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STEREOSPECIFIC SYNTHESIS OF METHYL VINYL KETONES

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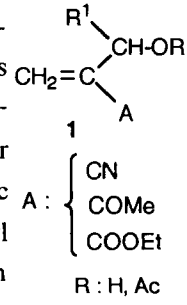
Abstract: *A stereospecific synthesis of enones **3** by coupling reaction of α-acetoxy alkyl methyl vinyl ketones **2** and Gilman or Grignard reagents in the presence of a catalytic amount of copper (I) salt at low temperature, is described.*

α,β-Unsaturated ketones[1-6] have attracted much attention as synthetic intermediates particularly in the most important areas of application such as Michael, Robinson annulations[8], hydrocyanations[9], heterodiene syntheses[10] and Diels-Alder cyclaodditions[11]. Although, new synthetic methods are reported regularly there is no general one which covers all the different types of vinyl ketones.

In connection with our studies on the reactivity of α-functional acrylic derivatives **1**[12-17], we have now extended its utility to provide a facile and stereospecific synthesis of α,β-unsaturated methyl ketones **3** involving the addition of dialkyl or diaryl cuprates or Grignard reagents in the presence of a catalytic amount of copper (I) salt at low temperature, to methyl vinyl ketones derivatives **2** in the appropriate solvent as indicated in scheme 1.



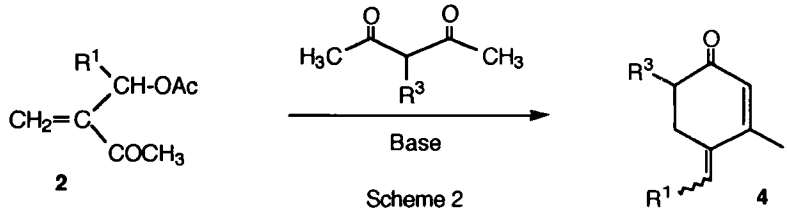
*To whom correspondence should be addressed.

Table : α-Alkyl α,β-unsaturated ketones **3a-i** from α-acetoxyalkyl methyl vinyl ketones **2**

R^1	$(R^2)_2CuM$ or $R^2M+\varepsilon Cu(I)$	Solvent(s)	T°C	Ketones *3a-i*	Yield(%)
CH_3	$(nBu)_2CuLi$	Et_2O	-78	***3a***	**80**
CH_3	$(C_6H_5)_2CuMgBr$	THF-Et_2O (1:1)	-78	***3b***	**70**
C_2H_5	nBuMgCl+5%Cu(I)*	THF	-50, - 0	***3c***	**85**
C_2H_5	$(nBu)_2CuLi$	Et_2O	-78	***3c***	**90**
C_2H_5	$(C_6H_5)_2CuMgBr$	THF-Et_2O (1:1)	-40, - 0	***3d***	**75**
C_6H_5	iPrMgCl+5%Cu(I)*	THF	-78	***3e***	**57**
C_6H_5	$(nBu)_2CuLi$	Et_2O	-78	***3f***	**88**
C_6H_5	$(C_6H_5)_2CuMgBr$	THF-Et_2O (1:1)	-78	***3g***	**84**
C_6H_5	$(Me)_2CuMgI$	Et_2O	-78	***3h***	**53**
C_6H_5	EtMgBr+5%Cu(I)*	THF	-78	***3i***	**58**

(*) Solution of $LiCuBr_2$ (1M) in THF was employed.

Organometallic reagents [Gilman: $(R^2)_2CuM$ and Grignard $(R^2M+\varepsilon Cu(I)]$ and reaction conditions have been designed so that addition occurs exclusively 1,4. The overall process consists in the nucleophilic Michael addition of these reagents to the carbon-carbon double bond of the vinylic ketones **2** leaving the acetate group and forming selectively the desired α-alkylated α,β-unsaturated ketones **3** in good yields. Configurational assignment was established by ^1H NMR spectroscopy, the configuration being supported by the abnormal downfield shift of the vinylic proton (δ>7ppm)[18,19].This methodology can be extended to the known reaction, coupling of **2** with aliphatic potassium β-diketone enolates in the same manner, as previously described[17]. The reaction leads to a "one pot" synthesis of γ-alkylidene α,β-cyclohex-2-en-1-ones derivatives **4** (Scheme 2) which will be the subject of our future reports.



Scheme 2

Experimental Section

Allylic acetates of type **2** have been prepared in high yields by the action of acetic anhydride in the presence of one drop of concentrated sulfuric acid in ether[16,20] at 0°C on the corresponding alcohols which can be prepared by DABCO-catalysed coupling of aldehydes with methyl vinyl ketone[13,14]. β-Diketones **3** are commercial grade or prepared according to Johnson's method[21]. Reaction progress and purity of products were monitored on an Intersmat 20M gas chromatograph using a 3mx3mm column packed with 10% SE 30. Thin-layer chromatography was performed on precoated silica gel plates (Merck F 254) and silica gel GEDURAN SI 60 (70-230mesh, Merck) was used for preparative chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Jeol C-HL 60 MHz and Bruker 300MHz instruments in $CDCl_3$ solution with TMS as the internal standard. Mass spectra were obtained on a VARIAN MAT 112 with double focalisation.

