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

REACTIONS OF 3-ALKYL AND ALICYCLIC α-ENONES WITH PHOSPHORYLATED ANIONS

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Abstract—Reaction of phosphonoester (**2**) and phosphononitrile (**3**) with 3-alkyl or alicyclic α-enones in THF—t-BuOK gives different products resulting mainly from primary C=C double bond attack. The reaction is very fast, compared with 3-aryl substituted analogs. These results are interpreted in terms of a transition state for which deconjugation (π energy loss due to hybridization change of reagent) has to be taken into account in addition to HOMO-LUMO interactions. A 3,3-disubstituted α-enone reacts slowly with phosphonitrile (**3**) at the carbonyl carbon, C=C double bond attack being inhibited by steric hindrance.

These results indicate the limitation of perturbation theory which only applies with certainty for very early transition states.

In the previous paper[1] we examined the regioselectivity of the attack of anionic reagents formed from phosphonates (**2** and **3**) on α-enones (**1 a–d**; R = Ar).

RCH = CHCOR′ $(EtO)_2P(O)CH_2COOEt$
4   2
1   **2**

$(EtO)_2P(O)CH_2CN$

3

In the present work, we extend this study to the case of alkyl substituted α-enones (**1e** and **1f**) and alicyclic α-enones (**4**, **5**, and **6**). As previously, we indicate in Table 1 the LUMO energy levels, carbonyl carbon positive charge q_2 and C_4 coefficient in LUMO calculated either by Hückel method or by an *ab initio* (STO 3 G basis) one, to take into account the geometric factors of the cyclic compounds. For comparison, we also indicate the calculated values for benzalacetone (**1c**) by both methods[2,3] and recall the values of chalcone (**1a**).

If perturbation theory applies, considering only LUMO energy levels and carbonyl carbon positive charge, one can expect the following behaviour—as explained in the previous paper.[1]

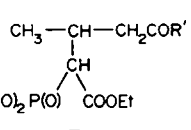
(1) Compound **1f** should give more carbonyl carbon attack than **1a**, **1e**, **4**, **5** or **6** as its carbonyl positive charge is higher.

(2) The rate of carbon-4 attack should be about the same for **1e** and **1c** and slower for **1f**, **4**, **5** or **6** as the LUMO levels are nearly the same for the first two and higher for the four others—as C_4 coefficients in the LUMO are similar.

We selected the same reaction conditions as with the aryl substituted enones (**1**; R = Ar).[1] Therefore, we examined firstly the reaction products in each case and determined which compound results from carbon-4 kinetic attack or carbonyl carbon reaction.

Reaction products. 1 Molar equivalent of phosphonate (**2** or **3**) was stirred with 1 molar equivalent t-BuOK in THF at room temperature, then 1 molar equivalent α-enone was added. The reaction was kept for about 30 min at room temperature (except **6** for which it was kept at −80°). After addition of water, the following compounds were obtained and characterized, according to the different ketones studied.

Crotonophenone (**1e**) only yielded **7e** and **8e** in nearly quantitative yield.



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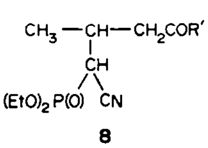

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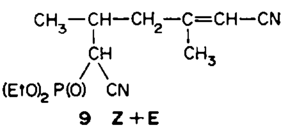
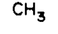
e: R′ = Ph
f: R′ = CH_3

3-Penten-2-one (**1f**) and phosphonate (**2**) yielded **7f** in a nearly quantitative yield. However, from the same α-enone and nitrile **3**, we obtained a mixture of nitriles (**9** and **10**) in the ratio 1/1, in a total yield of 50%, the remaining being starting enone.



9 Z + E



$$CH_3{-}CH{=}CH{-}\underset{\displaystyle CH_3}{\underset{|}{C}}{=}CH{-}CN$$

10

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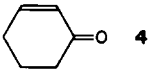
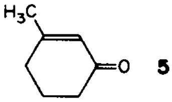
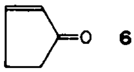
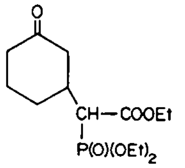
†This work is part of Bernard Deschamps these d'Etat No. A.O. 12.510.

