Rhodium-catalyzed carbene transfer reactions via thienylcarbene complexes generated from thiocarbamoyl-ene-yne compounds

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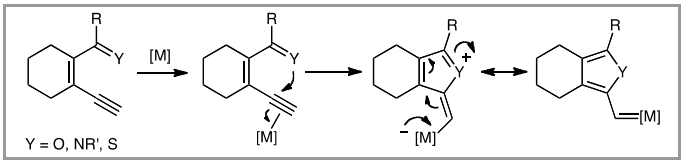
Received XXXX 2010

Abstract: Catalytic thienylcarbene transfer reactions have been developed. The rhodium-catalyzed reaction of alkenes, furans, and thiophenes with a thiocarbamoyl-ene-yne compound as a carbene source gave the cyclopropanation products or ring-opened products of heterocycles. These processes provide efficient synthetic methods for thiophene-containing complex molecules.

Key words: thiocarbamoyl-ene-yne, rhodium, carbene complex, cyclopropanation, ring-opening reaction

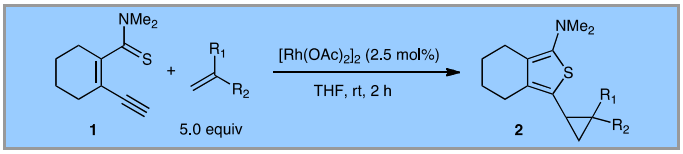
Transition metal-catalyzed transformations involving carbene complexes are powerful methods especially for carbon–carbon bond formation.[1] Although diazoalkanes have been widely used as some of the most common precursors for carbenoid generation,[2] such compounds must be handled carefully because of their explosive nature. The activation of alkynes by transition metal catalysts giving carbene complexes with cyclization or rearrangement has emerged as an alternative method.[3] Among them, reactions involving carbene complexes generated with the formation of furan or pyrrole rings as a driving force are efficient processes in terms of atom-efficiency (Scheme 1, Y = O, NR).[4] However, no such reaction with the formation of thiophene rings has been reported (Scheme 1, Y = S). Here we report the catalytic carbene transfer reactions via thienylcarbene complexes generated from thiocarbonyl-ene-yne compounds.



Scheme 1 Cyclization-induced generation of carbene complexes

Since thioaldehydes and thioketones are generally unstable, we employed an ene-yne compound with a thiocarbamoyl moiety (**1**)[5–8] as a substrate for the rhodium-catalyzed cyclopropanation of alkenes, which was reported by us using carbonyl-ene-ynes or imino-ene-ynes as carbene sources.[4] The reaction of thiocarbamoyl-ene-yne **1** with *tert*-butyl vinyl ether in the presence of 2.5 mol% of $[Rh(OAc)_2]_2$ at room temperature gave the expected thienylcyclopropane **2a** in 84% yield (Table 1, entry 1).[9,10] It turned out that the major diastereomer of product **2a** was *cis* isomer (*cis*/*trans* = 81/19). The reaction of **1** with styrene gave 91% yield of **2b**, which was in turn *trans*-rich mixture (*cis*/*trans* = 30/70; Table 1, entry 2). The reaction with 1,1-diphenylethylene also gave the corresponding cyclopropane **2c** in 80% yield (Table 1, entry 3).

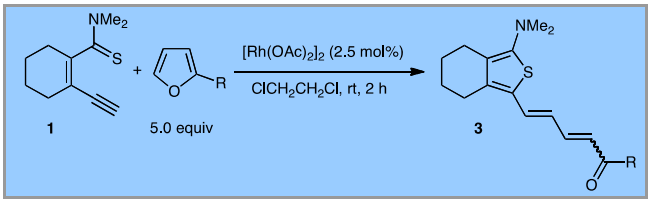
Table 1 Rhodium-catalyzed cyclopropanation of alkenes via a thienylcarbene complex[a]



Entry	R^1	R^2	Product	Yield[b] (cis/trans)[c]
1	O*t*-Bu	H	**2a**	84% (81/19)
2	Ph	H	**2b**	91% (30/70)
3	Ph	Ph	**2c**	80%

[a] The reaction was carried out with **1** (0.30 mmol), alkene (1.5 mmol), and $[Rh(OAc)_2]_2$ (2.5 mol%) in THF (3.0 mL) at rt for 2 h. [b] Isolated yield. [c] Determined by ^{1}H NMR.

