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AMINONITRILE AND CYANOHYDRIN ETHERS AS BENZOYL ANION EQUIVALENTS IN CONJUGATE ADDITIONS TO SUBSTITUTED α CYCLENONES : COMPARATIVE SYNTHETIC POTENTIALITIES.

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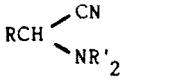
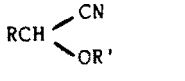
Abstract - Lithiated aminonitrile 1a and cyanohydrin ether 2a are good nucleophilic benzoyl equivalents in conjugate addition to α cyclenones. 1a is more sensitive to β substitution of the cyclenone than 2a, as in THF it does not react with 3-methyl substituted cyclohexenones 6a, b. From 2-methyl and 2-fluorocyclenones and 1a or 2a, cis 2-substituted 3-benzoylcyclanones are stereoselectively obtained, provided that mild unmasking conditions were used. The intermediate enolates trapping, leading to trans 2-substituted 3-benzoylcyclanones, is discussed, according to the nucleophilic reagent and the alkylating agent nature. A comparison with silyl ether cyanohydrin 2b shows the broader synthetic usefulness of 1a and 2a.

The use of masked acyl anion equivalents in the formation of carbon-carbon bonds has been shown as a powerful method in the development of synthesis strategies. Among the proposed reagents, N-dialkylaminonitriles 1 and protected cyanohydrins 2 have the advantage of the easy unmasking of the protected keto functionality [1].



1 a R = Ph
R' = CH_3

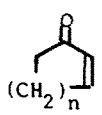


2 a R = Ph
R' = $CH(CH_3)OC_2H_5$
b R = Ph
R' = $SiMe_3$
c R = Ph
R' = CH_3

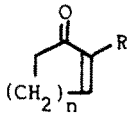
Few studies were previously published on conjugate additions of such reagents to α,β-unsaturated compounds [1], However, as Albright quoted, "Michael additions of α-aryldialkylaminoacetonitriles to cyclic α,β-unsaturated enones are unreported" and "studies comparing anions of protected cyanohydrins and anions of α-dialkylaminonitriles under similar reaction conditions have not been reported" : this is the purpose of the present work. Since Albright's review publication, three papers [2-4] on the reaction of anions of aminonitriles towards cyclic α enones appeared, in addition to those devoted to similar reactions from cyanohydrin ethers and an aminonitrile in aprotic conditions [5-8].

In the present study, the synthetic potentialities of aminonitrile 1a and cyanohydrin ether 2a, which are benzoyl equivalents, towards several differently substituted cyclic

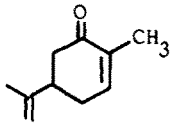
α-enones 3 - 7 will be compared [8c].



3 a n = 1
b n = 2
c n = 3



4 a n = 1 R = CH_3
b n = 2 R = CH_3
c n = 3 R = CH_3
d n = 3 R = F



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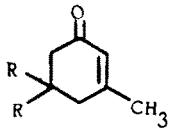
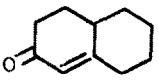


6 a R = H
b R = CH_3



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The results obtained will be also compared to those of Hünig and coworkers [6a], using 2b and ours using 2c [8b].

As aprotic conditions allow the "one pot" formation of two C-C bonds by trapping of the enolates formed after conjugate addition by alkylating agents, this possibility will also be examined : the interest of such a process when using cuprates has been emphasized in a recent review [9]. In the present case, as lithium enolates are formed without any other salt, the solvent problem frequently met with cuprates, is easily solved [10].

1 - Results

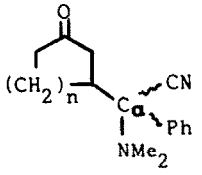
a) Conjugate addition - protonation.

The carbanionic reagents were generated in tetrahydrofuran (THF) at -78°C using either nBuLi in hexane or tBuLi in hexane as bases instead of LDA [5].

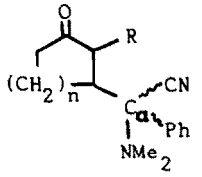
After addition of equimolar amounts of 2-cyclenone 3 - 7, the reaction was run at -78°C until completion, then quenched by a saturated aqueous NH_4Cl solution at low temperature and extracted by Et_2O. When the reaction was carried out from aminonitrile 1a, the products formed were either characterized before unmasking, or treated by an aqueous $AgNO_3$ solution (method A) [11] to regenerate the keto group. From cyanohydrin ether 2a, the ^1H spectrum of the crude reaction mixture is too complicated for analysis ; therefore, the keto group was unmasked either by H_2SO_4/EtOH followed by aqueous HONa according to literature [5,12] (method B) or by wet silica gel [13] followed by aqueous $NaHCO_3$ (method C). The results are in Table 1.

Identification of the products.

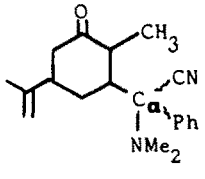
From aminonitrile 1a, ketonitriles 8 - 10 were only obtained : they were characterized by IR (ν_{CO}, ν_{CN}), ^1H and in some cases ^{13}C NMR, elemental analysis or mass spectra. 8a,



8 a n = 1
b n = 2
c n = 3



9 a n = 1 R = CH_3
b n = 2 R = CH_3
c n = 3 R = CH_3
d n = 3 R = F



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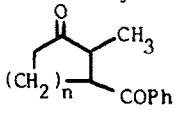
8b and 8c were mixtures of stereoisomers around C_3C_α as shown by ^{13}C NMR. 9a was a 1:1 mixture of stereoisomers around C_3C_α, with a cis relationship between the C_2 and C_3 substituents as shown by 400 MHz NMR ($^3J_{H_2H_3}$ = 8 Hz) [10b,14]. 9b, 9c and 10 were also mixtures of two 2,3 cis disubstituted isomers in the following ratios : 9b : 85/15 ; 9c : 70/30 ; 10 : 80/20. The major isomers were obtained pure by fractionate crystallization : their ^1H NMR spectrum allows the assignment of the cis relationship between C_2 and C_3 substituents (9b

$^3J_{H_2H_3}$ = 3.5 Hz ; 9c $^3J_{H_2H_3}$ < 1 Hz ; 10 $^3J_{H_2H_3}$ = 3.5 Hz)[15]. An X ray determination of 9c gave the configuration shown in Fig. 1 [16] (see experimental part).

