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Copper-Catalyzed Tandem Reactions of 1-(2-Iodoary)-2-yn-1-ones with Isocyanides for the Synthesis of 4-Oxo-indeno[1,2-*b*]pyrroles

Qian Cai,* Fengtao Zhou, Tianfeng Xu, Liangbing Fu, and Ke Ding*

Key Laboratory of Regenerative Biology and Institute of Chemical Bioology,
Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences,
No. 190 Kaiyuan Avenue, Guangzhou Science Park, Guangzhou, 510530, China

cai_qian@gibh.ac.cn; ding_ke@gibh.ac.cn

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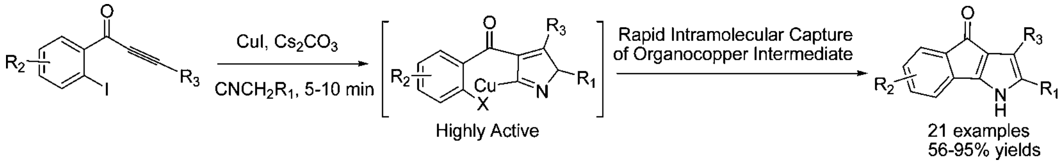
ABSTRACT



A novel copper-catalyzed tandem reaction of 1-(2-iodoaryl)-2-yn-1-ones with isocyanides is described. The reaction is through a formal [3 + 2] cycloaddition/coupling tandem process and leads to efficient formation of 4-oxo-indeno[1,2-*b*]pyrroles.

A large demand exists in drug discovery and other types of research programs for novel, structurally diverse molecules. This demand continues to stimulate the development of conceptually innovative synthetic strategies. Tandem or multicomponent reactions of isocyanides,[1] which form multiple bonds in a one-pot manner, have remarkable versatility in producing structurally appealing heterocycles. Since the time of the initial discoveries by Schöllkopf and Gerhart about 40 years ago,[2] α-metalated isocyanides have been observed to participate in various types of cycloaddition reactions that lead to a diverse array of nitrogen-heterocycles.[3] Recently, great progress has been made in the use of transition-metal-catalyzed reactions of isocyanides.[4,5] The transition-metal-catalyzed cycloaddition reactions of isocyanides with double or trible bonds were proposed to go through a formal [3 + 2] process involving organometal intermediates, which are highly active and undergo rapid protonation to form the stable cyclized products, such as pyrrolines, oxazolines, etc.[3−6] One example was independently reported by de Meijere et al.[5e] and Yamamoto et al.:[5f] oligosubstituted pyrroles can be readily prepared by using copper-catalyzed cycloaddtion reactions of isocyanides with electron-deficient alkynes. A cyclized organocopper intermediate was proposed to be invloved in these reactions. However, no further work extensions of these highly active organometal intermediates were reported. Perhaps this is

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[1] For comprehensive reviews, see: (a) Marcaccini, S.; Torroba, T. *Org. Prep. Proced. Int.* **1993**, *25*, 141. (b) Dömling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3168. (c) Dömling, A. *Chem. Rev.* **2006**, *106*, 17.

[2] Schöllkopf, U.; Gerhart, F. *Angew. Chem., Int. Ed.* **1968**, *7*, 805.

[3] For a review, see: Gulevich, A. V.; Zhdanko, A. G.; Orru, R. V. A.; Nenajdenko, V. G. *Chem. Rev.* **2010**, *110*, 5235.

[4] For representative examples of transition metal-catalyzed reaction of isocyanides, see: (a) Takaya, H.; Kojima, S.; Murahashi, S. *Org. Lett.* **2001**, *3*, 421. [Rh](b) Motoyama, Y.; Kawakami, H.; Shimozono, K.; Aoki, K.; Nishiyama, H. *Organometallic* **2002**, *21*, 3408. [Pt, Rh](c) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405. [Au](d) Sawamura, M.; Hamashima, H.; Ito, Y. *J. Org. Chem.* **1990**, *55*, 5935. [Ag].

