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Communication

Synthesis of polysubstituted pyrroles *via* a gold(I)-catalyzed tandem three-component reaction at room temperature

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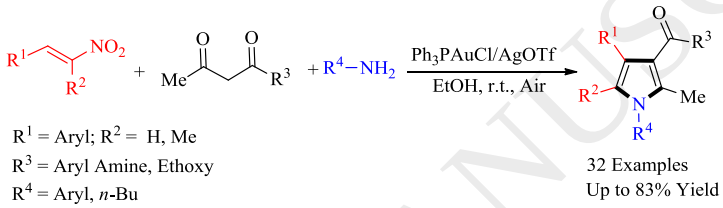
Graphical abstract



A gold(I)-catalyzed three-component reaction of β-nitrostyrenes with 1,3-dicarbonyl compounds and primary amines to form polysubstituted pyrroles has been developed at room temperature in ethanol. The key advantages of the three-component reaction are the mild reaction conditions and environmentally safer solvent

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ABSTRACT

A gold(I)-catalyzed three-component reaction of *β*-nitrostyrenes with 1,3-dicarbonyl compounds and primary amines to form polysubstituted pyrroles has been developed at room temperature in ethanol. The key advantages of the three-component reaction are the mild reaction conditions and environmentally safer solvent.

The polysubstituted pyrrole derivatives are important heterocycles that are embedded in a broad range of natural products, pharmaceutical agents and organic functional materials (Fig. 1) [1]. Accordingly, the construction of highly functionalized pyrroles has attracted significant attention of chemists [2]. Except for the classical methods such as Hantzsch [3], Paal-Knorr procedure [4], enormous efforts have been dedicated to the development of efficient methods for its preparation [5]. The development of general and efficient strategies for the synthesis of pyrroles from simple and readily available precursors in an atom- and step-economic manner is of great interest. Recently, three-component reactions have emerged as powerful tools toward the synthesis of polysubstituted pyrroles in a one-pot fashion [6]. One of the interesting strategies available for the synthesis of polysubstituted pyrroles involves the reaction between nitroalkenes, *β*-dicarbonyl compounds and amines using zirconocene dichloride, (diacetoxyiodo)benzene, $CeCl_3 \cdot 7H_2O$ or $FeCl_3$ as the catalyst [7]. Beyond that, Kumar *et al*. [8] developed a method for the synthesis of polysubstituted pyrroles in PEG-400 at 85 °C. Although this strategy has been well explored during the past few years, the reactions in many cases suffered from one or more drawbacks such as high temperature, harsh reaction conditions, environmentally non-benign solvents and toxicity. Contemplating on

this, we decided to study the reaction for an efficient, high yielding and commercially available catalyst in an environmentally safer solvent under mild conditions.

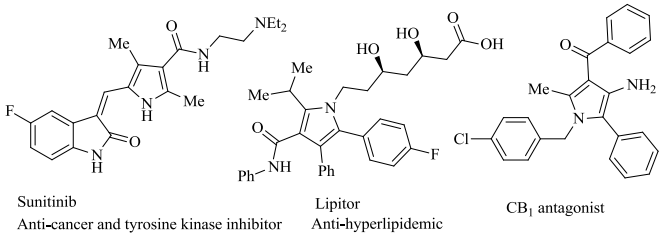


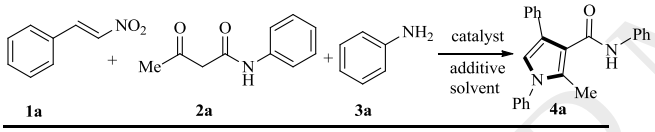
Fig. 1. Selected bioactive multisubstituted pyrroles.

The gold catalysis can certainly be considered "hot topics" in synthetic organic chemistry in recent years, since gold has its special catalytic character [9]. The homogeneous gold catalysis has emerged as a powerful tool for synthesizing a variety of important heterocycles under mild reaction conditions [10]. Herein we present our results on the gold(I)-catalyzed tandem multicomponent reaction of simple *β*-nitrostyrenes with 1,3-dicarbonyl compounds and primary amines for the synthesis of polysubstituted pyrroles in an environment-friendly ethanol medium at room temperature.

