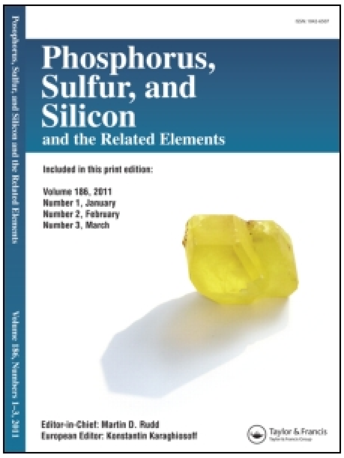

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

Alkylating Properties of Dialkyl Phosphites

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To cite this Article Gancarz, Roman(1994) 'Alkylating Properties of Dialkyl Phosphites', Phosphorus, Sulfur, and Silicon and the Related Elements, 92: 1, 193 — 199

To link to this Article: DOI: 10.1080/10426509408021472

URL: http://dx.doi.org/10.1080/10426509408021472

Phosphorus, Sulfur, and Silicon, 1994, Vol. 92, pp. 193-199
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ALKYLATING PROPERTIES OF DIALKYL PHOSPHITES

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(Received July 12, 1994; in final form August 4, 1994)

When the mixture of amines and dialkyl phosphites is used in the reaction, as for example in the Kabachnik Fields reaction, all possible N-alkylated products are formed. N-ethylation by diethyl phosphite is much slower than N-methylation by dimethyl phosphite and the latter can be easily formed via transesterification when the methanol is present in the mixture.

Key words: Amine alkylation, dialkyl phosphites, Kabachnik-Fields synthesis.

INTRODUCTION

Many organic and inorganic esters like sulfates or phosphates are used as alkylating agents of amines.[1-6] There are also reports on using other phosphorus oxy acids esters like phosphonates or phosphinates for alkylation of amines.[7-9] The general order of alkylating power among those oxy acid esters is: phosphate > phosphonate > phosphinate. Conversely aliphatic amines have been used for partial dealkylation of phosphoric and phosphonic esters[10-13] [Scheme I].

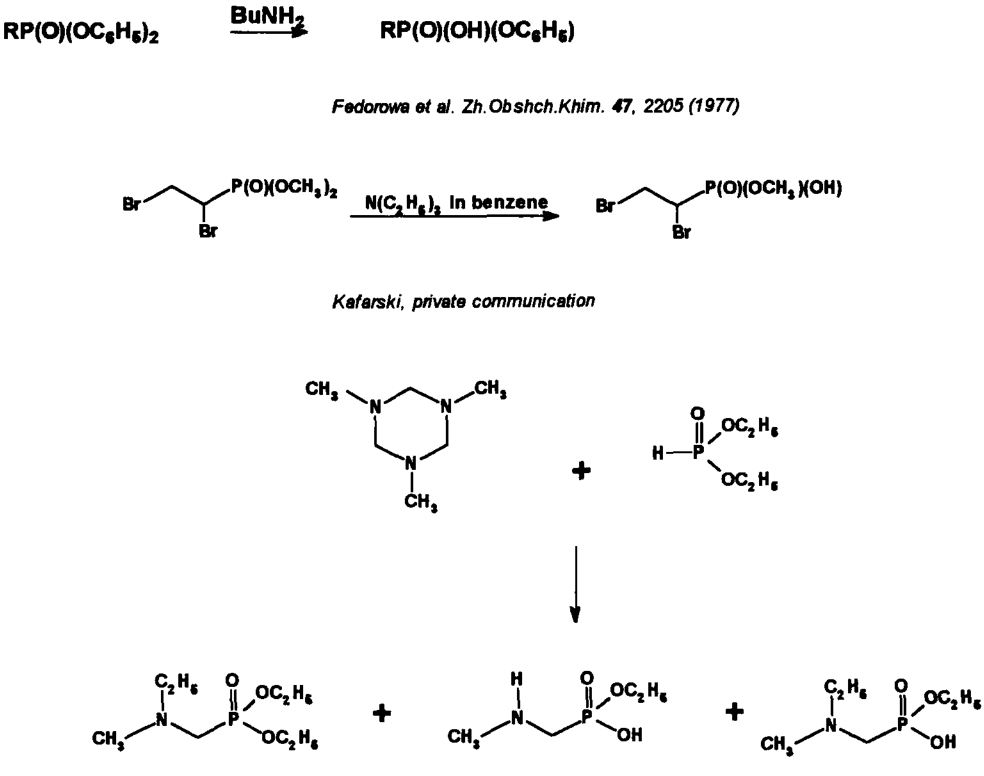
Dialkyl phosphites were reported as alkylating agents for nitrogen heterocyclic compounds. The reactions were carried out at temperatures above 150°C.[14] In some cases the formation on N-alkylated products were observed while phosphite was used as a reagent[15] [Scheme I].

