

1,6 ADDITION OF CARBANIONIC REAGENTS TO 10-METHYL HEXAHYDRONAPHTHALENONE.

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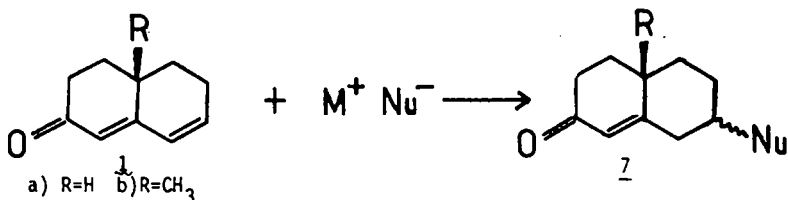
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Abstract. 1,6 addition of carbanionic reagents to bicyclic dienone **1** requires anionic activation: according to the acidity of the corresponding carbon acids, good yields in **7a**-adducts can be obtained either in THF-HMPA with *n*BuLi or *t*BuOK as bases or under solid-liquid phase transfer catalysis.

1,6 additions of carbon nucleophiles to bicyclic dienones such as **1** have been scarcely described in the literature. HUNIG and WEHNER¹ have studied the reaction of a silyloxycyanohydrin anion to **1a** (R = H); malonates², organomagnesium reagents with or without copper catalysis³⁻⁵ or organozirconium ones in the presence of nickel salts⁵ have also been used for such a purpose.

We have recently shown⁶ that 1,6 addition of lithiated arylacetonitriles or cyanohydrin ethers to **1b** (R = CH₃) requires anionic activation. In this paper, we generalize this study to carbon nucleophiles formed from phenylthioacetone **2**, dimethylaminophenylacetone **3**, phenylthioacetone **4** and *t*.butylacetoacetate **5**. In the previous study, the reaction was run in a mixture of tetrahydrofuran (THF) and hexamethylphosphorotriamide (HMPA), using *n*BuLi as a base to generate a loose carbanion-solvated lithium ion pair. As loose ion pairs can also be formed in phase transfer conditions, we focus this study on the possibility of performing such reactions in phase transfer catalysis (PTC) and extend it to the reaction of **1b** with diethylmalonate previously performed by YANAGITA and al.² in alcoholic medium.



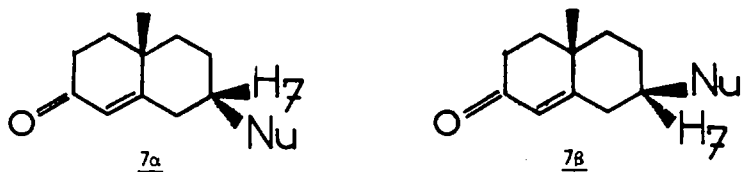
- 2** Nu = PhSCHCN
3 = PhC(CN)NMe₂
4 = PhSCHCOCH₃
5 = CH₃COCHCO₂tBu
6 = CH(CO₂Et)₂

Results and Discussion

The reactions were run either in a mixture of THF/HMPA, occasionally in THF only (method A) or in solid-liquid phase transfer conditions (PTC) (method B).

In the first case, (method A) the carbanionic reagent **2**, **3** or **4** was formed by action of *n*BuLi or of KOtBu on a solution of the corresponding carbon acid at low temperature, then equimolar amount of dienone **1b** was added. After aqueous treatment, the crude reaction product showed in IR 1660-1680 cm⁻¹ and in ¹H NMR two olefinic signals around 5.5 and 5.8 ppm, indicating the presence of a deconjugate cyclohexanone next to a conjugate one. The crude reaction mixture treated by Al₂O₃ according to literature³⁻⁶ led to conjugated ketones **7** identified by IR, ¹H NMR, M.S. and analysis after purification.

In the second case (method B), the reactions were run using equimolar amounts of carbon acids corresponding to **2-6** and dienone **1b** in the presence of solid K₂CO₃, KOH or KOtBu as bases, TEAC or Aliquat 336 as phase transfer agents with or without adding benzene to the organic phase. In these experiments, the conjugated ketones **7** were directly obtained.



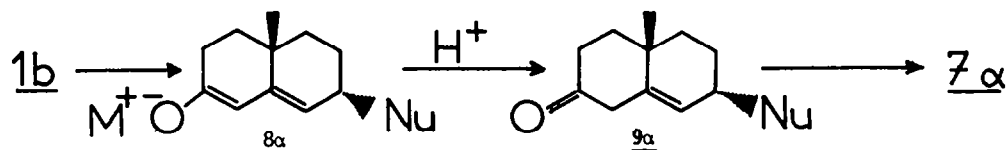
In all cases, the 7α isomers were predominantly formed but generally small amounts of 7β ones could be characterized in the crude reaction mixture. Their relative stereochemistry relies upon the values of H_6 and H_6' , coupling constants and on H_7 , $W_{1/2}$ (≈ 10 Hz for 7α isomers).

