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One-Pot Silver-Catalyzed and PIDA-Mediated Sequential Reactions: Synthesis of Polysubstituted Pyrroles Directly from Alkynoates and Amines

Weibing Liu, Huanfeng Jiang,* and Liangbin Huang

School of Chemistry and Chemical Engineering, South China University of Technology, Guangzhou 510640, P. R. China

jianghf@scut.edu.cn

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ABSTRACT

The addition/oxidative cyclization of alkynes with amines in the presence of $AgBF_4$ catalyst and PIDA oxidant leads to polysubstituted pyrroles. The reaction corresponds to the construction of a pyrrole fragment, which also provides a new way to the formation of C−C bonds.

Pyrroles are one of the most important classes of heterocyclic compounds as they are not only a key structural attribute of many bioactive natural products,[1] organic conducting materials,[2] and pharmaceutical substances[3] but also a useful and versatile building block in organic synthesis.[4] In this regard, there are many reports for the synthesis of pyrroles,[5] such as the classical Knorr reaction,[6] Hantzsch reaction,[7] and Paal−Knorr[8] condensation reaction. Recent strategies include palladium-, platinum-, copper-, and gold-catalyzed cycloisomerization, cyclization reactions of a variety of acyclic

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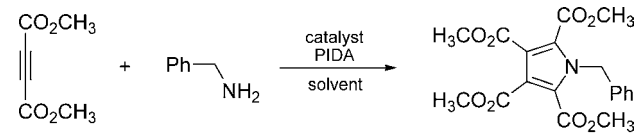
precursors,[9] reductive coupling,[10] aza-Wittig reactions,[11] multicomponent coupling methodologies,[12] and other multistep operations.[13] However, some of them usually present significant limitations, such as tedious workup, harsh nature of reaction conditions, low yields, long reaction times, or the requirement for an inert atmosphere. Therefore, the continuous studies for the synthesis of pyrroles in terms of efficient, environmentally benign, operational simplicity, economic viability, and high selectivity are still of great significance. Herein, we report an efficient and straightforward protocol under mild conditions to the synthesis of pyrroles, which is also a novel one-pot strategy for silver-catalyzed and PIDA-mediated sequential reactions.

At the outset of our studies, various silver catalysts were tested by heating the mixture of dimethyl but-2-ynedioate (**1a**) and benzylamine (**2a**) using PIDA as the oxidant in dioxane at 100 °C (Table 1), and the expected tetramethyl 1-benzyl-1*H*-pyrrole-2,3,4,5-tetracarboxylate (**3aa**) was indeed obtained. Among the salts we tested, silver tetrafluoroborate ($AgBF_4$) showed the highest activity for this reaction (Table 1, entries 1−5). A survey of solvents indicated that this reaction was sensitive to the solvent medium (Table 1, entries 6−10). Among the various solvents examined, dioxane, 1,2-dichloroethane (DCE), and acetonitrile (CH_3CN) were practical for this transformation (Table 1, entries 1, 9, and 10). The reaction time had an obvious effect on this reaction, and the suitable time was 3 h (Table 1, entries 1, 12, and 13). The dosage of PIDA had no significant impact on the reaction, and the best result was obtained when the amount of PIDA was 1.2 equiv (Table 1, entries 12, 14, and 15).

Table 1. Optimization of Reaction Conditions[a]



1a 2a 3aa

entry	catalyst (5 mol %)	solvent	temp (°C)	time (h)	yield[b] (%)
1	$AgBF_4$	dioxane	100	2	75
2	AgOTf	dioxane	100	2	29
3	$AgClO_4$	dioxane	100	2	49
4	$AgNO_3$	dioxane	100	2	32
5	Ag_2CO_3	dioxane	100	2	63
6	$AgBF_4$	toluene	100	2	41
7	$AgBF_4$	DMSO	100	2	27
8	$AgBF_4$	DMA	100	2	22
9	$AgBF_4$	DCE	80	2	65
10	$AgBF_4$	acetonitrile	80	2	72
12	$AgBF_4$	dioxane	100	3	85
13	$AgBF_4$	dioxane	100	4	85
14[c]	$AgBF_4$	dioxane	100	3	89
15[d]	$AgBF_4$	dioxane	100	3	88

[a] **1a** (0.50 mmol), **2a** (0.25 mmol), solvent (2 mL), PIDA (1.0 equiv). [b] GC yield. [c] PIDA (1.2 equiv). [d] PIDA (2.0 equiv).

