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Synthesis of indoles through acceptorless dehydrogenative coupling catalyzed by nickel on silica-alumina

Aubin Charvieux,^a Abdul Aziz Hammoud,^a Marie-Christine Duclos,^a Nicolas Duguet^{a,*} and Estelle Métay^{a,*}

^aUniv Lyon, Université Claude Bernard Lyon1, CNRS, INSA-Lyon, CPE-Lyon, Institut de Chimie et Biochimie Moléculaires et Supramoléculaires, ICBMS, UMR 5246, Equipe CAtalyse, SYNthèse et ENvironnement (CASyEN), Campus LyonTech La Doua, Bâtiment Lederer, 1 rue Victor Grignard, 69100 Villeurbanne, France.

* Corresponding author. Tel.: +33-472-485-507; e-mail: nicolas.duguet@univ-lyon1.fr

* Corresponding author. Tel.: +33-472-485-507; e-mail: estelle.metay@univ-lyon1.fr

ABSTRACT

The high atom-economical formation of indoles from anilines and diols was described with affordable and easy to handle Ni/SiO₂-Al₂O₃. After optimization, 2,3-dimethylindole was isolated with an excellent 98% yield in neat conditions. The scope of the reaction was studied and 13 indoles were isolated in 16-80% yields.

Keywords: Indole; Acceptorless dehydrogenative coupling; Heterogeneous nickel; Anilines; Diols

Introduction

The indole core is one of the most important heterocycle present in many natural products and bioactive compounds.¹ Moreover, indoles are also used as dyes² and functionalized materials.³ Because of these important properties, many synthetic methodologies have been developed, such as Fischer,⁴ Madelung⁵ or Bichler-Napieralski syntheses.⁶ More recently, transition metal-catalyzed methods have been also reported for the preparation of indoles, generally through an alkyne activation.⁷ Most of these methods require the use of prefunctionalized starting materials, thus producing stoichiometric amounts of waste.

Advantageously, the transition metal-catalyzed acceptorless dehydrogenative coupling methodology allows the synthesis of nitrogen-based heterocycles in a very atom economic way.⁸ More specifically, indoles can be formed using simple compounds such as anilines and vicinal diols, producing only hydrogen and water as coproducts. In their pioneer work reported in 1986, Watanabe *et al.* showed that RuCl₂(PPh₃)₃ catalyzes this reaction in dioxane at 180°C, though with a limited scope.⁹ Using SnCl₂ in quite similar conditions, Shim *et al.* extended the scope to abundant and cheap ethylene glycol, thus allowing the synthesis of indoles with no substituents in positions 2 and 3.¹⁰ More recently, other systems combining a metal-based complex and an acidic cocatalyst were also reported. For example, Ding *et al.* showed that [Ru(CO)₂(Xantphos)]₂ was an efficient catalyst in the presence of *para*-toluene sulfonic acid (PTSA) in *tert*-amyl alcohol at 120°C.¹¹ Madsen *et al.* demonstrated that [Cp*IrCl₂]₂ and MsOH can catalyze this reaction in neat conditions.¹² Very recently, Ballesteros-Garrido *et al.* reported Pt/Al₂O₃ as the first heterogeneous catalyst for this reaction.¹³ Used with ZnO, this catalyst allows the synthesis of indoles from ethylene glycol and anilines. Though most of the works previously cited gave good results, they are mostly based on the use of expensive noble metals and solvents, thus limiting their synthetic potential and sustainability. Recently, we demonstrated the efficiency of affordable and commercially available Ni/SiO₂-Al₂O₃ for the solvent-free α -alkylation of ketones with alcohols,¹⁴ including methanol,¹⁵ and for the *N*-alkylation of amides.¹⁶ Considering the

mechanistic similarities between the borrowing-hydrogen methodology¹⁷ and the acceptorless dehydrogenative coupling, we now report the solvent-free indole synthesis from anilines and diols catalyzed by Ni/SiO₂-Al₂O₃.

Results and discussion

Aniline **1a** (2 equivalents) and 2,3-butanediol **2a** were selected as model substrates and the reaction was performed with Ni/SiO₂-Al₂O₃ (10 mol%) at 175 °C for 15 hours in a pressure tube under air (Table 1).

