Microwave-Assisted Copper(II)-Catalyzed One-Pot Four-Component Synthesis of Multifunctionalized Dihydropyridines

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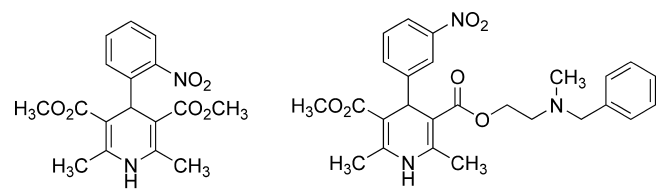
A fast and highly efficient copper-catalyzed multicomponent synthesis of 1,4-dihydropyridines under microwave irradiation is described. The protocol utilizes mild reaction conditions with low catalytic loading, leading to high yields. This methodology provides us with biologically active 1,4-dihydropyridine library for medicinal chemistry applications.

Introduction

Synthesis of bioactive molecules should preferably be facile, fast, and efficient with minimal workup.[1] To suite such requirements, multicomponent reactions that directly yield target molecules have attracted considerable attention in both organic and medicinal chemistry.[2] Many chemical processes require a large amount of energy from heating, which can have considerable adverse effects on the environment. Therefore, microwave technology is becoming increasingly attractive as an alternative energy source to assist reactions under milder conditions.[3] Microwave irradiation is an extremely powerful tool for reducing reaction time and increasing desired product yields, thus producing many efficient organic reactions.[4,5] Over the past few years our group has extensively focused on the development of new facile and efficient methodologies to synthesize bioactive compounds for medicinal chemistry applications.[6−8]

Multisubstituted 1,4-dihydropyridines (1,4-DHPs) are analogues of NADH coenzymes and have a wide range of biological activity with such derivatives proving to act as vasodilator, bronchodilator, antiatherosclerotic, antitumor, geroprotective, hepatoprotective, and antidiabetic agents.[9−14] The major biological significance of 1,4-DHPs is that they act as Ca^{2+} channel blockers enabling them to be important drugs in the treatment of cardiovascular disease including hypertension, as exemplified by nifedipine and nicardipine (Figure 1).[15,16] Recent studies have shown that these 1,4-DHP pharmacophores possess neuroprotectant and platelet antiaggregatory activities.[17,18] In addition, it has also been indicated that DHPs can be used in the treatment of Alzheimer's disease because of their antiischemic activity and can also be used as chemosensitizers in tumor therapy.[19] Hence, the development of new methods that lead to multisubstituted DHPs via an efficient and convenient procedure are of great interest for medicinal chemists.

Multicomponent reactions have proven to be a valuable asset in medicinal chemistry, drug design, and drug discovery because of their simplicity, efficiency, and high selectivity. Such protocols can reduce the number of steps and present advantages, such as low energy consumption and little to no waste production, leading to desired environmentally friendly processes. The multicomponent symmetrical 1,4-dihydropyridine yielding Hantzsch reaction was first established by Hantzsch in 1881 and has attracted considerable attention over the years because of its efficiency to yield bioactive dihydropyridines.[20] However, the classic reaction using aldehyde, ethylacetoacetate, and ammonia under acetic condition suffers from disadvantages, such as high temperatures, long reaction times, harsh reaction conditions, and incomplete conversion of reactants. Thus, over recent years significant effort has been made to find efficient procedures that maintain the simplicity of the Hantzsch reaction but produce better yields. A large number of optimized procedures have been reported by many research groups, the majority of them employed catalytic methods to synthesize DHPs. These protocols utilize ionic liquids,[21] triphenyl phospine,[22] iodine,[23] Baker's yeast,[24] silica-supported acids,[25] ceric ammonium nitrate (CAN),[26] organo-catalysts,[27−29] polymers,[30,31] and metal-triflates.[32−34] However, many of the methods still suffer from drawbacks, such as high reaction temperatures, incomplete conversion of reactants, expensive metal precursors, stoichiometric amounts of catalyst, environmentally toxic catalysts, or prolonged reaction time. In contrast, copper catalysts have become increasingly appealing because of their affordability, high activity, and low toxicity.



Nifedipine **Nicardipine**

Figure 1. Biologically active dihydropyridines.