[5] For representative copper-catalyzed reaction of isocyanides, see: (a) Lygin, A. V.; Larionov, O. V.; Korotkov, V. S.; de Meijere, A. *Chem.—Eur. J.* **2009**, *15*, 227. (b) Bonin, M.-A.; Giguère, D.; Roy, R. *Tetrahedron* **2007**, *63*, 4912. (c) Kanazawa, C.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2006**, *128*, 10662. (d) Benito-Garagorri, D.; Bocokiae, V.; Kirchner, K. *Tetrahedron Lett.* **2006**, *47*, 8641. (e) Larionov, O. V.; de Meijere, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 5664. (f) Kamijo, S.; Kanazawa, C.; Yamamoto, Y. *J. Am. Chem. Soc.* **2005**, *127*, 9260. (g) Ito, Y.; Matsurra, T.; Saegusa, T. *Tetrahedron Lett.* **1985**, *26*, 5781. (h) Saegusa, T.; Ito, Y.; Kinoshita, H.; Tomita, S. *J. Org. Chem.* **1971**, *36*, 3316.

[6] Schöllkopf, U. *Angew. Chem., Int. Ed.* **1977**, *16*, 339.

10.1021/ol102826f

because the organometal intermediate is too active to be available long enough for further transformation.

In the past decade, copper-catalyzed coupling reactions[7] have come into a renaissance. However, copper-catalyzed aryl C−C formation reactions are still great chanllenges and the reaction scope is relatively limited. Novel aryl C−C bond formation reactions are highly attractive in copper-catalyzed coupling chemistry. In conjunction with our continuing interest in the area of copper-catalyzed coupling chemistry,[8] we realized that the organocopper intermediate produced in isocyanide chemistry may also act as some kind of active substrate for further aryl C−C coupling.[9] Below, we describe the results of an effort aimed at exploring and developing a novel copper-catalyzed tandem reaction based on this hypothesis, which demonstrates that the process comprises a facile method for the synthesis of 4-oxo-indeno[1,2-*b*]pyrrole derivatives (Scheme 1).[10]

Scheme 1. Design of Copper-Catalzyed Tandem Reaction through Rapid Intramolecular Capture of Highly Active Organocopper Intermediate

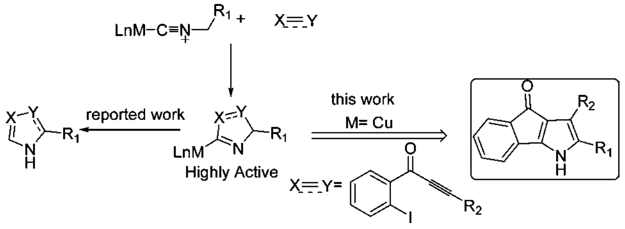
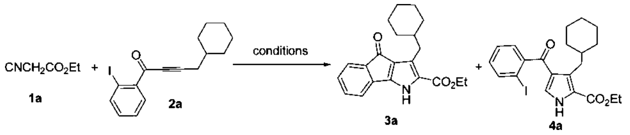


Table 1. Synthesis of Ethyl 3-(Cyclohexylmethyl)-4-oxo-1,4-dihydroindeno[1,2-*b*]pyrrole-2-carboxylate **3a** by Using the Copper-Catalyzed Tandem Reaction[a]



					yield[b]	
entry	catalyst	base	solvent	*t* (°C)	**3a**%	**4a**%
1		Cs_2CO_3	DMF	90	n.d.[c]	81[d]
2	CuI	−	DMF	100	n.d.[c]	15[d]
3	CuI	Cs_2CO_3	DMF	r.t.	62	35
4	CuI	Cs_2CO_3	DMF	60	76	20
5	**CuI**	$\mathbf{Cs_2CO_3}$	**DMF**	**90**	**93**	**trace**
6	CuBr	Cs_2CO_3	DMF	90	76	19
7	Cu_2O	Cs_2CO_3	DMF	90	n.d.[c]	40
8	CuI	Cs_2CO_3	Dioxane	90	n.d.[c]	90
9	CuI	Cs_2CO_3	MeCN	90	n.d.[c]	89
10	CuI	Cs_2CO_3	DMSO	90	77	15
11	CuI	K_2CO_3	DMF	90	20	75
12	CuI	NaOH	DMF	90	34	28

[a] **1a** (0.55 mmol, 1.1 equiv), **2a** (0.5 mmol, 1.0 equiv), catalyst (10 mol %), base, (1.0 mmol, 2.0 equiv), solvent (1 mL), 10 min. [b] Isolated yields. [c] No desired product was detected. [d] 2−6 h.

