Heteroatom Chemistry
Volume 22, Number 5, 2011

A Study on the Kabachnik–Fields Reaction of Benzaldehyde, Propylamine, and Diethyl Phosphite by In Situ Fourier Transform IR Spectroscopy

György Keglevich, András Fehérvári, and István Csontos

Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, 1521 Budapest, Hungary

Received 15 December 2010; revised 24 January 2011

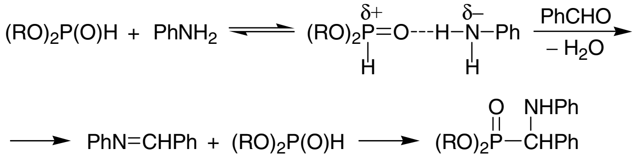
ABSTRACT: *The phospha-Mannich condensation of benzaldehyde, n-propylamine, and diethyl phosphite carried out at 80°C in acetonitrile takes place via the imine (PhC=N–Pr) intermediate as suggested by in situ FT-IR spectroscopy.* © 2011 Wiley Periodicals, Inc. Heteroatom Chem 22:599–604, 2011; View this article online at wileyonlinelibrary.com. DOI 10.1002/hc.20676

INTRODUCTION

In situ Fourier transform infra-red (FT-IR) spectroscopy is a useful tool in environment friendly chemistry, as it allows optimization of the reaction conditions via monitoring the concentration profile of the components [1–5]. The time-dependent IR spectra also allow the establishment of formal kinetics or equilibrium constants [6,7] as well as detection of intermediates [8,9]. In situ FT-IR spectroscopy has been applied only rarely in organophosphorus chemistry [5,10,11]. We wished to study the Kabachnik–Fields (phospha-Mannich) reaction [12,13] by in situ FT-IR spectroscopy to obtain information on the course of the three-component condensation reaction of an oxo compound, a primary or secondary amine, and a dialkyl phosphite. The resulting α-aminophosphonates are important, potentially biologically active substrates [14–17]. In our laboratory, the microwave(MW)-assisted synthesis of heterocyclic α-aminophosphates and α-aminophosphine oxides was investigated [18,19]. It was found that, in general, the simplest procedure involves solventless MW conditions, and there is no need for special (expensive and environment unfriendly) catalysts [20]. The course of the Kabachnik–Fields reaction is also of continuing interest. Cherkasov and Galkin studied the mechanism of the Kabachnik–Fields reaction in detail [21]. One possibility is that an imine is formed from the carbonyl compound and the (primary) amine, and then the dialkyl phosphite is added onto the C=N moiety of the imine. The other route that they considered involves the formation of an α-hydroxyphosphonate by the addition of the phosphite to the carbonyl group of the oxo component. Then the hydroxyphosphonate may undergo substitution by the amine to afford the α-aminophosphonate. Mainly on the basis of kinetic studies, it was thought that the mechanism is dependent on the nature of the reactants. For example, the condensation of aniline, benzaldehyde, and a dialkyl phosphite was shown to follow the “imine”

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

Contract grant sponsor: Hungarian Scientific Research Fund (OTKA).
Contract grant numbers: K067679 and K83118.
This work is connected to the scientific program of the “Development of quality-oriented and harmonized R+D+I strategy and functional model at BME” project. This project is supported by the New Hungary Development Plan (Project ID: TÁMOP-4.2.1/B-09/1/KMR-2010-0002).



SCHEME 1 [21,22]

mechanism. Interestingly, it was found that before the condensation of the aniline and the benzaldehyde, an H-bond is formed between the P=*O* function of the phosphite and the N*H* unit of the amine (Scheme 1) [21,22].

In another example, Cherkasov and Galkin suggested that the reaction of the more nucleophilic cyclohexylamine, benzaldehyde, and a dialkyl phosphite takes place via the "hydroxyphosphonate" route [21,23].

Later, however, Matveeva and Zefirov proved that the condensation of cyclohexylamine, benzaldehyde, and dialkyl phosphite follows the "imine route" and concluded that there is no experimental evidence for the hydroxyphosphonate route being involved [24].

