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A One Pot Synthesis of *(E)*-4-Alkylidene-2-Cyclohexen-1-ones

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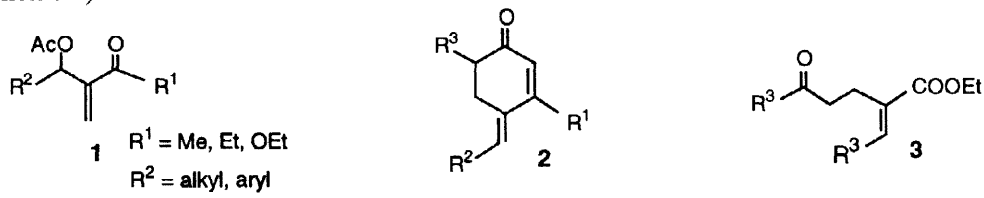
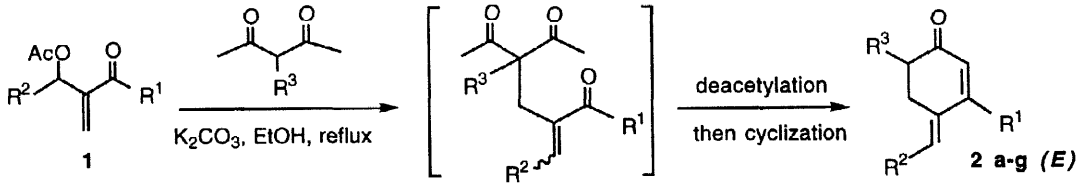
***Abstract** : A one pot synthesis of (E)-4-alkylidene-2-cyclohexen-1-ones 2 via a cross coupling of 2-(1-acetoxy alkyl) enones 1 and aliphatic 1,3-diketones in the presence of anhydrous potassium carbonate in absolute ethanol at reflux, is reported.*

The 4-alkylidene-2-cyclohexen-1-ones **2**[1-8] and some derivatives[9,10] represent the main structural feature of some natural and synthetic products[11-13] characterized by important biological activities[14] and considered as useful flavouring materials and perfumes[8]. Several multi-step methods for the synthesis of these products have been reported. In our ongoing project aimed to further illustrate the potentiality of Baylis-Hillman derivatives **1**[15-20] in organic chemistry, we wish to report a simple one pot synthesis of *(E)*-4-alkylidene-2-cyclohexen-1-ones **2** (Scheme 1).



Scheme 1

We have recently reported a stereospecific synthesis of alkylated enones[21] by coupling **1** with Grignard reagents mediated by copper (I) salt as catalyst. Related compounds **1** (R^1=OEt) were submitted at reflux of absolute ethanol to the action of 1,3-diketone enolates to give, through the use of anhydrous potassium carbonate as a base, 1,5-ketoesters **3**[22,23] in good yields. Therefore we expected 1,3-diketone enolates to react efficiently with 2-functional enones **1** (R^1=Me, Et) in the synthesis of 4-alkylidene-2-cyclohexen-1-ones **2** via the tandem three-step: S_N2' substitution-deacetylation-cyclization reactions (Scheme 2).



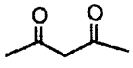
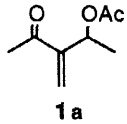
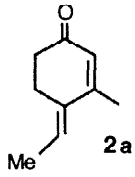
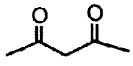
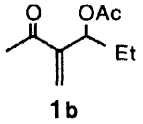
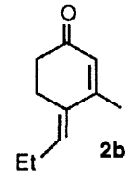
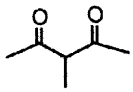
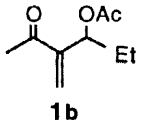
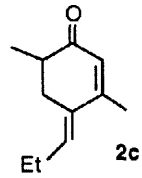
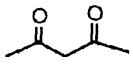
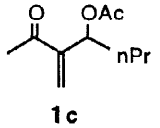
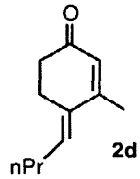
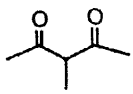
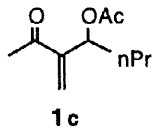
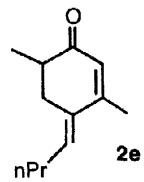
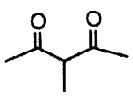
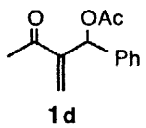
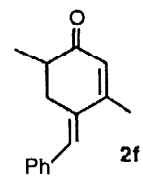
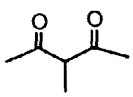
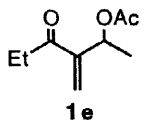
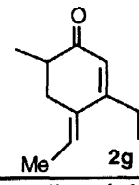
Scheme 2

