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Reactivity of 3,6-Dimethoxy-3,6-dimethylcyclohexa-1,4-diene (Part 3).[1] Regioselective α-Arylation of Ketones *via* their Silyl Enol Ethers

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Abstract: *The reaction of 3,6-dimethoxy-3,6-dimethylcyclohexa-1,4-diene (1) with an excess of different silyl enol ethers derived from ketones in the presence of zinc dichloride leads to the corresponding ketones regioselectively arylated at the α position.*

Introduction

The arylation of β-dicarbonyl compounds with aryl halides is a known reaction, which can be carried out in the presence of a base, and takes place through a S_NAr mechanism or *via* an aryne intermediate, depending on the activation of the aryl halide.[2] Other methodologies with the same substrates involve aryllead triacetate[3] or diaryliodonium salts,[4] the mechanism being apparently free radical. However, the arylation of simple carbonyl compounds has been much less investigated and has been carried out by (a) using aryl halides in ammonia containing sodium or potassium[6] or photochemically,[7] and (b) starting from aryl sulphides or aryl ammonium salts under the same conditions.[8] In the case of starting from silyl enol ethers derived from ketones, the arylation with aryl bromides can only be carried out, to our best knowledgement, using tributyltin fluoride in the presence of a catalytic amount of a palladium(II) compound.[9]

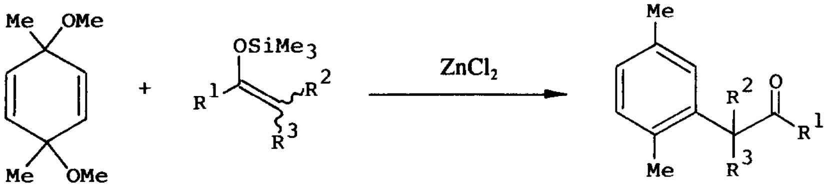
On the other hand, we have recently reported on the reactivity of 3,6-dimethoxy-3,6-dimethylcyclohexa-1,4-diene (**1**) (easily prepared from *p*-xylene by electrochemical oxidation[10] or chemically from *p*-quinone by methylation with methyllithium followed by treatment with methyl iodide[11]) towards nucleophilic reagents[12] or electron-rich aromatic compounds.[1] In this paper we study the ability of compound **1** acting as arylating electrophilic agent in the reaction with silyl enol ethers to give arylated ketones in a regioselective manner.

Results and Discussion

The reaction of a *cis/trans* mixture of 1[13] (*ca.* 1/1)[10] with an excess (1:10 molar ratio) of a silyl enol ether derived from a ketone[14,15] in the presence of a catalytic amount (1:0.07 molar ratio) of zinc dichloride in dichloromethane led to the corresponding α-arylated ketone (Scheme 1 and Table 1). In the case of using a mixture of regioisomeric silyl enol ethers the process afforded mainly the corresponding arylated ketone at the most substituted α-carbon atom (Table 1, entries 1 and 2); thus, for **3a** and **3b** the corresponding regioisomers **3a'** and **3b'** were obtained in 28 and 6% yield, respectively. It is necessary to use a large excess of the silyl derivative in order to minimize the decomposition of the starting material **1** by the Lewis acid;[1,12] in spite of that, in all the described reactions compound **3** is contaminated with 2,5-dimethylanisole arising from the mentioned decomposition of compound **1**, the both compounds being the only reaction products. The final separation and purification of compound **3** is very easy by column chromatography.

When the above described process was applied to silyl enol ethers derived from aldehydes,[14,15] the reaction failed leading to an intractable mixture of products containing always 2,5-dimethylanisole as the major one.

If one consider that compounds of the type **4** are now easily accesible chemically,[11] the here reported methodology permits the general preparation of α-arylated ketones in a regioselective manner.



1 **2**

3a: $R^1=R^2=\mathrm{Me}$, $R^3=\mathrm{H}$

3a': $R^1=\mathrm{Et}$, $R^2=R^3=\mathrm{H}$

3b: $R^1=R^2=R^3=\mathrm{Me}$

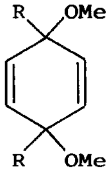
3b': $R^1=i\text{-Pr}$, $R^2=R^3=\mathrm{H}$

