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Combined Pd/C and Montmorillonite Catalysis for One-Pot Synthesis of Benzimidazoles

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Abstract

A series of nineteen benzimidazoles are prepared from *ortho*-nitroanilines via one-pot transfer hydrogenation, condensation, and dehydrogenation enabled by the concurrent use of two heterogeneous catalysts: montmorillonite-K10 and Pd/C. This strategy is further employed to accomplish a five-step, three-component synthesis of an antifungal benzimidazoquinazoline using a simple one-pot procedure.

Keywords

heterogeneous catalysis; heterocycles; synthetic methods; clays; benzimidazoles

Introduction

The use of multiple catalysts in one-pot reactions to achieve sequential transformations, termed ‘tandem concurrent catalysis’, is documented predominantly for homogeneous systems.^[1] Extension of this strategy to heterogeneous catalysts offers noteworthy advantages. In such cases, the inherent economic and environmental benefits of one-pot multistep sequences are paired with facile catalyst removal by filtration and opportunities for convenient catalyst recycling.^[2] Indeed, the development of multi-functional heterogeneous catalysts is enabling multistep transformations with remarkable efficiency.^[3] While incorporation of complex catalytic materials, such as polyfunctional mesoporous silicas,^[3d, 3i] into routine use in synthetic research laboratories is limited by catalyst availability, the pragmatic chemist can now choose from an abundance of simpler heterogeneous options.^[4] In principle, any two or more chemically compatible heterogeneous materials are potential tandem catalysts for one-pot multistep transformations. Herein we aim to draw attention to this underutilized strategy by demonstrating a facile preparation of benzimidazoles from *ortho*-nitroanilines and aldehydes enabled by the simultaneous use of two heterogeneous catalysts, palladium on carbon and the acid-treated clay montmorillonite-K10.^[5] Not only is the isolation of two intermediates avoided but products of high purity are recovered by simple filtration.

Benzimidazoles demonstrate wide ranging biological activities including efficacy against cancers,^[6] HIV,^[7] and HSV-1.^[8] Benzimidazole are most commonly prepared from *ortho*-arylenediamines which, in turn, are available via *ortho*-nitration of anilines and subsequent reduction of the nitro moiety.^[9] The two principal synthetic strategies for benzimidazole

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Supporting Information (see footnote on the first page of this article): General information, characterization data and copies of ¹H and ¹³C NMR spectra for compounds **5**, **10-28**, and **34**.

formation are: a) condensation of *ortho*-arylenediamines with carboxylic acids and derivatives thereof,^[10] and b) dehydrogenation of benzimidazoline intermediates generated from condensation of *ortho*-arylenediamines with aldehydes.^[11] The first of these methods entails acidic conditions and high temperatures while the second typically requires stoichiometric or excess oxidants. Catalytic aerobic methods have recently emerged as suitable green alternatives for benzimidazoline oxidation.^[12] Transition metal catalyzed aryl amination,^[13] C-H functionalization,^[14] and oxidation of alcohols,^[15] have also been employed in the efficient preparation of benzimidazoles.

Results and Discussion

We envisioned a three-step sequence starting from *ortho*-nitroaniline (**1**) where Pd/C would catalyze both the initial hydrogenation of the nitro moiety and the terminal benzimidazoline dehydrogenation, while montmorillonite-K10 would catalyze condensation of diamine (**2**) with an aldehyde (Scheme 1).

The reduction of the aryl nitro moiety via transfer hydrogenation over Pd/C is a well-documented process.^[16] The compatibility of montmorillonite-K10 and Pd/C has also been previously established.^[17] Thus, as anticipated, the reduction of *ortho*-nitroaniline in the presence of montmorillonite-K10 was readily accomplished in refluxing toluene with ammonium formate (>3 equiv.) as the hydrogen donor. Cyclohexene and ammonium acetate were also found to be suitable hydrogen donors but ammonium formate was preferred due to comparative ease of handling. We were pleased to observe that inclusion of benzaldehyde in this reaction mixture resulted in formation of the desired 2-phenyl benzimidazole **5** albeit in modest yield (65%) and contaminated by a small amount of the 1,2-disubstituted benzimidazole **6** (Table 1, Entry 1). A considerable amount of unreacted phenylenediamine was also recovered indicating that some of the benzaldehyde had likely undergone reduction.

