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Selective Construction of Polycyclic Spirooxindoles via $Cu(OTf)_2$/HOTf-catalyzed Domino Reaction of *o*-Arylalkynylacetophenones and 3-Phenacylideneoxindoles

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Under the combined catalysis of $Cu(OTf)_2$/HOTf, the domino annulation reaction of o-arylalkynyl acetophenones with 3-phenacylideneoxindoles in refluxing acetonitrile selectively afforded functionalized spiro[indoline-3,7'-tetrapheno[7,6-bc]furans] and spiro[indeno[1,2-*b*]naphtho[2,1-d]furan-7,3'-indolines] depending on electron effect of the substituents on both substrates.

Spirooxindolines are an important class of naturally occurring substances characterized by their important bioactivity and interesting structural properties.[1,2] Recently, these powerful units have emerged as interesting target compounds for synthesis because of their biological activities, which include cholinesterase inhibition,[3a] anticancer,[3b] antibacterial,[3b] and anti-inflammatory activities.[3c] Thus, many methods have been developed for the synthesis of compounds with these scaffolds as core structures.[4] In recent decades, *o*-alkynylarylcarbonyl series and their derivatives have been widely studied and utilized as versatile building blocks in organic synthesis[5], because these species undergo many transformations, containing nucleophilic addition reactions[6] and Diels–Alder cycloaddition reactions[7].

Scheme 1. Intramolecular Cyclization Reactions of *o*-Alkynylarylketones

As a member of the family of o-alkynylarylcarbonyl compounds, 2-alkynylarylketones also attract great interest from many chemists. The Lewis/Bronsted acid induced intramolecular electrophilic cyclization of 2-alkynylarylketones has proven to be a versatile synthetic approach to a variety of biologically interesting heterocycles and carbocycles. In general, the known cyclization processes of *o*-alkynylarylketones undergoing through isobenzofuranium intermediates are limited to simple nucleophilic additions, which exclusively lead to isobenzofuran derivatives (Scheme 1, path a).,[8] Alternately, the same isobenzopyrylium intermediate with *o*-alkynylarylketones, undergoes a cycloaddition with an alkene/alkyne moiety to generate polycyclic compounds (Scheme 1, path b).[9] Besides the two major reaction pathways, it is also known that *o*-alkynylarylketones preferentially undergo *C*-5-*exo*-dig cyclizations to form carbopalladation intermediates (Scheme 1, path c),[10] and undergo a *C*-6-*endo*-*dig* cyclizations to form the powerful intermediate naphthalenol (Scheme 1, path d),[11] but the domino reaction starting from this pathway has been no reported yet. A literature survey indicated that the synthesis of spirooxindoline derivatives using the *o*-alkynylarylketones still not been reported.

3-Phenacylideneoxindoles act as effective precursors for the synthesis of biologically important spirooxindole compounds[12] and have attracted much attention, including that of our group.[13] Various nucleophilic reactants have been shown to proceed smoothly with this interesting reaction unit.[13] Thus, the reaction diversity of the cycloaddition of the *o*-alkynylarylketones with 3-phenacylideneoxindoles led us to examine the reactivity of analogues of these two substrates. Herein, we report the multi-step cycloaddition reaction of the *o*-alkynylarylketones and 3-phenacylideneoxindoles via a $Cu(OTf)_2$/HOTf catalytic system for the efficient synthesis of complex spirooxindoline derivatives. The diversity of products controlled by the electronic properties of the reactants was systematically studied.

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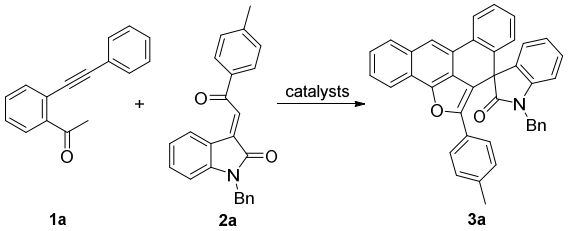
Table 1. Reaction Optimization for the Synthesis of **3a**[a]



