

ALKYLATION OF KETONES BY USE OF SOLID KOH IN DIMETHYL SULFOXIDE

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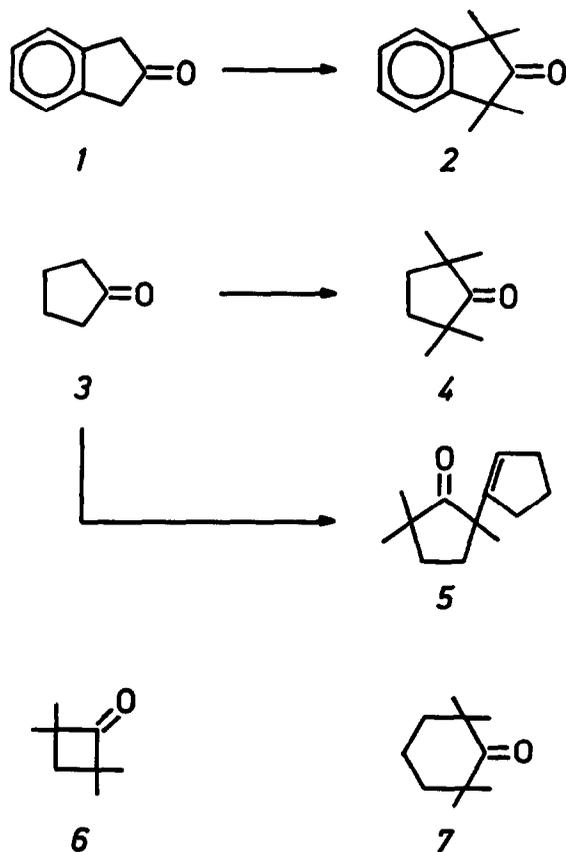
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Abstract: A mixture of solid KOH in dimethyl sulfoxide has a strong basicity, but only a low nucleophilicity and is used for α methylation of ketones. With this simple and inexpensive reagent complete methylation with yields up to 90% can be achieved.

Solid KOH in dimethyl sulfoxide (DMSO) is a very strong base with a pK_a -value of 27 or even higher.¹⁻³ On the other hand, the nucleophilicity of this reagent is low due to the low solubility of KOH in DMSO which allows only surface reactivity. Therefore, the mixture is especially prone as a base for nucleophilic displacement reactions. This simple and inexpensive reagent has already been used for the alkylation of OH groups in phenols and alcohols⁴⁻⁵ and of the nitrogens of carboxylic amides⁶ with high yields.

The reaction of ketones with an alkylation reagent in presence of strong bases is an attractive way for the preparation of peralkylated ketones. However, peralkylations are reported to be achieved by stepwise reactions.⁷ The use of NaH in THF is an essential improvement.⁸ Solid KOH has been applied in toluene as a solvent,⁹ but crown ether had to be added.

The basicity of the reagent KOH/DMSO is high enough for the direct alkylation of ketones in α position, and the preparation procedure can be carried out in a very simple manner.¹⁰ All reagents can be used without drying, for the solid KOH binds small amounts of water.¹⁻³ Technical grade KOH can be applied in pellets without further purification. Pulverization of the pellets will increase the reaction rate, but has only little influence on the yields of alkylation products. The presence of oxygen causes a slow decomposition of DMSO under the reaction conditions, but the exclusion of air is not essential. Methylation is carried out with methyl iodide as alkylating reagent. Dimethyl sulfate reacts with DMSO and gives a complex reaction mixture.



The methylation reaction can be carried out both with aliphatic and aromatic ketones (see table 1). 2-Indanone (1), for example, is methylated to the tetramethyl derivative 2 in 75% isolated yield. The aliphatic cyclopentanone (3) reacts to the tetramethyl derivative 4 in 90% yield at high reaction temperatures (60°C), whereas at room temperature, when cyclopentanone is first added to a mixture of KOH and DMSO and then methylated, the condensation product 5 is obtained.¹⁰ Cyclobutanone is tetraalkylated (see table 1). For these cases no di- or threemethylated products or other sideproducts were found. However, for the permethylation of cyclohexanone two alkylation runs are necessary, probably due to steric hindrance of the system. Acetone reacts to a mixture of products with mainly pinacolone (60%) and diisopropylketone (30%). Pinacolone mainly reacts to 2,2,4-trimethyl-2-pentanone, and acetophenone reacts to isopropyl-phenylketone. Furoine,¹¹ however, is alkylated at both oxygens forming 1,2-difuryl-1,2-dimethoxyethylene.^{12,13}

