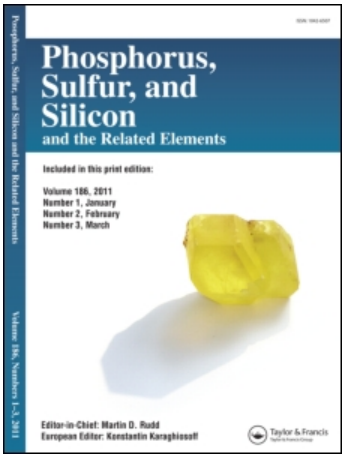

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PHOSPHORUS ANALOGUES OF AMINO ACIDS AND PEPTIDES XII[1] REACTION OF SODIUM DIETHYL PHOSPHITE WITH AROMATIC ALDAZINES AND HYDRAZONES

M. Topolski[a]; J. Rachonco[a]
[a] Department of Organic Chemistry, Technical University of Gdańsk, Gdańsk, Poland

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PHOSPHORUS ANALOGUES OF AMINO ACIDS AND PEPTIDES XII[1] REACTION OF SODIUM DIETHYL PHOSPHITE WITH AROMATIC ALDAZINES AND HYDRAZONES

M. TOPOLSKI and J. RACHON†

Department of Organic Chemistry, Technical University of Gdańsk, 80-952 Gdańsk 6, Poland

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The mechanism of the reaction of sodium diethyl phosphite with aromatic aldazines has been investigated. The initially formed monoaddition product (**4**) reacts with the excess of phosphorus reagent prior to the conceivable addition of diethyl phosphite to the C=N double bond. Cleavage of the N—N single bond is initiated by Single Electron Transfer from phosphite anion to the conjugated N=CH—Ph bond system. The scope of the reaction can be extended to other aromatic hydrazones. There is strong evidence to support the operation of a non-chain SET mechanism.

Key words: Single Electron Transfer; non-chain reaction; sodium diethyl phosphite; aromatic aldazines; benzoylhydrazones; N—N bond cleavage.

INTRODUCTION

In the early seventies an entirely new reduction process was discovered in our laboratory.[2] In search for a new route to aminophosphonic acids a reaction between benzaldazine and diethyl phosphite in the presence of its sodium salt was investigated. Surprisingly, instead of the expected mono- and diaddition reactions, a reduction of the nitrogen-nitrogen single bond took place. Two products, namely diethyl aminobenzylphosphonate (**1**) and its N-diethoxyphosphoryl derivative (**2**) were isolated.[3]

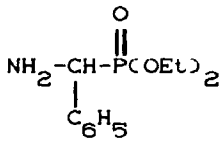
This unique reaction took place in the case of aromatic aldazines only; when aliphatic aldazines were employed the expected addition products could be isolated, both in our laboratory[4] and by Russian workers.[5]

The intriguing mechanism of the N—N single bond cleavage in aromatic aldazines has been recently scrutinized in our laboratory. The results of our study are presented herein.

RESULTS

Reaction of benzaldazine (**3**) with sodium diethyl phosphite (1.5 equivalent) and diethyl phosphite (2 equivalents) gave, after 2 days at room temperature in THF 67% of diethyl aminobenzylphosphonate (**1**) and 66% of its N-diethoxyphosphoryl derivative (**2**).

The reaction described above can be stopped after the monoaddition step. The monoaddition product (**4**) could be isolated in almost quantitative yield (92%)



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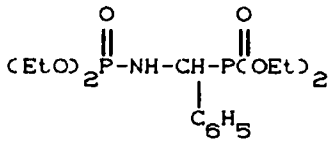

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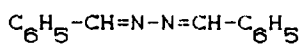

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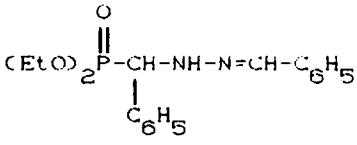

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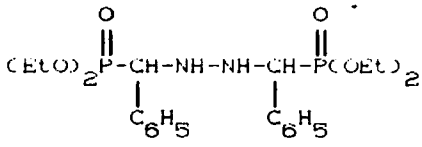


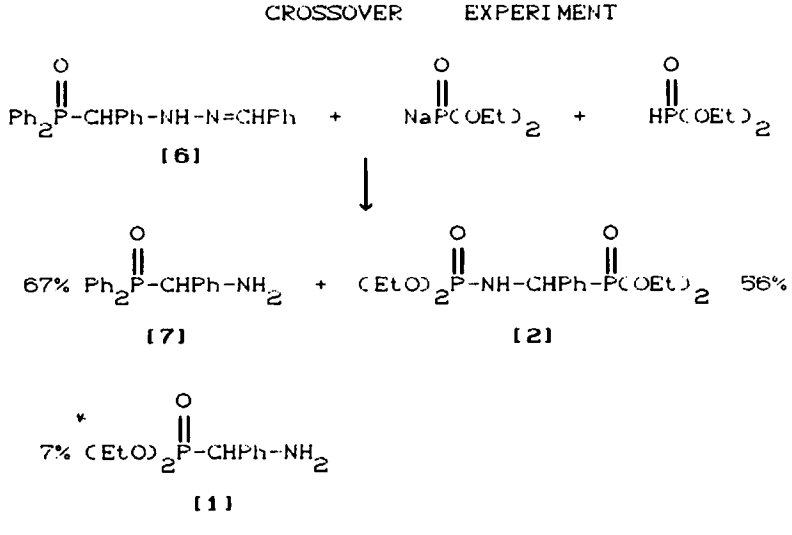
[5]

SCHEME 1

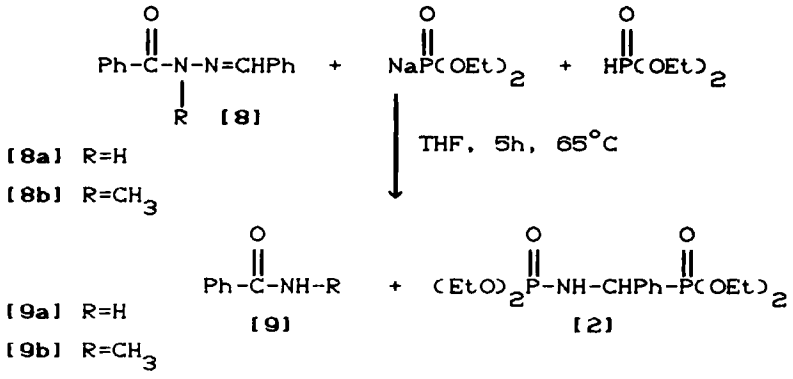
when benzaldazine was reacted, without solvent, with diethyl phosphite in the presence of catalytic amount of its sodium salt.

