Iron-catalyzed synthesis of polysubstituted pyrroles *via* [4C + 1N] cyclization of 4-acetylenic ketones with primary amines†‡

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A highly efficient iron-catalyzed approach to polysubstituted pyrroles has been developed through the [4C + 1N] cyclization of 4-acetylenic ketones with primary amines, leading to the synthesis of a variety of tetra- and fully-substituted pyrroles as well as fused pyrrole derivatives in good to excellent yields.

Pyrroles are among the most representative heteroaromatic compounds and are common structural motifs in many biologically active molecules and pharmaceutical substances, they are also widely employed as versatile building blocks in synthetic organic chemistry.[1,2] The interest in the pyrrole unit is exemplified by the great variety of procedures known for its synthesis.[3] Among them, the metal-catalyzed cyclization reactions have taken a dominant position, and a variety of metal species have been utilized in the synthesis of pyrroles, including Au, Ag, Pd, Pt, Rh, Ru, Cu, In, Mg, Zr, Co, Zn, Bi, Ni, Sc, and Yb.[4] Iron is one of the most abundant metals on Earth, and the study of iron-catalyzed reactions has received great attention in recent years,[5] however, reports on the iron-catalyzed reaction for the synthesis of pyrroles are still rare.[6] Moreover, the reported methods exhibit significant deficiencies, for example, using stoichiometric amounts of highly toxic carbonyl irons[7] and lacking the variation of substituents on the pyrrole ring due to the unity of starting materials.[8] More recently, Maiti *et al.* reported an iron(III)-catalyzed, operationally simple four-component coupling reaction of 1,3-dicarbonyl compounds, amines, aromatic aldehydes, and nitroalkanes, however, it generally required long reaction times and afforded pyrroles in low yields in most cases.[9] Therefore, the development of an efficient iron-catalyzed synthesis of pyrroles is highly desirable.

During our continued interest in the development of iron-catalyzed reactions for the synthesis of heterocycles,[10] we have noted the [4C + 1N] cyclization of 4-acetylenic ketones with primary amines acting as a straightforward approach to polysubstituted pyrrole derivatives. This route is attractive because both substrates are easily available. Until now, only a few catalysts have been utilized to catalyze this transformation, including gold, silver, palladium, and copper.[11] Iron salts have been used to catalyze relevant reactions but were unsuccessful. For example, when Zhan and co-workers employed $FeCl_3$ instead of $InCl_3$ in an indium-catalyzed multicomponent reaction of propargyl alcohols, β-dicarbonyl compounds and primary amine for the synthesis of pyrroles, the reaction was stuck at the step of 4-acetylenic ketone without further cyclization with amines.[12] Considering the many reactive species in the reaction mixture, which possibly deactivated the iron catalyst, we hypothesized that the cyclization of 4-acetylenic ketones with primary amines directly catalyzed by iron salts might be feasible. Further studies realized this idea. In this context, we wish to report results on the iron-catalyzed synthesis of polysubstituted pyrrole derivatives, including the achievement of a previously unexploited synthesis of fully-substituted pyrroles *via* this [4C + 1N] cyclization reaction. A mechanistic study disclosed an iron-catalyzed intramolecular hydroamination of the alkyne in the ring-closing step. To our knowledge, this is the first procedure for the synthesis of pyrroles using non-toxic iron salts as catalysts with high reaction efficiency, good to excellent yields, and a wide variation of substituents.

