Journal of Organometallic Chemistry 177 (1979) 17—26

ADDITION OF LITHIATED ANIONS FROM ARYLACETONITRILES TO α,β-UNSATURATED ALDEHYDES. SOLVENT EFFECT ON 1,2 VERSUS 1,4 ADDITION UNDER KINETIC AND/OR THERMODYNAMIC CONTROL *

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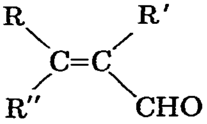
(Received April 2nd 1979)

Summary

In THF at —70° C lithiated anions from arylacetonitriles undergo exclusively 1,2 addition to α,β-unsaturated aldehydes under kinetically controlled conditions, while 1,4 addition can be observed in some cases under thermodynamically controlled conditions at higher temperature. In THF/HMPA at —70° C, competitive 1,2 and 1,4 additions take place in nearly all cases examined. when starting from a *p*-methoxy-substituted reagent, both reactions are kinetically controlled, while with unsubstituted and *m*-chloro-substituted reagents, kinetic and/or thermodynamic control of 1,4 addition occurs The application of this reaction to synthesis of γ-cyanoaldehydes is considered

Introduction

It is generally admitted [1,2] that organolithium reagents undergo 1,2 addition to α,β-unsaturated carbonyl compounds As α,β-unsaturated aldehydes of type I are more susceptible to 1,2 additions than α,β-unsaturated ketones [1,3] there are only a few examples in the literature of 1,4 additions to these compounds, either via Michael type reactions [4], Grignard reagents [5] or organocuprate additions [6] To our knowledge, only a single example of 1,4 addition of an organolithium reagent to α,β-unsaturated aldehydes has been postulated recently by Taschner and Kraus [7] as an intermediate process



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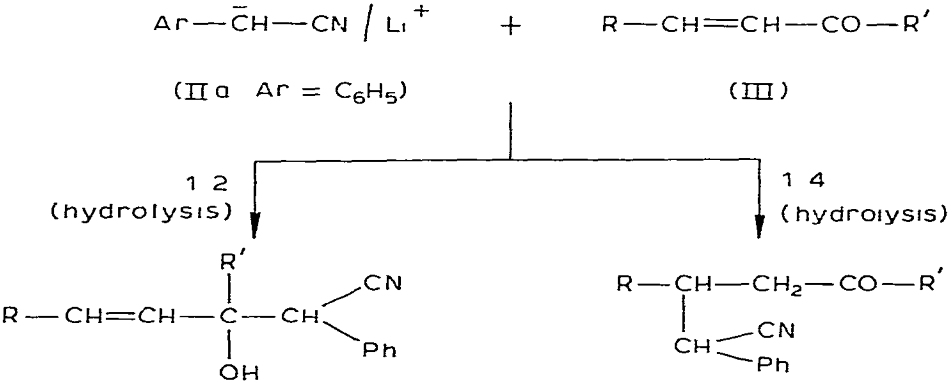
* Dédié au Professeur H Normant à l'occasion de son 72ème anniversaire le 25 juin 1979

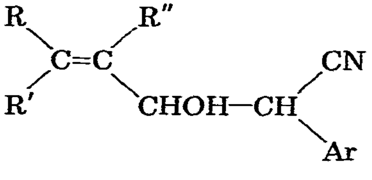
We have examined previously the reactions of lithiated phenylacetonitrile IIa with α-enones III [8] We noticed that 1 2 addition products can be obtained in diethylether or tetrahydrofuran (THF) at —70° C together with 1.4 addition products; however only 1,4 addition takes place in THF/hexamethylphosphotriamide (HMPA) mixtures (Scheme 1) Therefore. it seemed worthwhile to study the reactions of the same species (IIa). as well as those of electron-donating or electron-withdrawing substituted derivatives (i e *p*-methoxy (IIb) and *m*-chloro (IIc) analogs) with α,β-unsaturated aldehydes (I) We selected the following aldehydes crotonaldehyde (Ia. R = CH_3, R' = R'' = H), cinnamaldehyde (Ib R = Ph, R' = R'' = H), 3-methyl-2-butenal (Ic R = R' = CH_3, R'' = H) and methacrolein (Id· R = R' = H, R'' = CH_3).