When benzaldehyde addition was withheld until complete reduction of the nitro moiety (1 h), a modest improvement in yield was observed along with a drop in selectivity for **5** over **6** (Table 1, Entry 2).

Formation of the undesired 1,2-disubstituted benzimidazole, **6**, was a predictable complication. Under a variety of conditions, *ortho*-arylenediamines are documented to react with two aldehyde equivalents to yield 1,2-disubstituted benzimidazoles.^[18] This presumably proceeds via isomerization of intermediate **9** to benzimidazole **6** (Scheme 2). This aromatization has been previously proposed to proceed via 1,3-hydride shift.^[18c, 18d] However, given that suprafacial 1,3-hydride shifts are symmetry forbidden and the antarafacial pathway would be geometrically disfavoured, it is conceivable that an intermolecular hydride transfer may be occurring. Addition of two molar equivalents of benzaldehyde to our reaction did not yield exclusively **6** but rather a 1 : 1 mixture of **5** and **6** (Table 1, Entry 3).

Given the equilibrium between compounds **7** and **9** under acidic conditions, exclusive formation of the monosubstituted benzimidazole (**5**) requires that dehydrogenation of benzimidazoline (**7** to **5**) is favored over isomerization of **9** to **6** (Scheme 2). While a number of oxidants are known to mediate selective formation for **5** over **6** in such systems,^[11,12] dehydrogenation using Pd/C is not previously reported.

A brief screen of conditions for the reaction of phenylenediamine with benzaldehyde in the presence of both catalysts, revealed that selectivity between **5** and **6** was remarkably temperature-dependent (Table 2). Above 60 °C, a substantial amount of **6** was produced

while at or below room temperature the desired benzimidazole **5** was formed exclusively. In fact, when the reaction was performed in an ice bath (4 °C – rt) only trace formation of **6** was observed even in the presence of two equivalents of benzaldehyde (Table 2, Entry 6).

With the issue of selectivity resolved, a suitable set of conditions was established for the one-pot three-step reaction. The substrate is first treated with NH₄HCO₂ (3.3 equiv.), Pd/C (0.05 equiv. Pd), and montmorillonite-K10 (300 mg/mmol of substrate) in refluxing toluene for 1 hour to complete the reduction of the nitro moiety. Next the reaction is cooled and an aldehyde (1 equiv.) is added before stirring for a further 16 hours while allowing the reaction to warm from 4 °C to ambient temperature. Notably, we found that both Pd/C and montmorillonite-K10 are needed for high yielding benzimidazole synthesis but a some product formation (< 20%) was also observed in the absence of montmorillonite. Using the optimized procedure we prepared 19 benzimidazoles (**5**, **10-27** Table 3). as a mixture of tautomers that equilibrate at elevated temperatures (see supporting information). [d] 2-nitrophenol was used as the substrate.

The procedure was found to be suitable for a variety of electron-rich and -poor substituted benzaldehydes (**10-19**). These included three *ortho*-substituted benzaldehydes (**16**, **18**, **19**) as well meta-hydroxy benzaldehyde (**12**). Several aliphatic aldehydes were also found to be suitable substrates for the reaction (**20-24**) and alkyl substitution on the 1,2-nitroaniline substrate was tolerated (**13**, **24**, **26**). Three heteroaromatic aldehydes were also suitable substrates (**25-27**). When 2-nitrophenol and benzaldehyde were used as substrates, 2-phenyl benzoxazole (**28**) was obtained in low yield.

