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Heterogeneous Catalysis

Solvent-Free N-Alkylation of Amides with Alcohols Catalyzed by Nickel on Silica–Alumina

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Abstract: The N-alkylation of phenylacetamide with benzyl alcohol has been studied using Ni/SiO_2–Al_2O_3. In the optimized conditions, the desired product was isolated in an excellent 98 % yield. The reaction could advantageously be performed in neat conditions, with a slight excess of amide and a catalytic amount of base. These conditions were tested on a large range of amides and alcohols, affording 24 compounds in 13 to 99 % isolated yields.

The formation of an amide C–N bond is one of the key processes for the synthesis of peptides, pharmaceuticals, polymers and natural products.[1–4] Amides are generally synthesized by condensation of carboxylic acids (or their esters, anhydrides or acyl chloride analogs) with amines, or by the reaction between an amide and an aryl or aliphatic halide.[5–9] However, those methods exhibit a poor atom economy, as they inevitably lead to the formation of stoichiometric amounts of waste. Though less explored than the previously cited methods, reductive alkylation of amides with aldehydes has been reported by our group as a greener alternative,[10] along with other nitrogen nucleophiles.[11,12] A high hydrogen pressure is however required, and aldehydes generally need to be purified before use as they easily oxidize. The borrowing hydrogen methodology solves these issues, as it uses alcohols both as alkylating agents and hydrogen sources.[13–15] The N-alkylation of amides with alcohols has been firstly reported in the pioneer work of Watanabe et al. with $RuCl_2(PPh_3)_3$.[16] Shortly after, Jenner improved the yields and the scope of this reaction by including secondary alcohols with $RuCl_2(PBu_3)_3$ as a catalyst.[17] More recently, [Ru(*p*-cymene)Cl_2]$_2$ with DPEphos has been reported under microwave activation.[18] The N-alkylation of amides with alcohols has been mainly explored with homogeneous Ir catalysts, such as [Cp*IrCl_2]$_2$ (1 to 5 mol-%, at 130–160 °C).[19–21] The loading of the catalyst and the reaction temperature could be reduced by using a N–Heterocyclic Carbene–phosphine ligand[22] or a benzoxazolyl ligand,[23] thus improving the activity of the Ir catalyst. This reaction has also been reported with homogeneous Pd, using $Pd(OAc)_2$[24,25] or a heterobimetallic Pd–Sn catalyst,[26] and Rh, with the Wilkinson catalyst.[27,28] Only two examples of homogeneous non-noble metal complexes were reported, with $Cu(OAc)_2$[29] and a $NiBr_2$/phenanthroline catalytic system.[30] Whereas some of these catalytic system require toxic solvents such as toluene or *o*-xylene, a significant part of the previously cited examples does not require an additional solvent. However, in these cases, a large excess of alcohol (from 3 to 6 equivalents) is used. Few heterogeneous catalysts were used for the N-alkylation of amide with alcohols. An Ag/Mo oxide ($Ag_6Mo_{10}O_{33}$) was used by Shi et al.[31] However, the authors did not report any recyclability test for their catalyst. Kobayashi et al. reported an example of recyclable catalyst for this reaction, with polymer-incarcerated Au/Pd nanoparticles with carbon black as a secondary support, and $Ba(OTf)_2$ as an additive.[32] To this date, no non-noble metal based heterogeneous catalyst has been reported for this reaction. Our group has been investigating the efficiency of Ni/SiO_2–Al_2O_3 for the α-alkylation of ketones with alcohols, including methanol.[33,34] Furthermore, this catalyst has been fully characterized (see ESI). Herein, we report our new findings on the catalytic activity of Ni/SiO_2–Al_2O_3 for the solvent-free N-alkylation of amides with alcohols.