Table 1.

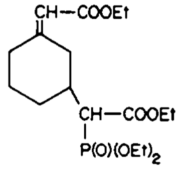
	Hückel method			*Ab initio* method		
	E_{LUMO}(β units)	$q_2{}^a$	C_4	E_{LUMO}(a.u.)	$q_2{}^b$	C_4
PhCH=CHCOPh **1a**	−0.132	+0.30	0.513			
PhCH=CHCOCH$_3$ **1c**	−0.226	+0.38	0.563	0.185	+0.190	0.475
CH$_3$CH=CHCOPh **1e**	−0.238	+0.31	0.558			
CH$_3$CH=CHCOCH$_3$ **1f**	−0.400	+0.43	0.670	0.231	+0.196	0.653
 **4**	−0.400	+0.43	0.670	0.229	+0.188	0.648
 **5**				0.234	+0.187	0.653
 **6**	−0.400	+0.43	0.670	0.232	+0.196	0.663

[a] π charge
[b] $(\sigma + \pi)$ charge

2-Cyclohexenone (**4**) and phosphonoester (**2**) yielded a complex mixture of starting enone **4** and compounds **11**, **12**, **13**.[†]



11



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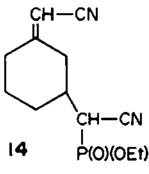
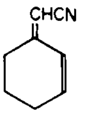
—Enone (**4**) and phosphononitrile (**3**) gave compound **14** (yield 40–45%) accompanied by starting material and trace amounts of **15**.



14



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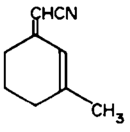
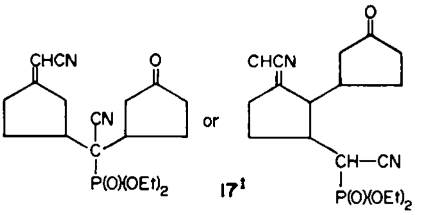
3-Methyl-2-cyclohexenone (**5**) and phosphononitrile (**3**) gave single product **16** (50% yield within 30 min at room temperature).

2-Cyclopentenone (**6**) and nitrile **3**, at −80° gave a single product **17**, accompanied by a small amount of polymers. At room temperature, extensive polymerization occurred.



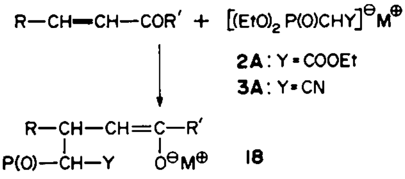
16



17[‡]

We checked, in all the cases, whatever reaction time, or temperature, all the compounds formed, therefore kinetic control was assured.

Mode of formation of reaction products. Formation of **7e**, **7f**, **8e** and **11** resulted from carbon 4 attack by the anionic reagents **2A** and **3A** and yielded enolates **18** which were protonated.

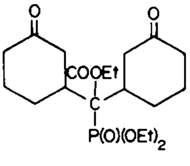


Formation of **13** resulted from a further reaction of enolate **18** on starting enone **3**: polycondensations have been described in cyclohexenones and cylopentenones and other analogous cases.[4]

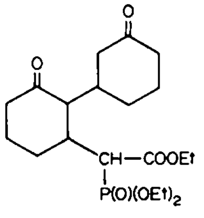
Formation of **10**, **15** and **16** resulted from carbonyl carbon attack: no product resulting from carbon 4 attack could be detected at any reaction time from ketone **5**. However, formation of **9**, **12** and **14** is not clear. There are two possibilities: (a) Carbon 4 attack should occur yielding to enolate **18** which could be protonated in the reaction medium giving **8f**, **11**, **19** and **20**. These ketones could then react with the anionic reagent **2A** or **3A** present in the medium.

