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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 10 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 15 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 activity² Lamellarin O (2), a pyrrole alkaloid from an Australian marine sponge, 20 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 broadspectrum fungicide structurally related to pyrrolnitrin.⁵ Licofelone (5) possesses significant analgesic, anti-25 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, 30 polysubstituted pyrrole derivatives also have been widely used as versatile building blocks in organic synthesis⁹ 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 35 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 Hantzsch¹⁶ reactions are well documented as the traditional 40 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-45 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 ⁵⁰ 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,1} Although a variety of methods have been recently developed for the synthesis of functionalized pyrrole ⁵⁵ 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.



60 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 1,2-65 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 1phenylpropane-1,2-dione (8a), 4-methoxyaniline (9a, PMP- NH_2), and benzaldehyde (10a) by using 4methylbenzenesulfonic acid monohydrate (TsOH'H₂O) 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 ⁵ 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 ¹⁰ 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

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Ph Ba	+ PMP-NH ₂ + 9a	PhCHO	Cat. (20 mol% solvent, rt) ┣ ₽h	NHPMP
					11a
Entry	Catalyst	Solvent	Temp. (°C)	Time (h)	Yield $(\%)^b$
1	TOULUO	CIL CI		40	67

5	2		രസ്	(h)	$(0/a)^b$
	T ON N O	arr al	(0)	(11)	(70)
1	TsOH·H ₂ O	CH_2CI_2	r.t.	48	57
2	CF ₃ CO ₂ H	CH_2Cl_2	r.t.	48	52
3	AcOH	CH_2Cl_2	r.t.	60	22
4	PhCO ₂ H	CH_2Cl_2	r.t.	96	26
5	CH ₃ SO ₃ H	CH_2Cl_2	r.t.	48	48
6	TsOH·H ₂ O	EtOH	r.t.	10	73
7	TsOH·H ₂ O	CH ₃ CN	r.t.	10	79
8	TsOH·H ₂ O	EA	r.t.	40	45
9	TsOH·H ₂ O	THF	r.t.	40	48
10	TsOH·H ₂ O	PhCH ₃	r.t.	40	57
11	TsOH·H ₂ O	DMF	r.t.	40	59
12	TsOH	CH ₃ CN	r.t.	10	80
13 ^c	TsOH·H ₂ O	CH ₃ CN	r.t.	12	62
14	TsOH·H ₂ O	CH ₃ CN	40	8	73
15	TsOH·H ₂ O	CH ₃ CN	60	6	58
16	TsOH·H ₂ O	CH ₃ CN	reflux	5	56
17^{d}	TsOH·H ₂ O	CH ₃ CN	r.t.	10	84
a D			1 0 1	0 (0 0	D DI (D

^{*a*} Reaction conditions: 1-phenylpropane-1,2-dione **8a** (0.2 mmol), PMP-NH₂ **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·H₂O 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 20 catalyst seemed to have some effect on the catalytic activity (Table 1, entries 2–5). Generally, the use of more acidic TsOH[•]H₂O, TFA and methanesulfonic acid as the catalyst afforded product **11a** in higher yield within a shorter reaction

- time. TsOH H_2O turned out to be the best catalyst candidate, ²⁵ delivering the desired product **11a** in 57% yield (Table 1,
- entry 1). The solvent played an important role in this threecomponent 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
- ³⁰ were observed by performing the reaction in toluene and N,Ndimethyl 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
- 35 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⁺H₂O was employed as the catalyst (Table 1, entry 12). Furthermore, upon adjusting the amount of TsOH⁺H₂O to 10 ⁴⁰ 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 ⁴⁵ 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 1-50 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 55 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 60 (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 electronwithdrawing (10d,e) group on the phenyl ring had no significant influence, and the corresponding pyrroles were 65 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 111 in acceptable yield (Table 2, entry 12). Additionally, cinnamaldehyde (10g) was also found to be 70 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 1phenylpropane-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 1-⁸⁰ phenylbutane-1,2-dione (8d) 1-phenyl-3-(4and 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 85 addition, aliphatic aldehyde, such as cyclohexanecarbaldehyde (10h), was also applicable but required changing the solvent to ethanol and adjusting the dosage of TsOH H₂O to one equivalent (Entry 18). We have also attempted the reactions of aliphatic amines and 1,2-diones, unfortunately, the ⁹⁰ corresponding polysubstituted pyrroles were not form at all under the current conditions. Thus, the brønsted acidcatalyzed three-component reaction of 1-arylpropan-1,2diketones with a broad range of arylamines and aldehydes

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

Table 2 Substrate scope of the organocatalyzed three-componentreactions a

Ar	$R + Ar^{1}-NH_{2} + R^{1}CHO - \frac{TsOHH}{CH}$	₂ O (20 mol%) I ₃ CN, rt R	R NHAr
8a-e	9a–g 10a–g		Ar' 11a–q
Entry	11 (Ar, Ar^1 , R, R^1)	Time	Yield
		[h]	(%)
1	11a (Ph, 4-MeOC ₆ H ₄ , H, Ph)	10	84
2	11b (Ph, 3 -MeOC ₆ H ₄ , H, Ph)	10	67
3	11c (Ph, 2-MeOC ₆ H ₄ , H, Ph)	12	73
4	11d (Ph, 4-MeC ₆ H ₄ , H, Ph)	10	79
5	11e (Ph, 4-BuC ₆ H ₄ , H, Ph)	10	70
6	11f (Ph, Ph, H, Ph)	10	84
7	11g (Ph, 4-FC ₆ H ₄ , H, Ph)	10	79
8	11h (Ph, 4-MeOC ₆ H ₄ , H, 4-MeC ₆ I	H ₄) 10	82
9	11i (Ph, 4-MeOC ₆ H ₄ , H, 2-MeC ₆ H	H_4) 10	76
10	11j (Ph, 4-MeOC ₆ H ₄ , H, 3-ClC ₆ H	I ₄) 10	86
11	11k (Ph, 4-MeOC ₆ H ₄ , H, 4-O ₂ NC ₆	H ₄) 10	87
12	111 (Ph, 4-MeOC ₆ H ₄ , H, 2-Furyl	1) 20	46
13	11m (Ph, 4-MeOC ₆ H ₄ , H, Styryl	ĺ) 20	54
14	11n (4-EtOC ₆ H ₄ , 4-MeOC ₆ H ₄ , H,	Ph) 10	81
15	110 (4-BrC ₆ H ₄ , 4-MeOC ₆ H ₄ , H, F	Ph) 10	83
16	11p (Ph, 4-MeOC ₆ H ₄ , Me, Ph)	20	67
17	11q (Ph, 4-MeOC ₆ H ₄ , 4-MeC ₆ H ₄ S,	Ph) 10	43
18 ^c	11r (Ph, 4-MeOC ₆ H ₄ , H, Cy)	10	42
^a Reaction	conditions: 1,2-diones 8 (0.2 mm	ol), arylamine	es 9 (0.44

^{*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)-2,5diphenyl-1*H*-pyrrol-3-amine **11a** was performed. The result is shown in Scheme 2. When 1.48 g of 1-phenylpropane-1,2dione **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 15 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 ²⁰ 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

²⁵ 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





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 40 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 45 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 55 Nankai University, Tianjin 300071, P. R. China. E-mail: z.h.zhou@nankai.edu.cn

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