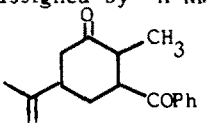
In the case of 9d ($^3J_{H_2H_3}$ < 1 Hz), obtained as a 70/30 mixture of two stereoisomers, we observed 10% of the trans analog ($^3J_{H_2H_3}$ = 8 Hz).

The stereoselectivity observed around C_3C_α from 8 - 10 can be under kinetic or thermodynamic control as aminonitriles can isomerize through iminium salts [17]. Indeed, we observed that, in $CDCl_3$ solution the single crystalline 9c isomer evolved towards a stereoisomeric 9c mixture. However, this crystalline isomer remained unchanged when a THF solution was treated at low temperature by aqueous NH_4Cl and extracted as previously : the epimerization thus only takes place in the presence of acid (which is present in $CDCl_3$) and therefore the observed stereoselectivity is probably under kinetic control.

From the pure crystalline isomers or from the previous mixtures, treatment by an aqueous $AgNO_3$ solution, generated the pure cis diketones 11b, 11c and 12 to which the stereochemistry has been assigned by ^1H NMR [15]



11 a n = 1
b n = 2
c n = 3



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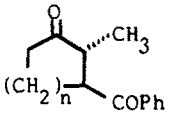
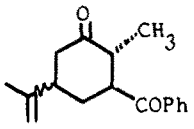


13 a n = 1
b n = 2
c n = 3



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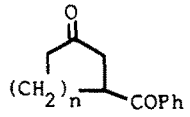
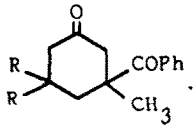
(11b $^3J_{H_2H_3}$ = 5 Hz ; 11c $^3J_{H_2H_3}$ = 2.75 Hz ; 12 $^3J_{H_2H_3}$ = 5 Hz) and by basic equilibration to cis/trans isomeric mixtures : 11b/13b : 20/80 ; 11c/13c : 30/70 ; 12/14 : < 5/95 (13b : $^3J_{H_2H_3}$ = 12 Hz [10], 13c : $^3J_{H_2H_3}$ = 10 Hz ; 14 2 isomers $^3J_{H_2H_3}$ = 12 and 10 Hz).

From 9a stereoisomeric mixtures treatment by aqueous $AgNO_3$ gave a 80/20 11a/13a mixture which was also characterized by ^1H NMR (11a $^3J_{H_2H_3}$ = 7.6 Hz) and by comparison with known data for 13a [10a] ($^3J_{H_2H_3}$ = 11Hz).

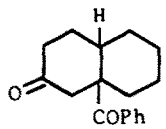
The other benzoyl-3 cyclanones 15 - 17 have been previously described [5,6,8,18]



15 a n = 1
b n = 2
c n = 3



16 a R = H
b R = CH_3



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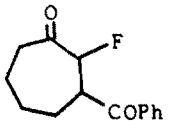
(except 15c). From 7 membered ring α-fluoroenone, 4d, a 18/19 : 90/10 mixture is obtained as shown by ^1H and ^{19}F NMR (18 $^3J_{H_2H_3}$ = 3 Hz ; 19 $^3J_{H_2H_3}$ = 8.5 Hz).



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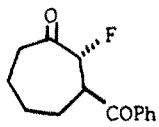

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From Table 1, it appears that aminonitrile 1a as well as cyanohydrin ether 2a are efficient benzoyl equivalents which give 1,4 adducts with good yields from 3-unsubstituted cyclenones 3a-c, leading easily to 3-benzoylcyclanones (entries 1-4). 2-methyl and 2-fluoro substituted cyclenones 4 (entries 5-12) also give 1,4 adducts in high yields.

Furthermore, cis 2-methyl-3-benzoylcyclanones can be obtained from 6 and 7 membered ring 2-methylcyclenones with a very good stereoselectivity (⩾97%), provided that mild unmasking conditions (method C) were used (entries 7,8,10,11,13) instead of method B (entry 9). A similar methodology also permits the stereoselective synthesis of cis 2-phenyl-3 benzoylcyclohexanone [19]. From 2-fluoro-2-cycloheptenone 4d, the stereoselectivity is not so high, as next to the cis isomer 18, 10% trans one 19 is obtained (entry 12) : the same stereoisomeric ratio is observed in the 1,4 adduct before $AgNO_3$ treatment.

Table I. Reaction of anionic reagents from 1a and 2a with cyclic α,β-unsaturated ketones.

Entry	α enone	Reagent	% Yield in adduct [a]	Unsmaking method	Product and	% Yield
1	3a	1a	>95 (85)	A	15a	>92
2	3b	1a	95 (80)	A	15b	90
3	3b	2a	-	B	15b	95 [7]
4	3c	1a	90 (75)	A	15c	86
5	4a	1a	90	A	11a + 13a [b]	85
6	4a	2a	90	C	11a + 13a [c]	80
7	4b	1a	85 (75)	A	11b [d]	80
8	4b	2a	90 (70)	C	11b [d]	85
9	4b	2a	90	B	11b + 13b [e]	85
10	4c	1a	85 (75)	A	11c [d]	79
11	4c	2a	88	C	11c [d]	80
12	4d	1a	87 (60)	A	18 + 19 [f]	80
13	5	1a	85 (75)	A	12 [d]	78
14	6a	1a	-	-	-	<5 [g]
15	6b	1a	-	-	-	<5 [g]
16	6b	2a	-	B	16b	88 [8a,b]
17	7	1a	-	-	-	<5 [g]
18	7	2a	-	B	17	85 [8a,b,18]

a) Yield determined by ^{1}H NMR (isolated).
b) 80/20 11a/13a mixture (isomers not separated).
c) 75/25 11a/13a mixture (not separated).
d) no trans isomer detected within ^{1}H NMR limits (<5%).
e) 50/50 11b/13b mixture (not separated).
f) 90/10 18/19 mixture (18 is obtained pure by crystallization).
g) Starting material recovered.

