SINGLE-STEP PREPARATION OF ALLYLIC SULFIDES HAVING 1-PHENYLTETRAZOLE-5-THIO GROUP FROM ALLYLIC ALCOHOLS USING <u>S</u>,<u>S</u>'-BIS(1-PHENYL-1<u>H</u>-TETRAZOL-5-YL) DITHIOCARBONATE AND REACTIONS INVOLVING THE ALLYLIC SULFIDES¹⁾

Kazuyoshi TAKEDA, Kanoko TSUBOYAMA, Katsumi TORII, Maki MURATA, and Haruo OGURA*

School of Parmaceutical Sciences, Kitasato University Shirokane, Minato-ku, Tokyo 108, Japan

Summary: The reaction of allylic alcohols and $\underline{S}, \underline{S}'-bis(1-phenyl-lH-tetrazol-5-yl)$ dithiocarbonate (1) gave allylic sulfides having 1-phenyltetrazole-5-thio group in a single step. Furthermore, these allylic sulfides could be applied to carbon-carbon bond and carbon-sulfur bond formations by using Grignard reagents or carbanions in the presence of a catalytic amount of copper(I) bromide or palladium (0), respectively.

Allylic sulfides have been used widely as intermediates for the formation of carboncarbon bond.²⁾ The allylic sulfides are synthesized by the reactions of allylic halides and mercapto compounds, allylic alcohols and tributylphosphine-disulfides or allylic carbonates and alkylthiotrimethylsilane in the presence of palladium as a catalyst.³⁾ In this paper we would like to report the one step procedure of the formation of allylic sulfides from allylic alcohols.

Recently, we have reported that $\underline{S}, \underline{S}'$ -bis(1-phenyl-1<u>H</u>-tetrazol-5-y1) dithiocarbonate (<u>1</u>) is a useful reagent for making esters, macrolactones, and peptides.¹⁾ We now found that this reagent (<u>1</u>) is useful for direct syntheses of allylic sulfides having 1-phenyltetrazole-5-thio group from allylic alcohols <u>2</u>. We also like to report the application of this allylic sulfides to the formation of carbon-carbon or carbon-sulfur bond.

The reaction of S,S'-bis(l-phenyl-l \underline{H} -tetrazol-5-yl) dithiocarbonate (<u>l</u>) with allylic alcohols 2 in the presence of tert-amine in acetonitrile or acetone at room temperature resulted in the liberation of carbon dioxide to give allylic sulfides 4 and/or 5 in good yields (see Scheme I).⁴⁾ In these reactions, interestingly, allylic sulfides <u>4</u> and/or <u>5</u> were formed <u>via</u> intermediate $\frac{3}{2}$ from allylic alcohols $\frac{2}{2}$ in high yields with the liberation of carbon dioxide. As expected, SN'-type products (5) were formed together with SN-type products (4) in the reaction of sec- or tert-allylic alcohols with the reagent (1) (Scheme I). This means that the allylic hydroxy groups attack the carbonyl group of reagent (1) and simultaneously 1-phenyltetrazole-5thio group (6) was eliminated by nucleophilic attack to α -carbon or γ -carbon. The results under various reaction conditions are summarized in Table II. The following observation and interpretations may deserve some comments. 1) Primary allylic alcohols gave allylic sulfides in good yields without migration of double bond, and configurations on β -carbon of geranyl (run 4) and neryl (run 5) were retained in these reactions. Therefore, these reactions occurred via SNtype reaction on α -carbon (run 1-8). 2) In the case of sec-allylic alcohols, the reaction of 3buten-l-ol with the reagent (1) gave two products which were SN-type and SN'-type products. NMR examination showed that the ratio of $\frac{4}{2}$ and $\frac{5}{2}$ was 2.0:1.0 at room temperature and 1.0:1.1 under refluxing conditions (run 9,10). The results appear to suggest that 4 is kineticallycontrolled product and the more stable 5 is the thermodynamically-controlled one. Furthermore, in the presence of 4-dimethylaminopyridine (DMAP), the ratio of 4 and 5 was 4.0:1.0 (run 11).

4106

These results also suggest that DMAP may be more effective than NEt₃ for kineticallycontrolled products. Of course, cyclic allylic alcohols gave cyclic allylic sulfides as the only product (run 12,13). 3) In linalool, $\underline{4}$ and $\underline{5}$ were obtained with 1.0:23.8 ratio for overnight reaction, and 1.0:13.7 ratio for 1 hr reaction (run 14,15). The ratios of $\underline{4}$ and $\underline{5}$ in time-course conditions may also be explicable for similar reasons as noted above. 4) Propargyl and benzylic alcohols also gave sulfides in good yields (run 16-19).



a) All of reactions were carried out at room temperature with the exception of run 10. The latter was carried out at refluxing temperature. Molar ratio of alcohol/amine/reagent (1) is 1/1/1.1. b) ST: $s \in \mathbb{N}$ c) Products were isolated by preparative TLC. d) The ratios were estimated by NMR. N = 0 The starting alcohols of run 14 and 15 were recovered in 40 and 60% yields, respectively. f) E,Z mixture.