Since the mixture of amine and dialkyl phosphite is frequently used in the reaction mixture, as for example, in the Kabachnik-Fields reaction, we decided to study if such alkylation processes are fast enough to compete with the main reaction.

In this paper we report that phosphites are quite good alkylating agents for amines and that N-alkylation of amines could be an alternative process to the main reaction when dialkyl phosphite is used in a mixture with amine.

RESULTS AND DISCUSSION

During the synthesis of aminophosphonates in a Kabachnik-Fields reaction especially with ketones of low reactivity like benzophenone, fluorenone or even acetophenone, the formation of N-alkylated amines as by-products were observed.[16] We have also found that during heating the amine and dialkyl phosphite at the same conditions all possible alkylated amines were formed. The results are presented in Table I. The data in the table show that aliphatic amines are alkylated



Fedorowa et al. Zh.Obshch.Khim. 47, 2205 (1977)

Kafarski, private communication

L. Maier, Phosphorus, Sulfur and Silicon; 62, 29 (1991)

SCHEME I

much easier than aromatic ones and that N-methylation undergoes much faster than N-ethylation.

The alcohol corresponding to the phosphite was used as a solvent in all experiments shown above. When a different alcohol is used then formation of a mixture of all possible alkylation products were found. A reaction of aniline or butylamine and diethyl phosphite in methanol (reflux 3 hours) can serve as an example. The reaction mixture contains the unsubstituted amine, N-methyl, N,N-dimethyl, N-ethyl, N-methyl-N-ethyl, N,N-diethyl derivatives in the ratio: 52:27:7:10:3:1 or 26:54:92:1:2:6 respectively. Such composition of the products indicates that amine promotes the transesterification process. Thus the following set of reaction takes place:

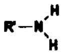
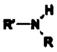
The transesterification process:

$$HP(O)(OC_2H_5)_2 + CH_3OH \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} HP(O)(OC_2H_5)(OCH_3) + C_2H_5OH$$

$$HP(O)(OC_2H_5)(OCH_3) + CH_3OH \underset{k_{-2}}{\overset{k_2}{\rightleftharpoons}} HP(O)(OCH_3)_2 + C_2H_5OH$$

TABLE I

Alkylation of amines (RNH_2) by dialkyl phosphites (methyl or ethyl)

Run No.	R	Dialkyl Phosphite	Reaction Time [hrs]	Solvent	Unreacted amine*	Alkylated Products*		
								
1	Bu	$HP(O)(OEt)_2$	1	EtOH	96	2	2	<1
2	Bu	$HP(O)(OMe)_2$	1	MeOH	22	58	20	<10
3	Bu	$HP(O)(OEt)_2$	7	EtOH	18	62	20	<10
4	Bu	$HP(O)(OMe)_2$	7	MeOH	4	41	54	<10
5	$PhCH_2$	$HP(O)(OEt)_2$	1	EtOH	73	27	0	0
6	$PhCH_2$	$HP(O)(OMe)_2$	1	MeOH	19	50	31	<10
7	Ph	$HP(O)(OEt)_2$	7	EtOH	90	10	0	0
8	Ph	$HP(O)(OMe)_2$	7	MeOH	25	34	41	<10

* given as a weight ratio

The alkylation by the dimethyl phosphite, methyl-ethyl phosphite or diethyl phosphite:

$$HP(O)(OCH_3)_2 + H_2NBu \xrightarrow{k_3} HP(O)(OCH_3)(OH) + CH_3NHBu$$

$$HP(O)(OCH_3)_2 + CH_3NHBu \xrightarrow{k_4} HP(O)(OCH_3)(OH) + (CH_3)_2NBu$$

$$HP(O)(OCH_3)_2 + (CH_3)_2NHBu \xrightarrow{k_5} HP(O)(OCH_3)(OH) + (CH_3)_3\overset{+}{N}Bu$$

$$HP(O)(OCH_3)(OC_2H_5) + H_2NBu \xrightarrow{k_3'} HP(O)(OC_2H_5)(OH) + CH_3NHBu$$

$$HP(O)(OCH_3)(OC_2H_5) + CH_3NHBu \xrightarrow{k_4'} HP(O)(OC_2H_5)(OH) + (CH_3)_2NBu$$

$$HP(O)(OCH_3)(OC_2H_5) + (CH_3)_2NHBu \xrightarrow{k_5'} HP(O)(OC_2H_5)(OH) + (CH_3)_3\overset{+}{N}Bu$$

Similar set of equations can be written for the N-ethylation.

