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Ruthenium-Catalyzed Cycloaddition of 1,6-Diynes with Isothiocyanates and Carbon Disulfide: First Transition-Metal Catalyzed [2 + 2 + 2] Cocyclotrimerization Involving C═S Double Bond

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Despite of continuous efforts, the development of transition-metal-mediated C−S bond formations have still remained as a challenging task, due to their difficulty as a result of the strong coordination of organosulfur compounds deactivating the mediators.[1] Among such reactions, the cocyclotrimerization of alkynes with a thiocarbonyl compound is of synthetic significance, because a C−S single bond as well as two C−C single bonds are simultaneously formed by a single operation. To the best of our knowledge, there is only a few example of such an interesting sulfur ring assembly[2,3] whereas thiocarbonyl compounds behave as more reactive dienophiles for Diels−Alder cycloaddition than the corresponding carbonyl compounds.[4] Yamazaki and co-workers reported that the reaction of a cobaltacyclopentadiene **1** and methyl isothiocyanate gave a thiopyridone in 10% yield,[5] but its structure was subsequently reassigned to (2*H*)-thiopyran-2-imine **2** (Scheme 1).[6] In addition to the isothiocyanate, carbon disulfide was also reacted with **1** to furnish a dithiopyrone **3** in 50% yield (Scheme 1).[5] To improve these interesting sulfur-heterocycle formations mediated by a *stoichiometric* amount of a transition metal into an environmentally benign catalytic variant, a serious problem might arise: the oxidative cyclization step to form a metallacyclopentadiene key intermediate such as **1** from two alkyne molecules is inhibited by the strong coordination of the thiocarbonyl components to the metal center. As a result, the aimed catalytic cycle becomes totally ineffective. In this context, we envisaged that a solution for this problem comes from the combination of α,*ω*-diynes, excellent precursors of metallacyclopentadienes,[7] and ruthenium catalyses, which have recently been employed for efficient catalytic C−S bond formations.[8] Herein, we wish to report our preliminary study on the *ruthenium-catalyzed cycloaddition* of 1,6-diynes **4** with isothiocyanates **5** or carbon disulfide **9** (Figure 1).

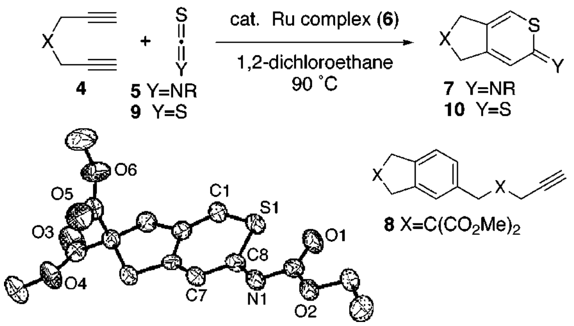

Figure 1. ORTEP diagram of **7aa** at 50% probability level. All hydrogens are omitted for clarity.

Scheme 1

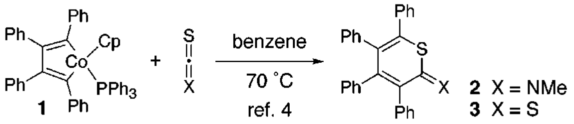

Table 1. Ruthenium-Catalyzed Cycloaddition of 1,6-Diyne **4a** with Isothiocyanates **5a**−**d**[a]

	isothiocyanate **5**			yield[b] (%)	
run	R (equiv)	catalyst/mol %	*t* (h)	**7**	**8**
1	**5a**/CO_2Et (1.2)	**6a**/10	3	**7aa**, 71	5
2	**5a**/CO_2Et (2)	**6a**/10	1.5	**7aa**, 79	trace
3[c]	**5a**/CO_2Et (1.2)	**6a**/10	3	**7aa**, 72	10
4	**5a**/CO_2Et (1.2)	**6b**/10	3.5	**7aa**, 68	9
5	**5a**/CO_2Et (1.2)	**6c**/10	21	**7aa**, 6	5
6	**5b**/COPh (1.2)	**6a**/10	24	**7ab**, 76	trace
7	**5c**/Ph (1.2)	**6a**/10	5	**7ac**, 88	3
8	**5c**/Ph (1.2)	**6a**/5	24	**7ac**, 51	trace
9	**5d**/Cy (1.2)	**6a**/10	24	**7ad**, 50	15

[a] All reactions were carried out with a dyne **4a** and isothiocyanates **5a**−**d** in 1,2-dichloroethane at 90 °C. [b] Isolated yields. [c] The reaction was carried out in benzene.

