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One-pot synthesis of 2-methyl-1,5-diaromatic-1*H*-pyrroles from styrene, acetone and arylamines using TBHP, copper(II) trifluoromethanesulfonate and sulfamic acid

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ABSTRACT

The one-pot copper/manganese co-catalyzed heterocyclization of arylamine derivatives with styrene and acetone to produce a series of 2-methyl-1,5-diaromatic-1*H*-pyrroles was investigated. The described reaction combines 1,4-dicarbonyl synthesis and Paal-Knorr type condensation reactions.

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Keywords: one-pot copper/manganese co-catalyzed pyrroles

Paal-Knorr

TBHP

Introduction

Pyrroles and their derivatives are important heterocyclic compounds, which, for example, are found in many natural products, biologically active compounds, and materials.¹ Additionally, pyrroles and their derivatives represent one of the most important pharmaceutical classes of N-heterocyclic compounds due to their remarkable anti-bacterial, anti-viral, antiinflammatory, antitumor, and antioxidant activities.³ As a result, many synthetic chemists have focused their attention on developing more efficient methods to obtain multi-substituted pyrroles. Due to the initial success of the Paal-Knorr condensation reaction of 1,4-dicarbonyl compounds with ammonia or primary amines, this method has become one of the most important and widely applied among the many developed strategies.⁴ However, synthetic routes towards 1,4-dicarbonyl compounds often suffer from shortcomings, such as the use of toxic solvents, difficult to obtain reactants, multistep reaction procedures, complex reaction conditions, high reaction temperatures, and long reaction times.⁵

Results and Discussion

Recently, Huang and Xie reported a cascade carbocarbonylation reaction of alkenes with ketones to generate 1,4dicarbonyl compounds, using an organocatalyst and transitionmetal catalyst and proceeding *via* a SOMO enamine.⁶ Subsequently, Klussmann and co-workers discovered a multicomponent radical addition of unactivated ketones and *tert*butyl hydroperoxide to vinyl arenes, proceeding *via* Brønsted acid catalyzed formation of ketone radicals for the synthesis of alkenyl peroxides.⁷ Lan and co-workers reported the direct and regioselective difunctionalization of alkenes to provide dual carbonyl groups *via* a free-radical pathway, representing the copper/manganese co-catalyzed direct oxidative coupling of vinylarenes with ketones *via* $C(sp^3)$ –H bond functionalization to generate 1,4-dicarbonyl compounds.⁸ These reports provide new methods and inspiration for the synthesis of 1,4-dicarbonyls.

To the best of our knowledge, none of these methods involve the one-pot synthesis of pyrroles using readily accessible starting materials. Therefore, based on the above research, we envisioned that multi-substituted pyrroles could be synthesized in one-pot from alkenes, acetone and arylamines *via* a combination of 1,4-

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dicarbonyl synthesis and Paal-Knorr type condensation reactions. 9



Scheme 1. Proposed method for pyrrole synthesis.

Table 1. Reaction condition screening.^a

| | | ² Catalysts, Co-catalyst, | | N - | |
|----------|--------------------------------------|--------------------------------------|-------------------|------------|--|
| <u> </u> | | Cyclization reagent | | | |
| 1 | 2 3 | | 4a 🔍 | ~ | |
| Entry | Catalyst | Co-catalyst | Cyclization | Yield 4a | |
| | | | reagent | $(\%)^{0}$ | |
| 1 | $MnCl_2 \cdot 4H_2O$ | | AcOH | 10 | |
| 2 | FeCl ₃ ·6H ₂ O | | AcOH | 15 | |
| 3 | $NiCl_2 \cdot 6H_2O$ | | AcOH | 12 | |
| 4 | CuBr ₂ | | AcOH | 11 | |
| 5 | CuCl ₂ | | AcOH | 8 | |
| 6 | $CuSO_4{\cdot}5H_2O$ | | AcOH | 14 | |
| 7 | $Cu(OTf)_2$ | | AcOH | 26 | |
| 8 | Cu(OAc) ₂ | | AcOH | 16 | |
| 9 | $Cu(OTf)_2$ | NiCl ₂ ·6H ₂ O | АсОН | 41 | |
| 10 | Cu(OTf) ₂ | $FeCl_3 \cdot 6H_2O$ | АсОН | 43 | |
| 11 | $Cu(OTf)_2$ | MnCl ₂ ·4H ₂ O | АсОН | 57 | |
| 12 | Cu(OTf) ₂ | CuBr ₂ | АсОН | 40 | |
| 13 | $Cu(OTf)_2$ | MnCl ₂ ·4H ₂ O | RuCl ₃ | 42 | |
| 14 | Cu(OTf) ₂ | MnCl ₂ ·4H ₂ O | HSO_3NH_2 | 68 | |
| 15 | Cu(OTf) ₂ | MnCl ₂ ·4H ₂ O | I_2 | 44 | |
| 16 | Cu(OTf) ₂ | MnCl ₂ ·4H ₂ O | $Bi(NO_3)_3 \\$ | 45 | |
| 17 | Cu(OTf) ₂ | MnCl ₂ ·4H ₂ O | TsOH | 43 | |

^aReagents and conditions: styrene **1** (0.5 mmol, 1 equiv.), acetone **2** (3 mL), aniline **3** (0.5 mmol,1 equiv.), Cu(OTf)₂ (5 mol%), MnCl₂·4H₂O (5 mol%), DBU (1.5 equiv.), TBHP (4 equiv., 70% in water), H₂NSO₃H (5 mol%), 60 $^{\circ}$ C, 24 h.