The N-alkylation of phenylacetamide **1a** with benzyl alcohol **2a** has been chosen as the model reaction for the initial investigation, leading to the formation of the desired product: *N*-benzyl-2-phenylacetamide **3a**. During this optimization, benzyl 2-phenyl acetate **4** was identified as the major by-product. The formation of the ester **4** is probably consequent to the nucleophilic addition of **2a** on **1a**, thus releasing ammonia. A range of bases was first tested, with a 2 to 1 ratio of amide **1a** to alcohol **2a**, 20 mol-% of 65 wt.-% Ni/SiO_2–Al_2O_3 and 10 mol-% of base. The reaction mixture was heated at 175 °C for 15 h, without added solvent (Table 1). AcOK, a weak base, allowed to obtain **3a** in 60 % GC ratio, with moderate selectivity as the ester **4** was formed in 17 % GC ratio (Table 1, Entry 1). Reaction with stronger bases such as *t*BuOK and KOH lead to good results, with 90 % ratio and high conversion (Table 1, Entries 2 and 3). K_3PO_4, used in our previous work, allowed the formation

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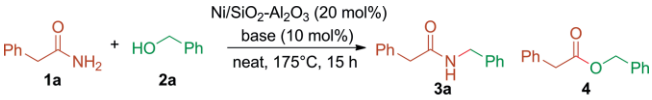
of **3a** in a 93 % ratio (Table 1, Entry 4). Some carbonates were then tested. Cs_2CO_3 afforded the product in 82 % ratio while it was obtained in 95 % ratio with Na_2CO_3 and K_2CO_3 (Table 1, Entries 5–7). The selectivity with Na_2CO_3 being slightly lower, K_2CO_3 was selected as the most suitable base for this reaction. Other parameters, such as nickel loading, **1a**/**2a** ratio and reaction conditions were then studied (Table 2). In an effort of increasing the greenness of this reaction, the quantity of the nickel catalyst was decreased to 10 mol-% Ni. Advantageously, it did not highly impact the formation of the desired product **3a**, as it was observed in an 81 % ratio (Table 2, Entry 1). Further reduction of the quantity of nickel was not found suitable for the reaction. Ratio of **1a**/**2a** was then decreased to 1.5 to 1, allowing to observe **3a** in 92 % ratio, with a 93 % conversion of **2a** (Table 2, Entry 2). Further decrease of this ratio to 1.2 to 1 impacted negatively the ratio of **3a** (82 %, Table 2, Entry 3). The conversion could be increased to 99 % by increasing the time to 20 h, thus affording the desired *N*-benzylated amide **3a** in an excellent 98 % isolated yield (Table 2, Entry 4). Decreasing the temperature to 160 °C highly impacted the kinetics of the reaction, as conversion of **2a** was only 47 % (Table 2, Entry 5). Blank experiments were then performed. As expected, the desired product was not formed when the reaction was run without nickel catalyst (Table 2, Entry 6). Small amounts of product were formed in the absence of base (Table 2, Entry 7). Interestingly, ester **4** was the major product in this case. The formation of the benzaldehyde intermediate by dehydrogenation of **2a** is most probably reversible. In the absence of base, the kinetics of the condensation of **1a** on **2a** is likely to be decreased, as the base is thought to catalyze this step and could also play a role in the dehydrogenation of **2a**. Consequently, from a macroscopic point of view, more benzyl alcohol **2a** is probably available, thus increasing the rate of the nucleophilic addition of **2a** on **1a**, leading to the formation of the corresponding ester. This ester could also be formed by the insertion of nickel in the C–N bond of **1a**, as reported by Garg et al.[35,36] New investigations would be required in order to confirm the capacity of $Ni/SiO_2–Al_2O_3$ to perform this insertion.