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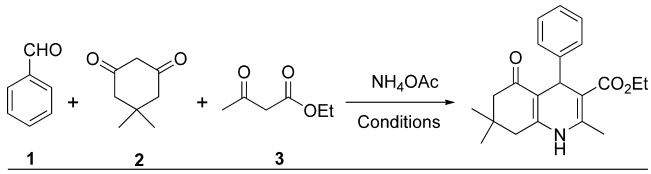
Table 1. Optimization of the Hantzsch Reaction[a]



1 2 3

entry	solvent	temperature (°C)	$Cu(OTf)_2$ catalyst (mol %)	time	yield (%)
1	DCM	rt	10	24 h	38
2	DCM	50	10	12 h	52
3	ACN	rt	10	24 h	45
4	ACN	70	10	12 h	55
5[b]	ACN	80	10	1 h	65
6	EtOH	rt	10	24 h	55
7	EtOH	70	10	12 h	82
8	EtOH	70	5	12 h	82
9[b]	EtOH	80	10	1 h	95
10[b]	EtOH	80	5	1 h	95
11[b]	EtOH	80	2	1 h	95
12[b]	EtOH	80	2	30 min	95
13[b]	**EtOH**	**100**	**2**	**15 min**	**95**
14[b]	EtOH	120	2	5 min	65

[a] Reaction conditions using benzaldehyde (1.0 mmol), ethyl acetoacetate (1.0 mmol), dimedone (1.0 mmol), ammonium acetate (1.0 mmol), solvent (2 mL) and $Cu(OTf)_2$ (0.1, 0.05, and 0.02 mmol). [b] Reactions under microwave irradiation, 200 W.

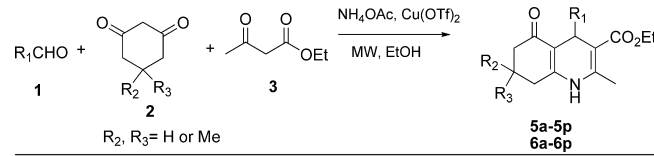
Copper can be used with considerable advantages including mild reaction conditions, high catalytic efficiency, shorter reaction times and no formation of byproduct. Recently, our group has developed a copper-catalyzed one-pot three-component synthesis of homoallylamines with great success.[35] In this study, we focus on the development of a new, fast, and efficient methodology utilizing microwave technology with a copper catalyst for the preparation of biologically active 1,4-dihydropyridine derivatives via a one step multicomponent reaction.

Results and Discussion

First, the establishment of the reaction conditions was undertaken by investigating the effect of different solvents, temperatures, reaction times and amounts of catalyst using benzaldehyde, ethylacetoacetate, dimedone, and ammonium acetate as standard components (Table 1).[36] Initially, a mixture of benzaldehyde, ethylacetoacetate, dimedone and ammonium acetate in dichloromethane was stirred in the presence of $Cu(OTf)_2$ (10 mol %) at room temperature for 24 h and the dihydropyridine product was produced in a low yield (38%) due to incomplete conversion of the reactants, leading to the assumption that more thermal energy may be needed. To focus on the effect of temperature and time, the reaction was carried out at 50 °C for 12 h, which allowed the heterocyclic product to form with a slightly higher yet unsatisfactory yield (52%).

Our attention then moved on to investigate the effect of solvents on the product yields, and dichloromethane was replaced by acetonitrile and ethanol. The reactions were stirred for 24 h at room temperature, and both solvents resulted in incomplete conversion of reactants; ethanol, however, gave higher yields. The temperature was then raised to 70 °C for both acetonitrile and ethanol and the mixture was stirred for 12 h. In the case of acetonitrile as the solvent,

Table 2. $Cu(OTf)_2$ Catalyzed Hantzsch Synthesis of Dihydropyridine Derivatives from Substituted Aromatic Aldehydes



