1,5-Addition of Halogens and Pseudohalogens to Cyclopropylthiocarbene–Chromium Complexes: A Stereocontrolled Synthesis of 1,4-Dihalo-1-alkene Derivatives

James W. Herndon* and Margaret D. Reid

Department of Chemistry and Biochemistry
University of Maryland
College Park, Maryland 20742-2021

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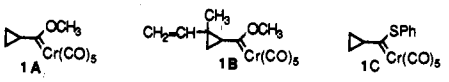
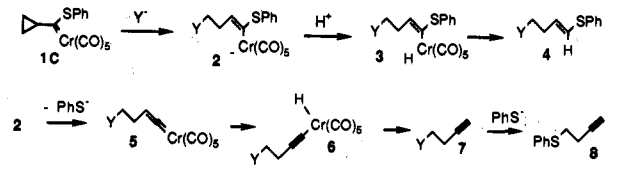
Electron-deficient cyclopropane derivatives readily undergo ring-opening reactions when treated with nucleophiles[1] or with Lewis acids and nucleophiles,[2] forming either γ-substituted carbonyl compounds or the analogous enol derivatives. Similar reaction processes have not been reported for simple cyclopropyl-substituted Fischer carbene complexes,[3,4] which might be susceptible to similar ring-opening reactions but ultimately provide γ-substituted carbene complexes or products derived therefrom. Herein we report our initial investigation into the reaction between cyclopropylcarbene–chromium complexes and halogens, which provides 1,4-dihalo-1-phenylthio-1-alkene derivatives in good yield with excellent control of stereochemistry.[5] These highly functionalized compounds are potentially valuable building blocks for organic synthesis since both the halogen and vinyl sulfide functionalities[6] are subject to further transformations.

Initially, the reaction of nucleophiles with cyclopropylcarbene–chromium complexes was examined. Ring-opened products were not observed when alkoxycarbene complexes **1A** or **1B** were treated with lithium dimethyl cuprate, sodium thiophenoxide, or tetrabutylammonium iodide. Cyclopropylthiocarbene complexes



were next tested in their reactions with nucleophiles since they should be more electrophilic.[7] Preparation of thiocarbene complex **1C** from the corresponding acylate complex,[7] acetyl chloride, and thiophenol at 0 °C led to vinyl sulfide **4** in 2% yield, along with complex **1C** in 81% yield (Scheme 1). Vinyl sulfide **4** was even more prevalent at longer reaction times. A mechanism for formation of vinyl sulfide **4** involving nucleophilic addition of chloride ion to the cyclopropane ring has been proposed in Scheme 1.[8] Reaction of thiocarbene complex **1C** with iodide ion (24 h, 25 °C, CH_2Cl_2) led to alkyne sulfide **8** in 99% yield; the mechanism

Scheme 1



Scheme 2

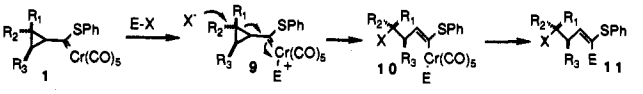
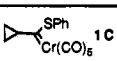
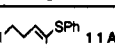
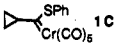
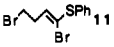
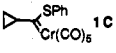
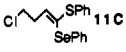
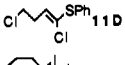
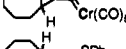
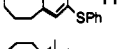
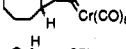
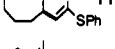
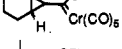
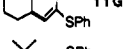
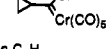
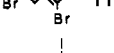
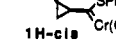
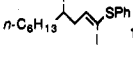
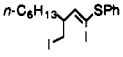
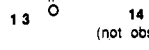
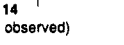


Table 1. Reaction of Cyclopropylcarbene Complexes with Halogens and Pseudohalogens[a]

entry	carbene complex	electrophile	products	yield	*Z*:*E* ratio[b]
A	 **1C**	I_2	 **11A**	72%[c]	>97:3
B[d]	 **1C**	Br_2	 **11B**	61%[c]	93:7
C	 **1C**	PhSeCl	 **11C**	46%[c]	52:48[e]
			 **11D**	39%[c]	97:3
D[f]	 **1D**	I_2	 **11E**	82%[c]	93:7
E	 **1E**	I_2	 **11F**	74%[c]	75:25
F[f]	 **1F**	I_2	 **11G**	87%[c]	72:28
G[d]	 **1G**	Br_2	 **11I**	22%	20:80
H[g]	 **1H-cis**	I_2	 **11J**	68%	17:83
			 **12J**	3%	<2:98
I	**1H-trans**	I_2	**11J**	54%	84:16
			12J	22%	96:4
J	**1A**	I_2	 **13**  **14** (not observed)	41%	

[a] For a procedure, see ref 13. [b] For a discussion of the *E*:*Z* assignment, see ref 14. [c] In this case isomers **11** and **12** are identical. [d] Pyridinium bromide was used as the Br_2 source. [e] The identity of the *E* and *Z* isomers could not be determined. [f] Synthesis of this compound provided only the exo isomer. [g] Contaminated with 8% of the trans isomer.

for this process involving metal vinylidenes[9] is outlined in Scheme 1. The presence or absence of acetic acid explains the diverging reaction pathways for carbene complex anion intermediate **2**. Only unsubstituted cyclopropylthiocarbene complex **1C** was reactive to iodide ion, probably because the nucleophilic addition step is less facile in more-substituted systems.