Under the optimized conditions, we explored the scope of the reaction, and the results are summarized in Table 2. Treatment of dimethyl but-2-ynedioate (**1a**) with various amines **2** furnished the corresponding pyrroles **3** in moderate to excellent isolated yields (Table 2, entries 1−12). As shown in Table 2, aromatic amines whether with electron-withdrawing groups or with electron-donating groups are all suitable for this protocol. Besides, the reaction appears quite tolerant with respect to the position of the substituent on the benzene ring of the aromatic amines. For example, the addition/oxidative cyclization of dimethyl but-2-ynedioate (**1a**) with *p*-toluidine (**2d**) or *m*-toluidine (**2e**) as well as dimethyl but-2-ynedioate (**1a**) with 4-chlorobenzenamine (**2g**) or 2-chlorobenzenamine (**2h**) led to pyrroles in reasonable yields (entries 4, 5, 7, and 8). However, the reaction is quite sensitive to the electronic contribution of the substituent on the benzene ring. For example, the reaction of dimethyl but-2-ynedioate (**1a**) with 4-methoxy-phenylamine (**2c**) afforded tetramethyl 1-(4-methoxyphenyl)-1*H*-pyrrole-2,3,4,5-tetracarboxylate (**3ac**) in 78% yield, while 4-fluorobenzenamine (**2f**) only resulted in tetramethyl 1-(4-fluorophenyl)-1*H*-pyrrole-2,3,4,5-tetracarboxylate (**3af**) in 53% yield. Interestingly, the amines bearing an aliphatic substituent proved to be a suitable partner. All the tested aliphatic amines resulted in excellent yields (Table 2, entries 1 and 9−12). Additionally, diethyl acetylenedicarboxylate (**1b**), methyl propiolate (**1c**), and ethyl but-2-ynoate (**1d**) can all react with benzylamine (**2a**) smoothly to give corresponding pyrroles in good yields (Table 2, entries 13−15).

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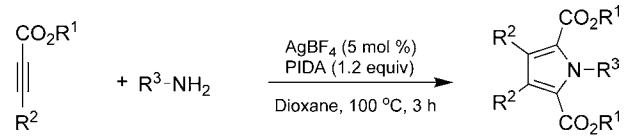
Table 2. Synthesis of Polysubstituted Pyrroles from Various Alkynoates and Amines[a]



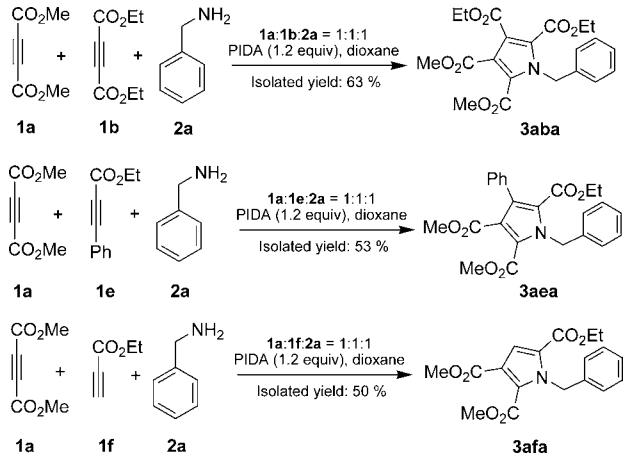
1a-1d 2a-2l 3aa-3al

	1	2		yield[b]
entry	(R^1; R^2)	(R^3)	product	(%)
1	**1a** (Me; CO_2Me)	**2a** ($PhCH_2$)	**3aa**	82
2	**1a**	**2b** (Ph)	**3ab**	67
3	**1a**	**2c** (p-$MeOC_6H_4$)	**3ac**	78
4	**1a**	**2d** (p-MeC_6H_4)	**3ad**	63
5	**1a**	**2e** (m-MeC_6H_4)	**3ae**	65
6	**1a**	**2f** (p-FC_6H_4)	**3af**	53
7	**1a**	**2g** (p-ClC_6H_4)	**3ag**	57
8	**1a**	**2h** (o-ClC_6H_4)	**3ah**	60
9	**1a**	**2i** (Me)	**3ai**	85
10	**1a**	**2j** (Et)	**3aj**	88
11	**1a**	**2k** [$(CH_2)_2CH_3$]	**3ak**	88
12	**1a**	**2l** [$(CH_2)_3CH_3$]	**3al**	87
13	**1b** (Et; CO_2Et)	**2a**	**3ba**	85
14	**1c** (Me; H)	**2a**	**3ca**	67
15	**1d** (Et; Me)	**2a**	**3da**	73

[a] **1** (1.0 mmol), **2** (0.5 mmol), PIDA (1.2 equiv), dioxane (2 mL). [b] Isolated yield.

