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FACTORS CONTROLLING THE REGIOSELECTIVITY OF ADDITIONS TO α-ENONES—III

REACTIONS OF 3-ARYL α-ENONES WITH PHOSPHORYLATED ANIONS

MONCEF COSSENTINI,[a] BERNARD DESCHAMPS,[a]† NGUYEN TRONG ANH[b] and JACQUELINE SEYDEN-PENNE[a]‡

[a] GR 12 du CNRS, BP 28, 94320 Thiais, France

[b] Laboratoire de chimie théorique, 91401 Orsay, France

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Abstract—Reaction of phosphonoester **2** and phosphononitrile **3** with chalcone and *p*-methoxychalcone in THF–t-BuOK at room temperature gives only the product resulting from C=C double bond attack. The same reagents with benzalacetone lead to mixture of products resulting from C=C double bond and carbonyl attack, though phosphine oxide **4** gives only the products of C=C attack. Dypnone gives products of carbonyl attack with **3** and does not react with **2**.

These results are discussed in terms of perturbation theory: C_4 attack increases with delocalization of the reagent's negative charge and lowering of the α-enone LUMO level.

α-Enones **1** are ambident electrophiles, their two reactive sites being carbons 2 and 4.

$$\underset{4}{R}CH=CH\underset{2}{CO}R' \qquad \mathbf{1}$$

We have previously examined the reactivity of two α-enones towards anionic nucleophiles derived from α-chloracetates and α-chloracetonitrile[1] in terms of the generalized perturbation theory,[2-4] considering that attack on carbon 2 (carbon 4) is charge-controlled (frontier-controlled). Our former results can be interpreted by a charge-controlled reaction when the nucleophile has a localized negative charge and a frontier controlled one when the nucleophile's charge is delocalized.

In the present work, this approach is applied to the reaction of α-enones with anionic reagents formed α to phosphorus.

The study of these reactions must enable us to check the following points.

(a) *Influence of the reagent structure.* A better delocalization of the negative charge will increase frontier control and therefore favour carbon 4 attack. As an ester group is more prone to conjugate with a negative charge than a nitrile,[5] the charge of the anion derived from **2** will be more delocalized than that of the anion derived from **3**.

$$\underset{\mathbf{2}}{(EtO)_2P(O)CH_2COOEt} \qquad \underset{\mathbf{3}}{(EtO)_2P(O)CH_2CN}$$

In phosphonate compounds, $(EtO)_2P(O)CH_2R$, interaction with the oxygen lone pairs raises the energy of the phosphorus *d* orbitals. Therefore, these orbitals are no longer good acceptors and cannot stabilize anions derived from **2** or **3**. However, replacing the EtO moiety by a phenyl group should permit a better delocalization and it is expected that the anionic species derived from **4** should give more carbon 4 attack than the corresponding reagent derived from **3**.

$$\underset{\mathbf{4}}{Ph_2P(O)CH_2CN}$$

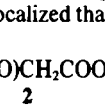
(b) *Influence of substrate structure.* An increase of frontier control is expected if the C_2 positive charge is decreased and/or the LUMO energy level is decreased and/or the C_4 coefficient in LUMO is increased.

We selected two series of α-enones:

(1) Aryl conjugated **1 a, b, c, d**, the reactivity of which is examined in this paper. Table 1 shows the LUMO levels, C_4 coefficient in LUMO and carbon 2 positive charge of these compounds.

(2) Alkyl substituted α-enones (R = alkyl), the reactivity of which is examined in the accompanying paper.[6]

Table 1.

	α-enone	E_{LUMO}[a]	q_2[a]	C_4[a]
1a	PhCH=CHCOPh	−0.132	+0.30	0.513
1b	CH_3O–C_6H_4–CH=CHCOPh	−0.183	+0.25	0.503
1c	PhCH=CHCOCH$_3$	−0.226	+0.38	0.563
1d		−0.191	+0.28	0.503

[a] Calculation by Hückel method.[7]

As perturbation theory gives only an estimation of the relative activation enthalpies of reactions, one has to ensure first that the reactions examined are under kinetic control. As it is applied here in its simplest form, it only takes into account variation of structural effects reactants but not the solvent, temperature and concentration. Therefore, these latter effects[4] need to be eliminated.

