



Synthesis of pyrrole-2,3,4,5-tetracarboxylates via a copper-catalyzed reaction of amine with but-2-ynedioate



Ling Zhang^{a,*}, Xianbo Wang^a, Shaoyu Li^b, Jie Wu^{b,*}

^a Department of Chemistry, Nanchang University, 999 Xuefu Road, Nanchang, Jiangxi 330031, China

^b Department of Chemistry, Fudan University, 220 Handan Road, Shanghai 200433, China

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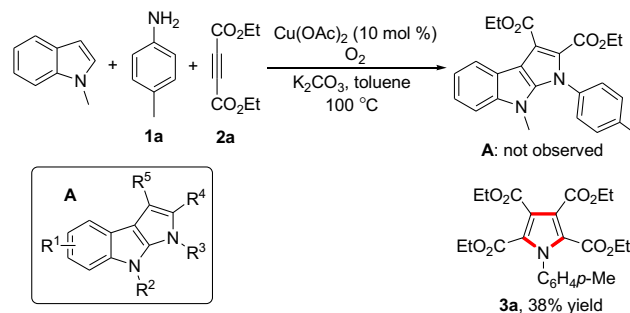
ABSTRACT

A copper-catalyzed reaction of amine with but-2-ynedioate gives rise to pyrrole-2,3,4,5-tetracarboxylates in moderate to good yields. The reaction proceeds in the presence of dioxygen with the formation of three bonds during the process.

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1. Introduction

It is well known that substituted pyrroles are an important class of heterocyclic compounds due to their remarkable biological and physical properties.¹ The pyrrole core can be found in many natural products (such as the lamellarin, ningalin, polycitane, lukianol, and storniamide classes of natural products),² as well as in agrochemicals (e.g., chlorfenapyr), pharmaceuticals (e.g., Lipitor), fluorescent dyes (e.g., BODIPY derivatives),³ and conducting polymers (e.g., polypyrroles).⁴ So far, cyclization reactions, such as the Knorr, Paal–Knorr, and Hantzsch reactions⁵ have been used as the most common route to pyrrole derivatives. Other strategies were also developed as alternative routes to pyrrole derivatives.^{6,7} Among the family of pyrroles, the dihydropyrrolo[2,3-*b*]indole core **A** has attracted much attention (Scheme 1), which is a widely distributed structural framework presented in a number of biologically active alkaloids⁸ (such as physostigmine,⁹ urchordamines,¹⁰ asperazine,¹¹ chimonanthines,¹² and leptosins¹³). Recently, we are interested in the construction of natural product-like compounds for different biological evaluations using tandem approaches.¹⁴ The interesting biological activities of the compounds with a dihydropyrrolo[2,3-*b*]indole core have made it as an attractive synthetic target. Therefore, we initiated a program for the generation of dihydropyrrolo[2,3-*b*]indole scaffold and its library construction.



Scheme 1. An unexpected reaction for the generation of pyrrole-2,3,4,5-tetracarboxylate.

The proposed synthetic route was presented in Scheme 1. Prompted by recent advances achieved in the [Cu]/O₂ system,^{15,16} we conceived that the dihydropyrrolo[2,3-*b*]indole scaffold could be constructed through a three-component reaction of indole, amine, and but-2-ynedioate under oxidative conditions. At the beginning, we studied a model reaction of 1-methylindole, *p*-toluidine **1a**, with diethyl but-2-ynedioate **2a** catalyzed by 10 mol% of Cu(OAc)₂ in the presence of dioxygen (Scheme 1). To our surprise, an unexpected pyrrole-2,3,4,5-tetracarboxylate **3a** was obtained instead of the desired dihydropyrrolo[2,3-*b*]indole **A**. From this result, we recognized that 1-methylindole was not involved in the reaction, and the pyrrole product **3a** came from the reaction of *p*-toluidine **1a** with 2.0 equiv of diethyl but-2-ynedioate **2a**.

* Corresponding authors. E-mail address: jie_wu@fudan.edu.cn (J. Wu).