Synthesis of (E) α-alkyl-α,β-unsaturated methyl ketones 3a-i

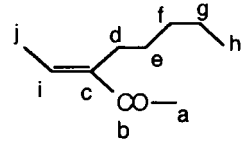
Cuprates addition to the allylic acetates 2: *General procedure*

A four-necked, round-bottomed flask, equipped with a mechanical stirrer, nitrogen inlet tube, and side-armed addition funnel, was cooled in nitrogen-bath to -30°C and charged with ether (60 mL) and cuprous iodide (12 mmol), which was followed by addition of n-butyllithium (25mmol, 1,6N in hexane). The mixture was stirred for 30 min then cooled at -78°C followed by the addition during 20 min

of the allylic acetate **2a** (10 mmol) dissolved in 10 mL of ether. After the addition was complete, the reaction mixture was stirred at -78°C for 30 min again, then quenched with saturated ammonium chloride solution and extracted with ether (3x30 mL). The organic layers combined were washed successively with aqueous $Na_2S_2O_3$ and brine. The organic layer was dried ($MgSO_4$) and the solvent was removed to leave an oil, which was distilled in vacuo, giving **3a** (1,23 g, 80%).

Grignard reagents addition to the allylic acetates 2: *General procedure*

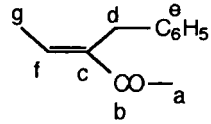
Using the conditions as described for the cuprates, Grignard reagent was added dropwise to the stirred mixture of allylic acetate 2 (10mmol), $LiCuBr_2$ (5%, 0.5mL) in 60 mL of THF at temperature (See Table).



(E)-3-Ethylidene octanone *3a*

bp: 48°C/1torr

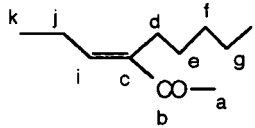
IR($CHCl_3$,vcm^{-1}): 1640(C=C) ; 1660(C=O). ^1H NMR($CDCl_3$,δppm): 0.84 (t, 3H, J=6Hz, CH_3); ; 1.28 (m, 6H, $3CH_2$); 1.83 (d; 3H, J=6Hz, CH_3) ; 2.03 (m, 2H, CH_2) ; 2.25 (s, 3H, CH_3CO); 6.69 (q; 1H, j=6Hz, -CH=). ^{13}C NMR($CDCl_3$,δppm): a: 25.63 ; b: 199.41 ; c: 143.68 ; d: 31.99 ; e: 28.69 ; f: 25.11 ; g: 22.59; h: 14.06 ; i: 138.31; j: 14.68. Mass m/z(%): 43(100) ; 55(40) ; 69(42) ; 83(16) ; 139(30) ; 154($M^{+\cdot}$, 4).



(E)-3-Ethylidene-4-phenylbutanone *3b*

(Silica gel, hexane then ether).

IR($CHCl_3$,vcm^{-1}): 1635(C=C) ; 1670(C=O) ; .^1H NMR($CDCl_3$,δppm): 1.93 (d; j=6,90Hz,3H,CH_3) ; 2.30 (s,3H,CH_3CO) ; 3.68 (s,2H,CH_2) ; 6.90 (q; j=6,90Hz,1H,-HC=) ; 7.20 (m, 5H,C_6H_5). ^{13}C NMR($CDCl_3$,δppm): a: 25.57 ; b: 198.92 ; c: 139.91 ; d: 30.51 ; e: 125.70 , 128.20, 139.74 ; f: 141.86 ; g: 15.10. Mass m/z(%): 43(100) ; 91(73) ; 115(16) ; 130(29) ; 131(33) ; 159(45) ; 174($M^{+\cdot}$, 40).

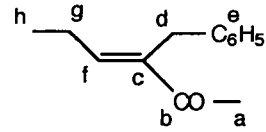


(E)-3-Propylidene octanone *3c*

bp: 63°C/0.1 torr

IR($CHCl_3$,vcm^{-1}): 1635(C=C) ; 1670(C=O). ^1H NMR($CDCl_3$,δppm): 0.88(t,3H,J=7Hz,CH_3) ; 1.09(t,3H,J=7Hz,CH_3); 1.28(m,6H,$3CH_2$); 2.26(m,4H,$2CH_2$); 2.28(s,3H,CH_3CO) ; 6.58(t,J=7Hz,1H,-CH=). ^{13}C NMR($CDCl_3$,δppm): a: 25.53 ; b:

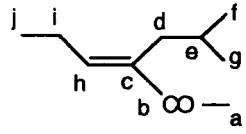
199.62 ; c: 141.83 ; d: 29.23 ; e: 25.25 ; f: 22.44 ; g: 22.17 ; h: 13.34 ; i: 145.14 ; j: 31.87 ; k: 13.92. Mass m/z(%): 43(100) ; 69(30) ; 83(14) ; 111(25) ; 139(24) ; 168($M^{+\cdot}$, 13).



