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# $\alpha$ -Methylation of ketones with methanol catalyzed by Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>

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**Abstract:**  $\alpha$ -Methylation of ketones with methanol catalyzed by a cheap and easy to handle Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> was explored herein. After optimization of the reaction between propiophenone and methanol, the desired product was obtained in 95% isolated yield. A wide range of ketones was methylated in the optimized conditions (16 examples). This procedure was extended to a three-component cross-benzylation-methylation of acetophenone.

#### Introduction

Methylation is an essential transformation for the synthesis of biologically active molecules.<sup>[1]</sup> However, classical methylating agents, such as methyl iodide, dimethylsulfate, or diazomethane, are highly toxic or explosive.<sup>[2]</sup> In recent years, methylation methods were developed with greener agents, such as CO2,<sup>[3]</sup> formic acid<sup>[4]</sup> or dimethyl carbonate.<sup>[5]</sup> Other alternative reagents such as dimethylsulfite<sup>[6]</sup> and trimethylphosphate<sup>[7]</sup> were also proposed by our group. The borrowing hydrogen methodology allows the use of alcohols as alkylating agents through an aldehyde intermediate, generating water as the sole byproduct.<sup>[8]</sup> However, this methodology has been mostly developed with benzylic and long chain aliphatic alcohols.<sup>[9]</sup> The most challenging one, the methylation with methanol has been less explored, possibly due to the high dehydrogenation energy of methanol ( $\Delta H = 84 \text{ kJ.mol}^{-1} \text{ vs. } 68 \text{ kJ.mol}^{-1}$  for ethanol).<sup>[10]</sup> And yet, methanol is a cheap, abundant and renewable molecule, as it can be also synthesized from H<sub>2</sub> and CO<sub>2</sub>.<sup>[11]</sup> In the past decade, methanol has been successfully used for the amethylation of ketones through the borrowing hydrogen methodology (Scheme 1). This reaction has been mainly reported with homogeneous Ir,<sup>[12]</sup> Ru<sup>[13]</sup> and Rh<sup>[14)</sup> complexes (Scheme 1a). More recently, it has been shown that non-noble metal complexes of Co,<sup>[15]</sup> Mn,<sup>[16]</sup> Ni<sup>[17]</sup> and Fe<sup>[18]</sup> could efficiently catalyze this reaction (Scheme 1b). Pd supported on polymers<sup>[19]</sup> and Pt/C<sup>[20]</sup> are the only examples of heterogeneous catalysts for the  $\alpha$ -methylation of ketones with methanol (Scheme 1c). Though most of these catalysts can be used in mild conditions, a large excess of base (up to 500 mol%) is generally required. Moreover, the works previously cited mostly rely on noble and

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expensive metals, and there is to date no example of non-noble metal heterogeneous catalysts. We have previously reported that Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> is an efficient, inexpensive and recyclable supported catalyst for the  $\alpha$ -alkylation of ketones by benzylic and long chain aliphatic alcohols.<sup>[21]</sup> Herein, we report the  $\alpha$ -methylation of ketones catalyzed by Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> using methanol as an alkylating agent (Scheme 1).



Scheme 1. a-Methylation of ketones with methanol.

#### **Results and Discussion**

Propiophenone 1a was selected as a model substrate for the optimization of the  $\alpha$ -methylation with methanol catalyzed by Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>. The base screening was carried out with 9 equivalents of MeOH, 20 mol% of Ni catalyst and 10 mol% of base. The mixture was heated at 175°C for 15h without added solvent (Table 1). Using KOAc gave a high selectivity but a low yield of the desired product 3a (13% GC ratio, Table 1, entry 1). Improved yields were obtained with <sup>t</sup>BuOLi and KOH (Table 1, entries 2-3). However, 2,4-dibenzoyl-pentane 4a was observed as a byproduct under these conditions. This undesired product is probably formed by the Michael addition of 1a on the product of aldol-condensation between formaldehyde and propiophenone. This kind of product has been previously observed by other groups.<sup>[14,16]</sup> Although a high conversion was obtained with K<sub>2</sub>CO<sub>3</sub>, the vield was still moderate (45% GC ratio, Table 1, entry 4). The use of K<sub>3</sub>PO<sub>4</sub> improved the ratio of **3a** to 66% and gave a high selectivity (Table 1, entry 5). This high selectivity was attributed to the drastic reduction of byproduct 4a. K<sub>3</sub>PO<sub>4</sub> was therefore selected as the most suitable base for this transformation. Other parameters of the reaction, such as the Ni catalyst and base loading, the temperature and the quantity of MeOH, were then optimized. Increasing the quantity of MeOH to 18 equivalents while keeping the same volume, increased the GC ratio of 3a to 74%, albeit with a reduced selectivity (Table 1, entry 6). The quantity of the nickel catalyst could be advantageously decreased to 10 mol%, affording the desired product 3a in a good 83% GC ratio (Table 1, entry 7). A further decrease of this loading to 5 mol% highly impacted the selectivity, as the desired product 3a was formed in 24% GC ratio, while the undesired product 4a was obtained in a 71% GC ratio (Table 1, entry 8). A slight increase of temperature to 185°C increased the GC ratio of 3a to 87% (Table 1, entry 9).

