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Copper-Catalyzed Complete Regio- and Stereoselective Cyclization of 1-Aryl-3-sulfanyl-4-oxahepta-1,6-diynes Triggered by Alkynylation

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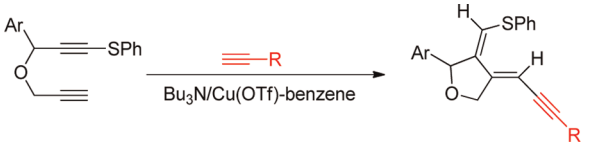
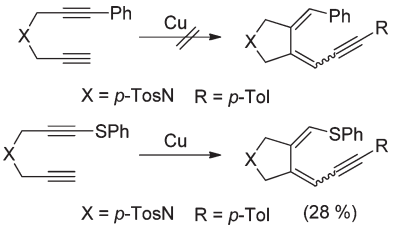
ABSTRACT



Copper(I)-catalyzed alkynylation–cyclization of 4-oxahepta-1,6-diynes 1 with a wide variety of terminal alkynes proceeded to give (3*E*,4*Z*)-3-(phenylsulfanylmethylene)-4-(2-propynylidene)tetrahydrofuran-2-yl]benzenes 2aa–he in high yields with complete regio- and stereoselectivity.

During the past decade, the direct utilization of 1,6-diynes in cyclizations and cycloisomerizations has been a significant challenge, and the application of these strategies to construct polysubstituted furans is especially attractive. A novel strategy of transition-metal-catalyzed cyclization of 1,6-diynes using alkynes such as [2 + 2 + 2] cycloadditions leading to benzenoides has been established.[1] The challenge is tuning the approach to a more attractive cyclization including a wide variety of functionalizations such as catalytic hydrogenation,[2] rhodium-catalyzed arylation,[3] carbon–carbon bond formation with ketones and enones leading to 1,2-dialkylidenecycloalkanes,[4] and ruthenium-catalyzed decarbonylation leading to alkylidenecycloalkanes.[5]

Scheme 1. Alkynylative Cyclization



Although some progress has been made in this field, there still remains a significant challenge in discovering a

† Gifu University.
‡ Kinki University.

(1) Recent reviews for [2 + 2 + 2] cycloaddition reactions: (a) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (b) Gandon, V.; Aubert, C.; Malacria, M. *Curr. Org. Chem.* **2005**, *9*, 1699. (c) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (d) Gandon, V.; Aubert, C.; Malacria, M. *Chem Commun.* **2006**, 2209. (e) Chopade, P. R.; Louie *J. Adv. Synth. Catal.* **2006**, *348*, 2307. (f) Tanaka, K. *Synlett* **2007**, 1977. (g) Tanaka, K. *Chem. Asian J.* **2009**, *4*, 508. (h) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (i) Shibata, T.; Tsuchikawa, K. *Org. Biomol. Chem.* **2008**, *6*, 1317. (j) Galan, B. R.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2830. (k) García-Rubín, S.; Varela, J. A.; Castedo, L.; Saá, C. *Chem.–Eur. J.* **2008**, *14*, 9772.

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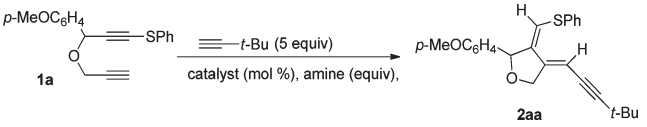
highly efficient cyclization and cycloisomerization triggered by other useful functionalizations.

Our previous investigations of sulfur-substituted 1,6-diynes with nucleophiles afforded cyclized furans through an alkoxylation or aryloxylation−cyclization process, even in metal-free reactions.[6] Next, we focused on the cyclization of 1,6-diynes triggered by alkynylation reactions because enynes, dienynes, and enediynes are the key units of a wide variety of important pharmacores such as neocarzinostatin,[7] C-1027,[8] calicheamicin,[9] kedarcidin chromophore,[10] and other enediyne chromophores.[11] Meanwhile, recent advances in alkynylations have explored the metal-catalyzed cross-dimerization of alkynes, which is a practical and direct method for generating enynes.[12] In continuation of our studies on the cyclizations of sulfur-substituted 1,6-diynes, which have a unique reactivity, we initially investigated the copper-catalyzed cyclization of sulfanyl 1,6-diynes. Surprisingly, the cyclization of phenyl-substituted 1,6-diyne did not proceed, as shown in Scheme 1. Here, we report a new copper(I)-catalyzed regio- and stereoselective alkynylation−cyclization of sulfanyl 1,6-diynes leading to 3,4-dialkylidenefurans bearing an alkynyl group.

