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Dianions of Acyclic β-Enamino Ketones and Electrophiles. 9. Synthesis and Reactivity of Phosphorylated Enaminones

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ABSTRACT: *Phosphorylated enaminones can be obtained by the reaction of enaminone dianions with diphenylphosphinoyl chloride. In most cases, the reaction gave a mixture of monosubstituted and disubstituted compounds. Disubstituted compounds show an interesting NMR spectrum. In fact, the methine proton appears as a broad signal whose chemical shift varies with concentration. The chemistry of the α′-derivatives partially parallels that of the corresponding silicon derivatives in reaction with aldehydes.* © 2000 John Wiley & Sons, Inc. Heteroatom Chem 11:1–5, 2000

INTRODUCTION

Some years ago, we were interested in the alkylation of enaminones [β-(monoalkylamino) α,β-unsaturated ketones]. We set up the conditions for the regioselective dimetallation of the *N*,α′ or the *N*,γ positions using two equivalents of lithium tetramethylpiperidide (LTMP) or methyllithium/tetramethylethylendiamine (MeLi/TMEDA), respectively [1]. Both dianions react with a large variety of carbon electrophiles leading to interesting polyfunctionalized heterocyclic and straight chain compounds [2].

More recently, [3] silicon electrophiles were successfully employed and they showed interesting proprieties in the synthesis of α′,β′-unsaturated diketones or β,γ-unsaturated ketones by reaction of the corresponding dianions with carbonyl compounds or by reaction with organocerium reagents, respectively [4]. However, this reaction suffers some drawbacks, such as the high instability of the γ-silylated enaminones that cannot be used in synthesis.

Due to the higher stability of phosphorus compounds and the parallelism between silicon and phosphorus derivatives in the formation of a double bond, we were able to explore the possibility of the synthesis of phosphorylated enaminones.

RESULTS AND DISCUSSION

Diphenylphosphinoyl chloride (**4**) offers the chance to obtain intermediates for the Wittig-Horner synthesis of alkenes, whose side products are more easily separated from the reaction medium than those of the classical Wittig reaction [5]. Therefore, it has been chosen among various phosphorus derivatives for this work. *N*,α- and *N*,γ-dianions of enaminones prepared according to the previously described standard procedure [1] were allowed to react with **4** at

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For part 8 of this series, see Ref [3].
Dedicated to Professor Alfred Schmidpeter on the occasion of his 70th birthday.

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room temperature and after the usual workup, the expected α' = (or γ)-phosphorylated enaminones were recovered (Scheme 1 and Table 1) in moderate to good overall yields.

In order to increase yields and to modify product distribution, the reaction with the cerium enolate of the enaminone obtained by transmetallation of **2b** or **3b** with dry cerium (III) chloride according to our procedure for the synthesis of phosphane oxides [6] was unsuccessfully attempted.

As shown in the scheme, the reaction often gave a mixture of mono and diphosphorylated compounds. Very likely, the reaction medium is basic enough to give a further metallation of the α' or the γ positions (a diphenylphosphinoyl group bound to the α' or γ position enhances the acidity of the remaining hydrogen atoms). The steric hindrance exerted by the nitrogen substituent at the γ position would surely influence the attack on the second molecule of **4**. It is more difficult to explain why mixtures of compounds are obtained in the α' position, where encumbering groups are not present. A third metallation reaction could be likely, but the hindrance of the two bulky diphenylphosphinoyl groups prevents a third attack.

The reaction requires, in fact, an excess of base larger than previously reported [2]. By use of stoichiometric amounts of base, starting material is recovered due to a transmetallation process between the unsubstituted dianion and the more acidic substituted monoanion, as in the reaction with carbonates [2g].

It should be noted that the γ methine hydrogen of compounds **8** gives a broad signal in the ^{1}H NMR spectrum, whose chemical shift varies with concentration. Therefore, we think that enolic forms of those compounds (**8′**, Scheme 2) might be more stable than those of the corresponding keto tautomer **8**.

However, the ^{13}C NMR spectrum of **8e** showed a signal at 42.6 ppm, which must be assigned to a methine carbon bound to two phosphorus atoms by DEPT analysis and multiplicity. In our knowledge, this is the first example of a hydrogen atom bound to a carbon atom that exhibits typical characteristics of a mobile hydrogen. However, it is not surprising if one realizes that this hydrogen atom is linked to three strong electron-withdrawing groups.