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Finally, increasing the quantity of MeOH to 21 equivalents led to an excellent 95% isolated yield for the desired product **3a** (Table 1, entry 10).

Table 1. α-Methylation of propiophenone catalyzed by Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>.<sup>[a]</sup>

Ph 1a	, + MeOH <b>2</b>	Ni/SiO <sub>2</sub> - base (10 175°C,	Al <sub>2</sub> O <sub>3</sub> mol%) 15 h	Ph Me 3a	Ph Me	O Ph
Entry	Base	Ni cat. (mol%)	<b>2</b> (eq)	Conv. (%) <sup>b)</sup>	<b>3a</b> GC ratio (%) <sup>c)</sup>	<b>4a</b> GC ratio (%) <sup>c)</sup>
1	KOAc	20	9	14	13	0
2	<sup>t</sup> BuOLi	20	9	28	24	4
3	КОН	20	9	69	46	20
4	K <sub>2</sub> CO <sub>3</sub>	20	9	82	45	36
5	K <sub>3</sub> PO <sub>4</sub>	20	9	78	66	6
6	K <sub>3</sub> PO <sub>4</sub>	20	18	98	74	24
7	K <sub>3</sub> PO <sub>4</sub>	10	18	>99	83	15
8	K <sub>3</sub> PO <sub>4</sub>	5	18	97	24	71
9	K <sub>3</sub> PO <sub>4</sub>	10	18	>99	87	9
10	$K_3PO_4$	10	21	98	97 ( <b>95</b> ) <sup>d)</sup>	0

[a] Reaction conditions: **1a** (1 equiv.), **2** (86.9 mmol, 3.6 mL),  $65wt\%Ni/SiO_2-Al_2O_3$ , base (10 mol%), under Ar atmosphere,  $175^\circ$ C, 15h. [b] GC conversion of **1a**. [c] 185°C. [d] isolated yield.

In order to evaluate the scalability of our methodology, the  $\alpha$ methylation of propiophenone with methanol was studied starting from 17.4 g of ketone (30-fold scale-up) in the optimized conditions (Scheme 2). The reaction was performed in a 300-mL autoclave reactor equipped with mechanical stirring. It was noticed that the reaction could run smoothly under air. After 72h at 185°C, the product was obtained in a 91% yield (18.6 g, 94% GC purity).



 $\begin{array}{l} \mbox{Scheme 2. Scale-up reaction. Reaction conditions: 1a (17.25 mL, 0.124 mol, 1 equiv.), 2 (108 mL, 2.61 mol, 21 equiv.), 65wt%Ni/SiO_2-Al_2O_3 (10 mol%, 1.14 g), K_3PO_4 (10 mol%, 2.64 g), under air, 185°C, in a 300 mL autoclave reactor, 72h. \\ \end{array}$ 

The scope of the  $\alpha$ -methylation of ketones was then investigated under the optimized conditions (Scheme 3). The reaction was firstly studied with acetophenones. Acetophenone and substituted acetophenones with para-electron-donating groups such as methyl and methoxy afforded good yields (73, 78 and 77%, **3b**, **3c** and **3f**).



**Scheme 3.** α-Methylation of various ketones with methanol: Scope and limitations. <sup>[a]</sup> Reaction conditions: **1b-o** (4.14 mmol, 1 equiv.), MeOH (86.9 mmol, 21 equiv.), 65wt%Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> (10 mol%), K<sub>3</sub>PO<sub>4</sub> (10 mol%), under Ar, 185°C, 15h unless otherwise noted. <sup>[b]</sup> 24h. <sup>[c]</sup> 24 : 76 mixture of diastereomer. <sup>[d]</sup> GC ratios.

