Efficient Regioselective Preparation of 2,6-Disubstituted Derivatives of 3-Acetoxy-5,5-dimethyl-2-cyclohexenone

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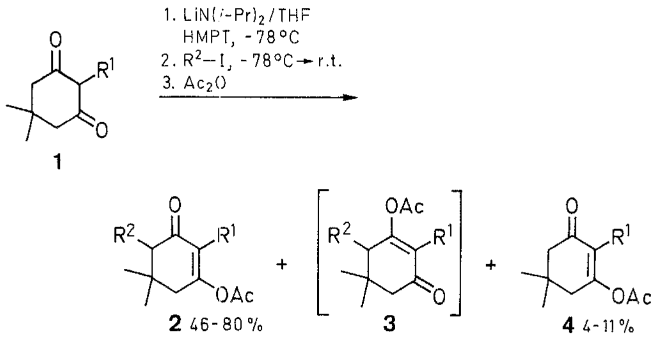
Low temperature generation of dianions of 2-alkylated derivatives of dimedone, followed by alkylation at C-4 and quenching of the reaction mixture with acetic anhydride at room temperature furnishes the least sterically hindered 2,6-dialkyl-3-acetoxy-5,5-dimethyl-2-cyclohexenones **2** with high selectivity in a one-pot process.

In connection with studies directed towards the synthesis of the taxane skeleton, we have described the kinetically controlled generation of dianionic intermediates from 1,3-cyclohexanediones and the subsequent alkylation of these to furnish 4-substituted 1,3-cyclohexanediones in good yield,[1] in a procedure complementary to those developed by Stork[2] and Pattenden.[3] In addition to regioselective alkylation, we demonstrated that quenching the reaction mixture under thermodynamic conditions with acetic anhydride furnishes a mixture of the two possible isomeric enol acetates, in which 6-alkyl-3-acetoxy-2-cyclohexenones are marginally favoured over the 4-alkylated isomers (ca. 2:1). Our rationale for this slight preference was based upon a consideration of the relative steric interactions present in the different isomers.

If our argument for thermodynamic control of the predominant enol acetate were indeed correct, use of *C*-2 substituted 1,3-cyclohexanediones **1** as starting materials in the above conversion would be predicted to result in far greater thermodynamic control of the relative proportions of isomeric enol acetates **2** and **3**, due to the buttressing effect of the *C*-2 and *C*-4 substituents. We now report the results of such a study, which both support our initial proposal and provide ready access to 2,6-disubstituted-3-acetoxy-2-cyclohexenone derivatives **2**, key intermediates in our strategy for taxane synthesis.[4]

Precursors **1**, readily available via photochemical 2-alkylation of dimedone with enol ethers,[5] were subjected to the conditions for dianion generation and alkylation, followed by quenching with acetic anhydride as described previously,[1] and the product mixtures examined by capillary GC and high-field NMR. In all cases investigated, the crude reaction mixtures were found to consist of one major product, corresponding to the desired isomer **2**, accompanied by lesser amounts of acetylated material **4** lacking the *C*-6 substituent. Material, which was tentatively assigned structure **3** on the basis of GC/MS analysis of the crude product mixtures, could also be detected in certain circumstances, but in no case was any such material isolable by chromatography. This may be due either to preferential hydroly-



1-4	R^1	R^2
a	CH_2CH_2OEt	*n*-Pr
b	CH_2CH_2OEt	CH_3
c	CH_2CH_2OEt	*i*-Pr
d	$CH_2CH(CH_3)OCH_3$	CH_3
e	$CH_2CH(CH_3)OCH_3$	*i*-Pr
f	$CH_2CH(n\text{-}C_4H_9)OSiMe_2Bu\text{-}t$	CH_3
g	$CH_2CH(n\text{-}C_4H_9)OSiMe_2Bu\text{-}t$	*i*-Pr

Table. Alkylation of 2-Substituted Dimedones[a,b]