First, we examined the reaction of diyne **1a**, which was easily prepared through the propargylation of 1-aryl-3-sulfanylpropargyl alcohol, with 3,3-dimethyl-1-butyne under typical conditions for usual coupling reactions; namely 5 mol % of $Pd(PPh_3)_4$−20 mol % CuI in toluene to give 4-[(4,4-dimethylpent-2-ynylene)-3-(phenylsulfanylmethylene)-2-furyl]-1-methoxybenzene (**2aa**) in 37% yield. As shown in entry 2 of Table 1, the same reaction in the presence of CuI alone gave a yield similar to that of **2aa**. Using the palladium catalyst in the absence of CuI, the cyclization reaction did not proceed (entry 4), and the starting diyne was recovered. On further screening of catalysts, amines, and solvents, we found that copper(I) and tributylamine were the most suitable catalyst and amine for alkynylation−cyclizations, respectively. The optimized conditions were used as shown in entry 6. In addition, we investigated the role of the solvent. Toluene was found to be the most effective solvent for the alkynylation−cyclizations. Other solvents such as dioxane, DMF, and DMSO gave poorer yields of **2aa**.

Table 1. Screening for Suitable Reaction Condition

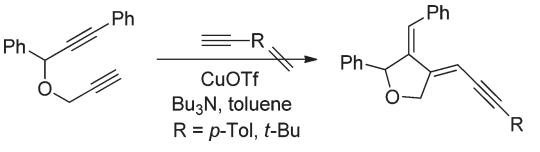


entry	conditions	% yield[b]
1	$Pd(PPh_3)_4$ (5), CuI (20), Et_3N (5), toluene, 5 h	37
2	CuI (20), Et_3N (5), toluene, 5 h	20
3	CuBr (10), Bu_3N (2.5), toluene, 1 h	33
4	$Pd(PPh_3)_4$ (10), Et_3N (5), toluene, 5 h	recov
5	$Cu(OAc)_2$ (10), Bu_3N (2.5), toluene, 5 h	recov
6	Cu(OTf)[a] (10), Bu_3N (2.5), toluene, 20 min	100
7	CuOTf (10), Bu_3N (2.5), dioxane, 15 min	37
8	CuOTf (10), Bu_3N (2.5), DMF, 15 min	49
9	CuOTf (10), C_5H_5N (6), DMF, 2 h	5
10	CuOTf (10), Et_3N (5), toluene, 10 min	48
11	CuOTf (10), DIPEA (3.5), DMF, 45 min	29
12	CuOTf (10), Bu_3N (2.5), Bu_4NHSO_4 (0.1), toluene−H_2O (10:1), 15 min	76
13	CuOTf (10), Bu_3N (2.5), benzene, 20 min	48
14	CuOTf (10), Bu_3N (2.5), DMSO, 20 min	–

[a] CuOTf was used as benzene complex. [b] The yield of the product **2aa** was the isolated yield.

Furthermore, including water as an additive resulted in a minor increase in the yield (entry 12). To clarify the unique alkynylation−cyclizations with complete regio- and stereoselectivity, we further investigated the copper-catalyzed alkynylation of 4-oxahepta-1,6-diyne bearing no sulfur functional groups with *p*-tolyl- and *tert*-butylacetylene; however, the corresponding dienynes were not obtained, and most of the diynes were recovered (Scheme 2). This shows that the organosulfur functional group on the terminal acetylene of the diynes plays an important role in catalytic alkynylation−cyclization. In all cases, the homocoupling product of **1a** was not observed.