As a preliminary study, *β*-nitrostyrene **1a**, acetoacetanilide **2a** and aniline **3a** were submitted to reaction in the presence of Ph_3PAuCl (5 mol%) in EtOH at room temperature, but the desired product 2-methyl-*N*,1,4-triphenyl-1*H*-pyrrole-3-carboxamide **4a** could be obtained only in a trace amount (Table 1, entry 1). The reaction was considerably promoted by using AgOTf (5 mol%) as an additive (Table 1, entry 2), while using AgOTf only resulted in lower reactivity (Table 1, entry 11). Changing the silver additives to $AgSbF_6$ and $AgBF_4$ did not give any satisfactory results (Table 1, entries 3 and 4). Obviously, the Ph_3PAuCl/AgOTf system exhibited better activity than Ph_3PAuCl or AgOTf alone, which might be because of the silver salt effect [11] and anion effect [12]. Besides, various other solvents such as DMF, PhMe, THF, MeCN, CH_2Cl_2, and 1,4-dioxane were also examined for this reaction, the result demonstrated that EtOH (Table 1, entry 2) was superior to other solvents (Table 1, entries 5-10). The catalyst $(Ph_3PAu)^+OTf^-$, which was prepared from Celite filtration of the Ph_3PAuCl/AgOTf mixtures also could also promote this reaction (entry 12). After the optimization process, the optimal reaction conditions was obtained, that is, *β*-nitrostyrene **1a**, acetoacetanilide **2a** and aniline **3a** were conducted in a tube at room temperature for 12 h with EtOH as solvent (Table 1, entry 2).

Table 1

Optimization of reaction conditions.[a]



1a **2a** **3a** **4a**

Entry	Catalyst (5 mol%)	Additive (5 mol%)	Solvent	Yield (%)[b]
1	Ph_3PAuCl	-	EtOH	7
2	Ph_3PAuCl	AgOTf	EtOH	79
3	Ph_3PAuCl	$AgSbF_6$	EtOH	71
4	Ph_3PAuCl	$AgBF_4$	EtOH	73
5	Ph_3PAuCl	AgOTf	DMF	18
6	Ph_3PAuCl	AgOTf	PhMe	65
7	Ph_3PAuCl	AgOTf	THF	32
8	Ph_3PAuCl	AgOTf	MeCN	48
9	Ph_3PAuCl	AgOTf	CH_2Cl_2	71
10	Ph_3PAuCl	AgOTf	1,4-Dioxane	15
11	-	AgOTf	EtOH	12
12 [c]	Ph_3PAuCl	AgOTf	EtOH	76

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.42 mmol), **3a** (0.42 mmol), catalyst (5 mol%), additive (5 mol%), solvent (2 mL), r.t., 12 h. AgOTf = silver trifluoromethanesulfonate.

[b] Isolated yield

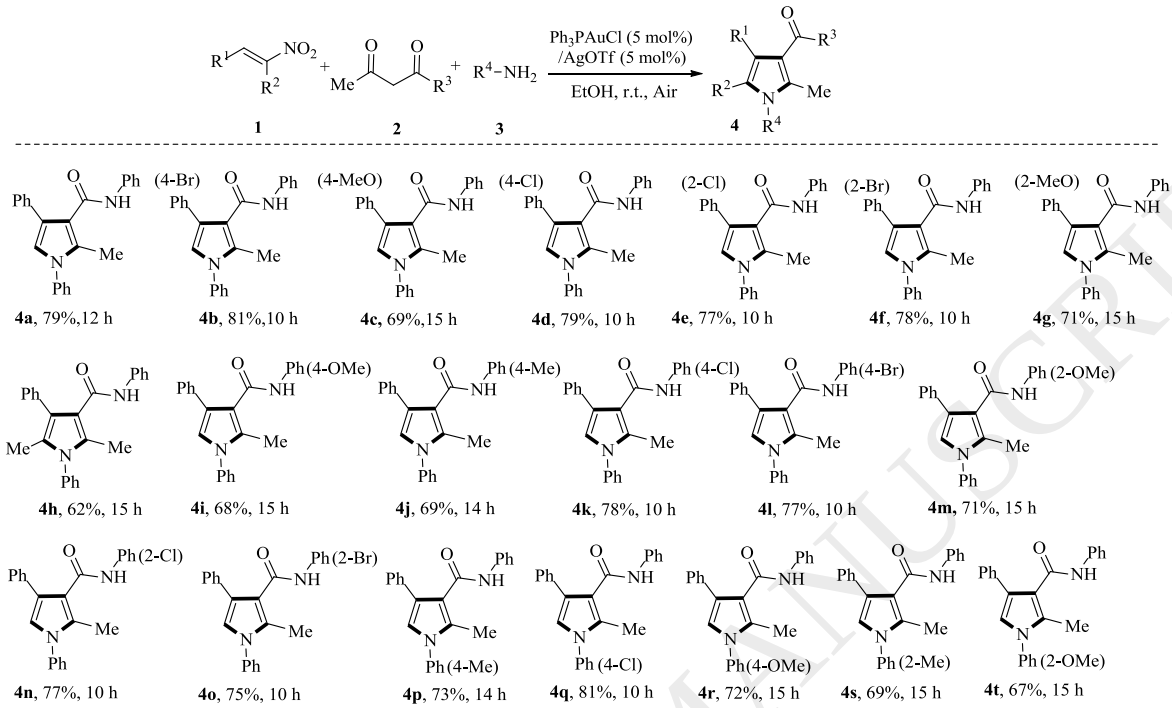
[c] Ph_3PAuCl and AgOTf in EtOH (2 mL) for 5 min, after filtration, then added **1a** (0.4 mmol), **2a** (0.42 mmol), **3a** (0.42 mmol), r.t., 12 h.

