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RING-FORMING REACTION VIA REGIOSELECTIVE INTRAMOLECULAR INSERTION BY (PHENYLTHIO)CARBENE INTO α C-H BOND OF ALKOXIDES

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Abstract: ω -(Phenylthio)- ω -chloroalkyl acetates were allowed to react with MeLi (3.2 equiv) to give 2-(phenylthio)cycloalkanols which were produced by the regioselective intramolecular insertion by (phenylthio)carbenes.

Intramolecular C-H insertion reaction by carbenes has been utilized as a powerful tool for the construction of highly strained molecules or cage systems that would be difficult to approach in other ways.¹ However, due to the lack of regioselectivity in carbenic insertion reactions and a facile 1,2-shift of hydrogen adjacent to the carbenic carbon, their use in organic synthesis has been limited only in the cases where molecular geometry locates a potential insertion site close to the carbene site.² Recently, we have disclosed a novel oxyanionic substituent effect that facilitates the insertion by various kinds of carbenes into α C-H bond of alkoxides.³ For the purpose of extending the scope of intramolecular insertion reactions, we examined a regiocontrolled intramolecular insertion into α C-H bond of alkoxides. In this paper, we wish to report the regioselective intramolecular insertion of ω -oxidoalkyl(phenyl-thio)carbenes that provides a novel synthetic route to 2-(phenylthio)alkanols (Scheme I).⁴

Scheme I



5-(Phenylthio)pentyl acetate (<u>1a</u>) was chlorinated with N-chlorosuccinimide in CCl₄, and the resulting chloride <u>2</u> was treated with MeLi (3.2 equiv) in THF at -80 °C. The mixture was allowed to warm to a room temperature to generate 4-oxidobutyl(phenylthio)carbene (<u>3</u>) which, in an intramolecular fassion, inserted regioselectively into the α C-H bond of the oxido group to give *cis*- and *trans*-2(phenylthio)cyclopentanol (<u>4a</u>) in 45% and 24% isolated yield, respectively (eq 1).





Reactions of (phenylthio)alkyl acetates $(\underline{1a-h})$ which have varying lengths of, or substituents on, the alkyl chain were performed under the similar reaction condition. The results are summarized in Table I.

The intramolecular insertion of 4-, 5-, and 6-oxidoalkyl(phenylthio)carbenes proceeded regioselectively to give the corresponding 2-(phenylthio)cycloalkanols. Among these, five-membered ring forming reactions proceeded most efficiently, demonstrating a synthetic potential of the present novel cyclization reaction. The directing effect of oxyanionic substitution is manifested not only by the above regioselectivity but also by the completely differnet course of the reaction for the *tert*-butyldimethylsilyloxy derivative 5 (entry 6) where 2-(phenylthio)tetrahydropyran was obatined but none of 4a. Except the reaction of 3-oxidopropyl(phenylthio)carbene (entry 9), formation of cyclic ethers was not observed.



Alternatively, the oxidoalkyl(phenylthio)carbenes can also be generated by the reaction of chloro(phenylthio)aldehyde with MeLi. 5-(Phenylthio)pentanal (<u>6</u>) was converted first to the chloride and then treated with 2.2 equiv of MeLi in THF to give 1-methyl-2-(phenylthio)cyclopentanol (<u>4b</u>) in 50% yield (eq 2).