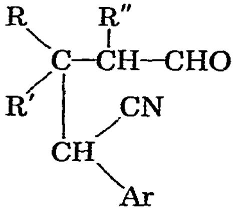
In our previous work [8], we showed that the 1,2 addition process is reversible at —70° C in THF and in THF/HMPA so that the 1,4 adduct could be formed in both cases under thermodynamic control. Therefore, we shall also examine the possibility of kinetic and/or thermodynamic control of the reactions studied.

Results

The reactions were carried out at —70° C and quenched by the addition of acid. The expected products are secondary allylic alcohols (IV· Ar = C_6H_5, V Ar = *p*-$CH_3OC_6H_4$ and VI: Ar = *m*-ClC_6H_4) resulting from 1,2 addition, and γ-cyanoaldehydes (VII. Ar = C_6H_5; VIII· Ar = *p*-$CH_3OC_6H_4$ and IX. Ar = *m*-ClC_6H_4) resulting from 1,4 addition



(IV, V, VI)



(VII, VIII, IX)

(a: R=CH_3, R'=R''=H; b: R=Ph, R'=R''=H, c. R=R'=CH_3, R''=H, d: R=R'=H, R''=CH_3)

TABLE 1

REACTION OF UNSATURATED ALDEHYDES I WITH LITHIATED ARYLACETONITRILES II (30 min at −70° C in THF/HMPA 80/20 v/v)

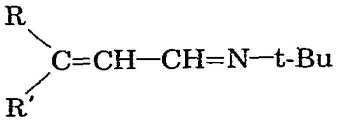
Run number	Starting aldehyde	Reagent	Total yield (%) [a]	1 2/1 4
1	Ia	IIa	75	IVa/VIIa 65/35
2		IIb	75	Va/VIIIa 55/45
3		IIc	55	VIa/IXa 35/65
4	Ib	IIa	75	IVb/VIIb 65/35
5		IIb	85	Vb/VIIIb 70/30
6	Ic	IIa	90	IVc/VIIc 75/25
7		IIb	$\geqslant$95	Vc/VIIIc >95/5
8	Id	IIa	80	IVa/VIId 25/75
9		IIb	$\geqslant$95	Vd/VIII 60/40
10		IIc	80	VId/IXd 15/85

[a] With respect to starting material (100%)

When the reactions were run in THF for 10 to 90 min only allylic alcohols IV, V and VIa—d were obtained with $\geqslant$80% yield as mixtures of *RS,RS* and *RS,SR* diastereoisomers which were detected by ^{1}H NMR but were not separated Their structure was assigned by IR (ν(OH) 3450, ν(C=C) 1620 and ν(C≡N) 2250 cm^{-1}) ^{1}H NMR (CHOH ca 4,5 and vinylic protons between 5 and 7 ppm), and mass spectroscopy after thick layer chromatographic purification Whatever the reaction time ($\leqslant$90 min), no compound other than IV, V, VI, and occasionally the starting materials, could be detected

When the reactions were run for 30 min in THF/HMPA (80/20 v/v), a mixture of diastereoisomeric allylic alcohols IV, V, VI and diastereoisomeric cyanoaldehydes VII, VIII, IX was obtained in nearly all cases The results are given in Table 1

For identification purposes, compounds VIIa and b, VIIIa, b and c and IXa were prepared by treating the corresponding α,β-unsaturated imines X with reagents IIa, b and c in THF/HMPA, followed by treatment with acid [9] They were also obtained eventually as mixtures of *RS,RS* and *RS,SR* stereoisomers which were not separated VIIc, IXb and IXc could not be obtained by this