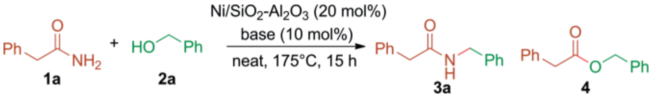
Table 1. Base screening for the N-alkylation of phenylacetamide **1a** with benzyl alcohol **2a** catalyzed by $Ni/SiO_2–Al_2O_3$.[a]



Entry	Base [mol-%]	GC conv.[b]	**3a**[c]	**4**[c]
1	AcOK	81	60	17
2	*t*BuOK	97	90	2
3	KOH	97	90	3
4	K_3PO_4	96	93	1
5	Cs_2CO_3	87	82	4
6	Na_2CO_3	> 99	95	< 1
7	K_2CO_3	96	95	< 1

[a] Reaction conditions: **1a** (19.32 mmol, 2 equiv.), **2a** (9.67 mmol, 1 equiv.), 65wt.-%$Ni/SiO_2–Al_2O_3$ (20 mol-%), base (10 mol-%), neat, 175 °C, 15 h. [b] GC conversion of **2a**. [c] GC ratio.

Table 2. Conditions screening for the N-alkylation of phenylacetamide **1a** with benzyl alcohol **2a** catalyzed by $Ni/SiO_2–Al_2O_3$.[a]

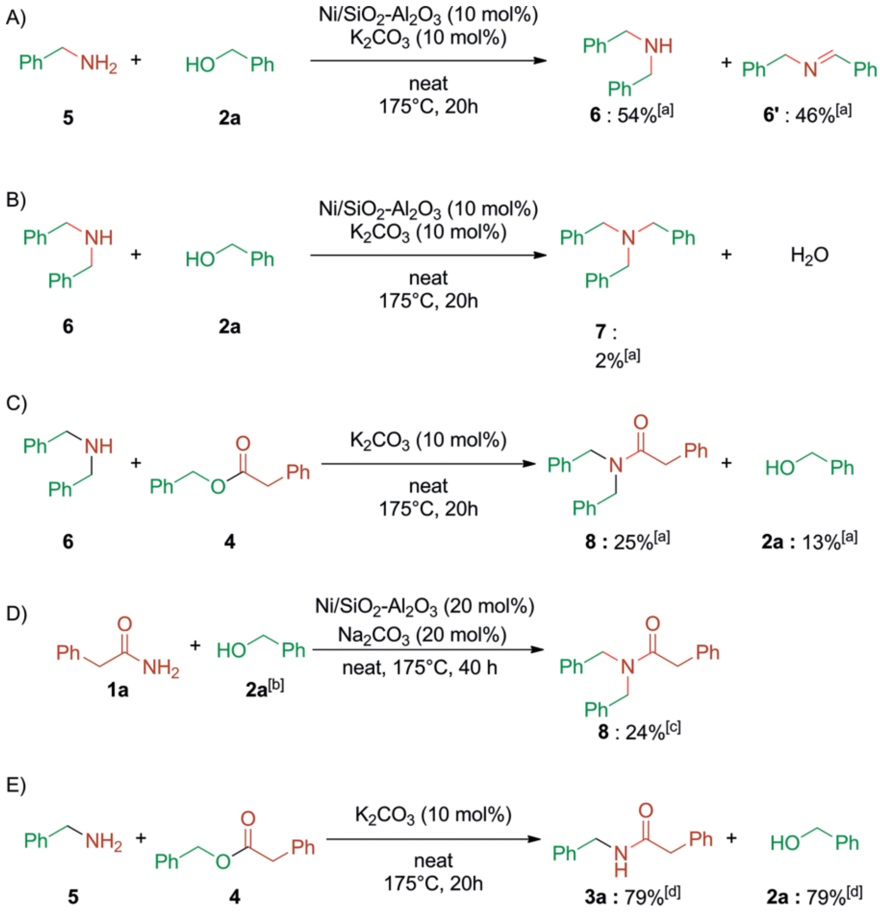


Entry[a]	**1a**/**2a** ratio	GC conv.[b]	**3a**[c]	**4**[c]
1	2:1	86	81	< 1
2	1.5:1	93	92	< 1
3	1.2:1	87	82	1
4[d]	1.5:1	99	99 (**98**)[e]	< 1
5[f]	1.5:1	47	42	5
6[g]	2:1	2	0	1
7[h]	2:1	59	19	31

[a] Reaction conditions: **1a** (19.32 mmol, 2 equiv.), **2a** (9.67 mmol, 1 equiv.), 65wt.-%$Ni/SiO_2–Al_2O_3$ (10 mol-%), K_2CO_3 (10 mol-%), neat, 175 °C, 15 h. [b] GC conversion of **2a**. [c] GC ratio. [d] 20 h. [e] Isolated yield. [f] 160 °C. [g] Ni: 0 mol-%. [h] K_2CO_3: 0 mol-%.

