CONJUGATE ADDITION OF GRIGNARD REAGENTS TO α-FUNCTIONAL ENONE PROMOTED BY $LiCuBr_2$

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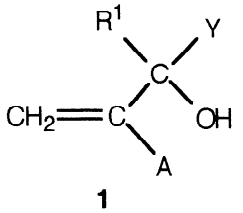
ABSTRACT

α-Functional methyl vinyl ketone **2** reacts with magnesium dialkyl cuprates generated in situ to produce the corresponding γ-ketoesters **3** in good yields.

RESUME

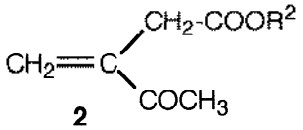
L'addition conjuguée d'organomagnésiens en présence de (3%) de $LiCuBr_2$ aux cétones vinyliques α-fonctionnelles de type **2** conduit aux γ-cétoesters **3** avec de bons rendements.

The Baylis-Hillman reaction[1-3] constitutes now a general synthetic method to access to multifunctional molecules **1** in forming carbon-carbon bond in α-position by coupling activated alkenes and some electrophiles in the presence of tertiary amines as catalyst[4-10]. We have recently described a convenient method for the preparation of α-functional enone **2**[11] via a deacylative condensation of monoalkylated β-diketones with 30% aqueous formaldehyde under heterogeneous conditions (Scheme 1).



1

Y = H , Me
R^1 = alkyl, COOEt, COMe
R^2 =Me, Et
A = COMe , COEt, COOEt, CN



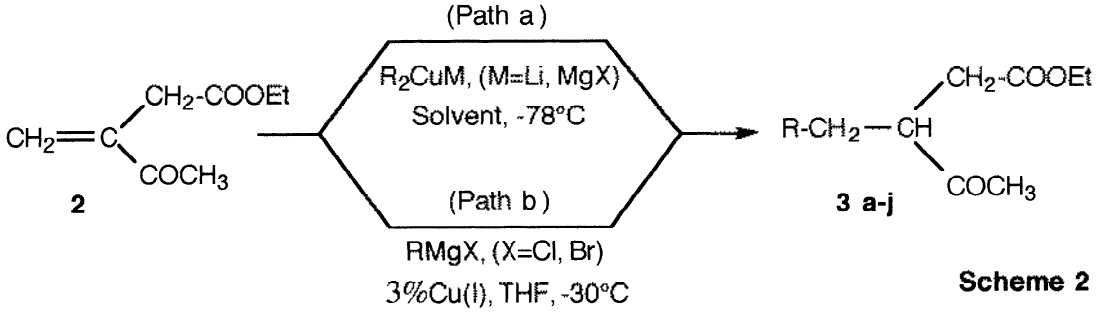
2

Scheme 1

In the light of our previous studies on the reaction of organocopper reagents to α-functional acrylic derivatives[12,13], we decided to examine the behaviour of enone **2** towards some magnesium dialkyl cuprates generated *in situ* . Simple enones are recognised as good Michael acceptors towards organocopper compounds[14-18] and lithium organocuprates (R_2CuLi : Gilman reagents)[19-21]. Unfortunately, the introduction of alkyl substituents at the β-position of enones prevents or frequently inhibits the conjugate addition. Some of these problems were solved by using higher order cuprates[22] $R_2Cu(CN)Li_2$, monoorganocopper reagents-phosphine ligand[23] $RCu.(nBu)_3P$,

$RCu.BF_3$ system[21-24], a combination of alkyllithium and bis-2,5-di-t-butyl-4-alkylphenoxide (MAD or MAT)[25] and more commonly, additives such as Me_2S[26], LiBr[27], TMSCl[28,29] or phosphorous derivatives e.g. HMPA[30], $(EtO)_3P$[31].