To further highlight the synthetic value of this general strategy we set out to synthesize a substituted dihydrobenzo[4,5]imidazo[1,2-c]quinazoline, **34**, using a one-pot, three-component, five-step sequence (Scheme 3). **34** has previously been shown to have narrow-spectrum anti-fungal activity against *E. Flocossum*.^[19] We envisioned a one-pot sequence whereby 4,5-dimethyl-2-nitroaniline (**29**) is initially reacted with *ortho*-nitrobenzaldehyde (**30**) to yield to benzimidazole **31** which is not isolated but rather subjected to a second nitro-reduction and condensation with *para*-anisaldehyde (**32**, Scheme 3).

Gratifyingly, the one-pot five-step procedure proceeded as planned giving the desired heterocyclic product (**34**) in 60% overall yield. We found that the last stage of the reaction sequence, condensation of anisaldehyde (**33**), required a mild elevation of temperature (40 °C) to proceed at a reasonable rate. We were cautious to avoid excessive heating at this stage due to the potential of further dehydrogenation of **34** or condensation between **34** and a second equivalent of anisaldehyde (**33**) followed by isomerization to the fully aromatic species (analogous to formation of **6**, Scheme 2). Although ¹H NMR analysis of the crude reaction mixture containing **33** suggested a trace amount of dehydrogenation of this product, we were unable to isolate any substantial byproducts of the reaction. From a procedural standpoint, this one-pot five-step synthesis of **33** was exceptionally facile requiring no workup apart from a single filtration followed by chromatographic purification of the product.

Conclusions

Synthetic innovation today increasingly stresses the themes of efficiency, procedural simplicity and minimal environmental impact. In this context multiple reactions conducted in one-pot, employing easily removable and reuseable heterogeneous catalysts, and non-polluting redox procedures constitute desirable tools with the potential to improve access to valuable compounds. We have combined these themes to prepare benzimidazoles from *ortho*-nitroanilines by means of a one-pot transfer hydrogenation, condensation, and

dehydrogenation sequence made possible by the concurrent use of montmorillonite-K10 and Pd/C. In this manner, nineteen benzimidazoles were prepared in good yields. The process was further extended to a one-pot, five-step, three-component synthesis of a bioactive tetracyclic benzimidazoquinazoline, **34**. With this methodology we hope to highlight the largely untapped potential of tandem concurrent heterogeneous catalysis to facilitate multi-step organic synthesis.

Experimental Section

General procedure for the one-pot three-step synthesis of **benzimidazoles 5, 10-27**: To 25 mL round bottom flask charged with a magnetic stir bar are added: the nitroaniline (1.00 mmol), ammonium formate (3.30 mmol), Montmorillonite-K10 (300 mg) and 5% Pd/C (106 mg, 0.05 mmol Pd). Solids remaining on the sides of the flask are then rinsed to the bottom with toluene (10 mL) to give a bright yellow solution interspersed with black heterogeneous particles. This reaction mixture is refluxed vigorously at 120°C for 1 hr. Effervescence of CO₂ is evidenced by a frothing of the reaction that is distinguishable from reflux. This settles after about 30 minutes. The resulting solution is colorless, interspersed with black heterogeneous particles. The reaction mixture is allowed to cool and 1.00 mmol of the desired aldehyde is added by micropipette (liquid) or funneled weighing paper (solid). The reaction mixture is stirred in an ice bath and allowed to warm to ambient temperature overnight (16 hrs). The reaction mixture is filtered through a pad of Celite and rinsed with methanol under mild air pressure. The solvent of the filtrate is then removed in vacuo to give the corresponding benzimidazole in typically high purity. All benzimidazoles were further purified by liquid chromatography using 1% methanol/99% dichloromethane as the eluent.