It is worthy of mention that the reaction of cyclohexylamine, benzaldehyde, and dibutylphosphine oxide, which can be regarded as an extended Kabachnik–Fields condensation, was shown to proceed according to the "imine" mechanism [21,25]. It seems to be probable that the actual mechanism is dependent on the components of the reaction, but the "imine" route is more general, than the pathway involving an "α-hydroxyphosphonate" intermediate [26]. Gancarz observed that a reversible formation of the α-hydroxyphosphonate may also occur, and at the same time if it is rearranged to the corresponding phosphate this is a "dead-end" route [27]. It can be said that in the Kabachnik–Fields reaction, a soft nucleophile, that is the dialkyl phosphite, and a hard nucleophile, that is the amine, compete for the electrophilic carbonyl compound. The softer the carbonyl compound is, the faster it reacts with the softer P-nucleophile and the slower it reacts with the harder amine nucleophile [28].

We wished to study the course of the phospha-Mannich reactions involving a primary aliphatic amine, an aromatic aldehyde, and a dialkyl phosphite as the reactants. In situ FT-IR spectroscopy seemed to be an appropriate tool in monitoring the target reaction.

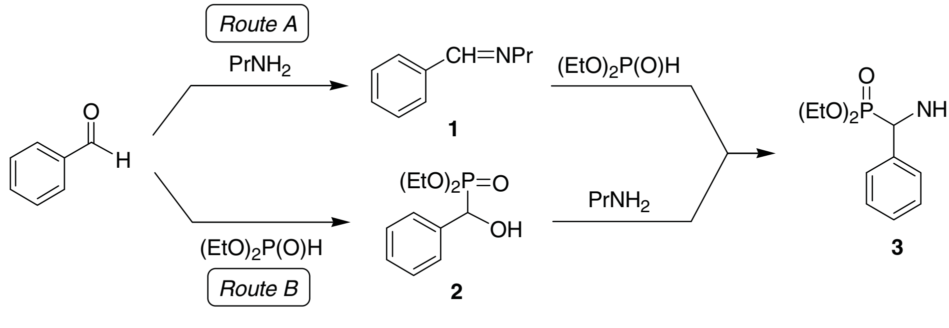
RESULTS AND DISCUSSION

The model reaction to be studied was the condensation of *n*-propylamine, benzaldehyde, and diethyl phosphite affording diethyl α-propylamino-α-phenyl-methylphosphonate (**3**) either via imine (Schiff base) **1** or α-hydroxyphosphonate **2** (Scheme 2).

According to earlier experiences, in most cases, "*Route A*" is the preferred pathway. For this, we wished to evaluate first the possibility of the imine pathway.

Schiff base **1** and α-aminophosphonate **3** were prepared in separate experiments, and the IR spectra of benzaldehyde, diethyl phosphite, imine **1,** and aminophosphonate **3** were recorded in acetonitrile solution. The spectra are shown in Fig. 1. Owing to its lack of IR absorption in the region of 800–1700 cm^{-1}, the spectrum of *n*-propylamine was not included.

The reagents benzaldehyde and diethyl phosphite revealed intense absorptions at 1702 or 980, 1042 and 1258 cm^{-1}, respectively. The peaks at 1702, 980/1042, and 1258 cm^{-1} are due to $\nu_{C=O}$, ν_{P-O-C}, and $\nu_{P=O}$ stretching vibrations, respectively. The imine (**1**) showed intense signals at 973 and 1648 cm^{-1}. As the first one overlaps with the peak of $(EtO)_2P(O)H$ at 980 cm^{-1}, the absorption at 1648 cm^{-1} that is due