Instead carbon 2 attack could take place, yielding a

[†] According to NMR, IR, MS data, compound **13** could have either formula **13a** or **13b** but we are not able to determine the exact structure.

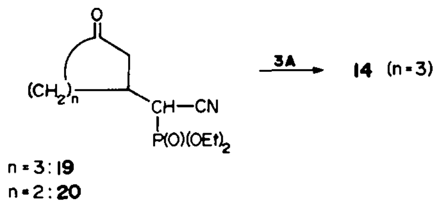


13a

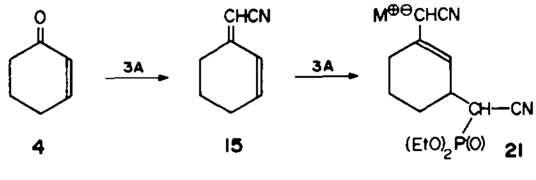


13b

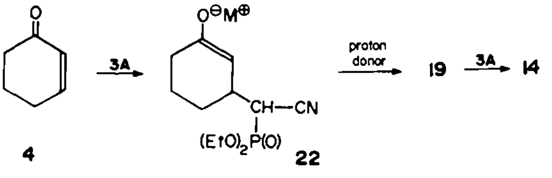
[‡] As in the case of **13**, NMR, IR and MS data do not permit to assign which is the exact structure.



diene such as **15** in the case of ketone **4**; carbon 4 attack following should then yield **21** the precursor of **14**.



The addition of anionic reagents α to phosphorus to α,γ-diene nitriles has not been described. We prepared dienes **10** and **15** and found that, under our reaction conditions, they remained unchanged. Therefore **14** resulted from a primary attack of carbon 4, giving enolate **22** which was protonated either by ketone **4**, t-BuOH present in the medium, or a proton α to the nitrile group to give **19** which reacted very rapidly with **3A** yielding **14**.



Though it is well known that nucleophilic reagents react faster with saturated ketones than with the corresponding α-enones,[5] we checked that reagent **3A** reacts faster with cyclohexanone than with 2-cyclohexenone **4**, which is in line with our interpretation. The yield of **14** (40–50%) obtained with the α-enone **4** and the phosphonate reagent reacting in equimolar amounts supports this mechanism. Using two equivalent phosphonate **3** and 1 molar equivalent t-BuOK per mole α-enone **4** gave **14** in a yield of >90%.

The reactions yielding **9** and **12** are the same. These two compounds were also obtained almost quantitatively when the molar ratio phosphonate : t-BuOK : α-enone was 2 : 1 : 1.

Formation of **17** resulted both from a further reaction of enolate **18** (or of the corresponding carbanion α to CN) on starting enone **6** giving a product analogous to **13** and a secondary attack of **3A** on one carbonyl carbon of **13**. Consequently, all these results show that formation of **9**, **12**, **13**, **14** and **17** involved a primary carbon 4 attack.

Therefore all the α-enones studied, except **5**, under kinetic control, suffered mainly primarily carbon 4 attack, but α-enone **1f** gave a slightly different result as equimolar amounts of phosphonate and t-BuOK gave diene **10** in addition to compound **9**.

Relative reactivities. In order to determine the scope of these reactions, we studied and relative reactivity of α-enones **1e**, **1f**, **1c**, **4** and **6** towards anionic reagent **3A**, admitting that the slow step of the process is carbon–carbon bond formation. We determined the reaction time and temperature at which half the starting α-enone **1e**, **1f** and **4** was consumed in the presence of 2 molar equivalents phosphonate **3** and 1 molar equivalent t-BuOK (initial α-enone concentration in THF: 0.1 mole l^{-1}). The following results were obtained: Half the α-enone **1e** was consumed after 5 min at −80°; in the case of α-enone **1f** and **4**, the same reaction advancement could be seen within 2 min at 0°. In the case of **6**, the reaction was even faster (quantitative yield within 2 min at −80°). From the previous results,[1] it appears that chalcone **1a** and benzalacetone **1c** are far less reactive. Enone **5** is also less reactive than the unsubstituted **4**.

