CHEMISTRY LETTERS, pp. 259-262, 1972. Published by the Chemical Society of Japan

SELECTIVE CARBON-CARBON BOND FORMING REACTION BY THE USE OF ALLYL 2-PYRIDYL SULFIDE DERIVATIVES —— TOTAL SYNTHESIS OF α-cis-BERGAMOTENE

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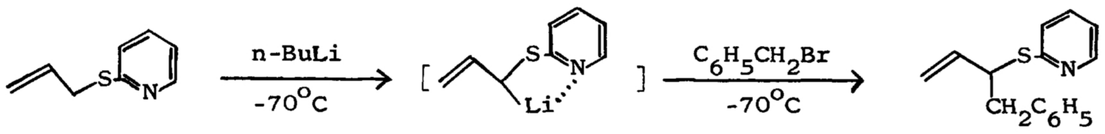
A convenient method for the selective formation of α-coupled allylic compounds was established by the alkylation of lithium salt of allylic 2-pyridyl sulfide with organic halide and the successive reductive desulfurization of the α-alkylated allylic sulfide with $CuCl_2$ and $LiAlH_4$. The method was successfully applied to the total synthesis of α-cis-bergamotene.

In general, it is known that alkylation of alkali metal derivative of allylic compound with organic halide always accompanies with some side reactions such as isomerization of double bond and halogen-metal interconversion$^{1)}$. Recently, it was found in our laboratory that the alkylation of an allyl compound with organic halide is carried out efficiently by utilizing the lithium salt of allyl 2-pyridyl sulfide, probably because of the stabilization of the salt by the formation of five membered chelate$^{2)}$. A successive reductive desulfurization of the alkylated product with $CuCl_2$ and $LiAlH_4$ provides the α-olefin in good yield almost without the isomerization of the double bond.

This communication reports the further investigation of the selective alkylation of allylic 2-pyridyl sulfide and of the reductive fission of 2-pyridylthio group with $CuCl_2$ and $LiAlH_4$, and its application to the synthesis of a sesquiterpene, α-cis-bergamotene.

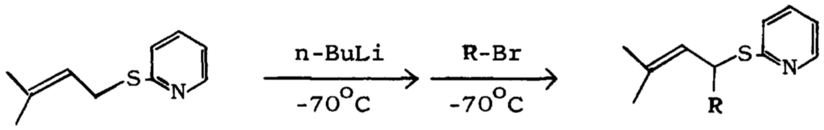
By the method previously described, the alkylation of allyl 2-pyridyl sulfide (I) was carried out at -25°- -15°C, and α-coupled sulfide (II) was obtained in 92-95% pure (γ-coupled product was contained slightly as by product). In order to improve the selectivity of alkylation, the reaction was tried under more mild condition. For example, allyl 2-pyridylsulfide (I) was treated with 1.05 equiv of n-butyllithium in tetrahydrofuran at -70°C under an argon atmosphere, and after 0.5 hr, an equiv of benzyl bromide was added dropwise at -70°C. After stirring for 0.5 hr at the temperature, the reaction mixture was hydrolyzed. Organic layer, on extraction with ether and distillation, gave α-coupled product, α-benzylallyl 2-pyridyl sulfide (II) in 79% yield. Satisfactory nmr, ir and analytical data were obtained and it was found by glpc examination that the α-coupled product (II) is contained in 99% pure.



(I) (II)

79% yield (99% pure)

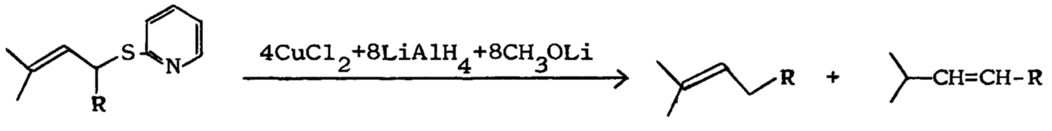
In a similar way, γ,γ-dimethylallyl 2-pyridyl sulfide (III) was converted into its lithium salt with n-butyllithium and successive alkylation with benzyl bromide or phenetyl bromide afforded the alkylated product in 89% or 77% yield, respectively. The nmr spectra of the products were identified with α-coupled sulfides (IV) and the glpc examinations showed that α-coupled products (IV) were contained in more than 99% pure.



