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Practical Copper-catalyzed Synthesis of Pyrroles under Solvent Free Condition

Tuan Thanh Dang[1,*], Nguyen Thi Son,[1] Hien Nguyen,[2] Cu Hong Hanh,[2] Nguyen Thi Thanh Chi,[2] Tran Quang Hung,[3] Nguyen Thi Thanh Huyen,[4] Ngo Thi Thuan,[1] Dang Van Do[1,*]

[1]*Faculty of Chemistry, VNU-Hanoi University of Science, 19 Le Thanh Tong, Hanoi, Vietnam*
[2]*Institute of Chemistry, Vietnamese Academy of Science and Technology (VAST), 18 Hoang Quoc Viet, Hanoi, Vietnam*
[3]*Faculty of Chemistry, Hanoi National University of Education, 136 Xuan Thuy, Cau Giay, Hanoi, Vietnam*
[4]*Chu Van An High School for Gifted Students, Lang Son*
**Email: dangthanhtuan@hus.edu.vn, dangdovan@hus.edu.vn*

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ABSTRACT

An efficient and practical method for the synthesis of pyrroles by Cu-catalyzed multicomponent reaction has been described. A range of highly functionalized pyrroles was prepared in good yields under solvent free condition.

Introduction

Pyrroles are considered as the important heterocycles, which appeared not only in many natural products, agrochemicals, advanced organic materials, bioactive molecules but also in current important drugs.[1,2] Several important drugs (Figure 1), including the Lipitor, Sunitinib, Ketorolac, Tolmetin contain pyrrole moiety in their core structures.[3] Until now, there are many efficient methods for the synthesis of pyrroles, in which, the Paal-Knorr, van Leusen, Hantzsch reactions have been known as the most conventional methods.[3] Recently, the metal-catalyzed syntheses of pyrroles have attracted many attention due to the efficiency and tolerance of functional groups.[4,5]

Alcohols are one of the promising non-hazardous and widely available starting materials for organic synthesis. They are generally used as nucleophiles and rarely utilized as electrophilic precursors for nucleophilic addition due to the high C-O bond dissociation energy (~90 kcal mol^{-1}).[6-8] Hence, alcohols are traditionally activated by converting the hydroxy functional group into a better leaving group such as sulfonates or halides, which lead to genotoxic issues. In a better and greener approach recently developed, the inactive alcohol is converted *in-situ* to a more reactive and highly electrophilic carbonyl intermediate by temporary removal of hydrogen towards nucleophilic addition reactions. This methodology is termed as "*Hydrogen borrowing*" (HB) which offers a mild and highly atom efficient way of activating alcohols using a substrate-selective catalyst that transfers hydrogen between the alcohol and the final product.[6-8] Transformations like *N*-alkylation of amines and alkylation of ketones using readily available alcohols are the two important

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transformations that utilize the advantage of this concept. Interestingly, the HB method could be combined with tandem condensation steps using cheap starting materials such as amines, ketones and alcohols in the synthesis of N-heterocycles. A series of important heterocycles was prepared using this method, for examples, benzimidazoles, pyrazines, quinoxalines, pyridines, quinolines and pyrroles.[10]

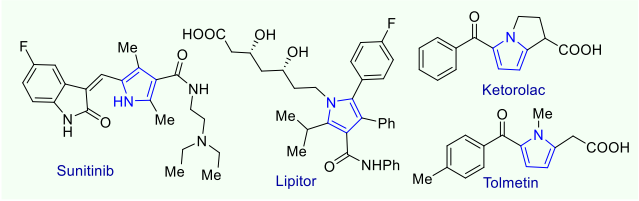

Figure 1: Several important drugs contain pyrrole core structure

In 2011, Crabtree *et al*. reported the first Ru-catalyzed synthesis of indoles by cyclization of amines and hexane-2,5-diol.[10] In 2013, Michlik and Kempe described an efficient Ir-catalyzed synthesis of highly functionalized pyrroles by the cyclization of amino alcohols with secondary alcohols.[11] In the same year, Milstein et al. also reported a similar protocol for the preparation of pyrroles in the employment of Ru pincer complexe as catalyst, developed by his group.[12] Recently, Beller and coworkers developed an interesting Ru-catalyzed three-component reaction for the synthesis of pyrroles.[13] Until now, all of reports on the synthesis of pyrrole derivatives using amines, alcohols and ketones based on expensive and toxic transition metals (Ir and Ru) as catalysts.[14] In our effort to develop cheap and less toxic catalysts for practical synthesis of pyrroles, herein, we would like to report an efficient Cu-catalyzed synthesis of pyrroles from cheap and commercially available ketones, amines and diols.

