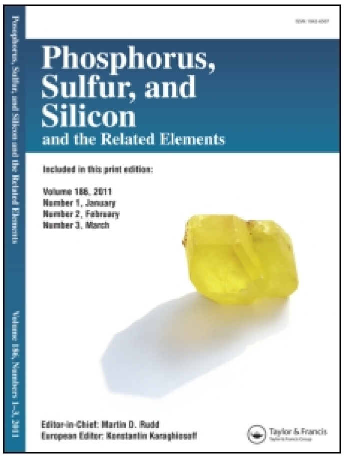

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UNEXPECTED PRODUCTS IN A KABACHNIKFIELDS SYNTHESIS OF AMINOPHOSPHONATES

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UNEXPECTED PRODUCTS IN A KABACHNIK-FIELDS SYNTHESIS OF AMINOPHOSPHONATES

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In a Kabachnik-Fields synthesis of aminophosphonates derived from aromatic ketones the formation of hydroxyphosphonates, their rearrangement to corresponding phosphates and amine promoted decomposition of the last, leads to a number of unexpected products, which in some cases could be the only products of the reaction.

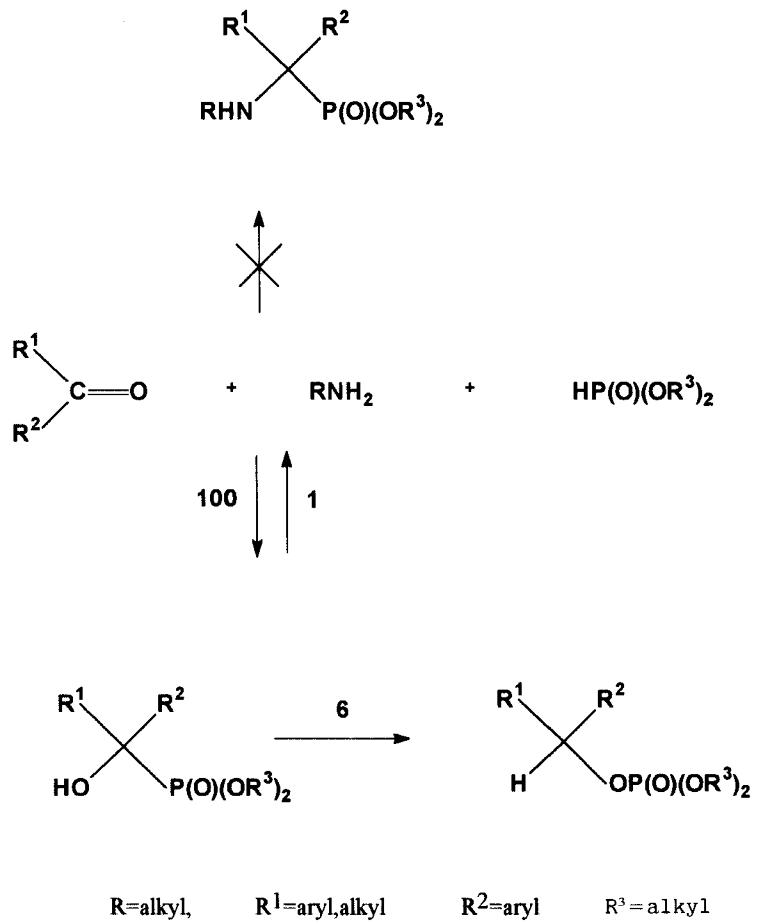
Key words: 1-Aminophosphonates; 1-hydroxyphosphonates; Kabachnik-Fields reaction; phosphonate-phosphate rearrangement.