However, from 2-methyl-2-cyclopentenone 4a, the unmasking of the keto group induces some epimerization : while in 9a, the 400 MHz ^{1}H NMR spectrum shows that the 2 and 3 substituents are in a cis relationship, treatment by aqueous $AgNO_3$ or aqueous $CuSO_4$ lead to a 11a/13a 80/20 mixture (entry 5). From cyanohydrin ether 2a, a similar result is obtained (entry 6) after treatment with wet silica gel.

When the β carbon of the α-cyclenone is disubstituted, the behaviour of the two reagents becomes different : aminonitrile 1a anion is no longer efficient (entries 14, 15, 17), while conjugate addition still takes place in the same conditions with a good yield from cyanohydrin ether 2a (entries 16, 18). However, the limitation of reagent 2a is met with 10-methyl-$\Delta^{1,9}$-2-octalone or 19-nortestosterone-17-silylether which were left unchanged [18b].

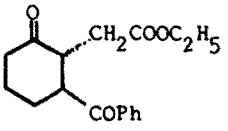
b) Conjugate addition-alkylation

The conjugate addition methyl iodide trapping could be realized in "one pot" in the presence of HMPA [10] from cyclenones 3a-c and cyanohydrin ether 2a, using t-BuLi as a base instead of LDA. Trans 2-methyl-3-benzoylcyclanones 13b,c could be prepared with a high

yield (≥90%) provided that unmasking of the keto group was done by method C. 13b was previously obtained with lower yield and stereoisomeric purity either from 3b and 2a but using method B for unmasking the keto group [8b] or by conjugate addition of lithiated phenylacetonitrile/ICH_3 trapping followed by PTC oxidation by molecular oxygen [10a]. The present methodologies are thus an improvement of the two previous ones.

ICH_3 trapping of the enolate resulting from conjugate addition of lithiated aminonitrile 1a did work only in the 5-membered ring series : 13a was obtained with a good yield. From the 6 and 7 membered ring cyclenones 3b and 3c, 13b and 13c + 11c were formed respectively next to the unsubstituted 1,4 adducts 15b and 15c and their corresponding methyl enolethers 20.

When using ethyl bromoacetate and after aqueous $AgNO_3$ treatment, trans 2-carboethoxymethyl-3-benzoylcyclohexanone 21 was obtained with a good yield and identified by IR, high field ^1H NMR ($^3J_{H_2H_3}$ = 11.5 Hz) and elemental analysis.



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Discussion

Several points observed during this study are worthy of comment :

a) The fact that 1,2 addition was never observed from lithiated 1a in THF at low temperature whatever the α-enone studied, a behaviour similar to the one previously observed with 2a [8a,b]. From literature, it appears that many carbanions α to nitriles give 1,2 addition to 2-cyclohexenone [2,5,6,20,22,23,24] or to 3-methyl-2-cyclohexenones [20,25] in similar conditions, even when their substituent allows charge delocalisation such as $[PhCHCN]^-Li^+$, [20]

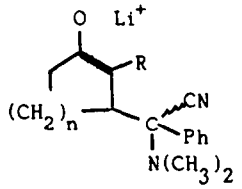
$[PhC(OCH_3)CN]^-Li^+$ [8b] , $\left[CH_2\dot{-}\ddot{C}H\dot{-}\ddot{C}\begin{matrix}CN\\NEt_2\end{matrix}\right]^-Li^+$ [7] or $[PhC(OSiMe_3)CN]^-Li^+$ [6].

The only examples where no 1,2 addition could either be seen, is the reaction of $\left[CH_3\dot{C}H\dot{-}\ddot{C}H\dot{-}\ddot{C}\begin{matrix}CN\\OCH(CH_3)OC_2H_5\end{matrix}\right]^-Li^+$ to several cyclohexenones in the same conditions[5,18a] or of $(EtS)_2CHCN$ to 2-cyclohexenone in the presence of KH in THF [26]. However, 1,2 addition of lithiated 1a to α,β-ethylenic aldehydes has been observed in our group in THF at -78°C [27]; it has also been observed with various β-substituted α-enones in the presence of Lewis acids, but next to 1,4 addition [28].

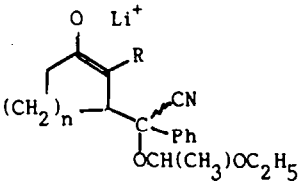
From all these results, it appears that there is a delicate balance between the different interactions which favor more or less 1,2 vs 1,4 addition.

- kinetic or thermodynamic control [21] ;
- bulkiness of the nucleophile [29] : aminonitrile 1a behaves as bulkier as the corresponding ethers 2b or 2c in THF, as it does not give any 1,2 addition ;
- steric hindrance around the carbonyl carbon : it is well known that α,β-ethylenic aldehydes always give more 1,2 addition than α-enones [21,29] : such is also the case for lithiated 1a which add 1,2 to aldehydes [27] ;
- repulsive interactions due interalia to the carbonyl lone pairs [30]; these factors are more important for α,β-unsaturated ketones. This can be alleviated by the influence of Lewis acids, which also activate the electrophile. This could explain why both 1,2 and 1,4 addition to 6a and 6b were observed in the presence of Lewis acids [28]. However, the β substituent plays a role as, from cyclohexenone 3b only 1,4 addition took place in similar conditions : earlier results from our group have shown that under Lewis acid catalysis 3-methyl 3-cyclohexenones 6a and 6b gave more 1,2 addition than 2-cyclohexenone 3b [31].

b) The very high stereoselectivity of the protonation of 2-methyl substituted enolates 21a and 22a, as only cis 2-methyl 3-substituted cyclanones were detected before or after unmasking under mild conditions. Therefore, protonation takes place on the side of the enolate opposite to the 3-substituent, whatever the ring size and without considering its aggregation state [32]. However, if $(iPr)_2NH$ is present in the reaction medium, when the carbanionic reagent is formed using LDA, this stereoselectivity is lost [10c].