We first discuss the reaction scheme, select experimental conditions and check if kinetic control is ensured.

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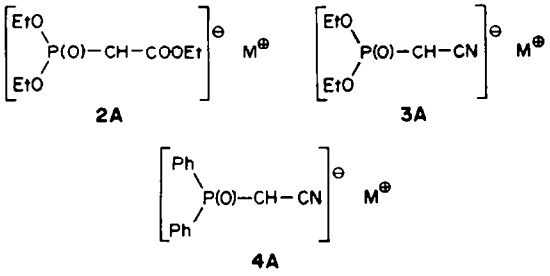
Reaction scheme

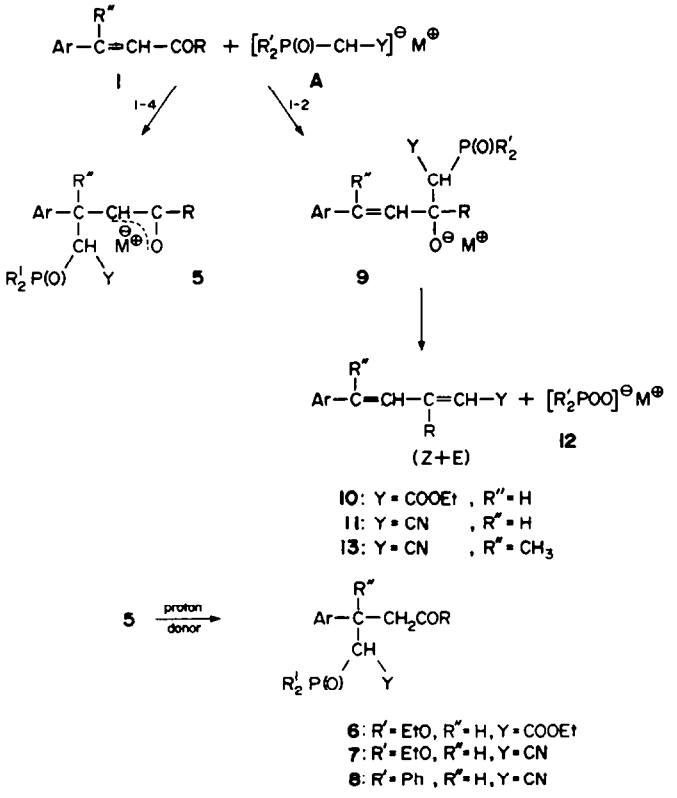
In basic medium, **2**, **3**, and **4** give anionic reagents **2A**, **3A** and **4A** which can attack either carbon 4 or carbon 2 of α-enones **1**.



Carbon 2 attack is a Wittig-Horner-Emmons reaction:[8] it gives alcoholates **9** which evolve *in situ* into dienes **10**, **11** or **13**, and phosphorus anion **12**.

Carbon 4 attack leads to enolates **5** which can be protonated, thus giving ketoesters **6** or ketonitriles **7** or **8**.

The general reaction scheme is the following:



Scheme 1.

We have prepared in good yields ketones **6**, **7**, **8** as well as dienes **10**, **11**, **13** (Experimental). All these compounds were purified and identified by physical methods.

Choice of experimental conditions

In order to compare rates of carbon 2 or carbon 4 attack, these two processes must be the slow ones of each reaction pathway: carbon 2 attack must be slower than decomposition of alcoholates **9** into olefins and carbon 4 attack slower than protonation.

Carbonyl attack (1–2 addition). Since stabilized ylids react faster with electroattracting *p*-substituted benzaldehydes than with electrodonating *p*-substituted ones, it has been concluded that the slow step of the Wittig reaction, in that precise case, is carbonyl attack.[9] We have found the same sensitivity for reagents **2A** and **3A**[10] to benzaldehyde substituents and conclude therefore that the slow step is likewise the carbonyl attack, and admit it also for ketones.

