Synthesis of cyclopentenones by tandem reactions of metallated alkyldiarylphosphazenes with DMAD and methyl maleate

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The reaction of lithium alkyldiarylphosphazenes with DMAD and methyl maleate affords cyclopentenones.

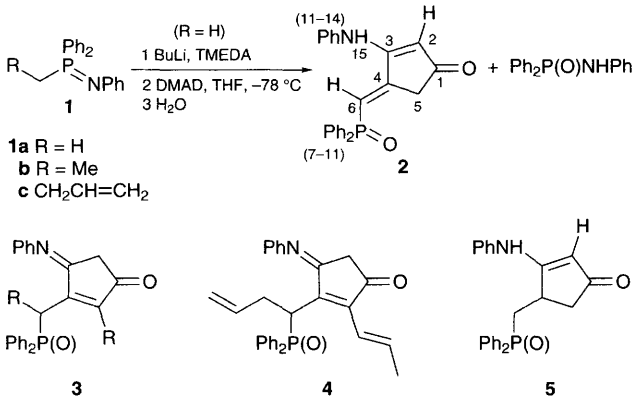
The P=N linkage of alkyldiarylphosphazenes can be considered as an isosteric function of the C=N double bond. This structural similarity applies, for example, to the observation of a phosphazene–aminoylide equilibrium[1] in suitable substituted phosphazene derivatives, analogous to the well known imine–enamine tautometry. An important consequence of the phosphazene *vs.* imine structural correlation is the ability of tuning the reactivity of alkyldiarylphosphazenes to the nitrogen or the carbon atom bonded to phosphorus with high selectivity depending on the reaction conditions. We have exploited this dual behaviour to introduce different functional groups in the alkyl chain of the starting phosphazene[2] as well as to synthesize several phosphole[3] and azaphosphinine heterocycles.[4] The synthetic strategy leading to these heterocycles involves the insertion of the triple bond of the dimethyl acetylenedicarboxylate (DMAD) into the phosphorus–nitrogen double bond, followed by an intramolecular cyclocondensation generally promoted by a base.

Recently, it has been shown that in lithium *N*-phenylmethylendiphenylphosphazene the cation is bonded to the nitrogen and methylene carbon atoms of the phosphazene.[5] We reasoned that by performing the addition of DMAD on the previously lithiated alkyldiarylphosphazene a new 1,2 λ^5-azaphosphinine could be obtained. To our surprise the reaction affords cyclopentenones instead of the expected phosphorus-containing heterocycle. The results are presented in this communication.

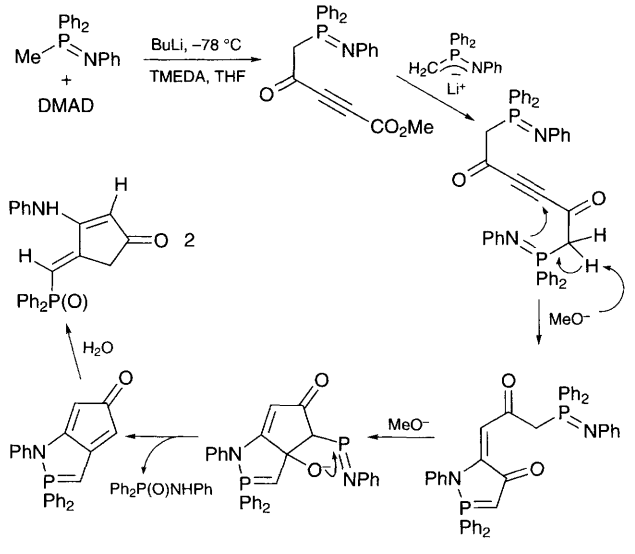
Alkyldiarylphosphazenes **1** are easily prepared through the Staudinger reaction between the respective phosphine and phenyl azide.[6] Phosphazene **1a** (3 mmol) in THF (15 ml) was lithiated with BuLi : TMEDA (3 mmol) at −20 °C for 30 min; then DMAD (3 mmol) in THF (5 ml) was added at −78 °C. The reaction mixture was allowed to warm to room temperature overnight. Subsequently aqueous work-up, solvent evaporation, purification by column chromatography (ethyl acetate as eluent) and recrystallization from hexane–CH_2Cl_2 afforded cyclopentenone **2** (45%)† and *N*-phenyldiphenylphosphonamide (43%). The structure of **2** indicates that two molecules of phosphazene have reacted with one molecule of DMAD. Therefore, when a molar ratio 2 : 2 : 1 of phosphazene : base : DMAD was used, cyclopentenone **2** was isolated in 85% yield (Scheme 1).

The structure of **2** was deduced from the 2D HMQC and HMBC spectra. The key entry are the correlations of the enamine proton at δ 5.68 (d, $^5J_{PH}$ = 2.8 Hz)‡ with all the carbon atoms which define the carbocyclic framework (δ 199.98, 164.1, 151.25, 107.14 and 38.42).§ The stereochemistry of the exocyclic double bond is assigned from the NOE enhancement observed for the signal of the *ortho* protons of the phenyl rings bonded to phosphorus when the methylene protons of the cyclopentenone are selectively saturated.

