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SHORT COMMUNICATION

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Copper(II)-Catalyzed [4+1] Annulation of Propargylamines with *N*,*O*-Acetals: Entry to the Synthesis of Polysubstituted Pyrrole Derivatives

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Described herein is the $CuCl_2$-catalyzed [4+1] annulation of a variety of propargylamines with *N*,*O*-acetals that function as a C1 unit, leading to the production of polysubstituted pyrrole derivatives. Three important features of the *N*,*O*-acetal during the [4+1] annulation series via *5-endo-dig* cyclization are described: an enolizable substituent adjacent to the central sp^3-carbon is required, the central sp^3-carbon displays the functions of both an electrophile and a nucleophile, and liberation of the secondary amine smoothly leads to the aromatization.

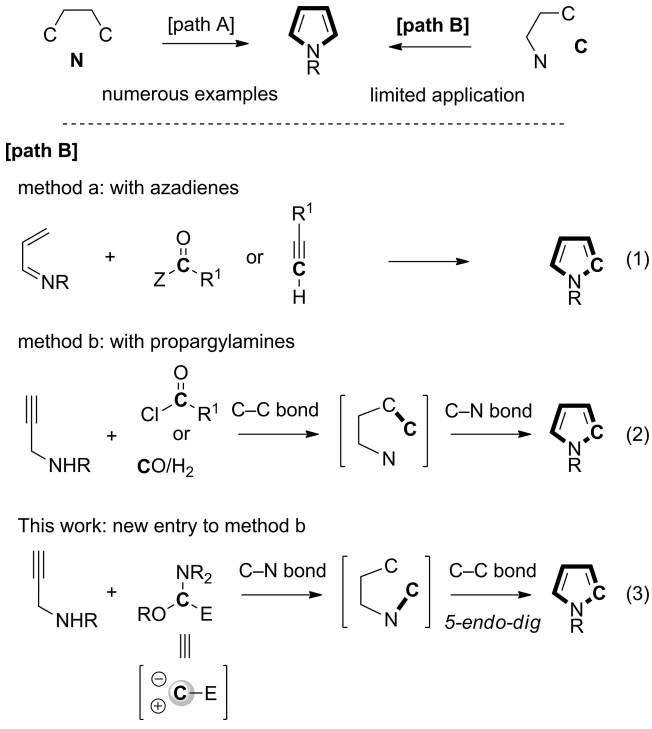
Introduction

The preparation of polysubstituted pyrrole derivatives has attracted considerable attention in organic and pharmaceutical chemistry, because the main framework of the nitrogen-containing five-membered rings occurs in many natural products, biologically active substances, and functional materials.[1] Hence, a number of approaches involving Hantzsch synthesis ([2+2+1] annulation),[2] Piloty–Robinson synthesis ([2+2+1] annulation),[3] and Barton–Zard synthesis ([3+2] annulation)[4] have been developed for the preparation of this unique skeleton.

Two well-known representative methods for the preparation of substituted pyrrole derivatives through [4+1] annulation (path A in Scheme 1) are the Parr–Knorr pyrrole method by the cyclocondensation of a 1,4-diketone with a primary amine or ammonia under acidic conditions[5] and the Clauson–Kaas reaction through the acid-promoted condensation of 2,5-dimethoxytetrahydrofuran and a primary amine.[6] In both [4+1] approaches, one of the five constituent atoms is constructed from a primary amine (or ammonia) as an N1 unit, and the remaining four atoms are derived from a carbon atom. On the basis of these approaches, a number of modified [4+1] preparations leading to the preparation of a pyrrole skeleton have been disclosed (path A in Scheme 1).[7]

In contrast to the above examples, an effective construction of a pyrrole framework by a combination of compounds composed of a [C–C–C–N] unit with a carbon-source compound as a C1 unit has not been investigated extensively and is limited to only a few methods (path B in Scheme 1). For example, Pedersen et al. reported that $NbCl_3$(DME) promoted the annulation of 1-azadine derivatives with esters or *N*,*N*-dimethylformamide (DMF), producing the pyrrole derivatives (path B1 in Scheme 1).[8]

Iwasawa and co-workers also disclosed a catalytic preparation of pyrrole derivatives via the Rh^I-catalyzed [4+1] annulation of 1-azadines with terminal alkynes (path B1 in Scheme 1).[9] Moreover, a phosphine-mediated annulation of 1-azadines with acid chlorides has been reported by



Scheme 1. Divergent approaches to a pyrrole framework via a [4+1] annulation.

