. 45, p. 1275.
7. Kim, M., Sanda, F., and Endo, T. *Pol. Bull*., 2001, vol. 46, p. 277.
8. Muller, P., Nury, P., and Bernardinelli, G., *Helv. Chim. Acta*, 2000, vol. 83, p. 843.
9. Lin, Ch., Fu, H., Tu, G., and Zhao, Yu., *Synth. Commun*., 2003, vol. 33, p. 2553; Nifant'ev, E.E., Blagoveshchenskii, V.S., Sokurenko, A.M., and Sklyarskii, L.S., *Zh. Obshch. Khim*., 1974, vol. 44, p. 108; Mucha, A., and Kafarski, P., *Tetrahedron* 1994, vol. 50, p. 12743; Brands, K.M.J., Wiedbrauk, K., Williams, J.M., Dolling, U.H., and Reider, P.J., *Tetrahedron Lett.,* 1998, vol. 39, p. 9583.
10. Mimura, M., Hayashida, M., Nomiyama, K., Ikegami, S., Iida, Ya., Tamura, M., Hiyama, Yo., and Oshishi, Yo., *Chem. Pharm. Bull.,* 1993, vol. 41, p. 1971.
11. Kotsikorou, E., Song, Yo., Chan, J.M.W., Faelens, S., Tovian, Z., Broderick, E., Bakalara, N., Docampo, R., and Oldfield, E., *J. Med. Chem*., 2005, vol. 48, p. 6128.
12. Kumar, G.D.K., Saenz, D., Lokesh, G.L., and Natarajan, A., *Tetrahedron Lett*., 2006, vol. 47, p. 6281.
13. Hammerschmidt, F. and Hanbauer, M., *J. Org. Chem*., 2000, vol. 65, p. 6121.
14. Lefort, L., Boogers, J.A.F., de Vries, A.H.M., and de Vries, J.G., *Org. Lett.,* 2004, vol. 6, p. 1733.
15. Jia, X., Li, X., Xu, L., Shi, Q., Yao, X., and Chan, A.S.C., *J. Org. Chem.,* 2003, vol. 68, p. 4539.
16. Quin, L.D. and Jankowskit, S., *J. Org. Chem*., 1994, vol. 59,

p. 4402.
17. Leitner, A., Shekhar, Sh., Pouy, M.J., and Hartwig, J.F., *J. Am. Chem. Soc*., 2005, vol. 127, p. 15506.
18. Alexakis, A., Rosset, S., Allamand, J., March, S., Guillen, F., and Benhaim, C., *Synlett*., 2001, p. 1375.
19. Atherton, F.R., Openshaw, H.T., and Todd, R.R., *J. Chem. Soc*., 1945, p. 660.
20. Warner, V.D., Mirth, D.B., and Dey, A.S., *J. Med. Chem*., 1973, vol. 16, p. 1185.
21. Lidstorm, P., Tierney, J., Wathey, B., and Westman, J., *Tetrahedron*, 2001, vol. 57, p. 9225.
22. Kabachnik, M.M., Zobnina, E.V., and Beletskaya, I.P., *Zh. Org. Khim.,* 2005, vol. 41, p. 517; Kabachnik, M.M., Zobnina, E.V., and Beletskaya, I.P., *Synlett*., 2005, p. 1393; Kabachnik, M.M., Minaeva, L.I., and Beletskaya, I.P., *Zh. Org. Khim.,* 2009, vol. 45, p. 1135; Kabachnik, M.M., Minaeva, L.I., and Beletskaya, I.P., *Synthesis*, 2009, vol. 14, p. 2357.