When Nu was PhSCHCN, two 7α isomers were isolated in a 1/1 ratio. With PhC(CN)NMe₂, the structural assignments were performed after treatment of the crude mixture by aqueous AgNO₃⁷, giving thus benzoyl ketones 7α and 7β (Nu = C(=O)Ph) in a 90/10 ratio identified by comparison with authentic samples⁶.

In the case of CH₃COCHCOOtBu, the reaction mixture was treated by p.toluenesulfonic acid in benzene at reflux, leading thus to a mixture of $7\alpha/7\beta$ in a 90/10 ratio (Nu = CH₂COCH₃). Pure 7α was obtained by fractionate crystallization. 7α (Nu = CH(COOEt)₂) was also obtained and identified by ¹H NMR spectrum (H_7 , $W_{1/2}$: 12 Hz) and comparison with literature data².

The results of the various experiments are in the Table : it appears that good yields in 1,6 adducts are generally obtained when the carbanionic reagent is loosely associated to its counterion : either in the presence of HMPA (entries 2, 5, 7) related to pure THF (entries 1, 6) or in PTC (entries 13, 15, 16). However, when the related carbon acid pK_a in DMSO is too high⁸ (>17), the reaction does not take place in PTC⁹ : when a weak base such as K₂CO₃ is used, starting material is recovered (entries 4, 8, 11) while with a stronger base (entries 3, 9, 12) dienone **1b** suffers polymerization. However a compromise could be found using KOtBu when adding an organic cosolvent (entry 13). The yields in 1,6 adduct in PTC either using phenylthioacetone (50%, entry 13) or diethylmalonate (75%, entry 16) are quite higher than those obtained in classical Michael conditions (respectively 30% entry 14 or 50%²).

The mechanism of the reaction can be the same as proposed in related cases³⁻⁵ : 1,6 addition of the anionic nucleophile preferentially on the α -face of **1b**, leading to dienolate **8 α** which is protonated, under kinetic control in non equilibrating conditions, into deconjugated ketone **9 α** . This ketone can be re-conjugated to 7α .



Indeed, the presence of **9** is observed by IR, and ¹H NMR (method A) before Al₂O₃ treatment, while in equilibrating conditions (method B), 7α is directly obtained.

The reaction only takes place with good yields when the nucleophile is poorly associated to its counter-ion, i.e. when it is not stabilized by tight ion-pairing (anionic activation).

Our results thus show the generality of the need of anionic activation for 1,6 additions of carbanions to **1b**, while 1,4 addition requires electrophilic assistance when α -enones are too sterically hindered¹⁰. According to the pK_a of the corresponding carbon acid, the reaction has to be performed either in the presence of a dipolar aprotic solvent such as HMPA or in PTC.

Acknowledgments : We are grateful to Jacqueline MARGUERITE who prepared dienone **1** and to Claude MERIENNE for the 400 MHz NMR ¹H spectra.

Table
 1-6 addition of anionic reagents to 1b

Entry	Reagent	Method (base)	Conditions	Yields % ^a
1		A (nBuLi)	-35°C	55 ^{b,c}
2	PhSCH ₂ CN	A (nBuLi)	+ HMPA, -30°C	>95 ^c
3		B (KOH)	Aliquat, 20 or 40°C	< 5 ^d
4		B (K ₂ CO ₃)	Aliquat, 20 or 40°C	< 5
5		A (nBuLi)	+ HMPA, -30°C	60 ^e
6	$\text{PhCH} \begin{cases} \text{CN} \\ \text{NMe}_2 \end{cases}$	A (KOtBu)	-30°C	40 ^e
7		A (KOtBu)	+ HMPA, -30°C	70 ^e
8		B (K ₂ CO ₃)	TEBAC 20 or 40°C with or without C ₆ H ₆	< 5
9		B (KOtBu)	Aliquat 20 or 40°C with or without C ₆ H ₆	< 5 ^d
10	PhSCH ₂ COCH ₃	A (KOtBu)	+ HMPA, -30°C	< 5
11		B (K ₂ CO ₃)	TEBAC, 40°C	< 5
12		B (KOtBu)	Aliquat, 40°C	< 10 ^d
13		B (KOtBu)	Aliquat, 40°C with C ₆ H ₆	50
14		NaOEt/EtOH	40°C	30
15	CH ₃ COCH ₂ COOtBu	B (K ₂ CO ₃)	TEBAC, 40°C with C ₆ H ₆	80 ^f
16	CH ₂ (COOEt) ₂	B (K ₂ CO ₃)	TEBAC, 40°C with C ₆ H ₆	75 ^c

a) Yields estimated by ¹H NMR after, if needed, Al₂O₃ recondensation. Complement to 100% is starting material unless quoted.