1 2 3 5a-5p 6a-6p

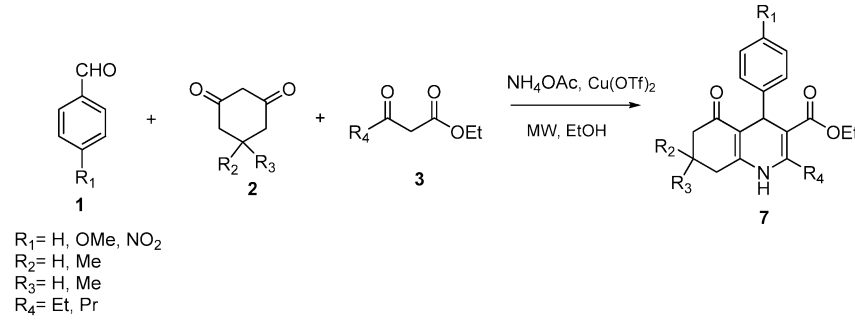
R_2, R_3= H or Me

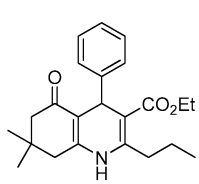
entry	R_1	R_2	R_3	product	yield (%)
1	C_6H_5	H	H	**5a**	95
2	4-MeC_6H_4	H	H	**5b**	quantitative
3	4-$NO_2C_6H_4$	H	H	**5c**	91
4	4-$OMeC_6H_4$	H	H	**5d**	98
5	4-$CO_2MeC_6H_4$	H	H	**5e**	92
6	4-ClC_6H_4	H	H	**5f**	90
7	4-$SMeC_6H_4$	H	H	**5g**	quantitative
8	3,4-$Me_2C_6H_3$	H	H	**5h**	88
9	3-OHC_6H_4	H	H	**5i**	98
10	2-$CF_3C_6H_4$	H	H	**5j**	95
11	2-furyl	H	H	**5k**	88
12	3-thiophenyl	H	H	**5l**	92
13	*n*-pentyl	H	H	**5m**	82
14	cyclohexyl	H	H	**5n**	90
15	2-$NO_2C_6H_4$	H	H	**5o**	82
16	1-naphthyl	H	H	**5p**	92
17	C_6H_5	Me	Me	**6a**	96
18	4-MeC_6H_4	Me	Me	**6b**	quantitative
19	4-$NO_2C_6H_4$	Me	Me	**6c**	92
20	4-$OMeC_6H_4$	Me	Me	**6d**	quantitative
21	4-ClC_6H_4	Me	Me	**6e**	98
22	4-$SMeC_6H_4$	Me	Me	**6f**	quantitative
23	3,4-$Me_2C_6H_3$	Me	Me	**6g**	92
24	3-OHC_6H_4	Me	Me	**6h**	90
25	2-$CF_3C_6H_4$	Me	Me	**6i**	87
26	C_5H_4N	Me	Me	**6j**	85
27	2-furyl	Me	Me	**6k**	93
28	3-thiophenyl	Me	Me	**6l**	86
29	*n*-pentyl	Me	Me	**6m**	94
30	cyclohexyl	Me	Me	**6n**	88
31	2-$NO_2C_6H_4$	Me	Me	**6o**	81
32	1-naphthyl	Me	Me	**6p**	91

the reaction led to decomposition of the product, therefore producing low yields (55%); however, ethanol produced the desired DHPs in a significantly higher yield (82%). We then focused on lowering the reaction time from 12 h, in which microwave irradiation was used because of its ability to lower reaction times and increase yields. A range of temperatures, times, and the amounts of catalysts were screened to optimize the one-pot multicomponent reaction. For both acetonitrile and ethanol, the reaction was then carried out using microwave irradiation at 80 °C for 1 h at 200 W. The reaction utilizing acetonitrile as a solvent suffered from incomplete conversion of reactants, as indicated by TLC monitoring and thus the reaction in ethanol produced the desired product in much higher yield (95%) than acetonitrile did (65%), proving ethanol to be the most effective solvent. At the same time, decreasing the amount of copper catalyst from 10 to 5 and 2 mol % did not show any significant impact on the product yield. The investigation at this point indicated that ethanol at 80 °C in the presence of 2 mol % $Cu(OTf)_2$ with a reaction time of 1 h under microwave irradiation were the appropriate conditions for the one-pot synthesis.