In addition to these methods for specific introduction of a hydrocarbon group to the β-position of activated enone **2**, which offers three electrophilic sites, we realize that organocuprates prepared *in situ* without additives, are proved to be selective reagents in the synthesis of the γ-alkylated-γ-ketoesters **3** (Scheme 2).



Scheme 2

RESULTS

From a synthetic point of view, two pathways were envisaged to realise conjugate addition of an organocopper reagent to enone **2**. Thus as shown in **path a**, the reaction of lithium and magnesium organocuprates and enone **2** (1:1.25 ratio) in ether or THF-Et_2O (1:1) at -78°C gives, after quenching with aqueous ammonium chloride solution, the desired conjugate addition products **3** in satisfactory yields (entries 1, 2, 6 and 7). This method suffers from severe disadvantages. For instance one equivalent of the organic group is inevitably wasted in addition to the extended reaction times (1 to 2 hours).

In order to decrease the reaction time (**path b**), we assumed that the key to effecting 1,4-addition to enone **2** lays simply in conducting the reaction using a slight excess of Grignard reagent (1.2 equiv. entries 2-7 except entries 4 and 10 where 1.7 to 2 equiv. of reagent were required) in the presence of copper (I) salt as catalyst. We first tested the catalytic activity of Cu(I) compounds including CuCl, CuBr and CuI which seemed to be effective, but the solubility of some of them in the solvent, in addition to the reaction complexity,were globally inconclusive. Thus, the introduction of 3 mol % of lithium dibromocuprate ($LiCuBr_2$) as catalyst in the reaction medium accelerates remarkably the over-all rate of the reaction (lower than 5 min, entries 2-10).This catalytic method was applied to various Grignard reagents as illustrated in the Table.

The results presented above indicate that, Gilman reagents and the more available Grignard reagents in the presence of catalytic amount of $LiCuBr_2$ led to the same products when they were especially coupled to α-functional enone **2** at low temperature. The latter method combines advantages such as simplicity, short reaction times and good yields. Finally, as it is apparent in the Table, yields of 1,4-adducts are not affected by the nature of the alkyl or the aryl halides (X=Cl, Br) from which Grignard reagents were prepared.

Table : Conjugate addition of Grignard reagents in the presence of $LiCuBr_2$ as catalyst to enone **2** .

Entry	Reagent (equiv.) R_2CuM/RM	$LiCuBr_2$* (mol %)	Solvent, T°C, time	1,4-Adduct 3a-j	Yield (%)
1	$(CH_3)_2CuMgI$ (1.25)	-	Et_2O-THF, -78°C, 2h	**3a**	89
2	C_2H_5MgBr (1.2) $(C_2H_5)_2CuMgBr$ (1.25)	3% -	THF, -30°C, 5min Et_2O-THF, -78°C, 2h	**3b**	59 75
3	iC_3H_7MgBr (1.2)	3%	THF, -30°C, 4 min	**3c**	75
4	nC_3H_7MgCl (1.2) nC_3H_7MgBr (1.2)	3% 3%	THF, -30°C, 5min THF, -30°C, 5min	**3d**	82 67
5	iC_3H_7MgCl (1.2) iC_3H_7MgBr (1.2)	3% 3%	THF, -30°C, 5min THF, -30°C, 5min	**3e**	77 95
6	nC_4H_9MgCl (1.2) nC_4H_9MgBr (1.2) nC_4H_9MgBr (1.2) $(nC_4H_9)_2CuLi$ (1.25)	3% 3% 3% -	THF, -30°C, 5min THF, -30°C, 5min Et_2O, -30°C, 5min Et_2O, -78°C, 1h	**3f**	59 80 69 85
7	tC_4H_9MgCl (1.2) tC_4H_9MgBr (1.2) $(tC_4H_9)_2CuLi$ (1.25)	3% 3% -	THF, -30°C, 5min THF, -30°C, 5min Et_2O, -78°C, 1.5h	**3g**	88 77 84
8	$cC_6H_{11}MgCl$ (2.8)	3%	THF, -30°C, 1.5h	**3h**	81
9	C_6H_5MgCl (1.2) C_6H_5MgBr (1.2)	3% 3%	THF, -30°C, 5min THF, -30°C, 5min	**3i**	73 85
10	$C_6H_5CH_2MgCl$ (2) $C_6H_5CH_2MgBr$ (1.9)	3% 3%	THF, -30°C, 2h THF, -30°C, 2h	**3j**	36 48