1a 2a 3a

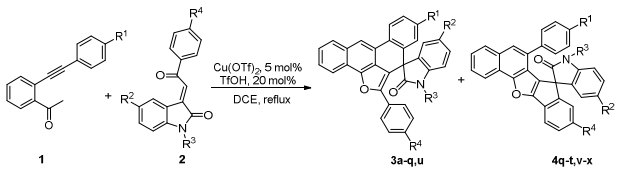
Entry	Catalysts (mol %)	Solvent	Yield (%) [b]
1	HOTf (5)	DCE	N.D.
2	$InCl_3 \cdot 4H_2O$ (5)	DCE	N.D.
3	$In(OTf)_3$ (5)	DCE	N.D.
4	$Cu(OTf)_2$ (5)	DCE	N.D.
5	$Cu(ClO_4)_2$ (5)	DCE	N.D.
6	$BF_3 \cdot Et_2O$ (5)	DCE	trace
7	$In(OTf)_3$ (5) + HOTf (10)	DCE	46
8	$InCl_3 \cdot 4H_2O$ (5) + HOTf (10)	DCE	45
9	$Cu(OTf)_2$ (5) + HOTf (10)	DCE	47
10	$Cu(ClO_4)_2$ (5) + HOTf (10)	DCE	trace
11	$Cu(OTf)_2$ (5) + HOTf (20)	DCE	81
12	$Cu(OTf)_2$ (5) + HOTf (20)	Tol	trace
13	$Cu(OTf)_2$ (5) + HOTf (20)	THF	trace
14	$Cu(OTf)_2$ (5) + HOTf (20)	CH_3CN	trace
15	$Cu(OTf)_2$ (5) + HOTf (20)	CH_2Cl_2	trace
16[c]	$Cu(OTf)_2$ (5) + HOTf (20)	DCE	82
17[d]	$Cu(OTf)_2$ (5) + HOTf (20)	DCE	trace
18[e]	$Cu(OTf)_2$ (5) + HOTf (20)	DCE	49

[a] reaction conditions unless otherwise stated: **1a** *o*-(alkynyl)arylketone (0.5 mmol, 0.110 g), **2a** 3-phenacylideneoxidole (0.5 mmol, 0.177 g), solvent (10 mL), reflux, 12 h reaction time, ND = not detected; [b] Isolated yield; [c] 24 h reaction time; [d] Reaction at room temperature; [e] Reaction under N_2 atmosphere.

Initially, *o*-phenylethynylacetophenone (**1a**) and 3-phenacylideneoxindole (**2a**) were chosen as the substrates for the model reaction. Various catalysts and solvents were examined (Table 1). HOTf and different Lewis acids in refluxing 1,2-dichloroethane (DCE) were found to be inefficient for this transformation (entries 1-5). When $BF_3 \cdot Et_2O$ was used as a catalyst in refluxing DCE, similar results were afforded (entry 6). When $In(OTf)_3$ and HOTf were combined as catalysts in refluxing DCE, the polycyclic spirooxindoline **3a** was formed in moderate yields (entry 7). Its molecular structure was assigned as the functionalized spiro[indoline-3,7′-tetrapheno[7,6-*bc*]furan] by spectroscopic methods. To improve the reaction, a combination of $InCl_3 \cdot 4H_2O$, $Cu(OTf)_2$, and $Cu(ClO_4)_2$/HOTf was tested in different ratios as a catalyst. The combination of 5 mol% of $In(OTf)_3$ or $Cu(OTf)_2$ with 10 mol% of HOTf gave the product **3a** in 45-47% yield (entries 8-9); however, $Cu(ClO_4)_2$ in refluxing DCE was still inefficient for this transformation, even with 10 mol% HOTf (Entry 10). When the combination of 20 mol% HOTf and 5 mol% $Cu(OTf)_2$ was employed in the reaction, the yield of product **3a** significantly increased to 81% (entry 11). The $Cu(OTf)_2$/HOTf catalyst in other solvents, such as toluene, THF, acetonitrile and CH_2Cl_2, also resulted in complex mixtures (entries 12-15). Prolonging the reaction time to 24 h led to an 82% yield (entry 16), and the reaction was not successful at room temperature. The reaction was only result in 49% yield under N_2 atmosphere. On the basis of these results, we found that the optimized reaction conditions for the domino reaction were the combination of $Cu(OTf)_2$/HOTf as a catalyst in refluxing DCE for approximately 12 h under air condition.