Other products were also observed in low amount during this optimization study, such as benzylamine **5**, dibenzylamine **6**, tribenzylamine **7** and *N*,*N*-dibenzyl-2-phenylacetamide **8**. The formation pathways of these products were studied. As previously mentioned, the formation of the ester **4** could produce ammonia as a coproduct. This reactive compound could be benzylated by benzyl alcohol through a borrowing hydrogen mechanism, as reported in the literature, thus leading to the formation of benzylamine.[37–40] This primary amine was successfully alkylated by benzyl alcohol in the optimized conditions, affording dibenzylamine (54 % GC ratio) and *N*-benzylidene-1-phenylmethanamine (46 % GC ratio) (Scheme 1, A). Dibenzylamine could be converted into tribenzylamine (2 % GC ratio) with benzyl alcohol in the same conditions (Scheme 1, B). These three amines could therefore be formed by consecutive borrowing hydrogen processes. *N*,*N*-dibenzyl-2-phenylacetamide **8** could *a priori* be produced by direct benzylation of the desired product **3a**. However, **8** was not observed when **3a** and benzyl alcohol were submitted to the optimized conditions. Interestingly, this product could be observed in a 25 % GC ratio by reaction between dibenzylamine and the ester **4** in alkaline conditions (K_2CO_3, 10 mol-%) at 175 °C during 20 h (Scheme 1, C). After some optimization, this product was isolated in 24 % yield. (Scheme 1, D) In the same manner, the desired product **3a** could be formed by reaction between benzylamine and the ester **4** in 79 % NMR ratio (Scheme 1, E). We have therefore demonstrated that di-N-alkylation of phenylacetamide could be performed indirectly through a borrowing hydrogen process. This reaction will be further investigated in next works.

A range of alcohols and amides was then tested to evaluate the versatility of the optimized conditions. Phenylacetamide **1a** was first *N*-alkylated by several alcohols (Figure 1). Some benzyl alcohols with electron-donating groups were first tested. Excellent yields were obtained with *p*-methoxy and *p*-methylbenzyl alcohols (**3b** and **3c** resp., 99 and 96 % yield). As expected, a slight decrease of yield was noticed with *m*- and *o*-methylbenzyl alcohols (**3d** and **3e** resp., 80 and 71 % yield), which could easily be explained by the increase of the steric hindrance induced by the methyl group. Benzyl alcohols bearing an electron-withdrawing group seemed less reactive, as a moderate 55 % yield was obtained with *p*-trifluoromethylbenzyl alcohol



Scheme 1. Study of the formation of the by-products. Starting materials were introduced in equimolar quantities, unless otherwise specified. [a] GC ratio. [b] 5 equiv. [c] Isolated yield. See ESI for full procedure. [d] ^1H NMR ratio.

(**3f**). *p*-Fluoro and *p*-chlorobenzyl alcohols afforded the desired product in good yields (**3g** and **3h** resp., 75 and 61 % yield). For *p*-chlorobenzyl alcohol, the dechlorinated product **3a** was observed in low amounts. Surprisingly, the desired reaction did not occur with *p*-bromobenzyl alcohol and *p*-bromobenzyl phenyl acetate was obtained as the main product, in low amounts. The N-alkylation of **1a** with a range of aliphatic alcohols was also investigated. Linear alcohols, such as ethanol, 1-propanol, 1-pentanol and 1-octanol gave good to low yields (**3i**, **3j**, **3k**, **3l** resp., 69, 46, 31, 13 % yield). It was observed that the yield of the desired products decreased and that the amount of ester increased when the chain length increased. This could partially be explained by the increase of nucleophilicity of linear alcohols with the increase of the chain length. The reaction 3-phenylpropan-1-ol afforded the desired product **3m** in a low 31 % yield while the ester was observed in high quantity. 2-Propanol and cyclohexanol gave the desired products in low and moderate yield (**3n** and **3o** resp., 26 and 58 % yield).