The monoaddition product (**4**) was also reduced by sodium diethyl phosphite (1.5 equivalent)/diethyl phosphite (1 equivalent) mixture when refluxed in THF (71% of diethyl aminobenzylphosphonate (**1**)).

When benzaldazine was reacted with diethyl-trimethylsilyl phosphite in the pres-



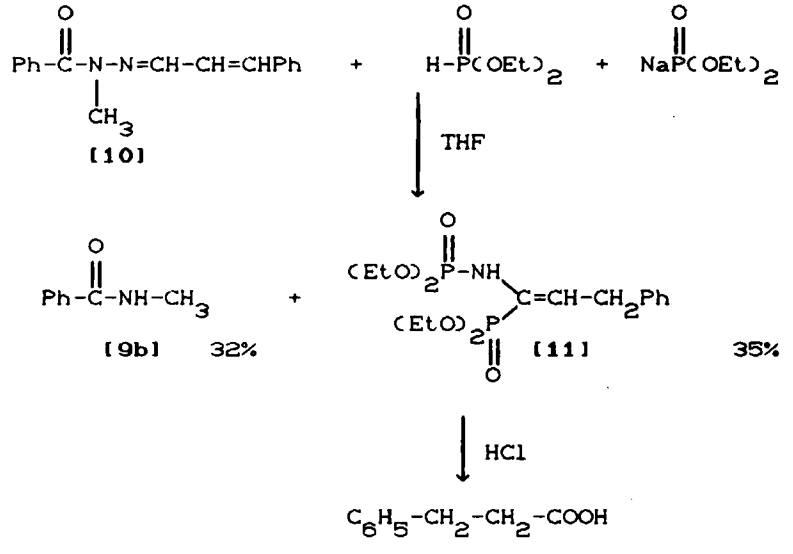
SCHEME 2



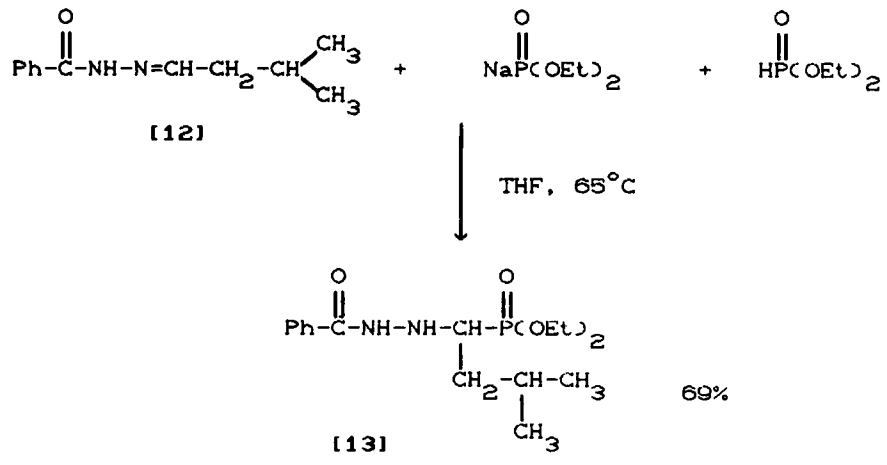
SCHEME 3

ence of titanium tetrachloride, the diaddition product (**5**) was obtained in 40% along with 18% of the monoaddition product (**4**). Compound (**5**) did not react at all with sodium diethyl phosphite-diethyl phosphite mixture (THF, 2 days, room temperature).

In the crossover experiment (Scheme 2), designed to distinguish between the possible ways of phosphorylation, we reacted sodium diethyl phosphite-diethyl phosphite mixture with compound (**6**) (obtained in the monoaddition reaction of diphenyl phosphine oxide to benzaldazine). Only one compound containing a P—N bond, namely diethyl N-diethoxyphosphorylaminobenzylphosphonate (**2**) was isolated (56%), along with aminobenzyldiphenylphosphine oxide (**7**) (67%) accompanied by small amount (7%) of diethyl aminobenzylphosphonate (**1**). The last product resulted from the reversibility of the monoaddition reaction under the basic condition employed.



SCHEME 4



SCHEME 5

In order to prove this, in a separate experiment the monoaddition product (**4**) was stirred with sodium hydride in THF for two days. Benzaldazine could be isolated, which must have resulted from the reversibility mentioned above.

In order to establish whether hydrazones of a general formula R—NH—N=CHPh undergo this type of reduction we attempted the reaction of benzaldehyde benzoylhydrazone (**8a**) with sodium diethyl phosphite-diethyl phosphite mixture. Only two products, i.e., benzamide (**9a**) and diethyl N-diethoxyphosphoryl aminobenzylphosphonate (**2**) were isolated in 76% and 70% of yield respectively.

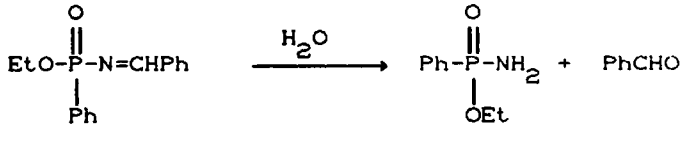
Similarly, benzaldehyde N-methylbenzoylhydrazone (**8b**) gave N-methylbenzamide (**9b**) (65%) and compound (**2**) (59%). This reaction was performed in the absence of the free diethyl phosphite.

Furthermore cinnamaldehyde benzoylhydrazone (**10**) gave reduction products (**9b**) and (**11**) as depicted in the scheme below.

On the contrary aliphatic hydrazone (**12**) gave only addition product (**13**) in 69% yield. No cleavage of N—N single bond was detected.

By condensing benzaldehyde with phosphoric acid diethyl ester amide, we obtained N-phosphorylated benzaldimine ((**17**), Scheme 8) which was reacted with diethyl phosphite under basic catalysis to yield 80% of the expected compound (**2**).

When the reaction between benzaldazine and P-phenyl ethyl phosphonite[6] was interrupted by the addition of water we were able to isolate benzaldehyde (**16**) and phenylphosphonic acid monoester amide (**15**) from the reaction mixture. Their presence must have resulted from the hydrolysis of the intermediate N-phosphorylated benzaldimine (**14**).



Scheme 6

Finally, the monoaddition product (**4**) was reduced by sodium diethyl phosphite-diethyl phosphite mixture under a variety of conditions. The results are present in the Table I.

Moreover complete retardation of the reaction was observed in the presence of equimolar amounts of tert.butyl amine and tert.butyl thiol. When the reaction was performed in an NMR tube and ^{31}P NMR was taken a CIDNP effect was observed. On the other hand no light influence on the reaction rate could be detected and no entrainment[7] was found.