Transition-metal-catalyzed cocyclotrimerization of two molecules of an alkyne and an isocyanate leading to a substituted pyridone has been accomplished using Co,[9] Ni,[10] and Rh[11] catalysts. Recently, we also reported the first example of the ruthenium-catalyzed cycloaddition of 1,6-diynes **4** with isocyanates furnishing bicyclic pyridones.[12] In contrast to isocyanates, corresponding sulfur analogues, isothiocyanates, has been scarcely employed for such a cocyclotrimerization with alkynes.[5] On the basis of our previous studies on the ruthenium catalyses,[12,13] we attempted the cycloaddition of a diyne **4a** (X = $C(CO_2Me)_2$) and an isothiocyanate **5a** (R═CO_2Et) using a ruthenium(II) complex, Cp*Ru(cod)Cl (**6a**) as a catalyst (Figure 1). In the presence of 10 mol % **6a**, a solution of **4a** and 1.2 equiv **5a** in 1,2-dichloroethane was heated at 90 °C for 3 h. The purification by silica gel chromatography afforded a product **7aa** along with a small amount of a diyne dimer **8** (Table 1, run 1). The ^1H and ^{13}C NMR spectra (see Supporting Information) as well as the molecular ion peak (MH^+ $m/z = 340$) of its FAB mass spectrum indicated that **7aa** is a 1:1 adduct of **4a** and **5a**. The formation of the (2*H*)-thiopyran ring was unequivocally determined by X-ray analysis as shown in Figure 1.[14] The S1−C1 and S1−C8 single bond distances are 1.722(3) and 1.758(3) Å, respectively, which are consistent with the typical Csp^2−S single bond distance (1.75 Å). The N1−C8 bond is a typical C═N double bond of 1.319(3) Å, and the ethoxycarbonyl group on the nitrogen atom is oriented toward the sulfur atom (vide infra).

It is noteworthy that only 1.2 equiv of **5a** chemoselectively gave **7aa** in good yield, suppressing the concomitant formation of **8** (Table 1, run 1). This is in contrast to the cycloaddition of **4** with isocyanates, in which 4 equiv of isocyanates were required to realize the chemoselective pyridone annulation.[12] The increased amount

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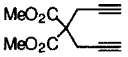
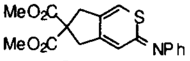
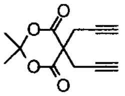
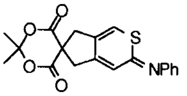
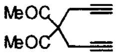
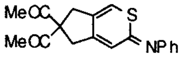
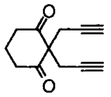
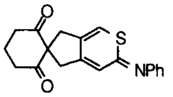
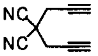
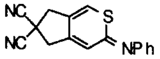
Table 2. Cp*Ru(cod) Cl-Catalyzed Cycloaddition of 1,6-Diynes **4a**−**e** with Phenylisothiocyanate **5c**[a]

run	diyne **4**/ *t*		**7** yield[b]	
1		**4a** /5 h		**7ac**, 88 %
2		**4b** / 9 h		**7bc**, 35%
3		**4c** /6 h		**7cc**, 74 %
4		**4d** / 8 h		**7dc**, 67%
5		**4e** /8 h		**7ec**, 58 %

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[a] All reactions were carried out with 10 mol % **6a**, diynes **4a**−**e** and an isothiocyanate **5c** (1.2 equiv) in 1,2-dichloroethane at 90 °C. [b] Isolated yields. [c] The reaction was carried out in benzene.

of **5a** gave a similar result (run 2). The cycloaddition also proceeded similarly in benzene (run 3), but the catalyst appeared to be deactivated in acetonitrile. Among various ruthenium complexes, Cp*Ru(cod)Cl (**6a**) exhibited the highest catalytic efficiency. A similar ruthenium(III) complex, $[Cp^*RuCl_2]_2$ (**6b**), proved to catalyze the cycloaddition, but the yield was slightly lowered (run 4). On the other hand, a Ru(II) complex without the Cp* ligand, $RuCl_2(CH_3CN)_2(cod)$ (**6c**), hardly catalyzed the cycloaddition, and other complexes such as $[RuCl_2(cod)]_n$ and $C_6Me_6Ru(cod)$ were totally ineffective toward the present cycloaddition.