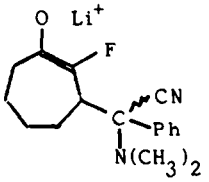
21 a) R = CH_3
b) R = H



22 a) R = CH_3
b) R = H

Such an observation is in line with our previous results [32] : we have shown that the stereoselectivity of 2,3-disubstituted endocyclic enolates protonation depends upon the ring size and the bulkiness of the 3-substituents. Aminonitrile and cyanohydrin ether moieties are bulky enough to induce the selective proton donor approach from the other side of the ring in all the cases studies (5,6,7 membered). Provided that the keto group unmasking conditions are mild enough, the cis 2,3 substituent relationship is maintained in diketones 11b, 11c, 12 and 18. However, in the 5-membered ring derivative 11a, some epimerization is observed : such an easy isomerization in this series has precedent in the literature [32-35].

The α-fluoro enolate 23 protonation is less selective : this could be due to the small size of the fluoro group, but this single result is only indicative and more examples are needed to determine what the trend is.



c) The alkylating agents trapping experiments are also in line with former results of the literature : conditions allowing regio and stereoselective trapping by ICH_3 of five membered ring enolates were easily realized [9,10b,34,35]. However, in the six and seven-membered ring series, such a trapping only worked well with the enolates 22b formed from cyanohydrin ether 3a ; it leads to mixtures with 21b (n = 2,3), due to the lesser reactivity of these species, an observation previously made for six membered ring enolates [34,35]. However, when using a more reactive electrophile, such as methyl bromoacetate [34] or PhSeCl [36], this limitation was no longer met.

Furthermore, use of tBuLi instead of LDA as a base to generate the carbanions prevented the presence in the reaction medium either of a diisopropylammonium salt with CH_3I [36a] or of an H-bonded complex between diisopropylamine and the lithiated enolate [36b] which could protonate the enolates before trapping and thus lower the yields in regioselectively monoalkylated compounds.

Conclusion

Aminonitrile 1a, as well as cyanohydrin 2a are powerful benzoyl anionic equivalents which give easily 1,4 adducts to cyclic enones in conditions where the resulting enolates can be trapped by various electrophiles in THF or in THF-HMPA. This renders them superior in use to silylether 2b which gives 1,4 addition to cyclenones only under thermodynamic control in diethylether [6], a solvent in which such a trapping is not possible. The limitation in use of aminonitrile 2a is its sensitivity to carbon-3 substitution of the cyclenone, a fact similar to those observed by Hünig with silyl ether 2b. Cyanohydrin ether 2a is far less sensitive to steric hindrance and has thus a broader domain of application.

Conditions of unmasking of the benzoyl moiety which do not induce any epimerization, except in the 5-membered ring series, have been determined : either aqueous $AgNO_3$ [11] for aminonitriles from 1a, or a new and mild method i.e. wet silica gel followed by aqueous sodium bicarbonate for cyanohydrin ethers from 2a. These techniques allowed the highly stereoselective preparation of several cis or trans 2-substituted-3-benzoylcyclohexanones and heptanones, provided that no protonation agent is present in the reaction medium i.e. the use of LDA is precluded to generate the carbanionic reagents.

Experimental Section

General. ^1H NMR spectra were recorded on a Perkin-Elmer R32 (90 MHz), a Bruker AM 250 (250 MHz) or a Cameca (400 MHz) spectrometer in $CDCl_3$ and are reported in δ from Me_4Si. IR spectra were recorded on a Perkin-Elmer Model 682 infrared spectrophotometer and the IR figures reported are ν max in cm^{-1}. Mass spectra were recorded on a Nermag R 10-10 mass spectrometer coupled with a OKI DP 125 chromatographer or on a Hewlett-Packard 5992A GC/MS system coupled with gas phase chromatography. Melting points were obtained on a Mettler FP 5 capillary melting point apparatus and are uncorrected. Preparative thin-layer chromatographies were performed on 0,5 mm x 20 cm X 20 cm Merck silica gel plates (60F-254). Merck silica gel 60 (70-230 mesh) was used for column chromatography. Tetrahydrofurane (THF) was freshly distilled from lithium aluminum hydride ($LiAlH_4$) under argon. Diethyl ether was also distilled from $LiAlH_4$. nButyllithium in hexane (1,6 M) or tButyllithium in hexane (1,6 M) were purchased from Janssen Chemica or Ega-Chemie. Hexamethylphosphorotriamide (HMPA) was purchased from Merck (spectroscopy quality) and was used without purification.2-Methyl-2-cyclopentenone (38), 2-methyl-2-cyclohexenone (39), 1(9) 2-octalone (40) were prepared according to the literature. 2-Cycloheptenone, 2-methyl-2-cycloheptenone and 2-fluoro-2-cycloheptenone were kindly given to us by Dr. L. Blanco. The other α-enones used are commercial. The N-dimethylphenylacetonitrile (41) and the cyanohydrin ether (5) were prepared according to the literature.

Enolate formation

All reactions concerning conjugate additions were run under a nitrogen atmosphere, the low temperature being maintained by a liquid nitrogen bath. In a three necked flask equipped with a mechanical stirrer, a thermometer, a rubber septum cap and a nitrogen entrance (glassware were previously oven dried and flamed out) 5 mmoles of 1a or 2a in 3 ml THF or in a mixture of 14 ml THF and 3,5 ml HMPA were introduced. The solution was cooled to -78°C or -65°C respectively and 5,2 mmoles of nBuLi or tBuLi were added dropwise via a syringe. After the addition was complete, the solution was stirred for 15 minutes and 5 mmoles of the α-enone in 2 ml THF were added.

Enolate protonation

After stirring for various times (5-25 min.) the enolate was protonated by a saturated NH_4Cl aqueous solution at -78°C or -65°C. After extractions with diethyl ether the organic phase was eventually washed with H_2O in order to remove HMPA, then with a saturated NaCl aqueous solution and dried over Na_2SO_4.

Enolate alkylation

1) Methylation was performed in THF-HMPA by adding an excess of ICH_3 (5 eq.) to the preformed enolates 21b (n = 1,2,3) and 22b (n = 2,3) and stirring the solution for 2,5 h at -30°C.
2) Ethyl bromoacetate trapping (1,5 eq.) of 21b (n = 2) was performed in THF-4 eq. HMPA/Li^+ after stirring the solution for 3 h at -30°C.