SCHEME 2

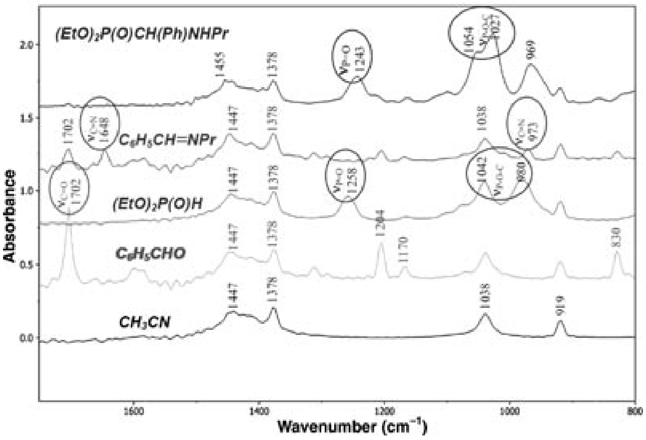


FIGURE 1 IR spectra of the reaction components measured in acetonitrile solution.

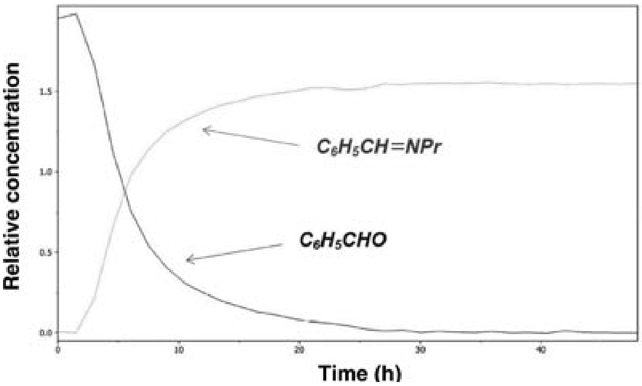


FIGURE 3 Concentration profile for the reaction of benzaldehyde with n-propylamine at 0°C in acetonitrile.

to the $\nu_{C=N}$ vibration remains for identification. The aminophosphonate **3** can be recognized from the signals at 1027 and 1054 cm^{-1} (both due to ν_{P-O-C} stretching vibration) and 1243 cm^{-1} ($\nu_{P=O}$).

In the first experiment, the formation of imine **1** was studied. Benzaldehyde and n-propylamine were reacted in acetonitrile at 0°C. On the basis of the decreasing absorption at 1702 cm^{-1} and the increasing signal at 1648 cm^{-1}, the change in the concentration of benzaldehyde and imine **1** could be followed well (Fig. 2).

The concentration profile for the reaction components, benzaldehyde, and imine **1** is shown in Fig. 3. The curves were obtained by deconvolution, which is the separation of the (overlapping) absorption bends of the reaction components. The formation of imine **1** was practically complete after 20 min.

The next experiment involved the reaction of Schiff base **1** with diethyl phosphite. We wished to evaluate the temperature at which the addition commences. For this, the acetonitrile solution of the reactants was heated gradually from room temperature to 80°C. The reaction started at 75°C, as was shown by the appearance of the absorbances at 1027 and 1054 cm^{-1} belonging to the ν_{P-O-C} vibration of aminophosphonate **3**. At the same time, the signals at 980, 1042, and 1258 cm^{-1} characteristic of diethyl phosphite and at 1648 cm^{-1} belonging to the imine (**1**) started decreasing when the temperature reached 75°C. The three-dimensional (3D) diagram of the above transformation is shown in Fig. 4. It can be concluded that the imine (**1**) and diethyl phosphite react at a temperature ≥75°C.

The next experiment was on a three-component equimolar reaction mixture and was carried out in two stages. The first spectrum was obtained on the acetonitrile solution of diethyl phosphite at 26°C. After recording of 3 and 11 spectra, the n-propylamine and benzaldehyde, respectively, were added. After the addition of benzaldehyde, the temperature rose

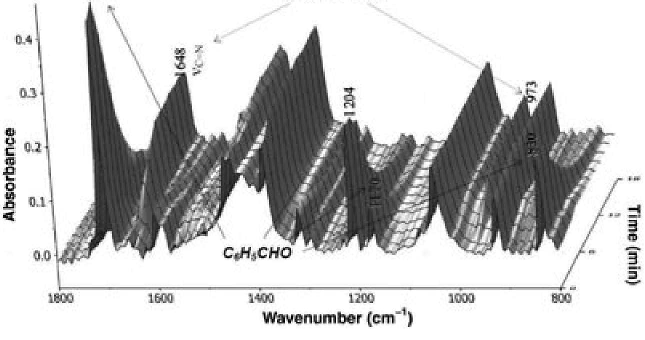


FIGURE 2 A segment of the time-dependent IR spectrum for the reaction of benzaldehyde with n-propylamine in acetonitrile at 0°C.

