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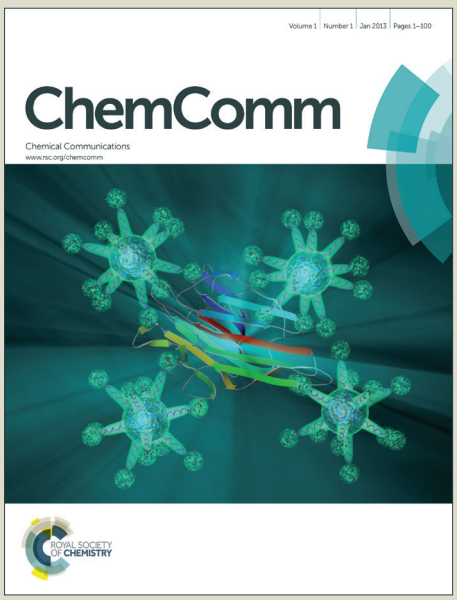

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Communication

Organocatalytic Multicomponent Synthesis of Polysubstituted Pyrroles from 1,2-diones, aldehydes and arylamines

Yin Zheng, Youming Wang, Zhenghong Zhou*

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We have developed an organocatalyzed three-component reaction of 1,2-diones, aldehydes and arylamines, which provide an efficient approach to access polysubstituted pyrroles. Under the catalysis of 4-methylbenzenesulfonic acid monohydrate, the reactions of a wide range of 1,2-diones, arylamines and aldehydes took place smoothly to generate the corresponding polysubstituted pyrroles in acceptable to good yields under mild reaction conditions.

Polysubstituted pyrroles are important as components in numerous biologically active compounds such as natural products, pharmaceuticals, and agrochemicals.[1] For example, Neolamellarin A (**1**), a metabolite isolated from the sponge Dendrilla nigra, demonstrated antitumor activity[2] Lamellarin O (**2**), a pyrrole alkaloid from an Australian marine sponge, was characterized as a selective inhibitor of breast cancer resistant protein (BCRP).[3] Pyrrolnitrin (**3**) functions as a systemic antifungal agent.[4] Fludioxonil (**4**) is a contact broad-spectrum fungicide structurally related to pyrrolnitrin.[5] Licofelone (**5**) possesses significant analgesic, anti-inflammatory, and antiasthmatic activities.[6] Apricoxib (**6**), a cyclooxygenase-2 (COX-2) inhibitor, exhibited antitumor activity.[7] Atorvastatin (**7**), an inhibitor of HMG-CoA reductase, is very widely used as a cholesterol-lowering agent, being one of the best-selling drugs in history.[8] Furthermore, polysubstituted pyrrole derivatives also have been widely used as versatile building blocks in organic synthesis[9] and as conducting polymers, molecular optics in the field of material science.[10] Consequently, the efficient assembly of this class of molecule is undoubtedly a significant objective in synthetic chemistry. Numerous different approaches for the construction of pyrrole derivatives from acyclic materials have arisen from over one century of intense research activity in this particular field.[11,12] The Knorr,[13] Paal–Knorr[14,15] and Hantzsch[16] reactions are well documented as the traditional methods to build pyrrole rings. Most of these methods are limited to the use of elaborately designed starting materials and suffer from low efficiency and selectivity. Recently, transition metal-catalyzed cyclization strategies have proven highly fruitful for the construction of pyrrole nucleus.[11b,d,12b-e,12g-k,12n] However, they suffer from several drawbacks such as complicated operations, harsh reaction conditions as tedious work-up procedures. As transition metals are required, which cause potential contamination of the products, this is particularly significant in the pharmaceutical industry.[17] In addition, due to their improved efficiency, reduced waste, and rapid access to structural diversity, multicomponent reactions (MCRs) has also been successfully employed for the synthesis of pyrroles.[11a,c,12f,l] Although a variety of methods have been recently developed for the synthesis of functionalized pyrrole derivatives, direct and practical access to novel and more exotic polyfunctionalized pyrroles from readily available feedstocks, especially in an atom and step economic manner, still remains challenging and highly desirable.