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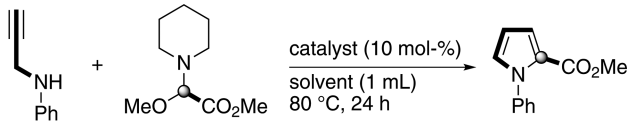
Arndtsen et al. (path B1 in Scheme 1).[10] In other approaches to [4+1] annulation, Müller has reported that a coupling of propargylamines and acid chlorides and subsequent intramolecular cyclocondensation of the alkynone intermediate leads to the preparation of pyrrole derivatives,[11] and the Rh-catalyzed hydroformylation of propargylamines with H_2/CO gas has been reported by Campi (path B2 in Scheme 1).[12] In both cases with a propargylamine, the terminal alkyne carbon is initially bonded to a C1 unit, followed by the intramolecular formation of a C–N bond to construct a pyrrole ring.

As a preliminary result, however, we developed the copper-catalyzed [5+1] annulation of 2-ethynylanilines with an *N*,*O*-acetal with an ester group, which functions as a glycine cation equivalent,[13] leading to the preparation of 2-ester-substituted quinoline derivatives, although the *N*,*O*-acetal used in this transformation was limited to a single substrate with the ester group.[14] Herein we report the unprecedented example of a copper-catalyzed [4+1] annulation of propargylamines with *N*,*O*-acetals, wherein the central sp^3-carbon functions as both an electrophile and a nucleophile, leading to the preparation of polysubstituted pyrrole derivatives via 5-*endo*-*dig* cyclization (path B3 in Scheme 1). The single-step preparation of nitrogen-containing aromatic heterocycles, such as pyrrole, via 5-*endo*-*dig* intramolecular cyclization is extremely rare compared with that of carbocycles through a Conia-ene-type cyclization.[15–17] The present method permits the unique preparation of a variety of polysubstituted pyrrole derivatives.

Results and Discussion

Initially, as a model reaction, the intermolecular annulation of *N*-phenylpropargylamine (**1a**) with *N*,*O*-acetal **2a**, which was prepared from methyl 2-bromo-2-methoxyacetate and piperidine,[18] was examined in the presence of a variety of metal catalysts in 1,4-dioxane (Table 1). For instance, when the reaction was carried out with group 2, 3, and 4 metals such as $MgCl_2$, $Yb(OTf)_3$, and $HfCl_4$ as catalysts, the expected annulation did not occur, and only decomposition of the *N*,*O*-acetal was observed (entries 1–3). Although late transition metals such as $FeCl_2$, $FeCl_3$, and $NiCl_2$ did not function as Lewis acids for the annulation, $CoCl_2$ gave a trace amount of the expected pyrrole derivative **3aa** (entries 4–7). $ZnCl_2$ also produced a small amount of the pyrrole, but group 13 metals, such as $GaCl_3$ and $InCl_3$, led to a complex mixture (entries 8–10). It is noteworthy that when the reaction was conducted with CuCl, the yield of the pyrrole was dramatically improved to 64% yield (entry 11). Also, the use of $CuCl_2$ increased the yield slightly (entry 12). However, CuBr and $CuBr_2$ led to a decrease in the product yield; in particular, a strong Lewis acidic $Cu(OTf)_2$ did not give the product (entries 13–15). Then, upon examination of several solvents such as THF, CH_3CN, and DMF, besides 1,4-dioxane, the most effective ones were found to be toluene and 1,2-dichloroethane (entries 16 and 17). Raising the reaction temperature to 100 °C shortened the reaction time to 2 h and decreased the equivalent of $CuCl_2$ to 5 mol-% (entries 18 and 19). When annulation was carried out by using a Brønsted acid, HCl, instead of $CuCl_2$, the corresponding pyrrole was not obtained, which definitively showed that copper(II) chloride effectively promoted the annulation series (entry 20).

Table 1. Examination of the reaction conditions.