$RR'C{=}CH{-}CH{=}N{-}t\text{-}Bu$

(X)

method however as the reaction does not work properly in these cases [9] and until now we had not tried to perform the reaction using the imine of methacrolein (Id)

The other γ-cyanoaldehydes (VIIc, VIId, VIIId and IXd) were obtained in a nearly pure form by thick layer chromatography of the reaction mixtures on SiO_2. They were identified by IR (ν(C=O) 1720, ν(C≡N) 2250 cm^{-1}) and ^{1}H NMR (δ(CHO) ca 9 5 ppm) The yields in allylic alcohols and γ-cyanoalde-

TABLE 2

REACTION OF UNSATURATED ALDEHYDES WITH LITHIATED ARYLACETONITRILES IN THF AT —70°C FOR 30 MIN FOLLOWED BY ADDITION OF HMPA AND FURTHER REACTION FOR 30 MIN AT —70°

Run number	Starting aldehyde	Reagent	1,2/1,4
11		IIa	IVa/VIIa 85/15 [a]
12	Ia	IIb	Va/VIIIa >95/5
13		IIc	VIa/IXa 75/25 [a]
14	Ib	IIa	IVb/VIIb 90/10
15		IIb	Vb/VIIIb >95/5
16	Ic	IIa	IVc/VIIc >95/5
17		IIb	Vc/VIIIc >95/5
18		IIa	IVd/VIId 65/35 [a]
19	Id	IIb	Vd/VIIId >95/5
20		IIc	VId/IXd 15/85

[a] Some arylacetonitrile is also present in the reaction mixture

hydes were determined by ^{1}H NMR (integration of the CH—OH and CHO proton signals, internal standard aromatic protons) The reactions of the *m*-chlorosubstituted reagent IIc and cinnamaldehyde Ib or 3-methyl-2-butenal Ic did not give good results, some experiments using acrolein give mainly polymers

From Table 1, it appears that significant amounts of 1,4 addition products are obtained except in the reaction of IIb with aldehyde Ic (run 7)

In order to check the eventual reversibility of 1,2 addition, we carried out the reactions for 30 min in THF at —70°C (conditions under which the allylic lithium alcoholates corresponding to IV, V and VI are formed in ⩾80% yield), then added HMPA and stirred the reaction mixture for a further 30 min at —70°C. It was then quenched and analyzed as previously The results are given in Table 2.

It appears that, in the presence of HMPA at —70°C, no conversion takes place for the *p*-methoxy lithiated derivatives (runs 12, 15, 17 and 19) For the unsubstituted derivatives, a slight conversion is noticed (except in run 16) as some γ-cyanoaldehyde is formed (runs 11, 14 and 18) as well as starting arylacetonitrile (runs 11 and 18), while with the *m*-chlorosubstituted ones complete conversion takes place (runs 13 and 20) γ-cyanoaldehydes are formed in 30 to 60% yield accompanied by *m*-chlorophenylacetonitrile (run 13)

We also performed two experiments in THF at —70°C and then raised the temperature to —30°C for 1 h without adding any other solvent under these conditions, and using methacrolein Id and anionic reagents IIa or IIc, we only obtained γ-cyanoaldehydes VIId and IXd (yield 70—75%), with no allylic alcohol.