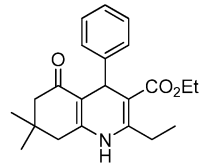
Next, we proceeded to lower the reaction time further to speed up the reaction and produce desirable yields therefore producing a more efficient reaction. The reaction mixture of benzaldehyde, ethylacetoacetate, dimedone, ammonium

Scheme 1. $Cu(OTf)_2$ Catalyzed Hantzsch Synthesis of Dihydropyridine Derivatives

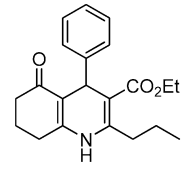




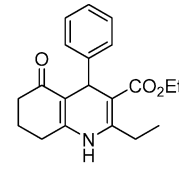
7a
96%



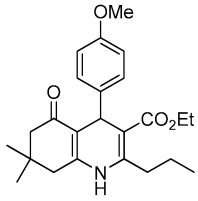
7b
quantitative



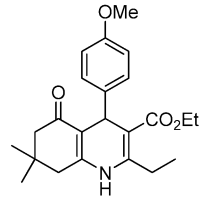
7c
95%



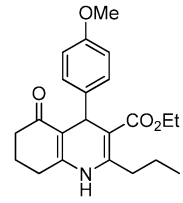
7d
95%



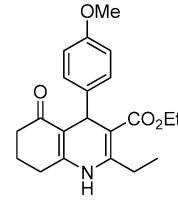
7e
93%



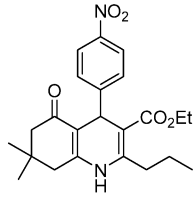
7f
quantitative



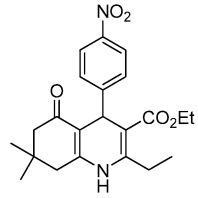
7g
98%



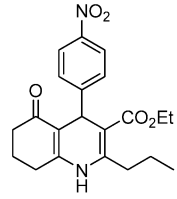
7h
quantitative



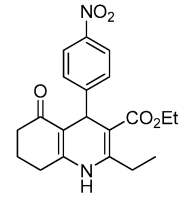
7i
89%



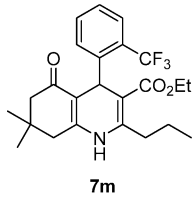
7j
96%



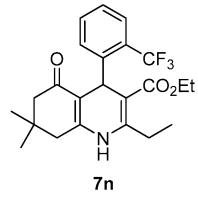
7k
90%



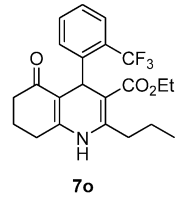
7l
91%



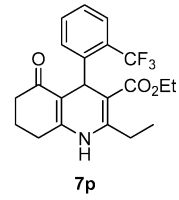
7m
95%



7n
90%



7o
92%



7p
92%

acetate, and $Cu(OTf)_2$ (2 mol %) in ethanol was stirred under microwave irradiation at 80 °C for 30 min, and the DHP product was produced with a similar yield (95%). The temperature was then raised to 100 °C and the reaction mixture was stirred for 15 min. Such changes produced the product in similar yields as comparing to that running at 80 °C (95%). When the reaction time was then lowered to 5 min at a temperature of 120 °C the resulting DHP product was obtained in a lower yield (65%), suggesting that the temperature was too high which led the components to decompose. From the above investigations, ethanol at 100 °C in the presence of 2 mol % $Cu(OTf)_2$ with a reaction time of 15 min under microwave irradiation at a power of 200 W was established as the optimized reaction conditions for the four-component, one-step synthesis.

Under the optimized conditions the copper-catalyzed reactions of a variety of substituted aldehydes were undertaken and a small library of DHPs was created (Table 2).

The reactions of different aldehydes possessing a range of substituents from electron-withdrawing (**6c**) to electron-donating (**6d**) produced the heterocyclic products in excellent yields, ranging from 82% to quantitative yields. Unsubstituted (**6a**), heteroaromatic (**6k**), and bulky aldehydes such as naphthal (**6p**) were also investigated and led to the production of the corresponding DHPs in excellent yields (81−96%). The use of aldehydes with electron-withdrawing substituents showed no significant effect on the yields of the corresponding DHPs when compared to reactions utilizing aldehydes, which possessed electron-donating substituents (compare compounds **6c** and **6d**) and also when compared to those that were unsubstituted and those possessing bulky substituents (compare compounds **6c** and **6a**, **6c**, and **6p**). We then proceeded to replace the dimedone with 1,3-cyclohexanedione and repeated the reaction with the same substituted aldehydes. Compared with the initial reaction utilizing dimedone, the reactions involving 1,3-cyclohexanedione produced the corresponding DHPs in equally high yields (82% to quantitative yields) (comparing compounds **5b** and **6b**) and similarly the nature of the aldehyde substituents showed no significant effect on the yields (compare compounds **5c** and **5d**, **5c** and **5a**, **5c** and **5p**).