DISCUSSION

The key problem we faced starting our research was to establish the actual sequence of steps in the reaction. The cleavage of the N—N single bond could conceivably take place as a first step (benzaldazine (**3**) would be directly reduced), as a second step (monoaddition product (**4**) would be reduced) or as a third step (diaddition product (**5**) would be reduced). Isolation of the monoaddition product (**4**) from the reaction of benzaldazine with diethyl phosphite-sodium diethyl phosphite mixture made it clear that the first possibility can be excluded.

Obviously the successful reduction of the monoaddition product does not distinguish between the two remaining possibilities. Therefore we synthesized the diaddition product (**5**) and subjected it to the reaction with sodium diethyl phosphite-diethyl phosphite mixture. No reaction occurred. Under the same conditions both the monoaddition product (**4**) and benzaldazine is reduced in good yield. Clearly the diaddition product may not be a key intermediate. The only possible conclusion is that the monoaddition product (**4**) is reduced.

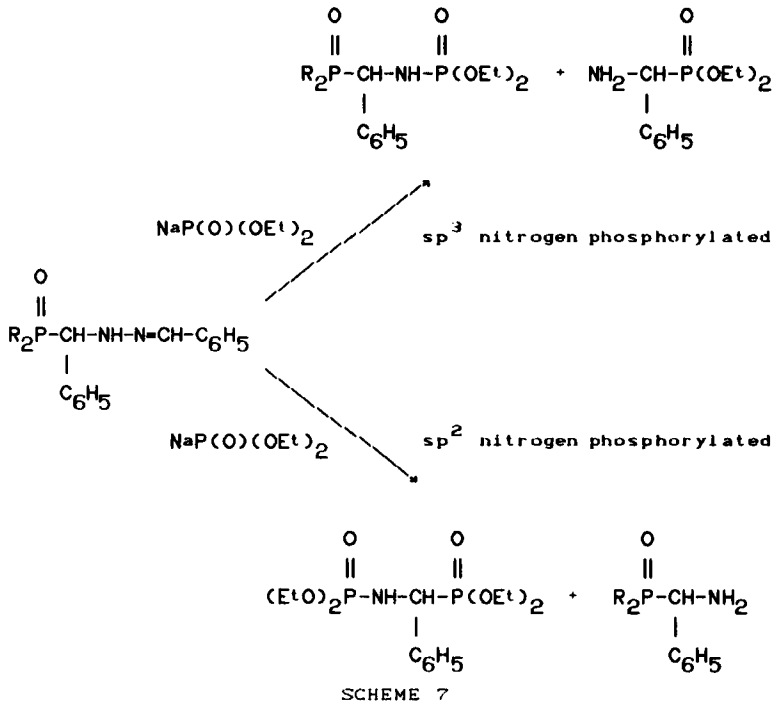
On the contrary to benzaldazine and to the diaddition product, compound (**4**) contains two different nitrogen atoms, and as a natural consequence two different reaction pathways (depicted below) can operate.

One can easily recognize that the two possible pathways are distinguishable when R is different from OEt, because, in such a case they lead to two different pairs of products. An unequivocal determination of their structure should explain which of the nitrogens is actually phosphorylated. In the crossover experiment we reduced compound (**6**) (scheme 2) and the two main products (**7**) and (**2**) were obtained strongly indicating that the imine type nitrogen is phosphorylated.

To check the scope and limitations of the reaction we decided to investigate whether this kind of reactivity can be observed in other hydrazone derivatives R—NH—N=CHR′. In such cases products of the reaction should be easily pre-

TABLE I

Conditions	Yield after 0.5 h	Yield after 2 h
Normal	31%	67%
Darkness	22–23%	53%
Inhibitor	—	55%
Darkness and inhibitor	—	50%



SCHEME 7

dictable: diethyl N-diethoxyphosphoryl aminoalkylphosphonate ought to be isolated in each case, along with the other compound of a general structure R—NH_2.

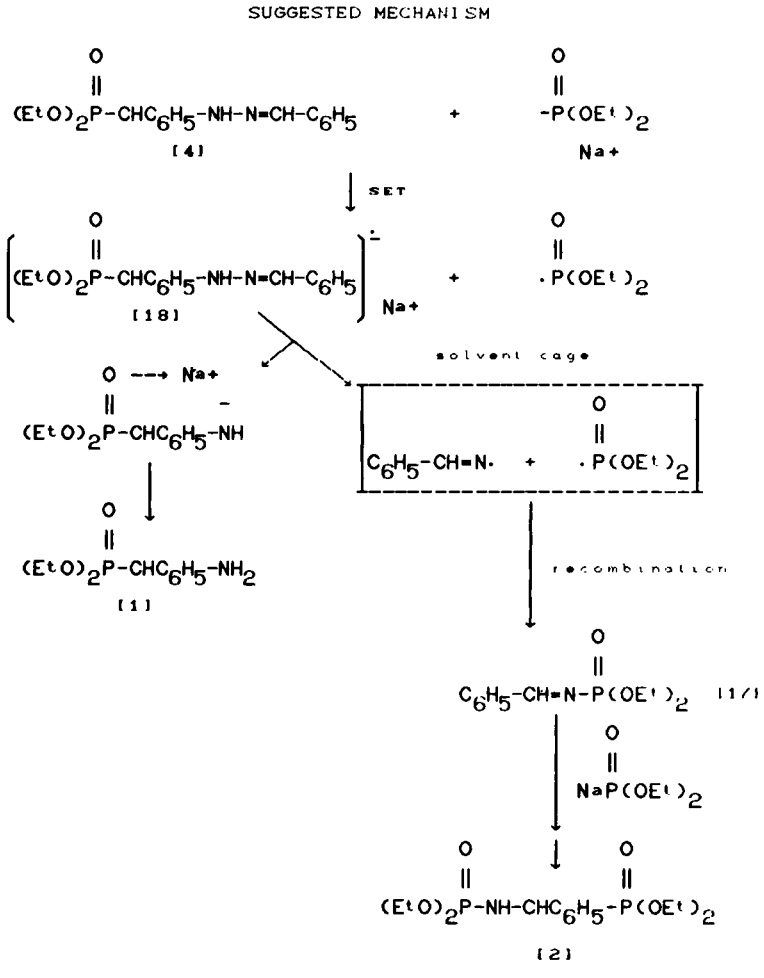
As a model compound for this study we chose benzaldehyde benzoylhydrazone (**8a**) (Scheme 3). According to our expectations it was smoothly reduced to give two expected products (**9a**) and (**2**) in good yields. Furthermore, essentially the same reaction was found when sodium diethyl phosphite was reacted with benzaldehyde N-methylbenzoylhydrazone (**8b**) (see Scheme 3). What is very important this reduction was conducted in the absence of the free diethyl phosphite. Thus sodium diethyl phosphite has a crucial meaning as a reducing agent. Moreover, beyond any doubts, a conceivable intermediacy of a hydride anion in the reaction mechanism may now be excluded.

