α-Cumylation of Ketones

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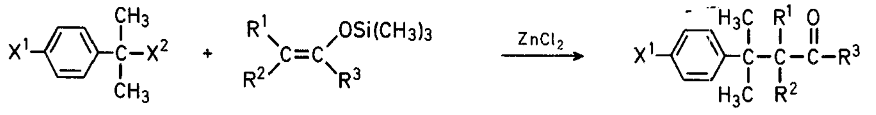
Methodology for the construction of compounds containing quarternary carbon atoms is of current interest[1]. Recently, procedures according to which carbonyl compounds can be α-*t*-alkylated with complex tertiary alkyl halides via the corresponding silyl enol ethers in the presence of titanium(IV) chloride have been described[2a,b]. We now show that α-cumylation of ketones is possible using catalytic amounts of mild Lewis acids such as zinc chloride.



1a $X^1 = H, X^2 = Cl$
b $X^1 = H, X^2 = OAc$
c $X^1 = O_2N, X^2 = Br$

2a $R^1 = H, R^2 = CH_3, R^3 = C_2H_5$
b $R^1, R^2 = CH_3, R^3 = i\text{-}C_3H_7$
c $R^1 = H, R^2\ R^3 = -(CH_2)_3-$
d $R^1, R^2 = H, R^3 = t\text{-}C_4H_9$
e $R^1 = CH_3, R^2\ R^3 = -(CH_2)_4-$

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Exploratory investigations were carried out with cumyl chloride (α,α-dimethylbenzyl chloride; **1a**) and the trimethylsilyl enol ether (**2c**) derived from cyclopentanone[3]. Whereas reaction in the presence of equivalent amounts of titanium chloride at −50 °C affords 2-cumylcyclopentanone to the extent of about 60%, use of catalytic amounts of zinc chloride or bismuth chloride at room temperature results in nearly quantitative conversion[4]. The relatively low yield in the former case has to do with competing Friedel-Crafts self-condensations induced by the more reactive Lewis acid. Using **1a** and the equivalent amount of **2**, structurally different α-cumylated ketones **3** are readily accessible (Table). It is noteworthy that the reaction is not restricted to cumyl chloride, the acetate **1b** functions equally well.

The analogous reaction with *p*-nitrocumyl bromide (**1c**) is not quite as smooth (40–60%). However, use of twice the amount of silyl enol ether **2** affords good yields based on **1c** (Table). Regiospecificity is demonstrated by the reaction of the "thermodynamic" silyl enol ether from 2-methylcyclohexanone, which yields the desired product **3** as the only regio-isomer. Finally, we note that the genesis of products **3** from **2b** and **2c** involves the formation of compounds **3** having *two neighboring* quarternary carbon atoms. The direct coupling of two tertiary carbon atoms to form hexasubstituted ethane derivatives is generally difficult by other means[1].

The present method is formally related to Kornblum's elegant procedure, in which cumyl halides containing electron-withdrawing groups react with the enolate anions derived from 1,3-dicarbonyl compounds and other delocalized anions[5]. The structural prerequisites are different, so that the two methods are complementary.

Table. Preparation of α-Cumylated Ketones **3**

Starting materials 1	2	Yield [%] of 3	m.p. [°C] or b.p. [°C]/torr	Molecular formula[a]	I.R. ν [cm⁻¹]	¹H-N.M.R. (CCl₄/TMS) δ [ppm]
1a	**2a**	80	59–61°/0.1	$C_{14}H_{20}O$ (204.3)	2980, 1700, 1600, 1580, 1490, 1230	0.73 (t, *J*=6 Hz, 3H); 0.92 (d, *J*=7.5 Hz, 3H); 1.30 (s, 3H); 1.33 (s, 3H); 1.5–2.3 (m, 2H); 2.80 (q, *J*=7.5 Hz, 1H); 7.0–7.4 (m, 5H)
1a	**2b**	65	31° (*n*-pentane)	$C_{16}H_{24}O$ (232.4)	2970, 1680, 1600, 1580, 1460, 1380, 1230	0.86 (d, *J*=6 Hz, 6H); 1.10 (s, 6H); 1.35 (s, 6H); 2.55 (sept, *J*=6 Hz, 1H); 7.0–7.4 (m, 5H)
1a	**2c**	78 (75)[b]	85–87°/0.1	$C_{14}H_{18}O$ (202.3)	2970, 1720, 1600, 1575, 1490	1.30 (s, 3H); 1.40 (s, 3H); 1.2–2.4 (m, 7H); 6.8–7.4 (m, 5H)
1b	**2d**	74	87–89°/0.1	$C_{15}H_{22}O$ (218.3)	2960, 1710, 1600, 1480, 1370, 1160, 700	1.00 (s, 9H); 1.43 (s, 6H); 2.68 (s, 2H); 6.9–7.6 (m, 5H)
1c	**2c**	80	—[c]	$C_{14}H_{17}NO_3$ (247.3)	2970, 1730, 1595, 1515, 1350, 860, 700	1.43 (s, 3H); 1.51 (s, 3H); 1.3–3.0 (m, 7H); 7.3–8.2 (m, 4H)
1c	**2d**	70	65° (ether)	$C_{15}H_{21}NO_3$ (263.3)	2970, 1700, 1600, 1520, 1460, 1345, 855, 700	1.00 (s, 9H); 1.40 (s, 6H); 2.86 (s, 2H); 7.2–8.2 (m, 4H)
1c	**2e**	76	68° (ether)	$C_{16}H_{21}NO_3$ (275.3)	2940, 1700, 1590, 1500, 1345, 850, 700	1.16 (s, 3H); 1.50 (s, 3H); 1.53 (s, 3H); 1.1–2.8 (m, 8H); 7.3–8.2 (m, 4H)

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[a] The microanalyses were in satisfactory agreement with the calculated values (C ±0.37, H ±0.24, N ±0.23).

[b] Yield from reaction of **2c** with **1b**.

[c] Isolated by column chromatography on silica gel, eluent: 3:1 petroleum ether (b.p. 40–60 °C)/ether.

0039-7881/80/1132-0941 $ 03.00

α-Cumylation of Ketones; General Procedure:

The cumyl chloride **1** (6.2 g, 0.04 mol) is added at room temperature within 2 min to a mixture of the silyl enol ether **2** (0.04 mol), anhydrous zinc chloride (400 mg), and dry dichloromethane (60 ml) in a round bottom flask under an atmosphere of nitrogen. After stirring for 1 h, the mixture is poured on to saturated sodium hydrogen carbonate solution (400 ml), the organic phase separated, and the aqueous phase washed with dichloromethane (2 × 50 ml). The combined organic phases are dried with sodium sulfate and concentrated using a rotary evaporator. The residue is distilled or crystallized (see Table). In case of *p*-nitrocumylation a double excess of silyl enol ether is used.

This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie.

Received: June 27, 1980

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