DISCUSSION OF RESULTS

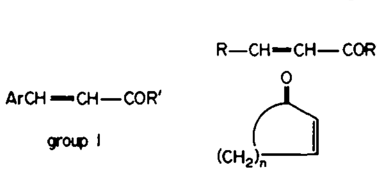
According to considerations based upon perturbation theory, we expected the following results:

(a) *Carbonyl attack.* The positive charge on enone **1f** being the highest in the series, it should give a high proportion of carbonyl attack: which it does with phosphononitrile **3**, but not with phosphonoester **2**. The cyclic enones have a smaller positive charge and no product resulting from carbonyl attack was found with **4** and **6** and just trace amounts from **4** and nitrile **3**. However 3-methyl-2-cyclohexenone **5** gave only carbonyl attack, though q_2 is the same as for **4**.

(b) *Carbon 4 attack.* According to LUMO energy levels and C_4 values (which are quite close), the rate of carbon 4 attack should be about the same for **1e** and **1c** and slower for **1f**, **4**, **5** and **6**. Our results are not in line with these expectations as **6** is the most reactive; **1e** reacts very fast—faster than **1c** and **1a**—the LUMO level of which is lower; **1f** and **4** react even faster than **1c** and **5** does not react at all.

Therefore, considering only carbonyl carbon q_2 and LUMO characteristics of all these enones, the reactivity of these electrophiles towards the anionic reagents cannot be predicted.†

If we compare carbon 4 reactivity of all the carbon 4 monosubstituted α-enones studied, they can be divided into two groups: aryl substituted ones (group 1) **1a**, **1b**, **1c** and alkyl substituted ones **1e**, **1f**, **4**, **6**, (group 2).



group 1
group 2

Carbon 4 attack is faster for group 2α-enones. One difference between the two groups is the possible loss of π energy at the transition state which is greater for group 1 than for group 2 when carbon 4 goes from sp^2 hybridization to sp^3 hybridization. Therefore, if α-enone hybridization is changing, the loss of π energy will be more important for group 1 enone transition state, thus raising their relative energy levels compared to group 2 enone transition states.[7,8] The importance of phenyl

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†More sophisticated calculations[15] show that, according to the nucleophile HOMO energy level, carbon 4 attack should be quite faster in the case of chalcone than in the case of 4-alkyl substituted α enones (high lying HOMO nucleophiles) or the reactivity is nearly the same whatever the α enone 4 substituent is (lower lying HOMO nucleophiles). However, no such a reversal of reactivity (4 alkyl substituted α enone being quite more reactive than chalcone) can be given by calculation.

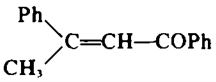
double bond deconjugation has already been used by Klein[9] and Iqbal and Jackson[10] to interpret the results of 1–4/1–2 addition of organometallics or hydrides to different α-enones. This factor can at least partly account for the difference in reactivity of the two groups.

If we consider that loss of π energy is about the same for the transition states of all group 1 ketones, interaction of HOMO and LUMO might then determine the reactivity order within this group, as previously observed.[1] In group 2 except α-enone **6** which is highly reactive, reactivity order also follows LUMO energy order: **1e** > **1f** and **4**.

A similar approach has been made by Mok and Nye[11] who examined the reactivity of various conjugated olefins in the Diels–Alder reaction. They showed that π energy loss is unimportant and the orbital interaction is the predominating factor, the behaviour being different from the present case. Recent results in our laboratory for the reaction of the series of α-enones studied in this paper and the anion of phenylacetonitrile, are also in line with Mok and Nye's observations[12]-loss of π conjugation must not to be taken into account to interpret reactivity orders.

The results we obtained with 3-methyl-2-cyclohexenone **5** show that carbon 4 attack is inhibited; only carbon 2 attack can be seen. This result is no longer in line with perturbation theory.

