Green Approaches for the Synthesis of Some Biologically Relevant Nitrogen-Containing Organic Compounds

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Doctor of philosophy

By

Vishal Singh

DEPARTMENT OF CHEMISTRY
INDIAN INSTITUTE OF TECHNOLOGY
(BANARAS HINDU UNIVERSITY)
VARANASI- 221005
INDIA

Roll No. 19051008 **Year 2024**

SUMMARY AND CONCLUSIONS

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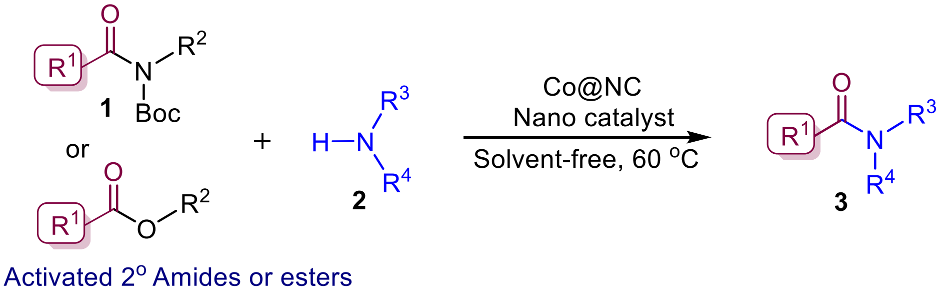
The primary purpose of this thesis is to develop new synthetic strategies employing microwave irradiation as a green, sustainable, and benign source of energy or conducting the reaction in solvent-free conditions. That gave higher yields due to reduced solvent interference and increased concentration of reactants. Overall, conducting reactions under solvent-free conditions and utilizing microwave irradiation represents a greener and more efficient approach to organic synthesis, offering numerous benefits in terms of reaction efficiency, yield, and environmental sustainability. This work focuses on developing greener transformation strategies for the synthesis of Nitrogen-Containing Organic Compounds in distinct ways.

The thesis entitled, "Green Approaches for the Synthesis of Some Biologically Relevant Nitrogen-Containing Organic Compounds" embodies the synthesis of biologically important compounds containing nitrogen atoms and their structural assignments. The contents of the thesis have been divided into five chapters.

Chapter 1 provides a general introduction and literature review of the synthesis and applications of some main classes of nitrogen-containing organic compounds such as acyclic nitrogen-containing compounds like amine, imine, oxime, amide and nitrogen-containing five-membered heterocyclic pyrrole, six-membered pyridine, pyrimidine and fused heterocycles such as indoles and benzimidazoles.

Chapter 2 describes a novel and efficient approach for transamidation of *N*-*tert*-butoxycarbonyl (*N*-Boc) activated secondary carboxamides, as well as the direct amidation of esters with amines using Co@NC nanocatalyst, in the solvent-free conditions. This technique exhibits exceptional selectivity in cleaving N–C/O–C, and resulting in the formation of amide bonds. The present methodology offers several benefits such as available cheap starting materials, solvent-free, mild reaction conditions, high atom economy, eco-friendly standards, excellent yields and magnetically separable and reusability of the catalyst (**Scheme A**).

The Co@NC magnetite nanoparticles were synthesized by the reported method and characterized by using different analytical and spectroscopic techniques such as FT-IR spectroscopy, XRD diffraction spectrum, SEM, TEM, EDAX and AFM analysis.



Scheme A

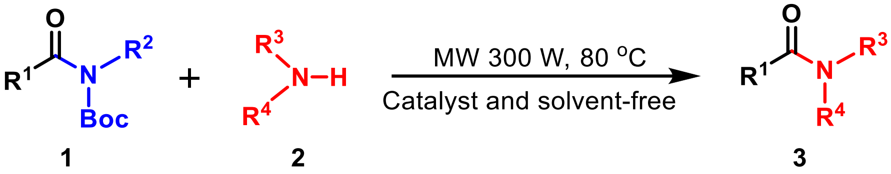
To determine the optimal conditions, *N*-*tert*-butylbenzoyl(benzyl)carbamate **1a** and morpholine **2a** were chosen as model substrates and reacted under various conditions. First, the reaction was performed without catalyst Co@NC in water as a solvent, at its reflux temperature for 2 h, but no desired product was obtained. Then, the reaction was carried out in the presence of Co@NC nano catalyst (1.0 mg), and refluxed in water for 2 h. The corresponding product, *N*-morpholino(phenyl) methanone **3a**, was formed in 40 % yield. Further to improve the yield, the reaction was tried with Co@NC nano catalyst in various solvents like ethanol, methanol, water, DMF, DMSO, toluene, xylene etc. and no satisfactory result was obtained. To our delight, the yield of product 3a was notably higher when conducted under solvent-free conditions at 60 °C. The reaction proceeded more efficiently, resulting in a 65% yield in just 30 minutes. This improvement may be attributed to the elevated concentration of reactants and their proximity in the absence of solvent.

