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Graphical Abstract





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Manganese (III) acetate mediated synthesis of polysubstituted pyrroles under solventfree ball milling

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ABSTRACT

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Keywords: Manganese (III) acetate Polysubstituted pyrroles Solvent free Ball milling Under solvent-free ball milling conditions, a simple and mild method was developed for efficient synthesis of 2,5-dimethyl-3,4-dicarboxylate-pyrroles and *N*-substituted 3,4-diphenylpyrroles via condensation-annulation of amines with acetoacetate and 2-phenylacetaldehyde, respectively. The use of cheap and safe $Mn(OAc)_3$ as a mediator, no use of commonly employed acetic acid as solvent, short reaction time and readily available starting materials make this protocol a good alternative to traditional synthesis of polysubstituted pyrroles.

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Polysubstituted pyrroles represent one of the most important class of heterocyclic compounds, which are found in a large number of natural and biologically active compounds and exhibit a broad range of bioactivities, such as antitumor, anti-inammatory, and antibiotic activities.¹ Furthermore, polysubstituted pyrroles are widely used as synthetic building blocks, pharmacophores, and various kinds of functional materials.² Therefore, it is a hot research topic in the area of organic synthetic chemistry to develop simple and efficient methods for synthesis of these molecules, especially for convenient one-step synthesis of polysubstituted pyrroles. Indeed, since the initial synthesis of pyrrole by Paal-Knorr reaction,³ a large number of methods have been developed for synthesis of polysubstituted pyrroles.^{4,5} Most of these approaches are sufficiently powerful, but they often involve special or expensive starting materials, preliminary preparation of some kind of intermediates or precursors, employment of noble- or heavy-metal catalysts, relatively high reaction temperature or long reaction time. To overcome these problems for more environmental and economical construction of such Nheterocycles, herein we wish to develop a straightforward protocol via Mn (III) acetate promoted radical cyclization^{6,7} under solvent-free ball milling.8,

Firstly, we selected a model reaction of ethyl acetoacetate (1a) with 4-methylaniline (2b) under solvent-free ball milling to optimize the reaction condition for synthesis of pyrrole **3b** (Table 1). In a typical procedure, all the reactants, together with a stainless ball (7.0 mm in diameter) were introduced into a stainless jar (25 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were sealed with screw caps, fixed on the vibration arms of a ball-milling

apparatus and were vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for 60 minutes.

As shown in Table 1, several oxidants were investigated which are often employed in dehydrogenative annulation reaction for traditional synthesis of nitrogen-containing heterocycles in solution. In contrast, Mn(OAc)₃ exhibited the best chemoselectivity and efficiency for generation of the desired product pyrrole **3b** (entry 9), while other oxidants either mainly promoted the formation of enamine 4b (entries 1-4) or resulted in significant side reactions (entries 5-8). In absence of any oxidant, the starting materials remained a lot, poorly affording enamine 4b (entry 10). When the Mn(OAc)₃ mediated reaction was carried out by heating in several organic solvents, it also suffered from serious side reactions and thus gave the desired product 3b in very poor yield (entries 11-13). Using this solventfree ball milling technique to perform such Mn(OAc)₃ mediated reaction, the desired product 3b was easily obtained in good-toexcellent yield. This efficiency may be somewhat related to the high mechanical energy and considerable heat caused by local high pressure, friction and shear strain during the high speed ball milling process. In traditional solution methods for Mn(OAc)₃ involved reactions, acetic acid is almost invariably used as solvent due to its poor solubility in other organic solvents. In those cases, the separation procedure is rather tedious since large quantities of aqueous sodium hydrogen carbonate have to be used to remove the acetic acid, and so considerable amounts of aqueous waste would be generated.

Employing the optimized $Mn(OAc)_3$ as the oxidant and solvent-free ball milling as the reaction condition, we therefore developed a general method¹⁰ for efficient synthesis of a series of polysubstituted pyrroles as shown in Table 2.

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"Reactions were carried out with **1a** (2.0 mmol), **2b** (1.0 mmol), and oxidant (2.0 mmol) at room temperature with a vibration frequency of 30 Hz for entries 1–10; heating in 10 mL solvent for entries 11–13.