(E)-3-Propylidene-4-phenylbutanone ***3d***

(Silica gel, hexane then ether)

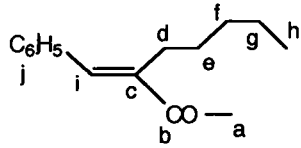
IR($CHCl_3$,νcm^{-1}): 1635(C=C) ; 1665(C=O). ^1H NMR($CDCl_3$,δppm): 1.07(d,3H,J=7Hz,CH_3) ; 2.23(s,3H,CH_3CO) ; 2.36(m,2H,CH_2) ; 3.67(s,2H,CH_2) ; 6.75(t,J=7Hz,-CH=) ; 7.20(m,5H,C_6H_5). ^{13}C NMR($CDCl_3$,δppm): a: 25.62 ; b: 199.24 ; c: 140.18 ; d: 30.85 ; e: 125.37 ; 128.44 ; 139.92 ; f: 146.78 ; g: 22.64 ; h: 13.07 . Mass m/z(%): 43(100) ; 65(13) ; 91(38) ; 77(8) ; 115(16) ; 145(20) ; 159(67) ; 188($M^{+\cdot}$, 57).



(E)-5-Methyl-3-propylidene hexanone ***3e***

(Silica gel, hexane then ether)

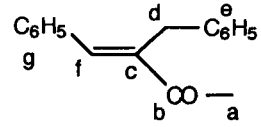
IR($CHCl_3$,νcm^{-1}): 1635(C=O) ; 1665(C=O) ; 1645(C=C). ^1H NMR($CDCl_3$, δppm): 0.84(d,6H,J=7Hz,$2CH_3$) ; 1.08(t,3H,J=7Hz,CH_3) ; 1.75(m,1H,-CH-) ; 2.18(d,2H,J=7Hz,CH_2) ; 2.27(m,2H,CH_2) ; 2.29(s,3H,CH_3CO) ; 6.70(t,1H,J=7Hz, -HC=). ^{13}C NMR($CDCl_3$,δppm): a: 25.70 ; b: 199.95 ; c: 140.73 ; d: 28.05 ; e: 34.00 ; f. g: 22.41 ; h: 145.92 ; i: 22.50 ; j: 13.29. Mass m/z(%): 43(96) ; 55(22) ; 69(42) ; 97(38) ; 11(100) ; 125(13) ; 154 ($M^{+\cdot}$, 63).



(E)-3-Benzylidene octanone ***3f***

bp: 114°C/1 torr

IR($CHCl_3$,νcm^{-1}): 1600(C=C) ; 1620(C=C) ; 1670(C=O). ^1H NMR($CDCl_3$,δppm): 0.89(t,3H,J=6,9Hz,CH_3) ; 1.32(m,6H,$3CH_2$) ; 2.46(s,3H,CH_3CO) ; 2.50(m,2H,CH_2) ; 7.39(m,5H,C_6H_5) ; 7.47(s,1H,-CH=). ^{13}C NMR($CDCl_3$,δppm): a: 26.14 ; b: 201.23 ; c: 136.80 ; d: 33,00 ; e: 28.81 ; f. g: 27.30 ; 27.10 ; h: 14.95 ; i: 140.28 ; j: 128.47; 129.16; 135.80. Mass m/z(%): 43(100) ; 57(1) ; 77(4) ; 91(32) ; 145(9) ; 159(20) ; 173(6) ; 201(10) ; 216($M^{+\cdot}$, 23).



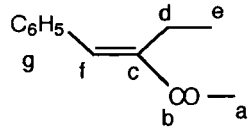
(E)-3-Benzylidene-4-phenylbutanone ***3g***

(Silica gel, hexane then ether)

IR($CHCl_3$,νcm^{-1}): 16200(C=C) ; 1625(C=C) ; 1670(C=O). ^1H NMR($CDCl_3$,δppm):

2.46(s,3H,CH_3CO) ; 3.95(s,2H,CH_2) ; 7.24(m,5H,C_6H_5) ; 7.35(m,5H,C_6H_5) ; 7.77(s,1H,-CH=). ^{13}C NMR($CDCl_3$,δppm): a: 26.26 ; b: 199.80 ; c: 139.83 ; d: 32.17; e.g: 139.46; 126.01; 128.60; 135.33; 127.92; 128.89; 129.20 ; f: 141.30. Mass m/z(%): 43(67) ; 91(50); 115(99) ; 157(21) ; 192(61) ;193 (31) , 221(22) ; 236($M^{+\cdot}$, 100).