1a (1.1 equiv.) **2a** (0.4 mmol) **3aa**

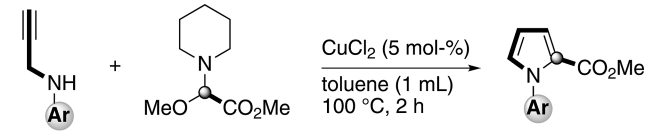
Entry	Catalyst	Solvent	Yield [%][a]
1	$MgCl_2$	1,4-dioxane	ND[b]
2	$Yb(OTf)_3$	1,4-dioxane	ND
3	$HfCl_4$	1,4-dioxane	ND
4	$FeCl_2$	1,4-dioxane	ND
5	$FeCl_3$	1,4-dioxane	ND
6	$CoCl_2$	1,4-dioxane	trace (19)[c]
7	$NiCl_2$	1,4-dioxane	ND
8	$ZnCl_2$	1,4-dioxane	trace
9	$GaCl_3$	1,4-dioxane	ND
10	$InCl_3$	1,4-dioxane	ND
11	CuCl	1,4-dioxane	64
12	$CuCl_2$	1,4-dioxane	(67)
13	CuBr	1,4-dioxane	53
14	$CuBr_2$	1,4-dioxane	48
15	$Cu(OTf)_2$	1,4-dioxane	trace
16	$CuCl_2$	1,2-DCE[g]	65
17	$CuCl_2$	toluene	72
18[d]	$CuCl_2$	toluene	80
19[e]	$CuCl_2$	toluene	(86)
20	HCl[f]	toluene	ND

[a] NMR (Isolated) yield. [b] ND: not determined. [c] $CoBr_2$ (10 mol-%). [d] 100 °C, 2 h. [e] **1a** (0.4 mmol), **2a** (0.44 mmol), $CuCl_2$ (5 mol-%), 100 °C, 2 h. [f] HCl in MeOH (2 M). [g] 1,2-Dichloroethane.

To expand the scope of this annulation, the reaction of propargylamines **1**, possessing a variety of aryl groups, with *N*,*O*-acetal **2a** was examined under the optimized conditions (Table 2). With no relationship to the electronic effect of an aryl group on propargylamines, most reactions were completed within 2 h to give the *N*-arylated 2-substituted pyrrole derivatives **3ba**–**3ma** in moderate to good yields. Also, the steric effect of an *o*-substituted methyl group did not have a strong effect on the chemical yield. However, when the reaction of propargylamine **1g**, which had a hydroxy group on the benzene ring, with *N*,*O*-acetal **2a** was treated under the optimized conditions, the expected pyrrole was not obtained. In this context, the use of propargylamine (**1n**) did not give the expected *N*-unsubstituted pyrrole (entry 13).

The preparation of 1,2-di- or 1,2,5-trisubstituted pyrrole derivatives was then examined with several propargylamines **1** that possessed a substituent group next to an amino group (Table 3). In most cases, when propargylamines possess either an aliphatic or an aromatic group, the corresponding 1,2,5-trisubstituted pyrrole

Table 2. The synthesis of *N*-arylated pyrrole derivatives using a variety of *N*-arylpropargylamines.



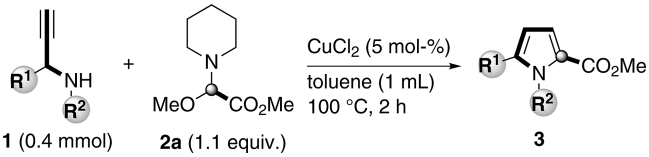
1 (0.4 mmol) **2a** (1.1 equiv.) **3**

Entry	Propargylamine **1** Ar		Yield of **3** [%][a]
1	**1b**	*o*-MeC_6H_4	**3ba** 86
2	**1c**	*m*-MeC_6H_4	**3ca** 80
3	**1d**	*p*-MeC_6H_4	**3da** 80
4	**1e**	*p*-$Me_2NC_6H_4$	**3ea** 81
5	**1f**	*p*-$MeOC_6H_4$	**3fa** 90
6	**1g**	*o*-HOC_6H_4	**3ga** CM[b]
7	**1h**	*p*-FC_6H_4	**3ha** 81
8	**1i**	*p*-ClC_6H_4	**3ia** 87
9	**1j**	*p*-BrC_6H_4	**3ja** 83
10	**1k**	*p*-$CF_3C_6H_4$	**3ka** 84
11	**1l**	*p*-AcC_6H_4	**3la** 77
12	**1m**	*p*-NCC_6H_4	**3ma** 70
13	**1n**	H	**3na** ND[c]

[a] Isolated yield. [b] CM: complex mixture. [c] ND: not determined.

derivatives **3pa**–**3ta** are produced in relatively good to excellent yields (entries 1–5). When the reaction was carried out with *N*-*tert*-butyl-substituted propargylamine **1o**, however, the yield of the corresponding 1,2-disubstituted pyrrole derivative **3ta** was 31% (entry 6). However, when several substituents, such as a phenyl, an *n*-butyl, an ester, and a trimethylsilyl group, were introduced into the terminal alkyne moiety on a propargylamine, the expected [4+1] annulation unfortunately did not occur to produce the corresponding pyrrole derivative with a decomposition of both starting materials. These results were probably due to the fact that a steric effect of the introduced substituent hindered the intramolecular cyclization of the expected intermediate.