All the compounds which were found to undergo the N—N bond cleavage reaction upon the action of sodium diethyl phosphite have invariably the same structural unit; a N=CHPh conjugated bond system is present in the molecule.[2,3,6,8] Additionally we discovered that the expected reduction process can also be observed when cinnamaldehyde benzoylhydrazone (**10**) is reacted with sodium diethyl phosphite (see Scheme 4).

On the contrary, and in full agreement with our predictions, isovaleraldehyde benzoylhydrazone (**12**) gave only addition product (**13**). No trace of reduction products could be detected.

At this stage we would like to suggest a new mechanism for the cleavage of N—N single bond. The following experimental facts were taken into account:

1) The monoaddition product (**4**) is reduced,
2) The imine type sp^2 nitrogen is phosphorylated,



SCHEME 8

3) A conjugated bonds system is indispensable (N=CHPh, N=CH—CH=CHPh).
4) Sodium diethyl phosphite is a reducing agent.

We suggest a single electron transfer from diethyl phosphite anion (a well known single electron donor)[9] to the conjugated N=CHPh bond system. The produced anion radical undergoes a heterolysis of the N—N single bond to give diethyl aminobenzylphosphonate and a radical pair composed of benzaldimine radical and diethoxyphosphoryl radical. In the next step the two radicals recombine to give the key intermediate N-phosphorylated benzaldimine (**17**), which reacts in the final step with diethyl phosphite to give the second reaction product (**2**).

To find evidence supporting the proposed mechanism we synthesized the key intermediate (**17**) and subjected it to the base catalysed reaction with diethyl phosphite. The anticipated addition reaction took place very easily, which means that N-phosphorylated imine can be the key intermediate. To prove its presence in the reaction mixture we reacted benzaldazine with sodium salt of P-phenyl ethyl phos-

phonite and interrupted the reaction by the addition of water. We were able to isolate two products, phenylphosphonic acid monoethyl ester amide **(15)** and benzaldehyde **(16)**, which must have resulted from the hydrolysis of the intermediate N-phosphorylated imine **(14)** (see Scheme 6).

In order to provide evidence for the SET mechanism we reduced the monoaddition product **(4)** under a variety of conditions (see Table I and below). We found that the reaction was slightly inhibited by catalytic amounts of di-tert.butyl nitroxide and when conducted in darkness. Apart from that, equimolar amounts of tert.butyl amine and tert-butyl thiol caused almost complete retardation of the reaction. All those results, together with the CIDNP effect unambiguously suggest a radical mechanism; if the ionic mechanism were operating we wouldn't have observed any influence of darkness, inhibitors (especially tert.butyl amine in equimolar amounts) shouldn't have stopped the reaction entirely and the CIDNP effect ought not to have been observed. At the same time we were unable to discover any measurable influence of light on the reaction rate. Moreover, no entrainment was observed. The two last effects, if positive, are considered to be good proofs for Single Electron Transfer chain processes.[10,11] The chain reactions are also much more retarded in darkness and by catalytic amounts of free radicals traps such as di-tert.butyl nitroxide.

To sum up we suggest a non chain Single Electron Transfer mechanism for the cleavage of N—N single bond in aromatic hydrazones upon the action of sodium diethyl phosphite. The non chain pathway for SET reaction has been well discerned by organic chemists during the last several years. Only a few examples can be found in the earlier literature.[12] Today however, this mechanism seems to be well recognised. Ashby and coworkers have thoroughly examined some well known organic reactions and provided evidence for the so called $S_{ET}2$ mechanism.[13,14] Katritzky[15,16] ascribed a non chain SET mechanism to the reaction of lithium 2-nitropropane with N-benzylpyridinium salts. Striking evidence for the radical and against ionic mechanism was included. According to Lewis[17] and Bordwell[18] the two mechanisms seem to be distinguishable and only rarely competitive. On the other hand several authors[19] were able to distinguish the non chain SET mechanism from the well known chain reaction.

So, there are several methods and experimental tests available to establish a non chain SET mechanism. Having analyzed both the literature material and our own results we postulate that this very mechanism operates in the case of N—N single bond reduction in aromatic hydrazones by sodium diethyl phosphite. Thus we suggest that the initially formed monoaddition product anion radical **(18)** undergoes a heterolysis of the N—N bond to give a radical pair which recombines within a solvent cage. As a consequence the cage recombination product **(17)** is preferentially obtained.

The tentatively postulated heterolysis of the N—N bond was supported in a separate experiment. We noticed that if the homolysis of the N—N bond had taken place an aminyl radical $(EtO)_2P(O)$-CHPh-NH· would have been produced.

So when the reaction was carried out in the absence of hydrogen donors (THF, diethyl phosphite) some typical radical processes (e.g., recombination) should have been observed. We reduced the monoaddition product **(4)** with sodium diethyl phosphite in the absence of the free diethyl phosphite and in benzene which is not

a hydrogen donor.[20] No products derived from the aminyl radical could be observed, which is in full agreement with the postulated heterolysis of the N—N bond.

CONCLUDING REMARKS

As a result of our study on the reaction between aromatic aldazines and sodium diethyl phosphite we were able to find that we are dealing with a SET initiated cleavage of the N—N bond followed by heterolysis of the intermediate anion radical. The produced radical pair gives a cage recombination product in a non chain process. The non chain SET mechanism is strongly indicated by only slight decrease of yield in darkness and when catalytic amounts of inhibitors are added. It was necessary to use equimolar amounts of inhibitors to stop the reaction almost entirely.

Additionally we examined some other hydrazone derivatives which should be reduced, according to our predictions, by sodium diethyl phosphite. In the preliminary experiments we were able to reduce benzaldehyde semicarbazone and benzaldehyde N-diethoxyphosphorylhydrazone.

Finally, we would like to stress, that the mechanism proposed herein explains the difference in reactivity between conjugated and aliphatic hydrazone systems towards sodium diethyl phosphite. The SET process is energetically favoured in the case of conjugated system possessing delocalized molecular orbitals.