The investigation was initiated by exploring the copper-catalyzed reaction of ethyl isocyanoacetate **1a** with 4-cyclohexyl-1-(2-iodophenyl)but-2-yn-1-one **2a**. No desired coupling product 4-oxo-indeno[1,2-*b*]pyrrole **3a** was detected in the absence of either a necessary base or copper catalyst, and the only product was the protonated pyrrole **4a** (Table 1, entries 1 and 2). However, with the assistance of Cs_2CO_3, the reaction was completed in several minutes and 62% of the desired product **3a** was obtained in DMF at room temperature, accompanied by 35% of protonolysis byproduct **4a** (Table 1, entry 3). Although the selectivity was low, however, it confirmed our assumption that the proposed highly active organocopper intermediate can be rapidly captured through an intramolecular aryl C−C coupling reaction, which greatly inspired us for further studies. In order to increase the selectivity of insertion to the aryl C−I bond, further screenings of reaction conditions were performed, which revealed that the combination of CuI, Cs_2CO_3, and DMF is the best choice for the tandem reaction and the reaction temperature played a critical role in the selectivity (Table 1, entry 5). We found that a higher temperature can greatly increase the ratio of coupling product **3a**, which can reach 73% at 60 °C and 93% at 90 °C, with only a trace amount of byproduct **4a** being detected. The use of other Cu(I) sources or organic solvents led to lower yields and/or poorer **3a**:**4a** selectivity (Table 1, entries 6−12).

An exploratory study evaluating the scope of the new methodology provided the results displayed in Table 2. The observations show that in most cases the desired 4-oxo-indeno[1,2-*b*]pyrrole products **3** are produced in good to excellent yields when using 1-(2-iodoaryl)ynones as substrates.[11] Alkyl and functionalized alkyl substituents on the alkyne moieties of the alkynylketones **2** were well tolerated, and the reactions selectively formed the desired tandem products **3** in excellent yields. However, when aryl groups are present on the alkyne carbons of **2**, the processes take place in only moderate yields (Table 2,

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[7] For recent reviews about copper-catalyzed coupling reactions, see: (a) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Beletskaya, I. P.; Cheprakov, A. V. *Coord. Chem. Rev.* **2004**, *248*, 2337. (c) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054. (d) Monnier, F.; Taillefer, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 6954. (e) Ma, D.; Cai, Q. *Acc. Chem. Soc.* **2008**, *41*, 1450.

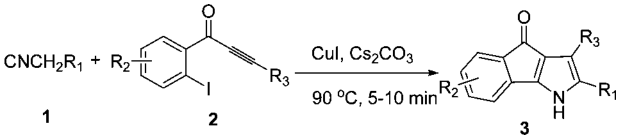
[8] (a) Cai, Q.; Li, Z.; Wei, J.; Fu, L.; Ha, C.; Pei, D.; Ding, K. *Org. Lett.* **2010**, *12*, 1500. (b) Li, Z.; Fu, L.; Wei, J.; Ha, C.; Pei, D.; Cai, Q.; Ding, K. *Synthesis* **2010**, 3289. (c) Cai, Q.; Li, Z.; Wei, J.; Ha, C.; Pei, D.; Ding, K. *Chem. Commun.* **2009**, 7581.

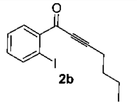
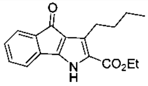
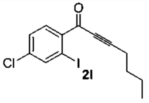
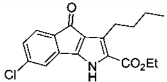
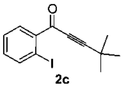
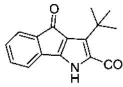
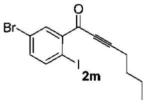
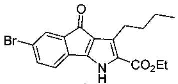
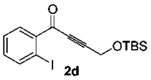
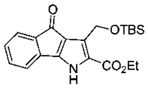
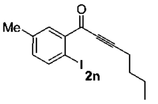
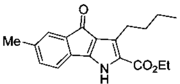
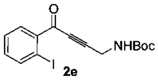
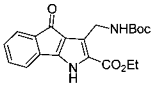
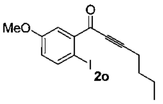
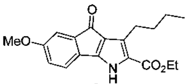
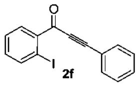
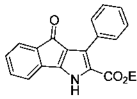
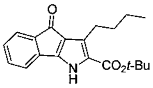
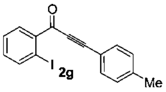
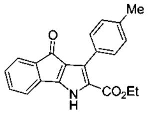
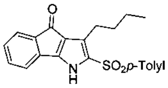
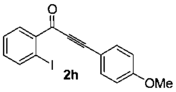
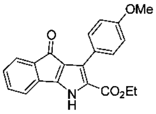
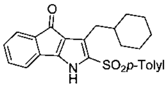
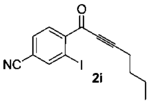
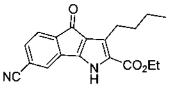
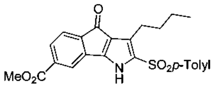
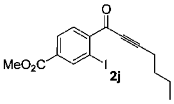
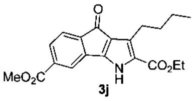
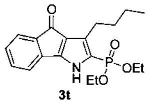
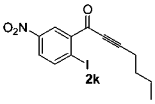
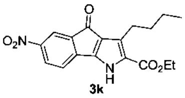
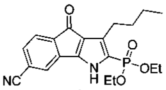
[9] In the reaction of o-iodophenols with ethyl propiolate, an intermediate cupriated benzofuran was proposed to go through intermolecular coupling with additional *o*-iodophenol in the presence of an excess of copper(I) *tert*-butoxide, and the product lactonized to isocoumestan. See: Haglund, O.; Nilsson, M. *Synlett.* **1991**, 723.