We tried without success to isolate the alcohols corresponding to **9** in several instances, using as we did with aldehydes[11] magnesium or lithium derivatives at low temperature.

Furthermore, according to our previous results,[11,12] reversibility of carbonyl attack by phosphonate anions was decreased when the reaction was performed in THF with K^+ as counterion rather than Li^+ or Na^+ and when the reaction temperature was lowered.

Therefore *we chose THF as solvent, K^+ as counterion and the reactions were run at room temperature* (as they are too slow at a lower temp).

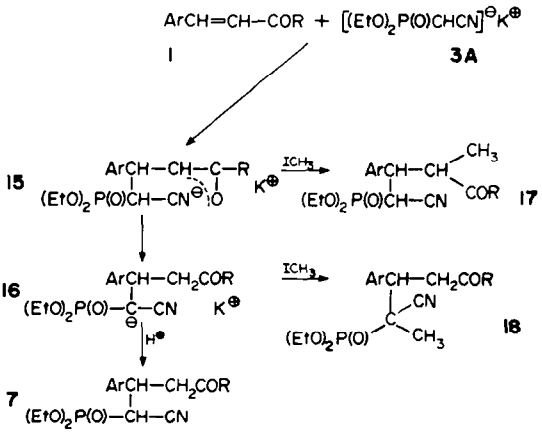
Carbon 4 attack. In our preliminary paper,[4] we have shown that formation of enolate **5** (Ar = Ph, R = CH_3, R′ = EtO, R″ = H, Y = COOEt) can be reversible. If such is the case, the product ratios will not correspond kinetic control and we must determine reaction conditions where reversibility can be neglected i.e. conditions where enolates generated from phosphonoketones **6a–c** and **7a–c** do not lead to starting materials (α-enones and phosphonates anions).

(a) *Ketoesters* **6a–c**. Adding one molar equivalent t-BuOK to ketoesters **6a–c**, we noticed some decomposition into starting ketone **1** and formation of dienes **10a–c**. However, performing the same experiment in the presence of one molar equivalent of ester **2**, after 30 min, neither formation of ketone **1** nor dienes **10** took place. However, reversibility was noticed over a long period of heating under reflux.

Therefore, *to determine the ratio* **6**/**10** *corresponding to* 1–4/1–2 *addition under kinetic control, the reaction must be performed within* 30 *min, from* 0.2 *mole ester* 2,0,1 mole t-BuOK, 0, 1 *mole enone* **1a–c**.

(b) *Ketonitriles* **7a–c** *and* **8c**. Treating ketonitriles **7a–c** and **8c** with one molar equivalent of t-BuOK did not give the starting ketone **1a–c** nor dienes **11** at room temperature. However, these compounds were formed by heating under reflux.

The lack of reversibility at room temperature in this case, may be due to the higher acidity of the protons α to CN than those α to COOR. Compounds **7** should give, in the presence of base, carbanions **16** instead of enolates **15**.



Scheme 2.

Furthermore, these carbanions **16** should be formed by a fast prototropy when α-enone **1** reacts with **3A**.

If this is the case, adding MeI either to the anion formed from **7** by addition of t-BuOK or to the reaction product of **1a–c** with **3A** before hydrolysis should lead to **17** if enolate **15** is present, or to **18** if **16** is formed. In both cases, we obtained only **18**, the structure of which was confirmed by a NMR coupling of Me protons with phosphorus. Therefore, *the reaction performed at room temperature, with t*-BuOK, *phosphonitrile* **3** *and ketones* **1a–c** *in molar equivalent was under kinetic control.* Indeed, we checked and found that the ratio **7**/**11** did not change with reaction time, in the presence or not of one molar excess of **3**; with phosphine oxide **4** and α-enone **1c**, the results were similar.

RESULTS AND DISCUSSION

Table 2 shows the yields of the products resulting from carbon 4 and carbon 2 attack under kinetic control.