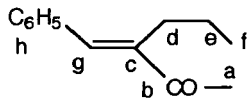
(E)-3-Benzylidene pentanone ***3h***



(Silica gel ; hexane : Ethyl acetate , 9:1)

IR($CHCl_3$,νcm^{-1}): 1620(C=C) ; 1660(C=O). ^1H NMR($CDCl_3$,δppm): 1.10(t,3H,J=7Hz,CH_3) ; 2.43(s,3H,CH_3CO) ; 2.53(m,2H,CH_2) ; 7.36(m,5H,C_6H_5) ; 7.45(s,1H,-CH=). ^{13}C NMR($CDCl_3$,δppm): a: 26.05 ; b: 199.97 ; c: 143.97 ; d: 19.53 ; e: 13.71 ; f: 139.29 ; g: 135.69; 128.49. 128.28. Mass m/z(%): 43(100) ; 65(11) ; 77(15) ; 91(86) ; 131(74) ; 159(51) ; 174($M^{+\cdot}$, 68).

(E)-3-Benzylidene hexanone ***3i***



(Silica gel ; hexane : Ethyl acetate , 8:2)

IR($CHCl_3$,νcm^{-1}): 1620 (C=C) ; 1660 (C=O). ^1H NMR($CDCl_3$,δppm): 0.93(t,3H,J=7Hz,CH_3) ; 1.43(m,2H,CH_2) ; 2.43(s,3H,CH_3CO) ; 2.43(m,2H,CH_2) ; 7.33(m,5H,C_6H_5) ; 7.40(s,1H,-CH=). ^{13}C NMR($CDCl_3$,δppm): a: 27.05 ; b: 201.19 ; c: 140.5 ; d: 29.33 ; e: 23.44 ; f: 15.23 ; g: 143.85 ; h: 136.78; 130.17; 129.49. Mass m/z(%): 43(100) ; 91(29) ; 145(24) ; 130(10) ; 159(15) ; 173(20) ; 188($M^{+\cdot}$, 24).

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References

1. Grieco, P.A., Boxler, D., Pogonowski, C.S. *Chem. Commun., 1974, 479.*
2. Floyd, J.C. *Tetrahedron Lett., 1974, 33, 2877.*
3. Trahanovski, W.S., Mullen, P.W. *J. Am. Chem. Soc, 1972, 94, 5086.*
4. Ksander, G.M., McMurry, J.E. *Tetrahedron Lett., 1976, 51, 4691.*
5. Croteau, A.A., Termini, J. *Tetrahedron Lett., 1983, 24, 2481.*
6. Moskal, J., Van leusen, A.M. *Tetrahedron Lett., 1984, 25, 2585.*
7. For leading references, see: *Comprehensive Organic Chemistry*, Barton & Ollis, Vol 1 (Stoddart, J.F., Ed.) p.1043.

8. *Comprehensive Organic Chemistry*, Barton & Ollis, Eds in chief, pergamon, Oxford 1979 and Waring in vol 1 (Stoddart, J.F., Ed.) p.1049.

9. Nagata, W., Yoshioka, M. *Org. React., 1977 25, 255.*

10. Desimoni, G., Tacconi, G. *Chem. Revs., 1975, 75, 561.*

11. Newton, J., in vol 6 (Dayton, J.C., Ed.) p. 895.

12. Villiéras, J., Rambaud, M. *Synthesis, 1982, 924.*

13. Amri, H., Villiéras, J. *Tetrahedron Lett., 1986, 27, 4307.*

14. Basavaiah, D., Bharati, T.K., Gowriswari, V.V.L. *Synth. Commun., 1987, 17, 1893.*

15. Amri, H., Rambaud, M., Villiéras, J. *J. Oganomet. Chem.,1986, 308, C27.*

16. Amri, H., Rambaud, M., Villiéras, J. *J. Oganomet. Chem.,1990, 384, 1.*

17. Beltaïef, I., Amri, H. *Synth. Commun., 1994, 24, 2003.*

18. Bull, L.B.,Culvenor, C.C.J., Dick, A.T. *The pyrolizidine Alkaloids, North Holland Publishing Co., Amsterdam, 1968.*

19. Pascual, C., Meier, J., Simon, W. *Helv. Chim. Acta, 1966, 49, 164.*

20. Drewes, S.E., Emslie, N.D. *J. Chem. Soc. Perkin trans. I, 1982, 2079.*

21. Johnson, A.W., Markham, E., Price, R. *Org. Syn., 1962, 42, 75.*

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