As the structure of this compound is fixed (s-*trans*), no important conformational change can be invoked to compare its reactivity with that of enone **4**, as we could tentatively do in the case of dypnone **1d**[1] which did not give any carbon 4 attack. It seems, thus, that only steric hindrance to carbon 4 attack can account for the lack of reactivity.



1d

CONCLUSIONS

The reaction of 3-aryl and 3-alkyl substituted α-enones with anionic reagents α to phosphorus **2A** and **3A** is essentially under orbital control. However, it is not possible to correlate carbon 4 reactivity with the LUMO characteristics of these α-enones. The transition states of these reactions probably involve rehybridization of the α-enone moiety and therefore, π energy loss of the system has to be considered; steric hindrance for carbon 4 di-substituted compounds must also have an effect.

Application of the generalized perturbation theory to chemical reactivity takes into account interactions between reagents at initial states.[6] Transition states are considered within the molecular complex approximation which may be adequate for early ones where neither loss of π energy nor steric factors are of prime importance, compared with orbital factors. However, if transition states are not so close to reactants on the reaction coordinate,† the loss of π energy and (or) steric hindrance may predominate over orbital factors.

EXPERIMENTAL

General data are given in the Experimental of the previous paper.[1]

Starting materials. α-Enones-**1e** were prepared according to Ref. 13; **1f** was an Aldrich product and redistilled ($Eb_{760\,mm\,Hg}$ = 124°); **4** and **6** were K.E.K. products; **5** was prepared according to Ref. 14 and distilled ($Eb._{24\,mm\,Hg}$ = 83°). See the previous paper[1] for the general technique.

Reaction of **16** *with phosphonate anion* **3A**. To 10^{-4} mole t-BuOK in 20 ml THF was added at room temp. 10^{-4} mole phosphonate **3**. After 30 min stirring under N_2 10 ⁴ mole (**Z** + **E**) mixture of **16** in 5 ml THF was added. After 30 min, unreacted **16** was obtained.

Half reaction time determination. The reaction was performed as usual (5×10^{-3} mole t-BuOK, 10^{-3} mole phosphonate then 5×10^{-3} mole α-enone in 50 ml THF). At variable times, an internal standard (PhCHO, 5×10^{-3} mole) was added and the mixture hydrolyzed. After the usual treatment, an NMR spectrum was run on the crude mixture which only consisted of starting α-enone, and described compounds (except with **6**, see text) and PhCHO.

Compound **1e** was determined by integration of PhCHO aldehydic proton and protons (**a**) of **6e**; **1f** by integration of aldehydic protons of PhCHO and protons (**a**) of **6f**; **4** by integration of aldehydic protons of PhCHO, ethylenic protons of remaining **4** and proton (**e**) of **12**.

Description of new compounds

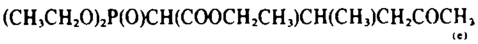
Infra-red spectra. For compounds **6e** and **6f** we noted the bands $\nu_{C=O}$(ketones): 1700 cm^{-1}; $\nu_{C=O}$(ester): 1735 cm^{-1}. For compounds **7e**, **8** and **12**, we noted the bands $\nu_{C=O}$: 1700 cm^{-1}; $\nu_{C\equiv N}$: 2250 cm^{-1}. In addition for **8** and **12** we noted the $\nu_{C\equiv N}$(conjugated): 2200 cm ¹. *NMR spectra.* We have underlined the NMR signal used to determine.

Compound **6e**.

$$(\underset{(b)}{CH_3}\underset{(d)}{CH_2}O)_2P(O)\underset{(c)}{CH}(COO\underset{(d)}{CH_2}\underset{(b)}{CH_3})\underset{(c)}{CH}(\underset{(a)}{CH_3})\underset{(c)}{CH_2}COPh$$

Analysis; NMR: δ = 1.05 ppm (m): *proton* (*a*)—δ = 1.30 ppm (t): *proton* (*b*)—δ = 2.6–4.0 ppm (m): protons (c)—δ = 4.15 ppm (m): protons (d).