Table 2 Rhodium-catalyzed ring-opening reaction of furans



Entry	R	Product	Yield (%)[b]
1	OMe	**3a**	90
2	Me	**3b**	48[c]
3	Et	**3c**	64[c]
4	4-MeC_6H_4	**3d**	80
5	4-MeOC_6H_4	**3e**	97
6	3-MeOC_6H_4	**3f**	94
7	2-MeOC_6H_4	**3g**	96
8	4-CNC_6H_4	**3h**	94
9	4-$CF_3C_6H_4$	**3i**	89

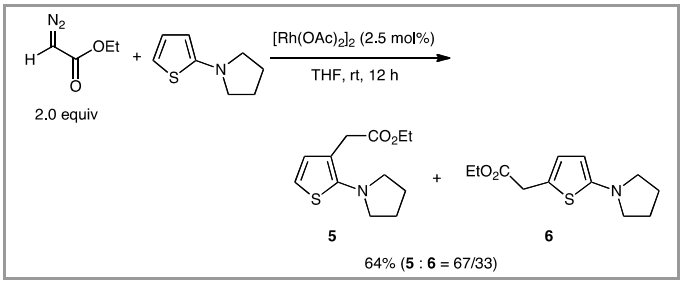
[a] The reaction was carried out with **1** (0.30 mmol), furan (1.5 mmol), and $[Rh(OAc)_2]_2$ (2.5 mol%) in 1,2-dichloroethane (3.0 mL) at rt for 2 h. [b] Isolated yield. [c] In THF.

In the reaction of furans with carbene complexes, we have to consider several pathways including

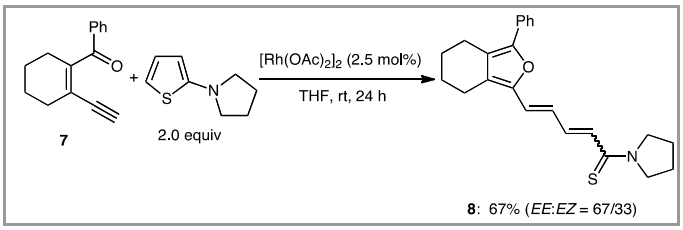
cyclopropanation, C–O insertion, and ring-opening of furans.[11] In some cases, the selective ring-opening reaction proceeds. A thienylcarbene complex generated from thiocarbamoyl-ene-yne is also expected to react with furans. Indeed, 2-methoxyfuran reacted with thiocarbamoyl-ene-yne **1** to give thienyldienoate **3a** in 90% yield (Table 2, entry 1).[12] This reaction is applicable to various 2-substituted furans to give the corresponding ring-opening products in the optimized solvents (THF or 1,2-dichloroethane). In the case of 2-alkylfurans, the products were obtained only in moderate yields (Table 2, entries 2,3). The reaction with aromatic-substituted furans at 2-position gave the dienone **3b**–**3g** in high yields (Table 2, entries 4–9).

We next examined the ring-opening reactions of thiophenes, which are anticipated to be less reactive than furans because of their resonance stability.[13] Under the above reaction conditions, the reaction of thiocarbamoyl-ene-yne **1** with 2-methoxythiophene gave the ring-opening product **4a** in 62% yield (Table 3, entry 1).[14,15] The instability of the methoxythiocarbonyl group of the product **4a** resulted in a low yield. Therefore, we employed 2-aminothiophenes,[16] which were expected to provide more stable products having thioamide moieties. As expected, the use of pyrrolidino-, piperidino-, diethylamino-, and morpholinothiophene resulted in high yields of the ring-opening products (Table 3, entries 2–5).[12]

Interestingly, ethyl diazoacetate, which is widely used as a common carbene source, showed a different reactivity from thiocarbamoyl-ene-yne **1** in the rhodium-catalyzed reaction with 2-aminothiophenes. As shown in Scheme 2, we examined the reaction of 2-pyrrolidinothiophene with ethyl diazoacetate under the above conditions, and found that C–H insertion[17] products were obtained as major products in 64% yield (3-substituted/5-substituted = 67/33). Other carbene sources were also examined.[18] Carbonyl-ene-yne compound **7**,[4a,c] a previously reported carbene source, was also reacted with 2-pyrrolidinothiophene. However, the yield of ring-opening product **8** was only 67% (Scheme 3).



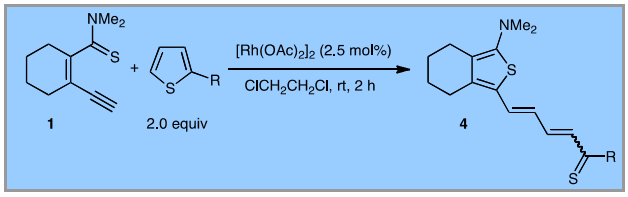
Scheme 2 Ring-opening reaction with ethyl diazoacetate



Scheme 3 Ring-opening reaction with carbonyl-ene-yne compound **7**

In summary, we have developed catalytic carbene transfer reactions via a thienylcarbene complex from thiocarbamoyl-ene-yne **1**. This type of carbene source was applicable to not only cyclopropanation reaction, which has been achieved by the use of furyl- or pyrrolylcarbene complexes, but also ring-opening reactions of furans and thiophenes. Especially, the ring-opening of 2-aminothiophenes succeeded specifically in the reaction of thiocarbamoyl-ene-yne **1**, while other carbene sources resulted in lower yields of ring-opening products or in the formation of C–H insertion products. Synthetic applications of thienylcarbene complexes to preparation of conjugated heterocycles are underway in our laboratory.

