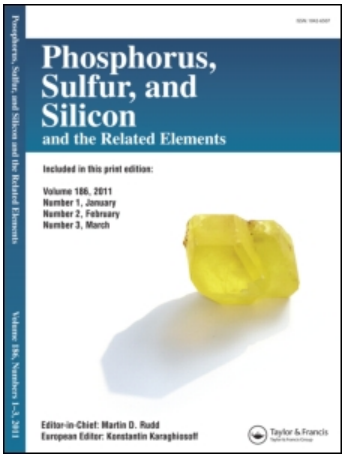


Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

INVESTIGATION OF THE STAUDINGER REACTION BETWEEN BICYCLIC PHOSPHITE AND DIAZO COMPOUNDS

Chengxin Pei[a]; Xuanlong Xu[a]
[a] Beijing Pharmaceutical Chemistry Institute, Beijing, P. R. China

To cite this Article Pei, Chengxin and Xu, Xuanlong(1993) 'INVESTIGATION OF THE STAUDINGER REACTION BETWEEN BICYCLIC PHOSPHITE AND DIAZO COMPOUNDS', Phosphorus, Sulfur, and Silicon and the Related Elements, 84: 1, 143 — 148
To link to this Article: DOI: 10.1080/10426509308034325
URL: http://dx.doi.org/10.1080/10426509308034325

Phosphorus, Sulfur, and Silicon, 1993, Vol. 84, pp. 143–148
Reprints available directly from the publisher
Photocopying permitted by license only

INVESTIGATION OF THE STAUDINGER REACTION BETWEEN BICYCLIC PHOSPHITE AND DIAZO COMPOUNDS

CHENGXIN PEI† and XUANLONG XU
Beijing Pharmaceutical Chemistry Institute, P.O. Box 1044-403, Beijing 102205, P. R. China

(Received June 30, 1993; in final form August 25, 1993)

Nine bicyclic phosphatazines were synthesized by the Staudinger reaction between bicyclic phosphite (1) and diazo compounds (2–5), the Elemental Analysis data, IR, ^{31}P NMR and Mass Spectral data of these compounds are reported. The reaction of diazoacetate with bicyclic phosphite was followed by ^{31}P NMR, the concentration-time curve was simulated by Optimal Approximation with a computer. It was found that this reaction consisted of two steps, the first step was second-order and the second was first-order. A possible mechanism is also proposed.

Key words: Staudinger reaction; bicyclic phosphite; phosphatazine; optimal approximation; NMR; IR.

INTRODUCTION

Kabachnik and his coworkers[1] have reported the synthesis of acyclic phosphatazines by the Staudinger reaction between diazo compounds and acyclic phosphite, but the reaction between diazo compounds and bicyclic phosphite has never been investigated. Since the skeleton structure of bicyclic phosphite is sterically defined, its Staudinger reaction may be somewhat different from that of the acyclic analogue.[2] Here we report the investigations of this reaction.

RESULTS AND DISCUSSION

(I) Staudinger Reaction Between Bicyclic Phosphite and Diazo Compound

When ethyl diazoacetate (2b) was treated with equal moles of bicyclic phosphite (1) at 45°C, the IR spectra showed that as the peak of diazo group at 2200 cm^{-1} diminished, a new one (at 1580 cm^{-1}) appeared. When the reactant was completely consumed (peak at 2200 cm^{-1} disappeared), the newly formed compound was isolated from the mixture and identified by IR, Mass Spectral data, ^{31}P NMR and Elemental Analysis to be bicyclic phosphatazine (6b). Later, nine more diazo compounds of four kinds (2–5) were treated similarly for the purpose of synthetic study and the following results were obtained (Table I). The reaction may be generally represented as shown in Scheme I.

From the synthetic results given in Table I, it was found that for most of these compounds, their Staudinger reaction with bicyclic phosphite was a suitable method

†Author to whom correspondence may be addressed.

TABLE I
Reaction between bicyclic phosphite and diazo compound

Compd. No.	Substituent R_1	Substituent R_2	T (℃)/t (hr.)	Solvents for recrys.	Yield (%)
2a	H	CO_2Me	45/7	benzene	27
2b	H	CO_2Et	45/16	benzene	39
2c	H	CO_2Pr-n	45/12	benzene	38
2d	H	CO_2Pr-i	45/12	benzene	62
2e	H	CO_2Bu-n	45/12	benzene	47
3f	H	COMe	45/24	benzene/octane	34
3g	H	COEt	45/50	benzene/octane	48
3h	H	COPr	45/60	benzene/octane	81
4i	CO_2Et	CO_2Et	45/166	benzene	37
5j	H	H	25/99	/	/

SCHEME I

for preparing the corresponding bicyclic phosphatazine, though the reaction conditions were much stricter. However, it is interesting to note diazomethane (5j) could react with acyclic phosphite easily to give acyclic phosphatazine.[1] When it was treated with bicyclic phosphite (1), the following IR spectra gave no peak in the corresponding band as the other diazo compounds did. After standing at room temperature for 99 hours, the reaction mixture was worked-up, and the reactant bicyclic phosphite (1) recovered completely. Did this result imply that only those diazo compounds with electon-attracting group connected with diazo group could react with bicyclic phosphite to give bicyclic phosphatazine?

