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α-t-BUTYLATION OF ALDEHYDES AND KETONES BY THE FRIEDEL-CRAFTS ALKYLATION OF TRIMETHYLSILYL ENOL ETHERS

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α-Alkylation of a ketone or aldehyde by the reaction of its enolate anion or its equivalent with an alkyl halide is one of the fundamental methods of carbon-carbon bond formation.[1] However, the method is limited to primary and secondary alkyl halides. When the alkyl group to be introduced is tertiary with a β-hydrogen (e.g. t-butyl), the demon of elimination predominates over substitution, thus leading to a low yield of the desired alkylation product. Hence, a general method for the introduction of a tertiary alkyl group α to a carbonyl function is lacking. Various approaches have been developed, but each has its own limitations.[2,3]

In view of the ready availability of trimethylsilyl enol ethers[4] and their facile reactions with electrophiles[5], we have examined the Friedel-Crafts alkylation of these enol ethers as a method of introducing the t-butyl group α to a carbonyl.[6] The following sequence has been successfully employed:

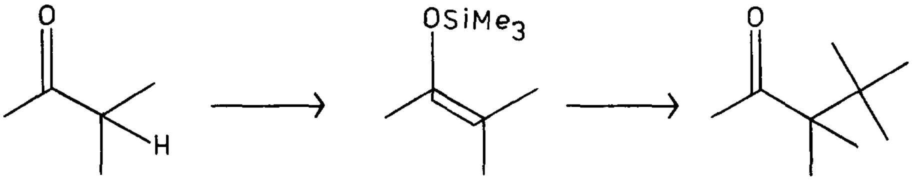
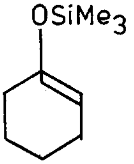
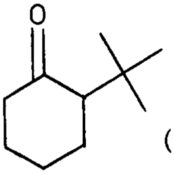
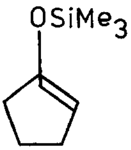
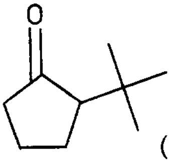
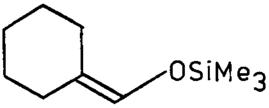
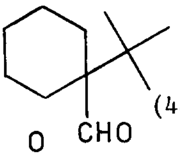
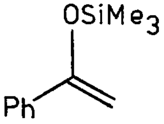
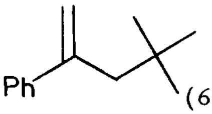
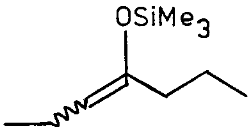
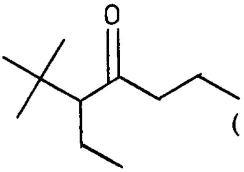


TABLE: PREPARATION OF SOME 2-t-BUTYLKETONES AND ALDEHYDES BY THE ALKYLATION OF SILYL ENOL ETHERS USING $TiCl_4$ IN A 1:1 SUBSTRATE/CATALYST RATIO

SILYL ENOL ETHER	TEMP. (°C)	REACTION TIME (hr)	PRODUCT[a] (B.P.)	% YIELD[b] (ISOLATED)[c]
	-23	2.5	 (67°C/1.6 mm)	48 (41)
	-23	3.0	 (44°C/3.5 mm)	59 (54)
	-23	2.5	 (48°C/0.75 mm)	40 (40)
	-78	2.5	 (66°C/0.7 mm)	43 (40)
	-23	2.5	 (32°C/0.8 mm)	- (31)

a. The product had spectroscopic data consistent with its structure. Its purity and molecular weight have been established by GC-MS.

b. Estimated by nmr using an internal standard.

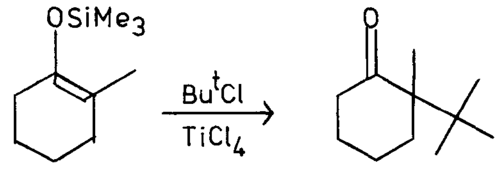
c. Isolated by distillation

Using 1-trimethylsiloxycyclohexene as the standard substrate, its reaction with t-butylchloride was examined using different catalysts.[7] The efficacy of the catalyst follows the order $TiCl_4 > ZnCl_2 > SnCl_4 > AlCl_3$. With $TiCl_4$ as the catalyst, a substrate/catalyst ratio of 1:1 gave the best yield. A reduction in the amount of catalyst led to a decreased yield. The effect of solvent on the reaction was quite dramatic with dichloromethane being the solvent of choice. The side product of the reaction appeared to be polymeric compounds due to condensation. Hence, lowering the concentration of the substrate had a beneficial effect on the yield up to a certain extent. Varying the reaction temperature between 25° to -78° had a moderate effect on the yield with lower temperatures being preferable.