Experimental

Chemicals

Commercially available reagents and solvents were used as received without further purification. For chromatographic purifications, technical-grade solvents were used. Reactions were magnetically stirred and monitored by thin layer chromatography (TLC) using *Merck Silica Gel 60 F254* plates.

NMR method for the characterization of pyrroles

^{1}H and ^{13}C NMR pyrrole products were measured in $CDCl_3$ solvent using cryoprobe on the Bruker Advance 400 (400 MHz, ^{1}H NMR; 101MHz, ^{13}C NMR). Chemical shifts δ were calculated by ppm value in the comparison to tetramethylsilane (TMS) with both ^{1}H và ^{13}C NMR. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal or as a combination of them. Coupling constants (*J*) are given in Hertz (Hz).

General procedures for the synthesis of pyrroles (4a-4k)

The Cu precursor CuBr (2.9 mg, 2 mol%), L4 (6.3 mg, 2.2 mol%), LiOH (20.0 mg, 1equiv.), amine (1.0 mmol), ketone (2.0 mmol) were added under argon gas in a Radleys carrousel reaction tube. After adding 1 mL of diol, carrousel tube was closed, put in the Radleys 12-place carrousel system and was degassed using argon gas. Then, carrousel tubes were opened to the argon line and heated to 140 °C under stirring in 24 h. The top part of the reaction tube was cooled at 10°C to prevent the evaporation of reactants. After the desired reaction time, the reaction mixture was cooled down to room temperature and diluted with acetonitrile (5 mL). Then, SiO_2 (500mg) was added into the crude mixture. The organic solvent was removed under vacuum and then the product was purified by column chromatography.

Typical compound (1-phenethyl-2-phenyl-1H-pyrrole (4a)

Followed the general procedure-1 using 2-phenylethan-1-amine (1.0 mmol), acetophenone (2 mmol) and ethylene glycol (1.0 mL) for 24h at 110 °C. Purification by flash chromatography (5% EtOAc/Hexane) gave 212.4 mg (86%) **4a** as yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz): δ= 7.28 (m, 2H), 7.22 (m, 3H), 7.12 (m, 3H), 6.88 (m, 2H), 6.63 (dd, *J* = 2.7, 1.8 Hz, 1H), 6.12 (m, 2H), 4.07 (m, 2H), 2.81 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ= 138.4, 134.5, 133.8, 129.1, 128.8, 128.6, 128.5, 127.1, 126.7, 122.1, 109.1, 108.0, 48.9, 38.2.

Results and discussion

Based on our experiences in the topic of hydrogen borrowing and Cu catalysis, we realized that LiOH would be a suitable base and Cu catalyst can show its excellent activity at high temperature (140 °C and above).[15,16] Therefore, in order to develop a practical procedure for the synthesis of pyrroles, we choose the reaction of 2-phenylethanamine, acetophenone and