This process was monitored by the NMR. The NMR spectra of the reaction products of the butylamine, diethyl phosphite and methanol in deuterated benzene are shown in Figure 1. Figure 2 shows the changes of the concentration of the reaction mixture components with time.

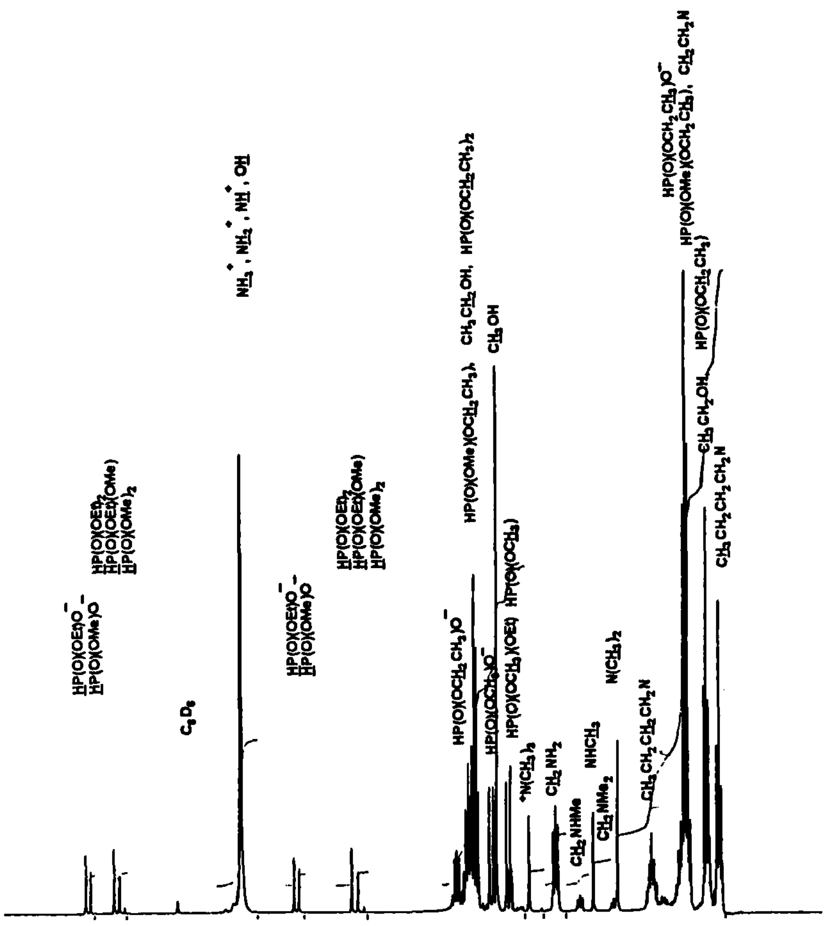


FIGURE 1 The NMR of the reaction mixture after 300 hrs at room temperature in C_6D_6.

Taking the ^{1}H-NMR spectra at several time intervals one can calculate the concentration of the products. Based on the reaction equations one can write a set of differential equation, then find a set of reaction rate constants that allows to fit the calculated compound concentration curves to the experimental ones.

In this way we have found that the transesterification rates in deuterated benzene at room temperature are $2.7 \cdot 10^{-2}$ and $4.0 \cdot 10^{-2}$ [min^{-1} mol^{-1}] for k_1 and k_2 respectively whereas the corresponding equilibria constants are 0.8 and 0.34. For the N-methylation the corresponding rates are $k_3 = 1.0 \cdot 10^{-4}$, $k'_3 = 5.0 \cdot 10^{-5}$ [min^{-1} mol^{-2}] for monomethylation, $k_4 = 1.65 \cdot 10^{-4}$, $k'_4 = 8.0 \cdot 10^{-5}$ [min^{-1} mol^{-2}] for N,N-dimethylation and $k_5 = 3 \cdot 10^{-4}$, $k'_5 = 1.5 \cdot 10^{-4}$ [min^{-1} mol^{-2}] for N,N,N trimethylation of *n*-butylamine. The N-ethylation is so slow in that conditions that only traces of N-ethylbutylamine are found in the reaction mixture. The estimated reaction rate of N-ethylation is of the order $1 \cdot 10^{-5}$ [min^{-1} mol^{-2}]. In the same conditions aminophosphonates are alkylated very slowly. In the experiments in which we tried to obtain the N-alkylated aminophosphonates, desired

