JOC*Note*

Synthesis of Cyclic Alkenyl Ethers via Intramolecular Cyclization of *O*-Alkynylbenzaldehydes. Importance of Combination between CuI Catalyst and DMF

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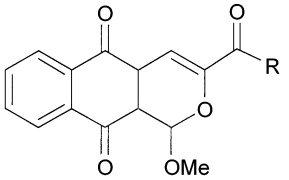
Abstract: An efficient and remarkably general method for the synthesis of cyclic alkenyl ethers via the Cu(I)-catalyzed intramolecular cyclization of *O*-alkynylbenzaldehydes has been developed. The survey of metal catalysts and solvents revealed that the combination of copper(I) iodide and DMF was the catalytic system of choice. The reaction most probably proceeds via the nucleophilic addition of alcohols **2** to *O*-alkynylbenzaldehydes **1** to generate the corresponding hemiacetals, and subsequent nucleophilic attack of the hemiacetal oxygen to the copper coordinated alkyne would give the annulation products **3**. In all cases, the reaction proceeded in a regiospecific manner leading to the six-membered endocyclic products via 6-*endo*-*dig* cyclization.

Cyclic alkenyl ethers are a class of important compounds possessing significant biological properties.[1] For example, BCH-2051 and its analogues have been found to be very effective antitumor chemotherapeutics (Scheme 1).[1e] Despite the high biological activity of this class of compounds, very few successful reports have been documented for the synthesis of cyclic alkenyl ethers.[2] Wang et al. succeeded in constructing the cyclic alkenyl ether derivatives; however, the process involved several steps.[1e,f] In this context, we have previously reported[3] a new method for the one-pot synthesis of cyclic alkenyl ethers from acetylenic aldehydes by using $Pd(OAc)_2$ as a dual role catalyst.[4] A successful application of this newly developed process has been demonstrated for the synthesis of BCH-2051.[5] A wide range of internal alkynes can be used as a substrate under this protocol;

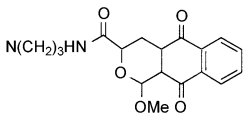
SCHEME 1



I. R = $NH(CH_2)_3N(CH_3)_2$ (BCH-2051)

II. R = OMe

III. R = NR^1R^2 [R^1 = H, R^2 = $N(CH_2)_4N(CH_3)_2$, $N(CH_2)_3OH$, $N(CH_2)_3OH$, $N(CH_2)_3Br$, $N(CH_2)_3S^+(CH_3)_2$, $N(CH_2)_2N^+(CH_3)_3$, $N(CH_2)_2N(C_4H_8)$,



R^1 = CH_3, R^2 = $N(CH_2)_2N(CH_3)_2$]

however, terminal alkynes gave the desired products in very low yields with the formation of unidentified by-products.[6]

The transition-metal-catalyzed synthesis of various heterocycles via cyclization of alkynes possessing a nucleophile in proximity to the triple bond is one of the most important processes in organic synthesis. The intramolecular annulations of alcohols,[7] carboxylic acids,[8] amines,[9] amides,[10] and imines[11] to a triple bond have been extensively investigated using transition metals as an effec-

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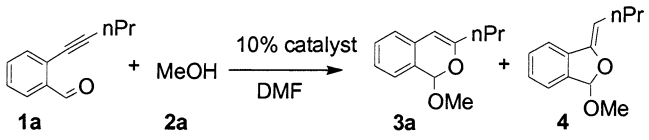
TABLE 1. Effect of the Catalysts for the Formation of Cyclic Alkenyl Ethers[a]

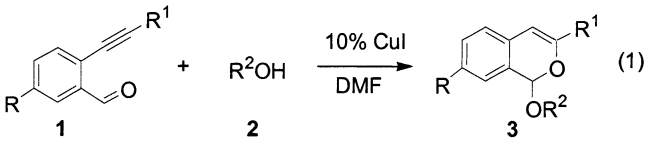


1a **2a** **3a** **4**

entry	catalyst (10%)	nmr YIELD (%)[b]	**3**:**4**
1	none	0[c]	–
2	CuBr	92	100:0
3	CuCl	97 (96)[d]	100:0
4	CuI	99 (97)[d]	100:0
5	$CuCl_2$	89	50:50[e]