Next, Lewis acid-assisted nucleophilic ring-opening reactions of cyclopropylcarbene complexes were investigated. The reaction of thiocarbene complexes and iodine was examined since electrophilic iodine could activate the carbene complex,[10] and then iodide anion could initiate the homo-Michael addition in the activated complex (Scheme 2). Treatment of complex **1C** with iodine led in high yield to formation of diiodo compound **11A**.

(1) For relevant reviews, see: (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72. (b) Wong, H. N. C.; Hon, M.-Y.; Tse, C.-W.; Yip, Y.-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198. (c) Lipshutz, B. H.; Sengupta, S. In *Organic Reactions*; Paquette, L. A., Ed.; Wiley and Sons: New York, 1992; Vol. 41, pp 135–631. (d) Hudlicky, T.; Reed, J. W. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Paquette, L. A., Eds.; Pergammon: Oxford, 1991; Vol. 5, pp 899–970.

(2) (a) Miller, R. D.; McKean, D. R. *J. Org. Chem.* **1981**, *46*, 2412–2414. (b) Caputo, R.; Ferreri, C.; Palumbo, G.; Wenkert, E. *Tetrahedron Lett.* **1984**, *25*, 577–578. (c) Beaulileu, P. L.; Kabo, A.; Garratt, D. G. *Can. J. Chem.* **1980**, *58*, 1014–1020. (d) Morrill, T. C.; Malsanta, S.; Warren, K. M.; Greenwald, B. E. *J. Org. Chem.* **1975**, *40*, 3032–3036. (e) Lambert, J. C.; Napoli, J. J.; Johnson, K. K.; Taba, K. N.; Packard, B. S. *J. Org. Chem.* **1985**, *50*, 1291–1295.

(3) A carbene complex is very electron-withdrawing group based on its pK_a value. Casey, C. P.; Boggs, R. A.; Anderson, R. L. *J. Am. Chem. Soc.* **1972**, *94*, 8947–8949.

(4) For nucleophilic ring opening of 1-carbonyl-substituted cyclopropylcarbyne–metal complexes, see: Carter, J. D.; Schoch, T. K.; McElwee-White, L. *Organometallics* **1992**, *11*, 3571–3578.

(5) Herndon, J. W.; Reid, M. D. *Abstracts of Papers*, 204th National Meeting of the American Chemical Society, Washington, DC, Fall, 1992 American Chemical Society: Washington, DC, 1992; ORGN 139.

(6) For example, (phenylthio)alkenes are easily converted to alkenyllithiums. Cohen, T.; Doubleday, M. D. *J. Org. Chem.* **1990**, *55*, 4784–4786.

(7) Yamashita, A.; Toy, A. *J. Org. Chem.* **1989**, *54*, 4481–4483.

(8) (a) For a review of metal–vinylidene complexes, see: Bruce, M. I.; Swincer, A. G. *Adv. Organomet. Chem.* **1983**, *22*, 59–128. (b) For facile C–S bond breaking in a thiocarbene complex, see: Katz, T. J.; Yang, G. X.-Q.; Rickman, B. H.; Iwashita, T. *J. Am. Chem. Soc.* **1993**, *115*, 2038–2039.

(9) A mechanism can be envisaged where the acetoxycarbene complex intermediate undergoes ring opening; however, the vinylic acetate should be the product in this reaction: Söderberg, B. C.; Turbeville, M. J. *Organometallics* **1991**, *10*, 3951–3953.

0002-7863/94/1516-0383$04.50/0

The reaction was general for a variety of cyclopropylthiocarbene complexes, as can be seen in Table 1. Compounds **11E** and **11G** were obtained as a single ring stereoisomer, assigned as the isomer having the trans relative configuration of substituents on the ring. This assignment was based on the large coupling (11.4 Hz) between the hydrogens at the stereogenic centers in **11G**. Trans cyclooctyl-fused complex **1E** led to a single ring stereoisomer, assigned as diiodide **11F**. In compounds **1G** and **1H**, which contain unsymmetrical cyclopropane rings, the more-substituted alkyl halide (corresponding to structure **11**, not **12**) was preferentially obtained. Alkoxycarbene complex **1A** was also reactive to iodine, but only the ester **13** was obtained and not the expected enol ether **14**.[11]

The mechanism outlined in Scheme 2 has been proposed for formation of the diiodide.[10] Nucleophilic attack occurs predominantly at the more-substituted carbon atom of the cyclopropane ring and with inversion of configuration. The regiochemical and stereochemical features of this reaction are reminiscent of the trimethylsilyl iodide-induced ring opening of cyclopropylketones.[2] This mechanism is further supported by the reaction of complex **1C** with phenylselenium chloride, where the chlorine ends up at the alkyl position and the phenylseleno group is at the alkenyl position in compound **11**. This product was accompanied by a secondary product, dichloride **11D**, which results from reaction of **11C** with phenylselenium chloride.