^b Yield was determined by HPLC analysis.

^cThe starting materials were completely consumed, accompanying with several side products.

^d Most of starting materials remained.

Table 2. Mn(OAc)₃-mediated synthesis of 2,5-dimethyl-3,4-dicarboxylate-pyrroles under solvent-free ball milling^{a, b}



^a Reactions were carried out with 1 (2.0 mmol), 2 (1.0 mmol), and Mn(OAc)₃·2H₂O (2.0 mmol) at room temperature with a vibration frequency of 30 Hz for 60 minutes.

^bIsolated yield combined from two parallel runs.

^cObtained from the reaction of preliminarily prepared enamine **4b** with isobutyl acetoacetate under standard condition.

From Table 2 we can see that anilines bearing electronwithdrawing groups or substituents at ortho position afforded relatively lower yield. Accordingly, ethyl acetoacetate exhibited higher efficiency than isobutyl acetoacetate due to obvious steric effect. It is worth pointing out that the corresponding *N*- unsubstituted pyrrole (**3j**, **3k**) can also be obtained in moderate yield when NH_4OAc was employed instead of anilines by following this protocol. Some other 1,3-dicarbonyl compounds including acetylacetone and 1,3-cyclohexanedione were also attempted. Unfortunately, the corresponding fully substituted

pyrroles cannot be obtained. These results demonstrate that only β -carbonyl esters work well in this reaction, which may be ascribed to the fact that the reactivity of β -enaminone is somewhat lower than that of β -enaminoester.

As to the mechanism of this reaction, we initially speculated that it may undergo through oxidative free radical coupling of acetoacetate in presence of $Mn(OAc)_3$ to generate intermediate 1,4-diketone,¹¹ which then could proceed via classical Paal–Knorr reaction with amine to afford the final pyrrole.^{3, 12} To verify the reaction mechanism, we performed some controlled experiments as outlined in Scheme 1. We first carried out the reaction of ethyl acetoacetate **1a** with equivalent $Mn(OAc)_3$ in absence of any amine under the standard condition, but it did not afford the proposed 1,4-diketone (<2% yield). This result denied our original hypothesis. On the other hand, direct ball milling of **1a** and equivalent aniline **2b** can easily generate enamine **4b**

even in absence of Mn(OAc)₃, though the conversion is very low. Therefore, we inferred that the formation of pyrrole 3b should go through addition-cyclization of 1a with in situ generated enamine 4b. To confirm this point, we treated preliminarily prepared enamine 4b with one equivalent 1a in presence of Mn(OAc)₃ under ball milling. As expected, pyrrole **3b** formed smoothly. But it should be emphasized that two molar equivalents of Mn(OAc)₃ are required for the completion of the reaction (93% yield), since one molar equivalent of Mn(OAc)₃ afforded only 46% yield. When enamine 4b was directly treated with equivalent $Mn(OAc)_3$ in absence of 1a under the standard condition, the reaction gave trace of 3b. In this case, 3b may be formed via addition-cyclization of enamine 4b with trace of 1a that was in situ generated from slight decomposition of 4b. It is also possible that 3b comes from the homodimerization of two enamines as reported.13



Table 3. Mn(OAc)₃-mediated synthesis of N-substituted 3,4-diphenylpyrroles under solvent-free ball milling^{a, b}



^a Reactions were carried out with 2-phenylacetaldehyde (2.0 mmol), **2** (1.0 mmol), and Mn(OAc)₃·2H₂O (2.0 mmol) at room temperature with a vibration frequency of 30 Hz for 60 minutes. ^b Isolated yield, average of two parallel runs. 4