INTRODUCTION

Aminophosphonates and aminophosphonic acids were almost unknown compounds still in 1968 but today they are a subject of more than 5000 papers. These compounds have received their great interest due to their biological activity. For the review see Reference 1. A reaction between ammonia or amine, dialkyl phosphite and the corresponding carbonyl compound, described by Kabachnik & Medved and Fields,[2–4] is one of the very first methods of aminophosphonate synthesis. This method has received the common name Kabachnik-Fields reaction and it is still commonly used especially for synthesis of N-substituted and N,N-disubstituted derivatives, despite the fact that in some cases yields of aminophosphonates are small, e.g. 12% (benzophenone)[5] and 0% (fluorenone derived substrates).[6] Based on the observation that hydroxyphosphonates are present in the mixture of ammonia or amine, carbonyl compound and dialkyl phosphite at room temperature,[2,4,7] it was postulated that the reaction proceeds via hydroxyphosphonates followed by the substitution of hydroxy group by the amino group. Pietrov,[8] however, presented arguments against that mechanism. Until today the mechanism of this reaction remains unclear.

RESULTS AND DISCUSSION

Recently we have found[9] that when aromatic ketone is used as a substrate the hydroxyphosphonate is formed reversibly but it irreversibly rearranges to the corresponding phosphate and thus makes aminophosphonate synthesis impossible, see Scheme 1. The numbers on Scheme 1 represent the relative rates of the reactions. The rearrangement reaction is 6–7 times faster than the reverse reaction leading back to the ketones, which in turn is about 100 times slower than formation of



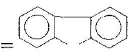
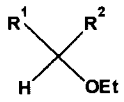
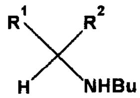
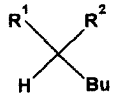
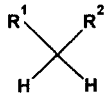
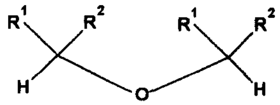
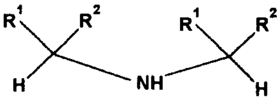
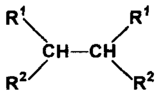
SCHEME 1

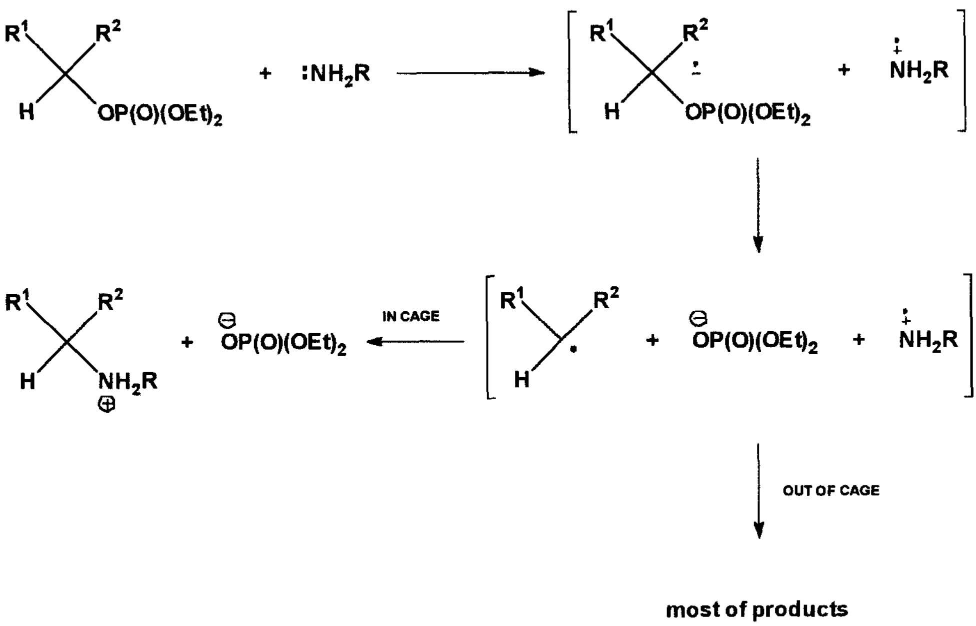
hydroxyphosphonate. Thus all or most of the ketone is used up before aminophosphonate is formed.

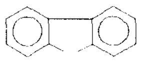
There are many examples in the literature that formation of phosphate could be reversed.[10] Thus we were interested in what happens with the phosphate formed in the Kabachnik-Fields condition in those cases when aminophosphonates are formed with low yields. The reaction may stop at that stage, or may slowly reverse to allow formation of aminophosphonates, or may go to some other direction forming some new compounds. In this paper we present the results of our investigation showing that the last reaction takes place. Heating of an equimolar mixture of carbonyl compound, amine and dialkyl phosphite at 70°C, with or without solvent in a typical Kabachnik-Fields reaction[4] yields phosphate irreversibly.

