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

INFLUENCE OF LITHIUM CATION ON PHOSPHONITRILES REACTIONS

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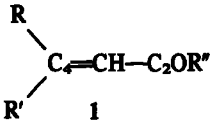
Abstract—Reaction of phosphononitrile 2 with a series of α-enones in THF–*n*-BuLi gives different results according to the enone nature. C_4-disubstituted enones are attacked at the carbonyl carbon; phenones and cyclopentenone are attacked at the double bond (except dypnone); benzalacetone, 3-penten-2-one and cyclohexenone give mixtures of C_2 and C_4 substituted products. Electrophilic assistance by complexation of the lithium cation by α-enone can be shown except for phenones.

In previous work[1] we studied the regioselectivity of attack of α-enones 1 by the anionic reagent 3 (M=K) formed from phosphonate 2, within the framework of Perturbation Theory applied to the Chemical Reactivity. We concluded that this reaction takes place under orbital control.


1

$(EtO)_2P(O)CH_2CN$ 2 $[(EtO)_2P(O)CHCN]^- M^+$ 3

We observed C_4 attack under kinetic control when the reaction is performed in THF, in the presence of potassium as a counterion. However, it has been observed that C_2 addition is generally favoured when lithium derivatives are used, rather than sodium, potassium or magnesium.[2] This change of regioselectivity can be explained by the aptitude of α-enone carbonyls for complexing a lithium cation, in an associating and not too basic solvent, such as THF. Handel and Pierre[3] noticed that, when reactions of hydrides and cyclohexenone were run in the presence of excess salts, complexing enones, the 1–2 addition ratio increased. Furthermore, in our laboratory, R. Sauvetre and J. Seyden-Penne[4] studied the reaction of the lithiated phenylacetonitrile 4 on α-enones: when the reaction is performed in a very basic and poorly associating medium (THF/HMPA mixture), C_4 attack is only obtained, but in THF, C_2 attack products appear in some cases.

$(PhCHCN)^-Li^+$
4

Ab initio calculations[5] about the molecule of acrolein, complexed or not by a lithium cation, give us some further information: 1–2 addition seems favoured when acrolein is complexed, as there is an inversion of carbon 2 and carbon 4 coefficients in its LUMO (while the coefficient of carbon 4 was the largest in the case of non-complexed acrolein, the carbon 2 one becomes the largest in the case of complexed acrolein). These calculations also indicate that acrolein LUMO energy level decreases when acrolein complexes Li^+, thus inducing an acceleration of the reaction, when compared to the case of no cation complexation.

A comparative study of α-enones reactivity towards 3 and 4 in poorly associating conditions[1,4] showed that the importance of the different factors involved is not the same for the two reagents; the reactivity of 4 attack on α-enones is mainly governed by HOMO–LUMO interactions (HOMO of the anion, LUMO of the enone), though steric effects on carbon 4 and π energy loss have also to be taken into account to interpret the reactions of 3. Therefore the possibility of lithium cation complexation by the α-enone could lead to different results according to the reagent nature.

Therefore, we examine in the present work the reaction of 3 (M=Li) with the α-enones previously studied 1a–i in THF. Moreover, we are hoping eventually to show electrophilic assistance, i.e. acceleration of the reaction due to Li^+ complexation, which could not be seen in the case of 4, as the reaction rates were too high.

Choice of experimental conditions-kinetic control. The mechanisms of the C_2 and C_4 attack processes were developed in our previous papers.[1] We demonstrated, there, that the first step of each reaction pathway is the slow one. To be assured that the reaction is under kinetic control, we have to verify that each of these first steps are irreversible:

C_4 *attack.* We have shown that, as with K^+ as a counterion, C_4 attack is irreversible in the presence of lithium cation.[b]

C_2 *attack.* In our preliminary studies on Horner–Emmons reaction,[6] we noticed that the reversibility factor increases when K^+ is replaced by Li^+, but decreases, whatever the cation is, when reaction temperature is lowered. Therefore, we performed the reaction at −80°C to minimize the reversibility factor. Some experiments were also run, on one hand at 0°C to compare with the results obtained with 3 (M=K), though the reversibility factor cannot be neglected and, on the other hand, at room temperature, as some ketones are not reactive under the previous conditions. In this latter case, kinetic control is

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[a] This work is part of Bernard Deschamps, These d'Etat No. A.O. 12.510.