The utilities of the allylic sulfides <u>4</u> which can be easily prepared as synthons by one step reaction were demostrated in the cross-coupling reactions with nucleophiles in the presence of CuBr or palladium (0) (Scheme II) (Table II). The cross-coupling reaction of the allylic sulfide is an important method for the carbon-carbon bond formation and various highly regioselective reactions in the presence of transition metal complex as catalysts. Only a few general methods for the cross-coupling reaction of allylic sulfide with Grignard reagent have been found in literatures. 2c, 2d, 5)

We examined the copper(I) bromide catalyzed cross-coupling reaction using the allylic sulfides 4 with the expectation that sulfur containing groups of allylic sulfides would directly be replaced by aryl or alkyl groups of the Grignard reagents. Geranyl or 2-cyclohexenyl sulfide with phenylmagnesium bromide afforded a cross-coupling product together with diphenyl as homo-coupling product in the presence of CuBr (run 20,26). Cinnamoyl sulfide gave a cross-coupling product and a small amount of dimer in the same catalyst (run 23). In these reactions, CuBr proved to be the best catalyst. The other catalysts such as nickel phosphine complexes gave only homo-coupling products. The reaction mechanism of copper complex as a catalyst may be somewhat different from that of nickel complex, while 4 equiv. of Grignard reagents gave the products in higher yields than same equiv. It is known that on mixing a Grignard reagent with a copper(I) halide the equilibria in equations (A) and (B) operate, and the two reagents rapidly equilibrate in two alternative ways. In these equilibria, the concentration of CuX controls the modes of equilibrium and the $RMgX + CuX \Longrightarrow RCu + MgX_{2}$ (A) $RCu + RMgX \rightleftharpoons (R_{2}Cu)^{-}MgX^{+}(B)$ mode exerts the influence on the regioselectivity of crosscoupling reaction, that is, in the presence of exess CuX, the cross-coupling reaction is predominant through SN'-type reaction by co-ordination of allylic sulfide with RCu (equation(A)), whereas the $(R_2Cu)^{-}Mgx^{+}$ may be formed through SN-type reaction in the case of a catalytic amount of $Cux.^{2d}$ (equation(B)) Since our reaction also gave only SN-type product in the presence of a catalytic amount of CuX, the effective reactant may be presumably $(R_2 Cu)^{-}MgX^{+}$.

On the other hand, the reaction of the allylic sulfides, and carbanion or sulfinate was carried out in a catalytic amount of palladium phosphine complexes. The palladium catalyzed reaction of allylic derivatives with carbanion $^{6)}$ or sulfinate, $^{7)}$ carried out in the presence of the phosphine ligand, is a good method for carbon-carbon or carbon-sulfur in sulfone formations. Under the presence of palladium-phosphine complex, the reaction of the allylic sulfide, and carbanion or sulfinate could also be adopted for the formation of carboncarbon bond or synthesis of allylic sulfone which is important as leaving group in nucleophilic displacement. ⁶⁾ Treatment of the allylic sulfide with a catalytic amount of $Pd(PPh_3)_4$ in the presence of a soft nuclephile such as sodium methyl phenylsulfonylacetate or sodium dimethyl malonate under refluxing in CH₂CN led to alkylation smoothly (run 21,24). Furthermore, in the reaction of π -allyl complex of the geranyl sulfide and sodium p-tolylsulfinate, as expected, coupling products were obtained in reasonable yields, though SN-type product 7 was formed together with SN'-type product 8 (ratio 1.0:4.6) (run 22). This result of ratio is different from that in Kotake's 7) report which used geranyl acetate and sodium p-tolylsulfinate in the presence of Pd(PPh3)4, and the difference could not be explained clearly. Cinnamoyl and 2-cyclohexenyl sulfide gave only one product in good yield (run 25,27).