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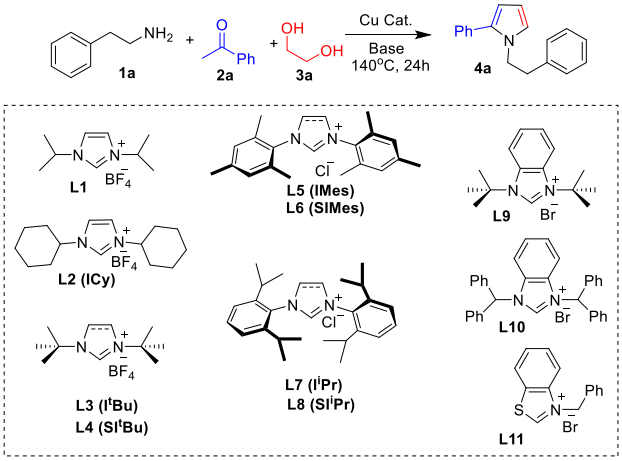
ethylene glycol in the presence of LiOH base as a model reaction for catalysts optimizations. The influence of key factors such as ligands, Cu precursors and bases were examined at 140 °C as described in Table 1. N-heterocyclic carbenes (NHCs) have been known as powerful ligands in the combination with transition metals to become efficient catalysts in organic transformations.[17] First, we envisioned that the presence of a N-heterocyclic carbene (NHC) ligand is necessary to promote dehydrogenation reaction. A series of NHC ligands in the combination with CuCl were screened, pyrrole product 4a was isolated in 65% yield in the employment of 2 mol % of Cu catalyst loading (Entry 5, Table 1). Then, several Cu sources were tested and CuBr seems to be the most suitable Cu precursor for this reaction. The employment of LiOH as a base was found to be crucial for the success of reaction. Further screenings with other ligands and L4 showed the best performance with 86% isolated yield of product (Entry 11, Table 1). When we changed different temperatures to 130 °C and 150 °C, the yields of reaction were decreased to 72 and 84 %, respectively (Entry 16, 17, Table 1). The use of high catalyst loading did not give higher yield of pyrrole product. Several bases have been examined in order to improve the yield of this reaction but did not improve the formation of desired product (Entry 18-20, Table 1).

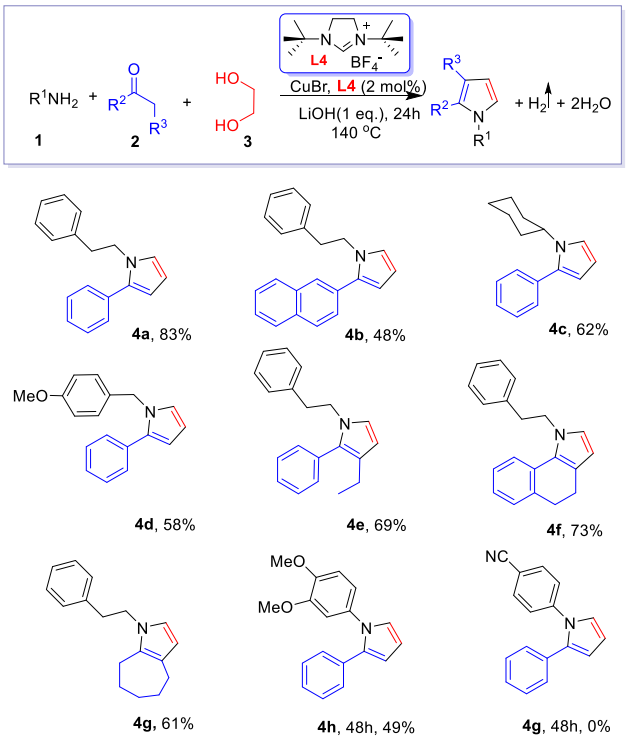
Table 1: Optimization for the Cu-catalyzed synthesis of 4a



Entry	Cu precursor (2 mol%)	Ligand (2 mol%)	Base (1 equiv.)	Temp. (°C)	Yield (%)[a]
1	CuCl	L7	LiOH	140	32
2	CuCl	L8	LiOH	140	24
3	CuCl	L5	LiOH	140	51
4	CuCl	L6	LiOH	140	44
5	CuCl	L1	LiOH	140	65
6	CuI	L1	LiOH	140	31
7	CuOAc	L1	LiOH	140	56
8	**CuBr**	**L1**	**LiOH**	**140**	**80**
8	**CuBr**	**-**	**LiOH**	**140**	**38**
9	CuBr	L2	LiOH	140	5
10	CuBr	L3	LiOH	140	40
11	**CuBr**	**L4**	**LiOH**	140	**86**
13	CuBr	L9	LiOH	140	65
14	CuBr	L10	LiOH	140	12
15	CuBr	L11	LiOH	140	36
16	CuBr	L4	LiOH	130	72
17	CuBr	L4	LiOH	150	84
18	CuBr	L4	KOH	140	49
19	CuBr	L4	KO*t*Bu	140	21
20	CuBr	L4	K_2CO_3	140	14

[a]Yield was calculated by ^{1}H NMR of the crude product using mesitylene as an internal standard

Table 2: Substrates scope of Cu-catalyzed synthesis of pyrroles



With optimized condition in hand, we extended the scope of substrates as described in Table 2. The reaction of acetophenone derivatives with different amines and ethylene glycol give a range of functionalized pyrroles in moderate to very good yields. In order to highly substituted pyrroles, some cyclic ketones were employed. The cyclization of tetralone and cycloheptanone gave desired products (4f, 4g) in 73% and 61% yield, respectively.