Table 3. The synthesis of 1,2-di- or 1,2,5-trisubstituted pyrrole derivatives using a variety of propargylamines.



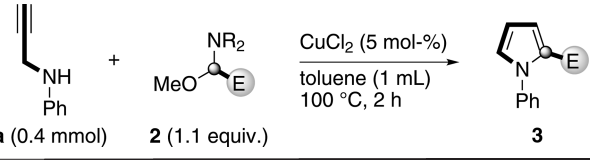
1 (0.4 mmol) **2a** (1.1 equiv.) **3**

Entry	Propargylamine **1** R^1	R^2	Yield of **3** [%][a]
1	**1o** $PhCH_2CH_2$	Ph	**3oa** 70
2	**1p** *c*-hexyl	Ph	**3pa** 60
3	**1q** Ph	Ph	**3qa** 90
4	**1r** *p*-MeC_6H_4	Ph	**3ra** 91
5	**1s** *p*-ClC_6H_4	Ph	**3sa** 77
6	**1t** H	*t*Bu	**3ta** 31

[a] Isolated yield.

To expand on the scope and overcome the limitations of *N*,*O*-acetal **2** as a substrate, the annulation of propargylamine **1a** with several other *N*,*O*-acetals was carried out under our optimized conditions (Table 4). Any type of amine moiety on *N*,*O*-acetal **2b** that functioned as a leaving group had no significant effect on the subsequent annulation (entry 1). The use of *N*,*O*-acetals with a ketone or an amide group produced the corresponding pyrrole derivatives **3ac** and **3ad** in moderate to good yields (entries 2 and 3). In contrast, when using *N*,*O*-acetals with a phenyl group or without a substituent, the desired annulation did not occur (entries 4 and 5). These results strongly implied that the enolization of an ester, a ketone, or an amide portion of an *N*,*O*-acetal is key in the [4 +1] annulation series.

Table 4. Scope and limitations of an *N*,*O*-acetal.

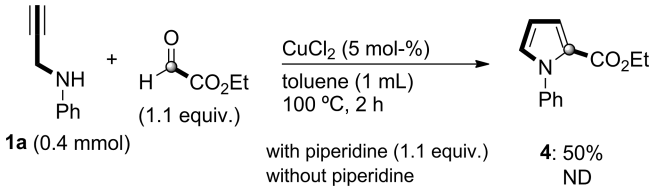


1a (0.4 mmol) **2** (1.1 equiv.) **3**

Entry	*N*,*O*-Acetal **2** R	E	Yield of **3** [%][a]
1	**2b** Et	CO_2Me	**3aa** 85
2[b]	**2c** $-(CH_2)_5-$	COPh	**3ac** 43
3[b]	**2d** $-(CH_2)_5-$	$CONR_2$[c]	**3ad** 58
4	**2e** $-(CH_2)_5-$	Ph	**3ae** ND[d]
5	**2f** $-(CH_2)_5-$	H	**3af** ND

[a] Isolated yield. [b] Unpurified *N*,*O*-acetal was used, because of decomposition during a common purification. [c] NR_2 = a piperidinyl group. [d] ND: not determined.

The direct preparation of a pyrrole derivative by the $CuCl_2$-catalyzed coupling of a propargylamine with a glyoxylate ester in the presence of a secondary amine was attempted (Scheme 2). First, when the reaction mixture of *N*-phenylpropargylamine (**1a**), ethyl glyoxylate, and piperidine was treated under our optimized conditions, the expected pyrrole derivative **4** was obtained in 50% yield. Without piperidine, however, the same conditions would not yield pyrrole **4**. These results definitely showed that an in situ formation of an *N*,*O*-hemiacetal intermediate from piperidine and ethyl glyoxylate initially occurs, then an intermolecular substitution of the hemiacetal intermediate with a propargylamine proceeds to produce the corresponding *N*,*N*-aminal intermediate.