Running the reaction for a prolonged time leads to many unexpected products containing no phosphorus atom. We also found that decomposition products are formed mainly from phosphate decomposition since the same products were observed when an equimolar amount of corresponding phosphate and amine was heated at 70°C for several hours. All decomposition compounds which were collected in experiments when benzophenone or fluorenone were used as carbonyl compounds account for more than 70%, based on the starting ketone and average data for the two studied carbonyl compounds collected in Table I. The amine is essential for the formation of these products, since heating of the phosphate alone in methanol or ethanol does not lead to decomposition. Only the starting material (i.e. phosphate) in these cases is isolated after the reaction. Decomposition is observed only when the amine is added to the solution. When benzophenone or fluorenone is used as carbonyl substrate, the corresponding aminophosphonates

TABLE I
Percentage amount of decomposition products

	$R^1=R^2=$Phenyl	$R^1,R^2=$ 
	**33**	**8**
	**35**	**34**
	**2**	**3**
	**0**	**25**
	**1·3**	**0**
	**3**	**0**
	**0**	**10**
Total	74%	80%



$R^1=R^2=$Phenyl ; $R^1,R^2=$  ; R=alkyl

SCHEME 2

are isolated in yields lower than 5%. Running the similar experiment for acetophenone yields about 65% of the aminophosphonate but the side reactions are far more complicated. This is due to the presence of α-hydrogens in phosphate, produced by rearrangement of hydroxyphosphonate, and the possibility of the elimination reaction[11,12] which complicates the decomposition pattern. We have not observed a substantial amount of decomposition products when acetone or another aliphatic ketone was used as a substrate. Yields of aminophosphonates in these cases were over 80%.

The mechanism of formation of decomposition products is now known. This reaction is now a subject of our studies. Based on the structure of the products we think that some radical process is involved in the formation of all products. It is possible that decomposition starts as a single electron transfer according to Scheme 2. This explains why the N-n-butylamine derivatives are major products of decomposition.

Amine radical cations are relatively easily formed and they were postulated as intermediates in many reactions, including a biochemical one. For one of the latest papers, see Reference 13.

EXPERIMENTAL

^{1}H-NMR spectra were taken on BRUKER WM 250 MHz spectrometer (ref. TMS) and TESLA BS-497 (100 MHz). IR spectra were recorded on Specord IR-75 spectrophotometer. Mass spectra were taken on GC-MS Hewlet Packard 5971 series II instrument equipped with gas chromatograph 5890 series II. Analytical TLC were carried out on silicagel GF_{254} Merck) with a different developing system: methylene chloride, chloroform, hexane or mixture thereof. Column or preparative TLC chromatography were performed on silicagel (Kieselgel 60, Merck) with the same eluent system as TLC. Fluorenone was purchased from Merck and purified by steam distillation. The fluorene was purchased from Fluka, n-butylamine and diethyl phosphite from Aldrich.

Ethoxy(diphenyl)methane, colorless oil, MS: *m/e* (212, 183, 167, 135, 105, 77); ^{1}H-NMR ($CDCl_3$): 7.75–7.10 (m, 10H, $\mathrm{Ar\underline{H}}$), 5.35 (s, 1H, $\mathrm{C\underline{H}}$), 3.09 (q, 2H, $\mathrm{C\underline{H}_2}$, $J_{\mathrm{H\text{-}H}}$ = 6.84 Hz), 1.26 (t, 3H, $\mathrm{C\underline{H}_3}$, $J_{\mathrm{H\text{-}H}}$ = 6.84 Hz), data identical with that for a compound obtained by the method described in Reference 14.