b) 1,2 Adduct present.

c) Only 7α isomer detected.

d) Presence of polymeric material.

e) Determination after aqueous AgNO₃ treatment 7α/7β (Nu = C₆H₅) 90/10.

f) Determination after treatment by TsOH in refluxing C₆H₆ 7α/7β (Nu = CH₂COCH₃) 90/10.

Experimental section

IR spectra were recorded with a Perkin-Elmer 157 or 682 infrared spectrometer and are expressed as ν_{\max} in cm^{-1} . ^1H NMR were run at 90 MHz on a R32 Perkin-Elmer, at 250 MHz on a Brüker AM250 and at 400 MHz on the experimental equipment of the I.E.F. (Orsay) and are reported in δ ppm (internal standard Me_4Si). Mass spectra were run on a Nermag R10-10 mass spectrometer. Preparative thick layer chromatographies were performed on 0.5 mm x 20 cm x 20 cm Merck silica gel plates (60F-254) the solvents were purified as previously described 6,7 and dienone **1b** prepared according to literature 4.

General procedure

a) In THF or THF-HMPA : In a flame-dried flask flushed by argon, 5 mmoles reagent **2**, **3**, or **4** were dissolved in 25 ml THF or 20 ml THF and 5 ml HMPA and cooled at -70°C by a nitrogen bath. 5 mmoles $n\text{BuLi}$ in hexane (Merck) or sublimated KOtBu (550 mg) dissolved in 2 ml of THF or HMPA were added. After 15 min stirring at -70°C , 5 mmoles **1b** (810 mg) were added via a syringe and the reaction mixture stirred at the indicated temperature during 3-5 hours.

The reaction was quenched by aqueous HCl solution, extracted by Et_2O ; the solvent was evaporated and the crude product dissolved into 20 ml CH_2Cl_2 ; 30 g Al_2O_3 were added (Ega Chemie 5016A) and the mixture stirred at room temperature for 2 hrs. After filtration, the alumina was washed with CH_2Cl_2 and the solvent evaporated. **7** (R = PhSCHCN as a 1/1 mixture of **7a** stereoisomers) was purified by TLC (eluent Et_2O /hexane = 70/30) (yield : 90%). **7** (R = PhC(CN)NMe₂) was characterized by ^1H NMR the crude product obtained in entries 5-7 was dissolved into THF- Et_2O then treated by aqueous AgNO_3 0.5N according to **7** leading to a **7a**/**7b** 90/10 mixture, which was identified according to literature 6 (yield: 70%).

b) In PTC : To a solution of 2.5 mmoles carbon acid **2**, **3**, **4**, **5** or **6** in 3 ml C_6H_6 , a small amount of TEBAQ or Aliquat 336 was added, then 2.5 mmoles solid $t\text{BuOK}$ (275 mg) KOH (140 mg) or K_2CO_3 (345 mg) and finally 2.5 mmoles dienone **1b** (405 mg) eventually dissolved in 10 ml of C_6H_6 . The reaction mixture was stirred for 2-3 hrs at $40-50^\circ\text{C}$, then diluted with Et_2O , washed with water, dried over MgSO_4 and concentrated.

- **7a** (R = $\text{CH}_3\text{COCH}(\text{SPh})$) was purified TLC so that one isomer could be obtained pure. The crude product obtained after the reaction of t -butylacetoacetate in PTC conditions (entry 15) was dissolved in 15 ml benzene and refluxed for 30 min after addition of a small amount of p -toluenesulfonic acid. After cooling, 25 ml Et_2O was added, the organic phase was washed with aqueous K_2CO_3 , water, dried and evaporated **7a** (R = CH_2COCH_3) was obtained by crystallization from hexane-ether (95/5).