Theoretically, the reaction is a nucleophilic addition of bicyclic phosphite to diazo bond in the diazo compounds. Since the nucleophilicity of bicyclic phosphite is very weak because of its skeleton structure, the activity of the diazo compound may be significant. The electron-attracting group at the α-carbon benefits the reaction. It is interesting to compare the reaction of diazo malonate (4i), with that of diazoacetate (2b). As discussed above, diazomalonate (4i) with two electron-attracting groups at the α-carbon, should be more reactive than diazoacetate (2b) for electronic reason. But, the synthesis study showed the opposite result, the former is more unreactive than the latter. So it seems that steric hindrance played an important role in the reaction.

TABLE II

Physical data of bicyclic phosphatazines

Compd. No.	Substituent R_1	Substituent R_2	^{31}P NMR (ppm)	IR(cm^{-1}) $\nu_{C=O}$, $\nu_{N=N}$	m/z	Elemental Analysis N%(calcd), P%(calcd)
6a	H	CO_2Me	15.0	1720, 1580	203(B), 262(M.$^+$)	10.90(10.70), 11.82(11.80)
6b	H	CO_2Et	15.7	1720, 1575	203(B), 274(M.$^+$)	10.39(10.10), 11.11(11.20)
6c	H	CO_2Pr-n	15.60	1730, 1580	203)B), 290(M.$^+$)	9.44(9.80), 10.75(10.70)
6d	H	CO_2Pr-i	16.0	1705, 1580	203(B), 290(M.$^+$)	9.60(9.80), 10.80(10.70)
6e	H	CO_2Bu-n	15.8	1720, 1580	203(B), 304(M.$^+$)	9.25(9.20), 9.90(10.20)
7f	H	COMe	17.1	1660, 1550	203(B), 246(M.$^+$)	11.50(11.40), 12.45(12.60)
7g	H	COEt	17.0	1655, 1550	203(B), 260(M.$^+$)	10.63(10.77), 12.08(11.92)
7h	H	COPr-n	17.1	1660, 1550	203(B), 274(M.$^+$)	10.20(10.22), 11.20(11.31)
8i	CO_2Et,	CO_2Et	15.6	1720, 1550	186(B), 348(M.$^+$)	8.10(8.05), 8.70(8.91)

(II) Kinetics of the Reaction Between Diazoacetate and Bicyclic Phosphite

The kinetics of Staudinger reactions concerning acyclic trivalent phosphorus compounds and organic azides (Scheme II) has been studied in detail.[3–6] It was reported that the reaction consisted of two steps: the first step followed second-order and the second step followed first-order.

$$R_3P + N_3R' \xrightarrow{\text{1st step}} R_3P{=}N{-}N{=}NR' \xrightarrow{\text{2nd step}} R_3P{=}NR' + N_2 \uparrow$$

SCHEME II

Less has been known about the kinetics of the reaction between phosphite and diazo compound (Scheme III). In order to gain kinetic information, the reaction of diazoacetate and bicyclic phosphite was chosen to be followed with ^{31}P NMR:

$$Et{-}C(CH_2O)_3P + N_2CHCOOR \rightarrow Et{-}C(CH_2O)_3P{=}N{-}N{=}CHCOOR$$

SCHEME III

Internal Standard ^{31}P NMR Quantitation Method was used to measure the concentration of products and reactants, the ratio of product concentration at different times to the initial concentration of reactant (α_x) were calculated, and α_x-t curves could be obtained (as in Figure 1). It was found (Figure 1) that the formation rates of the product phosphatazine were accelerated at the beginning, then the acceleration diminished gradually and slowed down.