Table 3 Rhodium-catalyzed ring-opening reaction of thiophenes



Entry	R	Time (h)	Product	Yield (%)[b]
1	OMe	16	**4a**	62
2	pyrrolidino	8	**4b**	91[c]
3	piperidino	8	**4c**	88[c]
4	diethylamino	6	**4d**	94[c]
5	morpholino	12	**4e**	76

[a] The reaction was carried out with **1** (0.30 mmol), thiophene (0.60 mmol), and $[Rh(OAc)_2]_2$ (2.5 mol%) in 1,2-dichloroethane (3.0 mL) at rt for 2 h. [b] Isolated yield. [c] In THF.

Acknowledgement

This work is supported by Grant-in-Aid for Scientific Research on Priority Areas ‘‘Synergistic Effects for Creation of Functional Molecules’’ (Area 459, No. 19027027) from the Ministry of Education, Culture, Sports, Science and Technology, Japan.

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(5) Thiocarbamoyl moiety was also used for the generation of vinylcarbene complexes. See: Ikeda, Y.; Murai, M.; Abo, T.; Miki, K.; Ohe, K. *Tetrahedron Lett.* **2007**, *48*, 6651.

(6) Thiocarbamoyl-ene-yne **1** was synthesized in two steps from 1,2-dibromocyclohexene, which was prepared according to the known procedure. See: Voigt, K.; von Zezschwitz, P.; Rosauer, K.; Lansky, A.; Adams, A.; Reiser, O.; de Meijere, A. *Eur. J. Org. Chem.* **1998**, 1521.

(7) **Synthesis of 1-bromo-2-trinethylsilylethynylcyclohex-1-ene.**
To a solution of trimethylsilylacetylene (1.96 g, 20 mmol) in toluene (40 mL) were added *tert*-butylamine (5 mL) and 1,2-dibromocyclohexene (9.6 g, 40 mmol) at room temperature under N_2. CuI (0.68 g, 3.6 mmol) and $Pd(PPh_3)_4$ (1.35 g 1.2 mmol) were added to the solution and the mixture was stirred at 60 °C for 2 h. The reaction mixture was filtered through a pad of silica gel with Et_2O. The filtrate was removed under reduced pressure and the residue was purified by column chromatography on silica gel with hexane to afford 1-bromo-2-trimethylsilylethynylcyclohex-1-ene (4.6 g. 18 mmol, 45%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.55 – 1.75 (m, 4H), 2.21 – 2.26 (m, 2H), 2.50 – 2.55 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ –0.1, 21.8, 24.1, 31.7, 36.3, 98.3, 104.9, 121.4, 129.8.

(8) **Synthesis of *N,N*-Dimethyl 2-ethynyl-1-cyclohexenethiocarboxamide (1).**
To a solution of 1-bromo-2-trinethylsilylethynylcyclohex-1-ene (2.56g, 10 mmol) in THF (20 mL) was added dropwise *n*-BuLi (7.5 mL, 12.0 mmol) at –78 °C under N_2. The mixture was stirred at –78 °C for 30 min, and then *N*,*N*-dimethylthiocarbamoyl chloride (1.5g, 15.0 mmol) was added to it. After further stirring at room temperature for 2 h, the organic solution was washed with water, and the aquous phase was extracted with Et_2O (10 mL × 3). The combined organic phase was dried over $MgSO_4$. The solvent was removed under reduced pressure. The residue was filtered through a pad of silica gel. The filtrate was removed under reduced pressure. To a solution of the residue in DMSO (20 mL) were added KF (0.59 g, 10 mmol) and water (1 mL). The mixture was stirred at room temperature for 2 h. The reaction mixture was poured into water, and the aqueous phase was extracted with Et_2O (10 mL x 3). The combined organic phase was dried over $MgSO_4$. The solvent was removed under reduce pressure, and the residue was purified by column chromatography on silica gel with hexane/AcOEt (v/v = 4/1) as an eluent to afford *N*,*N*-dimethyl 2-ethynyl-1-cyclohexenethiocarboxamide (640 mg, 3.3 mmol 33% yield) as a dark brown solid. Mp 42.1-43.0 °C; IR (KBr) 1061, 1123, 1140, 1395, 1520, 2858, 2931, 3223 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 – 1.79 (m, 4H), 2.01 – 2.07 (m, 1H), 2.20 – 2.26 (m, 2H), 2.68 – 2.78 (m, 1H), 3.04 (s, 1H), 3.28 (s, 3H), 3.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7, 21.8, 28.7, 29.0, 41.8, 41.9, 80.7, 82.4, 113.29, 147.7, 201.0. HRMS (FAB): calcd for $C_{11}H_{16}NS$ ($M+H^+$), 194.1003; found, 194.1003.