Benzoyl deprotection

Method A : 0.28 mmoles of aminonitrile adduct in 1 ml THF and 0,5 ml of diethyl ether were stirred with 0.5 ml of a 0.5N aqueous solution of $AgNO_3$ for 30 min. at room temperature. After extracting with diethyl ether, the organic phase was washed with a saturated aqueous NaCl solution and dried over Na_2SO_4.

Method B : 5 mmoles of cyanohydrin ether in 3 ml of ethanol were stirred with 1 ml of 5% H_2SO_4 for 10 min. at room temperature. After extraction with diethyl ether the organic phase was washed with a saturated aqueous NaCl solution.

Method C : A drop of a 15% aqueous H_2SO_4 solution was added on 273 mg of silica gel while stirring until the aqueous phase was completely adsorbed. Then 90 mg of the cyanohydrin adduct in solution with 1 ml of $CHCl_3$ were added and stirring continued for 30 min. The suspension was neutralized by adding 2 ml of a saturated aqueous $NaHCO_3$ solution and stirred for 30 min. at room temperature. After extracting with diethyl ether the organic phase was washed with a saturated aqueous NaCl solution and dried over Na_2SO_4. If the hydrolysis of the cyanohydrin ether was not complete the procedure was repeated.

Description of the products

8a mixture of two diastereoisomers isolated after recrystallization from Et2O (85%).

IR (CDCl3) : νCN : 2230 cm^{-1} ; νCO : 1745 cm^{-1}. ^1H NMR 400 MHz (CDCl3) δppm : 7.58 - 7.44 (m, 5H) aromatic protons ; 3.06 (m, 1H) H3 ; 2.36 (s, 6H) NMe2 8a1 ; 2.34 (s, 6H) NMe2 8a2 ; 2.3 - 1.47 (massif, 6H) cyclic protons. 13C NMR 15 MHz (CD3COCD3) : 26.29 and 24.39 (C4) ; 37.14 and 37.75 (C5); 39.26 and 42.72 (C2) ; 41.15 and 41.33 (N-CH3) ; 43.82 and 44.06 (C3) ; 117.51 and 117.49 (C N) ; 129.48; 129.91 ; 129.94 (Ph) ; 215 and 215.5 (C O). Anal. calcd for $C_{15}H_{18}N_2O$ % : C, 74.35 ; H, 7.49 ; N, 11.56; O, 6.60. Found : C, 74.30 ; H, 7.41 ; N, 11.45 ; O, 6.5.

8b mixture of two diastereoisomers isolated after recrystallization from Et2O (80%).

IR (CDCl3) : νCN : 2210 cm^{-1} ; νCO : 1720 cm^{-1}. ^1H NMR 400 MHz (CDCl3) δppm : 7.52 - 7.3 (m, 5H) aromatic protons ; 2.66 - 0.76 (massif, 15H) ; 2s at 2.29 and 2.27 (NMe2) are detected. 13C NMR 15 MHz (CD3COCD3) ppm : 209.56 and 208.73 (C O) ; 116.91 and 116.49 (C N). Anal. calcd for C16 H2ON2O % : C, 74.97 ; H, 7.86 ; N, 10.93 ; O, 6.24. Found : C, 74.90 ; H, 7.82 ; N, 10.90 ; O, 6.20.

8c mixture of two diastereoisomers isolated by crystallization from Et2O (75%).

IR (CDCl3) : νCN : 2210 cm^{-1} ; νCO : 1700 cm^{-1}. ^1H NMR 90 MHz (CDCl3) δppm : 7.55 - 7.30 (m, 5H) aromatic protons ; 3.10 - 1.15 (massif, 17H) ; 2s at 2.30 and 2.29 (NMe2) are detected. Anal. calcd. for C17H22N2O % : C, 75.52 ; H, 8.20 ; N, 10.36 ; O, 5.92. Found : C, 75.35 ; H, 8.39 ; N, 10.11 ; O, 6.00.

9a : oil mixture of two diastereoisomers 9a1 and 9a2 in 50/50 ratio (90%).

IR (film) : νCN : 2210 cm^{-1} ; νCO : 1745 cm^{-1}. ^1H NMR 400 MHz (CDCl3) δppm : 7.58 - 7.33 (m, 5H) aromatic protons ; 3.22 (q, 1H) H3 9a1 ; 3.15 (q, 1H) H3 9a2 ; 2.62 (m, ^3JH2H3 = 8 Hz, 1H) H2 9a2; 2.16 (m, ^3JH2H3 = 8 Hz, 1H) H2 9a1 ; 2.64 - 1.60 (massif, 10H) cyclic protons ; 2s at 2.25 and 2.26 (NMe2) are detected ; 1.22 (d, ^3JH2H3 = 8 Hz, 3H) CH3 $9a_2$; 1.15 (d, ^3JH2CH3 = 8 Hz, 3H) CH3 9a1.

9b : mixture of two diastereoisomers 9b1 and 9b2 in a 85/15 ratio.

9b1 was obtained by crystallization from diethyl ether (75%) : mp = 133-134°C.

IR (CDCl3) : νCN : 2240 cm^{-1} ; νCO : 1715 cm^{-1}. ^1H NMR 400 MHz (CDCl3) δppm : 7.54 - 7.34 (m, 5H) aromatic protons ; 2.92 (m, ^3JH2H3 = 5 Hz, 1H) H2 ; 2.58 (dt, ^3JH3H4 = 5 Hz, ^3JH3H4' = 10 Hz, 1H) H2 ; 2.58 (dt, ^3JH3H4 = 5 Hz, ^3JH3H4' = 10 Hz, 1H) H3 ; 2.50 - 1.44 (massif, 12H) ; 2.17 (s, 6H) NMe2 ; 0.75 (d, ^3JCH3H2 = 7 Hz, 3H) CH3. Anal. calcd for C17H22N2O % : C, 75.52 ; H, 8.20 ; N, 10.36 ; O, 5.92. Found : C, 75.53 ; H, 8.19 ; N, 10.50 ; O, 5.99.

9b2 detected by the CH3 = 0.92 (d, ^3JCH3H2 = 7 Hz, 3H) in the ^1H NMR spectrum of the mixture.