With the optimized reaction conditions in hand (Table 1, entry 2), we proceeded to explore the reaction scope with an array of *β*-nitrostyrenes, *β*-ketoamides and primary aromatic amines as shown in Scheme 1. The *β*-nitrostyrenes with electron-withdrawing substituents gave the corresponding products in higher yields, where as the *β*-nitrostyrenes with electron-donating substituents obtained a slight decrease in the yields for longer reaction time (**4b**, **4d**, **4e** and **4f** *vs.* **4c** and **4g**). The steric effects of the substituents located at *ortho* and *para* positions on the benzene ring of the *β*-nitrostyrenes did not show clear differences in terms of yields (**4b-4g**). In comparison with *β*-nitrostyrene (**1a**), (*E*)-(2-nitroprop-1-en-1-yl)benzene (**1h**) showed lower reactivity, possibly due to steric hindrance (**4a** *vs.* **4h**).

It was found that electron-withdrawing groups on the aromatic rings of *β*-ketoamides exhibited better activity and higher yields compared with their counterparts carrying electron-donating groups (**4k**, **4l**, **4n** and **4o** *vs.* **4i**, **4j** and **4m**). The steric effects of the

substituents located at ortho and para positions on the benzene ring of the *β*-ketoamides did not show significant differences, and offered the desired product **4i-4o** in moderate to good yields (**4i-4o**).

The aniline derivatives with electron-donating substituents were found to be less reactive than the counterparts with electron-withdrawing substituents (**4p**, **4r-t** *vs.* **4q**). Furthermore, in comparison with the aniline derivatives with substituents located at *para* positions, the aniline derivatives with substituents located at the *ortho* position gave a slightly decreased yield (**4p** *vs.* **4s**; **4r** *vs.* **4t**). Finally, the structure of representative compound **4h** and **4l** were ascertained by X-ray single crystal analysis, as represented in Fig. 2. The crystal data of **4h** (CCDC 1823466) and **4l** (1823465) are provided free of charge by The Cambridge Crystallographic Data Centre.



Scheme 1. Scope for the reaction of *β*-nitrostyrenes with *β*-ketoamides and primary aromatic amines under optimal conditions. Reaction conditions: *β*-nitrostyrene **1** (0.4 mmol), *β*-ketoamide **2** (0.42 mmol), primary aromatic amine **3** (0.42 mmol), EtOH (2.0 mL), r.t., 10-15 h. Yields are for the isolated products.

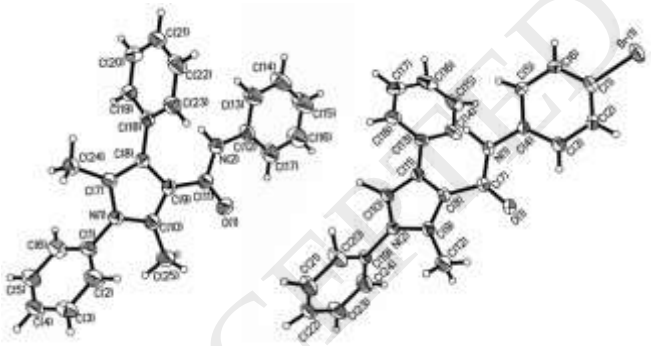
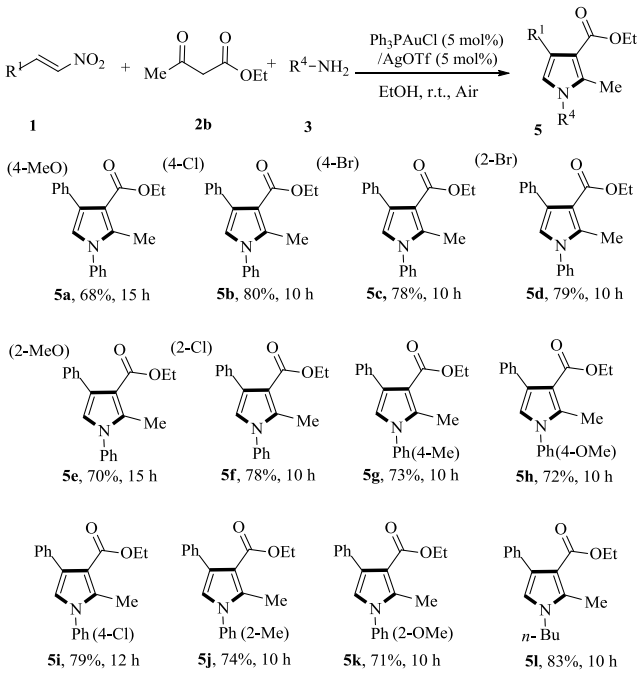