Discussion

Reversibility of the 1,2 addition

It is known that addition of allylic Grignard, organolithium or organozinc reagents to simple carbonyl compounds can be reversible [10], as can Reformatsky [11] and Ivanov [12] reactions and the 1,2 additions of some charge delocalized organolithium reagents to α-enones [8,13,14] Furthermore, reversibility is favoured in the presence of dipolar aprotic solvents or on raising the temperature [8,10,11,14]

From our results, it appears that 1,2 addition of lithiated arylacetonitriles IIa, b and c to α,β-unsaturated aldehydes I is irreversible in THF at —70°C as only allylic alcohols are obtained whatever the reaction time (30 to 90 min.). This is contradictory to our earlier results on the reaction of IIa with 2-cyclohexenone under the same temperature and time conditions, we showed the reversibility of addition to the C=O bond and the formation of a 1,4 adduct under thermodynamic control However, this lack of reversibility of formation of secondary alcoholates (from unsaturated aldehydes) compared with tertiary alcoholates (from α-enones) is in line with other literature results. Miginiac [10a] and Jacques [15] showed that the reactions of allylic organozinc derivatives and of Reformatsky-like reagents are much less reversible when performed with aldehydes than with ketones

The addition of HMPA, at —70°C, to allylic lithium alcoholates corresponding to IV and VI formed in THF, leads partly to 1,4 adducts and partly to starting arylacetonitriles in the case of unsubstituted or *m*-chloro-substituted derivatives (except for Ic (run 16)) These results show that 1,2 addition is partly reversible under these conditions For the reaction of 2-cyclohexenone and IIa [8] under similar conditions, we observed previously quantitative transformation of the 1,2 adduct to the 1,4 one Again, this comparison is in line with the previous results (vide supra) indicating the less important reversibility of formation of secondary lithium alcoholates compared with tertiary ones.

However, the *p*-methoxy-substituted lithium alcoholates corresponding to V remain unchanged at —70°C in this solvent mixture. Therefore, when starting from the electron-donating substituted reagent IIb 1,2 addition is irreversible under these conditions. The same observation is also valid for the reaction of 3-methyl-2-butenal (Ic) and the lithiated anion of phenylacetonitrile (IIa) (run 16)

To our knowledge this is the first time that the influence of the aromatic ring substituent of such a nucleophile on the reversibility of its condensation to carbonyl compounds has been demonstrated However, electron-withdrawing substituents on the aromatic ring of acetophenones are known to favour the reversibility of the Reformatsky reaction [16].

It is generally admitted that the transition state for the condensation of organolithium or Grignard reagents with carbonyl compounds is a reagent-like species [17a] and according to the microreversibility principle, the transition state of the retroprocess must have the same characteristics [17b] Thus, the more stable the anionic species, the more stable this transition state while at the same time the stability of the various lithium alcoholates is probably weakly affected by the substituent of the aryl ring. Therefore, the more stable the anionic species [*], the faster the retrocondensation.

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[*] The stabilization of the anionic species parallels its pK_a in DMSO the values for pK_a are IIa 22 2 IIb 23 4 and IIc 18 6 [18]

The two experiments run from methacrolein Id with IIa and IIc in pure THF, show that raising the temperature induces (as previously observed in related cases [8,14]), the formation of 1,4 adducts VIId—IXd thus increasing the reversibility of the 1,2 addition

1,2/1,4 addition kinetic versus thermodynamic control

In THF at —70° C, only 1,2 addition takes place with α,β-unsaturated aldehydes I whatever the anionic reagent (IIa, IIb or IIc) This reaction occurs under kinetic control, as no reversibility has been shown This is different from the results we previously obtained with IIa and 2-cyclohexenone in which 1,2 and 1,4 additions took place under the same conditions [8] This result was not unexpected, as it is well documented that α,β-unsaturated aldehydes are more susceptible to 1,2 additions than α-enones [1,3]

In THF/HMPA, at —70° C, kinetic control is also ensured for the reactions of lithiated *p*-methoxyphenyl acetonitrile IIb as the formation of allylic lithium alcoholates is irreversible Therefore, the formation of 1,4 adducts leading to γ-cyanoaldehydes VIIIa, b and d does take place under kinetic control [13], with concomittant 1,2 addition. This is in line with the theoretical approach to the question of 1,2 versus 1,4 addition to α,β-unsaturated carbonyl compounds [19,20]: Li^+ complexation by the C=O of the carbonyl compound favours 1,2 addition [19] In a strongly Li^+-solvating medium, where such a complexation is not possible, more 1,4 addition is to be expected [19,20]