In the initial attempts to screen the iron catalysts for the [4C + 1N] cyclization of 4-acetylenic ketones with primary amines, the reaction of 4-acetylenic ketone **1a1** and 4-chlorobenzenamine was selected as a model. A toluene solution of 4-acetylenic ketone **1a1** was allowed to react with 4-chlorobenzenamine (1.2 equivalents) at 60 °C in the presence of a catalytic amount of the iron salt (10 mol%). The representative data were summarized in Table 1. To our delight, on using iron halide salts such as $FeCl_3$ or $FeBr_3$ as catalysts, excellent yields of pyrrole **2a1** were obtained in 89 and 91% yields, respectively (entries 1 and 2). The structure of **2a1** was established by X-ray analysis (CCDC 792079†). $Fe(OTf)_3$ gave a similarly high yield of **2a1** in a short time, whereas 10 mol% CF_3SO_3H produced **2a1** in 78% yield in 18 h but with 10% substrate **1a1** recovered (entries 3 and 4), which confirmed that the iron salt is the active catalyst. $Fe(acac)_3$ afforded a mixture of pyrrole **2a1** and unreacted substrate **1a1** with the ratio of 43% to 57% determined by ^{1}H-NMR analysis of reaction mixture (entry 5). Interestingly, the oxidation state of iron appears to have no influence on the catalysis, because the $FeCl_2$ afforded a similar yield of **2a1** to that under a nitrogen atmosphere which could to a large extent protect $FeCl_2$ from oxidizing to $FeCl_3$ (entries 6, 7). Other iron sources such as Fe_2O_3 and Fe powder all gave poor yields of pyrrole **2a1**, and most of the substrate **1a1** was recovered (entries 8, 9). Furthermore, upon decreasing the amount of $FeCl_3$ catalyst to 0.1 mol%, the reaction still proceeded smoothly, affording **2a1**

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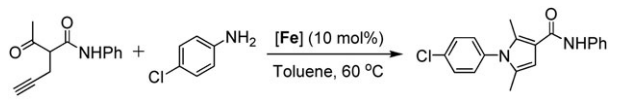
‡ Dedicated to Professor Michael Famulok on the occasion of his 50th birthday.

Table 1 Screening the iron catalyst[a]



1a1 2a1

Entry	Fe source	Time (h)	**2a1** Yield (%)[b]
1	$FeCl_3$	1.5	89
2	$FeBr_3$	1.5	91
3	$Fe(OTf)_3$	1.8	86
4	CF_3SO_3H	18	78 (10)[b]
5	$Fe(acac)_3$	24	43 (57)[c]
6	$FeCl_2$	2.0	83
7	$FeCl_2$[d]	3.0	80
8	Fe_2O_3	24	40 (60)[c]
9	Fe	24	33 (67)[c]
10	$FeCl_3$[e]	10	81

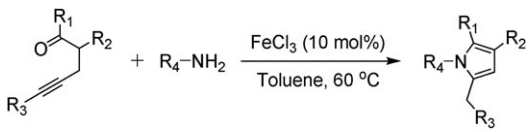
[a] Reactions were performed with 4-acetylenic ketone **1a1** (1.0 mmol), 4-chlorobenzenamine (1.2 mmol), and [Fe] catalyst (10 mol%) in toluene (1 mL) at 60 °C. [b] Isolated yields. [c] Ratio of the product **2a** to the recovered reactant **1a1** in parentheses was determined by ^{1}H-NMR analysis of crude reaction mixture. [d] Under nitrogen protection. [e] 0.1 mol% $FeCl_3$ was used.

in 81% yield, albeit within a much longer reaction time (entry 10). Considering the reaction efficiency, we thus chose the condition of 10 mol% $FeCl_3$ as a catalyst for the following study.