9c : mixture of two diastereoisomers 9c1 and 9c2 in a 70/30 ratio.

9c1 was isolated by crystallization from diethyl ether (75%) : mp : 133-134°C.

IR (CDCl3) : νCN : 2220 cm^{-1} ; νCO : 1700 cm^{-1}. ^1H NMR 400 MHz (CDCl3) δppm : 7.52 - 7.32 (m, 5H) aromatic protons ; 2.86 (q, 3 ^3JH2H3 ≤ 1 Hz, 1H) H2 ; 2.58 - 1.41 (massif, 14H) ; 2.26 (s, 6H) NMe2; 0.33 (d, ^3JH2CH3 = 7 Hz, 3H) CH3. Anal. calcd for C18H24N2O % : C, 76.02 ; H, 8.51 ; N, 9.85 ; O, 5.62. Found : C, 76.08 ; H, 8.55 ; N, 10.07 ; O, 5.79.

9c2 was characterized by the following signals in the ^1H NMR spectrum of the mixture: 3.09 (q, ^3JH2H3 ≤ 1 Hz, 1H) H2 ; 2.31 (s, 6H) NMe2 ; 0.65 (d, ^3JH2CH3 = 7 Hz, 3H) CH3.

Cis 9d : mixture of two diastereoisomers 9d1 and 9d2 in a 62/38 ratio.

9d1 was isolated by crystallization from diethyl ether (60%) ; mp : 95-96°C.

IR (CDCl3) : νCN : 2220 cm^{-1} ; νCO : 1720 cm^{-1}. ^1H NMR 400 MHz (CDCl3) δppm : 7.6 - 7.3 (m, 5H) aromatic protons ; 5.25 (d broad, ^3JH2H3 ≤ 1 Hz, ^2JH2F = 54 Hz, 1H) H2 ; 2.5 (s, 6H) NMe2. 19F RMN 84,6 MHz (CDCl3) ppm : dd -125 ppm, ^3JFH3 = 30 Hz. Anal. calcd for C17H21N2FO % : C, 70.81; H, 7.34 ; N, 9.72 ; F, 6.59. Found : C, 71.02 ; H, 7.37 ; N, 9.78 ; F, 6.12.

9d2 characterized by the following signals deduced from the ^1H NMR spectrum of the mixture : 5.5 (d broad, ^3JH2H3 ≤ 1 Hz, ^2JH2F = 54 Hz, 1H) H2. The trans isomer was characterized by the following signals deduced from the 1H NMR of the mixture : 4.78 (dd, ^3JH2H3 = 8 Hz ,^2JHF = 50 Hz, 1H) H2; 2.35 (s, 6H) NMe2.

Cis 10 : mixture of two diastereoisomers 10l and 10l2 in a 80/20 ratio.

10l was isolated by crystallization from diethyl ether (75%) ; mp : 127-128°C.

IR (CDCl3) : νCN : 2240 cm^{-1} ; νCO : 1710 cm^{-1} ; νC=C : 1650 cm^{-1}. ^1H NMR 400 MHz (CDCl3) δppm : 7.56 - 7.38 (m, 5H) aromatic protons ; 4.79 (s, 1H) and 4.76 (s, 1H) vinylic protons ; 2.93 (m, ^3JH2H3= 3.5 Hz, 1H) H_2 ; 2.65 (dt, ^3JH3Heq = 3,5 Hz, ^3JH3Hax = 12 Hz, 1H) H3 ; 2.43 (m, ^2JH6axH6eq = 14.5 Hz, ^3JH6axH5ax = 14.5 Hz, 1H) H6ax ; 2.28 (m, 1H) H6eq ; 2.22 (m, ^3JH5axH4ax = 11 Hz, ^3JH5axH4eq= 2 Hz, 1H) H5 ; 2.20 (s, 6H) NMe2 ; 2.0 (m, 1H) H4eq ; 1.85 (m, 1H) H4ax ; 1.73 (s, 3H) CH2 C CH3; 0.77 (d, 3H) CH3. Anal. calcd for C20H26N2O % : C, 77.38 ; H, 8.44 ; N, 9.02 ; O, 5.15. Found : C,

77.47 ; H, 8.45 ; N, 9.05 ; O, 5.41.

IQ2 was characterized by the following signals deduced from the ^{1}H NMR of the mixture: 2.22 (s, 6H) NMe2 ; 0.95 (d, 3H) CH3.

3-Benzoylcyclopentanone 15a purified by thin layer chromatography (ether/hexane = 70/30) (92%).

IR (film) : CO : 1745 cm^{-1}, 1680 cm^{-1}. ^{1}H NMR 90 MHz (CDCl3) δ ppm : 8.05 - 7.95 (m, 2H) and 7.65 - 7.45 (m, 3H) aromatic protons ; 4.15 (m, 1H) H3 ; 2.7 - 2.0 (massif, 6H) cyclic protons. M.S. for C12H12O2 : 188.

3- Benzoylcycloheptanone 15c oil purified by thin layer chromatography (ether/hexane = 70/30) (86%).

IR (film): νCO : 1700 - 1690 cm^{-1}. ^{1}H NMR 400 MHz (CDCl3) δ ppm : 8.0 - 7.9 (m, 2H) and 7.6 - 7.45 (m, 3H) aromatic protons ; 3.62 (tt, ^{3}JH3H4ax = 11 Hz, ^{3}JH3H4eq = 3 Hz, 1H) H3 ; 2.95 (dd, ^{3}JH2H3 = 11 Hz, Jgem = 14 Hz, 1H) H2ax ; 2.75 - 1.20 (massif, 10H) cyclic protons.

Cis 2-methyl-3-benzoylcyclopentanone 11a :

IR (film) : νCO : 1745 cm^{-1}, 1680 cm^{-1}. ^{1}H NMR 400 MHz (CDCl3) δ ppm : signals deduced from the cis/trans mixture : 7.9 - 7.8 (m, 2H) and 7.6 - 7.42 (m, 3H) aromatic protons ; 4.25 (m, 1H) H3 ; 2.55 (m, ^{3}JH2H3 = 7.6 Hz, 1H) H3 ; 2.53 - 1.78 (massif, 4H) cyclic protons ; 0.98 (d, ^{3}JH2CH3 = 7 Hz, 3H) CH3. M.S. for C13H14O2 : 202.