[b] The C_4 attack product 6 replaced in the presence of *n*-BuLi in THF remains unchanged.

justified *a posteriori*, as we only obtain dienes (see later on).

The products formed in these reactions are noted in Table 1: dienes **5** result from C_2 attack; compounds **6** result from C_4 attack; compounds **7** are formed by a primary C_4 attack followed by a secondary attack of **3** on intermediates **6** (the mechanism of **7** formation is detailed in Ref. 1b). All these products were isolated and identified by ^{1}H NMR, IR and mass spectra. **5a**, **5b**, **5d**, **5e**, **5f**, **5i**, **6a**, **6c**, **7d**, **7e**, **7h** and **8h** are described in Ref. 1; **5g** is described in the experimental part of this paper.

RESULTS

The reactions are run with molar equivalents of α-enone and lithium derivative **3** (prepared by action of *n*-BuLi on phosphonate **2**) in the absence (starting from **1a**, **1b**, **1c**, **1f**, **1g**, **1i**) or in the presence[c] (starting from **1d**, **1e**, **1h**) of one molar equivalent of phosphonate **2**.

We report in the tables the yields of products obtained when the reaction is performed with lithium as a counterion, compared with the experiments performed in the same conditions with potassium as a cation. The yields are determined by ^{1}H NMR using an internal standard (PhCHO).

Changing K^+ to Li^+, we can note that:

(a) no change of regioselectivity is observed, using **1a**, **1c** and **1i**, which are phenyl-substituted on carbon 2 (exp. 3, 10, 16, 19). The reaction rate is slightly decreased.

(b) no change of regioselectivity could be expected using **1f** and **1g**, the carbon 4 of which is disubstituted (exp. 17, 18): as with K^+ as a counterion, C_2 attack is observed; however, we observe an acceleration of the reaction.

(c) with **1b**, **1d**, **1e**, as in the case of **4**, we obtain a mixture of carbonyl and double bond attack products, varying with reaction temperature (exp. 2, 4, 5, 11, 13, 14). The global reaction is accelerated. This overall acceleration is very important for **1d** and **1e** at −80°C.

(d) when **1h** is considered (exp. 8), C_4 attack is always obtained, but the reaction rate is too high to be estimated.

DISCUSSION

Since the reactions are not run under exactly the same conditions, we performed the reaction of **2** with the same α-enones in phase transfer catalysis conditions using tetra-*n*-butylammonium as a large cation. We always observed the same results as with **3** (M=K), showing that the ion pair anion-K can be considered as loose. We also verified that, when the reaction of **3** (M=Li) was run in a THF/HMPA mixture with **1b** at 0°C or **1d** at −80°C, the results (yield and regioselectivity) were the same as when we used K^+ in THF. We can then safely compare the reactivity of **3** (M=K, THF) with these of **4** (M=Li, THF/HMPA). Consequently, in all cases, the reactions can be considered as performed either with a poorly associating cation (**3**, K^+, THF; **4** in THF/HMPA mixture where Li^+ is solvated by HMPA), or in an associating medium (**3** and **4**, Li^+ in THF).

The study of the reaction of phosphonate anion **3** on α-enones showed that the complexation of Li^+ by α-enone can have two effects: a change of regioselectivity and an acceleration of the global reaction.

These enones can be classified into three groups:

(a) When their carbonyl carbon bear a phenyl group, there is no Li^+ complexation.[d] No change of regioselectivity is observed whatever anionic reagent is: C_4 attack always takes place (except for dypnone **1i** which is a C_4 disubstituted enone: see later on). The reaction rate decreases changing K^+ to Li^+: the ion pair anion–Li^+ can be tighter than the anion–K^+ one, then slightly less reactive.[7,8]

(b) When their carbon 4 is disubstituted,1-2 addition always takes place, C_4 attack never occurs: steric hindrance is the predominating phenomenon inhibiting it. It is very different from Sauvetre and Seyden-Penne results[4] who showed that it has no influence in the reaction of **4**. Electrophilic assistance is observed: when lithium cation is involved reactions are accelerated.