2. Results/discussion

With this interesting result in hand, we started to explore the optimal conditions for this transformation (Table 1). Initially, the reaction was screened in various solvents in the presence of K_2CO_3 as base under reflux (Table 1, entries 1–5). The reaction worked efficiently in acetonitrile at 85 °C, which afforded the corresponding product **3a** in 41% yield (Table 1, entry 4). Different bases were examined subsequently (Table 1, entries 6–12). It seemed that the reaction using cesium carbonate gave a better result (58% yield) compared with other bases employed, although a comparable yield (57%) was obtained when *t*-BuONa was used in the reaction (Table 1, entry 12). The yield was increased to 74% when the reaction occurred at 70 °C (Table 1, entry 13). No better yields were obtained by evaluation of other copper salts (Table 1, entries 15–20). A control experiment without the addition of copper catalyst resulted in no reaction (Table 1, entry 21). The efficiency was retarded when the amount of copper(II) acetate was reduced to 5 mol% or the reaction was performed in air (Table 1, entries 22 and 23).

Table 1
Initial studies for the copper-catalyzed reaction of *p*-toluidine **1a** with diethyl but-2-ynedioate **2a**

Entry	[Cu]	Base	Solvent	Temp (°C)	Yield ^a (%)
1	Cu(OAc) ₂	K ₂ CO ₃	Toluene	100	38
2	Cu(OAc) ₂	K ₂ CO ₃	DMF	100	25
3	Cu(OAc) ₂	K ₂ CO ₃	1,4-Dioxane	100	27
4	Cu(OAc) ₂	K ₂ CO ₃	MeCN	85	41
5	Cu(OAc) ₂	K ₂ CO ₃	DCE	85	37
6	Cu(OAc) ₂	K ₃ PO ₄	MeCN	85	48
7	Cu(OAc) ₂	Cs ₂ CO ₃	MeCN	85	58
8	Cu(OAc) ₂	CSOAc	MeCN	85	35
9	Cu(OAc) ₂	NaOH	MeCN	85	54
10	Cu(OAc) ₂	DBU	MeCN	85	30
11	Cu(OAc) ₂	DABCO	MeCN	85	54
12	Cu(OAc) ₂	<i>t</i> -BuONa	MeCN	85	57
13	Cu(OAc) ₂	Cs ₂ CO ₃	MeCN	70	74
14	Cu(OAc) ₂	Cs ₂ CO ₃	MeCN	50	56
15	Cu(OTf) ₂	Cs ₂ CO ₃	MeCN	70	33
16	CuBr	Cs ₂ CO ₃	MeCN	70	44
17	CuI	Cs ₂ CO ₃	MeCN	70	47
18	CuCl	Cs ₂ CO ₃	MeCN	70	19
19	CuCl ₂	Cs ₂ CO ₃	MeCN	70	Trace
20	CuBr ₂	Cs ₂ CO ₃	MeCN	70	21
21	—	Cs ₂ CO ₃	MeCN	70	NR
22 ^b	Cu(OAc) ₂	Cs ₂ CO ₃	MeCN	70	42
23 ^c	Cu(OAc) ₂	Cs ₂ CO ₃	MeCN	70	25