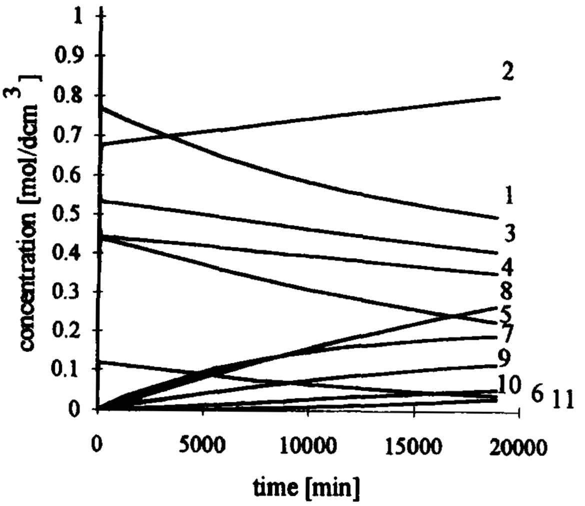


FIGURE 2 The change of the concentration of the reaction mixture components. 1-butylamine, 2-ethanol, 3-methanol, 4-diethyl phosphite, 5-methylethylphosphite, 6-dimethyl phosphite, 7-N-methylbutylamine, 8-monoethylphosphite, 9-monomethylphosphite, 10-N,N-dimethylbutylamine, 11-N,N,N-trimethylbutylammonium ion.

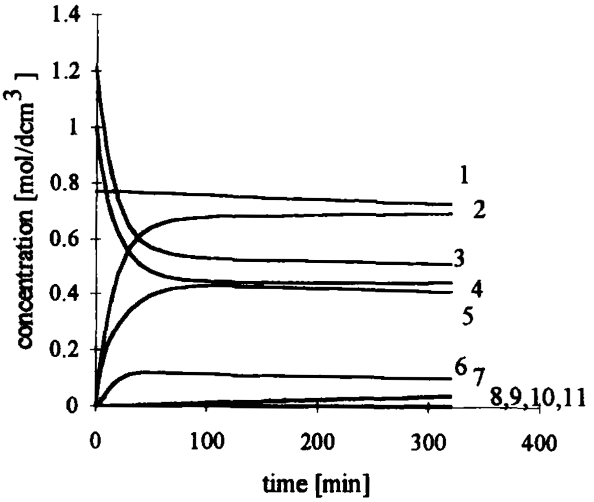


FIGURE 3 The change of the concentration of the reaction mixture components for the first 400 minutes. 1-butylamine, 2-ethanol, 3-methanol, 4-diethyl phosphite, 5-methylethylphosphite, 6-dimethyl phosphite, 7-N-methylbutylamine, 8-monoethylphosphite, 9-monomethylphosphite, 10-N,N-dimethylbutylamine, 11-N,N,N-trimethylbutylammonium ion.

products were formed in a very small yield even if the reaction mixture was refluxed in alcohol for a prolonged time.

EXPERIMENTAL

N-ethylation

A mixture of equimolar amounts of amine and dialkyl phosphite was refluxed in the appropriate alcohol for a time shown in the Table I. After that the mixture was diluted with 10% sodium carbonate solution and extracted with diethyl ether. The etheral solution was dried over sodium carbonate and analysed by GC and GC/MS spectra on GC-MS Hewlet Packard 5971 Series II instrument. The amount of trialkylated products was evaluated as a difference between the starting amine concentration and the total amount of amines in the etheral solution. The yield of amines in etheral solution was estimated with respect to the known amount of mesitylene added as an internal standard.