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

Experimental Section

α-Functionnal enone **2** has been prepared in high yield according to the reference 11. 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 β-alkylated-γ-ketoesters 3a-j

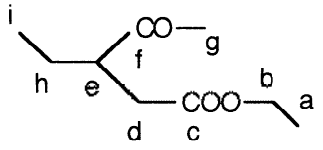
Cuprates addition to the α-functional enone 2: *General procedure*

A four-necked, round-bottomed flask, equipped with a mechanical stirrer, nitrogen inlet tube, and side-armed addition funnel, was cooled in a nitrogen-bath to -30°C and charged with ether (40 mL) and cuprous iodide (12,5 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 30 min of the enone **2** (10 mmol) dissolved in 10 mL of ether. After the addition was complete, the reaction mixture was stirred at -78°C for 1 hour again, then quenched with saturated ammonium chloride solution and extracted with ether (3x30 mL). The organic layers combined were washed with brine then dried over $MgSO_4$. The solvent was removed to leave an oil, which was distilled in vacuo, giving **3 f** (85%).

Grignard reagents addition to enone 2: *General procedure*

Using the conditions as described for the cuprates, Grignard reagent was added dropwise to the stirred mixture of enone **2** (10mmol), $LiCuBr_2$ (3%, 0.3mL) in 40 mL of THF (or Et_2O) at -30°C.

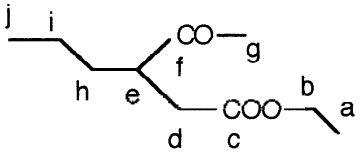
Ethyl 3-ethyl-4-oxopentanoate *3 a*



bp: 126°C/47torr

IR($CHCl_3$,νcm^{-1}): 1710(C=O) ; 1720(C=O). **^{1}H** NMR($CDCl_3$,δppm): 0.85 (t, 3H, J=7Hz, CH_3) ; 1.2 (t, 3H, J=7Hz, CH_3) ;1.4 (m, 2H, CH_2) ; 2.3 (s, 3H, CH_3CO) ; 2.0-3.3 (m, 3H, CH-CH_2-CO) ; 4.07 (q, 2H, j=7Hz, CH_2).

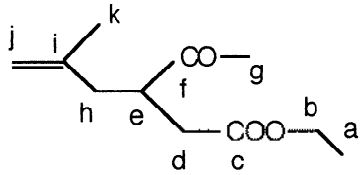
Ethyl 3-propyl-4-oxopentanoate *3 b*



bp: 74°C/1torr

IR($CHCl_3$,νcm^{-1}): 1714(C=O) ; 1731(C=O) ; .**^{1}H** NMR($CDCl_3$,δppm): 0.9 (t,3H j=7Hz,CH_3) ; 1.2 (t,3H j=7Hz,CH_3) ; 1.3 - 1.5 (m, 4H, $(CH_2)_2$) ; 2.2 (s,3H,CH_3CO); 2.3-3.1 (m,3H,(CH-CH_2-CO) ; 4.1 (q,2H, j=7Hz,CH_2) . **^{1} ^{3}C** NMR($CDCl_3$,δppm): a: 13.7 ; b: 60.0 ; c: 172.0 ; d: 34.8 ; e: 47.2 ; f: 210.5 ; g: 29.0 ; h: 33.0 ; i: 19.7 ; j: 13.6. Mass **m/z**(%): 27(21) ; 29(28) ; 41(21) ; 43(100) ; 55(20) ; 69(19) ; 73(20) ; 98(20) ; 101(21) ; 141(18) ; 144(22) .