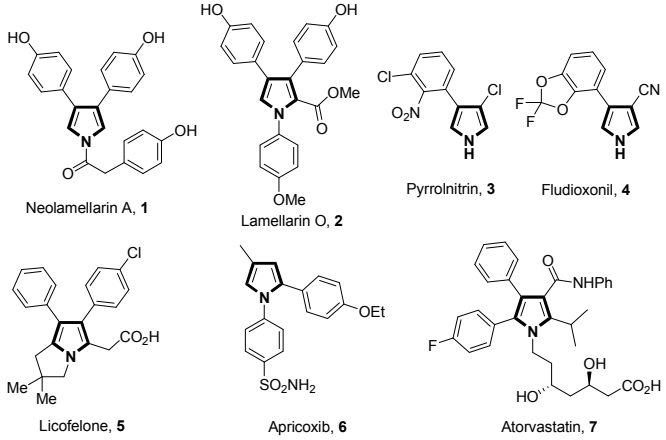
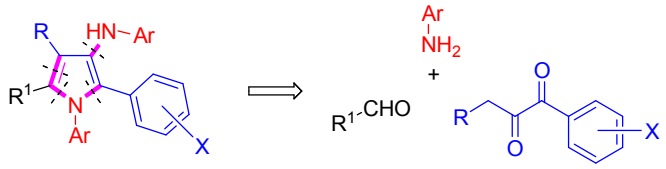


Figure 1. Arylpyrrole-derived natural products and pharmaceuticals

As a part of our ongoing research on the development of approaches to biorelevant heterocycles,[18] we were interested in the rapid construction of a polysubstituted pyrrole ring via the organocatalyzed three-component reaction of aryl 1,2-diketones, aldehydes and aromatic amines. The reaction involves the assembling of the pyrrole core from [1+1+3] atom fragments (Scheme1).

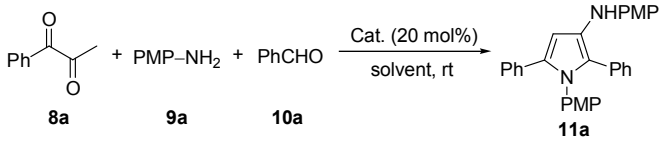


Scheme 1 Synthesis of pyrroles via MCRs

Our initial efforts focussed on the reaction of 1-phenylpropane-1,2-dione (**8a**), 4-methoxyaniline (**9a,** PMP–NH_2), and benzaldehyde (**10a**) by using 4-

methylbenzenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) as the catalyst in dichloromethane at room temperature. To our delight, we indeed obtained the corresponding polysubstituted pyrrole **11a** in moderate yield (Table 1, entry 1). The structure of **11a** was further unequivocally confirmed by X-ray analysis of the corresponding amide derivative **12** (see ESI).[19] Notably, this three-component reaction demonstrated a high bond-forming efficiency, four new bonds were formed in a single synthetic operation, and thereby increasing molecular diversity and complexity in a fast and often experimentally simple fashion. This interesting transformation to the pyrrole heterocycles encouraged us to further examine the feasibility of this efficient three-component reaction.

Table 1 Optimization of the reaction conditions [a]



Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield (%)[b]
1	$TsOH{\cdot}H_2O$	CH_2Cl_2	r.t.	48	57
2	CF_3CO_2H	CH_2Cl_2	r.t.	48	52
3	AcOH	CH_2Cl_2	r.t.	60	22
4	$PhCO_2H$	CH_2Cl_2	r.t.	96	26
5	CH_3SO_3H	CH_2Cl_2	r.t.	48	48
6	$TsOH{\cdot}H_2O$	EtOH	r.t.	10	73
7	$TsOH{\cdot}H_2O$	CH_3CN	r.t.	10	79
8	$TsOH{\cdot}H_2O$	EA	r.t.	40	45
9	$TsOH{\cdot}H_2O$	THF	r.t.	40	48
10	$TsOH{\cdot}H_2O$	$PhCH_3$	r.t.	40	57
11	$TsOH{\cdot}H_2O$	DMF	r.t.	40	59
12	TsOH	CH_3CN	r.t.	10	80
13[c]	$TsOH{\cdot}H_2O$	CH_3CN	r.t.	12	62
14	$TsOH{\cdot}H_2O$	CH_3CN	40	8	73
15	$TsOH{\cdot}H_2O$	CH_3CN	60	6	58
16	$TsOH{\cdot}H_2O$	CH_3CN	reflux	5	56
17[d]	$TsOH{\cdot}H_2O$	CH_3CN	r.t.	10	84