Table 1. Acid screening for the formation of 2,3-dimethylindole **3a** catalyzed by Ni/SiO₂-Al₂O₃.^a

| Entry | Acid | 2a Conv. ^b | 3a ^b | 4 ^b |
|-------|-----------------------------------|------------------------------|------------------------|-----------------------|
| 1 | - | > 99 | < 1 | 65 |
| 2 | AcOH | 77 | 16 | 46 |
| 3 | TFA | 96 | 56 | 27 |
| 4 | BF ₃ ·OEt ₂ | 93 | 62 | 14 |
| 5 | Aquivion PW98 ^c | 24 | 22 | < 1 |
| 6 | Amberlyst 35 dry ^d | 73 | 40 | 30 |
| 7 | TfOH | 98 | 81 | 14 |
| 8 | MsOH | 95 | 77 | 11 |
| 9 | PTSA | 91 | 75 | 8 |

^a Reaction conditions: **1a** (21.9 mmol, 2 equiv), **2a** (10.9 mmol, 1 equiv), 65 wt% Ni/SiO₂-Al₂O₃ (10 mol%), acid (10 mol%), neat, under air, 175°C, 15h, pressure tube. ^b GC conversion and ratios. ^c 1 mol%. ^d 210 mg.

Without any acidic co-catalyst, the conversion was complete but the desired product 2,3-dimethylindole **3a** was not formed and only 3-(phenylamino)butan-2-one **4** was observed as the major compound (Table 1, entry 1). According to the generally accepted mechanism for the formation of **3a**, diol **2a** is first dehydrogenated

by the metal catalyst, and hydrogen is released.¹² The corresponding hydroxyketone then undergoes a condensation with aniline **1a**, giving water as a byproduct, thus forming intermediate **4** after subsequent tautomerism. The last step is an acid catalyzed Friedel-Crafts type cyclisation, leading to the formation of the desired indole **3a**. Therefore, our result indicates that the silica-alumina support is not acidic enough to catalyze the final cyclization step. Therefore, several acids (10 mol%) were tested. AcOH gave a low GC ratio for the desired product, while intermediate **4** was observed as the major product (16 and 46% GC ratio respectively, Table 1, entry 2). Trifluoroacetic acid and boron trifluoride etherate gave **3a** in moderate quantities, with 56% and 62% GC ratio respectively (Table 1, entries 3 and 4). In order to evaluate the efficiency of a completely heterogeneous catalytic system, two heterogeneous acids were tested (Table 1, entries 5 and 6). A high selectivity but low conversion was observed with Aquivion PW98 (Table 1, entry 5). Amberlyst 35 dry allowed the formation of 40% GC ratio of **3a** (Table 1, entry 6). The efficiency of three sulfonic acid, TfOH, MsOH and PTSA, was then evaluated, leading to high GC ratios for **3a** (81, 77 and 75% respectively, Table 1, entries 7-9). The selectivity obtained with these acids being very similar, PTSA was selected as the best acid co-catalyst, for economical and practical reasons.

Parameters such as PTSA and nickel loading, aniline quantity, temperature and reactor type were then optimized (Table 2). The nickel quantity was first decreased to 5 mol%, giving a total selectivity for the desired product but a moderate 55% conversion (Table 2, entry 1). As expected, decreasing the PTSA loading to 5 mol% resulted in a decrease of **3a** GC ratio and an increase of intermediate **4** GC ratio, at total conversion (Table 2, entry 2). Increasing PTSA loading to 20 mol% did not significantly improve the results (81% GC ratio, Table 2, entry 3). Further increase of PTSA loading to 50 mol% did not allow any conversion. In this case, the mixture after reaction was green and transparent, instead of black and opaque for all other experiments, indicating that nickel was probably dissolved under these conditions. An important decrease of **3a** GC ratio to 56% was observed when the quantity of aniline **1a** was reduced to 1.5 equivalent (Table 2, entry 4). Decreasing the temperature to 150°C led to a decrease of **3a** GC ratio to 68% (Table 2, entry 5). When the reaction time was extended to 24 hours, no improvement was observed (72% **3a** GC ratio, Table 2, entry 6).

Table 2. Optimization of reaction parameters.^a

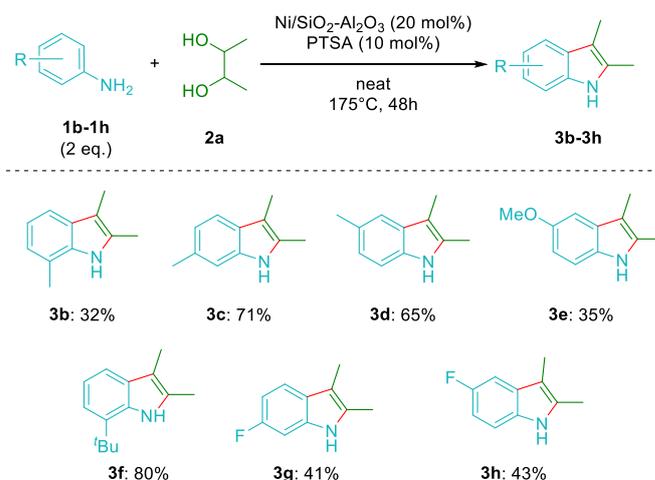


| Entry | PTSA (mol%) | 2a Conv. ^b | 3a ^b | 4 ^b |
|------------------|-------------|------------------------------|------------------------|-----------------------|
| 1 ^c | 10 | 55 | 55 | < 1 |
| 2 | 5 | 98 | 60 | 29 |
| 3 | 20 | 96 | 81 | 6 |
| 4 ^d | 10 | 93 | 56 | 15 |
| 5 ^e | 10 | 88 | 68 | 10 |
| 6 ^f | 10 | 97 | 72 | 12 |
| 7 ^g | 10 | 96 | 86 | 3 |
| 8 ^{g,h} | 10 | >99 | >99 (98) ⁱ | < 1 |