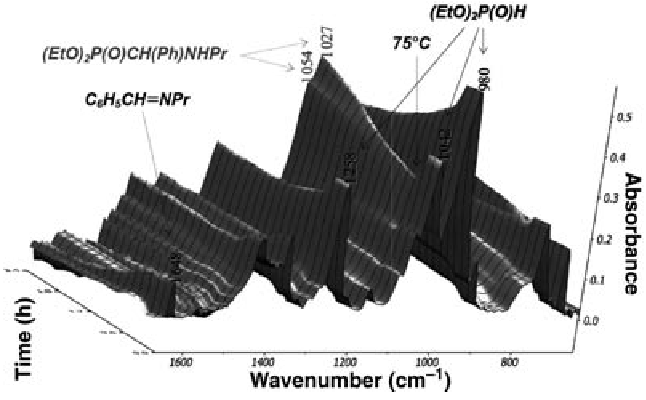


FIGURE 4 A segment of the time-dependent IR spectrum for the reaction of imine **1** with diethyl phosphite in acetonitrile.

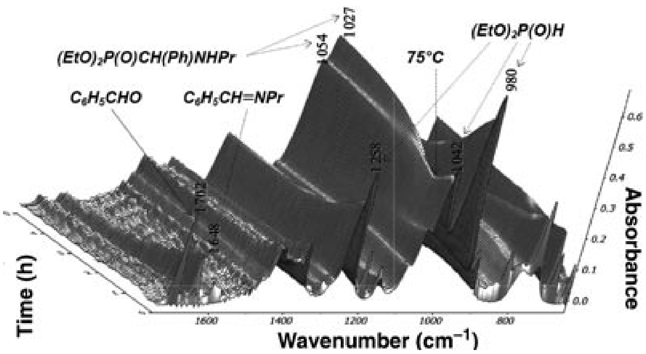


FIGURE 5 A segment of the time-dependent IR spectrum for the Kabachnik–Fields reaction of diethyl phosphite, *n*-propylamine, and benzaldehyde in acetonitrile carried out in two stages.

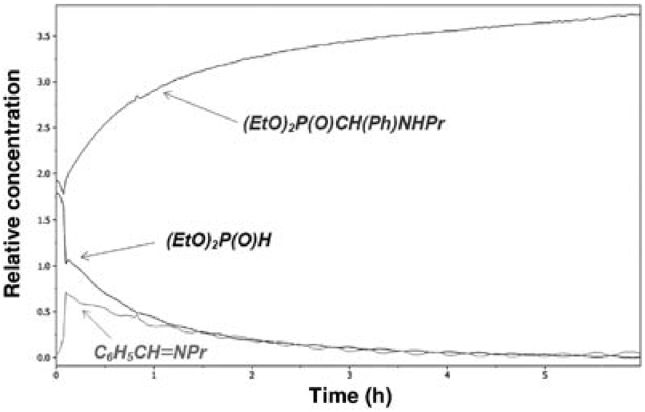


FIGURE 7 Concentration profile for the Kabachnik–Fields reaction studied at 80°C in acetonitrile.

from 26 to 36°C. Simultaneously, the benzaldehyde was consumed and the imine appeared as shown by the peak at 1648 cm^{-1}. The temperature was then gradually increased by heating. At 75°C, the imine (**1**) gradually disappeared, but the aminophosphonate appeared as suggested by the signals at 1027 and 1054 cm^{-1}. The 3D diagram obtained is shown in Fig. 5.