Kinetic Run

A mixture of butylamine, diethyl phosphite and methanol was kept in deuterated benzene in the NMR tube at 25°C and the ^{1}H NMR spectra were taken on WM 250 MHz Brucker instrument after certain periods of time. The concentration of a particular reaction mixture component was calculated from the spectra. The following compounds were identified in the spectra:

diethyl phosphite; ^{1}H-NMR (C_6D_6): 6.51 (d, 1H, $\underline{H}P$, J_{HP} = 691 Hz), 3.80, 3.76 (2xq, 4H, $C\underline{H}_2$, J_{HH} = 7.05, J_{HP} = 9.17 Hz), 0.95 (t, 6H, $C\underline{H}_3$, J_{HH} = 7.05)
dimethyl phosphite; ^{1}H-NMR (C_6D_6): 6.38 (d, 1H, $\underline{H}P$, J_{HP} = 697 Hz), 3.26 (d, 6H, $C\underline{H}_3$, J_{HP} = 11.91 Hz)
monoethyl phosphite; ^{1}H-NMR (C_6D_6): 7.06 (d, 1H, $\underline{H}P$, J_{HP} = 605 Hz), 3.90, 3.88 (2xq, 2H, $C\underline{H}_2$, J_{HH} = 7.38, J_{HP} = 8.11 Hz), 1.20 (t, 3H, $C\underline{H}_3$, J_{HH} = 7.38 Hz)
monomethyl phosphite; ^{1}H-NMR (C_6D_6): 6.95 (d, 1H, $\underline{H}P$, J_{HP} = 606 Hz), 3.48 (d, 3H, $C\underline{H}_3$, J_{HP} = 11.95 Hz)
methyl ethyl phosphite; ^{1}H-NMR (C_6D_6): 6.45 (d, 1H, $\underline{H}P$, J_{HP} = 694 Hz), 3.73, 3.71 (2xd, $C\underline{H}_2$, J_{HH} = 6.80 Hz, J_{HP} = 9.13 Hz), 3.28 (d, 3H, $C\underline{H}_3O$, J_{HP} = 11.93), 0.94 (t, 6H, CH_3, J_{HH} = 6.80 Hz)
butylamine; ^{1}H-NMR (C_6D_6): 2.75 (t, 2H, $C\underline{H}_2N$, J_{HH} = 7.50 Hz), 1.63 (m, $C\underline{H}_2CH_2N$), 1.26 (m, $C\underline{H}_2CH_2CH_2N$), 0.81 (t, $C\underline{H}_3$, J_{HH} = 7.33 Hz)
N-methylbutylamine; ^{1}H-NMR (C_6D_6): 2.47 (t, 2H, $C\underline{H}_2N$, J_{HH} = 7.93), 2.30 (s, 3H, $C\underline{H}_3$), 1.63 (m, 2H, $C\underline{H}_2CH_2N$), 1.26 (m, 2H, $C\underline{H}_2CH_2CH_2N$), 0.81 (t, 3H, $C\underline{H}_3$, J_{HH} = 7.33 Hz)
N, N-dimethylbutylamine, ^{1}H-NMR (C_6D_6): 2.05 (t, 2H, $C\underline{H}_2N$, J_{HH} = 7.79), 2.00 (s, 6H, $C\underline{H}_3$), 1.63 (m, 2H, $C\underline{H}_2CH_2N$), 1.26 (m, 2H, $C\underline{H}_2CH_2CH_2N$), 0.81 (t, 3H, $C\underline{H}_3$, J_{HH} = 7.33 Hz)
N,N,N-trimethylbutylamine ion, ^{1}H-NMR (C_6D_6): 3.14 (t, 2H, $C\underline{H}_2N$, J_{HH} = 7.80), 3.04 (s, 9H, $C\underline{H}_3$), 1.63 (m, 2H, $C\underline{H}_2CH_2N$), 1.26 (m, 2H, $C\underline{H}_2CH_2CH_2N$), 0.81 (t, 3H, $C\underline{H}_3$, J_{HH} = 7.33 Hz)
methanol, 3.42 (s, $C\underline{H}_3$)
ethanol, 3.68 (q, 2H, $C\underline{H}_2$, J_{HH} = 7.03), 1.18 (t, 3H, CH_3, J_{HH} = 7.03 Hz)

Calculation of the Reaction Rates

For each reaction the differential equation was formulated. For the whole process we have a set of the differential equations which can not be solved analytically. Thus the whole studied reaction time was divided to intervals equal 1 sek and the concentration of the species at the end of time interval t_2 was calculated by approximating the expression for the reaction rate $dc/dt = k \cdot c$ by $\Delta x/\Delta t = c_{t_2} - c_{t_1}/t_2 - t_1 = k \cdot c_{t_1}$. From the last equation the approximate concentration at the end of time interval is calculated, which in turn is used as the initial concentration in the next time interval. Thus the curves of the concentration change of every species can be simulated. Then a set of rate constants is found by iterative procedure until the best fit is formed. The quality of the fit is calculated as the sum of squared deviation of the calculated and experimental values.

ACKNOWLEDGEMENTS

This work was supported by a grant from Komitet Badań Naukowych.

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