Further, all optimizations were conducted under solvent-free conditions. Subsequently, the influence of temperature on the reaction's advancement was examined, on increasing the temperature up to 90 °C did not yield any significant alteration in the product yield. However, decreasing the temperature below 60^0C resulted in a reduction in the product yield. The study then investigated the impact of varying catalyst loading, ranging from 1 to 7 mg. As the amount of catalyst increased, so did the yield, with 5 mg emerging as the optimal amount. To assess the significance of the Co@NC nano catalyst, the reaction was conducted at 60 °C without the catalyst under solvent-free conditions. Even after 180 minutes, no product was obtained, indicating the essential role of the Co@NC catalyst in the transamidation of secondary amides.

Having optimized reaction conditions in hand, the general utility and efficiency of Co@NC nano-catalyzed transamidation reaction was explored with various Boc-protected aromatic and aliphatic amides and alkyl/aryl esters with different aliphatic, aromatic, cyclic, acyclic, sterically hindered amines. All amines reacted smoothly under these optimized reaction conditions and good to excellent yields were obtained (81-94%).

The reusability of Co@NC nanocatalyst was also examined under the optimized reaction conditions up to 6 runs. Comparison of FT-IR, EDAX, and XRD images of the fresh and recycled catalyst Co@NC has shown that the reaction conditions do not affect the structure and chemical nature of the catalyst.

Chapter 3 explores a simple environmentally benign and highly efficient catalyst and additive-free transamidation of *tert*-butyloxycarbonyl (Boc) activated secondary amides under controlled microwave irradiation in solvent-free conditions (**Scheme B**).

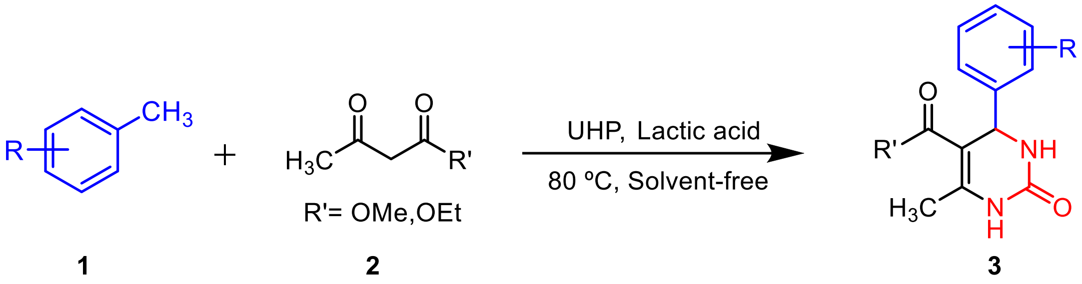


Scheme B

To optimize the reaction conditions for transamidation of secondary amide the reaction was carried out using *N*-Boc, *N*-phenylbenzamide **1a** (1.0 mmol), and piperidine **2a** (1.5 mmol) as a model substrate. Various reaction parameters were optimized under microwave irradiation on the model reaction. At the outset, the optimization experiments were carried out at 150W power and at 60^{o}C under solvent-free conditions in the presence of different polar protic or polar aprotic solvents in all cases it gave the product phenyl(piperidin-1-yl)methanone **3a** but the yield of the product was not satisfactory (30-55%). Surprisingly in solvent-free condition at 60^{o}C, 150 W gave the product **3a** in 62% yield in a shorter reaction time of 15 min. Next, we investigated the effect of microwave power a better yield of 80% was obtained at 300 W in 10 min. Interestingly the reaction at 80 ^{o}C under solvent-free conditions was driven to completion with the desired product **3a** to a maximum yield of 93% in 8 min at 300 W. To understand the assistance effect of microwave the model reaction was conducted under the same reaction conditions in the conventional heating method (without microwave) it gave only 20 % yield of the product **3a** even after 4 h.

The feasibility of this methodology was explored over a variety of *N*-Boc activated aliphatic, and aromatic amides with a series of electron-donating, electron-withdrawing, primary, secondary aromatic, aliphatic amines, and amino acids and found that they reacted smoothly under optimized reaction conditions. Transamidation of a structurally diverse set of amides and amines was accomplished in good to excellent yields. This method provides several advantages such as highly readily available substrates, solvent-free media, operational simplicity, mild reaction conditions, high product yields, wide functional group tolerance, and eco-safety.

Chapter 4 describes a simple and environmentally friendly one-pot multicomponent synthesis of biologically fascinating dihydropyridine-2(1*H*)-one derivative by the reaction of methyl arenes, as a surrogate of aldehydes, active methylene compounds and in *situ* generation of urea, and eco-friendly lactic acid as a green catalyst in solvent-free conditions via the Biginelli reaction (**Scheme C**).