Scheme 2. Attempts of 1,3-diphenyl-4-oxahpeta-1,6-diyne to alkynylation−cyclyzation



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Next, we investigated the scope of the alkynylation–cyclization reaction of 1,6-diynes with terminal acetylenes, and the results are shown in Table 2. In most cases, the reaction of diynes with aromatic acetylenes proceeded smoothly; however, the reaction with ethynylpyridine was totally ineffective (entries 1–4). Propargyl aldehyde diethyl acetal and propargyl alcohol formed adducts **2af** and **2ag**, entries 5 and 6, respectively, in a stereospecific manner. Notably, the reactions with 3-methyl-1-butyn-3-ol and ethynylcycloalkanols, for example, were complete in 10–20 min at room temperature. The reactions with bulky cyclododecanol and ethynylestradiol were also effective in giving both dienynes **2al** and **2am** in good yields (entries 11 and 12, respectively). The reaction with the secondary propargylic alcohol exclusively formed dienyne **2an** (entry 13). However, 4-azahepta-6-en-1-yne, a secondary propargylamine, did not undergo tandem cyclization to give the corresponding dienyne **2ao** in good yield (entry 14). We also examined reactions of diynes bearing other aromatic substituents in conjunction with similar acetylenes. The introduction of electron-withdrawing substituents in **1b** (Ar = *p*-FC_6H_4), **1c** (Ar = *p*-ClC_6H_4), and **1d** (Ar = *p*-BrC_6H_4) had a positive effect on the reaction outcome and formed the corresponding products after a relatively short reaction time (1–4 h) (entries 15–21).

All of the cyclized compounds **2aa**–**he** showed similar NMR spectroscopic properties. The NMR spectrum of **2ba** indicated the presence of two trisubstituted olefin moieties, and the observed small J values (J = 1.7 Hz for the single-proton doublet at δ_H 6.07 and J = 2.6 and 2.3 Hz for the one-proton doublet of doublets at δ_H 6.34, which correlates to the two olefinic protons at C3′ and C4′, respectively) were ascribed to allylic couplings between the α-methine proton at C2 and the methylene protons at C5. Finally, the structure of **2ba** was confirmed by single-crystal X-ray analysis, as shown in Figure 1.[13]

The substrate 3-(2-thienyl)-4-oxahepta-1,6-diyne **1h** was highly reactive in the alkynylation–cyclizations; therefore, *p*-tolyl-, 2-thienyl-, and cycloalkanol-substituted 1,3-dien-5-ynes (**2ha**–**hd**, respectively) were readily formed (entries 26–29). In addition, 1-octyn-3-ol participated effectively and exclusively afforded the adduct **2he** (entry 30).

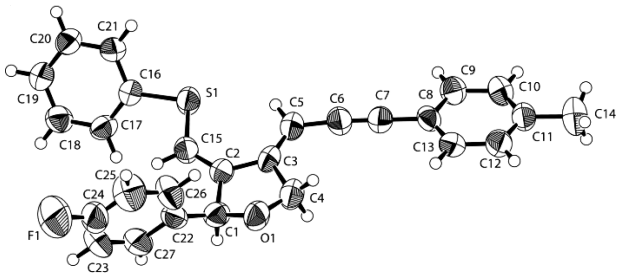

Figure 1. Perspective view of compound **2ba** with 50% ellipsoide probability.

The mechanism for the copper-catalyzed cyclizations of 1,6-diynes would be significantly different from that of base-mediated cyclization.[14] We propose a plausible mechanism for the copper-catalyzed alkynylation–cyclization, as shown in Scheme 3. First, the terminal acetylene is activated by the Cu(I) catalyst to form the alkynylcopper reagent **4**, which reacts with the diyne **3**, via an anti-addition at the terminal acetylene, to give an enyne copper species **5**. Second, intramolecular cyclization of **5** occurs in a stereospecific manner, resulting in dienyne **6**, which is highly stabilized by the organosulfur functional group. Third, the π-alkyne complex between the dienyl copper **6** and another acetylene-forming intermediate **7** undergoes ligand coupling to give product **8**. Finally, the alkynylcopper reagent **4** regenerated to induce the next catalytic cycle of the alkynylative cyclization. To obtain further information supporting this mechanism, we performed the reaction of diyne **1a** with phenylacetylene-d_1 to form doubly deuterated product **8a** (deuterated at both H3′ and H4′) with a high deuterium ratio. The results show that interconversion between acetylene **3** and acetylide **3′** takes place under the reaction conditions and that the last step involves the ligand coupling of intermediate **7** via the π-complex with the intermolecular acetylene or a simple deuteration in the presence of a large excess of phenylacetylene-d_1.[15]