[a] Methanol 2.91 mmol) was added to a solution of **1** (0.58 mmol) and catalyst (10 mol %) in DMF (0.2 mL) and the mixture was heated at 70 °C for 4 h. [b] Yields were determined by ^{1}H NMR spectroscopy with dibromo-methane as an internal standard. [c] Starting material recovered. [d] Isolated yields are shown in parentheses. [e] Ratio was determined by the ^{1}H NMR spectra of a crude mixture.

tive catalyst. Our own interest in this type of annulation reaction[12] has prompted us to investigate a robust catalytic system, which can tolerate terminal alkynes, for the synthesis of cyclic alkenyl ethers. Herein we report an entirely novel method for the synthesis of cyclic alkenyl ethers **3** from *O*-alkynylbenzaldehydes **1** and alcohols **2** using CuI as a catalyst and DMF as a solvent (eq 1).



1 **2** **3** (1)

After detailed investigation on the catalysts and solvents, we found that the combination of copper salts and DMF gave very good results. The results are summarized in Table 1. The reaction of **1a** with methanol **2a** in the absence of catalysts did not give the desired product at all, the starting material being recovered (entry 1). As shown in entry 2, the use of CuBr as a catalyst gave the product **3a** in 92% yield. The use of CuCl as a catalyst afforded **3a** in 97% yield (entry 3). When CuI was employed as a catalyst, the desired product **3a** was formed in 99% yield (entry 4). Although the yields of the reactions shown in entries 3 and 4 were comparable, we preferred the latter catalyst because of the cleanness of the process judging from the ^{1}H NMR spectrum of the crude reaction mixture. The use of Cu(II) salts such as $CuCl_2$, however, led to a mixture of **3a** and **4** in a ratio of 1:1, as shown by the ^{1}H NMR spectrum of the crude reaction mixture (entry 5).

Since the optimum reaction conditions (**1a**/**2a**/CuI = 1:1.5:0.1) for the formation of **3a** were in hand, we investigated the annulation reaction of various *O*-alkynylbenzaldehydes **1** (eq 1). The results are summarized in Table 2. Treatment of **1a** with *n*-butanol **2b** under the standard conditions gave the desired product **3b** in an essentially quantitative yield (entry 1). The reaction of homoallyl alcohol **2c** with **1a** also proceeded smoothly to produce **3c** in 82% yield (entry 2). The reaction of the secondary alcohol *i*-PrOH with **1a** proceeded without problem to give the product **3d** in an excellent yield (entry 3). It should be noted that benzyl alcohol reacted with **1a** to afford the desired product **3e** in 51% yield even after heating at 100 °C for 12 h; the starting material was recovered in 31% yield (entry 4). All additional attempts to increase the yield in this reaction, however, proved to be futile. It should be worth mentioning that the terminal alkyne **1b** was tolerated under the reaction conditions and the reaction of **1b** with **2a** and **2d** gave the products **3f** and **3g** in 99% and 98% yield, respectively (entries 5 and 6). This result is in contrast to the previous result[3] that the reaction of **1b** with methanol, in the presence of $Pd(OAc)_2$ catalyst, gave the product **3f** in 22% yield along with a complex mixture of products.[6] Upon treatment with MeOH and *i*-PrOH, the substrate **1c** with a CF_3 group at the para position of the alkyne moiety gave the products **3h** and **3i**, respectively, in excellent yields (entries 7 and 8). The *O*-acetylenic benzaldehyde **1d** underwent smooth annulation reaction to produce **3l** in 91% yield (entry 9). The trimethylsilyl-substituted alkyne **1e** also underwent the annulation, but the TMS group did not survive under these conditions (entry 10). Employing the phenyl-substituted alkyne **1f** as a substrate, the annulation proceeded well with methanol and *i*-PrOH to give the products **3k** and **3l**, respectively (entries 11 and 12). The methoxy methyl substituted alkyne **1g** was found to be a good substrate for this annulation reaction, giving **3m** and **3n** in 88% and 92% yields, respectively (entries 13 and 14).