Table 2. Products formed after 30 min reaction at 20°C (completion to 100% is starting ketone) molar conc. of α-enone: 0.1 M, KO t-Bu: 0.1 M, **2**: 0.2 M or **3**: 0.1 M

Exp. No.	α enone	reagent	Products % 1–4	1–2	1–4/1–2
1	**1a**	**2A**	90	<2	**6a/10a** ≥ 45
2	**1b**	**2A**	90	<2	**6b/10b** ≥ 45
3	**1c**	**2A**	35	15	**6c/10c** ~ 1.5
4	**1d**	**2A**	No reaction		
5	**1a**	**3A**	70	5	**7a/11a** ~ 15
6	**1b**	**3A**	60	10	**7b/11b** ~ 6
7	**1c**	**3A**	30	55	**7c/11c** ~ 0.5
8	**1d**	**3A**	<2	30	
9	**1c**	**4A**	40	<2	**8c/11c** ≥ 20

From this Table we can notice that:

(1) For a given ketone, reagent **2A** and **4A** gave more carbon 4 attack than reagent **3A**. With reagent **2A** and ketone **1a** and **1b**, no dienes **10** were found, though with reagent **3A** a small amount of dienes **11** was observed.

(2) With reagents **2A** and **3A**, α-enone **1c** always gave more carbonyl attack than α-enones **1b** and **1a**. It may be noted that dypnone **1d** either did not react (with **2A**) or gave only carbonyl attack (with **3A**).

In first approximation, these results are in line with our expectations concerning reagents structures in the reactions with enones **1a–c**. The greater charge delocalization on the anionic reagent, the greater frontier control and the more favoured carbon 4 attack: ester reagent **2A** gave more carbon 4 attack than nitrile **3A**; phosphine oxide **4A** gave more carbon 4 attack than **3A** and in fact even more than **2A**.

If we consider these α-enones, only benzalacetone **1c** has a relatively high q_2: it is also the only ketone which gave substantial amounts of dienes at room temperature. α-enones **1a** and **1b** both have lower carbonyl q_2 and LUMO levels: carbonyl attack is less favored; carbon 4 attack is more important.

The case of dypnone **1d** may seem singular: its carbonyl reactivity is in line with our expectations as the more localized reagent **3A** reacts faster than the more delocalized one **2A**. On the other hand, its carbon 4 reactivity is lower than expected: its LUMO energy level and C_4 are close to those of **1b** and one could expect as much carbon 4 attack as with **1b**, and more than with **1c**. However, dypnone **1d** is a 3-substituted α-enone and it is well known that Michaël like reactions are then slower.[13]

In conclusion, these results are in good agreement with the application of perturbation theory to chemical reactivity in the case of α-enones and anionic nucleophiles. The only possible exception is dypnone which is not reactive on carbon 4: this lack of reactivity has been usually attributed to steric hindrance.[13] However, this can be done to conformational deconjugation of C=C and carbonyl double bonds. This point will be discussed in the following paper.[6]

EXPERIMENTAL

NMR spectra were performed on VARIAN A 60 D or T 60 in CCl_4 (TMS internal standard). We quote analysis when a correct microanalysis corresponds to new compounds. THF was purified by distillation over KOH then over LAH.

Starting materials. Phosphonates **2** and **3** were prepared according to Ref. 14 and phosphine oxide **4** was prepared according to Ref. 15.

Compounds **1a**. Fluka product was recrystallized from EtOH (F = 54°); **1b** was prepared by condensation of acetophenone and anisaldehyde in the presence of KOH in EtOH–H_2O at room temp. during 1 hr (70% yield). Recrystallisation from EtOH (F = 79°); **1c**: Fluka product was recrystallized from hexane (F = 36°); **1d** was prepared by the action of gazeous HCl (70 g) on acetophenone (500 g) at room temp. during 2 days. Then 50 g glacial AcOH was added. The mixture was distilled under reduced pressure. ($Eb_{10\,mm\,Hg}$ = 200°), yield: 40%.

General technique. To 5×10^{-3} mole t-BuOK in 40 ml THF, at room temp., 5×10^{-3} mole phosphonate **2** or **3** or phosphine oxide **4** was added. The mixture was stirred under N_2 during 30 min; 5×10^{-3} mole α-enone in 10 ml THF was then added.