Trans 2-methyl-3-benzoylcyclopentanone 13a : oil isolated by thin layer chromatography (silica gel, éther/hexane = 70/30) (85%).

IR (film) : νCO : 1745 cm^{-1}, 1680 cm^{-1}. ^{1}H NMR 400 MHz (CDCl3) δ ppm : 8.03 - 7.99 (massif, 2H) and 7.64 - 7.50 (massif, 3H) aromatic protons ; 3.70 (m, 1H) H3 ; 2.80 (m, ^{3}JH2H3 = 11 Hz, 1H) H2 ; 2.58 - 1.90 (massif, 4H) cyclic protons ; 1.12 (d, ^{3}JH2CH3 = 7 Hz, 3H) CH3. M.S. for C13H14O2 : 202.

Cis 2-methyl-3-benzoylcyclohexanone 11b : oil isolated by thin layer chromatography (silica gel, ether/hexane = 70/30) (80%).

IR (film) : νCO : 1715 cm^{-1}, 1685 cm^{-1}. ^{1}H NMR 400 MHz (CDCl3) δ ppm : 8 - 7.9 (massif, 2H) and 7.6 - 7.42 (massif, 3H) aromatic protons ; 4.20 (q, ^{3}JH3H4ax = ^{3}JH3H4eq = 5 Hz, 1H) H3 ; 2.75 (m, ^{3}JH2H3 = 5 Hz, 1H) H2 ; 2.73 - 1.72 (massif, 6H) cyclic protons ; 1.05 (d, ^{3}JH2CH3 = 7 Hz, 3H) CH3. M.S. for C14H16O2 : 216.

Cis 2-methyl-3-benzoylcycloheptanone 11c : purified by crystallization from diethyl ether (79%) ; mp : 97 - 98°C.

IR (CDCl3) : νCO : 1700, 1690 cm^{-1}. ^{1}H NMR 400 MHz (CDCl3) δ ppm : 8 - 7.9 (massif, 2H) and 7.58 - 7.3 (massif, 3H) aromatic protons ; 3.93 (m, ^{3}JH3H4 = 4 Hz, ^{3}JH3H4' = 6 Hz, 1H) H3 ; 2.79 (qd, ^{3}JH2H3 = 2.75 Hz, 1H) H2 ; 2.72 - 1.43 (massif, 8H, cyclic protons ; 1.07 (d, ^{3}JH2CH3 = 6.75 Hz, 3H) CH3. Anal. calcd for C15H18O2 % : C, 78.23 ; H, 7.88 ; O, 13.89. Found : C, 78.37 ; H, 7.83 ; O, 14.13.

Trans 2-methyl-3-benzoyl cycloheptanone 13c : purified by thin layer chromatography (silica gel, ether/hexane = 70/30) (85%). Analysed in the presence of the cis 11c.

IR (CDCl3) : νCO : 1750 - 1690 cm^{-1}. ^{1}H NMR 400 MHz (CDCl3) δ ppm : 8 - 7.9 (massif, 2H) and 7.6 - 7.3 (massif, 3H) aromatic protons ; 3.36 (m, 2H) H2+H3 ; 2.26 - 1.48 (m, 8H) cyclic protons ; 1.02 (d, 3H, ^{3}JCH3H2 = 6.25 Hz) CH3. ^{1}H NMR 400 MHz (CDCl3 - C6D6) : ^{3}JH2H3 = 10 Hz.

Trans 2-methyl-3-benzoylcyclohexanone 13b : oil isolated by thin layer chromatography (silica gel, ether/hexane = 70/30) (85%).

IR (film) : νCO : 1715 cm^{-1}, 1685 cm^{-1}. ^{1}H NMR 250 MHz (CDCl3) δ ppm : 8.0 - 7.9 (massif, 2H) and 7.6 - 7.42 (massif, 3H) aromatic protons ; 3.52 (td, 1H) H3 ; 3.0 (m, ^{3}JH2H3 = 11 Hz, 1H) H2 ; 2.57 - 1.1 (m, 6H) cyclic protons ; 0.97 (d, ^{3}JH2CH3 = 6.75 Hz) CH3.

Cis 2-fluoro 3-benzoylcycloheptanone 11d purified by crystallization from diethyl ether (80%) ; mp : 101 - 102°C.

IR (CDCl3) : νCO : 1720 cm^{-1} ; 1690 cm^{-1}. ^{1}H NMR 400 MHz (CDCl3) δ ppm : 7.95 - 7.92 (massif, 2H) and 7.58 - 7.42 (massif, 3H) aromatic protons ; 5.20 (dd, ^{3}JH2H3 = 3 Hz, ^{2}JH2F = 47 Hz, 1H) H2 ; 4.16 (m, 1H) H3 ; 2.78 - 1.25 (massif, 8H) cyclic protons. 19F NMR 84,6 MHz (CDCl3) ppm : -113 (dd). Anal. calcd. for C14H15FO2 % : C, 71.78 ; H, 6.45 ; F, 8.11. Found : C, 71.85 ; H, 6.48 ; F, 8.16.

Trans 2-fluoro-3-benzoylcycloheptanoone 13d characterized by the following signals in the ^{1}H NMR spectrum of the mixture 11d+13d.

^{1}H NMR 400 MHz (CDCl3) δ ppm : 5 - 6.9 (dd, ^{3}JH2H3 = 8.5 Hz, ^{2}JH2F = 48 Hz, 1H) H2 ; 3.83 (m, 1H) H3. 19F NMR 84,6 MHz (CDCl3) ppm : -110 (dd). ^{3}JFH3 = 12 Hz.

Cis 2-methyl-3-benzoyl-5-isopropenylcyclohexanone 12 : purified by crystallization from diethyl ether (78%) ; mp : 64 -65°C.