[10] For some examples of syntheses of indeno[1,2-*b*]pyrrole systems, see: (a) Lash, T. D.; Quizon-Colquitt, D. M.; Shiner, C. M.; Nguyen, T. H.; Hu, Z. *Energy Fuels* **1993**, *7*, 172. (b) Chatterjie, N.; Shapiro, R.; Quo, S.-G.; Stephani, R. A. *Tetrahedron Lett.* **1975**, *30*, 2535. (c) Azizian, J.; Hatamjafari, F.; Karimi, A. R.; Shaabanzadeh, M. *Synthesis* **2006**, *5*, 765. (d) Wollweber, H.-J.; Wentrup, C. *J. Org. Chem.* **1985**, *50*, 2041. (e) Bös, M.; Jenck, F.; Martin, J. R.; Moreau, J.-L.; Sleight, A. J.; Wichmann, J.; Widmer, U. *J. Med. Chem.* **1997**, *40*, 2762.

[11] Poor results were obtained (25−30% yields) when 1-(2-bromophenyl)ynones were used as substrates.

Table 2. Investigation of the Scope of Reactions of 1-(2-Iodoaryl)-2-yne-1-ones **2** with Isocyanides **1** Leading to Formation of 4-Oxo-indeno[1,2-*b*]pyrroles **3**[a]



entry	substrate **2**	product	yield (%)[b]	entry	substrate **2**	product	yield (%)
1	 **2b**	 **3b**	95[c]	11	 **2l**	 **3l**	80
2	 **2c**	 **3c**	90[c]	12	 **2m**	 **3m**	82
3	 **2d**	 **3d**	85	13	 **2n**	 **3n**	80
4	 **2e**	 **3e**	81	14	 **2o**	 **3o**	81
5	 **2f**	 **3f**	65[d]	15	2b	 **3p**	91
6	 **2g**	 **3g**	65[d]	16	2b	 **3q**	65
7	 **2h**	 **3h**	64[d]	17	2a	 **3r**	61
8	 **2i**	 **3i**	88	18	2b	 **3s**	65
9	 **2j**	 **3j**	87	19	2b	 **3t**	62
10	 **2k**	 **3k**	78	20	2b	 **3u**	56

[a] For entries 1−14, ethyl isocyanoacetate **1a** wa used; for entry 15, *tert*-butyl isocyanoacetate **1b** was used; for entries 16−18, TOSMIC **1c** was used; for entries 19−20, diethyl isocyanomethylphosphonate **1d** was used. [b] Isolated yields. [c] For 1-(2-bromophenyl)-2-yn-1-ones, about 25−30% yields of coupling products **3b** and **3c** were isolated. [d] About 20−30% of corresponding uncoupling byproducts were isolated.

3f−3h), and about 30% of the protonated byproducts were isolated. The results also show that the electronic properties of the 1-(2-iodophenyl) ring have little effect on the reaction. Specifically, reactions of 1-(2-iodoaryl)but-2-yn-1-ones **2**, containing both electron-donating and -withdrawing substituents (e.g., cyano, alkoxycarbonyl, nitro, halo, alkyl, and alkoxyl) on the iodophenyl ring, occur smoothly to produce the corresponding products **3i−3o** in good yields. Furthermore, other isocyanides (e.g., *tert*-butyl isocyanoacetate, tosylmethyl isocyanide, and diethyl isocyanomethylphosphonate) also participate in tandem reactions with a variety of 1-(2-iodoaryl)-2-yne-1-ones to produce the corresponding products **3n−3p** in moderate to good yields.