(9) In sharp contrast, the reaction of carbamoyl-ene-yne compounds with a chromium complex gives not furyl carbene-chromium complexes but pyranylidene-chromium complexes. Theoretical investigations are in progress and will be published in due course. See: (a) Ohe, K.; Miki, K.; Yokoi, T.; Nishino, F.; Uemura, S. *Organometallics* **2000**, 19, 5525. (b) Miki, K.; Yokoi, T; Nishino, F.; Ohe, K.; Uemura, S. *J. Organomet. Chem*. **2002,** *645*, 228.

(10) The use of platinum or gold catalyst precursors ($PtCl_2$, AuCl, $AuCl_3$) was not effective in this reaction.

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(12) **Typical procedure for rhodium-catalyzed ring-opening reaction of thiocarbamoyl-ene-yne 1 with 2-methoxyfuran**
To a solution of $[Rh(OAc)_2]_2$ (3.3 mg, 0.0075 mmol) in anhydrous 1,2-dichloroethane (3.0 mL) were added thiocarbamoyl-ene-yne **1** (59 mg. 0.30 mmol) and 2-methoxyfuran (150 mg, 1.50 mmol) under N_2. The mixture was stirred at room temperature for appropriate time. The mixture was diluted with EtOAc (10 mL), and the solution was evaporated under reduced pressure. The residue was purified by column chromatography on silica gel with hexane/AcOEt (v/v = 10/1).
Compound 3a (90% yield, 1*E*,4*E*/1*Z*,4*E* = 99/1); an orange solid; mp 108.5-109.5 °C; IR (KBr) 877, 1008, 1237, 1332, 1394, 1590, 1701, 2831, 2938 cm^{-1}; (1*E*,4*E*)-**3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 – 1.78 (m, 4H), 2.41 – 2.56 (m, 2H), 2.62 – 2.71 (m, 2H), 2.79 (s, 6H), 3.73 (s, 3H), 5.80 (d, *J* = 15.0 Hz, 1H), 6.38 (dd, *J* = 15.0, 11.3 Hz, 1H), 6.96 (d, *J* = 15.0 Hz, 1H), 7.39 (dd, *J* = 15.0, 11.3 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.9, 23.2, 25.2, 25.4, 44.7, 51.2, 116.7, 120.5, 123.5, 124.5, 132.1, 140.9, 145.7, 154.9, 167.9. (1*Z*,4*E*)-**3a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.63 – 1.78 (m, 4H), 2.41 – 2.56 (m, 2H), 2.62 – 2.71 (m, 2H), 2.82 (s, 6H), 3.76 (s, 3H), 5.51 (d, *J* = 11.5 Hz, 1H), 6.66 (dd, *J* = 11.5, 11.5 Hz, 1H), 6.89 (d, *J* = 15.0 Hz, 1H), 7.69 (dd, *J* = 15.0, 11.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.1, 23.1, 25.2, 25.4, 44.8, 50.1, 112.7, 119.8, 123.9, 124.3, 133.0, 140.9, 146.0, 155.3, 167.4; Anal. Calcd for $C_{16}H_{21}NO_2S$: C, 65.95; H, 7.26. Found: C, 66.06; H, 7.22.
Compound 4e (76% yield); a red solid; mp 79.0-80.0 °C; IR (KBr) 1119, 1269, 1396, 1558 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 – 1.75 (m, 4H), 2.50 - 2.55 (m, 2H), 2.68 – 2.77 (m, 2H), 2.80 (s, 6H), 3.78 (br s, 8H), 4.20 – 4.40 (m, 2H,), 6.45 (t, *J* = 13.2 Hz, 1H), 6.52 (d, *J* = 14.2 Hz, 1H), 7.03 (d, *J* = 15.1 Hz, 1H), 7.73 (t, *J* = 12.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.2, 22.9, 23.2, 25.2, 25.5, 44.7, 50.3, 65.8, 66.6, 121.5, 123.3, 124.0, 124.7, 131.9, 141.1, 147.9, 154.8, 194.9. HRMS (FAB): calcd for $C_{19}H_{26}N_2OS_2$ (M^+), 362.1487; found, 362.1473.

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(18) The reaction of 1,1-dimethyl-2-propynyl acetate and 2-pyrrolidinothiophene in the presence of $[RuCl_2(CO)_3]_2$ or $PtCl_2$ as a catalyst gave no ring-opening product.

Compared with ref. 13, the reactivity of 2-aminothiophenes towards ring-opening seems to be lower than that of furans or 2-methoxythiophene.