(c) In the other cases, concerning regioselectivity change, while the results were very clear starting from **4** (this reagent gives only C_4 attack in strongly cation solvating medium, and, C_2 and C_4 attack in associating conditions, 1-2 attack then being favoured as expected), they are more complicated starting from **3**.[e] As a matter of fact, when changing medium, we always observe, as in the case of **4**, an increase of 1-2 products ratios, but we sometimes observe a more important increase in C_4 attack ratio (starting from **1e** at −80°C or **1b** at 0°C). With **3** (M=Li), decreasing reaction temperature, we observe an increase of carbonyl attack for **1b** and **1d**, but an increase of double bond attack for **1e**. Particularly, **1d** and **1e** have different behaviour in the case of Li^+, while they behave the same in the case of K^+. It is known that these two enones can present a geometry difference: **1e** reacts only under a *s-trans* conformation while **1d** can react under a *s-cis* conformation, which can modify the mechanism (cyclic or not cyclic) of C_2 and C_4 attack.

For these enones, electrophilic assistance occurs: the global reaction is accelerated. The complexation of Li^+ by α-enones favours carbonyl attack as well as double bond attack according to the enone, though calculations[5] predicted a greater 1-2 process acceleration than a C_4 one. Double bond attack rate also increased when **4** was opposed to isophoron **1g**, when complexation takes place.

We'll not discuss the case of cyclopentenone **1h**, as the reaction is too fast, whatever the conditions are.[f]

Calculations do not seem sufficient to completely explain and predict the reactivity of **3** towards all the α-enones.

Synthetic applications. Dienes are synthetized using *n*-BuLi at −80°C (for **5b** and **5d**), 0°C (for **5e**) and 20°C (for **5f**, **5g** and **5i**). Double bond attack products **6a** and **6c** are obtained using *t*-BuOK (or *n*-BuLi for **6c**) at 0°C. Compounds **7d** and **7e** resulting from a C_4 attack (leading to compounds as **6**) followed by a secondary attack of the anion **3** on the carbonyl of **6**, are synthetized using *t*-BuOK at 0°C.

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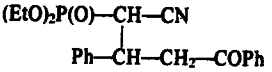
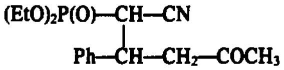
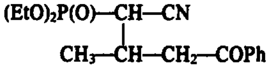
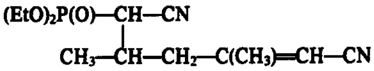
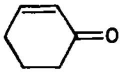
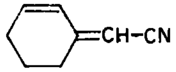
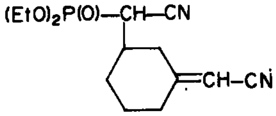
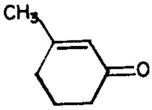
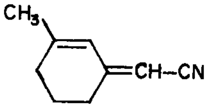
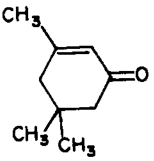
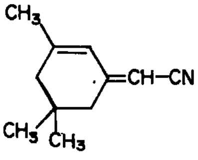
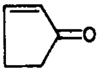
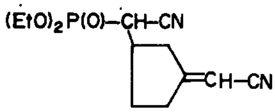
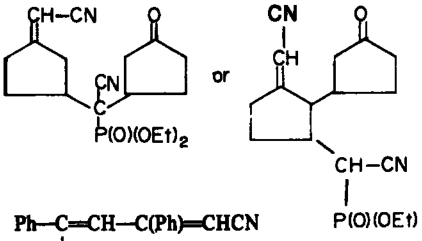
[c] The excess of **2** is necessary when the primary C_4 attack is followed by a secondary carbonyl attack leading to compounds **7**.

[d] Some studies by physico-chemistry methods showed that the carbonyl of these phenones was less basic than ketones which have no phenyl substituent.[9]

[e] The difference of regioselectivity between **3** (M=K) and **3** (M=Li) cannot be attributed to a difference of structure of these two species. Bottin, Seyden-Penne and Simmonin[10] demonstrated that the structure of **3** is nearly the same if it is associated to K^+ or Li^+.

[f] The greatest reactivity of cyclopentenone has also been observed with others nucleophiles such as **4** or hydrides.

Table 1.