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Based on the results from these controlled experiments, accompanying with related literatures on Mn(OAc)3-promoted generation of carbon-centered radicals from carbonyl compounds and their oxidative addition-cyclization to alkenes,⁶ we speculate that the reactions mainly go through a mechanism as shown in Scheme 2, which may involve the following steps: (a) formation of enamine 4 from acetoacetate 1 and amine 2; (b) generation of Mn(III)-enolate I from 1 promoted by equivalent $Mn(OAc)_3$; (c) generation of carbon-centered radical II via free radical addition of I to enamine 4; (d) formation of enamine III via oxidative elimination with another equivalent $Mn(OAc)_3;$ (e) intramolecular Aldol-like condensation and dehydration to achieve the formation of final product 3. This mechanism is further supported by a fact that the reaction of preliminarily prepared enamine 4b with equivalent isobutyl acetoacetate under the standard condition smoothly afforded the corresponding pyrrole 31 in 81% yield (Table 2). This result demonstrates a potential alternative of this protocol to synthesis of 3,4asymmetric-disubsitutied-pyrroles. But anyway, we cannot definitely exclude that maybe minor products are formed through reported mechanism of homodimerization from enamines.¹³⁻¹⁶

Then we extended this method to synthesize N-substituted 3,4diphenylpyrroles by using 2-phenylacetaldehyde instead of acetoacetates.¹⁰ As expected, a series of N-substituted 3,4diphenylpyrroles were obtained by following this mild and efficient protocol (Table 3). This reaction was firstly reported by Jia et al, in which they employed AgOAc as mediator by refluxing in THF for 8 hours (25-80% yields).¹³ Huang, Deng and co-workers has developed a Cu(OTf)2-promoted method, but the substrates were limited within alkylamines.¹⁴ Recently, Wan, Wen and co-workers employed TBHP to achieve this reaction, which can only be applied to anilines.¹⁵ Herein, we achieved this transformation using cheap and safe Mn(OAc)₃ as mediator under solvent-free ball milling at room temperature for only one hour, and the desired products were obtained in good to excellent yields (53-93%). As shown in Table 3, this method exhibited wide scope for amine 2, in which both anilines bearing either electro-donating or electro-withdrawing groups and aliphatic amines worked well. Other alkyl aldehydes such as nbutylaldehyde and phenylpropylaldehyde were also tried, but the reaction didn't work as desired to afford the corresponding products. Maybe the employed aldehydes require the β-phenyl group to form the enolate to facilitate the reaction. As to this reaction mechanism, it should go through homodimerization of two enamines as other papers demonstrate.¹³⁻¹⁶

In conclusion, a simple and mild method has been developed by using solvent-free ball milling technique for efficient synthesis of polysubstituted pyrroles via Mn(OAc)₃-mediated oxidative radical annulation. Following this method, a series of 2,5-dimethyl-3,4-dicarboxylate-pyrroles and *N*-substituted 3,4diphenylpyrroles were successfully synthesized in moderate to excellent yields from various amines, acetoacetate and 2phenylacetaldehyde, respectively. The advantages including use of cheap and safe Mn(OAc)₃ as mediator, no use of commonly employed acetic acid as solvent, short reaction time and readily available starting materials make this protocol a good alternative to traditional synthesis of polysubstituted pyrroles.

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Supplementary data

Supplementary data (experimental procedure, characterization data and NMR spectra of the products) associated with this article can be found, in the online version, at XXX.

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- 10. General procedure for solvent-free ball milling synthesis of pyrrole 3 and 5: Acetoacetate 1 or 2-phenylacetaldehyde (2.0 mmol), amine 2 (1.0 mmol) and Mn(OAc)₃·2H₂O (2.0 mmol), together with a stainless ball of 7.0 mm in diameter, were introduced into a stainless jar (25 mL). The same mixture was also introduced into a second parallel jar. The two reaction vessels were sealed with screw caps, fixed on the vibration arms of a ball-milling apparatus (mixer mill MM400, Retsch GmbH, Haan, Germany) and were vibrated vigorously at a rate of 1800 rounds per minute (30 Hz) at room temperature for 60 minutes. The mixture was diluted with EtOAc and water. The aqueous layer was dried over magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with

EtOAc/petroleum ether as the eluent, affording the desired product **3** or **5** as yellow solid. For characterization data of all products, see: Supplementary data.

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Highlights:

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1. Polysubstituted pyrroles are synthesized under mechanochemical ball milling.

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2. Solvent-free radical cyclization is efficiently accomplished mediated by Mn(OAc)₃.

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- The mechanism involves radical addition, oxidative elimination and condensation. 3.
- 4. The method exhibits mild condition, short time, simple work up and broad scope.

-or