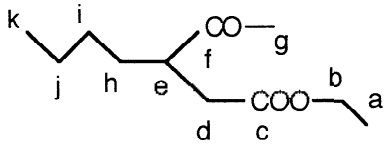
Ethyl 3-(2-methylprop-2-én)yl-4-oxopentanoate *3 c*



bp: 71.4°C/1torr

IR($CHCl_3$,νcm^{-1}): 1649(C=C) ;1714(C=O) ; 1735(C=O) ; .**^{1}H** NMR($CDCl_3$,δppm): 1.2 (t,3H j=7Hz,CH_3) ; 1.73 (m, 3H ,CH_3-C=) ; 2.1 (s,3H,CH_3CO) ; 2.26-3.33 (m,5H,CH_2-CH-CH_2) ; 4.06 (q,2H, j=7Hz,CH_2) 4.7, 4.83 (2m, 2H ,CH_2=C) . **^{13}C** NMR($CDCl_3$,δppm): a: 13.9 ; b: 60.3 ; c: 172.1 ; d: 39.4 ; e: 45.6 ; f: 210.3 ; g: 29.4 ; h: 34.8 ; i: 141.5 ; j: 113.4 ; k: 21.6. Mass **m/z**(%): 27(21) ; 29(32) ; 39(41) ; 41(20) ;43(100) ; 55(21) ; 67(13) ; 81(21) ; 82(17) ; 95(12) ; 109(29) ; 135(11) .

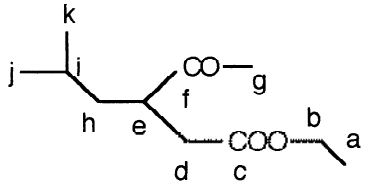
Ethyl 3-butyl-4-oxopentanoate *3 d*



bp: 76°C/1.2torr

IR($CHCl_3$,νcm^{-1}): 1713(C=O) ; 1729(C=O) ; .**^{1}H** NMR($CDCl_3$,δppm): 0.9 (t,3H j=6Hz,CH_3) ; 1.0 - 1.66 (m, 9H ,$(CH_2)_3$ et CH_3) ; 2.16 (s,3H,CH_3CO) ; 2.33-3 (m,3H,CH-CH_2-CO) ; 4.07 (q,2H, j=7Hz,CH_2) . **^{13}C** NMR($CDCl_3$,δppm): a: 13.8 ; b: 60.2 ; c: 172.1 ; d: 35.0 ; e: 47.5 ; f: 210.7 ; g: 28.7 ; h: 29.2 ; i: 30.7 ; j : 22.4 ; k: 13.5. Mass **m/z**(%): 27(23) ; 29(36) ; 39(12) ; 41(24) ;43(100) ; 55(27) ; 69(12) ; 71(12) ; 73(17) ; 83(12) ; 98(30) ; 101(20) ; 111(10) ; 115(23) ; 144(23) ; 155(17) .

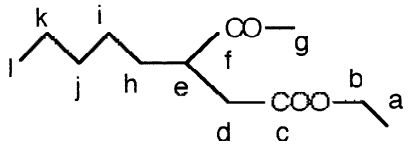
Ethyl 3-isobutyl-4-oxopentanoate *3 e*



bp: 62°C/1torr

IR($CHCl_3$,νcm^{-1}): 1713(C=O) ; 1722(C=O) ; .**^{1}H** NMR($CDCl_3$,δppm): 0.92 (dd,6H , j=6Hz,$(CH_3)_2$-C) ; 1.23 (t,3H j=7Hz,CH_3) ; 1.52 (m, 1H , -CH-) ; 2.23 (s,3H,CH_3CO) ; 2.29-3.4 (m,3H,CH-CH_2-CO) ; 4.07 (q,2H, j=7Hz,CH_2) . **^{13}C** NMR($CDCl_3$,δppm): a: 13.9 ; b: 60.3 ; c: 172.1 ; d: 40.3 ; e: 45.8 ; f: 211.0 ; g: 29.1 ; h: 35.4 ; i: 25.6 ; j , k: : 22.1 , 22.6. Mass **m/z**(%): 27(18) ; 29(23) ; 39(10) ; 41(26) ;43(100) ; 55(16) ; 69(13) ; 73(13) ; 98(26) ; 115(20) ; 144(17) .