In order to test the reactivity of these compounds in Wittig-Horner reactions, the reaction of **5b** with butylcerium chloride was performed under the same reaction conditions reported for silicon derivatives [4b]. Unfortunately, the reaction did not work, and starting material was recovered unaltered. This result provides further evidence of the encumbering effect exerted by the substituents on the reactive position of the enaminone. On the other hand, an acid-base reaction between the organometallic species and the enaminone system is very unlikely. It is in fact reported, [7] that β-ketophosphine oxides are selectively alkylated by organocerium reagents without affecting the acidic methylene between the phosphorus atom and the carbonyl moiety. The reaction of dianions of **5b** and **7b** was then performed with benzaldehyde according to the reaction conditions reported for the corresponding silylated enaminones [4a]. Only the reaction of **5b** successfully afforded the expected α',β'-unsaturated enaminone. The reaction is much slower than the one with silicon derivatives, requiring an overnight period of standing instead of 2 hours. Moreover the new alkene is formed in the *E* configuration.

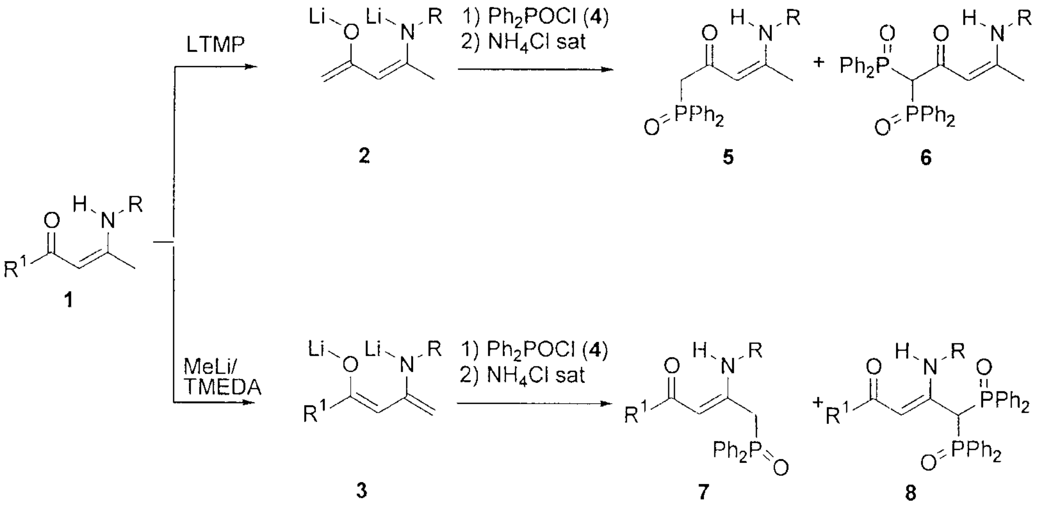
In the reaction of silicon derivatives, a *Z,E* isomerization occured after an elimination to form the alkene when the reaction mixture was allowed to stand overnight. However, in the reaction of **5b**, the *E* isomer is already present at the beginning of the reaction, thus demonstrating that a different transition state is involved in comparison to that reported with silicon derivatives.

In conclusion, a new class of phosphorus derivatives is now available. As with silicon derivatives, they can be valuable intermediates for the synthesis of α',β'-unsaturated enaminones or diketones. They can also be employed in the Warren modification of the Wittig-Horner alkene synthesis [8], since there are known methods to reduce selectively the carbonyl moiety in the presence of diphenylphosphinoyl groups [9].

EXPERIMENTAL

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 MHz and 75 MHz, respectively, with a Brucker WM300 instrument. Chemical shifts are given in ppm from Me_4Si. Coupling constants are given in Hertz. IR spectra were recorded with a Perkin-Elmer Paragon 1000 PC FTIR spectrometer. FAB-MS were recorded with a VG-ZAB spectrometer. Melting points are uncorrected and were determined with a Kofler hot stage.

Tetrahydrofuran (THF) was dried by refluxing it over sodium wire until the blue color of benzophenone ketyl persisted and then by distillation into a dry receiver under a nitrogen atmosphere immediately before use. *N,α'* And *N,γ*-dianions were prepared as previously described [1], but 3.5 equivalents of base were used instead of 2.5.