Product(s)	Yield (%)		GC Ratio	bp[c] (°C)/ mbar	Molecular Formula[d]	MS-CI *m/z* (%)	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
	2	**4**	**2:3**				
a	69	–	100:0	116/1.7	$C_{17}H_{28}O_4$ (296.4)	297 (100, M+H$^+$); 255 (31); 253 (18)	0.91 (t, 3H, *J* = 7, $CH_2CH_2C\underline{H}_3$); 0.98, 1.07 [2s, 3H each, $(CH_3)_2$]; 1.16 (t, 3H, *J* = 7, $OCH_2C\underline{H}_3$); 1.31–1.59 (m, 4H, $C\underline{H}_2C\underline{H}_2CH_3$); 2.04 (dd, 1H, *J* = 10, 3, H-6); 2.22 (s, 3H, CH_3CO); 2.31 (d, 1H, *J* = 18, H-4); 2.40–2.60 (m, 2H, $C\underline{H}_2CH_2O$); 2.55 (d, 1H, *J* = 18, H-4); 3.35 (t, 2H, *J* = 7, $C\underline{H}_2OEt$); 3.44 (q, 2H, *J* = 7, $OC\underline{H}_2CH_3$)
b	80	–	91:9	150–160/ 1.3	$C_{15}H_{24}O_4$ (268.3)	269 (100, M+H$^+$)	0.93, 1.08 [2s, 6H, $(CH_3)_2$]; 1.08 (d, 3H, *J* = 7, $CHC\underline{H}_3$); 1.16 (t, 3H, *J* = 7, $OCH_2C\underline{H}_3$); 2.22 (s, 3H, CH_3CO); 2.26 (q, 1H, *J* = 7, H-6); 2.38 (br d, 1H, *J* = 18, H-4); 2.50 (br t, 2H, *J* = 7, $C\underline{H}_2CH_2O$); 2.57 (br d, 1H, *J* = 18, H-4); 3.37 (t, 2H, *J* = 7.2, $C\underline{H}_2OEt$); 3.44 (q, 2H, *J* = 7, $OC\underline{H}_2CH_3$)
c	67	11	96:4	150–160/ 1.3	$C_{17}H_{28}O_4$ (296.4)	297 (100, M+H$^+$); 255 (25)	1.05, 1.06 [2d, 6H, *J* = 6.8, $CH(C\underline{H}_3)_2$]; 1.06, 1.11 [2s, 6H, $(CH_3)_2$]; 1.16 (t, 3H, *J* = 7, $OCH_2C\underline{H}_3$); 1.95 (d, 1H, *J* = 3.9, H-6); 2.03–2.09 [m, 1H, $C\underline{H}(CH_3)_2$]; 2.12 (br d, 1H, *J* = 18, H-4); 2.21 (s, 3H, CH_3CO); 2.44, 2.58 (2 × br dt, 2H, *J* = 13, 7, $C\underline{H}_2CH_2O$); 2.82 (br d, 1H, *J* = 18, H-4); 3.38 (t, 1H, *J* = 7.2, $C\underline{H}_2OEt$); 3.44 (q, 2H, *J* = 7, $OC\underline{H}_2CH_3$)
d[f]	65	4	93:7	140–150/ 1.3	$C_{15}H_{24}O_4$ (268.3)	269 (100, M+H$^+$); 227 (24); 195 (21)	0.93, 0.94 [2s, 3H, 1 CH_3 of $(CH_3)_2$]; 1.05–1.10 [m, 9H, 1 CH_3 of $(CH_3)_2$ + $CHC\underline{H}_3$ + $C\underline{H}_3CHOCH_3$]; 2.21 (s, 3H, CH_3CO); 2.22–2.64 (m, 5H, ring CH_2 + $C\underline{H}_2CHOCH_3$ + H-6); 3.29, 3.30 (2s, 3H, OCH_3); 3.32–3.45 (m, 1H, $C\underline{H}OCH_3$)

Table. (continued)

Product(s)	Yield (%)		GC Ratio	bp[c] (°C)/ mbar	Molecular Formula[d]	MS-CI m/z (%)	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, J (Hz)
	2	**4**	**2 : 3**				
e[f]	76	8	97 : 3	150–160/ 1.3	$C_{17}H_{28}O_4$ (296.4)	297 (100, M + H$^+$); 255 (17); 223 (20)	0.87–0.92 [m, 3H, 1CH_3 of $(CH_3)_2$]; 1.05–1.11 [m, 12H, 1CH_3 of $(CH_3)_2$, $CH(C\underline{H}_3)_2$, $C\underline{H}_3CHOCH_3$]; 2.20, 2.21 (2s, 3H, CH_3CO); 1.95–2.63 [m, 5H, H-4, H-6, $C\underline{H}(CH_3)_2$, $C\underline{H}_2CHOMe$); 2.80, 2.88 (2br d, 1H, J = 18, H-4); 3.27, 3.30 (2s, 3H, OCH_3); 3.31–3.50 (m, 1H, $C\underline{H}OCH_3$)
f[f]	46	5	96 : 4	170–180/ 1.3	$C_{23}H_{42}O_4Si$ (410.7)	411 (100, M + H$^+$)	0.058, 0.066, 0.073, 0.098 [4s, 6H, $Si(CH_3)_2$]; 0.87 [t, 3H, J = 6.8, $(CH_2)_3C\underline{H}_3$]; 0.89 (s, 9H, t-C_4H_9); 0.92, 1.08 [2s, 6H, $(CH_3)_2$]; 1.08 (d, 3H, J = 7, $CHC\underline{H}_3$); 1.16–1.47 [m, 6H, $(C\underline{H}_2)_3CH_3$]; 2.22 (s, 3H, CH_3CO); 2.18–2.44 (m, 4H, H-4 + H-6 + $C\underline{H}_2CHOSi$); 2.56, 2.58 (2br d, 1H, J = 18, H-4); 3.68, 3.82 (m, 1H, CHOSi)
g[f]	60	11	100 : 0	180–190/ 1.3	$C_{25}H_{46}O_4Si$ (438.7)	439 (100, M + H$^+$); 397 (20); 339 (32); 307 (53)	0.09, 0.10, 0.13, 0.14 [4s, 6H, rel. int. ca. 1 : 5 : 1 : 5, $Si(CH_3)_2$]; 0.86 (d, J = 6.8) and 0.91 (s) superimposed on 0.84–0.92 (m) [15H, t-C_4H_9, 1CH_3 of $CH(C\underline{H}_3)_2$, $(CH_2)_3C\underline{H}_3$]; 1.05 [s, 3H, 1CH_3 of $(CH_3)_2$]; 1.06 [d, 3H, J = 6.8, 1CH_3 of $CH(C\underline{H}_3)_2$]; 1.11 [s, 3H, 1CH_3 of $(CH_3)_2$]; 1.17–1.51 [m, 6H, $(C\underline{H}_2)_3CH_3$]; 1.94 (d, 1H, J = 3.9, H-6); 2.22 (s, 3H, CH_3CO); 2.01–2.48 [m, 4H, H-4, $C\underline{H}_2CHOSi$, $C\underline{H}(CH_3)_2$]; 2.77, 2.84 (2br d, 1H, rel. int. ca. 1 : 5, J = 18, H-4); 3.65–3.76, 3.84–3.94 (2m, 1H, rel. int. ca. 1 : 5, CHOSi)