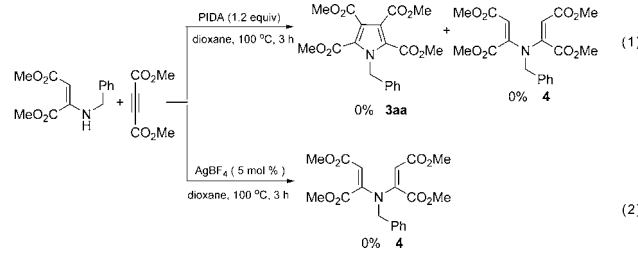
In light of the encouraging results, we then examined the scope of the sequential reactions of benzylamine with the crossed alkynoates. The reaction of dimethyl but-2-ynedioate (**1a**) with diethyl acetylenedicarboxylate (**1b**) and benzylamine (**2a**) led to 2,3-diethyl 4,5-dimethyl 1-benzyl-1*H*-pyrrole-2,3,4,5-tetracarboxylate (**3aba**) in 63% isolated yield (Scheme 1). Alternatively, **1e** and **1f** can also give reasonable

Scheme 1. Diversity of Polysubstituted Pyrrole Synthesis



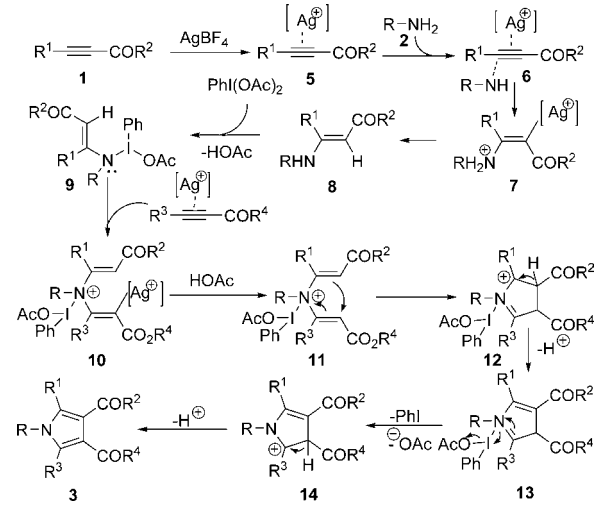
yields of the desired polysubstituted pyrroles. The successful sequential reactions are depicted in Scheme 1, which revealed that various substituted pyrroles can be designed and constructed via the control of the starting materials of alkyne.

To probe the mechanism of reaction, dimethyl 2-(benzylamino)maleate was employed to react with dimethyl but-2-ynedioate using PIDA as the oxidant in dioxane for 3 h at 100 °C; however, neither the desired product **3aa** nor the hydroamination product **4** of dimethyl 2-(benzylamino)maleate with dimethyl but-2-ynedioate was detected [eq 1]. Additionally, compound **4** which should be formed from the hydroamination of dimethyl 2-(benzylamino)maleate with dimethyl but-2-ynedioate was also not detected by GC/MS, even with 5 mol % of $AgBF_4$ as the catalyst [eq 2]. These results indicated that **4** could not be a potential intermediate in the transformation.



On the basis of these preliminary results, a plausible mechanism of this addition/oxidative cyclization was hypothesized as shown in Scheme 2. The first step involved

Scheme 2. Mechanistic Rationale for the Addition/Oxidative Cyclization Reaction



an activation of the C−C triple bond of the alkyne by Ag(I) to form intermediate **5**, which was followed by the addition of benzylamine resulting in the formation of enamine intermediate **8** and regeneration of the silver(I) catalyst. The intermediate **9**, generated by the action of the mild oxidant PIDA on amides **8**,[14] reacts with another activated alkyne and residue to a new intermediate **10**. The C−Ag bond in the intermediate **10** is protonated by acetic acid, and

nitrenium ion **11** is produced, which undergoes electrocyclic ring closure to give the carbocation **12** and the subsequent proton elimination to afford **13**.[15] Then, the C−I bond in **13** cleaves with concomitant electron-transfer to give another carbocation **14** by losing one molecule of iodobenzene and one molecule of acetate ion. Finally, the product **3** was formed by proton elimination.

In summary, we have established a facile and highly efficient C−N and C−C bond formation method to construct a pyrrole framework directly. In this protocol, various amines and alkynoates are suitable for this novel addition/oxidative cyclization sequential reaction. Therefore, this methodology not only provides a simple and convenient way to construct polysubstituted pyrrole derivatives but also opens a brand new way to build C−C and C−N bonds in a one-pot reaction. Furthermore, the readily accessible substrates, relatively cheap oxidant PIDA, and silver catalyst and moderate to excellent yields make the present reaction potentially useful in organic synthesis. Now, studies are ongoing in our laboratory to better understand the reaction mechanism and apply this C−C bond formation method to the synthesis of other heterocyclic compounds.

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Note Added after ASAP Publication. There was an error in the Table 1 graphic in the version published ASAP December 11, 2009; the corrected version published ASAP December 15, 2009.

Supporting Information Available: Full experimental details and copies of NMR spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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