On the basis of the experimental data, optimal approximation with computer is used to simulate the α_x-t curves. As a result of the simulation, the reaction, though it looks similar to the first step of the general Staudinger reaction, followed different kinetics from the latter. It did not follow second-order kinetics, but consisted of

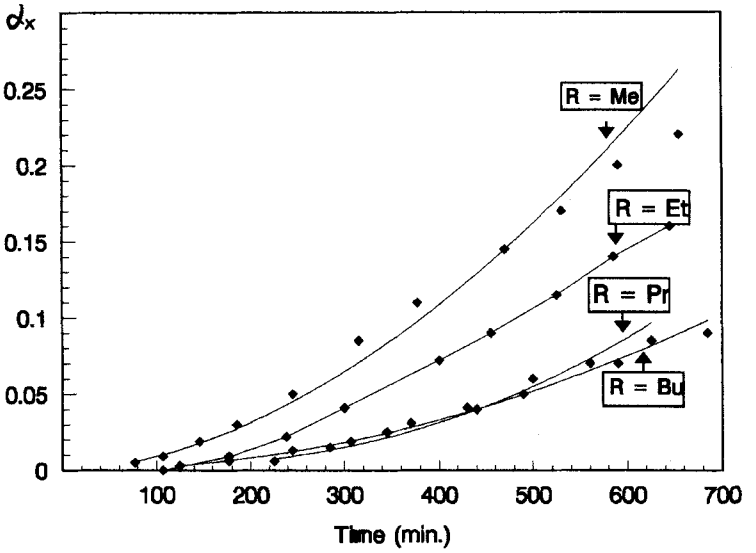


FIGURE 1 The reaction curves of diazo compound and bicyclic phosphite.

TABLE III

Rate constants calculated by optimal approximation

R	C_0 (mol/l)	k_{+1} ($mol^{-1}min^{-1}$)	k_{-1} (min^{-1})	k_2 (min^{-1})
Me	3.82	$2.7*10^{-4}$	$1.8*10^{-4}$	$2.8*10^{-3}$
Et	3.62	$2.4*10^{-4}$	$1.4*10^{-4}$	$2.8*10^{-3}$
Pr-n	3.45	$2.7*10^{-4}$	$1.5*10^{-4}$	$1.2*10^{-3}$
Bu-n	3.29	$3.5*10^{-4}$	$1.9*10^{-4}$	$6.3*10^{-4}$

two steps: the first step is an equilibrium process following second-order kinetics, the second step following first-order. The mechanism may be proposed as follows (Scheme IV):

$$Et{-}C(CH_2O)_3P + N_2CHCOOR \underset{k_{-1}}{\overset{k_{+1}}{\rightleftharpoons}} \text{Intermediate} \xrightarrow{k_2}$$

$$Et{-}C(CH_2O)_3P{=}N{-}N{=}CHCOOR$$

SCHEME IV

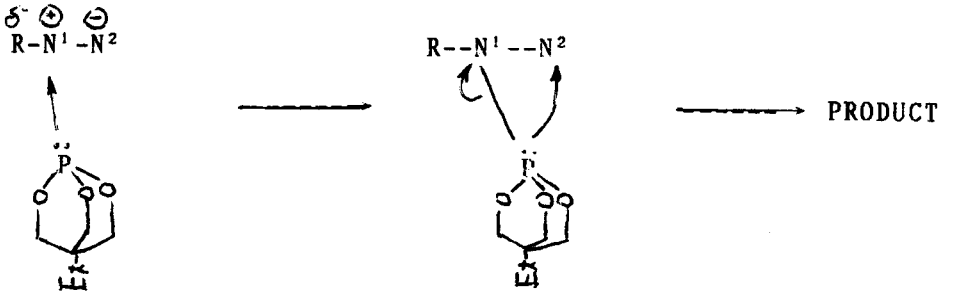
The rate constants k_{+1}, k_{-1} and k_2 estimated are given in Table III.

The identity of the intermediate is a very interesting problem. According to the

literature,[7] the diazo compounds have the following electric charge distribution:

$$\overset{\delta^-}{CH_2}\!-\!\overset{\oplus}{N^1}\!-\!\overset{\delta^-}{N^2}$$

Since the N^2 atom is negatively charged, the nucleophilic attack of the negatively charged P-atom in bicyclic phosphite on N^2 may be forbidden. Nevertheless, the N^1 atom is positively charged, the nucleophilic attack of the P-atom on it may be allowed and result in the formation of the intermediate, this intermediate could rearrange to the product as shown in Scheme V.



SCHEME V A possible mechanism.

This mechanism could also explain why the steric hinderance at the α-carbon atom had such an important influence on the reaction. Because the P atom in the bicyclic phosphite first attacked the N^1 atom, the substituent at α-carbon atom might make the attack difficult.

CONCLUSION

The Staudinger reaction between bicyclic phosphite and diazo compounds with an electron-attracting group at the α-carbon atom could give the corresponding bicyclic phosphatazines. The reaction is more difficult than that of acyclic phosphite. The kinetics of this reaction are somewhat different from that of the first step of the general Staudinger reaction, it consists of two steps: the first step is second-order and the second step is first-order.