0040-4039/98/$19.00
PII: S0040-4039(97)10593-7

The reaction with a series of 1,3-diketones and aliphatic 2-functional enones **1** as Michael acceptors was examined. The results are summarised in table 1.

Due to their nucleophilicity, 1,3-diketones enolates proceed through a conjugate addition-elimination which leads to the rapid consumption of the starting Michael acceptors **1a-e** (5 minutes) yielding a triketonic intermediate which may be isolated. Thus, the 1,3-diketone moiety of the intermediate was cleaved *in situ* in the presence of ethanol into new 1,5-dicarbonyl compounds[22,23] followed by a base catalysed intramolecular aldol condensation leading to 4-alkylidene-2-cyclohexen-1-ones[24] **2a-g** *(E)*. In conclusion, we believe that this simple procedure may serve as a useful alternative to the existing methods described above. It compares favourably with them in terms of mild reaction conditions, low cost and reproducibility.

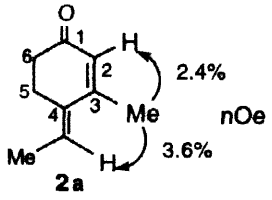
Table 1: *One pot synthesis of (E)-4-alkylidene-2-cyclohexen-1-ones* ***2 a-g***

Entry	1,3-Diketone	Enone **1 a-e**	Time (h)	Products **2 a-g**	Yield (%)
1		 **1a**	2	 **2a**	58
2		 **1b**	2	 **2b**	71
3		 **1b**	2,5	 **2c**	63
4		 **1c**	1	 **2d**	65
5		 **1c**	4	 **2e**	70
6		 **1d**	1	 **2f**	47
7		 **1e**	12	 **2g**	61

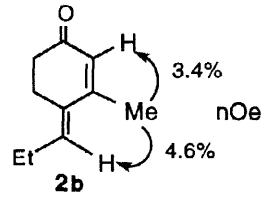
All the yields refer to pure compounds **2a-g**, *isolated chromatographically and characterized by IR,* ^{1}H, ^{13}C *NMR and mass spectrometry.*

For the assignment of the configuration of products **2a-g**, examination of nOe spectra of compounds **2a** and **2b** after irradiation of the methyl protons at C-3 respectively at 2.4 and 2.05 resulted respectively in (2.7 and 3.6%) and (3.4 and 4.6%) enhancement of the vinylic protons at C-2 and alkylidene groups (Scheme 3). The enhancement could only be rationalized if the alkylidene groups was in *(E)*-configuration.

A typical experimental procedure follows: To a mixture of enone **1a** (10 mmol) and anhydrous potassium carbonate (13 mmol) in absolute ethanol (8 mL), was added 2,4-pentanedione (11 mmol). The mixture was stirred at 80°C for a given time (TLC, GC, see table 1). After removing ethanol (and ethyl acetate a by-product) in vacuo, the residue was shaken with water to dissolve the salts. The resulting mixture was extracted three times with 40 mL of ether. The organic phase was dried on $MgSO_4$, concentrated and the crude product **2a** was purified by flash chromatography (EtOAc/Hexane, 3:7).