Finally, an acetonitrile solution of diethyl phosphite and *n*-propylamine was heated to 80°C, and benzaldehyde was then added. Collection of the spectra was started when all the three components were in the flask. The benzaldehyde could not be detected as it was converted instantly to Schiff base **1**, which, in turn, was transformed to aminophosphonate **3** by reaction with diethyl phosphite. The intermediate (**1**) appearing at 1648 cm^{-1} could be seen clearly for ca. 3 h. The maximum concentration could be seen after 10 min. The 3D diagram for the phospha-Mannich reaction carried out in acetonitrile at 80°C is shown in Fig. 6. No absorption at 3268 cm^{-1} characteristic to the stretching vibration of the hydroxy group of α-hydroxyphosphonate **2** could be detected during the course of the reaction.

The above experiment serves as direct evidence for the pathway via Schiff base **1** ("Route A" in Scheme 2) in the case of the three-component condensation under discussion. So far, only kinetic studies have been published in respect of the mechanism of other Kabachnik–Fields reactions [21]. The course of the phospha-Mannich reactions may obviously depend on the nature of the starting materials [21–24].

The relative concentration–time diagram obtained after deconvolution is shown in Fig. 7. The intermediacy of imine **1** can be seen clearly, and it can be established that the reaction time is approximately 4 h.

It was also possible to reproduce the IR spectra of the reaction components, such as diethyl phosphite, Schiff base **1**, and aminophosphonate **3** (Fig. 8 and Table 1). It can be seen that the real IR spectra

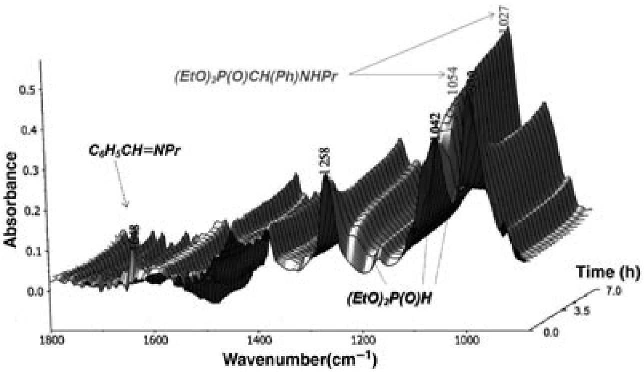


FIGURE 6 A segment of the time-dependent IR spectrum for the Kabachnik–Fields reaction of diethyl phosphite, *n*-propylamine, and benzaldehyde at 80°C in acetonitrile.

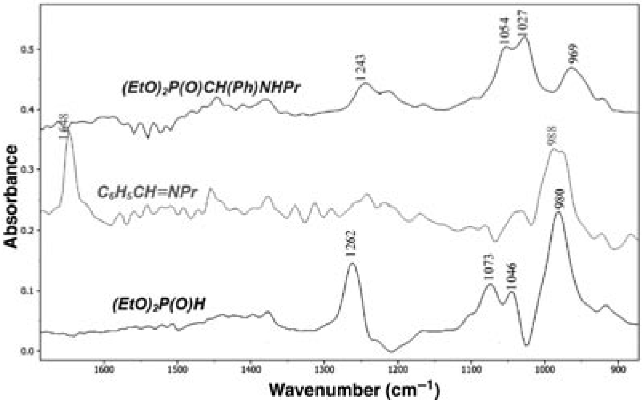


FIGURE 8 IR spectra for the reaction components obtained from the 3D diagram after deconvolution.

TABLE 1 IR Absorptions Measured and Obtained from the 3D Diagram after Deconvolution (in cm^{-1})

$(EtO)_2P(O)H$		$C_6H_5CH{=}NPr$		$(EtO)_2P(O)CH(Ph)NHPr$	
Calculated	Measured	Calculated	Measured	Calculated	Measured
		1648	1648		
1262	1258			1243	1243
1073	1077			1054	1053
1046	1042			1027	1027
980	980	988	973	969	969

are almost identical to those obtained by deconvolution (Fig. 1 vs. Fig. 8).