SCHEME 1

TABLE 1 Reaction of Dianions of Enaminones (**1a–d**) and Diphenylphosphinoyl Chloride (**4**) at Room Temperature followed by Quenching with Saturated Ammonium Chloride

Entry	*Dianion*	*R*	*R*^{1}	*Products*	*Overall Yield* (%)	Ratio (*mono/di*)
1	**2a**	i-Pr	Me	**5a** + **6a**	49	4/1
2	**2b**	Ph	Me	**5b**	58	—
3	**2c**	c-C_5H_9	Me	**5c** + **6c**	46	3/2
4	**2d**	c-C_6H_{11}	Me	**5d**	49	—
5	**3b**	Ph	Me	**7b**	71	—
6	**3c**	c-C_5H_9	Me	**7c**	49	—
7	**3d**	c-C_6H_{11}	Me	**7d** + **8d**	62	2/1
8	**3e**	i-Pr	Ph	**8e**	58	—

SCHEME 2

Reaction of α'*-Dianions* 2 *with Diphenylphosphinoyl Chloride* 4

A THF (10 mL) solution of 4 (7.5 mmol) was dropped into a THF solution of the α'-dianion (5 mmol) at room temperature under a dry nitrogen atmosphere and with stirring. The mixture was stirred for 30 minutes and was then treated with saturated NH_4Cl solution followed by extraction with diethyl ether and then three times with dichloromethane. The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography was performed on the crude products on a short silica gel column (chloroform:methanol 97.5:2.5 as eluant). Yields are tabulated in Table 1.

4-(N-Isopropylamino)-1-(diphenylphosphinoyl)-pent-3-en-2-one 5a *Foam.* ^{1}H NMR ($CDCl_3$): δ 1.16 (d, J = 6.2, 6H ($\underline{CH_3}$)$_2$CH), 1.88 (s, 3H CH_3), 3.38 (d, J_{HP} = 14.9, 2H CH_2PO), 3.61 (m, 1H $\underline{CH}(CH_3)_2$), 5,28 (s, 1H CH=), 7.40–7.61 (m, 6 H Ar), 7.68–7.88 (m, 4H Ar) 11.1 (brs, 1H NH). FAB ν^+: m/z 342 (M + H$^+$), 243, 201. Anal Calcd for $C_{20}H_{24}NO_2P$: C, 70.37; H, 7.09; N, 4.10%. Found: C, 70.40; H, 7.10; N, 4.10%.

4-(N-Isopropylamino)-1,1-bis(diphenylphosphinoyl)pent-3-en-2-one 6a *Foam.* ^{1}H NMR ($CDCl_3$): δ 1.17 (d, J = 6.6, 6H ($\underline{CH_3}$)$_2$CH), 2.04 (s, 3H CH_3), 3.35 (m, 1H $\underline{CH}(CH_3)_2$, 5.16 (s, 1H CH=), 5.55 (brs, 2H NH and CHP_2) 7.27–7.62 (m, 12H Ar), 7.66–7.90 (m, 8H Ar). FAB ν^+: m/z 542 (M + H$^+$), 342, 259, 243, 201. Anal Calcd for $C_{32}H_{33}NO_3P_2$: C, 70.97; H, 6.14; N, 2.59%. Found: C, 71.00; H, 6.11; N, 2.60%.

4-(N-Phenylamino)-1-(diphenylphosphinoyl)-pent-3-en-2-one 5b. M.p. 154–155°C. ^{1}H NMR ($CDCl_3$) δ 1.94 (s, 3H CH_3), 3.49 (d, J_{HP} = 14.5, 2H CH_2P), 5.38 (s, 1H CH=), 7.06–7.83 (m, 15H Ar), 12.25 (brs, 1H NH). m/z (EI, %) 375 (M$^+$, 89), 335 (19), 243 (80), 215 (100), 201 (81), 173 (43), 160 (54), 133 (70), 110 (69), 93 (19), 77 (95). Anal Calcd for $C_{23}H_{22}NO_2P$: C, 73.57; H, 5.91; N, 3.73%. Found: C, 73.55; H, 5.88; N, 3.75%.

4-(N-Cyclopentylamino)-1-(diphenylphosphinoyl)pent-3-en-2-one 5c *Foam.* ^{1}H NMR ($CDCl_3$): δ

1.40–1.75 (m, 9H cyclopentyl), 1.88 (s, 3H CH_3), 3.38 (d, J_{HP} = 14.6, 2H CH_2PO), 5.08 (s, 1H CH=), 7.35–7.60 (m, 6H Ar), 7.71–7.90 (m, 4H Ar), 11.51 (brs, 1H NH). FAB v^+: *m/z* 368 (M+H$^+$), 243, 201, 185. Anal Calcd for $C_{22}H_{26}NO_2P$: C, 71.92; H, 7.13; N, 3.81%. Found: C, 71.96; H, 7.10; N, 3.83%.