α-Enone	Products formed at the time of the reaction of 3 (M=Li)
1a Ph-CH=CH-COPh	6a  $\begin{array}{l}(EtO)_2P(O){-}CH{-}CN\\ \qquad\qquad\ \mid\\ \quad Ph{-}CH{-}CH_2{-}COPh\end{array}$
1b Ph-CH=CH-COCH$_3$	5b Ph—CH=CH—C(CH$_3$)=CH—CN
	6b  $\begin{array}{l}(EtO)_2P(O){-}CH{-}CN\\ \qquad\qquad\ \mid\\ \quad Ph{-}CH{-}CH_2{-}COCH_3\end{array}$
1c CH$_3$-CH=CH-COPh	6c  $\begin{array}{l}(EtO)_2P(O){-}CH{-}CN\\ \qquad\qquad\ \mid\\ \quad CH_3{-}CH{-}CH_2{-}COPh\end{array}$
1d CH$_3$-CH=CH-COCH$_3$	5d CH$_3$—CH=CH—C(CH$_3$)=CH—CN
	7d  $\begin{array}{l}(EtO)_2P(O){-}CH{-}CN\\ \qquad\qquad\ \mid\\ \quad CH_3{-}CH{-}CH_2{-}C(CH_3){=}CH{-}CN\end{array}$
1e 	5e 
	7e 
1f 	5f 
1g 	5g 
1h 	7h 
	8h 
1i Ph-C(CH$_3$)=CH-COPh	5i $\begin{array}{l}Ph{-}C{=}CH{-}C(Ph){=}CHCN\\ \quad\ \mid\\ \quad CH_3\end{array}$

CONCLUSIONS

Complexation is then a further factor which influences the regioselectivity of nucleophilic reagents attack on α-enones under orbital control. It must be added to those described in our previous papers,[1] ie.

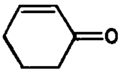
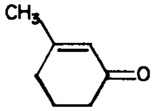
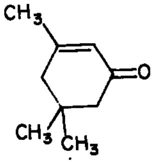
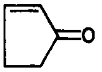
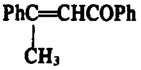
HOMO–LUMO interactions. The double bond attack rate increases when the difference between the nucleophilic reagent's HOMO energy level and the enone's LUMO one decreases.

π Energy loss. When the carbon 4 of α-enone bears a conjugated substituent such as an aryl, attack of the double bond promotes π conjugation breaking and the energy loss may lead to a decrease of reaction rate.

Steric effect. When the carbon 4 of α-enone is disubstituted, the C$_4$ attack may be slowed.

When electrophilic assistance is involved (if lithium cation is complexed by α-enone), the global reaction rate increases. This acceleration is observed for carbonyl attack, as expected, and also in some cases for double bond attack. In some, but not all cases, reversal of reacting sites does occur. When electrophilic assistance does not take place (no complexation of the cation by enone), the factors determining the regioselectivity depend on the anion nature, as previously proposed;[1,4] they are only HOMO–LUMO interactions for 4, π energy loss and C$_4$ steric hindrance added to HOMO–

Table 2. Yields of products formed from 3 after 5 min reaction at −80°C (completion to 100% is starting α-enone)

α-Enone	Exp.	Li⁺ Global yield %	Li⁺ C_4 products %	Li⁺ C_2 products %	K⁺ Global yield %	K⁺ C_4 products %	K⁺ C_2 products %
1a $PhCH{=}CHCOPh$	1	0	0	0	0	0	0
1b $PhCH{=}CHCOCH_3$	2	20	0	**5b**: 20	5	0	**5b**: 5
1c $CH_3CH{=}CHCOPh$	3	30	**6c**: 30	0	50	**6c**: 50	0
1d $CH_3CH{=}CHCOCH_3$	4	35	**7d**: 7	**5d**: 28	0	0	0
1e 	5	50	**7e**: 40	**5e**: 10	0	0	0
1f 	6	0	0	0	0	0	0
1g 	7	0	0	0	0	0	0
1h 	8	100	**7h** + **8h**: 100	0	100	**7h** + **8h**: 100	0
1i  $Ph\underset{CH_3}{C}{=}CHCOPh$	9	0	0	0	0	0	0

We indicate 0 when no product can be detected in NMR.

Table 3. Yields of products formed from 3 after 2 min reaction at 0°C (completion to 100% is starting α-enone)

α-Enone	Exp.	Li⁺ Global yield %	Li⁺ %C_4 products	Li⁺ %C_2 products	K⁺ Global yield %	K⁺ %C_4 products	K⁺ %C_2 products
1a	10	0	0	0	0	0	0
1b	11	55	**6b**: 20	**5b**: 35	25	**6b**: 5	**5b**: 20
1c	12	100	**6c**: 100	0	100	**6c**: 100	0
1d	13	65	**7d**: 50	**5d**: 15	50	**7d**: 40	**5d**: 10
1e	14	70	**7e**: 15	**5e**: 55	50	**7e**: 50	0
1f	15	0	0	0	0	0	0

We indicate 0 when no product can be detected in NMR.