After a variable reaction time, water and ether were added. The inorganic layer was separated washed three times with water and dried over Na_2SO_4.

The solvent was evaporated and the crude mixture analyzed by NMR in CCl_4 after eventual addition of an internal standard (PhCHO) for quantitative determinations.

For preparative purpose, we performed thick layer chromatography over SiO_2. Elution by a mixture hexane 80–ether 20.

Description of new compounds. IR: phosphono ketones: for nitriles we noted bands: $\nu_{C=O} = 1700\,cm^{-1}$, $\nu_{C\equiv N} = 2250\,cm^{-1}$ and for esters: $\nu_{C=O}$(ester) = 1735 cm^{-1}. NMR: We have underlined the NMR signal used for determination.

Dienes

Compound **10a**. Ethyl 3,5-diphenyl-2,4-pentadiene-oate

$$\underset{(b)}{PhCH=CH}-C(Ph)=\underset{(a)}{CH}-COOCH_2CH_3 \text{ (Z + E isomers)}$$

Analysis; NMR: δ = 5.70 ppm (broad s): proton (a) $-\delta$ = 6.70 ppm (d) proton (b).

Compound **11a**. 3,5-Diphenyl-2,4- pentadiene nitrile (**Z + E** isomers)

$$Ph-\underset{(b)}{CH=CH}-C(Ph)=\underset{(a)}{CH}-CN$$

Analysis; NMR: $\delta = 5.25(\boldsymbol{E}) - 5.50(\boldsymbol{Z})$ ppm (broad s): *proton* (*a*)—$\delta = 6.75(\boldsymbol{E}) - 6.53(\boldsymbol{Z})$ ppm (d): proton (b).

Compound **11b**. 5 - *p* - Anisyl - 3 - phenyl - 2,4 - pentadiene nitrile (**Z + E** isomers)

$$\underset{(a)}{p\text{-}CH_3O-C_6H_4}-\underset{(b)}{CH=CH}-C(Ph)=\underset{(c)}{CH}-CN$$

Analysis; NMR: δ = 3.72(s): proton (a)—$\delta = 5.20(\boldsymbol{E}) - 5.47(\boldsymbol{Z})$ ppm (broad s) *proton* (*c*)—δ = 6.47(d): proton (b).

Compound **10c**. Ethyl 3 - methyl - 5phenyl - 2,4 - pentadiene - oate (**Z + E** isomers)

$$Ph-\underset{(b)}{CH=CH}-\underset{(a)}{C(CH_3)}=\underset{(b)}{CH}-COOCH_2CH_3$$

Analysis; NMR: $\delta = 2.08(\boldsymbol{Z}) - 2.35(\boldsymbol{E})$ ppm (d): *proton* (*a*)—δ = $5.60(\boldsymbol{Z}) - 5.75(\boldsymbol{E})$ ppm (broad s): *proton* (*b*).

Compound **11c**. 3 - Methyl - 5 - phenyl - 2,4 pentadiene nitrile (**Z + E** isomers)

$$Ph-\underset{(b)}{CH=CH}-\underset{(a)}{C(CH_3)}=\underset{(b)}{CH}-CN$$

Analysis; **Z** isomer is purified by cristallization from pentane (F = 64°) **E** isomer is separated by preparative vapor phase chromatography, oily. NMR: δ = 2.11 ppm (d): *proton* (*a*) $^4J_{ab}$ = 1.25 Hz $-\delta$ = 5.13 (broad s): *proton* (*b*). **E** isomer: δ = 2.23 ppm (d): *proton* (*a*) $^4J_{ab}$ = 0.75 Hz $-\delta$ = 5.23 ppm (broad s): *proton* (*b*).