4-(N-Cyclopentylamino)-1,1-bis(diphenylphosphinoyl)pent-3-en-2-one **6c** *Foam.* ^{1}H NMR: δ 1.23–1.41 (m, 5H cyclopentyl), 1.43–1.62 (m, 4H cyclopentyl), 1.72 (s, 3H CH_3), 3.41 (brs, 2H NH and CHP_2), 5.29 (s, 1H CH=), 7.35–7.62 (m, 12H Ar), 7.70–7.88 (m, 8H Ar)10.80 (brs, 1H NH). FAB v^+: *m/z* 568 (M+H$^+$), 326, 259, 243, 201. Anal Calcd for $C_{34}H_{35}NO_3P_2$: C, 71.95; H, 6.22; N, 2.47%. Found: C, 71.90; H, 6.22; N, 2.50%.

4-(N-Cyclohexylamino)-1-(diphenylphosphinoyl)pent-3-en-2-one **5d** *Foam.* ^{1}H NMR ($CDCl_3$): δ 1.00–1.70 (m, 11H cyclopentyl), 1.72 (s, 3H CH_3), 3.40 (d, J_{HP} = 14.49, 2H CH_2PO), 5.29 (s, 1H CH=), 7.35–7.90 (m, 10H Ar), 10.40 (brs, 1H NH). FAB v^+: *m/z* 382 (M+H$^+$), 300, 244, 201. Anal Calcd for $C_{23}H_{28}NO_2P$: C, 72.42; H, 7.40; N, 3.67%. Found: C, 72.46; H, 7.37; N, 3.68%.

Reaction of γ-Dianions **3** *with Diphenylphosphinoyl Chloride* **4**

A THF (10 mL) solution of **4** (7.5 mmol) was dropped into a THF solution of the γ-dianion (5 mmol) at room temperature under a dry nitrogen atmosphere with stirring. The mixture was stirred for 30 minutes and then treated with saturated NH_4Cl solution, extracted with diethyl ether, and then again three times with dichloromethane. The combined organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography was performed on the crude products on a short silica gel column (chloroform:methanol 97.5:2.5 as eluant). Yields are tabulated in Table 1.

4-(N-Phenylamino)-5-(diphenylphosphinoyl)-pent-3-en-2-one **7b** *Foam.* ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3H CH_3CO), 3.38 (d, J_{HP} = 13.7, 2H CH_2PO), 5.34 (s, 1H CH=), 6.93–7.90 (m, 15 H Ar), 10.2 (brs, 1H NH). FAB v^+: *m/z* 376 (M+H$^+$), 334, 201, 158, 118. Anal Calcd for $C_{23}H_{22}NO_2P$: C, 73.57; H, 5.91; N, 3.73%. Found: C, 73.60; H, 5.90; N, 3.72%.

4-(N-Cyclopentylamino)-5-(diphenylphosphinoyl)pent-3-en-2-one **7c** *Foam.* ^{1}H NMR ($CDCl_3$): δ 1.22–2.00 (m, 9H cyclopentyl), 1.85 (s, 3H CH_3CO), 3.35 (d, J_{HP} = 14.5, 2H CH_2PO), 5.04 (s, 1H CH=), 7.01–7.59 (m, 6H Ar), 7.61–7.96 (m, 4H Ar), 10.7 (brs, 1H NH). FAB v^+: *m/z* 368 (M+H$^+$), 243, 201, 185. Anal Calcd for $C_{22}H_{26}NO_2P$: C, 71.92; H, 7.13; N, 3.81%. Found: C, 71.94; H, 7.15; N, 3.80%.

4-(N-Cyclohexylamino)-5-(diphenylphosphinoyl)pent-3-en-2-one **7d** *Foam.* ^{1}H NMR ($CDCl_3$): δ 0.80–2.40 (m, 11H cyclohexyl), 1.72 (s, 3H CH_3CO), 3.39 (d, J_{HP} = 14.49, 2H CH_2PO), 5.30 (s, 1H CH=), 7.00–8.00 (m, 10H Ar), 9.80 (brs, 1H NH). FAB v^+: *m/z* 382 (M+H$^+$), 380, 275, 201. Anal Calcd for $C_{23}H_{28}NO_2P$: C, 72.42; H, 7.40; N, 3.67%. Found: C, 72.40; H, 7.42; N, 3.68%.