In summary, the Kabachnik–Fields reaction of benzaldehyde, *n*-propylamine, and diethyl phosphite carried out at 80°C in the acetonitrile solution could be monitored successfully by in situ FT-IR spectroscopy, and the intermediacy of the corresponding Schiff base was pointed out suggesting that benzaldehyde and *n*-propylamine react with each other in the first step. We plan to study phospha-Mannich condensations of other types as well.

EXPERIMENTAL

Equipment

In situ FT-IR measurements were carried out using a ReactIR 1000 equipment. The diamond measuring head was placed in a 100-mL four-necked flask equipped with a dropping funnel, a condenser, a thermometer, and a magnetic stirrer. The temperature was maintained by using an appropriately adjusted water bath.

Synthesis of Imine **1**

10.2 mL (100.0 mmol) of benzaldehyde and 8.2 mL (100.0 mmol) of *n*-propylamine was measured together at 26°C, and the mixture was stirred for 24 h. Then the mixture was kept under vacuum to afford 14.2 g (96%) of Schiff base **1**. IR (neat) 693, 969, 1451, 1647, 2961 cm^{-1}.

Synthesis of α-Hydroxyphosphonate **2**

A mixture of 3.0 mL (29.5 mmol) of benzaldehyde, 3.8 mL (29.5 mmol) of diethyl phosphite, and 2.8 g Na_2CO_3 (as the catalyst) in 30 mL of toluene was heated at 110°C for 6 h. Then the solid was filtered off, and the filtrate was evaporated. The residue was washed with 2 × 10 mL of ether to give 6.2 g (86%) of α-hydroxyphosphonate **2**. ^{31}P NMR δ ($CDCl_3$) 21.5, δ_P[29] 22.0; IR (KBr) 701, 962, 1026, 1050, 1228, 1451, 2989, 3268.

Synthesis of Diethyl α-Phenyl-α-propylamino-methylphosphonate (**3**)

6.1 mL (60.0 mmol) of benzaldehyde, 5.0 mL (61.0 mmol) of *n*-propylamine, and 7.7 mL (60.0 mmol) of diethyl phosphite was heated at 80°C for 22 h. The mixture was passed through a short silica gel column using 3% methanol in chloroform as the eluant to furnish 12.8 g (75%) of aminophosphonate **3**. ^{31}P NMR δ ($CDCl_3$) 23.7, δ_P[30] 24.1; IR (neat) 700, 966, 1028, 1057, 1243, 1454, 2970 cm^{-1}.

Monitoring the Reaction of Benzaldehyde with n-Propylamine

To 5.1 mL (50.0 mmol) of benzaldehyde in 25 mL of acetonitrile, 4.1 mL (50 mmol) of *n*-propylamine was added dropwise at 0°C over a period of 2 min with external ice-cooling and vigorous stirring. The reaction was complete after 15 min. The reaction took place as shown in Fig. 2.

Monitoring the Reaction of Schiff Base **1** *with Diethyl Phosphite*

To 7.4 g (50.0 mmol) of imine **1** in 25 mL of acetonitrile, 6.4 mL (50.0 mmol) of diethyl phosphite was added dropwise at 26°C on intensive stirring. After complete addition, the mixture was heated gradually from 26°C by a water bath. The addition reaction commenced at 75°C, as shown in Fig. 4.

Monitoring the Phospha-Mannich Reaction Carried Out at 26 → 75°C

To the mixture of 7.7 mL (60.0 mmol) of diethyl phosphite in 30 mL of acetonitrile, 5.0 mL (61.0 mmol) *n*-propylamine and 6.1 mL (60.0 mmol) of benzaldehyde were added, whereupon the temperature increased from 26 to 36°C due to the formation of imine **1**. The mixture was then heated with a water bath until the temperature reached 75°C. At this temperature, the addition reaction took place gradually as shown in Fig. 5.

Monitoring the Phospha-Mannich Reaction Carried Out at 75°C

The above reaction was repeated by adding the benzaldehyde to the mixture of diethyl phosphite and *n*-propylamine in acetonitrile at 80°C. The resulting 3D diagram is shown in Fig. 6.