Finally, we investigated a similar addition–cyclization of 4-oxahepta-1,6-diynes, as shown in Scheme 4. The details of reactions with alkoxides and aryl oxides are described in our previous paper.[6] To clarify the trends of the reactions, other nucleophiles were examined. Under basic conditions, some nucleophiles such as tosyl hydrazide, ammonium acetate, and ammonium benzoate reacted with diynes to give 4-hydrazinomethyl **9**, acetoxymethyl **10**, and benzoyloxymethylfurans **11**, respectively. We further explored the palladium-catalyzed hydroamination–cyclizations leading to pyrrolidinomethyl **12a** (n = 0), piperidinomethyl **12b** (n = 1), and benzimidazolylfurans **13**.

In conclusion, we have demonstrated the first cyclization of terminal alkynes and 1,6-diynes leading to sulfanyl-substituted 1,3-dien-5-ynes catalyzed by copper(I). We

(13) X-ray crystallographic analysis: single crystals of products **2ba** were obtained by slow crystallization from a mixture of CH_2Cl_2 and *n*-hexane as pale yellow prisms. Data of **2ba** were taken on a Rigaku RAXIS RAPID imaging plate area detector with graphite monochromated Mo-Ka radiation (λ = 0.71075 Å). A total of 11010 reflections (5056 unique, R_{int} = 0.015) were collected at a temperature of 23 °C to a maximum 2θ value of 55°. The structure of **2ba** was solved by heavy-atom Patterson methods, and full-matrix least-squares refinement on F^2 was employed with anisotropic thermal parameters for all non-hydrogen atoms. All calculations were performed using the CrystalStructure 3.8 crystal structure analysis package, Rigaku and Rigaku/MSC. ORTEP drawings of **2ba** are shown in Figure 1. Crystal data for **2ba**: triclinic, space group P-1, a = 10.1433(11) Å, b = 10.4317(9) Å, c = 12.4818(12) Å, α = 76.579(3)°, β = 65.075(3)°, γ = 69.380(3)°, V = 1115.53(19) Å^3, Z = 2, μ(Mo Kα) = 1.68 cm^{-1}, $F(000)$ = 432, D_c = 1.228 g/cm^3, crystal dimensions: 0.35 × 0.22 × 0.20 mm. Final $R1$ [I > 2.00σ(I)], R (all reflections) and R_{w2} (all reflections) values were 0.0578, 0.0904, and 0.1845, respectively. The maximum and minimum peaks in the difference map were 0.35 and −0.45 e$^-$ Å^{-3}, respectively. The data for **2ba** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC842918. For further details on the crystal structure, see the CIF of compound **2ba**.

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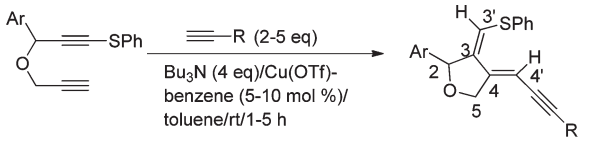
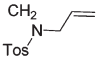
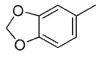
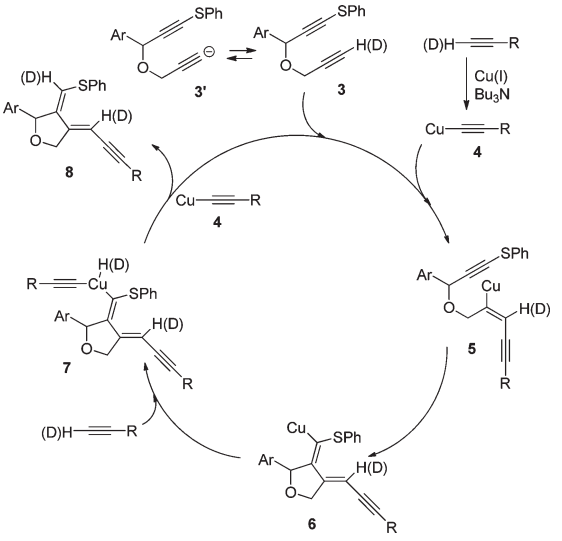
Table 2. Cyclization of 4-Oxahepta-1,6-diynes Using Versatile Terminal Alkynes