Butyl(diphenylmethyl)amine hydrochloride, mp. 217–218°C, (lit.[15] 195–197°C); MS, (for free amine): *m/e*, (239, 196, 182, 167, 152, 139, 91, 77); ^{1}H-NMR ($CDCl_3$): 7.77–7.21 (m, 10H, $\mathrm{Ar\underline{H}}$), 5.22 (s, 1H, $\mathrm{N\underline{H}}$), 4.83 (s, 1H, $\mathrm{C\underline{H}}$), 2.61 (t, 2H, $\mathrm{C\underline{H}_2N}$, $J_{\mathrm{H\text{-}H}}$ = 7.33 Hz), 1.5–1.05 (m, 4H, $\mathrm{C\underline{H}_2{-}C\underline{H}_2}$), 0.87 (t, 3H, $\mathrm{C\underline{H}_3}$, $J_{\mathrm{H\text{-}H}}$ = 5.87 Hz). MS, NMR data identical with that for a compound obtained by the method described in Reference 15.

Bis(diphenylmethyl)ether, mp. 105–107°C, (lit.[16] 107–107.5°C); MS: *m/e*, (330, 183, 167, 105, 77); ^{1}H-NMR ($CDCl_3$): 7.79–7.01 (m, 20H, $\mathrm{Ar\underline{H}}$), 5.25 (s, 1H, $\mathrm{C\underline{H}}$). Data identical with that for a compound obtained by the method described in Reference 16.

Bis(diphenylmethyl)amine, mp. 153–154°C, (lit.[17] 138–143°C); MS: *m/e*, (347, 167, 152, 77); ^{1}H-NMR ($CDCl_3$): 7.79–7.01 (m, 20H, $\mathrm{Ar\underline{H}}$), 5.25 (s, 1H, $\mathrm{C\underline{H}}$). MS, NMR data identical with that for a compound obtained by the method described in Reference 17.

Butyl(fluoren-9-yl)amine, colorless oil, MS: *m/e*, (237, 222, 180, 165, 115); ^{1}H-NMR ($CDCl_3$): 7.79–7.20 (m, 8H, $\mathrm{Ar\underline{H}}$), 4.93 (s, 1H, $\mathrm{C\underline{H}}$), 2.40 (t, 2H, $\mathrm{C\underline{H}_2N}$, $J_{\mathrm{H\text{-}H}}$ = 6.10 Hz), 2.25 (s, 1H, $\mathrm{N\underline{H}}$), 1.75–1.05 (m, 4H, $\mathrm{C\underline{H}_2C\underline{H}_2CH_3}$), 0.83 (t, 3H, $\mathrm{C\underline{H}_3}$, $J_{\mathrm{H\text{-}H}}$ = 6.10 Hz).

9,9'-difluorenyl, mp. 245–246°C (lit.[19], 245–246°C), MS *m/e* (330, 165, 139, 115). Compound identical with that obtained by the method described in Reference 19.

9-H-fluorene, mp. 114–116°C, MS: *m/e*, (166, 139, 115, 83). Compound identical with the one commercially available.

Due to their small amount in the reaction mixture the following compounds were identified by the GC/MS and their spectra were in good agreement with that for the compounds obtained by the literature method:

Butyl(diphenyl)methane, MS: *m/e*, (224, 167, 152, 91, 77).[20]
9-Butylfluorene, MS: *m/e*, (222, 165, 77).[21]
9-Ethoxyfluorene, MS: *m/e*, (210, 181, 165, 152, 82).[23]
Hydroxyphosphonates and phosphates were prepared by the procedures described in the literature.[22]

Kabachnik-Fields reaction. A mixture of carbonyl compound, diethyl phosphite, and n-butylamine were heated in ethanol or without solvent at 70°C for 6 hrs. At that time, when benzophenone or fluorenone was used as a carbonyl substrate, we observed as a main product the corresponding phosphate. To study the decomposition reaction the heating was continued until no phosphate was detected on TLC (it takes about 12 hrs). After that time the reaction mixture was separated to acidic, neutral and basic fractions by a standard technique or in another experiment the mixture was separated by preparative TLC or column chromatography. We did not observe substantial differences in the mixture contents using different separation techniques. The isolated compounds were analysed by NMR, IR, and MS and compared with the compounds obtained by the literature methods.

Phosphate decomposition. A mixture of phosphate and n-butylamine (molar ratio 1:2) was heated for 12 hrs at 70°C. After that time the mixture was separated by column chromatography and analysed as described above.

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