EXPERIMENTAL

Diethyl phosphite was purchased from Fluka and distilled before use. Sodium hydride (Fluka) was washed from paraffin oil with hexane. Tetrahydrofuran was dried with sodium-potassium alloy. Melting points were uncorrected. Mass spectra (FD) were recorded on a Varian MAT 711 apparatus. IR spectra were taken on a Jena-Zeiss IR 10 apparatus. ^{1}H NMR spectra were recorded with a Varian apparatus at 60 or 300 MHz. ^{31}P NMR spectra were recorded with a Bruker (300 MHz) apparatus. MN-Kieselgel 60 was employed for column chromatography.

Reaction of benzaldazine (**3**) *with sodium diethyl-phosphite diethyl phosphite mixture.* Diethyl phosphite (4.2 mL, 35 mmoles) was added dropwise with stirring to the suspension of sodium hydride (360 mg, 15 mmoles) in THF (25 mL). When the evolution of hydrogen had ceased, benzaldazine (2.08 g, 10 mmoles) was added in one portion. The reaction mixture was stirred two days at room temperature and diluted with methylene chloride (25 mL). The organic phase was then extracted with 5% $KHSO_4$ solution (3 × 25 mL), and dried over $MgSO_4$. The solvent was removed and the residue separated using column chromatography (ethyl acetate isopropyl alcohol 2:1) to yield 2.53 g. (66%) of diethyl N-diethoxyphosphorylaminobenzylphosphonate (**2**).

M.p. 56–57°C.

$C_{15}H_{27}NO_6P$ (379.37)	calcd:	C 47.49	H 7.19%
	found:	C 47.58	H 7.54%

IR (KBr) υ = 3230 (NH), 1230 (P=O), 1040 (P—O—C) cm^{-1}. ^{1}H NMR, 60 MHz, (CCl_4) δ = 0.67–1.47 (*m*, 12H; CH_3); 3.27–4.73 (*m*, 9H: CH_2, CH); 5.53 (ddd, *J*=5 Hz, *J*=12 Hz, *J*=12 Hz, 1H; NH); 6.97–7.53 (m, 5H: C_6H_5).

The acidic aqueous solution was neutralized with $NaHCO_3$ and extracted with methylene chloride (3 × 25 mL). The methylene chloride extract was dried over $MgSO_4$ and the solvent was removed in vacuo. The residue was dissolved in diethyl ether and dry hydrogen chloride solution in diethyl ether was added. The precipitated product was filtered, washed with ether and recristallized from EtOH-ether to yield 1.86 g, (67%).

M.p. 159–160°C (EtOH-ether), Lit 161°C.[2]

IR (KBr) υ = 3300–2800 (NH_3^+), 1250 (P=O), 1040 (P—O—C) cm^{-1}. ^{1}H NMR, 60 MHz, (D_6-DMSO) δ = 0.90–1.40 (*m*, 6H; CH_3); 3.77–4.50 (*m*, 4H, CH_2); 5.07 (*d*, 1H, *J*=18 Hz, CH); 7.50–7.90 (*m*, 5H, C_6H_5); 9.47 (*s*, 3H; NH_3^+).

Diethyl N-benzylidenohydrazinobenzylphosphonate (**4**). Benzaldazine (10.4 g, 50 mmoles) was added to the solution of 2 mmoles of sodium diethyl phosphite (obtained by reacting sodium with diethyl phosphite) in diethyl phosphite (10.6 mL, 75 mmoles). The reaction flask was vigorously shaken, the temperature being kept below 50°C by occasional cooling. Hexane (100 mL) was then added and the reaction flask was put aside for crystallization. The product was filtered and recrystallized from CCl_4-hexane to yield 15.9 g (92%) of (**4**).

M.p. 110–111°C (CCl_4-hexane) Lit 113–115°C.[21]

IR (KBr) υ = 3220 (NH), 1585 (C=N), 1240 (P=O), 1030 (P—O—C) cm^{-1}.

^1H NMR, 60 MHz, ($CDCl_3$) δ = 0.75–1.38 (*m*, 6 H, CH_3); 3.25–4.38 (*m*, 4 H, CH_2); 4.90 (*d*, *J*=22 Hz, 1 H, CH); 6.17 (*s*, 1 H, NH); 7.00–7.58 (*m*, 10 H, C_6H_5); 7.60 (*s*, 1 H, CH=N).

Reaction of the monoaddition product (**4**) *with sodium diethyl phosphite-diethyl phosphite mixture.* Diethyl phosphite (4.2 mL, 35 mmoles) was added dropwise with stirring to the suspension of sodium hydride (360 mg, 15 mmoles) in THF (25 mL). When the evolution of hydrogen had ceased, the monoaddition product (3.46 g, 10 mmoles) was added in one portion. The reaction mixture was refluxed for two hours and diluted with methylene chloride (25 mL). The organic phase was then extracted with 5% $KHSO_4$ solution (3 × 25 mL). The acidic aqueous solution was neutralized with $NaHCO_3$ and extracted with methylene chloride (3 × 25 mL). The methylene chloride extract was dried over $MgSO_4$ and the solvent removed in vacuo. The residue was dissolved in diethyl ether and dry hydrogen chloride solution in diethyl ether was added. The precipitated product was filtered, washed with ether and recristallized from EtOH-ether to yield 1.95 g, (71%).

M.p. 159–161°C (EtOH-ether), Lit 161°C.[2]

Tetraethyl 1,1'(hydrazino)-N,N'-bis-benzylphosphonate (**5**)*-the diaddition product.* Titanium tetrachloride (1.21 mL, 11 mmoles) was added dropwise with stirring to the suspension of benzaldazine (2.08 g, 10 mmoles) in diethyl trimethylsilyl phosphite (11.4 mL, 50 mmoles). The reaction mixture was stirred for three hours at room temperature and methanol (50 mL) was added. After 24 hours the solvent was removed under reduced pressure and the products were separated using flash chromatography (isopropyl alcohol-hexane 1:3). Two products were isolated: the monoaddition product (**4**) (0.62 g, 18%, M.p. 110°C, Lit 113–115°C),[21] and the diaddition product (**5**) (1.93 g, 40%).

$C_{22}H_{34}N_2O_6P_2$ (482.52)	calcd:	C 54.76	H 7.12%
	found:	C 54.43	H 6.97%

MS (FD, 70 EV) 482. IR (KBr) υ = 3200 (NH), 1240 (P=O), 1040 (P—O—C) cm^{-1}.

^1H NMR, 60 MHz, (CCl_4) δ = 0.77–1.43 (*m*, 12 H, CH_3); 3.47–4.27 (*m*, 8 H, CH_2); 4.70 (*d*, *J*=20 Hz, 1 H, CH); 4.80 (*d*, *J*=20 Hz, 1 H, CH); 6.63 (*s*, 1 H, NH); 7.03–7.53 (*m*, 10 H, C_6H_5).