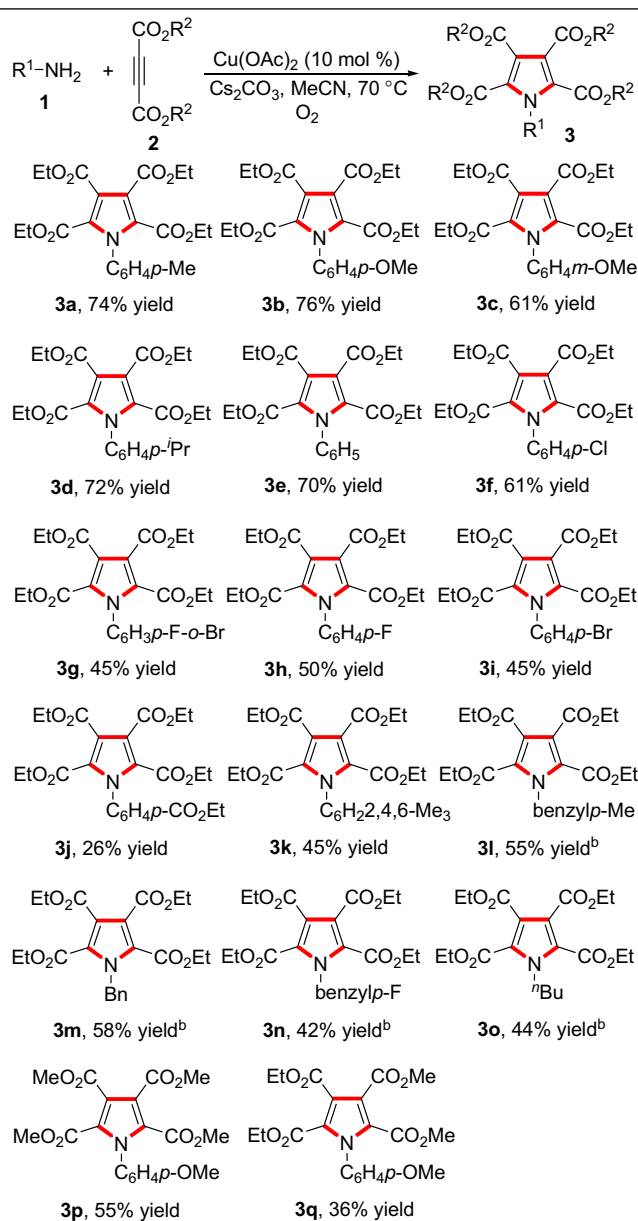
^a Isolated yield based on *p*-toluidine **1a**.

^b In the presence of 5 mol% of Cu(OAc)₂.

^c The reaction occurred in air.

The scope of this copper(II)-catalyzed tandem reaction of amines **1** with but-2-ynedioates **2** was then investigated under the optimized conditions (10 mol% of Cu(OAc)₂, Cs₂CO₃, MeCN, O₂ (balloon), 70 °C). The results are exemplified in Table 2. A range of pyrrole-2,3,4,5-tetracarboxylates **3** were obtained in moderate to good yields. Various anilines **1** were demonstrated to be tolerated in the transformation. However, the nature of the substituents on the aromatic ring of anilines **1** had effects for the final outcome. For instance, compound **3b** was furnished in 76% yield when 4-methoxybenzenamine was used in the reaction of diethyl but-2-ynedioate **2a**, while pyrrole-2,3,4,5-tetracarboxylate **3i** was generated in 45% yield when 4-bromobenzenamine was employed as a replacement. The ester group attached on the aniline was found to

Table 2
Synthesis of pyrrole-2,3,4,5-tetracarboxylates **3** via Cu(OAc)₂-catalyzed reaction of amine **1** with but-2-ynedioate **2**^a



^a Isolated yield based on amine **1**. ^b K₃PO₄ was used as the base.

be compatible under the standard conditions although the yield was low (**3j**, 26% yield). We also examined the steric bulky 2,4,6-trimethylaniline in the reaction with diethyl but-2-ynedioate **2a**, which produced the corresponding product **3k** in 45% yield. The yields were very low when aliphatic amines were utilized in the reactions. We thus re-explored the optimal conditions of aliphatic amines with but-2-ynedioate **2**. Finally, we identified the reactions worked efficiently when K₃PO₄ was used as the base. For instance, pyrrole-2,3,4,5-tetracarboxylate **3m** was formed in 58% yield when benzyl amine was involved in the reaction of diethyl but-2-ynedioate **2a**. *n*-Butyl amine was also a good reactant in this transformation, which gave rise to the expected product **3o** in 44% yield. 4-Methoxybenzenamine reacted with dimethyl but-2-ynedioate leading to the desired pyrrole **3p** in 55% yield. The structure of tetramethyl 1-(4-methoxyphenyl)-pyrrole-2,3,4,5-tetracarboxylate **3p** was unambiguously illustrated by X-ray diffraction analysis

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