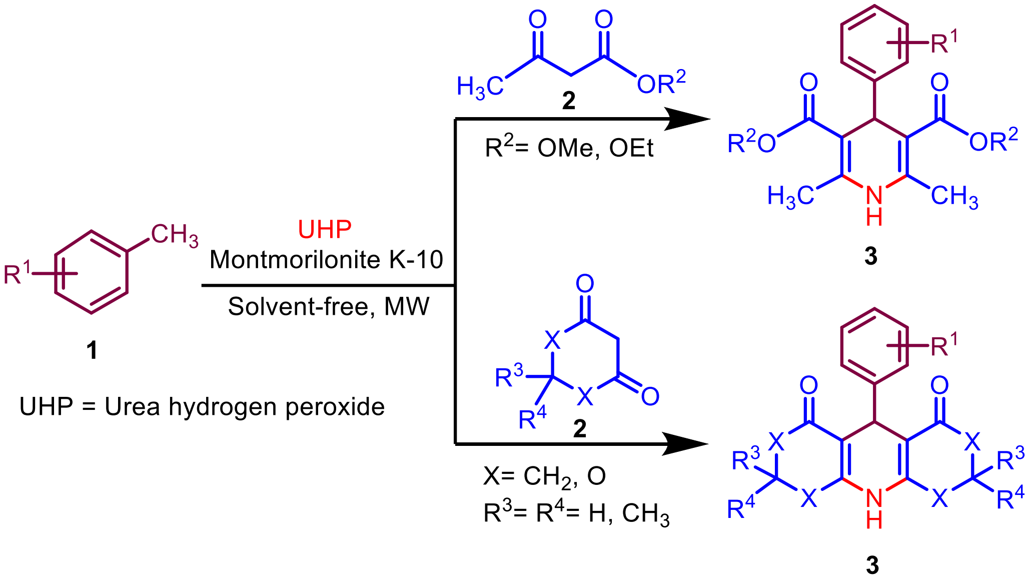


Scheme C

At the outset, in order to optimize the reaction conditions stoichiometric ratio of toluene **1a**, methyl acetoacetate **2a** and urea-hydrogen peroxide (UHP) were taken as the model reaction. Various parameters like solvents, amount of UHP, catalysts, and catalyst loading were investigated to find out, optimum conditions for the synthesis of tetrahydropyrimidine derivatives. The model reaction was carried out with lactic acid as a catalyst in the presence of different solvents at their reflux temperature and in solvent-free conditions to compare the effectiveness of this methodology, in solvent-free conditions a dramatically high yield of product **3a** (methyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate) was obtained.

The best result was obtained with 3 mmol of UHP and 20 mol% of catalyst lactic acid in solvent-free conditions, the yield of the product was (89%) in 2h. The feasibility of this methodology was explored over a variety of methyl arenes, also with different active methylene compounds such as methyl acetoacetate and ethyl acetoacetate it gave excellent yields under optimized reaction conditions. The salient features of the present methodology are environmentally benign mild reaction conditions, invaluable bio-based green catalyst, aerobic conditions easy isolation, high atom economy, and good to excellent yield of the products, without the use of chromatographic separation technique.

Chapter 5 presents an efficient and streamlined Montmorrilonite K-10 (MK-10) catalyzed synthesis for diverse Hantzsch 1,4-dihydropyridine derivatives under microwave irradiation in solvent-free conditions. The procedure entails the reaction of methyl arynes as a sustainable surrogate of aryl aldehydes, active methylene compounds, and urea hydrogen peroxide (UHP) as an oxidizing agent as well as a source of ammonia (**Scheme D**).



Scheme D

To optimize the reaction conditions toluene **1a** (1.0 mmol), ethyl acetoacetate **2a** (3.0 mmol) and urea-hydrogen peroxide with MK-10 were chosen as model substrates and different reaction parameters were optimized such as solvent, amount of UHP, amount of catalyst, microwave power and reaction temperature.

Various solvents were tested at 200 W in the presence of 2 mmol of UHP and 10 mg, MK-10 catalyst at fixed temperature of 50 °C for 60 min, but the yield of product **3a** (diethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate) was not satisfactory. Surprisingly, 60 % yield of the product was obtained it gave a in 30 min when the reaction was performed under solvent-free conditions. Next, we have optimized the microwave power by increasing the microwave power from 200 MW to 350 MW. The maximum yield 75 % of the product **3a** was obtained at 300 MW power in 20 min. Thereafter, the effect of the temperature on the yield of the model compound **3a** was investigated and at 60^{o}C it gave 80% in 15 min. A remarkable enhancement in the yield (85%) was obtained with 20 mg loading of the catalyst. In continuation of the solvent, temperature and catalyst loading optimization, the amount of UHP was also studied. On increasing the amount of UHP from 2 to 5 mmol, a 95 % yield of the desired product **3a** was obtained with 4 mmol of UHP in 15 min.

Afterwards, to extend the scope of substrates, various methyl arenes and heterocyclic methyl arenes were treated with acyclic active methylene compounds (e.g. ethyl acetoacetate, methyl acetoacetate) and cyclic active methylene compounds (e.g. 1,3 cyclohexanedione, dimedone and meldrum acid) for the synthesis of dihydropyridines. Methyl arenes containing electron-donating or electron-withdrawing groups were tested in the reaction and gave the desired product in good to excellent yields under optimized reaction conditions. The highlights of the present methodology are low-cost starting materials, high atom-economic strategy, simple with cleaner reaction profile, and high yield of products in shorter reaction time which builds a genuinely green protocol.

All the products have been fully characterized on the basis of their spectroscopic (^{1}H NMR, ^{13}C NMR and mass spectra) data. Plausible mechanisms for different transformations have also been proposed.