However, from 3-methyl-2-butenal Ic only 1,2 addition is observed, showing the effect of substitution of the carbon—carbon double bond

Starting from the unsubstituted reagent IIa or from the *m*-chloro-substituted derivative IIc, in THF/HMPA at —70° C the formation of γ-cyanoaldehydes VII and IX can take place under kinetic and/or thermodynamic control as we have demonstrated the reversibility of the 1,2 addition under those conditions Furthermore, raising the temperature to —30° C in pure THF when the reaction is performed with methacrolein Id, induces 1,4 addition under thermodynamic control, allowing the synthesis of γ-cyanoaldehydes VIId and IXd with good yields. This synthetic method is actually being put to general use [9]

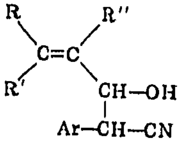
Conclusion

We have been able to demonstrate the formation of γ-cyanoaldehydes VIIa—d, VIIIa, b and d, and IXa and d by 1,4 addition of lithiated arylacetonitriles IIa, b and c to α,β-unsaturated aldehydes Ia—d in THF/HMPA at —70° C Depending on the electron donating or electron withdrawing character of the aromatic substituent of the carbanionic reagent, 1,4 addition takes place under kinetic and/or thermodynamic control This is one of the first examples of 1,4 addition of lithiated carbanionic species to α,β-unsaturated carbonyl compounds under kinetic control [13] Application of the reaction to the synthesis of some γ-cyanoaldehydes is under investigation.

Experimental

The solvents were purified by careful distillation over $LiAlH_4$ (THF) or CaH_2 (HMPT) under nitrogen. The IR spectra were run on a Perkin Elmer 157 spec-

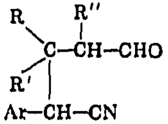
TABLE 3



Product	RF	δ(R) [a]	δ(R')	δ(R'')	δ(CH—CN)	δ(CH—OH)	δ(Ar)	δ(OCH$_3$)
IVa	0 50	1 63(d)(^3J 7 Hz)	5 5(m)		3 7(d)(^3J 6 Hz)	4 25(m)	7 26(s, br)	
					3 9(d)(^3J 7 Hz)			
Va	0 63	1 66(d)(^3J 7 Hz)	5 5(m)		3 7(d)(^3J 6 Hz)	4 15(m)	6 93(q)	3 73(s)
VIa	0 38	1 66(d)(^3J 7 Hz)	5 46(m)		3 83(d)(^3J 6 Hz)	4 2(m)	7 16(s, br)	
IVb	0 4	7 2(m)		6 13(m)	3 46(d)(^3J 6 Hz)	4 5(t)	7 2(s, br)	
Vb	0 45	7 1(m)		6 73(m)	3 9(d)(^3J 6 Hz)	4 5(m)	6 9(q)	3 70(s)
IVc	0 52	1 23(s) and 2 3(s)		5 3(d)(^3J 6 Hz)	4(d)(^3J 6 Hz)	4 6(t)	7 26(s, br)	
		1 36(s) and 2 3(s)		5 16(d)(^3J 7 Hz)	3 76(d)(^3J 7 Hz)	1 55(t)(^3J 7 Hz)		
Vc	0 6	1 43(s) and 1 66(s)		5 13(d)(^3J 8 Hz)	3 6	4.4(m)	6 9(q)	3 65(s)
		1 26(s) and 1 66(s)		5 3				
IVd	0 47	4 80(s, br)		1 63(s)	3 5(d)(^3J 6 Hz)	4 2(d)(^3J 6 Hz)	7 2(s, br)	
Vd	0 27	4 80(s, br)		1 63(s)	3 76(d)(^3J 6 Hz)	4 16(d)(^3J 6 Hz)	6 9(q)	3 66(s)
VId	0 37	4 80(s, br)		1 65(s)	3 80(d)(^3J 6 Hz)	4 16(d)(^3J 6 Hz)	7 1(s, br)	