Table 4. Yields of products formed from 3 after 60 min reaction at 20°C (completion to 100% is starting enone)

α-Enone	Exp.	Li⁺ C_4 products yield %	Li⁺ C_2 products yield %	K⁺ C_4 products yield %	K⁺ C_2 products yield %
1a	16	**6a**: 35	0	**6a**: 95	0
1f	17	0	**5f**: 80	0	**5f**: 60
1g	18	0	**5g**: 30	0	0
1i	19	0	**5i**: 30	0	**5i**: 45

We indicate 0 when no product can be detected in NMR.

LUMO interactions for 3. In the first case, the reaction transition state can be considered as "reactant like"; in the later case, it does not occur so early in the reaction path, the steric effect being important and the great influence of π energy loss involving an enone hybridization change. As for cycloadditions, examined by Huisgen,[11] the double bond reactivity of α-enones can bring us precious informations on the position of transition state on the reaction coordinates.

EXPERIMENTAL

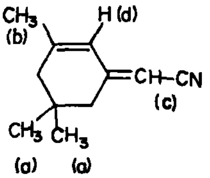
NMR spectra were performed on Varian A 60 D or T 60 in CCl_4 (TMS internal standard). We quote analysis when a correct microanalysis corresponds to a new compound. THF was purified by distillation over KOH then over LiAlH$_4$.

Starting materials. Phosphonate **2** was prepared according to Ref. 12. Compounds: **1a**: Fluka product, recrystallized from EtOH (F = 54°C); **1b**: Fluka product recrystallized from hexane (F = 36°C); **1c**: was prepared according to Ref. 13; **1d**: Aldrich product redistilled (Eb$_{760\ \mathrm{mm\ Hg}}$ = 124°C); **1e** and **1h**: KEK products; **1f**: was prepared according to Ref. 14 and distilled (Eb$_{24\ \mathrm{mm\ Hg}}$ = 83°C); **1g**: Schuchart product; **1l**: its synthesis is described in Ref. 1a.

General technique. To 5×10^{-3} mole *t*-BuOK or *n*-BuLi in 40 ml THF at variable temperature, 5×10^{-3} mole phosphonate **2** (in the case of **1a**, **1b**, **1c**, **1f**, **1g** and **1l**) or 10^{-2} mole **2** (in the case of **1d**, **1e** and **1h**) was added. The mixture was stirred under nitrogen during 30 min, 5×10^{-3} mole α-enone was then added. After variable reaction time, were added water, ether and eventually an internal standard (PhCHO) for quantitative determinations. The organic layer was separated, washed three times with water and dried over sodium sulfate. The solvent was evaporated and the crude mixture analysed by ^{1}H NMR in CCl$_4$.

Reactions in phase transfer catalysis conditions. To a solution of tetra *n*-butyl ammonium bromide (10^{-2} mole) in 0.5 N aqueous sodium hydroxide (50 ml) is added a solution of phosphonate **2** (10^{-2} mole) and α-enone (10^{-2} mole) in dichloromethane (50 ml). The mixture is stirred at room temperature for 1 h with **1d**, **1e**, **1h** and 6 h with **1a** and **1b**. The organic layer is separated, washed with water and dried over sodium sulfate. The reaction product is analysed as previously done. We obtain the same products as with *t*-BuOK as a base, but the reaction conditions are not so drastic as with *t*-BuOK (while the reaction with **1h** must be performed with *t*-BuOK at −80°C to avoid polymerization of the α-enone, it occurs at room temperature in phase transfer catalysis conditions).

Description of compounds. **5b**, **5d**, **5e**, **5f**, **5l**, **6a**, **6c**, **7d**, **7e**, **7h** and **8h** are described in Ref. 1. New compound: **5g**, separated by thick layer chromatography over SiO$_2$. Elution by a mixture hexane 95–ether 5. *Analysis.* ^{1}H NMR: (a) s, δ = 0.83 ppm for one isomer and 0.87 ppm for the other isomer; (b) s, δ = 1.83 ppm; (c) broad s, δ = 4.85 ppm for one isomer and 4.93 ppm for the other; (d) broad s, δ = 5.94 ppm for one isomer and 6.30 ppm for the other.



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