Under the optimal conditions (Table 1, entry 1), we started to explore the scope of the iron-catalyzed cyclization. A range of tetrasubstituted pyrroles were firstly prepared starting from the 4-acetylenic ketones **1a**, and the results are summarized in Table 2. The variation of R_2 groups on **1a** including amide, keto, ester, and aryl groups all furnished the desired products **2a1–2a7** in high to excellent yields within short times (entries 1–7). The R_1 group appears to be tolerant to bulky aromatic groups, thus product **2b1** was formed in nearly the same efficiency as **2b2** (entries 8, 9). The internal alkyne was also applicable to this iron-catalyzed procedure, yielding 84% **2c** (entry 10). Treatment of 4-acetylenic ketones **1a1** with various primary amines furnished the corresponding tetrasubstituted pyrroles **2d** in good to excellent isolated yields (entries 11–21). Aromatic amines whether with electron-withdrawing groups or with electron-donating groups are all suitable for this protocol (**2d1–2d5**). Additionally, the sterically hindered 2,6-diisopropylaniline as well as the fused aromatic naphthalen-2-amine proved to be suitable partners (**2d6** and **2d7**). All of the tested aliphatic amines resulted in excellent yields of pyrroles **2d8–2d11** (82%–91%). Noticeably, most of the pyrroles **2** contain a characteristic 3-carboxamide group. The pyrrole-3-carboxamide was found to be a key subunit in therapeutically active compounds,[13] for example, the well-known cholesterol-reducing drug Lipitor®. Thus, we have provided an efficient access to such kinds of compounds.

Catalytic approaches to fully-substituted pyrroles remains scarce;[14] on the other hand, the [4C + 1N] strategy of 4-acetylenic ketones with primary amines has yet to be exploited for the synthesis of fully-substituted pyrroles, so we decided to achieve this aim by using the iron-catalyzed procedure. As shown in Table 3, all the 4-acetylenic ketones **1b** with representative variation of substituents reacted smoothly with aromatic or alkyl primary amines, affording the corresponding fully-substituted **3a–3f** in high yields.

Table 2 Iron-catalyzed synthesis of tetrasubstituted pyrroles[a]

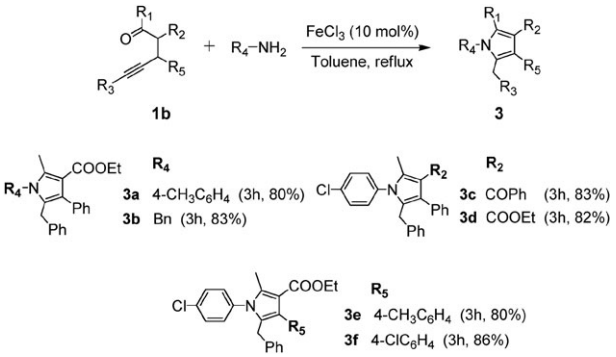


1a 2

Entry	R_1	R_2	R_3	R_4	Time (h)	**2**	Yield (%)[b]
1	Me	CONHPh	H	4-ClPh	1.5	**2a1**	89
2	Me	CONH(4-MePh)	H	4-ClPh	1.5	**2a2**	87
3	Me	CONH(4-ClPh)	H	4-ClPh	1.5	**2a3**	78
4	Me	COPh	H	4-ClPh	1.5	**2a4**	89
5	Me	COMe	H	4-ClPh	1.0	**2a5**	91
6	Me	COOEt	H	4-ClPh	1.0	**2a6**	90
7	Me	4-MeOPh	H	4-ClPh	1.5	**2a7**	78
8	4-MeOPh	CONH(4-MePh)	H	4-ClPh	2	**2b1**	81
9	Et	CONH(4-MePh)	H	4-ClPh	1.5	**2b2**	84
10	Me	CONHPh	Et	4-ClPh	1.5	**2c**	84
11	Me	CONHPh	H	Ph	1.5	**2d1**	86
12	Me	CONHPh	H	4-MePh	2	**2d2**	83
13	Me	CONHPh	H	2,4-diMeOPh	5	**2d3**	82
14	Me	CONHPh	H	2-ClPh	1.5	**2d4**	90
15	Me	CONHPh	H	3-ClPh	1.5	**2d5**	92
16	Me	CONHPh	H	2,6-di(*i*-Pr)Ph	4	**2d6**	79
17	Me	CONHPh	H	2-Naphthyl	4	**2d7**	79
18	Me	CONHPh	H	Bn	1.5	**2d8**	87
19	Me	CONHPh	H	Cyclohexyl	2	**2d9**	82
20	Me	CONHPh	H	*n*-Bu	2.5	**2d10**	83
21	Me	CONHPh	H	$(MeO)_2CHCH_2$	2	**2d11**	91

[a] Reactions were performed with 4-acetylenic ketones **1a** (1.0 mmol), amines (1.2 mmol), and $FeCl_3$ (10 mol%) in Toluene (1 mL) at 60 °C. [b] Isolated yields.