Our attention then focused on replacing ethylacetoacetate in the one-step synthesis (Scheme 1). In the reaction of benzaldehyde, ethyl acetoacetate, dimedone, and ammonium acetate the β-ketoester was replaced by ethyl propionylacetate and the corresponding DHP (**7b**) was produced in quantitative yields. At the same time, ethyl butyrylacetate was employed to replace ethyl acetoacetate, and the corresponding DHP, **7a**, was formed in similarly high yields (95%). This methodology was also tested with electron-donating (OMe) and electron-withdrawing (NO_2) substituted benzaldehydes which yielded the desired products, **7e**, **7f**, **7i**, and **7j**, in noticeably high quantities (89% to quantitative). The electron-withdrawing NO_2 group seemed to have little effect on the DHP yield when compared to the electron donating OMe product and also the unsubstituted product (compare compounds **7f** and **7j**, **7f**, and **7b**).

The dimedone component was then replaced with 1,3-cyclohexanedione and the reactions with the ethyl acetoacetate substitution were repeated. The resulting DHPs (**7c**, **7d**, **7g**, **7h**, **7k**, **7l**) were synthesized in equally high yields (90% to quantitative yields) (compare compounds **7a** and **7c**), and the electron-withdrawing nitro (NO_2) group exhibited little effect on the yield when compared to the electron-donating methoxy (OMe) product and the unsubstituted product (compare compounds **7l** and **7d**, **7l** and **7h**). In medicinal chemistry, fluorine-containing components are used because of their useful biological functions. Therefore, we carried out the reactions with 2-trifluoromethyl benzaldehyde and the resulting 1,4-dihydropyridine compounds **7m**−**7p** were produced with similar yields (90−95%).

The products were characterized by ^{1}H NMR, ^{13}C NMR, HR-MS, and IR spectroscopy and indicated the copper catalyzed reaction yielded pure compounds. The structure of the ethyl 4-cyclohexyl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate motif was further confirmed by X-ray crystallography (Figure 2, **5n**).

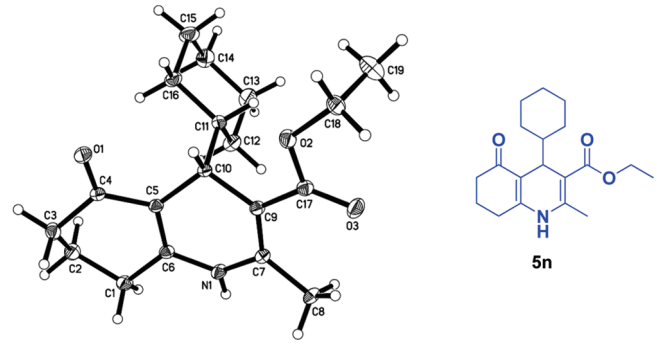


Figure 2. X-ray crystal structure of ethyl 4-cyclohexyl-2-methyl-5-oxo-1,4,5,6,7,8-hexahydroquinoline-3-carboxylate (**5n**).

Conclusion

In conclusion, we have developed a simple and efficient method to generate a range of DHP analogues in excellent yields via a microwave-assisted one-pot four-component reaction. The protocol utilizes $Cu(OTf)_2$ in small quantities and mild reaction conditions avoiding workup and column purification. Reaction times were considerably reduced and product yields increased up to quantitative yields under microwave irradiation. This methodology can be exploited to construct new multisubstituted DHPs, which are of great interest due to their extensive pharmaceutical and biological applications. Currently, biological tests of the synthesized 1,4-DHP analogues are in progress in our laboratory.

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Supporting Information Available. Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(36) In our experiments, ammonium acetate was taken as a standard reaction component. Other ammonia salts, such as NH_4Cl, NH_4NO_3, etc., should also work for our methodology but not result in extra structural diversity into the products.

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