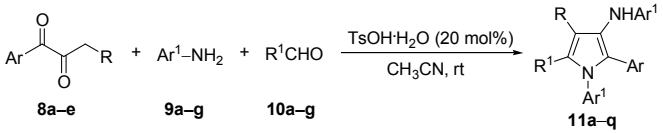
[a] Reaction conditions: 1-phenylpropane-1,2-dione **8a** (0.2 mmol), PMP-NH_2 **9a** (0.4 mmol), and benzaldehyde **10a** (0.2 mmol) in 1 mL of dichloromethane at room temperature in the presence of 20 mol% of catalyst. [b] Isolated yield. [c] The loading of $TsOH{\cdot}H_2O$ is 10 mol%. [d] 0.44 mmol of **9a** was employed.

Further evaluating of other brønsted acid catalysts, such as trifuoroacetic acid (TFA), acetic acid, benzoic acid and methanesulfonic acid, revealed that the acid strength of the catalyst seemed to have some effect on the catalytic activity (Table 1, entries 2–5). Generally, the use of more acidic $TsOH{\cdot}H_2O$, TFA and methanesulfonic acid as the catalyst afforded product **11a** in higher yield within a shorter reaction time. $TsOH{\cdot}H_2O$ turned out to be the best catalyst candidate, delivering the desired product **11a** in 57% yield (Table 1, entry 1). The solvent played an important role in this three-component reaction. Much better yields were obtained by changing dichloromethane to polar solvent ethanol (Table 1, entry 6) and acetonitrile (Table 1, entry 7). Comparable yields were observed by performing the reaction in toluene and *N*,*N*-dimethyl formamide (DMF) (Table 1, entries 10 and 11), whilst slightly decreased yields were achieved in ethyl acetate and tetrahydrofuran (THF) (Entries 8 and 9). Among the evaluated solvents, acetonitrile proved superior to all others leading to a highly efficient synthesis of **11a** (Table 1, entry 7). Under otherwise identical reaction conditions, similar yield was obtained when anhydrous TsOH rather than $TsOH{\cdot}H_2O$ was employed as the catalyst (Table 1, entry 12). Furthermore, upon adjusting the amount of $TsOH{\cdot}H_2O$ to 10 mol%, the reaction still proceeded smoothly, albeit with a slightly decreased yield (Table 1, entry 13). In addition, the reaction temperature also distinctly influenced the reaction. In general, increasing the reaction temperature accelerated the reaction but decreased the yield of product **11a** (Table 1, entry 7 vs. entries 14–16). Finally, a slight excess of **9a** (2.2 equivalent to **8a**) was proven to be beneficial to the reaction (Table 1, entry 17 vs. entry 7).