We have prepared a number of 2-t-butyl ketones by the alkylation of the corresponding silyl enol ethers (Table). A typical procedure is described for 2-t-butylcyclopentanone. To a stirred solution of $TiCl_4$ (0.033 moles) in dry CH_2Cl_2 (100 ml) at -23°, under nitrogen, was added dropwise a solution of t-butylchloride (0.066 moles) in CH_2Cl_2 (50 ml), followed by a solution of 1-trimethylsiloxycyclopentene (0.033 moles) in CH_2Cl_2 (100 ml). The mixture was stirred for 3 hr and hydrolysed with 40 ml aqueous sodium bicarbonate solution. The resultant mixture was extracted with CCl_4 and washed three times with aqueous sodium bicarbonate solution. The organic phase was dried and vacuum distilled to give 2-t-butylcyclopentanone, as a clear liquid, b.p. 44° C/3.5 mm, in 54% yield.

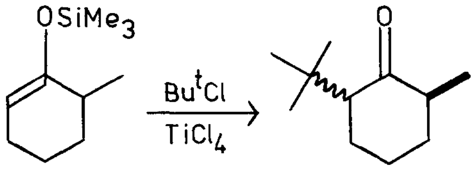
In the α-t-butylation of acetophenone (Table, entry 4) there was no indication of alkylation of the aromatic ring. Of particular interest is the reaction of cyclohexanecarboxaldehyde (Table, entry 3). This alkylation involved the introduction of a tertiary butyl group into an existing tertiary carbon. The product was obtained in reasonable yield in spite of the anticipated steric hindrance.

We have also examined the regioselectivity of this method of α-t-butylation. 2-Methylcyclohexanone was converted regioselectively into the two isomeric enol silyl ethers, **1** and **2** according to published procedures.[4] Under identical



1 **3**

(**1**/**2**=88:12)[8] (48% yield)



2 **4** a cis
b trans

(**1**/**2**=11:89) (58% yield)

conditions (-78° C, 4 hr), **1** was t-butylated to give **3**, whereas **2** was alkylated to give **4** as a mixture of cis- and trans- stereoisomers (**4a** and **4b**) in nearly equal amounts. The three compounds, **3**, **4a** and **4b**, could be resolved by GLC (10% SE-30 ULTRAPHASE column, 80° C). It was possible to establish that the alkylation was entirely regiospecific and there was no isomerisation of **1** and **2** under the reaction conditions.

The Friedel-Crafts t-butylation of silyl enol ethers, therefore, constitutes a useful supplement to the other methods of α-alkylation of aldehydes and ketones.

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References and Footnotes

(1) H.O. House, Modern Synthetic Reactions, 2nd ed., W.A. Benjamin, Merlo Park, 1972.

(2) G.H. Posner and J.J. Sterling, J. Amer. Chem. Soc., **95**, 3076 (1973).

(3) E.J. Corey and R.H.K. Chen, Tetrahedron Letters, 3817 (1973).

(4) H.O. House, L.J. Czuba, M. Gall and H. Olmstead, J. Org. Chem., **34**, 2324 (1969).

(5) For recent work on the reactions of trimethylsilyl enol ethers with carbon electrophiles, see E. Nakamura, T. Murofushi, M, Shimizu and I. Kuwajima, J. Amer. Chem. Soc., **98**, 2346 (1974) and E. Nakamura and I. Kawajima, ibid. **99**, 961 (1977).

(6) For the introduction of a t-butyl group into 1,3-dicarbonyl compounds under Friedel-Crafts conditions, see P. Boldt, H. Militzen, W. Thielecke and L. Schultz, Liebigs Ann. Chem., **718**, 101 (1968).

(7) For a general discussion of the Friedel-Crafts conditions, see G. Olah, Friedel-Crafts and Related Reactions, Interscience, New York, 1964.

(8) The regioselectivity in the preparation of **1** is better than that reported by House and his co-workers.[4] The conditions used by us were essentially the same but with a reaction time of 66 hr at reflux temperature (as opposed to 48 hr[4]). Distillation through a Vigreux column gave an isomeric ratio **1**/**2** of 88:12 in 78% yield.