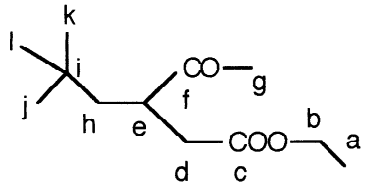
Ethyl 3-pentyl-4-oxopentanoate *3 f*



bp: 82°C/1torr

IR($CHCl_3$,νcm^{-1}): 1714(C=O) ; 1731(C=O) ; .**^{1}H** NMR($CDCl_3$,δppm): 0.8 - 1.8 (m,14H ,CH_3 et $CH_3(CH_2)_4$) ; 2.2 (s,3H,CH_3CO) ; 2.33-3.1 (m,3H,CH-CH_2-CO) ; 4.0 (q,2H, j=7Hz,CH_2) . **^{13}C** NMR($CDCl_3$,δppm): a : 13.9 ; b: 60.2 ; c: 172.2 ; d: 34.9 ; e: 47.6 ; f: 210.6 ; g : 29.2 ; h: 31.0, i:31.5 ; j: 26.3 , k: 22.1 ; i : 13.8 . Mass **m/z**(%): 27(21) ; 29(36) ; 43(100) ; 55(31) ; 71(14) ; 73(15) ; 98(40) ; 101(23) ; 144(31) ;169(12) ;144(31) ;215(M^+) ; 232(M + $NH4^+$).

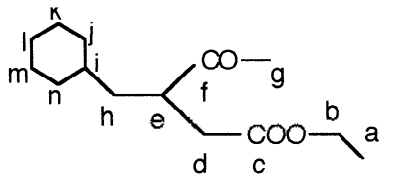
Ethyl 3-(2,2-dimethyl propane)yl-4-oxopentanoate *3 g*



bp:76°C/1torr

IR($CHCl_3$,νcm^{-1}): 1713(C=O) ; 1729(C=O) ; .**^{1}H** NMR($CDCl_3$,δppm): 0.9 (s,9H ,$(CH_3)_3$-C) ; 1.0 - 1.6 (m, 5H , CH_3 et CH_2-tBu) ;2.2 (s,3H,CH_3CO) ; 2.33-3.13 (m,3H,CH-CH_2-CO) ; 4.06 (q,2H, j=7Hz,CH_2) . **^{13}C** NMR($CDCl_3$,δppm): a: 13.9 ; b: 60.3 ; c: 171.8 ; d: 44.0 ; e: 44.2 ; f: 210.5 ; g: 28.8 ; h: 37.4; i: 30.8 ; j , k , l : 29.3 . Mass **m/z**(%): 27(15) ; 29(35) ; 39(13) ; 41(40) ;43(100) ; 55(21) ; 57(42) ; 73(21) ; 83(12) ; 111(16) ; 115(43) ; 153(13) ; 157(16) ; 169(10) ; 215(M^+).