A tentative mechanism to explain the formation of **2** would involve the following steps (Scheme 2). First, the lithiated phosphazene would be regioselectively added through the Cα of the P=N to a methoxycarbonyl group of DMAD. The methoxycarbonyl group remaining in the intermediate formed can further react with the second equivalent of lithium methylendiphenylphosphazene affording an activated acetylene derivative containing two methylenephosphazenyl moieties. This process also produce 2 equiv. of lithium methoxide. The LiOMe promotes cyclization to a $2\lambda^5$-azaphosphole heterocycle by abstracting a methylene proton followed by delocalization of the negative charge through the P=N bond and subsequent Michael addition to the acetylenic triple bond. A second equivalent of LiOMe would react similarly by metallating the methylene carbon of the phosphazenyl substituent of the azaphosphole, which is then added to the 1,5 carbonyl carbon. The new intermediate formed has a negatively charged oxygen in a β-position with a phosphazenyl moiety. This atomic arrangement could generate a carbon–carbon double bond



Scheme 1



Scheme 2

through a Horner-type elimination,[7] yielding *N*-phenyldiphenylphosphonamide and a bicyclic azaphosphole heterocycle. Aqueous work-up of the reaction would hydrolyse the P–N bond of the azaphosphole and, finally, a 1,3-proton shift would afford the cyclopentenone **2**.

We suggest that a tandem reaction occurs, which is driven by an alkyldiarylphosphazene involving successively the carbon and nitrogen atoms adjacent to the phosphorus, a process unprecedented in the literature.[8] Moreover, this would be also the first report on the participation of a λ^5-phosphazene in a Horner-type reaction.[9]

For phosphazenes **1b** (R = Me) and **1c** (R = allyl) the isolated cyclopentenones are stabilized as the isomers **3** showing a preference for the imine tautomer of the nitrogen substituent as well as the endocyclic carbon–carbon double bond formed in the final step of the reaction, favoured because it is now tetrasubstituted. Additionally, for R = allyl a mixture of two isomers **3b** and **4** was obtained.¶ Clearly, cyclopentenone **4** arises from a 1,3-proton shift of the homoallyl substituent of the carbocycle **3b** probably promoted by the extended conjugation achieved. The reaction seems to be very sensitive to steric effects. Thus, only moderate yields of **3** and **4** are obtained (Table 1). For R = Pr^i no reaction is observed and the same occurs for R = Ph and CH_2=CH. In the last cases the delocalization of the carbanion through the adjacent carbon π-system may contribute to the decreased reactivity.

The reaction of phosphazene **1a** with methyl maleate or methyl fumarate under the same experimental conditions mentioned above proceeds in the same way and cyclopentenone **5** was obtained, although in low yields (Table 1). The reaction of phosphazenes **1b,c** with these alkenes afforded only intractable mixtures.

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Table 1 Cyclopentenones **2–5**

Compound	Mp/°C	δ_P	Yield (%)[a]
2	207.8	23.92	85
3a[b]	213.4	33.01	28
3b[c]	—	31.68	30[d]
4	—	31.65	30[d]
5	208.9	31.16	20

[a] Yield of purified products from DMAD. [b] R = Me. [c] R = CH_2CH=CH_2. [d] Overall yield of the mixture **3b**/**4**.

Footnotes

† Elemental analysis and spectroscopic data were in agreement with the structures proposed. *Spectroscopic data* for compound **2**: ^{1}H NMR ($CDCl_3$; 400 MHz) (refer to Scheme 1 for numbering scheme); δ 2.68 (t, 2 H, $^4J_{HH}$ 1.8, $^4J_{PH}$ 1.8 Hz, 5-H_2), 5.68 (d, 1 H, $^5J_{PH}$ 2.8 Hz, 2-H), 7.02–7.06 (m, 1 H, 14-H), 7.11–7.14 (m, 2 H, 2 × 12-H), 7.15 (dd, 1 H, $^1J_{PH}$ 16, $^4J_{PH}$ 1.8 Hz), 7.17–7.23 (m, 2 H, 2 × 13-H), 7.30–7.50 (m, 6 H, 4 × 9-H and 2 × 10-H), 7.54–7.62 (m, 4 H, 4 × 8-H) and 9.02 (br s, 1 H, 15-H); ^{13}C NMR ($CDCl_3$; 100.61 MHz); δ 38.42 (C-2), 106.23 (C-3), 114.2 (d, *J* 101.1 Hz, C-6); 122.17 (C-12), 124.99 (C-14), 128.7 (d, *J* 12.2 Hz, C-9), 129.16 (C-13), 130.89 (d, *J* 10.0 Hz, C-8), 132.5 (d, *J* 106.1 Hz, C-7), 132.07 (C-10), 139.4 (C-11), 151.27 (d, *J* 3.0 Hz, C-4), 164.10 (d, *J* 16.6 Hz, C-3) and 199.98 (C-1); ^{31}P NMR ($CDCl_3$; 161.97 MHz); δ 23.92; MS *m*/*z*; 385 (M^+, 31), 261 (17) and 201 (100).

‡ ^{1}H, ^{31}P Coupling constants were established based on the ^{1}H NMR spectrum acquired with ^{31}P-decoupling. Homonuclear ^{1}H, ^{1}H scalar couplings were ascertained by a series of homodecoupling experiments.

§ The structural assignment is in agreement with the ^{1}H, ^{31}P and ^{13}C, ^{31}P coupling constants measured, and is further confirmed by the cross peaks observed for the methylene protons (with the carbons at δ 199.98, 164.10, 151.25 and 114.20), the methine proton adjacent to the phosphorus atom (with the carbons at δ 164.10, 151.25 and 38.42) as well as the correlations of the NH (with the carbons at δ 151.25, 122.17 and 106.23).

¶ Their structures have been assigned through analyses of the 2D ^{1}H, ^{13}C HMQC and HMBC correlation spectra.

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