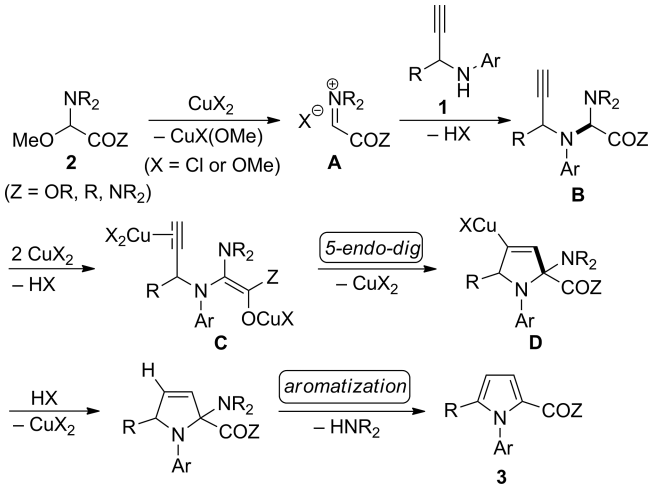


1a (0.4 mmol)

Scheme 2. Copper(II)-catalyzed direct coupling reaction of *N*-phenylpropargylamine with ethyl glyoxylate.

On the basis of these results, a plausible mechanism for the [4+1] annulation of propargylamines with *N*,*O*-acetals is shown in Scheme 3. First, the copper catalyst activates an oxygen atom of *N*,*O*-acetal **2** to generate iminium intermediate **A**. Second, the nitrogen atom on propargylamine **1**

nucleophilically attacks the iminium, which leads to the production of *N*,*N*-aminal intermediate **B**. Third, the reaction of the intermediate with the copper catalyst generates copper enolate intermediate **C**, and the intermediate undergoes *5-endo-dig* intramolecular cyclization to construct the nitrogen-containing five-membered ring skeleton **D**. This mechanism also implies that the copper catalyst would simultaneously activate a relatively soft electrophile, a carbon–carbon triple bond moiety on intermediate **C**, facilitating intramolecular cyclization. This discussion is supported by the fact that an *N*,*O*-acetal either with a non-enolizable group, such as a phenyl or a nitrile group, or without a substituted group did not yield the expected pyrrole derivative (see Table 4) and that the expected [4+1] annulation did not proceed without the copper catalyst. Finally, both protonation and aromatization through the liberation of a secondary amine of ring product **D** occurred to produce the corresponding pyrrole derivative **3**, along with a regeneration of the copper(II) catalyst.



Scheme 3. A plausible reaction mechanism for copper-catalyzed [4+1] annulation.

Conclusions

In summary, we have demonstrated the copper(II)-catalyzed [4+1] annulation of propargylamines with *N*,*O*-acetals that possess an ester, a ketone, and an amide unit, leading to the facile production of polysubstituted pyrrole derivatives. The key to this [4+1] annulation series is the use of an *N*,*O*-acetal that can be enolizable. Also, we have disclosed significant results: (1) with the copper catalyst, these *N*,*O*-acetals effectively function as a C1 unit of a pyrrole skeleton; (2) the central sp^3-carbon displays the functions of both an electrophile and a nucleophile; and (3) the annulation series was achieved through both *5-endo-dig* cyclization and a subsequent aromatization. Furthermore, we have demonstrated the copper(II)-catalyzed direct coupling reaction of a propargylamine and ethyl glyoxylate in the presence of a secondary amine, leading to the production of a pyrrole derivative.

Experimental Section

General Procedure for the Synthesis of Pyrrole Derivatives with 1 and 2: In a glove box, $CuCl_2$ (0.0200 mmol, 2.69 mg) was weighed directly into a screw-glass vial. The vial was sealed with a PTFE sealed screw cap under a N_2 atmosphere and was removed from the glove box. To the vial were successively added a magnetic stirring bar, distilled toluene (1 mL), propargylamine **1** (0.400 mmol), and *N*,*O*-acetal **2** (0.440 mmol). The solution was stirred at 100 °C for 2 h. After the reaction, the resultant mixture was filtered through a pad of silica gel. The filtrate was purified by silica gel chromatography (hexane/AcOEt = 9:1) to give the corresponding pyrrole derivative **3**.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures and characterization data for the products obtained by this method and copies of the ^1H and ^{13}C NMR spectra of the products.

Acknowledgments

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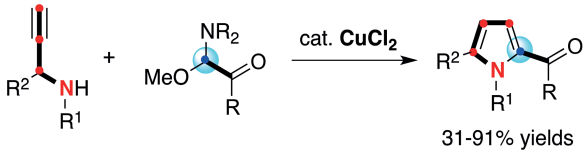
Pyrrole Synthesis



A $CuCl_2$-catalyzed [4+1] annulation of propargylamines with *N*,*O*-acetals having an ester, a ketone, and an amide moiety, leading to the facile preparation of polysubstituted pyrrole derivatives is presented. This annulation series was achieved through *5-endo-dig* cyclization and subsequent aromatization in one pot.

Keywords: Annulation / Pyrroles / Acetals / Copper / Propargylamines / Cyclization