Compound **13**. 3,5 - Diphenyl - 5 - methyl - 2,4 - pentadiene nitrile (**Z + E** isomers)

$$Ph-\underset{(a)}{C(CH_3)}=\underset{(c)}{CH}-C(Ph)=\underset{(b)}{CH}-CN$$

Analysis; NMR: **Z** isomer: δ = 1.96 ppm, $^4J_{ac}$ = 1.25 Hz, (d): proton (a)—δ = 5.58 ppm(d): *proton* (*b*)—δ = 6.58 ppm(m) proton (c). **E** isomer: δ = 1.96 ppm, $^4J_{ac}$ = 0.75 Hz (d): proton (a)—δ = 5.38 ppm: *proton* (*b*)—δ = 6.38 (m) proton (c).

Phosphonoketones

Compound **6a**.

$$\underset{(a)}{(CH_3CH_2O)_2}\underset{(b)}{P(O)}\underset{(b)}{CH}(\underset{(b)}{COOCH_2}\underset{(a)}{CH_3})\underset{(b)}{CH}(Ph)\underset{(b)}{CH_2}COPh$$

Analysis; NMR: δ = 1.2 ppm, $^3J_{ab}$ = 7 Hz (t): *protons* (*a*)—δ = 3.40 to 4.40 ppm (m): protons (b).

Compound **7a**.

$$(CH_3CH_2O)_2P(O)CH(CN)CH(Ph)CH_2COPh$$

Analysis; Mass Spectrum: M^+ = 385; NMR: the spectrum is the same type as **6a**.

Compound **6b**.

$$\underset{(a)}{(CH_3CH_2O)_2}\underset{(b)}{P(O)}\underset{(b)}{CH}(\underset{(b)}{COOCH_2}\underset{(a)}{CH_3})\underset{(b)}{CH}(\underset{(c)}{CH_3O-C_6H_4})\underset{(b)}{CH_2}COPh$$

Analysis; NMR: δ = 1.20 ppm (m): *proton* (*a*)—δ = 3.64 ppm (s): proton (c) δ = 3.40–4.40 ppm (m): protons (b).

Compound **7b**.

$$(CH_3CH_2O)_2P(O)CH(CN)CH(CH_3O-C_6H_4)CH_2COPh$$

Analysis; NMR: the spectrum is the same type as **6b**.

Compound **6c**.

$$\underset{(a)}{(CH_3CH_2O)_2}\underset{(b)}{P(O)}\underset{(b)}{CH}(\underset{(b)}{COOCH_2}\underset{(a)}{CH_3})\underset{(b)}{CH}(Ph)\underset{(b)}{CH_2}\underset{(c)}{COCH_3}$$

Analysis; NMR: δ = 1.20 ppm (m): *protons* (*a*) $^3J_{ab}$ = 7 Hz $-\delta$ = 1.93 ppm (s): *proton* (*c*)—δ = 2.80–4.40 ppm (m): protons (b).

Compound **7c**.

$$(CH_3CH_2O)P(O)CH(CN)CH(Ph)CH_2\underset{(c)}{COCH_3}$$

One pure isomer is isolated by crystallization from ether (F = 98°). Analysis; NMR: same spectrum as **6c** except δ = 2.11 ppm (s): *proton* (*c*).

Compound **8**.

$$(Ph)_2P(O)\underset{(b)}{CH}(CN)\underset{(b)}{CH}(Ph)\underset{(b)}{CH_2}\underset{(a)}{COCH_3}$$

One pure isomer is isolated by crystallisation from ether at 0° (F = 198°). Analysis; IR: $\nu_{C=O}$ = 1720 cm^{-1}; NMR: δ = 2.05 ppm (s): *proton* (*a*) δ = 3.20–3.75 ppm (m): protons (b).

Compound **18**.

$$\underset{(a)}{(CH_3CH_2O)_2}\underset{(b)}{P(O)}\underset{(c)}{C(CH_3)}(CN)\underset{(d)}{CH}(Ph)\underset{(d)}{CH_2}COPh$$

One pure isomer was isolated by crystallisation at 0° from an ether 70-pentane 30 mixture. NMR: δ = 1.27 ppm (t): *proton* (*a*) $^3J_{ab}$ = 7 Hz $-\delta$ = 1.67 ppm (d): *proton* (*c*) $^3J_{P-C}$ = 16 Hz $-\delta$ = 3.50–4.50 ppm (m): protons (d).

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