Attempted reaction between the diaddition product (**5**) *and sodium diethyl phosphite-diethyl phosphite mixture.* Diethyl phosphite (0.39 mL) was added to the suspension of sodium hydride (36 mg, 1.5 mmol) in THF (5 mL). When the evolution of hydrogen had ceased the diaddition product (**5**) (482 mg, 1 mmol) was added in THF (2 mL). The reaction mixture was stirred for 2 days at room temperature. No reduction products could be detected after that time by TLC. The starting material (**5**) was isolated using Flash Chromatography in 92% of yield.

(N-benzylidenohydrazino-)benzyldiphenylphosphine oxide (**6**). Diphenylphosphine oxide[22] (2.02 g, 10 mmoles) was added to the solution of benzaldazine (2.08 g, 10 mmoles) in ether (25 mL). The reaction flask was kept overnight in a refrigerator and the solid product was filtered, washed with ether and recrystallized from THF-hexane to yield 2.6 g, (63%) of (**6**).

M.p. 136–138°C (THF-hexane).

$C_{26}H_{23}N_2OP$ (M = 410.48)	calcd:	C 76.07	H 5.66%
	found:	C 75.45	H 5.86%

IR (KBr) υ = 3200 (NH), 1180 (P=O) cm^{-1}.

^1H NMR, 60 MHz, ($CDCl_3$) δ = 5.62 (*d*, *J*=10 Hz, 1H, CH); 6.80–7.63 (*m*, 21 H, NH, C_6H_5); 7.73 (*s*, 1 H, CH=N).

Reaction of (N-benzylidenohydrazino-)benzyldiphenylphosphine oxide (**6**) *with sodium diethyl phosphite diethyl phosphite mixture. The crossover experiment.* Diethyl phosphite (1.6 mL, 12.5 mmoles) was added to the suspension of sodium hydride (180 mg 7.5 mmoles) in THF (25 mL). When the evolution of hydrogen had ceased compound (**6**) (2.05 g 5 mmoles) was added in THF (15 mL). The reaction mixture was stirred for two days at room temperature. The solvent was then removed under reduced pressure and the residue was separated using column chromatography (hexane-isopropyl alcohol 20:1).

The following compounds were obtained:

Diethyl N-diethoxyphosphorylaminobenzylphosphonate (**2**) 1.06 g. (56%) M.p. 56–57°C. Spectral data were identical with those of an authentic sample.

α-aminobenzyldiphenylphosphine oxide (**7**)

1.05 g, (67%), M.p. 115–117°C,

$C_{19}H_{18}NOP$ (307.31)	calcd:	C 74.25	H 5.90%
	found:	C 74.23	H 5.81%

IR (KBr) υ = 3390 (NH_2), 1180 (P=O) cm^{-1}.

^1H NMR, 60 MHz, ($CDCl_3$) δ = 2.37 (*s*, 2 H, NH_2); 4.67 (*d*, *J*=8 Hz, 1H, CH); 7.00–8.07 (*m*, 15 H, C_6H_5).

Diethyl aminobenzylphosphonate (**1**) (identified as its HCl salt).

90 mg. (7%), M.p. 160–161°C Lit 161°C.[2]

IR (KBr) υ = 3300–2800 (NH_3^+), 1250 (P=O), 1040 (P—O—C) cm^{-1}.

^1H NMR, 60 MHz, (D_6-DMSO) δ = 0.90–1.40 (*m*, 6H, CH_3); 3.77–4.50 (*m*, 4 H, CH_2); 5.07 (*d*, 1 H, *J*=18 Hz, CH); 7.50–7.90 (*m*, 5H, C_6H_5); 9.47 (*s*, 3 H, NH_3^+).

Reaction of (N-benzylidenohydrazino-)benzyldiphenylphosphine oxide (**6**) *with sodium hydride in THF. Reversibility of the monoaddition reaction.* Compound (**6**) (1.32 g, 3.2 mmoles) was added to the suspension of sodium hydride (120 mg, 5 mmoles) in THF (25 mL), and the reaction mixture was stirred for two days at room temperature. 30 mg of benzaldazine (4.5%) was isolated from the reaction mixture using Column chromatography (hexane-methylene chloride)

M.p. 91–92°C Lit 93°C.[23]

Preparation of N-methylbenzoylhydrazones of benzaldehyde (**8b**) *and cinnamaldehyde* (**10**). Benzoylhydrazone of benzaldehyde[24] or cinnamaldehyde[24] (10 mmoles) was added dropwise with stirring to the slurry of sodium hydride (240 mg, 10 mmol) in THF (25 mL). When the evolution of hydrogen had ceased methyl iodide (0.62 mL, 10 mmol) was added and the mixture was stirred overnight at room temperature. The reaction mixture was diluted with CH_2Cl_2 and washed with water. The organic phase was then dried with $MgSO_4$ and evaporated to dryness. The residue was purified using "Flash Chromatography" (ethyl acetate) to give respectively:

Benzaldehyde N-methylbenzoylhydrazone (**8b**) 1.47 g (62%)

M.p. 81–82°C Lit M.p. 82°C.[25] IR (KBr) υ = 1680 (C=O) cm^{-1}.

^1H NMR, 60 MHz, ($CDCl_3$) δ = 3.50 (*s*, 3 H, CH_3); 7.13–7.77 (*m*, 11 H, CH=N, C_6H_5).

Cinnamaldehyde N-methylbenzoylhydrazone (**10**) 2.16 g, (82%).

M.p. 74–76°C; MS (FD, 70 EV) 264 for $C_{17}H_{16}N_2O$. IR (KBr) υ = 1670 cm^{-1} (C=O).

^1H NMR, 60 MHz, (CCl_4) δ = 3.30 (*s*, 3H, CH_3); 6.55, 6.66 (ds, 2 H, CH=CH); 7.00–7.65 (*m*, 11 H, N=CH, C_6H_5).

Reaction of benzoylhydrazones (**8a**, *or* **10**) *with sodium diethyl phosphite diethyl phosphite mixture.* Diethyl phosphite (1.6 mL, 12.5 mmol) was added dropwise with stirring to the slurry of sodium hydride (180 mg, 7.5 mmoles) in THF (25 mL). To the obtained solution the benzoylhydrazone (**8a**, **10**, respectively), (5 mmoles) was added and the whole mixture was refluxed for 5 hours, washed with brine, dried and evaporated to dryness. The oily residue was separated using column chromatography (ethyl acetate- isopropyl alcohol).

The following compounds were obtained: in the case of benzaldehyde benzoylhydrazone (**8a**): benzamide (**9a**) 0.46 g, (76%). M.p. 126°C (water) Lit M.p. 125°C.[26]

IR (KBr) υ = 3360, 3170 (NH_2), 1630 (amide I), 1600 (amide II), 1390 (amide III).