Description of new compounds

7a-(1-Phenylthio-1-cyanomethyl)-10-methyl-1,2,3,6,7,8,9-H-3-naphtalenone (**7a**, Nu = $\text{CHCN}(\text{SPh})$) mixture of 2 stereoisomers from which one isomer is obtained pure by TLC on Al_2O_3 . m.p. = 142.4°C (EtOH) $\text{C}_{18}\text{H}_{21}\text{NOS}$ = 312; M.S. m/z = 312; I.R. (CHCl_3) : 2930 (CH), 2220 (CN), 1665 (CO) for both isomers; ^1H NMR (400 MHz, CDCl_3) : pure **7a** : 1.27, s, 3H (CH₃); 1.4, m, 1H (H₉); 1.6, m, 1H (H_{9'}); 1.81, m, 2H (H₁, H_{1'}); 1.92, m, 1H (H₈); 2.05, m, 1H (H_{8'}); 2.17, m, 1H (H₇); 2.36, m, 1H (H₂); 2.48, m, 1H (H_{2'}); 2.61, m, 1H (H₆); 2.9, m, 1H (H_{6'}); 3.56, d, 1H (H₄), $^3\text{J}_{\text{H}_7\text{H}_4} = 5.5$ Hz; 5.83, s, 1H (H₄); 7.39 - 7.84, AA'BB'C system, 5H (aromatic protons).

The following coupling constants were determined in C_6D_6 : $^3\text{J}_{\text{H}_6\text{H}_7} = 2.2$ and $^3\text{J}_{\text{H}_6'\text{H}_7} = 5.8$ Hz showing that H₇ is equatorial.

7a (deduced from the mixture) : 2.55, m, 1H (H₆); 2.75, m, 1H (H_{6'}); 3.5, d, 1H (H₄), $^3\text{J}_{\text{H}_7\text{H}_4} = 5.5$ Hz; 5.86, s, 1H (H₄). From C_6D_6 solution $^3\text{J}_{\text{H}_6\text{H}_7} = 2.5$ and $^3\text{J}_{\text{H}_6'\text{H}_7} = 6.3$ Hz.

7-Cyanomethyl-10-méthyl-1,2,3,6,7,8,9-H-3-naphtalenone (**7a** (Nu = CH_2CN) : Obtained by refluxing 130 mg of the mixture of stereoisomers obtained above in 10 ml ethylacetate in the presence of 1 g Raney Nickel for 4-5 hrs. After filtration and evaporation of the solvent and TLC chromatography (eluent: ether/hexane 70/30), a single compound is obtained (yield : 65%). m.p. = 68°C , $\text{C}_{13}\text{H}_{17}\text{NO}$ = 204; M.S. m/z = 204; I.R. (CHCl_3) : 2930 (CH), 2225 (CN), 1660 (CO); ^1H NMR (90 MHz, CDCl_3) : 1.25, s, 3H (CH₃); 1.5 - 2.75, m, 13H (cyclic protons + CH_2CN); 5.2, s, 1H (H₄). Analysis calc. % : C = 76.8; H = 8.43; N = 6.89; found % : C = 76.73; H = 8.66; N = 6.69.

7a-Acetonyl-10-methyl-1,2,3,6,7,8,9-H-3-naphtalenone **7a** (Nu = CH_2COCH_3). m.p. = 114.5°C (hexane/ether : 95/5); $\text{C}_{14}\text{H}_{20}\text{O}_2$ = 220; M.S. m/z = 220; I.R. : 1715; 1660 (CO); ^1H NMR (400 MHz, CDCl_3) : 1.26, s, 3H (CH₃); 1.49 - 2.65, m, 8H (cyclic protons); 2.08, m, 1H (H_{6e}); 2.13, s, 3H (COCH₃); 2.41, m, 1H (H₇), $\text{W}_{1/2}$ determined after H₄ and H₆ irradiation : 7 Hz; 2.59, m, 2H (CH₂CO); 2.65, m, 1H (H_{6a}); 5.71, s, 1H (H₄). Analysis calc. % : C = 76.32; H = 9.15; found % : C = 76.47; H = 9.19.

7a-Acetonyl-10-methyl-1,2,3,6,7,8,9-H-3-naphtalenone **7a** (Nu = CH_2COCH_3); ^1H NMR (90 MHz, CDCl_3), deduced from the spectrum of the mixture **7a**+**7b** : 1.15, s, 3H (CH₃); 5.65, s, 1H (H₄).

7a(Dicarboethoxymethyl)-10-methyl-1,2,3,6,7,8,9-H-3-naphtalenone **7** (Nu = $\text{CH}(\text{COOEt})_2$); ^1H NMR (400 MHz, CDCl_3) : 1.26, t, 3H (CH₂CH₃); 1.27, s, 3H (10-CH₃); 1.56 - 2.65, m, 9H (cyclic protons); 2.65, m, 1H (H₆); 2.75, m, 1H (H₇), $\text{W}_{1/2}$ determined after H₄ irradiation : 12 Hz; 3.38, d, 1H (H₄), $^3\text{J}_{\text{H}_7\text{H}_4} = 12$ Hz; 4.18, q, 2H (CH₂CH₃); 5.64, s, 1H (H₄).

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