A proposed mechanism is shown in Scheme 2. The initial step is most probably in situ formation of the hemiacetal **5**. There are two conceivable pathways to reach the hemiacetal **5**: (i) The activation of aldehyde occurs through the coordination of Cu(I) to aldehyde oxygen, which facilitates the addition of methanol (path A).[14] (ii) DMF may act as a Lewis base which deprotonates a proton from methanol thereby facilitating the nucleophilic addition of methanol oxygen to the aldehyde (path B). We were interested in the question of whether the acetalization proceeds through Lewis acid-catalyzed or Lewis base-catalyzed process. To clarify this point, a mixture of **1a**, methanol **2a**, and 10% CuI was heated at 80 °C in benzene, but only very trace amounts of the product were detected in the ^{1}H NMR spectrum of the crude reaction mixture even after 12 h; the starting material was recovered almost quantitatively. However, when 2 equiv of triethylamine was added to the reaction mixture, the reaction proceeded and the desired product **3a** was obtained in 70% yield. These experiments suggest

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(13) See the Supporting Information for ^{1}H NMR of the crude reaction mixture.

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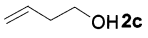
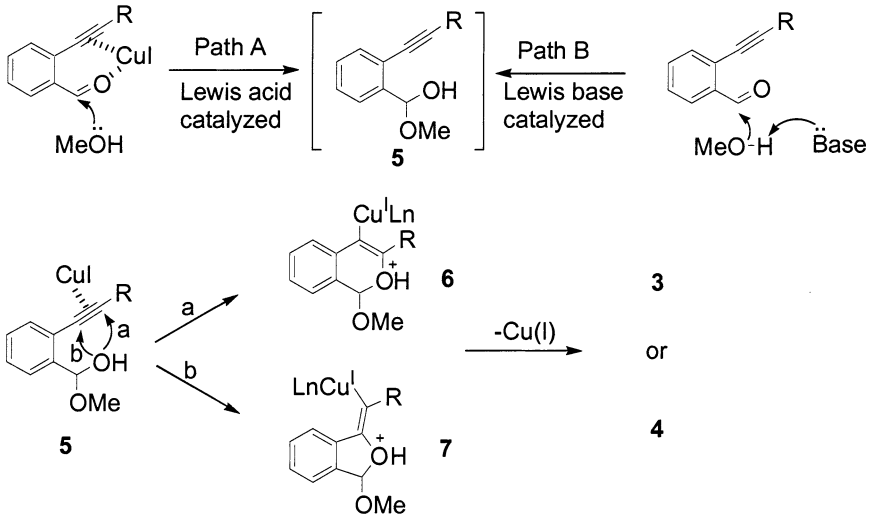
TABLE 2. CuI-Catalyzed Cyclization Reaction of *O*-Alkynylbenzaldehydes[a]

entry	substrate	R	R^1	R^2OH (**2**)	product (**3**)	yield (%)[b]
1	**1a**	H	n-Pr	^{n}BuOH **2b**	**3b**	97
2	**1a**	H	n-Pr	 **2c**	**3c**	82
3	**1a**	H	n-Pr	*i*PrOH **2d**	**3d**	98
4[c]	**1a**	H	n-Pr	BnOH **2e**	**3e**	53
5	**1b**	H	H	MeOH **2a**	**3f**	99
6	**1b**	H	H	*i*PrOH **2d**	**3g**	98
7	**1c**	CF_3	n-Pr	MeOH **2a**	**3h**	93
8	**1c**	CF_3	n-Pr	*i*PrOH **2d**	**3i**	85
9	**1d**	H	n-Bu	MeOH **2a**	**3j**	87
10	**1e**	H	TMS	MeOH **2a**	**3f**	91
11	**1f**	H	Ph	MeOH **2a**	**3k**	93
12	**1f**	H	Ph	*i*PrOH **2d**	**3l**	91
13	**1g**	H	CH_2OMe	MeOH **2a**	**3m**	88
14	**1g**	H	CH_2OMe	*i*PrOH **2d**	**3n**	92