With the optimized reaction conditions (Table 1, entry 14) in hand, we examined the substrate scope. The results are summarized in Table 2. *o*-(Phenylethynyl)acetophenone and its 4-methyl- and 4-methoxy-substituted derivatives reacted smoothly with various 2-phenacylideneoxindolines to give the expected spiro[indoline-3,7′-tetrapheno[7,6-*bc*]furans] **3a**-**3p** in 61-91% yields (Table 2, entries 1-16), On these case, the substituents on 3-phenacylideneoxindoles showed marginal effect on the reaction. When *o*-(4-fluorophenylethynyl)acetophenone was used in the reaction, the reaction afforded the expected spiro compound **3q** in only 16% yield (Table 2, Entries 17). Another unexpected spiro[indeno[1,2-*b*]naphtho[2,1-*d*]furan-7,3′-indoline] **4q** was obtained in 36% yield, which was clearly produced from the sequential annulation reaction of the phenyl group of the 3-phenacylidene moiety with the carbon atom at the 3-position of the oxindoline. Additionally, the yield of product **3r** was too low to isolate, and the cyclopentyl spirooxindole **4r** was obtained in 43% yield (Table 2, entry 18). Similarly, the *o*-(4-chlorophenylethynyl)acetophenone also resulted in the cyclopentyl spirooxindoles **4s** and **4t** in moderate yields (Table 2, entries 19-20). However, both substrate **1** and substrate **2** bearing *p*-chloro groups resulted in a complex mixture of products, from which the cyclohexyl spirooxindole **3u** was separated out in 5% yield (Table 2, entry 21). The substrates bearing electron-withdrawing *p*-nitro groups predominately gave the corresponding spiro[indeno[1,2-*b*]naphtho[2,1-*d*]furan-7,3′-indoline] **4t-4x** in 55-66% yields (Table 2, entries 22-24), whereas the normal spiro compounds **3t-3x** were not obtained from the reaction system. These results clearly

Table 2 Substrate scope [a]



1 2 3a-q,u 4q-t,v-x

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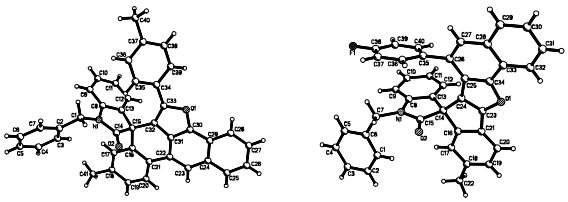
Entry	R^1	R^2	R^3	R^4	Compd (Yield, %) [b]	
1	H	H	Bn	CH_3	**3a** (81)	-
2	H	H	Bn	Cl	**3b** (84)	-
3	H	Cl	Bn	Cl	**3c** (80)	-
4	H	Cl	Bn	CH_3	**3d** (76)	-
5	H	CH_3	Bn	OCH_3	**3e** (76)	-
6	H	H	Bn	NO_2	**3f** (90)	
7	H	Cl	Bn	H	**3g** (91)	
8	CH_3	H	Bn	CH_3	**3h** (82)	-
9	CH_3	H	Bn	Cl	**3i** (87)	-
10	CH_3	Cl	Bn	Cl	**3j** (79)	-
11	OCH_3	H	Bn	CH_3	**3k** (83)	-
12	OCH_3	Cl	Bn	CH_3	**3l** (64)	-
13	OCH_3	Cl	Bn	Cl	**3m** (77)	-
14	OCH_3	F	Bn	CH_3	**3n** (80)	-
15	OCH_3	CH_3	Bn	H	**3o** (74)	-
16	OCH_3	Cl	*n*-Bu	OCH_3	**3p** (61)	-
17	F	H	Bn	CH_3	**3q** (16)	**4q** (36)
18	F	F	Bn	CH_3	-	**4r** (43)
19	Cl	H	Bn	CH_3	-	**4s** (51)
20	Cl	CH_3	Bn	OCH_3	-	**4t** (62)
21	Cl	CH_3	Bn	Cl	**3u** (5)	
22	NO_2	H	Bn	CH_3	-	**4v** (59)
23	NO_2	CH_3	Bn	OCH_3	-	**4w** (66)
24	NO_2	Cl	*n*-Bu	OCH_3	-	**4x** (55)