To determine the appropriate reaction system, we began by examining styrene, acetone and aniline as model substrates in the presence of DBU (1.5 equiv.) and TBHP (4 equiv., 70% in water) under various reaction conditions. Upon comparing a series of transition-metal catalysts (Table 1, entries 1–8), the desired multi-substituted pyrrole product **4a** was formed in 26% yield in the presence of Cu(OTf)₂ (Table 1, entry 7). An improved yield was obtained when MnCl₂•4H₂O was added as a co-catalyst (Table 1, entry 11); other co-catalysts gave lower yields (Table 1, entries 9, 10, and 12). Additionally, various cyclization reagents were explored (Entries 13-17). To our delight, **4a** was formed in 68% yield when sulfamic acid was used (Table 1, entry 14). Based on these results, the optimal conditions were as follows: alkene **1** (0.5 mmol, 1 equiv.), acetone **2** (3 mL), aniline **3** (0.5 mmol, 1 equiv.), $Cu(OTf)_2$ (5 mol%), $MnCl_2 \cdot 4H_2O$ (5 mol%), DBU (1.5 equiv.), TBHP (4 equiv., 70% in water), HSO_3NH_2 (5 mol%), 60 °C.

Table 2. Scope for the reaction of arylamines with acetone and styrenes.^{a,b}



^aReagents and conditions: styrene **1** (0.5 mmol, 1 equiv.), acetone **2** (3 mL), aniline **3** (0.5 mmol,1 equiv.), Cu(OTf)₂ (5 mol%), MnCl₂·4H₂O (5 mol%), DBU (1.5 equiv.), TBHP (4 equiv., 70% in water), H₂NSO₃H (5 mol%), 60 $^{\circ}$ C, 24 h. ^bIsolated yield.

°30 h.

Using the optimized reaction conditions,¹⁰ a series of substituted anilines were explored (Table 2). In most cases, the reactions of para-alkylanilines or para-alkoxyanilines with acetone and styrene were complete within 30 h and gave the corresponding pyrroles 4b-e in moderate yields (62-69%). The yields of ortho-substituted anilines were lower compared to para-methyl-substituted or para-methoxy-substituted alkenes (4f-h). Moderate yields were also obtained when anilines were substituted with a halogen, regardless of the position of the halosubstituent (4i-u). The yields of substituted anilines and their chemical reactivities were concluded to be as follows: para > *meta* > *ortho*. Anilines possessing electron-donating substituents such as CH₃ and CH₃O, smoothly gave the corresponding products, however, anilines possessing electron-withdrawing substituents such as CI-, Br-, I-, and CF3-, gave the corresponding products in lower yields. Therefore, it can be

^bIsolated yield.

concluded that this reaction was affected by both electronic and steric factors.

Additionally, other aromatic amines such as 1H-pyrazol-3amine (4v, 63%) or substituted styrenes such as 4-chlorostyrene (4w, 67%) and 4-methylstyrene (4x, 57%) were transformed into the corresponding products. However, the heterocyclic alkenes 4vinylpyridine, 2-vinylpyridine and 2-vinylthiophene did not proceed or reacted with low yields.



Scheme 2. Comparison of one-pot and two step routes for the formation of 4a.

Finally, the one-pot reaction and the stepwise synthesis of compound 4a was compared (Scheme 2). The reaction of styrene, acetone and aniline, as depicted in Table 2, gave the corresponding pyrrole in 68% yield (24 h) using the one-pot method and in 64% yield (>36 h) if 1-phenylpentane-1,4-dione was purified before the cyclization step. Compared to stepwise synthesis, the one-pot method has the advantages of higher yield, shorter reaction time, and simple operation. More importantly, the one-pot method allows the direct synthesis of multi-substituted pyrroles using simple and inexpensive reactants.



Scheme 3 Possible mechanistic pathway.

Based on our experimental results and previous investigations, ^{8,9} a plausible mechanism is shown in Scheme 3. Initially, in the presence of the catalyst, when *t*-BuOOH is added to the ketone, a *tert*-butyloxy radical **A** and a ketone radical **B** can be formed (eq. 1). A fast equilibrium exists between the *tert*-butyloxy radical and the *tert*-butylperoxyl radical (eq. 2), favoring the latter species. Addition of **B** to the styrene double bond would form a transient radical **D**, which reacts with the peroxy radical **C** to generate intermediate **E**. Intermediate **E** can then form the corresponding 1,4-diketone **F** in the presence of the Cu/Mn catalyst or DBU.⁸ Subsequently, 1,4-diketone **F** reacts with aniline under sulfamic acid catalysis to form enamine intermediate **I**. Finally, intermediate **I** is transformed to the target product **4a** *via* dehydration.

Conclusion

In summary, we have developed a simple and efficient onepot synthesis of 2-methyl-1,5-diaromatic-1*H*-pyrroles, *via* the reaction of various arylamine with acetones and styrenes. The reaction afforded the corresponding products in moderate yields with good functional group tolerance. This strategy offers a new method to directly synthesize multi-substituted pyrroles using simple and inexpensive reactants *via* a combination of 1,4-dicarbonyl synthesis and Paal-Knorr type condensation reactions.

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/

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10. Synthesis of 2-methyl-1,5-diphenyl-1H-pyrrole (4); Typical Procedure: Cu(OTf)2 (5 mol%), MnCl2·4H2O (5 mol%), DBU (1.5 Accepted equiv.) and aqueous TBHP (4 equiv., 70% in water) were sequentially added to a mixture of styrene (0.5 mmol, 1 equiv.) and acetone (3 mL). The reaction was heated at 60 °C for 20 h, then cooled to room

Highlights

One-pot method is developed for the formation of 2-Methyl-

1,5-diaromatic-1H-pyrrole.

Accembra The features include mild conditions and broad substrate

scope.

Graphical Abstract