^1H NMR, 60 MHz, (D_6-DMSO) δ = 6.93 (*s*, 2 H, NH_2); 7.20–8.00 (*m*, 5 H, C_6H_5).

Diethyl N-diethoxyphosphorylaminobenzylphosphonate (**2**) 1.33 g, 70%. M.p. 58°C. spectral data were identical with those of an authentic sample.

in the case of cinnamaldehyde benzoylhydrazone (**10**)

N-methylbenzamide (**9b**). 220 mg, (32%) M.p. 76–77°C Lit 78°C.[27] IR (KBr) υ = 3350 (NH), 1650 (amide I), 1580 (amide II) cm^{-1}.

^1H NMR, 60 MHz, ($CDCl_3$) δ = 2.87, 2.93 (two singlets, 3 H, CH_3); 6.73 (*s*, 1 H, NH); 7.13–7.80 (*m*, 5 H, C_6H_5).

Diethyl 1-(N-diethoxyphosphorylamino)-3-phenyl-1-propenylphosphonate (**11**); 710 mg, (35%). MS (FD, 70 EV) 405 for $C_{17}H_{28}NP_2O_6$. IR (KBr) υ = 3190 (NH), 1250 (P=O), 1040 (P—O—C) cm^{-1}.

^{31}P NMR ($CDCl_3$) δ = 3.66 (*d*, *J*=15 Hz, P—N), 14.99 (*d*, *J*=15 Hz, P—C).

^1H NMR, 60 MHz, (CCl_4), δ = 0.90–1.35 (*m*, 12 H, CH_3); 1.57 (dd, *J*=7 Hz, *J*=4 Hz, 2 H, CH_2); 3.70–4.20 (*m*, 8 H, O—CH_2); 5.57 (dd, *J*=7 Hz, *J*=7 Hz, 1 H, NH); 6.10 (*m*, 1 H, CH=); 7.10 (*s*, 5 H, C_6H_5).

Compound (**11**) was hydrolyzed with 2 N hydrochloric acid (100°C, 6 hrs.) to give β-phenylpropionic acid in 66% yield. M.p. 47–48°C Lit 48°C.[28] IR (KBr) υ = 1730 (C=O) cm^{-1}.

^{1}H NMR, 60 MHz, (CCl_4), δ = 2.30–3.00 (*m*, 4 H, CH_2-CH_2); 7.10 (*s*, 5 H, C_6H_5); 10.80 (*s*, 1 H, COOH).

Reaction of N-methylbenzoylhydrazone (**8b**) *with sodium diethyl phosphite.* Diethyl phosphite (0.95 mL, 7.5 mmol) of diethyl phosphite was added dropwise with stirring to the slurry of sodium hydride (180 mg, 7.5 mmoles) in THF (25 mL). To the obtained solution N-methylbenzoylhydrazone (**8b**) (1.19 g, 5 mmoles) was added and the whole mixture was refluxed for 5 hours, washed with brine, dried and evaporated to dryness. The oily residue was separated using column chromatography (ethyl acetate-isopropyl alcohol).

The following compounds were obtained: N-methylbenzamide (**9b**); 220 mg (65%). M.p. 76–77°C Lit 78°C.[27] IR (KBr) ν = 3350 (NH), 1650 (amide I), 1580 (amide II) cm^{-1}.

^{1}H NMR, 60 MHz, ($CDCl_3$) δ = 2.87, 2.93 (two singlets, 3 H, CH_3); 6.73 (*s*, 1 H, NH); 7.13–7.80 (*m*, 5 H, C_6H_5).

Diethyl N-diethoxyphosphorylaminobenzylphosphonate (**2**) 560 mg, (59%). M.p. 58°C. spectral data were identical with those of an authentic sample.

Reaction of isovaleraldehyde benzoylhydrazone (**12**) *with sodium diethyl phosphite.* Diethyl phosphite (1.6 mL, 12.5 mmol) was added dropwise with stirring to the suspension of sodium hydride (180 mg, 7.5 mmol) in THF (25 mL). Isovaleraldehyde benzoylhydrazone (**12**)[29] (1.02 g, 5 mmol) was added to the obtained solution and the whole mixture was refluxed for 5 hours. After work-up only addition product, namely diethyl 1-(N_β-benzoyl)-hydrazine-3-methylbutylphosphonate (**13**) was isolated using column chromatography (hexane-ethyl acetate) 0.83 g, (69%).

$C_{16}H_{27}N_2O_4P$ (342.42)	calcd: C 56.12	H 7.96%
	found: C 55.71	H 8.05%

MS (FD, 70 EV): 342.

IR (KBr) ν = 3280 (NH), 1660 (C=O), 1240 (P=O), 1040 (P—O—C), cm^{-1}.

^{1}H NMR, 300 MHz, ($CDCl_3$) δ = 0.933 (*d*, *J*=2, 8 Hz, 3 H, $\underline{CH_3}$—CH); 0.956 (*d*, *J*=2, 8 Hz, 3 H, $\underline{CH_3}$—CH); 1.342 (dt, *J*=3 Hz, *J*=13, 5 Hz, 6 H, O—CH_2—$\underline{CH_3}$); 1.670 (tq, *J*=2, 8 Hz, *J*=6, OHz, 1 H, $\underline{CH}$—CH_3); 1.840–2.020 (*m*, 4 H, NH, CH_2); 3.358 (dt, *J*=12 Hz, *J*=4, 5 Hz, 1 H, CH—P); 4.080–4.210 (*m*, 4 H, O—CH_2); 7.190–7.430 (*m*, 5 H, C_6H_5).

Hydrolysis with 6 N hydrochloric acid (100°C, 6 hrs.) gave 1-hydrazine-3-methylbuthylphosphonic acid: M.p. 175–176°C Lit 175–177°C.[4] IR (KBr) ν = 3300–2600 (NH_3^+, NH, OH), 1150.1130 (PO_2—), 1010 (P—OH) cm^{-1}.

^{1}H NMR, 60 MHz, (TFA) δ = 0.90 (*d*, *J*=6 Hz, 6 H, CH_3); 1.15–1.90 (*m*, 3 H, CH_2, $\underline{CH}$—CH_3); 3.37 (dt, *J*=9 Hz, *J*=9 Hz, 1 H, CH—P).