There have been a few reports on the stereochemical aspect of the intramolecular C-H insertion of flexible systems.^{2,5} In the present study, we determined the stereochemistry of products except entry 8.⁶ The intramolecular insertion by 5-oxidoalkyl(phenylthio)carbenes showed a *cis* stereoselectivity with respect to phenylthio and hydroxyl group. On the other hand, the reaction of 5-oxidopentyl(pehnylthio)carbene produced the *trans* product selectively. It should be noted that the *cis* selectivity is not based on a simple steric factor because an alkyl substituent at the α position to the oxido group did not affect the selectivity (see entries 2 and 3). As a possible explanation, we propose that in the transition state as depicted in Figure I, the oxido group interacts with the carbenic carbon and the insertion proceeds selectively into

Entry	Starting Material	Products ^b (Isolated Yield) ^C
1	<u>1a; PhS(CH</u> ₂) ₅ -OAc	$\underline{4a}^{d}; \xrightarrow{PhS}_{HO} (45\%) \xrightarrow{PhS}_{HO} (24\%)$
2	$\frac{1}{10}; PhS(CH_2)_4^{CH_3}CH-OAc$	$\underline{4b}; \qquad \underbrace{PhS}_{HO} \ PhS$
3	$\frac{1c}{1}; PhS(CH_2)_4^2 CH-OAc$	$\underline{4c}; \xrightarrow{\text{PhS}}_{\text{HO}} \underbrace{42\%}_{\text{Bu}} \xrightarrow{\text{PhS}}_{\text{HO}} \underbrace{42\%}_{\text{Bu}} \xrightarrow{\text{PhS}}_{\text{HO}} \underbrace{(21\%)}_{\text{Bu}}$
4	$\frac{1d}{1}; PhS(CH_2)_3^{CHCH_2OAc}$	$\underline{4d}; \qquad \underbrace{PhS}_{HO} \underbrace{(42\%)}_{Me} \underbrace{(42\%)}_{HO} \underbrace{(10\%)}_{Me} \underbrace{(10\%)}_{HO} \underbrace{(16\%)}_{Me}$
5 ^e	$\underbrace{\underline{1e}; \operatorname{PhS(CH}_{2})_{3}}_{\operatorname{AcO}}$	$\underbrace{\underline{A}}_{PhS} \xrightarrow{H}_{OH} \underbrace{\underline{B}}_{(49\%)} \underbrace{\underline{C}}_{H}$
6 ^f	$\frac{5}{5}$; PhS(CH ₂) ₅ -OSi(Me ₂) ^t Bu	$PhS \longrightarrow (30\%)$
7 ^e	$\frac{1f}{2}$; PhS(CH ₂) ₆ -OAc	$\underline{4f};^{g} \xrightarrow{\text{PhS}}_{\text{HO}} (7\%) \xrightarrow{\text{PhS}}_{\text{HO}} (23\%)$
8	$\underline{1g}$; PhS(CH ₂) ₇ -OAc	$\underline{4g}$; ^h $PhS \longrightarrow (8\%)$
9	<u>1h;</u> PhS(CH ₂) ₄ -OAc	$PhS \longrightarrow (54\%)$

Table I Intramolecular Insertion by (Phenylthio)carbenes into α C-H Bond of Alkoxides^a

a) Unless otherwise noted, reactions were performed by the same procedure described in the text. b) All showed satisfactory spectral (IR, ¹HNMR, and mass) and high resolution mass spectral data. c) Overall yields based on (phenylthio)alkyl acetate 1. d) Reference (4). e) After the addition of MeLi (2 equiv) at -85 °C, n-BuLi (1.1 equiv) was separately added at -85 °C (entry 5) or -40 °C (entry 7). f) 1.3 Equiv of MeLi was used. After the reaction, the crude mixture was treated with n-Bu4NF in THF. g) Vebel, J. J.; Miasezewski, R. F.; Arlt, R. E. J. Org. Chem. 1977, 42, 585. h) The stereochemistry was not determined.

the proximal pseudo axial $_{lpha}$ C-H bond. In entries 2 and 3 where R¹ is an alkvl group, and in entry 4 where \mathbb{R}^2 is methyl, the substitutent would take the pseudo equatorial position, and hence the major products have the geometry as shown in Table I. The proposed transition state is further supported by the exclusive formation of the $_{cis}$ insertion product 4e in entry 5 where α C-H bond is sterically constrained to take an axial position (see Figure I). The reversal in stereoselectivity in the six-membered ring formation (entry 6) may be explained by a sterically unfavorable interaction between the oxido group and the carbenic carbon.