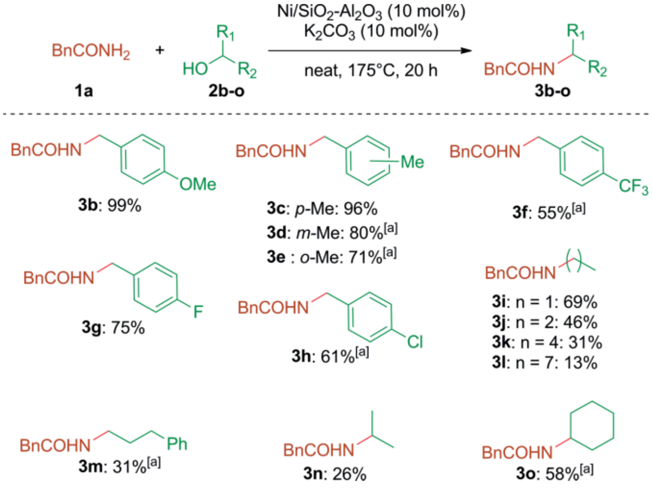


Figure 1. N-alkylation of phenylacetamide with alcohols catalyzed by $Ni/SiO_2–Al_2O_3$. Reaction conditions: **1a** (19.32 mmol), **2b–o** (12.88 mmol), 65wt.-%Ni/$SiO_2–Al_2O_3$ (10 mol-%), K_2CO_3 (10 mol-%), neat, 175 °C, 20 h unless otherwise specified. [a] 60 h.

A range of amides was also *N*-alkylated with benzyl alcohol in the optimized conditions (Figure 2). Phenylacetamides bearing electron-withdrawing substituents on the aromatic ring gave high to excellent yields. The reaction using 4-methoxyphenylacetamide gave the desired product **3p** in an excellent 94 % yield. *Para-*, *meta-*, and *ortho*-phenylacetamides gave the desired product in very good yields (89 %, 84 % and 88 % for **3q**, **3r** and **3s** resp.). A good 61 % yield was obtained with *para*-chlorophenylacetamide. Interestingly, dechlorination of the starting material or the desired product was negligible. A good yield was obtained with benzamide (**3u**, 76 %), while *N*-benzylnicotinamide was formed in moderate yield (**3v**, 39 %). 1-naphthylacetamide gave the desired product **3w** in a moderate 60 % yield. A good result was obtained with acetamide, affording the desired product **3x** in 79 % yield. A sulfonamide, *para*-tolylsulfonamide was engaged in reaction with benzyl alcohol in the optimized conditions to afford the desired *N*-benzylated product in a good yield (**3y**, 63 %).

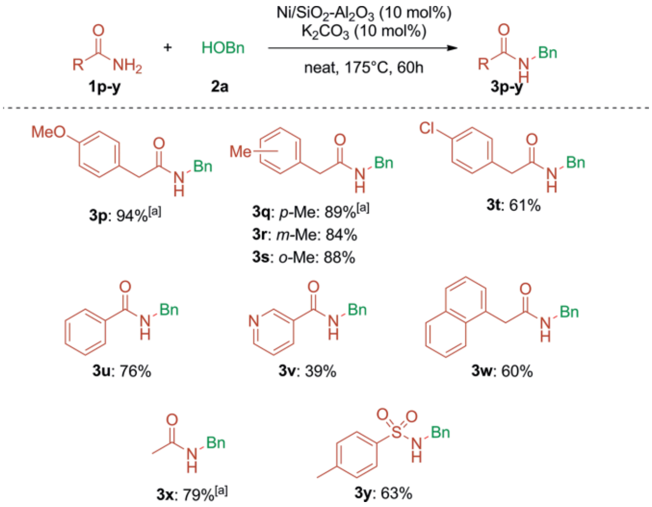


Figure 2. *N*-alkylation of various amides with benzyl alcohol catalyzed by $Ni/SiO_2–Al_2O_3$. Reaction conditions: **1p–y** (19.32 mmol), **2a** (12.88 mmol), 65 wt.-%$Ni/SiO_2–Al_2O_3$ (10 mol-%), K_2CO_3 (10 mol-%), neat, 175 °C, 60 h unless otherwise specified. [a] 20 h.