With the optimized reaction conditions in hand, we firstly set out to test the reactivity of other arylamines with 1-phenylpropane-1,2-dione (**8a**) and benzaldehyde (**10a**). As shown in Table 2, the reaction was readily extended to a variety of arylamines, and electron-withdrawing, neutral and electron-donating substituents were well tolerated under the reaction conditions (Table 2, entries 2–7). The substitution pattern demonstrated some influence on the yield of the reaction. For example, compared with the para-methoxy substituted arylamine **9a**, which affording the product **11a** in 84% yield, slightly decreased yields were observed for the ortho- and meta-methoxysubstituted substrates **9b** and **9c** (Table 2, entry 1 vs. entries 2 and 3). Next, we focussed our attention on investigating the scope with regard to the aldehyde. Introducing an electrondonating (**10b,c**) or electron-withdrawing (**10d,e**) group on the phenyl ring had no significant influence, and the corresponding pyrroles were obtained in good yields (Table 2, entries 8–11). Electron-rich heteroarylaldehyde containing 2-furyl group (**10f**) was also subjected to the three-component reaction, leading to the corresponding products **11l** in acceptable yield (Table 2, entry 12). Additionally, cinnamaldehyde (**10g**) was also found to be a suitable reaction partner, furnishing the desired product **11m** with a slightly decreased yield (Table 2, entry 13). To further explore the synthetic utility of this reaction, the scope of 1-phenylpropane-1,2-diones **8** was investigated as well. Both of the electron-donating (**8b**) and electronwithdrawing (**8c**) groups on the 1-aryl ring of the 1-phenylpropane-1,2-diones were well tolerated and provided the corresponding pyrroles **11n**, **11o** in desirable yields (Table 2, entries 14 and 15, 81 and 83%, respectively). Also worthy of note is the observation that in place of 1-arylpropane-1,2-diones **8a–c**, both 1-phenylbutane-1,2-dione (**8d**) and 1-phenyl-3-(4-methylphenylthio)propane-1,2-dione (**8e**) readily participated in the reaction with 4-methoxyaniline **9a** and benzaldehyde **10a**, giving rise to fully substituted pyrroles **12p** and **12q** in 67 and 43% yield, respectively (Table 2, entries 16 and 17). In addition, aliphatic aldehyde, such as cyclohexanecarbaldehyde (**10h**), was also applicable but required changing the solvent to ethanol and adjusting the dosage of $TsOH{\cdot}H_2O$ to one equivalent (Entry 18). We have also attempted the reactions of aliphatic amines and 1,2-diones, unfortunately, the corresponding polysubstituted pyrroles were not form at all under the current conditions. Thus, the brønsted acid-catalyzed three-component reaction of 1-arylpropan-1,2-diketones with a broad range of arylamines and aldehydes

provides a powerful method for the synthesis of tetrasubstituted and fully substituted pyrroles.

Table 2 Substrate scope of the organocatalyzed three-component reactions [a]

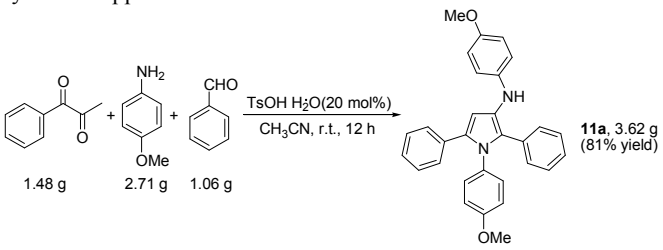


8a–e **9a–g** **10a–g** **11a–q**

Entry	**11** (Ar, Ar^1, R, R^1)	Time [h]	Yield (%)[b]
1	**11a** (Ph, 4-$MeOC_6H_4$, H, Ph)	10	84
2	**11b** (Ph, 3-$MeOC_6H_4$, H, Ph)	10	67
3	**11c** (Ph, 2-$MeOC_6H_4$, H, Ph)	12	73
4	**11d** (Ph, 4-MeC_6H_4, H, Ph)	10	79
5	**11e** (Ph, 4-BuC_6H_4, H, Ph)	10	70
6	**11f** (Ph, Ph, H, Ph)	10	84
7	**11g** (Ph, 4-FC_6H_4, H, Ph)	10	79
8	**11h** (Ph, 4-$MeOC_6H_4$, H, 4-MeC_6H_4)	10	82
9	**11i** (Ph, 4-$MeOC_6H_4$, H, 2-MeC_6H_4)	10	76
10	**11j** (Ph, 4-$MeOC_6H_4$, H, 3-ClC_6H_4)	10	86
11	**11k** (Ph, 4-$MeOC_6H_4$, H, 4-$O_2NC_6H_4$)	10	87
12	**11l** (Ph, 4-$MeOC_6H_4$, H, 2-Furyl)	20	46
13	**11m** (Ph, 4-$MeOC_6H_4$, H, Styryl)	20	54
14	**11n** (4-$EtOC_6H_4$, 4-$MeOC_6H_4$, H, Ph)	10	81
15	**11o** (4-BrC_6H_4, 4-$MeOC_6H_4$, H, Ph)	10	83
16	**11p** (Ph, 4-$MeOC_6H_4$, Me, Ph)	20	67
17	**11q** (Ph, 4-$MeOC_6H_4$, 4-MeC_6H_4S, Ph)	10	43
18[c]	**11r** (Ph, 4-$MeOC_6H_4$, H, Cy)	10	42