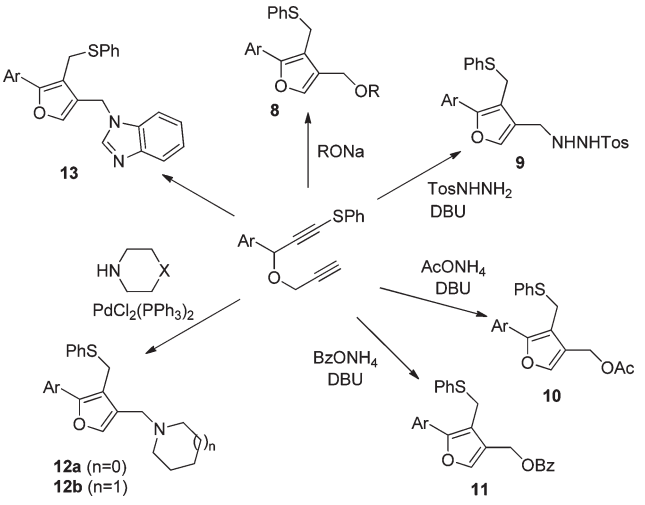
entry	diyne (Ar)	product (R)	yield [%]
1	**1a** *p*-$MeOC_6H_4$	**2ab** *p*-Tol	82
2	**1a**	**2ac** *p*-FC_6H_5	60
3	**1a**	**2ad** 2-thienyl	62
4	**1a**	**2ae** 2-pyridyl	—
5	**1a**	**2af** $CH(OEt)_2$	67
6	**1a**	**2ag** CH_2OH	51
7	**1a**	**2ah** $C(OH)Me_2$	88
8	**1a**	 **2ai**	94
9	**1a**	 **2aj**	77
10	**1a**	 **2ak**	41
11	**1a**	 **2al**	74
12	**1a**	—CH(OH)estradiol **2am**	54
13	**1a**	**2an** CH(OH)Ph	85
14	**1a**	 **2ao**	62
15	*p*-FC_6H_4 **1b**	**2ba** *p*-Tol	66
16	**1b**	**2bb** $C(OH)Me_2$	60
17	**1b**	**2bc** CH(OH)Ph	65
18	*p*-ClC_6H_4 **1c**	**2ca** *t*-Bu	63
19	**1c**	**2cb** *p*-Tol	55
20	**1c**	 **2cc**	66
21	*p*-BrC_6H_4**1d**	**2da** *t*-Bu	67
22	2,4,6-$Me_3C_6H_2$**1e**	**2ea** $C(OH)Me_2$	71
23	**1e**	 **2eb**	77
24	1-naphthyl **1f**	**2fa** *t*-Bu	70
25	 **1g**	**2ga** *p*-FC_6H_5	67
26	 **1h**	**2ha** *p*-Tol	59
27	**1h**	 **2hb**	51
28	**1h**	 **2hc**	80
29	**1h**	 **2hd**	62
30	**1h**	**2he** $CH(OH)(CH_2)_4Me$	63[a]

[a] 3*E*-Isomer was observed in 16%.

Scheme 3. Proposed Mechanism for Cyclization



Scheme 4. Transformations of Alkynylated Tetrahydrofurans



are now investigating further reactions of alkynylation–cyclizations of sulfur-substituted 1,6-diynes bearing non-aromatic substituents and other cyclizations triggered by aminations. These results will be reported elsewhere.

Acknowledgment. This paper is dedicated to Professor Shinzoh Kagabu on the occasion of his retirement from Gifu University.

Supporting Information Available. Experimental details and spectral data for all of the new compounds, ^1H and ^{13}C NMR spectral data of all compounds, and X-ray data for compound **2ba** (CIF). This material is available free of charge via the Internet via Internet at http://pubs.acs.org.

The authors declare no competing financial interest.