3c: $R^1=t\text{-Bu}$, $R^2=R^3=\mathrm{H}$

3d: $R^1=\mathrm{Et}$, $R^2=\mathrm{H}$, $R^3=\mathrm{Me}$

3e: $R^1\text{-}R^2=(CH_2)_3$, $R^3=\mathrm{H}$

3f: $R^1\text{-}R^2=(CH_2)_4$, $R^3=\mathrm{H}$



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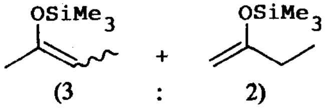
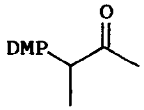
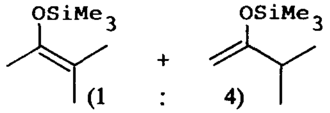
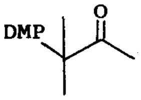
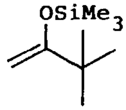
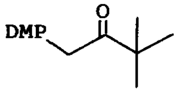
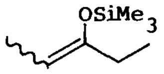
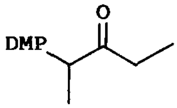
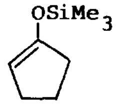
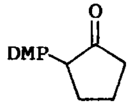
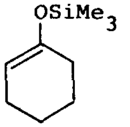
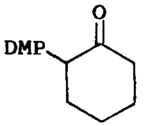
Scheme 1.

Table 1. Preparation of Compounds 3

Entry	Silyl enol ether 2	Product 3[a]		
		Structure[b]	no.	Yield (%)[c]
1	 (3 : 2)		3a[d]	42
2	 (1 : 4)		3b[e]	35
3			3c	38
4			3d	61
5			3e	41
6			3f	52

[a] All products 3 were >95% pure (g.l.c. and 300 MHz ^{1}H n.m.r.). [b] DMP= 2,5-dimethylphenyl. [c] Isolated yield after column chromatography based on the starting material 1. [d] A 28% of the other regioisomer [1-(2,5-dimethylphenyl)butanone (3a')] was also obtained. [e] A 6% of the other regioisomer [1-(2,5-dimethylphenyl)-3-methylbutanone (3b')] was also obtained.

Experimental

General.- For general information see references 1 and 12. Retention times (t_r) were obtained with a Hewlett Packard HP-5890 instrument equipped with a 12 m WCOT capillary column (0.22 mm diam., 0.2 μm film thickness OV-101 stationary phase) using nitrogen (2 ml/min) as the carrier gas, $T_{injector}$=270°C, T_{column}=60°C (3 min) and 60-270°C (10°C/min). ^{1}H and ^{13}C n.m.r. were recorded on a Bruker AC-300 spectrometer using $CDCl_3$ as solvent and $SiMe_4$ as internal standard. Hexane/ethyl acetate (9/1) was used as eluant in t.l.c. for R_f values. Starting silyl enol ethers were prepared according to the literature methods.[14,15]

Preparation of Compounds **3**. *General Procedure*.- A solution of 3,6-dimethoxy-3,6-dimethylcyclohexa-1,4-diene (**1**) (1 mmol), the corresponding trimethylsilyl enol ether **2** (10 mmol), dichloromethane (5 ml), and zinc dichloride (0.07 mmol) was stirred overnight at room temperature. The resulting mixture was then hydrolyzed with water (2 ml), extracted with ether (3x3 ml), and the organic layer dried over sodium sulfate. Solvents and the excess of trimethylsilyl enol ether were evaporated (15 torr) and the resulting residue was purified by column chromatography (silica gel; hexane/ethyl acetate: 98/2) to yield the corresponding products **3**.

3-(2,5-Dimethylphenyl)butanone (**3a**): t_r=11.83 min, R_f=0.39; ν_{max} (film) 3020, 1605 (HC=C), and 1705 cm^{-1} (C=O); δ_H 1.35 (3 H, d, *J*=6.8, *Me*CH), 2.02 (3 H, s, MeCO), 2.30, 2.35 (6 H, 2s, 2x*Me*Ar), 3.91 (1 H, q, *J*=6.8, C*H*Me), 6.86 (1 H, s, 6-ArH), 6.99, and 7.10 (2 H, 2 d, *J*=7.6, 3,4-ArH); δ_C 16.6 (*Me*CH), 19.2, 21.0 (2x*Me*Ar), 28.4 (*Me*CO), 49.7 (*C*HMe), 127.5, 127.7, 130.7, 132.5, 136.2, 138.9 (ArC), and 209.3 (C=O); *m/z* 177 (M^++1, 3%), 176 (M^+, 24), 133 (100), 131 (18), 128 (10), 118 (19), 117 (54), 115 (60), 105 (36), 103 (19), 91 (62), 89 (11), 79 (13), 78 (14), 77 (33), 65 (14), 63 (15), 51 (13), 43 (95), and 42 (10) (Found: M^+, 176.1193. $C_{12}H_{16}O$ requires M, 176.1202).