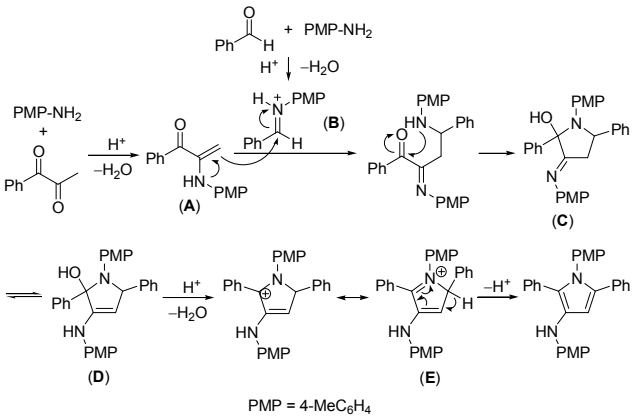
[a] Reaction conditions: 1,2-diones **8** (0.2 mmol), arylamines **9** (0.44 mmol), and aldehydes **10** (0.2 mmol) in 1 mL of acetonitrile in the presence of 20 mol% of $TsOH·H_2O$. [b] Isolated yield. [c] The reacton was performed in the presence of 1 equivalent of $TsOH·H_2O$ in 2 mL of ethanol.

To prove the practicality of this 'one-pot' reaction system, a gram-scale synthesis of the *N*,1-Bis(4-methoxyphenyl)-2,5-diphenyl-1*H*-pyrrol-3-amine **11a** was performed. The result is shown in Scheme 2. When 1.48 g of 1-phenylpropane-1,2-dione **8a**, 2.71 g of 4-methoxyaniline **9a** and 1.06 g of benzaldehyde **10a** were loaded, 3.62 g of polysubstituted pyrrole **11a** was obtained (81% yield). Thus, the metal-free and high efficiency make this reaction possess extensive synthesis applications.



Scheme 2 Gram-scale synthesis of polysubstituted pyrrole **11a**

On the basis of the above-described results, we propose that this multicomponent domino reaction proceeds by the mechanism shown in Scheme 3. First, the nucleophilic addition of enamine intermediate **A** formed by the reaction of 1-phenylpropan-1,2-dione and 4-methoxyaniline to the in situ formed iminium **B** from benzaldehyde and 4-methoxyaniline, followed by the intramolecular nucleophilic attack by the amine to afford the aminoalcohol intermediate **C** with the aid of acid catalyst. After the acid catalyzed tautormerization of the imine form aminoalcohol **C** to the corresponding enamine form **D**, the protonated aminoalcohol **D** loses a molecule of water to generate the relatively stable conjugate iminium ion (**E**), and then the removal of a proton generates the pyrrole nucleus.[20]



Scheme 3 Proposed reaction mechanism

In conclusion, we have developed an efficient, facile and practical one-pot procedure for the synthesis of polysubstituted pyrroles. This transformation features easy accessibility of starting materials, good functional group tolerance and transition metal free. A wide variety of poly-substituted pyrroles were obtained in acceptable to good yields in an environmentally benign manner under quite mild conditions. From a synthetic point of view, this protocol represents an extremely simple and efficient way to construct polysubstituted pyrroles in good yields. We believe that this efficient three-component reaction protocol is attractive for the preparation of a diverse range of tetra- and fully substituted pyrroles.

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Notes and references

Institute and State Key Laboratory of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering Nankai University, Tianjin 300071, P. R. China. E-mail: z.h.zhou@nankai.edu.cn

† Electronic Supplementary Information (ESI) available: [Experimental procedures, characterization of the products and copies of NMR, HRMS spectra of the products]. See DOI: 10.1039/b000000x/

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