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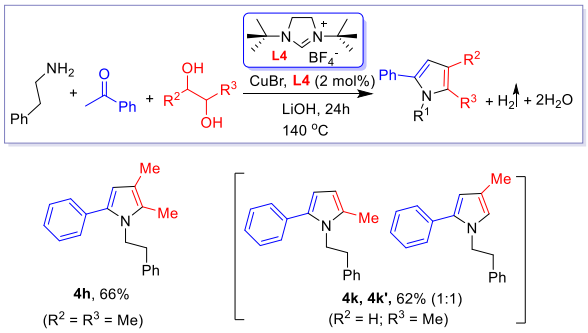
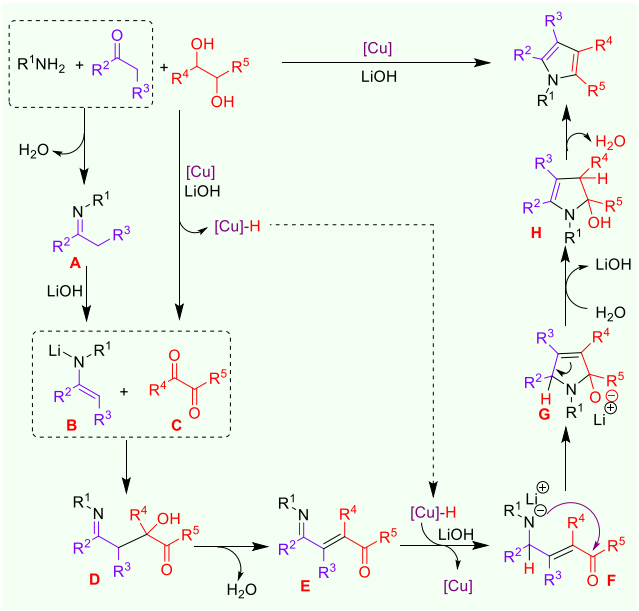
Interestingly, less active aromatic amine could be used as a useful component in this reaction affording to desired pyrrole in 49% yield after two days of reaction. Unfortunately, the reaction using 4-aminobenzonitrile did not give any trace of pyrrole product after 48h due to the low nucleophilic property of starting material.

We continued extending reactions with different substituted diols which could give highly substituted pyrroles in Table 3. Reaction of 2-phenylethanamine, acetophenone with butane-2,3-diol resulted in corestponding pyrrole **4h** in 66% isolated yield. Besides, the cyclization with propane-1,2-diol gave an unseparated mixture of two regioisomers **4k, 4k'** (1:1) in 62% yield. The ratio of regioisomers was confirmed by ^{1}H NMR.

Table 3: Substrates scope of Cu-catalyzed synthesis of highly substituted pyrroles



A possible reaction pathway is proposed in Scheme 1 on the basis of the results obtained and the available literature on similar Cu-catalyzed transformations.



Scheme 1: Proposed reaction pathway to the formation of pyrrole

First, the condensation reaction of amine with ketone occured to form imine A which was converted to aza-enolate B by LiOH base. Simultaneously, the diketone C was in situ-formed by the role of copper-NHC catalyst and generates the catalytically active [Cu]-H species. After that, aza-enolate compound B react easily with the diketone compound C to give intermediate D which was converted to highly conjugated ketone E by the dehydration reaction. Then, the reduction of imine group on intermediate E by in situ-generated [Cu]–H to generates the intermediate F, which followed the intramolecular cyclization reaction of amine group with ketone to form the cyclized product G. The effective formation of pyrrole product may occur via the double bond shift and then dehydration steps which require harsh reaction condition at 140 °C.

Conclusion

Herein, we have disclosed a practical and efficient homogeneous CuBr-NHC catalyst system for the synthesis of highly functionalized pyrroles *via* the multi component reaction using simple, less expensive amines, ketones, and diols under argon. Our robust procedure is highly beneficial in the comparison to previous expensive transition metals-catalyzed syntheses of pyrroles.

Acknowledgments

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