One-pot, five step procedure for the synthesis of 6-(4-methoxyphenyl)-9,10-dimethyl-5,6-dihydrobenzo[4,5]imidazo[1,2-c]quinazoline (**34**): To 25 mL round bottom flask equipped with a magnetic stir bar are added: 166.9 mg of 5-dimethyl-2-nitroaniline (1.00 mmol), 208.7 mg of ammonium formate (3.31 mmol), 300 mg of Montmorillonite-K10 and 108.7 mg of 5% Pd/C (0.05 mmol Pd). Solids remaining on the sides of the flask are then rinsed to the bottom with 10 mL toluene. This mixture is refluxed vigorously at 120°C for 1 hr. Effervescence of CO₂ is observed. This reaction mixture is cooled to room and 151.5 mg 2-nitrobenzaldehyde (1.00 mmol) is added by funneled weighing paper. The resulting yellow reaction mixture is stirred in an ice bath and allowed to warm to room temperature overnight (16 hrs). To this mixture (containing **31**) is added 208.6 mg of ammonium formate (3.31 mmol) by funneled weighing paper, after which the reaction is again refluxed vigorously at 120°C for 1 hr to yield a colorless solution interspersed with black heterogeneous particles. To this is added 138.8 mg *p*-anisaldehyde (1.02 mmol) by micropipette, yielding a yellow mixture. This reaction is heated at 40°C in an oil bath for an 16 hrs to yield a colorless solution of the crude benzimidazoquinazoline (**34**) interspersed with black heterogeneous particles. The reaction mixture is filtered through a pad of Celite pad and rinsed with methanol. The solvent is removed *in vacuo* and the product is purified by chromatography (1% methanol / 99% dichloromethane as eluent). Yield 215.3 mg (60%, mp 111-114 °C); yellow solid; R_f 0.70 (5%MeOH-95%DCM); ¹H NMR (500 MHz, DMSO-*d*₆) δ 7.90 (dd, 1H, J = 8.0 Hz, 1.5 Hz), 7.45-7.39 (m, 2H), 7.23-7.18 (m, 1H), 7.17-7.11 (m, 2H), 6.94-6.90 (m, 2H), 6.89-6.85 (m, 2H), 6.84-6.77 (m, 2H), 3.69 (s, 3H), 2.27 (s, 3H), 2.21 (s, 3H); ¹³C NMR (125 MHz, DMSO-*d*₆) δ 159.5, 146.1, 142.8, 142.4, 132.7, 131.3, 131.1, 130.5, 130.4, 127.1, 124.3, 118.7, 118.0, 114.7, 114.0, 112.3, 110.6, 67.3, 55.1, 20.1, 19.8. These data are in agreement with reported literature values.^[19]

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Proposed one-pot synthesis of benzimidazoles.

Scheme 2.
Rationale for formation of benzimidazole **6**.

Scheme 3.

One-pot, five step synthesis of anti-fungal agent **34**.

Table 1

Initial attempted one-pot benzimidazole synthesis.

Entry	Conditions	Yield ^[a] (5+6)	Ratio (5:6)
1	PhCHO (1.0 equiv. added at start of reaction)	65 %	50 : 1
2	Reflux 1 hour, then PhCHO (1.0 equiv.), then reflux 16 hours	71 %	8 : 1
2	Reflux 1 hour, then PhCHO (2.0 equiv.), then reflux 16 hours	85 %	1 : 1

^[a]Yield after chromatography (5 + 6 were co-eluted).

Table 2Optimization of selectivity of benzimidazole **5** over **6**.

Entry	Conditions	Ratio of 5 : 6 ^[a]
1	120 °C, 1 h	4 : 1
2	60 °C, 16 h	4 : 1
3	45 °C, 16 h	20 : 1
4	22 °C, 16 h	>100 : 1
5	4 °C - rt, 16 h	>100 : 1
6	4 °C - rt, 16 h, 2 equiv. of PhCHO	100 : 1

^[a] Determined by ¹H NMR spectroscopy of crude reaction mixture.

Table 3

One-pot synthesis of benzimidazoles.

[a] Reaction conditions: substrate (1.0 mmol), NH₄CHO₂ (3.3 equiv.), Mont-K10 (300 mg), Pd/C (0.05 equiv. Pd), reflux, 1 h; then aldehyde (1 equiv.), 4 °C - rt, 16 h [b] Isolated yield after chromatography. [c] Isolated as a mixture of tautomers that equilibrate at elevated temperatures (see supporting information). [d] 2-nitrophenol was used as the substrate.