IR (CDCl3) : νCO : 1710 cm^{-1} ; 1685 cm^{-1} ; νC=C : 1650 cm^{-1}. ^1H NMR 400 MHz (CDCl3) δppm : 7.93 - 7.90 (massif, 2H) and 7.60 - 7.43 (massif, 3H) aromatic protons ; 4.83 (s, 2H) vinylic protons ; 3.85 (m, $^3J_{H3H4ax}$ = 12 Hz ; $^3J_{H3H4eq}$ = 4 Hz, 1H) H3 ; 2.88 (m, $^3J_{H2H3}$ = 5 Hz, 1H) H2 ; 2.44 (m, $^3J_{H6H5}$ = 13 Hz, 1H) H6ax ; 2.37 (m, 1H) H5 ; 2.29 (m, 1H) H6eq ; 2.13 (m, 1H) H4ax ; 1.85 (m, 1H) H4eq ; 1.78 (s, 3H) C=C-CH3 ; 0.97 (d, $^3J_{H2CH3}$ = 7 Hz, 3H) CH3. Anal. calcd. for C17H20O2 % : C, 79.65 ; H, 7.86 ; O, 12.48. Found : C, 79.59 ; H, 7.82 ; O, 12.38.

Trans 2-methyl-3-benzoyl-5-isopropenylcyclohexanone 14 ; oil : mixture of two diastereoisomers 141 and 142 in a 80/20 ratio.

^1H NMR (CDCl3) δppm : 8.0 - 7.9 (massif, 2H) and 7.63 - 7.46 (m, 3H) aromatic protons ; 4.77 (m, 2H) vinylic protons ; 3.65 (td, $^3J_{H3H4eq}$ = 4 Hz, $^3J_{H3H4ax}$ = 10 Hz, 1H) H3 142 ; 3.55 (td, $^3J_{H3H4eq}$ = 4 Hz, $^3J_{H3H4ax}$ = 12 Hz) H3 141 ; 3.0 (m, $^3J_{H2H3}$ = 12 Hz, 1H) H2 141 ; 2.95 (m, $^3J_{H2H3}$ = 10 Hz) H2 142 ; 2.67 - 1.26 (m, 8H) cyclic protons ; 1.07 (d, $^3J_{H2CH3}$ = 6.5 Hz, 3H) CH3 142 ; 0.97 (d, J_{H2CH3} = 6.5 Hz, 3H) CH3 141.

Trans 3-benzoyl 2-carbethoxy methyl cyclohexanone 21. Recrystallized from diethyl ether (85%) ; mp : 71-72°C.

IR ($CDCl_3$) : νCO(ester) : 1740 - 1730 cm^{-1} ; νCO : 1715 cm^{-1} ; νCOPh : 1680 cm^{-1}. ^1H NMR 250 MHz (CDCl3) ppm : 8.0 - 7.94 (m, 2H) and 7.65 - 7.45 (m, 3H) aromatic protons ; 4.08 (q, 2H) CH_2CH_3; 3.95 (td, $^3J_{H3H4ax}$ = 11.7 Hz, $^3J_{H3H4eq}$ = 3 Hz, 1H) H3 ; 3.41 (m, $^3J_{H2H3}$ = 11.7 Hz, 1H) H2 ; 2.42 (ABX system, 2H) C_2CH_2 ; 2.55 - 1.70 (m, 6H) cyclic protons ; 1.19 (t, $^3J_{CH3CH2}$ = 6.8 Hz, 3H) CH_2CH_3. Anal. calcd. for C17H20O4 % : C, 70.82 ; H, 6.99 ; O, 22.19. Found : C, 70.38 ; H, 7.04 ; O, 22.49.

1-Methoxy-3-benzoyl-cyclohexene 20b isolated by column chromatography (ether/hexane = 20/80).

IR (film) : νCOPh : 1680 cm^{-1} ; νC=C : 1660 cm^{-1}. ^1H NMR 90 MHz (CDCl3) δppm : 8.0 - 7.9 (m, 2H) and 7.6 - 7.3 (m, 3H) aromatic protons ; 4.65 (d, 1H) vinylic proton ; 4.1 (m, 1H) H3 ; 3.45 (s, 3H) OCH_3; 2.6 - 1.6 (m, 6H) cyclic protons. M.S. for C14H16O2: 216 (M^+) ; 201 (M^+-CH_3) ; 185 (M^+-OCH_3).

1-Methoxy-3-benzoyl-cycloheptene 20c isolated by column chromatography (ether/hexane = 20/80).

IR (film) : νCOPh : 1690 cm^{-1} ; νC=C : 1670 cm^{-1}. ^1H NMR 90 MHz (CDCl3) δppm : 8.0 - 7.87 (m, 2H) and 7.65 - 7.3 (m, 3H) aromatic protons ; 4.92 (d, 1H) vinylic proton ; 4.1 (m, 1H) H3 ; 3.42 (s, 3H) OCH_3 ; 2.2 - 1.4 (m, 8H) cyclic protons. M.S. for C15H18O2 : 230 (M^+) ; 215 (M^+-CH_3) ; 199 (M^+-OCH_3).

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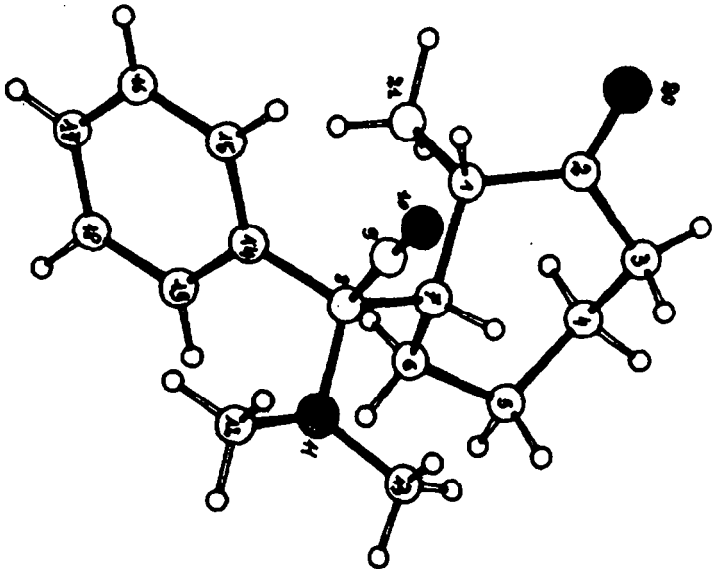

Figure 1