EXPERIMENTAL

^{31}P NMR spectra were taken on Varian FT-800A Spectrometer with 85% aqueous solution of phosphoric acid as standard, Mass Spectral data were obtained on a JEOL JMS-300 Spectrometer. IR data were detected on BE 558B Spectrometer. Elemental Analysis were performed by the Analysis Laboratory, Beijing Pharmaceutical Chemistry Institute.

The kinetic measurement: Bicyclic phosphite and diazoacetate were mixed at equal mole ratio without any solvent, and then added to a 10 mm NMR tube. A capillary tube contained 85% H_3PO_4 aqueous solution was placed in, and the ^{31}P NMR spectra was measured under normal conditions.

Synthesis of 4-ethyl bicyclic phosphite (1)[7]: To a 250 ml three-necked flask with stirrer, thermometer and distillation equipment, 38.0 g (0.32 mol) newly distilled triethyl phosphite, 41.0 g (0.32 mol) 2,2-

bis(hydroxylmethyl) propanol and 0.5 ml triethylamine were added. The mixture was then heated to 100°C with stirring, kept the temperature until the methanol produced in the reaction was distilled off. The residue was distilled under reduced pressure. Yield 30.8 g (65%). b.p. 92–95°C, m.p. 55–6°C.

Synthesis of diazo compounds: Diazoacetates (2),[8] diazoketones (3),[9] diazomalonates (4)[10] and diazomethane (5j)[11] were synthesized by literature methods.

Synthesis of 1-acetatyl 4-ethyl bicyclic phosphatazine (6a–6e): To a 25 ml flask, 0.05 mol diazoacetate and 8.1 g (0.05 mol) 4-ethyl bicyclic phosphite (1) were placed, the flask was flushed with dry nitrogen. The mixture was kept at 45°C in an oil-bath until it solidified. The solid was crushed, washed with 7 ml cool benzene and then recrystallized in dry benzene. A colorless crystal could be obtained with the yield of 40–80%.

Synthesis of 1-alkylketonyl 4-ethyl bicyclic phosphatazine (7f–7h): 0.05 mol of bicyclic phosphite (1) and 0.05 mol of diazomethyl ketone were mixed at room temperature and the flask was then flushed with dry nitrogen. The mixture was kept at 45°C in an oil-bath until it solidified. The solid was crushed, washed with 7 ml cool benzene and then recrystallized in dry benzene-octane. A colorless crystal could be obtained with the yield of 30–80%.

Synthesis of 1-malonatyl 4-ethyl bicyclic phosphatazine (9i): 3.7 g (0.023 mol) of diethyl diazomalonate (4i) and 0.023 mol 4-ethyl bicyclic phosphite (1) were mixed at room temperature and the flask was then flushed with dry nitrogen. The mixture was kept at 45°C in an oil-bath until it solidified. The solid was crushed, washed with 7 ml cool benzene and then recrystallized in dry benzene. 3.0 g of colorless crystal was obtained, yield 37%.

Reaction of diazomethane (5j) *with 4-ethyl bicyclic phosphite* (1): A solution of 0.33 g (0.05 mol) diazomethane in 50 ml ether was mixed with 0.5 g (0.03 mol) of 4-ethyl bicyclic phosphite at room temperature and the moisture was removed with dry nitrogen. The mixture was kept at room temperature for 99 hr. After the evaporation of the solvent, the reactant (1) was recovered.

REFERENCES

1. M. I. Kabachnik, *et al.*, *Dokl. Akad. Nauk SSSR*, **106,** 473 (1956).
2. G. Lei, *et al.*, *Phosphorus, Sulfur, and Silicon*, **66,** 101 (1992).
3. H. Staudinger and E. Hauser, *Helv. Chim. Acta*, **4,** 861 (1921).
4. Y. G. Gololobov, *et al.*, *Tetrahedron*, **37,** 437 (1981).
5. H. Goldwhite, *et al.*, *J. Chem. Soc., Dalton*, 16 (1975).
6. J. E. Leffler and R. D. Temple, *J. Am. Chem. Soc.*, **89,** 5235 (1967).
7. W. S. Wadsworth, *et al.*, *J. Am. Chem. Soc.*, **84,** 610 (1962).
8. N. E. Searle, *Org. Syn., Coll.*, **4,** 424 (1963).
9. W. E. Bachmann and W. S. Struve, *Org. Reaction*, **1,** 38 (1942).
10. M. Regitz, *Chem. Ber.*, **99,** 3128 (1966).
11. F. Arndt, *Org. Syn., Coll.*, **2,** 165 (1943).