4-(N-Cyclohexylamino)-5,5-bis(diphenylphosphinoyl)pent-3-en-2-one **8d** *Foam.* ^{1}H NMR ($CDCl_3$): δ 0.80–2.00 (m, 11H cyclohexyl), 1.89 (s, 3H CH_3CO), 2.51 (brs, 2H $CH(POPh_2)_2$ and NH), 5.30 (s, 1H CH=), 6.90–7.90 (m, 20H Ar), FAB v^+: *m/z* 582 (M+H$^+$), 340, 219, 201. Anal Calcd for $C_{35}H_{37}NO_3P_2$: C, 72.28; H, 6.41; N, 2.41%. Found: C, 72.25; H, 6.40; N, 2.44%.

3-(N-Isopropylamino)-1-phenyl-4,4-bis(diphenylphosphinoyl)but-2-en-1-one **8e**. M.p. 159–160°C. ^{1}H NMR ($CDCl_3$) δ 1.00 (d, J = 6.4, 6H $(CH_3)_2CH$), 3.05 (brd, 2H $CH(POPh_2)_2$ and NH), 3.44 (dhept, 1H CHNH), 5.24 (s, 1H CH=) 7.11–7.81 (m, 25H, Ar). ^{13}C NMR δ 21.3 (s, 2C $(CH_3)_2CH$), 42.6 (t, J = 51, 1C $CH(POPh_2)_2$), 45.3 (s, 1C $CH(CH_3)_2$, 93.1 (s, 1C $\underline{C}H{=}C$), 126.9–131.9 (m, 30C 5Ar), 190.5 (s, 1C PhCO). FAB v^+: *m/z* (%) 604 (M+H$^+$, 48), 402 (53), 376 (30), 201 (79), 105 (100). Anal Calcd for $C_{37}H_{35}NO_3P_2$, C, 73.62; H, 5.84; N, 2.32%. Found: C, 73.60; H, 5.82; N, 2.30%.

Reaction of Cerium Salts of Dianions **2b** *or* **3b** *with Diphenylphosphinoyl Chloride* **4**

A sample reaction was performed by transmetallation of lithium dianions **2b** or **3b** with dry cerium (III) chloride according to our procedure for the synthesis of phosphane oxides [6]. No reaction was detected.

Reaction of **5b** *with Benzaldehyde*

A TMEDA (5 mL) solution of benzaldehyde (5 mmol) was dropped into a THF (10 mL) solution of the α'-dianion of **5b** (5 mmol) prepared as previously described [1] at −78°C under stirring in a nitrogen atmosphere. After 2 hours, the attempted reaction was monitored by thin-layer chromatography (TLC) but no significative evidence of reaction was detected.

The mixture was then allowed to stand in a freezer overnight before treatment with saturated NH_4Cl solution. Then it was extracted three times with diethyl ether; the organic layers were dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography was performed on the crude product on a short silica gel column (hexane:ethyl acetate 8:2 as eluant). The recovered product was recognized to be (1*E*,4*Z*)-5-(*N*-phenylamino)-1-(phenyl)hexa-1,4-dien-3-one by comparison of its physical data with that in the literature [4a].

Reaction of **5b** *with Butylcerium Chloride*

A THF (10 mL) solution of **5b** (4 mmol) was dropped into butylcerium chloride prepared from equimolecular amounts of butyllithium and dry cerium (III) chloride (5 mmol) [4b] at −78°C under stirring in a nitrogen atmosphere. Stirring was continued for 48 hours and the temperature was allowed to rise to room temperature. The attempted reaction was monitored by TLC but no significant evidence of reaction was detected.

Reaction of **7b** *with Benzaldehyde*

A TMEDA (5 mL) solution of benzaldehyde (5 mmol) was dropped into a THF (10 mL) solution of the γ-dianion of **7b** (5 mmol) prepared as previously described [1] at −78°C under stirring in a nitrogen atmosphere. After 2 hours the putative reaction was monitored by TLC but no significative evidence of reaction was detected. The mixture was then allowed to stand in a freezer overnight and then to stir for 48 hours at room temperature before treatment with saturated NH_4Cl solution. After the usual workup, starting materials were quantitatively recovered.

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