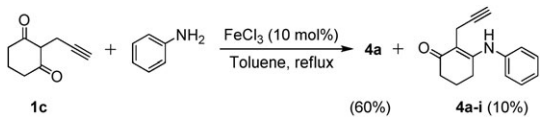
Table 3 Iron-catalyzed synthesis of fully-substituted pyrroles[a]



[a] Reactions were performed with 4-acetylenic ketones **1b** (1.0 mmol), amines (1.2 mmol), and $FeCl_3$ (10 mol%) in toluene (1 mL) at reflux.

Compared with the conditions for the synthesis of tetrasubstituted pyrroles, this reaction needed to be heated at reflux to reach a fast transformation, otherwise, the substrates can not disappear, which indicated that the presence of aromatic R_5 group heavily affected the cyclization efficiency. Overall, the iron-catalyzed procedure constitutes a straightforward alternative to the limited catalytic approaches to the synthesis of fully-substituted pyrroles that are presently available.

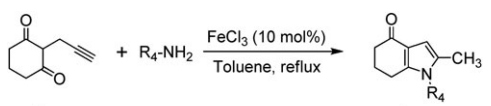
Cyclic ketone **1c** was applied to the iron-catalyzed cyclization with representative amines under the above conditions (10 mol% $FeCl_3$, toluene, reflux), to our delight, the corresponding fused pyrrole 6,7-dihydro-4-indolones **4** were also produced in good yields within short times (Table 4, entries 1–4).



(1)

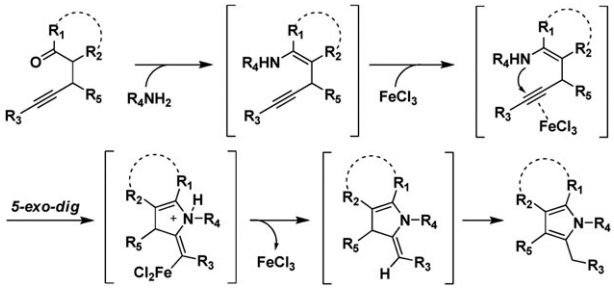
To investigate the reaction mechanism, the reaction of compound **1c** with 4-chlorobenzenamine was quenched at half way. In addition to the pyrrole **4a** (60%), an enaminone **4a–i** was isolated in 10% yield (eq. (1)). In an independent experiment, the enaminone **4a–i** was quickly converted into **4a** in the presence of 10 mol% $FeCl_3$ in refluxing toluene, which indicated that **4a–i** is the precursor for pyrrole **4a** and the ring closure proceeded through an iron-catalyzed intramolecular hydroamination of alkynes.[15]

Table 4 Iron-catalyzed synthesis of fused pyrroles[a]



Entry	R_4	Time (h)	4	Yield (%)[b]
1	Ph	0.5	**4a**	71
2	4-ClC_6H_4	0.5	**4b**	75
3	4-MeC_6H_4	0.6	**4c**	70
4	Bn	0.6	**4d**	75

[a] Reactions were performed with 4-acetylenic ketones **1c** (1.0 mmol), amines (1.2 mmol), and $FeCl_3$ (10 mol%) in toluene (1 mL) at reflux. [b] Isolated yields.



Scheme 1 A plausible reaction mechanism.

Based on the above result as well as other annulation processes involving the metal-catalyzed intramolecular hydroamination of alkynes,[16] a mechanistic proposal for this iron-catalyzed process is depicted in Scheme 1. The enamine was first formed by the condensation of carbonyl group and primary amine with the release of one H_2O. Subsequently, the regioselective 5-*exo-dig* annulation took place through an iron-catalyzed intramolecular hydroamination of alkynes followed by isomerization to give pyrroles.

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