Tetrahedron Letters, Vol. 34, No. 1, pp. 145-148, 1993
Printed in Great Britain

0040-4039/93 $5.00 + .00
Pergamon Press Ltd

FAILURE OF AMINOPHOSPHONATE SYNTHESIS DUE TO FACILE HYDROXYPHOSPHONATE - PHOSPHATE REARRANGEMENT

ROMAN GANCARZ* , IRENA GANCARZ**
* *Institute of Organic and Physical Chemistry*
** *Institute of Organic Technology and Plastics*
Technical University of Wroclaw, Wybrzeze Wyspianskiego 27,
50-370 WROCLAW, POLAND

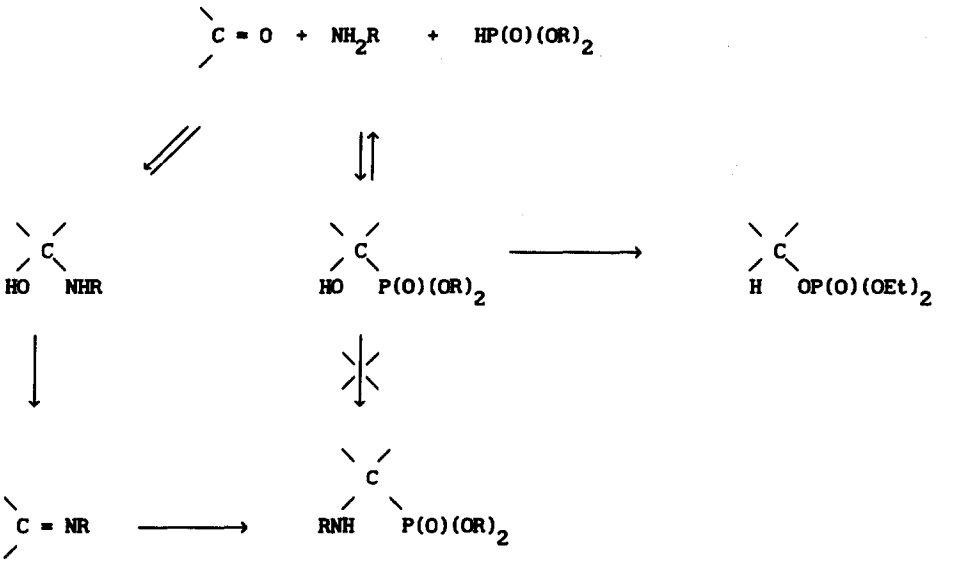
Abstract In a Kabachnik-Fields synthesis of aminophosphonates amines can catalyse the formation of hydroxyphosphonates, and their further rearrangement to phosphates, unabling the formation of aminophosphonates.

Aminophosphonates and aminophosphonic acids were almost uknown 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 [1].

One of the very first methods of aminophosphonates synthesis appears to be the one described by Kabachnik & Medved [2-3]. These compounds were obtained in a reaction between ammonia, dialkyl phosphite and corresponding carbonyl compound. A little bit later Fields [4] presented a method of synthesis of N-mono- and N,N- disubstituted aminophosphonates in a similar manner, replacing ammonia with the corresponding amine. These methods have received the common name Kabachnik-Fields reaction and are still important especially for synthesis of N-substituted derivatives. Yields of aminophosphonates vary from 40-47% (acetone) [5], 12% (benzophenone) [5] to 0% (fluorenone derived substrates) [6]. Since Kabachnik & Medved [2] have found that hydroxyphosphonates are present in the mixture of ammonia, carbonyl compound and dialkyl phosphite at room temperature they postulated that the reaction undergoes via hydroxyphosphonates followed by the substitution of hydroxy group by amino group. Pietrov [7] however presented arguments that aminophosphonates are not formed in a hydroxy group substitution reaction but rather due to reversibility of the hydroxyphosphonate formation. Based on the Fields idea [4], he postulated that aminophosphonates are formed via hydroxyamines or imines. The possible reactions are presented in the Scheme below. (Scheme 1)

To that scheme we added the path leading to phosphate. It was not postulated by the mentioned authors. It is known in the literature [8] and as we believe it is a reason of many failures of aminophosphonate synthesis especially when

diaryl ketones are used as a carbonyl substrates.