For p-methoxyacetophenone, time was increased to 24h in order to obtain a good yield: in 15h, the mono- $\alpha$ -methylated product was obtained with 23% yield along with the desired product (43% yield). The effect of steric hindrance on the aromatic ring was studied with methyl group. A slight decrease of the yield was observed from the para to ortho position (78-66% from 3c to 3e). A ketone with two electron-donating group, 3',4'dimethoxyacetophenone, gave product 3g in a moderate yield (47%). p-Trifluoromethylacetophenone was tested, affording a mixture of mono- $\alpha$ -methylated product **3h** (11%) and di- $\alpha$ methylated product 3h' (14%), both in low yield. Surprisingly, pchloroacetophenone gave mono-methylated product 3i as the sole product, in a very low yield (5%). In this case, the conversion was low and dehalogenation product was obtained only in traces. Reaction with 1- and 2-acetonaphthones afforded the desired products 3j and 3k in good yields (60 and 73%). More hindered ketones were finally tested. Butyrophenone and α-tetralone gave 3I and 3m in good yields (80 and 89%). α-Tetralones with electron-donating groups, such as 5,7-dimethyl-1-tetralone and 6-methoxy-1-tetralone afforded the desired

products 3n and 3o in good yields (85 and 64%). Interestingly, with 6-methoxy-1-tetralone, low amounts of 6-methoxy-2,4dimethylnaphthalen-1-ol were observed as a by-product. Some aliphatic ketones were also tested. Reaction with cyclohexanone afforded the dimethylated product 3p in 24% yield, as a 76 : 24 mixture of diastereomers. The monomethylation product was not observed. 2-Octanone underwent total conversion under the reaction conditions, affording four different products as a mixture. Monomethylated product 3q was obtained in 31% GC yield, dimethylated compounds 3q' and 3q" in 27% and 18% GC yield respectively and the trimethylated product 3q" in 24% GC yield. Selectivity toward one particular compound could not be improved by increasing/decreasing the time or the amount of MeOH nor changing the nature of the base. Some other ketones were tested, such as p-fluoroacetophenone, pbromoacetophenone, 1-phenylbutane-1,3-dione, dibenzoylmethane, p-nitroacetophenone and 4-acetylcyanide, but the desired products could not be obtained (see SI for more details).

In order to further explore the possibilities of the reactions of alcohols with ketones catalyzed by  $Ni/SiO_2-Al_2O_3$ , the three-component cross-benzylation-methylation of acetophenone with benzyl alcohols and methanol was studied (Scheme 4).



Scheme 4. Cross-benzylation-methylation of acetophenone with benzyl alcohols and methanol. Reaction conditions: 1b (4.14 mmol, 1 equiv.), 5 (8.28 mmol, 2 equiv.), MeOH (86.9 mmol, 21 equiv.),  $65wt\%Ni/SiO_2-Al_2O_3$  (10 mol%), K<sub>3</sub>PO<sub>4</sub> (10 mol%), under Ar atmosphere,  $185^{\circ}C$ , 15h.

The reactions between acetophenone **1b**, methanol and either benzyl alcohol **5a** or 4-methoxybenzyl alcohol **5b** successfully gave **6a** and **6b** in good yields (56% and 58%, respectively). Such reactions have already been studied by other groups with expensive noble metal catalyst only, such as Ru,<sup>[13b]</sup> Ir<sup>[12a]</sup> and Pd.<sup>[19b]</sup> Therefore, the promising results in this work constitute the first example of a three-component cross-alkylation-methylation of ketones with methanol and higher alcohols catalyzed by a supported non-noble metal.

Finally, the recyclability of the Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> catalyst was studied with the model reaction, over 4 runs (Figure 1). The catalyst was filtered between each run, washed with water and acetone, dried in an oven and reengaged for the next run (see ESI for the full procedure). In these conditions, a 58% GC ratio for the desired product **3a** was initially obtained with the fresh catalyst. However, this yield could not be maintained during the 3 other runs: it was divided by about 2 after each run. In each run, formation of **4a** was observed, which explains the difference between the GC ratio of **3a** and the conversion of **1a**.



Figure 1. Recycling study of the Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> for the  $\alpha$ -methylation of propiophenone.

