ALKYLATION OF KETONES BY USE OF SOLID KOH IN DIMETHYL SULFOXIDE

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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 a
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.\textsuperscript{1-3} On the other hand, the nucleophilicity of this re-
agent is low due to the low solubility of KOH in DMSO which allows only sur-
face 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 alcohols\textsuperscript{4-5}
and of the nitrogens of carboxylic amides\textsuperscript{6} 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.\textsuperscript{7}
The use of NaH in THF is an essential improvement.\textsuperscript{8} Solid KOH has been appli-
cated in toluene as a solvent,\textsuperscript{9} but crown ether had to be added.

The basicity of the reagent KOH/DMSO is high enough for the direct al-
kylation of ketones in $\alpha$ position, and the preparation procedure can be car-
rried out in a very simple manner.\textsuperscript{10} All reagents can be used without drying,
for the solid KOH binds small amounts of water.\textsuperscript{1-3} Technical grade KOH can be
applied in pellets without further purification. Pulverization of the pel-
lets will increase the reaction rate, but has only little influence on the
yields of alkylation products. The presence of oxygen causes a slow decompo-
sition of DMSO under the reaction conditions, but the exclusion of air is not
essential. Methylation is carried out with methyl iodide as alkylation re-
agent. Dimethyl sulfate reacts with DMSO and gives a complex reaction mix-
ture.
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. 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, however, is alkylated at both oxygens forming 1,2-difuryl-1,2-dimethoxyethylene.
### Table 1: Methylation of ketones with methyl iodide in KOH/DMSO

<table>
<thead>
<tr>
<th>Ketone</th>
<th>Reaction Product</th>
<th>Yield [%]</th>
<th>Boiling Point</th>
</tr>
</thead>
<tbody>
<tr>
<td>cyclobutanone</td>
<td>2,2,4,4-tetramethylcyclobutanone</td>
<td>49</td>
<td>128-130°C</td>
</tr>
<tr>
<td>cyclopentanone</td>
<td>2,2,5,5-tetramethylcyclopentanone</td>
<td>90</td>
<td>38-39°C/12 Torr</td>
</tr>
<tr>
<td>cyclohexanone</td>
<td>2,2,6,6-tetramethylcyclohexanone</td>
<td>34</td>
<td>60-46°C/15 Torr</td>
</tr>
<tr>
<td>2-indanone</td>
<td>1,1,3,3-tetramethylindan-2-one</td>
<td>75</td>
<td>108-112°C/15 Torr</td>
</tr>
<tr>
<td>pinacolone</td>
<td>2,2,4-trimethylpentan-3-one</td>
<td>70°</td>
<td></td>
</tr>
<tr>
<td>acetophenone</td>
<td>2-methylpropiophenone</td>
<td>77°</td>
<td>93-99°C/1 Torr</td>
</tr>
</tbody>
</table>

a) $^1$H-NMR(CD$_3$Cl$_2$): $\delta$ = 1.21(s, 4 CH$_3$), 1.78(s, CH$_3$).  
- b) $^1$H-NMR(CD$_3$Cl$_2$): $\delta$ = 1.04(s, 4 CH$_3$), 1.77(s, 2 CH$_2$).  
- c) two runs - $^1$H-NMR(CD$_3$Cl$_2$): $\delta$ = 1.12(s, 4 CH$_3$), 1.70(m, 3 CH$_2$).  
- 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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**REFERENCES**

Dedicated to Prof. Dr. Ch. Rüchardt on the occasion of his 60th birthday.

10) B.p. 105°C. - C₁₃H₂₀O (192.3) calc. C 81.20 H 10.48 found 80.93 H 10.48.  
- IR(film): $\nu$ = 2959cm⁻¹ s, 2868s, 1735s.  
- $^1$H-NMR (CD$_3$Cl$_2$): $\delta$ = 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).  
- $^{13}$C-NMR(CD$_3$Cl$_2$): $\delta$ = 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).
12) M.p. 108-110°C. - IR(KBr): ν = 3150 cm⁻¹ w, 3115w, 3000w, 2960w, 2930m, 2830m, 1640w, 1560w, 1483w, 1450w, 1430w, 1268s, 1220m, 1200s, 1140s, 1075s, 1015s. - ¹H-NMR (CDCl₃): δ = 3.70(s,6H), 6.34(dd,J=3Hz,J=1.8Hz,2H) 6.70(d,J=3Hz,2H) 7.43(d,J=1.8Hz,2H). - MS(70eV): m/z (%) = 221(12), 220(86,M⁺), 206(11), 205(86), 177(30), 95(100), 39(25).


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 ¹H-NMR-spectroscopically pure tetramethylcycloalkanones, which can be further purified by distillation.


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