REFERENCES

[1] Ende, D. J.; Preigh, M. J. Curr Opin Drug Disc 2000, 3, 699.
[2] Pintar, A.; Batista, J.; Levec, J. Analyst 2002, 127, 1535.
[3] Rein, A. J. SPIE—Optically Based Methods Process Anal 1992, 1681, 49.
[4] Sheridan, R. E.; Rein, A. J. Res Dev 1991, 33, 100.
[5] Yamagiwa, N.; Abiko, Y.; Sugita, M.; Tian, J.; Matsunaga, S.; Shibasaki, M. Tetrahedron: Asymmetry 2006, 17, 566.
[6] Keglevich, G.; Csontos, I.; Novák, T.; Mucsi, Z.; Marosi, G.; Greiner, I. Hung Chem J 2006, 112, 114.
[7] Sallay, P.; Szilágyi, N.; Csontos, I.; Keglevich, G. Per Politechn Chem Eng 2009, 53, 9.
[8] Keglevich, G.; Csontos, I.; Szilágyi, N.; Greiner, I. Chem Eng Technol 2008, 31, 421.
[9] Keglevich, G.; Csontos, I.; Szilágyi, N. Spec Lett 2009, 42, 67.
[10] Keglevich, G.; Puskás, R. E.; Grün, A.; Csontos, I.; Phosphorus, Sulfur, Silicon 2010, 185, 832.
[11] Keglevich, G.; Puskás, R. E.; Grün, A.; Csontos, I.; Greiner, I. Phosphorus, Sulfur, Silicon 2010, 185, 2333.
[12] Fields, L. K. J Am Chem Soc 1952, 74, 1528.
[13] Kabachnik, M. I.; Medved, T. Y. Dokl Akad Nauk SSSR 1952, 83, 689.
[14] Kafarski, P.; Lejczak, B. Curr Med Chem Anti-Cancer Agents 2001, 1, 301.
[15] Sienczyk, M.; Oleksyszyn, J. Curr Med Chem 2009, 16, 1673.
[16] Liu, W.; Rogers, C. J.; Fisher, A. J.; Toney, M. D. Biochemistry 2002, 41, 12320.
[17] Grembecka, J.; Mucha, A.; Cierpicki, T.; Kafarski, P. J Med Chem 2003, 46, 2641.
[18] Prauda, I.; Greiner, I.; Ludányi, K.; Keglevich, G. Synthetic Commun 2007, 37, 317.
[19] Keglevich, G.; Szekrényi, A.; Sipos, M.; Ludányi, K.; Greiner, I. Heteroatom Chem 2008, 19, 207.
[20] Keglevich, G.; Szekrényi, A. Lett Org Chem 2008, 5, 616.
[21] Cherkasov, R. A.; Galkin, V. I. Russ Chem Rev 1998, 67, 857 (Usp Khim 1998, 67, 940; in Russian).
[22] Galkin, V. I.; Zvereva, E. R.; Sobanov, A. A.; Galkina, I. V.; Cherkasov, R. A. Zh Obshch Khim 1993, 63, 2225.
[23] Galkina, I. V.; Sobanov, A. A.; Galkin, V. I.; Cherkasov, R. A. Russ J Gen Chem 1998, 68, 1398 (Zh Obshch Khim 1998, 68, 1465; in Russian).
[24] Matveeva, E. D.; Zefirov, N. S. Doklady Chem 2008, 420, 137 (Dokl Akad Nauk 2008, 420, 492; in Russian).
[25] Galkina, I. V.; Galkin, V. I.; Cherkasov, R. A. Zh Obshch Khim 1998, 68, 1469.
[26] Zefirov, N. S.; Matveeva, E. D. ARKIVOC 2008, (i), 1.
[27] Gancarz, R.; Gancarz, I. Tetrahedron Lett 1993, 34, 145.
[28] Gancarz, R. Tetrahedron 1995, 51, 10627.
[29] Nesterov, V. V.; Kolodyazhnyi, O. I. Russ J Gen Chem 2005, 75, 1161 (Zh Obshch Khim 2005, 75, 1225; in Russian).
[30] Qian, C.; Huang, T. J Org Chem 1998, 63, 4125.