Table 1: Methylation of ketones with methyl iodide in KOH/DMSO.¹⁴

ketone	reaction product	yield[%]	boiling point
cyclobutanone ¹⁵	2,2,4,4-tetramethylcyclobutanone ^{16,a}	49	128-130°C
cyclopentanone	2,2,5,5-tetramethylcyclopentanone ^b	90	38-39°C/12 Torr
cyclohexanone	2,2,6,6-tetramethylcyclohexanone ^c	34	60-46°C/15 Torr
2-indanone ¹⁷	1,1,3,3-tetramethylindan-2-one	75	108-112°C/15 Torr ^d
pinacolone	2,2,4-trimethylpentan-3-one	70 ^e	
acetophenone	2-methylpropiophenone	77 ^f	93-99°C/1 Torr

a) ¹H-NMR(CDCl₃): δ = 1.21(s, 4 CH₃), 1.78(s, CH₂). - b) ¹H-NMR(CDCl₃): δ = 1.04(s, 4 CH₃), 1.77(s, 2 CH₂). - c) two runs - ¹H-NMR(CDCl₃): δ = 1.12(s, 4 CH₃), 1.70(m, 3 CH₂). - d) solid-state distillation; m.p. 76°C from methanol. - e) a mixture of 39% 2,2,4,4-tetramethylpentan-3-one, 41% 2,2,4-trimethylpentan-3-one, and 20% 2-methylpentanone. f) the rest is pivalophenone. -

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- 10) B.p. 105°C. - C₁₃H₂₀O (192.3) calc. C 81.20 H 10.48 found 80.93 H 10.48. - IR(film): ν = 2959cm⁻¹ s, 2868m, 1735s. - ¹H-NMR (CDCl₃): δ = 1.05(s, 3H), 1.06(s, 3H), 1.18(s, 3H), 1.60-1.90, 2.10-2.35(m, 10H), 5.4(m, 1H). - ¹³C-NMR(CDCl₃) δ = 22.7(q), 25.1(q), 25.3(q), 23.4(t), 31.8(t), 32.4(t), 32.9(t), 45.2(s), 51.7(s), 125.4(d), 145.2(s).
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- 12) M.p. 108-110°C. - IR(KBr): $\nu = 3150\text{cm}^{-1}$ w, 3115w, 3000w, 2960w, 2930m, 2830m, 1640w, 1560w, 1483w, 1450w, 1430w, 1268s, 1220m, 1200s, 1140s, 1075s, 1015s. - $^1\text{H-NMR}$ (CDCl_3): $\delta = 3.70(\text{s}, 6\text{H}), 6.43(\text{dd}, J=3\text{Hz}, J=1.8\text{Hz}, 2\text{H}), 6.70(\text{d}, J=3\text{Hz}, 2\text{H}), 7.43(\text{d}, J=1.8\text{Hz}, 2\text{H})$. - MS(70eV): m/z (%) = 221(12), 220(86, M^+), 206(11), 205(86), 177(30), 95(100), 39(25).
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- 14) General Procedure - In a three-necked flask containing a reflux condenser, a mechanical stirrer and a dropping funnel a mixture of 0.10 mol ketone and 50 ml (0.80 mol) methyl iodide is added to a suspension of 112 g (2.00 mol) potassium hydroxide (pellets, scales, or powder) in 190 ml dimethyl sulfoxide under stirring at 50-60°C. After initial heating the temperature of the reaction mixture is kept within this temperature range by means of the exothermic reaction. After the addition, stirring is continued for an hour, and the slurry is poured into 500 ml of ice water. The product is extracted with pentane (3x70 ml), the organic layer washed twice with water and dried over magnesium sulfate. Evaporation of the solvent gives the $^1\text{H-NMR}$ -spectroscopically pure tetramethylcycloalkanones, which can be further purified by distillation.
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