In summary, we have shown that 1,5-addition of halogens (and pseudohalogens) to cyclopropylcarbene complexes proceeds very predictably with a high degree of stereocontrol and regiocontrol for formation of the alkenyl iodide, and in some cases with a high degree of stereoselectivity in formation of the trisubstituted alkene.[12] We are further examining the range of nucleophiles and electrophiles which add to this system and determining what factors affect the *E*:*Z* ratio of the alkenes.

(10) In some ligand environments, heptacoordinate Cr(II) species are quite stable. Mialki, W. S.; Wigley, D. E.; Wood, T. E.; Walton, R. A. *Inorg. Chem.* **1982**, *21*, 480–485. Electrophilic activation of the carbene complex might also be achieved by initial electrophilic attack at sulfur, followed by subsequent transfer to chromium.

(11) For a related hydrolysis of α-halovinyl ethers to esters, see: Helwig, R.; Hanack, M. *Chem. Ber.* **1985**, *118*, 1008–1021.

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Supplementary Material Available: Procedures and characterization of the products in Table 1 and Scheme 1; detailed discussion of alkene geometry assignment (10 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(12) Trisubstituted alkenes have previously been prepared stereoselectively by a cyclopropane ring-opening process: Brady, S. F.; Ilton, M. A.; Johnson, W.S. *J. Am. Chem. Soc.* **1968**, *90*, 2882–2889.

(13) To a solution of iodine (0.0149 g, 0.059 mmol) in dichloromethane (3 mL) at −20 °C under nitrogen was added dropwise a solution of carbene complex **1D** (0.0214 g, 0.0491 mmol) in dichloromethane (2 mL). The reaction was stirred for 10 h at −20 °C, after which time the solution was dark green. The crude reaction mixture was filtered through Celite, washing with 19:1 hexane: ethyl acetate. After removal of the solvent on a rotary evaporator, final purification of the residue was achieved by flash chromatography on silica gel using pure hexane as the eluent. An off-white solid (0.020 g, 82% yield, mp 76–78 °C) identified as compound **11E** was obtained. ^{1}H NMR ($CDCl_3$): major isomer, δ 6.15 (d, 1 H, J = 9.8 Hz), 3.15 (m, 1 H); minor isomer, δ 6.65 (d, 1 H, J = 9.8 Hz), 3.55 (m, 1 H); both isomers, δ 7.19 (m, 5 H), 4.48 (dt, 1 H, J = 11.2, 4.2 Hz), 2.18 (m, 2 H), 1.71–1.43 (m, 10 H). Irradiate at δ 6.15: δ 3.15 (dt, J = 11.2, 4.2 Hz). Irradiate at δ 3.15: δ 6.15 (s), 4.38 (dd, J = 11.2, 4.2 Hz). The integration suggests that a 93:7 ratio of alkene stereoisomers was obtained. ^{13}C NMR ($CDCl_3$): δ 153.1, 135.4, 130.5, 129.1, 127.4, 91.3, 55.2, 41.6, 35.3, 31.8, 27.7, 26.6, 26.2, 25.7 (the peaks for the minor isomer did not appear). MS (EI) m/z (relative intensity): 498 (M, 26.8), 371 (100), 275 (92), 244 (38), 147 (86), 127 (43). HRMS: calcd for $C_{16}H_{20}I_2S$, 497.9375, found, 497.9386.

(14) *E*:*Z* assignment: Halogen–metal exchange (*n*-BuLi, −78 °C) of **11G** (72:28 *Z*:*E* mixture) or **11A** (97:3 *Z*:*E* mixture) followed by protonation led to the expected vinyl sulfides (72:28 *E*:*Z* mixture from **11G** and only the *E* isomer from **11A**). In both cases, the major isomer was determined to be *E* on the basis of the large coupling constant (14.8 Hz) between the alkene protons. Assuming that replacement of iodide by hydrogen under these conditions proceeds with retention of configuration,[15] it can be inferred that the major isomers produced in the synthesis of **11G** and **11A** were the *Z* isomers. In both **11A** and **11G**, the alkene hydrogen in the *Z* isomer has a considerably greater chemical shift ($\Delta\delta \simeq 0.5$), and this correlation was employed to assign the *E*:*Z* geometry in all the other cases.

(15) Curtin, D. Y.; Harris, E. E. *J. Am. Chem. Soc.* **1951**, *73*, 4519–4521.