Compound **6f**.



$$(CH_3CH_2O)_2P(O)CH(COOCH_2CH_3)CH(CH_3)CH_2CO\underset{(e)}{CH_3}$$

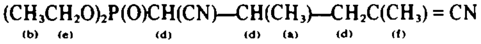
NMR: same spectrum as **6e**; in addition, we noted δ = 1.85 ppm (d): proton (e).

Compound **7e**.

$(CH_3CH_2O)_2P(O)CH(CN)CH(CH_3)—CH_2COPh$

Analysis. NMR: the spectrum is the same as **6e**.

Compound **8e**.

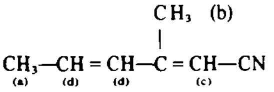


$$(\underset{(b)}{CH_3}\underset{(e)}{CH_2}O)_2P(O)\underset{(d)}{CH}(CN)—\underset{(d)}{CH}(\underset{(a)}{CH_3})—\underset{(d)}{CH_2}C(\underset{(f)}{CH_3}) = CN$$

(Z + E mixture)

NMR: δ = 1.20 ppm (m): protons (a)—δ = 1.30 ppm (t): protons (b)—δ = 2.10 ppm (d): protons (c)—δ = 2.6–4.0 ppm (m): protons (d)—δ = 4.15 ppm (m): protons (e)—δ = 5.20 ppm (broad s): *proton f*.

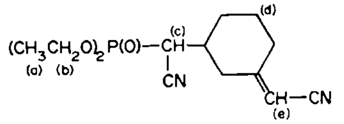
Compound **10**.



$$\underset{(a)}{CH_3}—\underset{(d)}{CH} = \underset{(d)}{CH}—\overset{\overset{CH_3\ (b)}{|}}{C} = \underset{(c)}{CH}—CN$$

NMR: δ = 1.95 ppm (d): protons (a)—δ = 2.11 ppm (s): protons (b)—δ = 5.06 ppm (broad s): *proton* (*c*)—δ = 6.0–6.9 ppm (m): protons (d).

Compound **12**.



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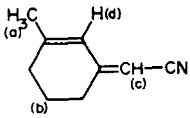
†This does not mean however that they are product-like.

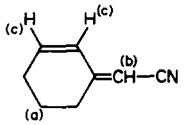
Mass spectrum $M^+ = 296$; Analysis; NMR: $\delta = 1.30$ ppm (t): protons (a)—$\delta = 2.2$ ppm (m): cyclic protons (d)—$\delta = 4.15$ ppm (m): protons (b)—$\delta = 5.15$ ppm (broad s): *proton* (*e*).

Compound **13**..



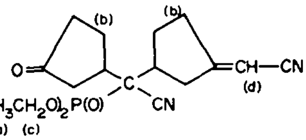
Analysis; NMR: $\delta = 1.9$ ppm (d): proton (a)—$\delta = 2.2$ ppm (m): cyclic protons (b)—$\delta = 4.85$ ppm (broad s): *proton* (*c*)—$\delta = 5.95$ and 6.50 ppm (broad s): protons (d): (two signals corresponding to the **Z** and **E** isomers).

Compound **16**. This compound is prepared according to the general technique[1] but replacing t-BuOK by t-BuOLi.



NMR: $\delta = 2.2$ ppm (m): cyclic protons (a)—$\delta = 5.00$ ppm (broad s): proton (b)—$\delta = 6.2$–6.9 ppm (m): system corresponding to protons (c).

Compound **17**.



Mass spectra: $M^+ = 364$; NMR: $\delta = 1.37$ ppm (t): protons (a)—$\delta = 1.5$–3.5 ppm (m) cyclic protons (b)—$\delta = 4.2$ ppm (m): protons (c)—$\delta = 5.2$ ppm (broad s) proton (d); Infra red: $\nu_{C\equiv N} = 2200\ \mathrm{cm}^{-1}$, $\nu_{C=O} = 1730\ \mathrm{cm}^{-1}$.

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