1-(2,5-Dimethylphenyl)butanone (**3a'**): t_r=12.01 min, R_f=0.39; ν_{max} (film) 3020, 1605 (HC=C), and 1705 cm^{-1} (C=O); δ_H 1.05 (3 H, t, *J*=7.3, *Me*CH$_2$), 2.21, 2.31 (6 H, 2 s, 2x*Me*Ar), 2.43 (2 H, q, *J*=7.3, C*H*$_2$Me), 3.67 (2 H, s, CH$_2$CO), and 6.94-7.11 (3 H, m, ArH); δ_C 7.8 (*Me*CH$_2$), 19.6, 20.9 (*Me*Ar), 35.1 (*C*H$_2$Me), 47.9 (*C*H$_2$CO), 126.8, 127.9, 130.3, 133.1, 133.5, 135.6 (ArC), and 209.2 (C=O); *m/z* 176 (M^+, 23%), 120 (11), 119 (81), 118 (13), 117 (41), 115 (43), 104 (40), 103 (39), 102 (10), 92 (12), 91 (100), 89 (12), 79 (10), 78 (32), 77 (54), 65 (25), 63 (22), 53 (12), 52 (11), 51 (24), and 41 (10).

3-Methyl-3-(2,5-dimethylphenyl)butanone (**3b**): t_r=13.02 min, R_f=0.50; ν_{max} (film) 3040, 1605 (HC=C), and 1700 cm^{-1} (C=O); δ_H 1.46 (6 H, s, *Me*$_2$CAr), 1.94 (3 H, s, MeCO), 2.14, 2.35 (6 H, 2 s, 2x*Me*Ar), and 7.02-7.20 (3 H, m, ArH); δ_C 19.8, 21.3 (2x*Me*Ar), 25.3 (*Me*$_2$CAr), 25.6 (*Me*CO), 52.8 (*C*Ar), 126.4, 127.6, 132.0, 132.9, 135.7, 142.4 (ArC), and 205.5 (C=O); *m/z* 191 (M^++1, 3%), 190 (M^+, 23), 148 (11), 147 (96), 131 (12), 129 (13), 119 (100), 117 (18), 116 (13), 115 (32), 107 (27), 105 (20), 91 (38), 77 (16), 43 (19), and 41 (11).

1-(2,5-Dimethylphenyl)-3-methylbutanone (**3b'**): t_r=13.53 min, R_f=0.50; ν_{max} (film) 3040, 1605 (HC=C), and 1700 cm^{-1} (C=O); δ_H 1.11 (6 H, d, *J*=6.9, *Me*$_2$CH), 2.17, 2.29 (6 H, 2 s, 2x*Me*Ar), 2.70-2.80 (1 H, m, C*H*Me$_2$), 3.80 (2 H, s, CH$_2$), and 7.02-7.20 (3 H, m, ArH); δ_C 18.5 (*Me*$_2$CH), 19.2, 21.0 (2x*Me*Ar), 39.9 (*C*HMe$_2$), 45.9 (CH$_2$), 126.7, 127.7, 130.2, 130.9, 131.3, 133.5 (ArC), and 206.5 (C=O); *m/z* 191 (M^++1, 5%), 190 (M^+, 32), 120 (19), 119 (88), 117 (13), 115 (15), 104 (12), 103 (11), 91 (33), 77 (19), 71 (73), 43 (100), and 41 (22).

3,3-Dimethyl-1-(2,5-dimethylphenyl)butanone (3c): t_r=14.39 min, R_f=0.65; ν_{max} (film) 3030, 1610 (HC=C), and 1700 cm^{-1} (C=O); δ_H 1.24 (9 H, s, CMe$_3$), 2.14, 2.28 (6 H, 2 s, 2x *Me*Ar), 3.80 (2 H, s, CH$_2$), 6.84 (1 H, s, 6-ArH), 6.97, and 7.05 (2 H, 2 d, *J*=7.7, 3,4-ArH); δ_C 19.1, 20.9 (2x*Me*Ar), 26.7 (*Me*$_3$C), 41.4 (*C*Me$_3$), 44.5 (CH$_2$), 127.7, 130.1, 131.1, 133.4, 133.5, 135.2 (ArC), and 212.8 (C=O); *m/z* 205 (M^++1, 4%), 204 (M^+, 26), 120 (20), 119 (94), 118 (14), 117 (40), 115 (41), 105 (15), 104 (43), 103 (36), 92 (10), 91 (96), 79 (14), 78 (30), 77 (46), 65 (21), 63 (13), 57 (95), 53 (11), 52 (7), 51 (16), 42 (14), and 41 (100) (Found: M^+, 204.1537. $C_{14}H_{20}O$ requires M, 204.1515).