[a] reaction conditions: 3-phenacylideneoxidole (0.5 mmol), *o*-(alkynyl)arylketone (0.5 mmol), HOTf (0.1 mmol, 0.015 g), $Cu(OTf)_2$ (0.025 mmol, 0.090 g) in DCE (10 mL), reflux, 12 hrs; under air condition [b] Isolated yield.

indicate that the electronic effect of the substituents not only affected the yields of the products, but also determined the reaction pathways. The structures of the spiro compounds **3a-3u** and **4q-4x** were fully characterized by IR, HRMS, and ^{1}H and ^{13}C NMR spectroscopy. The single-crystal structures of the seven spiro compounds **3h** (Figure 1), **3j**, **3k**, **3m**, **4q** (Figure 1), **4r**, and **4v** were successfully determined by X-ray diffraction.

On the basis of the aforementioned experimental results and previously reported similar works, [4] a plausible mechanism was proposed, as shown in Scheme 1. Firstly, an enol intermediate (**A**) was formed in the presence of stronger acid HOTf. Then, under the catalysis of $Cu(OTf)_2$, the coordination of Cu^{2+} to the C-C triple bond increased its electrophilic reactivity, which is drawn in intermediate **(B).** Thus, intermediate **(C)** was formed in the presence of the strong acid HOTf and strong Lewis acid $Cu(OTf)_2$, which in turn converted to the naphthalenol **(D)** by isomerization.[11a] In the presence of the catalyst $Cu(OTf)_2$, the addition of naphthalenol (**D**) to 3-phenacylideneoxindole **2** produced an adduct (**E**). The acid-catalyzed intramolecular dehydration of the adduct (**E**) afforded a naphtho[1,2-*b*]furan (**F**), and the oxidation of (**F**) was easily occurred at tertiary carbon position afforded corresponding 3-hydroxyoxindole (**G**) under air atmosphere. The further intramolecular Friedel–Crafts alkylation depended on the properties of the two aryl groups R^1 and R^4 in the intermediate (**G**). When R^1 = H, *p*-CH_3, or *p*-OCH_3, the FC alkylation reaction of the carbon atom at the 3-position of the oxindoline moiety on the activated aryl group R^1 resulted in the cyclohexyl spirooxindole **3**. When R^1 = *p*-F, *p*-Cl, or *p*-NO_2, the aryl ring connecting R^1 was deactivated and the FC alkylation on it was obviously inhibited. An alternative FC alkylation of the aryl group R^4 gave the cyclopentyl spirooxindole **4**. When both R^1 and R^4 were electron-withdrawing chloro or nitro groups, the FC alkylations on both of the deactivated aryl rings were suppressed. Thus, the reaction resulted in a mixture of products, from which the intermediate of naphtho[1,2-*b*]furan (**G**) was separated as a stable product.

To shed some light on the proposed reaction mechanism, some control experiments were carried out. Firstly, the reaction of proposed intermediate 3-(*p*-tolyl)naphthalen-1-ol (**D1)** with 3-(*p*-nitrophenacylidene)oxindoline **2a** resulted in polycyclic spirooxindoline **3h** in 78% yield, which strongly supported the mechanism proceeding through the reaction between naphthalenol and 3-phenacylideneoxindoles (**eq. 1** in Scheme 2). Secondly, the reaction of *o*-(4-chlorophenylethynyl)acetophenone **1f** with 3-(*p*-nitrophenacylidene)oxindoline **2b** resulted in naphtho[1,2-b]furan (**F1)** in only 6% yield, which also showed that the electron-withdrawing groups on both aryl groups strongly prevented the sequential FC alkylation reaction (**eq. 2** in Scheme 2). The single-crystal structures of compound (**F1)** was also determined by X-ray diffraction. Notably, Peddinti's group recently reported a $BF_3{\cdot}OEt_2$-mediated cyclization of β-naphthol with 3-phenacylideneoxindoles to give the benzofuran derivatives without the sequential annulation reaction,[15] which certifies the formation of 3-aryl-1-naphthalenol (**D**) in our reaction.