[a] The reactions of aldehydes **1** (0.5 mmol) with alcohols **2** (0.75 mmol) in the presence of CuI (0.05 mmol) were carried out in 70 °C in DMF (0.2 mL). [b] Isolated yields. [c] The reaction was heated at 100 °C for 12 h.

SCHEME 2 Plausible Mechanism for the Formation of Cyclic Alkenyl Ethers

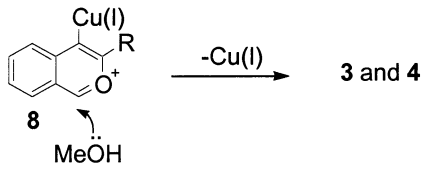


that the Lewis base mechanism (path B) operates in the acetalization process.[15] Once the hemiacetal formed, the next step would be the activation of alkyne by CuI through π-coordination which favors the cyclization of −OH to alkyne leading to the formation of vinylcopper species **6** and **7**. Subsequently, protonation with regeneration of the Cu(I) catalyst produces the cyclic alkenyl ethers **3** and **4**.

Another conceivable pathway is that the resonance-stabilized oxonium ion **8**, formed by the nucleophilic attack of aldehydic oxygen to the copper-coordinated alkynes, would be trapped by the alcohol to give the products **3** and **4** (Scheme 3). Irrespective of the precise mechanism, we are now in a position to synthesize a variety of isochromene skeletons. It should be noted that the regioselectivity was always 100% favoring 6-*endo-dig* cyclization (mode a). No formation of a regioisomeric side product due to 5-*exo-dig* cyclization (mode b) was observed in contrast to the previously reported cases wherein the cyclization of the alkynoic acids proceeded

(15) CuI is not soluble in DMF, benzene, and benzene−Et_3N. Accordingly, the reactivity difference is not due to the solubility difference of the solvents.

SCHEME 3. Trapping of the Oxonium Ion by Alcohol



with 5-*exo*-*dig* cyclization predominantly or in major amount.[8]

In conclusion, we have developed a general method for the synthesis of cyclic alkenyl ethers via the Cu(I) catalyzed intramolecular cyclization of *O*-alkynylbenzaldehydes. The yields are essentially quantitative or very high in most cases, and the regioselectivity was always 100% favoring the 6-*endo*-*dig* cyclization. Moreover, terminal alkynes are tolerated under the reaction conditions. The method reported herein will be applicable for the synthesis of numerous analogues of BCH-2051. Experiments directed toward the application of this approach to other heterocyclic targets, as well as the synthesis of natural products, are now underway in our laboratory.

Experimental Section

The preparation of **3a** is representative. To a mixture of *O*-alkynylbenzaldehyde **1a** (0.100 g, 0.5813 mmol), MeOH (0.028 g, 0.8720 mmol), and Cu(I)I (0.011 g, 0.0581 mmol) was added DMF (0.2 mL), and the mixture was stirred for 8 h at 70 °C. Water (20 mL) was added, and the product was extracted with ethyl acetate. The extracts were washed with water and dried over anhydrous sodium sulfate. The solvent was removed, and the residue was then filtered through a short silica gel column using hexane/AcOEt 98:2 as an eluent to give the pure sample of **3a** (0.115 g, 97%).

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Supporting Information Available: Experimental details, characterization data, and ^{1}H NMR spectra of newly synthesized compounds **3a**−**e**,**g**−**i**,**m**,**n**. This material is available free of charge via the Internet at http://pubs.acs.org.

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