2a



2b

Scheme 3

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24. Spectral data of products **2 a-g**:

2a : ν_{max} neat/cm^{-1} 1620 and 1660; δ_H (300MHz, $CDCl_3$) 1.86 (3H, d, J = 6.90Hz), 2.04 (3H, d, J = 1.10Hz), 2.47-2.70 (4H, 2t), 5.83 (1H, s), 6.07 (1H, q, J = 6.90Hz) ; ^{13}C-NMR (75MHz, $CDCl_3$) δ: 14.0 ($\underline{C}H_3$-CH=), 20.1 ($\underline{C}H_3$-C=), 24.2 ($\underline{C}H_2$-C=), 36.6 ($\underline{C}H_2$-CO), 125.6 (=H$\underline{C}$-CO), 127.4 ($\underline{C}$H=C), 134.4 ($\underline{C}$=CH-CH$_3$), 155.4 ($\underline{C}$=CH), 199.4 (C=O) ; MS (70eV) : m/z = 136 ($M^{+\cdot}$ 88), 121 (24), 108 (19), 93 (100), 91 (32), 80 (37), 77 (35).

2b : ν_{max} neat/cm^{-1} 1620 and 1650 ; δ_H (300MHz, $CDCl_3$) 1.08 (3H, t, J = 7.40Hz), 2.05 (3H, d, J = 1.07Hz), 2.28 (2H, m), 2.4 -2.70 (4H, 2t), 5.85 (1H, s), 5.95 (1H, q, J = 7.30Hz) ; ^{13}C-NMR (75MHz, $CDCl_3$) δ: 13.7 ($\underline{C}H_3$-CH$_2$), 20.2 ($\underline{C}H_3$-C=), 21.7 (CH$_3$-$\underline{C}H_2$), 24.5 ($\underline{C}H_2$-C=), 36.9 ($\underline{C}H_2$-CO), 126.0 (=H$\underline{C}$-CO), 133.2 ($\underline{C}$H=C), 134.9 (CH=$\underline{C}$), 155.6 ($\underline{C}$=CH), 199.5 (C=O) ; MS (70eV) : m/z = 150 ($M^{+\cdot}$, 99), 135(16), 122(37), 121(22), 108(44), 107(81), 93(70), 91(53), 80(13), 79(100).

2c : ν_{max} neat/cm^{-1} 1630 and 1670 ; δ_H (300MHz, $CDCl_3$) 1.08 (3H, t, J = 6Hz), 1.14 (3H, d, J = 6.70Hz), 2.04 (3H, d, 1.15Hz), 2.23 (4H, m), 2.83 (1H, dd), 5.81 (1H, s), 5.96 (1H, t) ; ^{13}C-NMR (75MHz, $CDCl_3$) δ: 13.8 (CH_2-$\underline{C}H_3$), 15.5 ($\underline{C}H_3$-CH), 19.9 (CH$_3$-C=), 21.7 ($\underline{C}H_2$-CH$_3$), 32.8 ($\underline{C}H_2$-C=), 40.6 ($\underline{C}$H-CO), 125.3 ($\underline{C}$H=C), 133.1 (C=$\underline{C}$H-CH$_2$), 134.9 ($\underline{C}$=CH-CH$_2$), 154.7 (CH=$\underline{C}$), 202.2 (C=O), MS (70eV) : m/z = 164 ($M^{+\cdot}$, 100), 149(10), 136(61), 135(72), 122(25), 121(73), 108(21), 107(82), 93(46), 91(51), 79(87), 77(41), 35(14).

2d : ν_{max} neat/cm^{-1} 1630 and 1660 ; δ_H (300MHz, $CDCl_3$) 0.99 (3H, m), 1.50 (2H, m), 2.21 (2H, m), 2.42 et 2.46 (4H, 2m), 5.86 (1H, s), 5.98 (1H, t) ; ^{13}C-NMR (75MHz, $CDCl_3$) δ: 13.7 ($\underline{C}H_3$-CH$_2$), 20.2 ($\underline{C}H_2$-CH$_3$), 22.3 ($\underline{C}H_3$-C=), 24.7 (CH-$\underline{C}H_2$), 30.3 (=C-$\underline{C}H_2$), 36.8 ($\underline{C}H_2$-CO), 125.9 ($\underline{C}$H-CO), 133.2 (=$\underline{C}$H-CH$_2$), 133.8 (=$\underline{C}$-CH$_2$), 155.6 (=$\underline{C}$-CH$_3$), 199.5 (C=O) ; MS (70eV) : m/z = 164 ($M^{+\cdot}$, 85), 108(19), 135(14), 122(86), 121(26), 107(66), 93(65), 91(56), 79(100), 77(40).