2-(2,5-Dimethylphenyl)-3-pentanone (3d): t_r=12.98 min, R_f=0.54; ν_{max} (film) 3030, 1610 (HC=C), and 1705 cm^{-1} (C=O); δ_H 1.07 (3 H, t, *J*=7.3, *Me*CH$_2$), 1.43 (3 H, d, *J*=6.9, *Me*CH), 2.37, 2.43 (6 H, 2 s, 2x*Me*Ar), 2.38 (2 H, q, *J*=7.3, C*H*$_2$Me), 4.02 (1 H, q, *J*=6.9, C*H*Me), 6.94 (1 H, s, 6-ArH), 7.05, and 7.17 (2 H, 2 d, *J*=7.9, 3,4-ArH); δ_C 8.0 (*Me*CH$_2$), 16.8 (*Me*CH), 19.2, 20.9 (2x*Me*Ar), 34.1 (*C*H$_2$Me), 48.5 (CH), 127.5, 127.6, 130.6, 132.4, 136.0, 139.2 (ArC), and 212.0 (C=O); *m/z* 191 (M^++1, 3%), 190 (M^+, 23), 134 (15), 133 (100), 131 (12), 117 (22), 115 (22), 105 (21), 91 (25), 77 (12), and 57 (20) (Found: M^+, 190.1355. $C_{13}H_{18}O$ requires M, 190.1358).

2-(2,5-Dimethylphenyl)cyclopentanone (3e): t_r=15.70 min, R_f=0.33; ν_{max} (film) 3020, 1610 (HC=C), and 1730 cm^{-1} (C=O); δ_H 1.93-2.06, 2.17-2.21 [4 H, 2 m, (C*H*$_2$)$_2$CH$_2$CO], 2.26, 2.28 (6 H, 2 s, 2xMe), 2.46-2.52 (2 H, m, CH$_2$CO), 3.47, 3.50 (1 H, 2d, *J*=8.7, CHCO), 6.80 (1 H, s, 6-ArH), 6.95, and 7.06 (2 H, 2 d, *J*=7.4, 3,4-ArH); δ_C 19.4, 21.0 (2xMe), 21.1 (*C*H$_2$CH$_2$CO), 31.8 (*C*H$_2$CHAr), 38.8 (*C*H$_2$CO), 53.0 (Ar*C*HCHO), 127.7, 128.1, 130.4, 133.5, 135.6, and 137.3 (ArC); *m/z* 188 (M^+, 15%), 145 (21), 132 (72), 131 (22), 129 (22), 128 (28), 118 (12), 117 (100), 116 (24), 115 (71), 105 (10), 103 (18), 91 (56), 78 (13), 77 (27), 65 (15), 63 (14), 51 (17), and 42 (10) (Found: M^+, 188.1210. $C_{13}H_{16}O$ requires M, 188.1202).

2-(2,5-Dimethylphenyl)cyclohexanone (3f):[16] t_r=17.20 min, R_f=0.23; ν_{max} (film) 3010, 1610 (HC=C), and 1700 cm^{-1} (C=O); δ_H 1.83-1.86, 2.05-2.10, 2.20-2.23 [6 H, 3 m, (C*H*$_2$)$_3$CH$_2$CO], 2.16, 2.29 (6 H, 2 s, 2xMe), 2.47-2.53 (2 H, m, CH$_2$CO), 3.71, 3.76 (1 H, 2 d, *J*=5.2, CHCO), and 6.93-7.04 (3 H, m, ArH); δ_C 19.6, 21.0 (2xMe), 25.9 (*C*H$_2$CH$_2$CH), 27.8 (*C*H$_2$CH$_2$CO), 34.2 (*C*H$_2$CH), 77.2 (*C*HCO), 126.7, 127.5, 127.6, 128.4, 130.1, 131.1 (ArC), and 210.1 (C=O); *m/z* 203 (M^++1, 12%), 202 (M^+, 78), 184 (10), 160 (10), 159 (75), 158 (31), 146 (15), 145 (100), 143 (40), 132 (33), 131 (40), 130 (23), 129 (32), 128 (34), 127 (11), 119 (38), 117 (56), 116 (24), 115 (70), 106 (13), 105 (36), 103 (12), 91 (58), 77 (27), 65 (12), 63 (10), 51 (10), 42 (31), and 41 (14).[17]

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