References and Notes

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- A highly selective intramolecular 1,5-insertion by α -diazo- β -ketoesters catalized by Rh(II) acetate has been reported recently: (a) Taber, D. F.; Petty, E. H. J. Org. Chem. 1982, 47, 4808. (b) Taber, D. F.; Raman, K. J. Am. Chem. Soc. 1983, 105, 5935. (a) Harada, T.; Oku, A. J. Am. Chem. Soc. 1981, 103, 5965. (b) Harada, T.; Akiba, E.; Oku, A. Ibid. 1983, 105, 2771. (c) Harada, T.; Nozaki, Y.; Oku, A. Tetrahedron Lett. 1983, 24, 5665. (d) Harada, T.; Nozaki, Y.; Yamaura, Y.; Oku, A. J. Am. Chem. Soc. 1985, 107, 2189. Recently, T. Cohen and his coworkers have reported a formation of 2-(phenylthio)cyclopentapol (36% yield) in the reaction of 4-oxidobutyl (3)
- (4) (phenylthio)cyclopentanol (36% yield) in the reaction of 4-oxidobutyl (phenylthio)carbene generated from 5,5-diphenylthiopentanol by the action of sec-BuLi; Cohen, T.; Ritter, R. H.; Ouellette, D. J. Am. Chem. soc. 1982, 104, 7142. Regitz, M.; Ruter, J. Chem. Ber. 1969, 102, 3877. The trans isomer of 4b and 4e were prepared by the reaction of 1,2-epoxy-
- (5)

Fig I

- (6) 1-methylcyclopentane and cis-6,7-epoxybicyclo[4,3,0]nonane⁷ with sodium phenyl thiolate, respectively. The stereochemistry of cis- and trans-4c was determined by the comparison of their ¹H NMR (200 MHz) spectra with was determined by the comparison of their ⁴H NMR (200 MHz) spectra with those of *cis*- and *trans*-4b. Protons attached to C-2 are appearing at; *cis*-4b; 3.30 (d,d, J = 8.5 and 9.8 Hz), *trans*-4b; 3.48 (m), *cis*-4c; 3.30 (d,d, J = 8.0 and 9.8 Hz), and *trans*-4c; 3.50 (m). The relative configu-ration in the three isomers of 4d with respect to methyl and hydroxyl group was determined after the desulfurization by Raney Ni (W-4). In an epimeric pair of 4d-A and 4d-C, 1-H of 4d-C resonates at an upper field (δ 3.48) by 0.2 ppm than that of 4d-A does because of the shielding effect of C-1 and C-3 substituents both *cis* to this proton.⁶ Moreover, the larger values of $J_{+,0}$ (8.0 Hz) and $J_{+,1}$ (3.8 Hz) in 4d-C than those of 4d-A larger values of J_{12} (8.0 Hz) and J_{15} ($\sqrt{8}$ Hz) in 4d-C than those of 4d-A (J_{12} = 5.2 Hz, J_{15} = $\sqrt{5}$ Hz) verifies the above assignment. The downfield shift of the resonance of 1-H in 4d-B (δ 3.77) in comparison with that of $\frac{4d-A}{2}$ and $\frac{4d-C}{2}$ together with the relatively small values of coupling constans ($J_{12} = 3.4$ and $J_{15} = 3.4$) supports its *cis*, *cis* configuration.⁸ Crandall, J. K.; Magaha, H. S.; Henderson, M. A.; Widener, R. K., Tharp, G. A. J. org. Chem. 1982, 47, 5372. (a) Gaudemer, A. In "Stereochemistry"; Kagan, H. B., Ed.; Georg Thieme Bublichered. Stattaget 1077 Val. L. p. 92 (b) Bai. M.W. J. org. Chem. (7)
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