3h **4q**

Figure. 1 Molecular structure of spiro compound **3h** and **4q**

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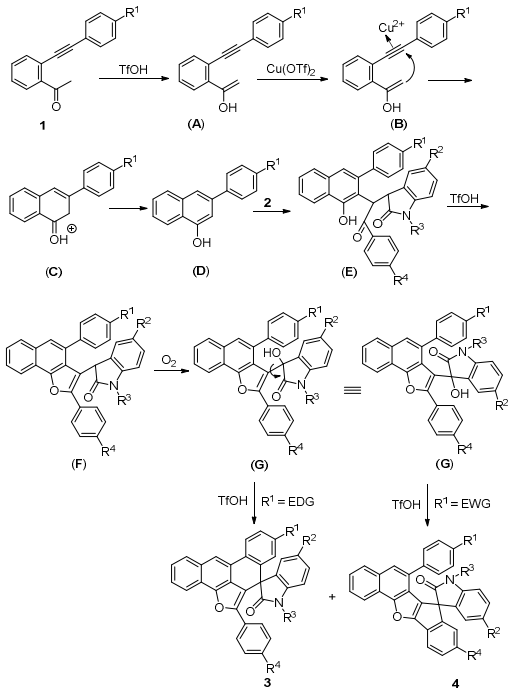
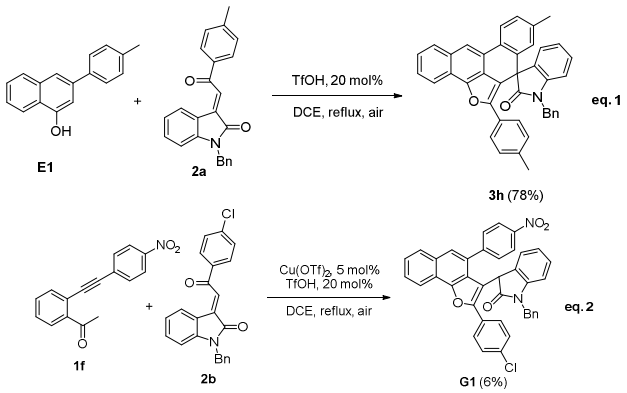


Scheme 2 Plausible reaction mechanism for domino reaction



Scheme 3 Control Experiments

Conclusions

In summary, we systematically investigated $Cu(OTf)_2$/HOTf-catalyzed domino reactions of *o*-(alkynyl)aryl ketones with 3-phenacylideneoxindoles and found very interesting reaction outcomes depending on the structures of the substrates. The reaction mechanism was clearly elucidated by the isolation of reaction intermediates and some control experiments. This domino reaction not only provided an efficient method for the syntheses of functionalized spiro[indoline-3,7′-tetrapheno[7,6-*bc*]furans] and spiro[indeno[1,2-*b*]naphtho[2,1-*d*]furan-7,3′-indolines], but also established the practical application of the domino C–C coupling reaction in organic synthesis. Further studies on the domino coupling reactions for the synthesis of polycyclic systems are in progress.

Supporting Information

Experimental procedures, analytical data, and copies of the ^1H and ^{13}C NMR spectra, HRMS spectra for all new products (3a-3s and 4o-4v, 6a, G1) (PDF). Single-crystal X-ray data for 3h (CCDC 1523295), 3j (CCDC 1523296), 3k (CCDC 1523297), 3m (CCDC 1523298), 4q (CCDC 1523299), 4r (CCDC 1523300), 4v (CCDC 1523301), G1 (CCDC 1526533).

Notes and references

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Selective Construction of Polycyclic Spirooxindoles via $Cu(OTf)_2$/HOTf-catalyzed Domino Reaction of *o*-Arylalkynylacetophenones and 3-Phenacylideneoxindoles

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