The recyclability of the Ni catalyst was studied with the model reaction over 5 runs (Figure 3). The reactions were performed in 6 h, at incomplete conversion, in order to detect efficiently a potential loss of catalytic activity. After each run, the crude mixture was filtered through Millipore paper (1 µm) and the catalyst was washed with acetone and water, dried and reengaged into reaction. The mass of the recycled catalyst was measured each time and the quantities of the other components of the reaction were recalculated accordingly. During this study, the desired product was virtually obtained as the sole product, as its GC selectivity was always greater than 98 %. After 6 hours of reaction, GC ratio of **3a** was 54 % after the first run. Surprisingly, this ratio increased until run #3, reaching 82 %. The ratio then decreases rapidly (run# 5: 41 %). The catalyst seems first to undergo an activation, then a deactivation. It is noteworthy that the mass of the catalyst after each run decreases quickly, from 115 mg (run# 1) to 66 mg (run# 5). Interestingly, 11 mg of nickel were detected in the solution obtained by hot filtration after 6 h of reaction. This value corresponds to a loss of 14.7 % of the initial mass, highlighting a leaching of the catalyst into solution. The actual nickel loading on the catalyst support probably decreases in the course of the different runs due to this leaching. Further studies will be undertaken in order to establish the cause of these observations.

In conclusion, we performed the first N-alkylation of amides with alcohols promoted by a non-noble heterogeneous catalyst: nickel on silica-alumina. The reaction conditions were optimized with benzyl alcohol and phenylacetamide as model substrates. The desired product was isolated in an excellent 98 % yield, with a slight excess of phenylacetamide (1.5 equiv.), 10 mol-% of $Ni/SiO_2–Al_2O_3$ and K_2CO_3 in 20 h at 175 °C without any solvent. The study of the reaction pathways leading to the reaction by-products was performed. The scope of the reaction was investigated with a range of amides and alcohols, affording 24 *N*-alkylated amides in 13 to 99 % isolated yield.

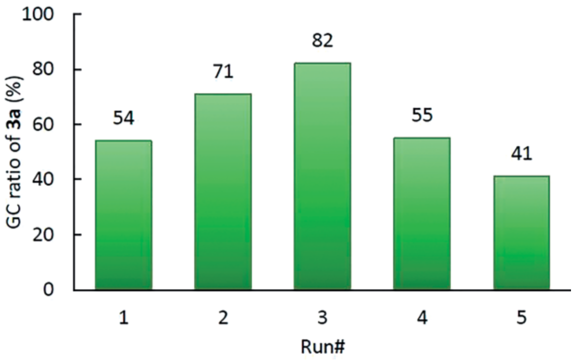


Figure 3. Recycling study of the nickel catalyst for the N-alkylation of phenylacetamide with benzyl alcohol.

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Keywords: N-alkylation · Amides · Alcohols · Nickel · Heterogeneous catalysis

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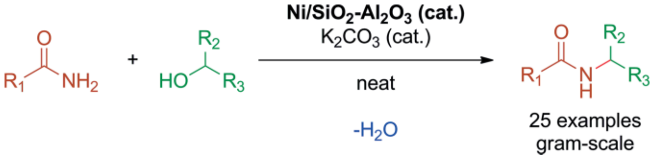

To date, the N-alkylation of amides with alcohols has not been studied with non-noble metal base heterogeneous catalyst. Herein, a range of amide was efficiently N-alkylated with various alcohols using cheap and easy to handle Ni/SiO_2-Al_2O_3.

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