^a Reaction conditions: **1a** (21.9 mmol, 2 equiv), **2a** (10.9 mmol, 1 equiv), 65 wt% Ni/SiO₂-Al₂O₃ (10 mol%), PTSA, neat, under air, 175°C, 15h, pressure tube. ^b GC conversion and ratios. ^c Ni/SiO₂-Al₂O₃ (5 mol%). ^d **1a** (1.5 eq.). ^e 150°C. ^f 24 h. ^g Open air reflux apparatus. ^h Ni/SiO₂-Al₂O₃ (20 mol%). ⁱ Isolated yield.

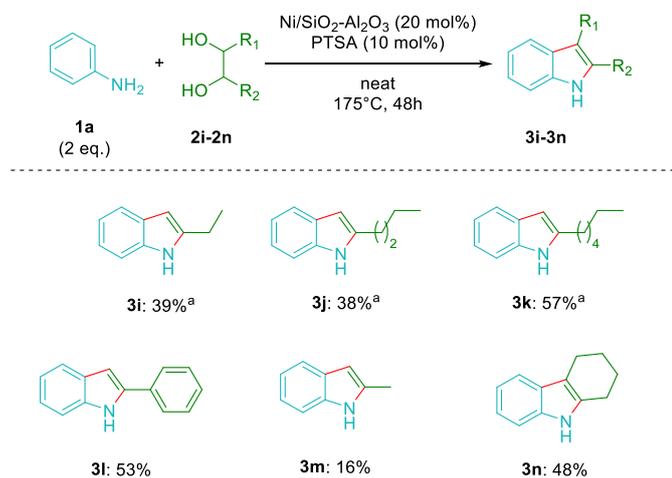
Performing the reaction in an open air reflux apparatus instead of a pressure tube increased the GC ratio of **3a** to 86% (Table 2, entry 7). The hydrogen release from the nickel catalyst is probably faster in this case, thus improving the desired reaction. In the same type of apparatus, increasing the nickel loading to 20 mol% led to an excellent conversion and selectivity towards indole **3a** (Table 2, entry 8). Under these conditions, the desired product was isolated with 98% yield, on a gram-scale.

The scope and limitations were investigated under the optimized conditions using 2,3-butanediol **2a** and a range of diversely substituted anilines (Scheme 1). In order to ensure an acceptable conversion for the majority of substrates, the reaction time was extended to 48 hours. Different toluidines were first tested. *Ortho*-toluidine led to the formation of **3b** in a moderate 32% isolated yield. Good results were obtained with *meta*- and *para*-toluidine as the corresponding products were isolated in 71% (**3c**) and 65% (**3d**) yield, respectively. Surprisingly, among anisidines, only *para*-anisidine afforded the desired product **3e**, in a moderate 35% yield. Low conversion of diol **2a** was observed with *ortho*- and *meta*-anisidines and the desired products could not be detected. Those anisidines could be strong chelating agents, thus poisoning the nickel catalyst. Despite its strong steric hindrance, a good 80% yield (**3f**) was obtained from 2-*tert*-butylaniline. *Meta*- and *para*-fluoroanilines gave the desired products **3g** and **3h** in moderate yields (41% and 43% respectively). Indeed, for these two examples, some degree of hydrodefluorination¹⁸ occurs as indole **3a** was observed in low quantities.



Scheme 1. Synthesis of indoles from various anilines and 2,3-butanediol. Reaction conditions: **1b-1h** (21.9 mmol, 2 equiv), **2a** (10.9 mmol, 1 equiv), 65 wt% Ni/SiO₂-Al₂O₃ (20 mol%), PTSA (10 mol%), neat, under air, 175°C, 24h, open air reflux apparatus. Isolated yields.

Different indoles were then formed from aniline and various vicinal diols (Scheme 2). Terminal diols such as 1,2-butanediol, 1,2-hexanediol and 1,2-octanediol gave the desired products in moderate yield (39%, 38% and 57% respectively). 1-Phenylethane-1,2-diol allowed to form the corresponding product **3l** with a moderate 53% yield. The desired product **3m** was obtained from 1,2-propanediol with a low 16% yield. For these five unsymmetrical diols, only one product was obtained selectively, as the other potential regioisomer was not observed. A moderate 48% yield (**3n**) was also obtained with 1,2-cyclohexanediol. Finally, the dehydrogenative coupling of anilines and 1,3-diols was also attempted. However, no satisfying results were obtained using the standard conditions.