An ICP analysis showed the presence of soluble Ni species in the filtrate obtained after 3h of reaction between 1a and MeOH in the optimized conditions. (NB: hot filtration could not be performed due to the low boiling point of MeOH). The concentration of soluble Ni in this filtrate was found to be 14.23 mg.L<sup>-1</sup>, which corresponds to 59 µg of Ni, namely 0.03% of the initial nickel quantity. In order to assess the activity of the soluble Ni species, the filtrate was heated at 185°C for 12h. The contents of the crude mixture before filtration and after filtration and heating were compared, showing slight differences. GC conversion of 1a increased from 23% to 33%. GC ratio of 3a slightly increased, from 26% to 29%, while GC ratio of 4a increase from 41% to 48%. The increase of conversion of 1a and GC ratio of 4a could be explained by the presence of dissolved formaldehyde in the filtrate, which makes the formation of 4a possible. The increase of GC ratio of 1a does not seem significant. These observations show that the leaching of the catalyst does not play a decisive role in the deactivation of the recycled catalyst. The recyclability of the Ni catalyst for the  $\alpha$ -methylation of ketones with methanol is in contrast with the excellent recyclability of the same catalyst for the alkylation of acetophenones with other alcohols.<sup>21</sup> Further studies will be performed to fully understand how the catalyst deactivates in the presence of methanol under these conditions.

#### Conclusions

To conclude, we have demonstrated that cheap and easy to handle Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> could efficiently catalyze the  $\alpha$ -methylation of propiophenone with methanol using catalytic amount of K<sub>3</sub>PO<sub>4</sub> (10 mol%). In the optimized conditions, the desired product was obtained in 95% isolated yield. This model reaction was successfully scaled-up to afford 18.6 g of product (91% yield). The scope of the reaction was explored and a range of methylated products was obtained (16 examples). Finally, we

have shown that the method developed here could be incorporated in a three-component cross-benzylationmethylation of acetophenone using benzyl alcohols and methanol simultaneously.

#### **Experimental Section**

General procedure for the  $\alpha$ -methylation of ketones by methanol catalyzed by nickel supported on silica alumina in the optimized conditions. 65wt% Ni/SiO<sub>2</sub>,Al<sub>2</sub>O<sub>3</sub> (38 mg, 0.1 equiv) and K<sub>3</sub>PO<sub>4</sub> (88 mg, 0.1 equiv), ketone (4.14 mmol, 1 equiv) and MeOH (3.6 mL, 86.9 mmol, 21 equiv) were introduced in that order in a 15 mL pressure tube, which was then sealed with a cap. The mixture was stirred at 185°C for 15h. After this duration, a sample of the crude mixture was diluted in ethyl acetate, filtered and analyzed by GC. 2-3 g of silica was added to the crude mixture, which was then concentrated under reduced pressure and purified by flash chromatography (ethyl acetate/cyclohexane) to afford the desired compounds. See Supporting Information for the characterisation of all compounds. It should be noted that this procedure includes risks due to the high pressure, which could lead, in the case of a damaged pressure tube, to its explosion. Therefore, this reaction should only be done under a protective shield.

Procedure for scaled-up  $\alpha$ -methylation of propiophenone by methanol catalyzed by nickel supported on silica alumina in the optimized conditions. 65wt% Ni/SiO<sub>2</sub>,Al<sub>2</sub>O<sub>3</sub> (1.14 g, 0.1 equiv) and K<sub>3</sub>PO<sub>4</sub> (2.04 g, 0.1 equiv), propiophenone (17.25 mL, 132 mmol, 1 equiv) and MeOH (108 mL, 2.78 mol, 21 equiv) were introduced in that order in a 300 mL autoclave reactor, which was then sealed. The mixture was mechanically stirred (~1200 rpm) at 185°C for 72h. After reaction, the mixture was filtered on Millipore filter (0.1 µm) on the solids were washed with MeOH. The filtrate was concentrated under reduced pressure and the desired product was distilled in the rotary evaporator. 18.6 g of the desired product were obtained (91% yield, 94% GC purity).

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The  $\alpha$ -methylation of ketones with methanol is a challenging topic due to the high dehydrogenation energy of methanol. Herein, we demonstrate that a range of ketones could be efficiently alkylated with methanol using a cheap and easy to handle Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub> catalyst. A cross-benzylation-methylation of acetophenone is also reported.

#### Methylation

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α-Methylation of ketones with methanol catalyzed by Ni/SiO<sub>2</sub>-Al<sub>2</sub>O<sub>3</sub>