2e : ν_{max} neat/cm^{-1} 1630 and 1665 ; δ_H (300MHz, $CDCl_3$) 0.96 (3H, t, J = 7.30Hz), 1.15 (3H, d, J = 7.70Hz), 1.50 (2H, m), 2.04(3H, d, J = 1.10Hz), 2.26 (4H, m), 2.84 (1H, dd), 5.84 (1H, s), 5.98 (1H, t) ; ^{13}C-NMR (75MHz, $CDCl_3$) δ: 13.5 ($\underline{C}H_3$-CH$_2$), 13.6 (CH-$\underline{C}H_3$), 19.8 ($\underline{C}H_2$-CH$_3$), 22.3 ($\underline{C}H_3$-C=), 30.2 (CH-$\underline{C}H_2$), 32.8 (=C-$\underline{C}H_2$), 40.5 ($\underline{C}$H-CH$_3$), 125.1 (=$\underline{C}$H-CO), 133.6 (=$\underline{C}$H-CH$_2$), 134.3 (=$\underline{C}$-CH$_2$), 154.5 (=$\underline{C}$-CH$_3$), 201.9 (C=O) ; MS (70eV) : m/z = 178 ($M^{+\cdot}$, 100), 149(18), 136(68), 135(80), 122(20), 121(98), 108(87), 107(48), 93(92), 91(53), 79(49), 77(49).

2f : ν_{max} neat/cm^{-1} 1590, 1600, 1651 and 1670 ; δ_H (300MHz, $CDCl_3$) 1.12(3H, d, J = 6.60Hz), 2.17 (3H, d, J = 1.10Hz), 2.56 (2H, m), 3.14 (1H, m), 5.95 (1H, s), 6.93(1H, s), 7.38 (5H, m) ; ^{13}C-NMR (75MHz, $CDCl_3$) δ: 15.4 (CH-$\underline{C}H_3$), 20.4 ($\underline{C}H_3$-C=), 34.9 (=C-$\underline{C}H_2$), 40.9 ($\underline{C}$H-CH$_3$), 136.5 (=$\underline{C}$-CH$_2$), 126.8, 127.6, 128.3, 129.1, 131.2, 135.7 ($\underline{C}_6H_5$), 154.5 (=$\underline{C}$-CH$_3$), 201.7 (CO), MS (70eV) : m/z = 164 ($M^{+\cdot}$, 100), 149(10), 136(61), 135(72), 122(25), 121(73), 108(21), 107(82), 93(46), 91(51), 79(87), 77(41), 35(14).

2g : ν_{max} neat/cm^{-1} 1630 and 1665 ; δ_H (300MHz, $CDCl_3$) 1.13 (6H, m), 1.86 (3H, d, J = 7Hz), 2.40 (4H, m), 2.84 (1H, dd), 5.80 (1H, s), 6.10 (1H, q, J = 7Hz) ; ^{13}C-NMR (75MHz, $CDCl_3$) δ: 12.7 (CH_2-$\underline{C}H_3$), 14.1 ($\underline{C}H_3$-CH), 15.4 (=CH-$\underline{C}H_3$), 25.3 ($\underline{C}H_2$-CH$_3$), 32.9 ($\underline{C}H_2$-CH), 40.6 ($\underline{C}$H-CH$_3$), 122.9 (=$\underline{C}$H-CO), 126.4 (=$\underline{C}$H-CH$_3$), 133.4 ($\underline{C}$=CH-CH$_3$), 159.9 (=$\underline{C}$-CH$_2$), 202.5 (C=O).