Scheme 1, R=alkil, aryl

We observed the reaction progress by NMR and kinetic methods. In all NMR experiments 1:1:1 (mole ratio) mixture of ketone, butylamine and diethylphosphite in C_6D_6 was left in room temperature for 72 hrs and in separate experiments for 3 hrs at 55-60°C. There were no substantial differences indicating that the reaction course is different in these two NMR experiments, only at higher temperatures the greater progress of the reaction was observed. We also run the reaction, by mixing the equimolar amounts of reagents and heating the mixture at 60°C for three hrs. The calculated yields of aminophosphonates for all experiments were about 87%, 46%, 20%, 0% and yields of hydroxyphosphonate and phosphate measured together were about 0%, 8%, 60% and 95% for acetone, acetophenone, benzophenone and fluorenone, respectively. The products identity was proved by their independent syntheses and comparison of the spectra with that in the studied mixture [9].

Replacing butylamine or any aliphatic amine with aniline or N-ethylaniline led to over 70% of aminophosphonates also when fluorenone was used as a carbonyl compound. It was found in a separate experiment that while heating fluorenone with phosphite at 80-90°C for several hours, only traces of hydroxyphosphonates were obtained. It was also shown that while heating the fluorenone with primary amine (no matter if it is aliphatic or aromatic) in the absence of phosphite the only product was coresponding imine, N-substituted fluorenylimine. We can explain it as follow. Aromatic amines as weak basic species do not "activate"

the dialkyl phosphites, and the reaction proceeds via hydroxyamine-imine path. The conditions are dramatically changed when any alkylamine appears. They are much stronger bases and they "activate" the dialkyl phosphite in a manner proposed by Springs & Haake [10] (path A or B).

$$(RO)_2P(O)^- + N^+H_3R \xleftarrow{A} HP(O)(O)(OR)_2 + NH_2R \xrightarrow{B} (RO)_2POH \quad :NH_2R$$

Such activated dialkyl phosphites react with ketone forming hydroxyphosphonates. Reversibility of this reaction should still allow the formation of aminophosphonate unless in another competing reaction like phosphonate - phosphate rearrangement, only phosphate is formed irreversibly as a final product. Since fluorenone behaves differently (gives only hydroxyphosphonate) we studied this reaction also by kinetic methods, as the kinetics of hydroxyphosphonate formation and its rearrangement to phosphate can prove the above conclusion. The hydroxyphosphonate formation was observed as a dissappearance of fluorenone (λ =400 nm) in methanol with an excess of amine and phosphite (100 times) with respect to fluorenone. The obtained data are presented in Table 1.

Table 1

amine	$k_{obs}[sek^{-1}] \times 10^2$	pK
t-butylamine	1.672 ± 0.036	10.83
isopropylamine	1.457 ± 0.011	-
n-propylamine	1.212 ± 0.017	10.71
n-butylamine	1.064 ± 0.025	10.77
benzylamine	0.332 ± 0.0035	9.33
diisopropylamine	0.939 ± 0.0057	10.96
diethylamine	0.841 ± 0.0013	10.49
piperidine	0.778 ± 0.010	11.12
dibutylamine	0.676 ± 0.0010	-
morpholine	0.046 ± 0.003	8.33
triethylamine	0.295 ± 0.0012	11.01
tributylamine	0.057 ± 0.0014	-

Considering the primary, secondary and tertiary amines seperately one can see that primary aliphatic amines are the strongest catalyst, whereas secondary and especially tertiary amines are much weaker catalysts.

As shown also in Table 1 formation of hydroxyphosphonate is rather fast process, but it should allow the formation of aminophosphonates as long as it is reversible. This reversibility was observed monitoring fluorenone formation at λ= 400 nm (c_1) when the excess of amine (100 times) was added to the solution of hydroxyphosphonate (c_o). The complete reversibility should be manifested by formation of the corresponding amount of fluorenone (c_o). The ratio of (c_1/c_o)(see Table 2) is a measure of reversibility vs. rearangement.