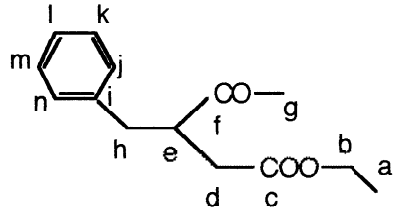
Ethyl 3-cyclohexyl methyl-4-oxopentanoate *3 h*



bp:102°C/1torr

IR($CHCl_3$,νcm^{-1}): 1713(C=O) ; 1722(C=O) ; .**^{1}H** NMR($CDCl_3$,δppm): 1.0-2.2 (2m, 16H, C_6H_{11}-CH_2 et CH_3) ;2.3 (s,3H,CH_3CO) ; 2.33-3.00 (m,3H,CH-CH_2-CO) ; 4.07 (q,2H, j=7Hz,CH_2) . **^{13}C** NMR($CDCl_3$,δppm): a: 13.8; b: 60.2 ; c: 172.0 ; d: 38.6 ; e: 44.9 ; f: 210.8 ; g: 34.9; h: 35.3 ; i : 29.0 j , n: 25.8 , 26.1 ; k , m : 32.6 ; 33.4 ; l : 25.7 . Mass **m/z**(%): 27(15) ; 29(28) ; 39(15) ; 41(42) ;43(100) ; 53(10) ; 55(52) ; 67(24) ; 71(21) ;73(16) ; 81(14) ; 83(10) ; 88(13) ; 98(72) ; 101(11) ; 111(16) ; 115(16) ; 144(71) ; 155(14) ; 195(12) .

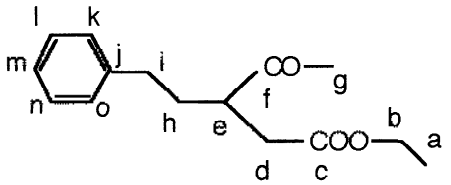
Ethyl 3-benzyl-4-oxopentanoate *3 i*



(Silica gel, hexane then ether).

IR($CHCl_3$,νcm^{-1}): 1603(C=C) ; 1713(C=O) ; 1729(C=O).**^{1}H** NMR($CDCl_3$,δppm): 1.2 (t, 3H, j=7Hz, CH_3) ; 2.1 (s,3H,CH_3CO) ; 2.33-3.50 (m,5H,CH_2-CH-CH_2) ; 4.07 (q,2H, j=7Hz,CH_2) ; 7.2 (m, 5H, C_6H_5). **^{13}C** NMR($CDCl_3$,δppm): a: 14.0 ; b: 60.5 ; c: 172.1; d: 37.5 ; e: 49.5 ; f: 210.7 ; g: 30.2; h: 35.3 ; i : 138.2 j , n: 128.5 ; k , m : 128.8 ; l : 126.6 . Mass **m/z**(%): 27(12) ; 29(23) ; 39(12) ; 43(83) ; 65(23) ; 91(93) ; 104(10) ; 115(24) ; 117(59) ; 118(11) ; 129(11) ; 145(100) ; 146(24) ; 147(76) ; 188(20) ; 189(12) ; 234(12) ; 266(M + NH_4^+).

Ethyl 3-(2-phenyl ethane)yl-4-oxopentanoate *3 j*



(Silica gel, hexane then ether).

IR($CHCl_3$,νcm^{-1}): 1602(C=C) ; 1713(C=O) ; 1728(C=O).**^{1}H** NMR($CDCl_3$,δppm): 1.23 (t, 3H, j=7Hz, CH_3) ; 1.46 - 2.10 (m,2H,CH_2-ϕ) ;2.21 (s,3H,CH_3CO) ; 2.4-3.6 (m,5H,CH_2-CH-CH_2) ; 4.08 (q,2H, j=7Hz,CH_2) ; 7.2 (m, 5H, C_6H_5). **^{13}C** NMR($CDCl_3$,δppm): a: 13.8; b: 60.3 ; c: 171.9; d: 32.8 ; e: 47.1 ; f: 210.3 ; g: 29.2; h: 32.5 ; i : 34.9 j : 140.7 ; k , o : 128.0 , 128.1 ; l , n: 128.1 , 128.2 ; m : 125.9. Mass **m/z**(%): 27(14) ; 29(29) ; 43(95) ; 65(21) ; 71(26) ; 91(65) ; 98(100) ; 104(21) ; 143(13) ; 144(59) .

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