Finally, the cross-coupling reaction of the allylic sulfide having l-phenyltetrazole-5thio group with Grignard reagent could be applied to the synthesis of dendrolasin, which was isolated from mandibular gland of the ant <u>Lasius</u> (D<u>endrolasius</u>) <u>fulginosus</u> Latr. ⁸⁾ The geranyl sulfide (run 4) was treated with 3-furylmethylmagnesium bromide ⁹⁾ in the presence of a catalytic amount of CuBr, at -78°C. The yield of dendrolasin was 86%. In this reaction, we confirmed a trace of isomer other than desired dendrolasin by NMR examination.

```
4108
```



a) 4PhMgBr/THF, CuBr llmol%, R.T. 3hr. b) 4CH3OCOCCH(Na)SO2Ph/CH3CN, Pd(Ph3P)4 3.8mol%, Reflux for 6hr. c) 4NaSO₂-Ph-CH₃(p)/MeOH,THF, Pd(Ph₃P)₄ 6.1mo1%, Reflux for 24hr. d) 4PhMgBr/THF, CuBr llmol%, R.T. overnight. e) 4(MeOOC)2CHNa/THF, Pd(dba)2 lmol%, DPPE 2.5mol%, Reflux for lhr. f) 4NaSO₂-Ph-CH₃(p)/MeOH,THF, Pd(Ph₃P)₄ 4.3mo1%, Reflux for 6hr. g) 4PhMgBr/THF, CuBr llmol% R.T. 4hr. h) 4NaSO2-Ph-CH3(p)/MeOH-THF, Pd(Ph3P)4 4.3mol%, Reflux for 4hr. i) All products were isolated by preparative TLC. j) Yield of isolated products. k) Estimated by NMR examinations. 1) E, Z mixture.

References and notes

1) This consitutes part XVI of a series entitled. Studies on Activating Methods of Functional

- Groups. Part XV.; K. Takeda, K. Tsuboyama, H. Takayanagi, and H. Ogura, <u>Synthesis</u>, <u>560</u> (1987).
 (a) For General Review; E. Block, "Reactions of Organosulfur Compounds", Academic Press, New York 1978. (b) D.A. Evans and G. C. Andrews, <u>Acc. Chem. Res.</u>, <u>7</u>, 147 (1974); (c) H. Okamura and H. Takei, Tetrahedron Lett., 3425 (1979); (d) V. Calo, L. Lopez, and W. F. Carlucci, J. Chem. Soc., Perkin Trans I, 2953 (1983).
- 3) B. M. Trost and T. S. Scanlan, Tetrahedron Lett., 27, 4141 (1986)
- 4) A typical experimental procedure for the preparation of allylic sulfide is described as follows: to a CH₃CN (10ml) solution of geranio1 (154mg, 1mmol) and reagent (1) (420mg, 1.1mmol) was sucessively added a solution of NEt3 (101mg, 1mmol) in CH3CN (0.5ml) at room temperature for 24hr. Reaction mixture was evaporated and AcOEt was added to residue. AcOEt layer was washed with 4%NaHCO3, H2O, 1N-HC1, and brine, dried over sodium sulfate. Organic layer was evaporated and the oily product was separated by preparative TLC (Benzene:Acetone=300:1), 280mg (89%), M.S. (m/2) M⁺ 314. Anal. Calcd for C₁₇H₂₂N₄S, C,64.93, H,7.05, N,17.81. Found, C,64.97, H,7.06, N,18.00, IRvcm⁻¹ (neat), 2920 (CH), 1600 (Ph), NMR δ ppm (CDC1₃), 1.58 (3H,s, C7-CH₃), 1.65 (3H,s,C7'-CH₃), 1.75 (3H,s,C3-CH₃), 1.98-2.10 (4H,m,-CH₂CH₂-), 4.07 (2H,d, J=8.0Hz,CH2-S), 5.01-5.06 (1H,m,C6-H), 5.40 (1H,t,J=8.0Hz,C2-H), 7.50-7.61 (5H,m,Ph). NOE was observed between C3-CH3 and C1-H2 at 5.3%, but it was nothing between C3-CH3 and C2-H, therefore, we determined trans configuration was assigned to the double bond system.
- 5) (a) Y. Gendrean, J. F. Normat, and J. Villieras, J. Organomet. Chem., 142, 1 (1977). (b) P. Barsanti, V. Calo, L. Lopez, G. Marchese, F. Naso, and G. Pesce, J. Chem. Soc., Chem. Commun., 1978, 1085.
- 6) For General Review; R. F. Heck, "Palladium Reagents in Organic Syntheses", Academic Press, London 1985.
- 7) K. Inomata, T. Yamamoto, and H. Kotake, Chem. Lett., 1357 (1981).
- 8) A. Quilico, F. Piozzi, and M. Pavan, Tetrahedron, 1, 177 (1957).
- 9) S. Araki and Y. Butsugan, Bull. Chem. Soc. Jpn., 56, 1446 (1983). They synthezied dendrolasin by using geranyl diethyl phosphate and 3-furylmethylmagnesium bromide in the presence of CuI in 64% yield together with regio isomer in 17% yield.

(Received in Japan 11 March 1988)