Scheme 2. Synthesis of indoles from various anilines and 2,3-butanediol. Reaction conditions: **1a** (21.9 mmol, 2 equiv), **2i-2n** (10.9 mmol, 1 equiv), 65 wt% Ni/SiO₂-Al₂O₃ (20 mol%), PTSA (10 mol%), neat, under air, 175°C, 24h, open air reflux apparatus. Isolated yields. ^a Reaction performed in a pressure tube.

In order to evaluate the robustness of the nickel catalyst, its recyclability was studied for the formation of 2,3-dimethylindole **3a** from aniline **1a** and 2,3-butanediol **2a**, at incomplete conversion (reaction time: 5 hours) (Figure 1).

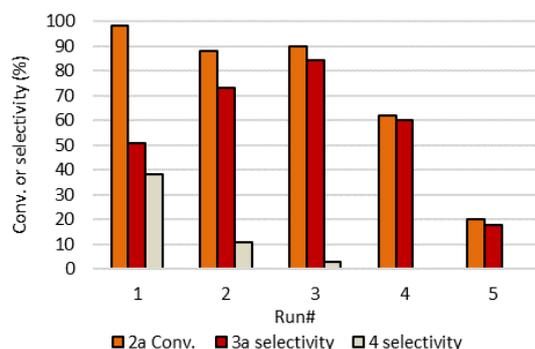


Figure 1. Recyclability study of Ni/SiO₂-Al₂O₃ for the formation of 2,3-dimethylindole **3a** from aniline **1a** and 2,3-butanediol **2a** performed at incomplete conversion (reaction time = 5h). Conversion and selectivity were determined by GC.

Between each run, the reaction mixture was filtrated on Millipore paper (1 μm) and the catalyst was washed with water, acetone and diethyl ether, dried and weighted. The quantities of the other compounds were calculated accordingly and a new reaction was performed. The selectivity of indole **3a** first increased from 51 to 84% from run 1 to run 3. Then, a decrease was observed until run 5 (18%). From these results, the catalyst seems to undergo an activation, then a deactivation. As observed during the optimization, PTSA could dissolve the catalyst. This dissolution could at first activate the nickel catalyst, then deactivate it as the Ni / support ratio decreases. Further studies would be necessary to fully understand this phenomenon.

Conclusion

In conclusion, we demonstrated that Ni/SiO₂-Al₂O₃ can efficiently catalyze the formation of 2,3-dimethylindole from aniline and 2,3-butanediol through an acceptorless dehydrogenative coupling in neat conditions in an excellent 98% isolated yield. The optimized conditions were then applied to a

range of anilines and vicinal diols, allowing the formation of diversily-substituted indoles in 16-80% yields (13 examples).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data (procedures, characterization data, ¹H and ¹³C NMR) to this article can be found online.

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19. **General procedure for indole synthesis from aniline and 1,2-diol catalyzed by nickel supported on silica-alumina.** 1,2-Diol (10.9 mmol, 1 equiv.), 65 wt% Ni/SiO₂-Al₂O₃ (198 mg, 0.2 equiv.),

aniline (21.9 mmol, 2 equiv.) and PTSA (209 mg, 0.1 equiv.) were introduced in that order in a 50 mL round bottom flask, which was then equipped with an open condenser. The mixture was stirred at 175 °C for 48 h. After this time, a sample of the crude mixture was diluted in ethyl acetate, filtered and analyzed by GC. Silica (2-3 g) was added to the crude mixture, which was then concentrated under reduced pressure and purified by flash chromatography (ethyl acetate/cyclohexane 5 : 95) to afford the desired product. The characterization data is given for a representative example, see supporting information for the characterization of all other products. **2,3-Dimethyl-1H-indole** (3a, CAS#91-55-4): 1.420 g, GC purity 96%, 89% yield, yellowish solid, mp = 108 °C; ¹H NMR (300 MHz, DMSO-*d*₆): δ = 2.15 (s, 3H, CH₃), 2.30 (s, 3H, CH₃), 6.89-7.00 (m, 2H, 2CH), 7.22 (dt, *J* = 8.0, 0.9, 1H, CH), 7.34 (ddd, *J* = 7.4, 1.6, 0.8, 1H, CH), 10.62 (s, 1H, NH); ¹³C NMR (75 MHz, DMSO-*d*₆): δ = 8.3 (CH₃), 11.2 (CH₃), 105.0 (C), 110.2 (CH), 117.3 (CH), 118.0 (CH), 119.9 (CH), 129.0 (C), 131.3 (C), 135.2 (C); HRMS (ESI⁺) [M+H]⁺ C₁₀H₁₁N: requires 146.0964, found 146.0963 (1.1 ppm).