[a] Chemical shifts (δ) are given in ppm

TABLE 4



Product	RF	δ(R) [a]	δ(R')	δ(R'')	δ(CH–R'')	δ(CH–CN)	δ(CHO)	δ(Ar)	δ(OCH$_3$)
VIIa	0 36	1(d)(^3J 7 Hz) 0 9(d)(^3J 7 Hz)	2,52(m)		2 5(m)	3 8(d)(^3J 6 Hz) 3 9(d)(^3J 6 Hz)	9 16(s) 9 56(s)	7 26(s, br)	
VIIIb	0 36	1(d)(^3J 7 Hz) 0 9(d)(^3J 7 Hz)	2 50(m)		2 50(m)	3 6(d)(^3J 6 Hz)	9 44(s) 9 55(s)	6 9(q)	3 66(s)
IXa	0 4	1 06(d)(^3J 7 Hz) 0 93(d)(^3J 7 Hz)	2 6(m)		2 6(m)	3 8(d)(^3J 6 Hz) 4(d)(^3J 6 Hz)	9 73(s) 9 80(s)	7 2(s, br)	
VIIb	0 53	7,2	3 4(m)		3(m)	4 2(d)(^3J 6 Hz) 4(d)(^3J 6 Hz)	9 50(s) 9 43(s)	7 2(s br)	
VIIIb	0 35	7 2	3 65(m)		3 1(m) 2 7(m)	4 2(d)(^3J 6 Hz) 4(d)(^3J 6 Hz)	9 66(s) 9 76	6 9(q)	3 7(s)
VIIc	0 51	1 05(s) and 1 17(s)			2 38(m)	4(s)	9 66(t)(^3J 2 5 Hz)		
VIIIc	0,34	1 11(s) and 1 27(s)			2 30(m)	3 93(s)	9 67(t)(^3J 2 5 Hz)	7(q)	3 88(s)
VIId	0 55	2(m)		1 20(d)(^3J 7 Hz)		3 7(m)	9 55(s) 9 65(s)	7 2(s br)	
VIIId	0 26	2(m)		1 20(d)(^3J 7 Hz)		3 8(m)	9 55(s) 9 60(s)	6 95(q)	3 75(s)
IXd	0 41	1 8(m)		1 20(d)(^3J 7 Hz)		3 7(m)	9 55(s) 9 65(s)	7 2(s, br)	

[a] Chemical shifts (δ) are given in ppm

trophotometer and NMR spectra on Varian T-60 in CCl_4 or $CDCl_3$ (TMS as internal standard) except in the cases of VIIc and VIIIc which were measured on a Bruckner 90 MH spectrometer in $CDCl_3$.

General technique

n-BuLi (5×10^{-3} mol in hexane) was added to 5×10^{-3} mol arylacetonitrile dissolved in 25 cm^3 THF or 25 cm^3 THF/HMPA (80/20 v/v) under argon at −70°C After 15—20 min stirring, 5×10^{-3} mol aldehyde dissolved in 3—5 cm^3 THF was added from a syringe via a rubber septum, while the temperature was maintained at −70°C After 30 min of further stirring, hydrolysis was carried out by rapid quenching with 10% aqueous HCl Ether extraction was followed by washing with NaCl-saturated water The organic layer was separated, dried over $MgSO_4$, and the solvent evaporated The crude product was analyzed by IR and NMR

Final purification of the compounds was carried out by thick layer chromatography on SiO_2 (eluant ether (60)/hexane (40)). The IR characteristics are in the text All the compounds gave satisfactory mass spectra ^1H NMR data and R_FH (SiO_2) of compounds IV, V and VI, and VII, VIII and IX are given in Tables 3 and 4

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