Based on the experimental observations and literature precedent, the plausible mechanism for the cascade process shown in Figure 1 is proposed. In this pathway, reaction of the isocyanide with CuI in the presence of base forms the cuprioisocyanide A or its tautomer A′. This intermediate reacts through a formal [3 + 2] cycloaddition process with the 1-(2-iodoaryl)ynones to generate the organocopper intermediate B which is then transformed to intermediates C by intramolecular insertion of Cu into the aryl C−I bond. The pyrrole byproducts are produced by competitive protonolysis of B.[12] Intermediate D along with A or A′ are then generated from C to end the catalytic cycle. Finally, 4-oxo-indeno[1,2-*b*]pyrroles are produced by tautomerization.

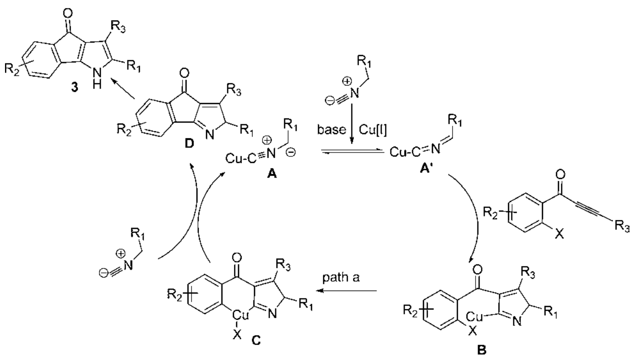
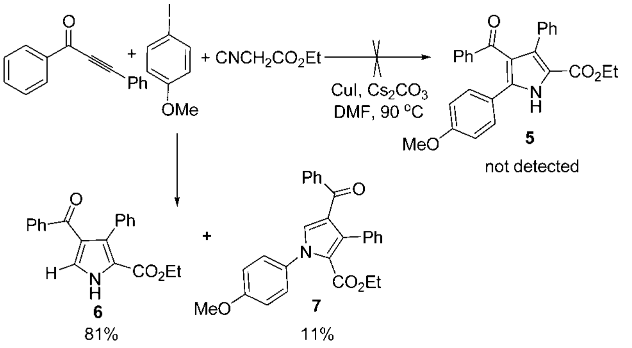


Figure 1. A plausible mechanism for the copper-catalyzed tandem reaction.

Although we successfully captured the proposed organocopper intermediate intramolecularly, our attempt for intermolecular capture failed. As shown in Scheme 2, by adding a large excess of 4-iodoanisole (10 equiv) into the copper-catalyzed reaction of ethyl isocyanoacetate with 1,3-diphenylprop-2-yn-1-one, no corresponding intermolecular C−C coupling product **5** was detected after 24 h at 90 °C. The products isolated were protonated product **6** and *N*-arylated product **7**. We thought the reason for this is that the copper-catalyzed intermolecular C−C coupling is much slower when compared with intramolecular C−C coupling, while the proposed organocopper intermediate was quickly protonated under the reaction conditions and did not proceed in the intermolecular C−C coupling reactions.

Scheme 2. Failure of Attempt for Intermolecular Capture of Organocopper Intermediate



In summary, the investigation described here is a successful example of the rapid intramolecular capture of a highly active organocopper intermediate produced in the formal [3 + 2] cycloaddition of isocyanides to ynones, which lead to the formation of an intramolecular aryl C−C bond. This reaction also represents a new type of copper-catalyzed tandem reaction, which offered a simple and efficient method for the synthesis of 4-oxo-indeno[1,2-*b*]pyrroles. The process takes place efficiently when a variety of 1-(2-iodoaryl)-2-yne-1-ones are used, and it displays a wide functional group compatibility. Further studies and applications of this methodology are currently underway in our laboratory.

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Supporting Information Available: Full experimental procedures, characterization data for all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[12] The pyrrole byproducts cannot be transformed into 4-oxo-indeno[1,2-*b*]pyrroles under the copper-catalyzed reaction conditions. This observation indicates that formation of the highly reactive organocopper intermediate is required in order for the tandem process to take place.