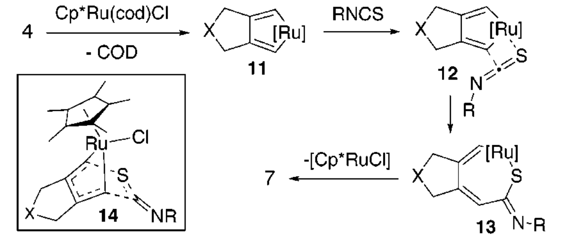
Under the optimized reaction conditions, several isothiocyanates were subjected to the cycloaddition with **4a**. Upon heating a solution of **4a** and benzoyl isothiocyanate (**5b**) for 24 h, the desired cycloadduct **7ab** was almost exclusively obtained in 76% yield (run 6). Similarly, phenyl isothiocyanate (**5c**) gave **7ac** in the highest yield of 88% (run 7). The reaction, however, did not complete within 24 h and the yield was lowered to 51% with a reduced catalyst loading of 5 mol % (run 8). Cyclohexyl isothiocyanate (**5d**) also gave the corresponding thiopyranimine **7ad** albeit in moderate yield, accompanying the formation of **8** in 15% yield (run 9). Exceptionally, *tert*-butyl isothiocyanate gave no cycloadduct under the same reaction conditions.

The generality of the novel [2 + 2 + 2] cycloaddition involving a C═S double bond was subsequently examined with regard to the diyne substrate as summarized in Table 2. In the same manner for **4a** (run 1), a cyclic diester analogue **4b** was reacted with **5c** for 9 h to afford **7bc** in 35% yield (run 2). Similarly, 1,2-diketones **4c** and **4d**, or a malononitrile derivative **4e** gave the corresponding thiopyranimines **7cc**, **7dc**, and **7ec** in 58−74% yields (runs 3−5). These results demonstrated the wide functional group compatibility of the ruthenium catalysis. On the contrary, a tosylamide **4f** (X = NTs) and an ether **4g** (X = O) failed to undergo cycloaddition with **5c**. Accordingly, the thiopyran annulation cannot proceed without the aid of the Thorpe-Ingold effect induced by the tertiary center at 4-position of the diynes,[15] which facilitates the oxidative cyclization of the diynes on the ruthenium center (vide infra).

In addition to the isothiocyanates, carbon disulfide (**9**) can be involved in the cycloaddition with the diyne (Figure 1). In the presence of 10 mol % **6a**, a solution of **4a** in CS_2/1,2-dichloroethane (2:3 v/v) was heated at 90 °C for 6 h to furnish the expected bicyclic dithiopyrone **10** in 50% yield along with a recovered **4a** (24%).

A plausible mechanism for the catalytic formation of the thiopyranimines **7** was outlined in Scheme 2. The catalytic cycle starts with the oxidative cyclization of a 1,6-diyne **4** on the ruthenium center to form a ruthenacyclopentadiene **11**. Subsequently, an isothiocyanate **5** was inserted into the Ru−C bond in such a way that the strongly coordinating sulfur atom is oriented toward the ruthenium center (in **12**). At this stage, the R group on the nitrogen atom is placed far from the ruthenacycle to minimize the steric repulsion between them. The reductive elimination of a [Cp*RuCl] fragment from an intermediate **13** affords a thiopyranimine **7**. The Diels−Alder cycloaddition of **11** with an isothiocyanate via **14** might be an alternative route to **7**.[16]

Scheme 2



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Supporting Information Available: Experimental procedures and analytical data for **7** and **10** (PDF). An X-ray crystallographic file (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) Crystallographic data for $C_{15}H_{17}NO_6S$ (**7aa**): The space group is $P2_1/n$, monoclinic, with unit-cell dimensions $a = 6.9808(10)$ Å, $b = 11.2342(16)$ Å, $c = 20.146(3)$ Å, $\beta = 90.057$ °, $V = 1579.9(4)$ Å^3, $Z = 4$, $D_{calc} = 1.427$ Mg/m^3. Intensity data were collected at 293 K on a Bruker SMART APEX diffractometer with Mo Kα radiation and graphite monochromator. The structure was solved by direct methods and refined by the full-matrix least-squares on F^2 (SHELXTL). A total 7657 reflections were measured and 2279 were independent. Final $R_1 = 0.0541$, $wR_2 = 0.1460$ ($I > 2\sigma(I)$), and GOF = 0.637 (for all data, $R_1 = 0.05921$, $wR_2 = 0.1556$). Full details are described in the Supporting Information.
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