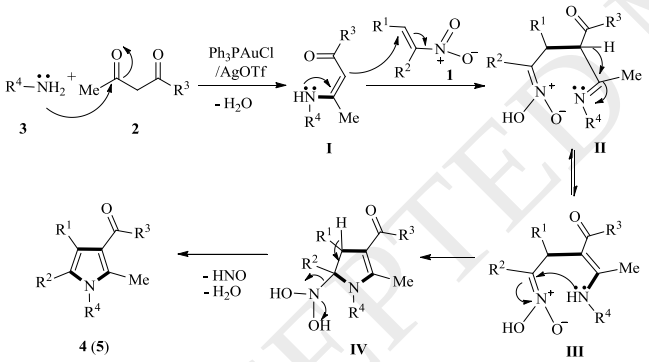
Fig. 2. ORTEP diagram of compounds **4h** and **4l**.

Furthermore, ethyl acetoacetate **2b**, another 1,3-dicarbonyl compound, was examined to probe the generality of this method, and the results are given in Scheme 2. Ethyl acetoacetate **2b**, *β*-nitrostyrenes **1**, and primary amines **3** participated in this reaction readily. A wide variation in aromatic groups of *β*-nitrostyrenes were tolerated in this procedure, the ones with electron-withdrawing gave the corresponding pyrroles in higher yields within shorter reaction time than those with electron-donating groups (**5b-f** *vs.* **5a** and **5e**). Both the aromatic amine with electron-withdrawing groups (**5i**) and the aromatic amine with electron-donating groups (**5g, 5h, 5j** and **5k**) gave the corresponding pyrroles in good yields. In addition, n-butylamine could also participate in the multicomponent reaction to produce the desired product **5l** in good yield (**5l**).



Scheme 2. Scope for the reaction of *β*-nitrostyrenes with ethyl acetoacetate and primary amines under optimal conditions. Reaction conditions: *β*-nitrostyrene **1** (0.4 mmol), ethyl acetoacetate **2b** (0.42 mmol), primary amine **3** (0.42 mmol), EtOH (2.0 mL), 10-15 h. Yields are for the isolated products. For **5l**, *n*-butylamine **3** (0.42 mmol), ethyl acetoacetate **2b** (0.42 mmol), Ph_3PAuCl (5 mol%), AgOTf (5 mol%) in 2.0 mL of EtOH for 1 h, then added *β*-nitrostyrene **1** (0.4 mmol) at room temperature for another 9 h.

A mechanistic proposal for this reaction is depicted in Scheme 3 based on results described above and other reported literatures [13]. In the presence of Ph_3PAuCl and AgOTf [12], the 1,3-dicarbonyl compound **2** is attacked by primary amine **3** to form the key intermediate **I** [14], which undergoes the Michael addition with *β*-nitrostyrene **1** to generate the intermediate **II**. **II** undergoes an imine-enamine tautomerization to give the resulting intermediate **III**, which processes an intramolecular attack through the nitrogen atom on the enamine, followed by an elimination reaction to gain the substituted pyrrole **4** (**5**) [15].



Scheme 3. Plausible reaction mechanism.

In summary, we have developed an efficient gold(I)-catalyzed three-component reaction between nitroalkenes, 1,3-dicarbonyl compounds, and primary amines, leading to the concise and flexible synthesis of polysubstituted pyrroles. The reactions were carried out under mild reaction conditions in an ethanol medium at room temperature. The products are cleanly obtained in moderate to good yields, resulting in an appealing alternative for accessing polysubstituted pyrroles.

Acknowledgments

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