Preparation of N-diethoxyphosphorylbenzaldimine (**17**). Phosphoric acid diethyl ester amide[30] (10.44 g, 68 mmoles), benzaldehyde (7.06 mL, 70 mmoles) and triethylamine (33.4 mL, 240 mmoles) was dissolved in methylene chloride (200 mL). The reaction mixture was then cooled to −70°C and titanium tetrachloride (4.4 mL, 40 mmoles) was added dropwise with stirring. The mixture was allowed to reach room temperature, filtered through Celite, evaporated to dryness and the residue extracted with ether. Evaporation of ether yielded N-diethoxyphosphorylbenzaldimine (**17**) (11.45 g, 70%). MS (FD, 70 EV) 241 for $C_{11}H_{15}NO_3P$

IR (film) ν = 1610 (C=N), 1250 (P=O), 1040 (P—O—C) cm^{-1}.

^{1}H NMR, 60 MHz, (CCl_4) δ = 3.27 (*t*, *J*=7 Hz, 6 H, CH_3); 4.10 (dq, *J*=7 Hz, *J*=10 Hz, 4 H, Ch_2); 7.23–8.00 (*m*, 5 H, C_6H_5); 8.93 (*d*, *J*=32 Hz, 1 H, CH=N).

Reaction of diethyl phosphite with N-phosphorylated benzaldimine (**17**). Diethyl phosphite (0.65 mL, 5 mmoles) was added to the suspension of sodium hydride (120 mg, 5 mmoles) in THF 20 mL. When the evolution of hydrogen had ceased, N-phosphorylated benzaldimine (**17**) (1.20 g, 5 mmoles) was added in THF (5 mL). The reaction mixture was stirred for an hour, diluted with methylene chloride (50 mL) and washed with water (50 mL). The organic phase was separated, dried over $MgSO_4$ and the solvents evaporated in vacuo. The residue was then purified using column chromatography (isopropyl alcohol) to yield 1.52 g. (80%) of diethyl N-diethoxyphosphorylaminobenzylphosphonate (**2**) M.p. 58°C. Spectral data were identical with those of an authentic sample.

Reaction of benzaldazine with P-phenyl ethyl phosphonite sodium salt-interruption by the addition of water. P-phenyl ethyl phosphonite[31] (3.4 g, 20 mmoles) was added to the slurry of sodium hydride (180 mg, 7.5 mmoles) in THF (50 mL). When the vigorous evolution of hydrogen was over, benzaldazine (1.04 g, 5 mmoles) was added and the reaction mixture was refluxed for half an hour. The reaction flask was then cooled and water (2 mL) containing acetic acid (0.45 mL, 7.5 mmoles) was added. The

reaction mixture was dried over $MgSO_4$, evaporated to dryness and separated using column chromatography (isopropyl alcohol-hexane) to yield: Benzaldehyde (**16**) 35 mg (6.5%). IR (film) υ = 1710 (C=O) cm^{-1}.

^1H NMR, 60 MHz, (CCl_4) δ = 7.27–8.07 (*m*, 5 H, C_6H_5); 10.00 (*s*, 1 H, CH).

dinitrophenylhydrazone M.p. 235–236°C Lit 235°C.[32]

Phenylphosphonic acid monoethyl ester amide (**15**), 32 mg, (3.5%); M.p. 127°C Lit. 127°C.[33] MS (FD, 70 EV) 185 for $C_8H_{12}NO_2P$. IR (KBr) υ = 3350, 3260 (NH_2), 1220 (P=O), 1050 (P—O—C) cm^{-1}.

^1H NMR, 60 MHz, ($CDCl_3$) δ = 1.13 (*t*, *J*=7 Hz, 3 H, CH_3); 3.80 (dq, *J*=7 Hz, *J*=8 Hz, 2 H, CH_2); 4.60 (*d*, *J*=7 Hz, 2 H, NH_2); 7.07–7.83 (*m*, 5 H, C_6H_5).

Reduction of the monoaddition product (**4**) *under a variety of conditions. Searching for evidence supporting the non chain SET mechanism.* . Diethyl phosphite (1.6 mL, 12.5 mmoles) was added to the suspension of sodium hydride (180 mg, 7.5 mmoles) in THF (25 mL). The monoaddition product (**4**) (1.73 g, 5 mmoles) was then added and the whole mixture was refluxed for the time indicated in Table I unless otherwise stated. The reaction mixture was diluted with methylene chloride (50 mL) and washed with water (50 mL). The organic layer was then dried over $MgSO_4$, and the solvents evaporated under reduced pressure. The residue was dissolved in ether and the product, diethyl aminobenzylphosphonate (**1**) was precipitated upon the action of hydrogen chloride solution in ether. Yields and conditions for the reactions carried out under normal conditions, in darkness and in the presence of catalytic amounts of inhibitor (di-tert.butyl nitroxide,[34] 30 molar percent) are summarized in Table I. Moreover we found that light (500W bulb) had no influence on the reaction rate; after 30 min. 420 mg (30%) of diethyl aminobenzylphosphonate hydrochloride was isolated.

Additionally, when the reaction described above was conducted in the presence of tert.butyl thiol (0.54 mL, 5 mmoles) only 140 mg (10% of product (**1**) could be isolated and when tert.butyl amine (0.52 mL, 5 mmoles) was employed as an inhibitor we did not isolate any reduction product at all.

CIDNP experiment. Diethyl phosphite (0.26 mL, 2 mmoles) was added to the suspension of sodium hydride (24 mg, 1 mmol) in C_6D_6 in an NMR tube. The monoaddition product (**4**) (346 mg, 1 mmol) was then added and the reaction mixture after being kept for an hour at room temperature, was cooled to 0°C. ^{31}P NMR spectrum was then taken which contained an emission signal at 110 ppm (85% H_3PO_4 as reference).

Attempted entrainment experiment. Diethyl malonate (1.52 mL, 10 mmoles) and diethyl phosphite (0.065 mL, 0.5 mmol) were added to the suspension of sodium hydride (144 mg, 11 mmoles) in THF (25 mL). The monoaddition product (**4**) (1.73 g, 5 mmoles) was then added and the reaction mixture was refluxed for two hours at room temperature. No reaction between diethyl malonate and the monoaddition product (**4**) could be detected. The starting material (**4**) was isolated.

Reaction of the monoaddition product (**4**) *with sodium diethyl phosphite in benzene.* Diethyl phosphite (0.91 mL, 7 mmoles) was added to the suspension of sodium hydride (190 mg, 8 mmoles) in benzene (20 mL). The monoaddition product (**4**) (1.22 g, 3.5 mmoles) was then added and the reaction mixture was stirred for two days at room temperature. After usual work-up compounds (**1**) (735 mg, 75%) and (**2**) (930 mg, 70%) were isolated. No diaddition product (**5**) could be detected by TLC. It should have been present in the reaction mixture, had the homolysis of the N—N bond taken place.

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