[a] Bp, molecular formula, MS and ^{1}H-NMR data assembled in the Table refer to isolated products **2a–g**. The isolated yields of **2** and **4** are compared, and GC ratio of **2 : 3** are given in the Table as discussed in the text.

[b] IR (film) for compounds **2a–g**: ν = 1768–1765 (enol acetate carbonyl), 1670–1660 (α,β-unsaturated carbonyl) cm^{-1}.

[c] Kugelrohr oven temperature.

[d] Satisfactory microanalyses obtained: C ±0.36, H ±0.36.

[e] Measured at 300 MHz.

[f] Obtained as diastereoisomeric mixtures.

sis of these isomers on silica gel or their conversion to the more stable materials. The desired products **2** were isolated in good yield in each case by chromatography (Table).

Assignment of structures **2** to the major isolated products was possible by examination of the NMR spectra, which showed a long range coupling between the ring methylene protons at C-4 and the α-methylene protons of the 2-substituent. Additional evidence could be obtained from a study of the long range C–H couplings using the COLOC sequence[6] by which the O-substituted alkene carbon was shown to be coupled to the methylene protons at C-4 but not to the methine at C-6.

The products **2d–f** were shown by GC and NMR analysis to consist of mixtures of diastereoisomers. Increasing the substitution at the α-carbon of the 6-alkyl substituent or the β-position of the 2-substituent served to augment the ratios **2**:**3** as determined by GC, providing further evidence for the conclusion that product formation is controlled by steric effects (Table).

In conclusion, the procedure described herein permits the preparation of 2,6-disubstituted derivatives of 3-acetoxy-2-cyclohexenones in one pot. All the procedures are amenable to medium scale work (20–50 mmol).

The 2-substituted derivatives of dimedone were prepared according to the published procedure.[3] All other materials were obtained from Aldrich Chemical Company and purified as appropriate before use. All products gave spectroscopic and microanalytical data in accord with their assigned structures (Table). Capillary GC analysis was performed using a 12 m BP10 column, temperature program 100–240°C/10°C min^{-1}.

2,6-Dialkyl-3-Acetoxy-5,5-dimethyl-2-cyclohexenones 2; General Procedure:

A solution of the dione **1** (1 mmol) in HMPT (0.6 mL) and dry THF (1.0 mL) is added dropwise over 5 min to a stirred solution of lithium diisopropylamide (2.2 mmol) in dry THF (3.5 mL) at −78°C under an atmosphere of nitrogen. After stirring for 30 min at −78°C, the alkyl iodide (1.1 mmol) is added, and the mixture allowed to reach room temperature over 16–18 h. The mixture is quenched with acetic anhydride (0.2 mL), and stirred for 1 h at room temperature. The mixture is diluted with ether, and washed with 2 M HCl (or sat. aq. NH_4Cl solution in the case of **2f, g**). The aqueous washings are reextracted with ether, the combined organic extract dried ($MgSO_4$), and concentrated under reduced pressure. The pure product **2** is obtained by column chromatography on silica gel [ether/petroleum ether (bp 30–40°C)].

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