Table 2

amine \ ester	dimethyl	diethyl	diisopropyl
triethylamine	0.13	0.15	0.19
n-butylamine	0.13	0.14	0.17
t-butylamine	0.12	0.16	0.15

Data in Table 2 show that the hydroxyphosphonate formation is reversed only in about 12-19% which means that it is 6-8 times slower than the phosphonate-phosphate rearangement, for all amines and all phosphonates used. The observed rate constants are of order $6.2*10^{-4}$ and $1.0*10^{-4}$ [sek^{-1}] for the rearrangement and reverse reaction respectively. Thus they are about two orders slower than the forward reaction. We also found that phosphates are formed irreversibly for all studied ketones and further heating of the reaction mixture does not lead to the ketone but to a decomposition products [6].

Thus the phosphonate-phosphate rearrangement path is like a 'sink', by which the ketone is used up. For aromatic and especialy diaromatic ketones and aliphatic amines this path becomes so fast that it is imposible to obtain a desired aminophosphonate in a good yield by heating a mixture of three reagents, as is usually done. In this case one must follow two step synthesis: preparation of imine, followed by addition of phosphite.

References

1. P.Kafarski & P.Mastalerz, *Beitr.Wirkst.Forsch.*, **H21**,1,(1984)
2. M.J.Kabachnik & T.Medved, *Izv.Akad.Nauk.SSSR,Ser.Chim.*, **1953**,1126
3. M.J.Kabachnik & T.Medved, *Izv.Akad.Nauk.SSSR,Ser.Chim.*, **1954**,1024
4. E.K.Fields, *J.Am.Chem.Soc.*,**74**,1528 (1952)
5. T.J.Medved & M.T.Kabachnik, *Doklady Akad.Nauk SSSR*, **84**,717,(1952)
6. R.Gancarz, to be published
7. K.A.Petrov,V.A.Tchauzov,T.S.Yerokhina, *Zh.Obsch.Khim.*, **45** ,737,(1975)
8. see for example A.F.Janzen,T.G.Smyrl, *Can.J.Chem.*,**50**,1205 (1972)
9. For example:
   Synthesis of *diethyl-9-hydroxyfluorene-9-yl-phosphate*. Equimolar amounts of fluorenone, diethyl phosphite and n-butylamine was allowed to stay in the room temperature for 20 minutes, then product was crystalised from 1:1 mixture of toluene and hexane; mp 146-147°C, yield 90%, 1H-NMR($CDCL_3$); 8.13-7.25(m,8H,ArH), 5.25(s,1H,OH), 4.13-3.63(m,4H,CH_2), 1.03(t,6H,CH_3).
   Synthesis of *diethyl (fluoren-9-yl)-phosphate*. Eequimolar amounts of fluorenone, diethyl phosphite and butylamine was let to stand for 24 hours. Product was crystalised from hexane; mp. 48-49°C, yield 80%, 1H-NMR ($CDCl_3$); 7.87-7.19(m,8H,ArH), 6.21(d,1H,CH,J_{HP}=9Hz), 4.25,4.13(d*q,4H,CH_2), 4.13(t,6H,CH_3).
   see also H.Timmler,J.Kurtz,*Chem.Ber.*,**104**,3740,(1971);R.Gancarz,J.S.Wieczorek *J.Prakt.Chemie* **322**,213(1980);R.Gancarz et al.,*J.Prakt.Chemie*,**329**(1),165(1987), R.Gancarz et al., *J.Prakt.Chemie*,**326**,349(1984); and references cited therein.
10. B.Springs & P.Haake, *J.Org.Chem.*,**42**,472 (1977)

The part of the work was presented on a poster session of XII International Conference on Phosphorus, Chemistry, July 1992, Touluse, FRANCE

(Received in UK 20 October 1992)