(III) (IV)

IV a) $R=C_6H_5CH_2$ 89% yield (>99% pure)
b) $R=C_6H_5CH_2CH_2$ 77% yield (>99% pure)

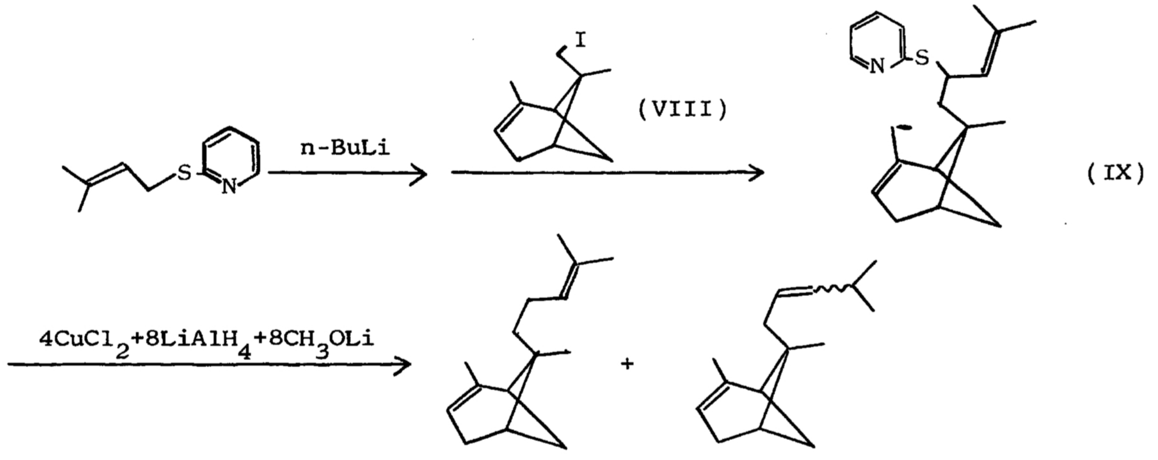
In the previous report$^{2)}$, the useful method of reductive desulfurization of sulfides by the use of $CuCl_2$ and $LiAlH_4$ was described, and the treatment of α-benzylallyl 2-pyridyl sulfide with 4 equiv of $CuCl_2$ and 8 equiv of $LiAlH_4$ in tetrahydrofuran gave the reduction product, 1-phenyl-3-butene, without accompanying the isomerization as the migration of double bond. On the other hand, when the reductive desulfurization of γ,γ-dimethylallyl derivative (IV) was tried in the same manner, the reduction product (V) was not obtained, but viscus oil which was distilled at higher b.p. was yielded. However, it was found that the additional use of lithium methoxide with $CuCl_2$ and $LiAlH_4$ afforded the desired reduction product (V) in good yield. For instance, tetrahydrofuan solution of 4 equiv of $CuCl_2$, 8 equivs of $LiAlH_4$ and lithium methoxide was stirred for 1 hr under an argon atmosphere, then α-benzyl-γ,γ-dimethylallyl 2-pyridylsulfide (IVa) was added dropwise into the reaction mixture under refluxing. After stirring for 1 hr, the reaction mixture was hydrolyzed and reduction product was obtained in 77% yield on filtration chromatography through silica gel and distillation. By glpc examination, it was shown that the product contained two components in 78:22 ratio. The nmr spectrum of each component, which was separated by glpc, showed that the major compenent is desired 1-phenyl-4-methyl-3-pentene (Va) and the minor component is the isomer, 1-phenyl-4-methyl-2-pentene (VIa). The reduction of IVb was tried in a similar way, and the reduction products,(Vb) and (VIb), were obtained in 87% yield.



(IV) (V) (VI)

	Yield of Reduction Product		Isomer Ration (V:VI)
a)	$R=C_6H_5CH_2$	77%	78 : 22
b)	$R=C_6H_5CH_2CH_2$	87%	77 : 23

Finally, the selective alkylation and reductive fission of allylic 2-pyridylsulfide described above were applied to the total synthesis of α-cis-bergamotene (VII)[3]. The treatment of γ,γ-dimethylallyl 2-pyridylsulfide with n-butyllithium in tetrahydrofuran at -70°C under an argon atmosphere and the addition of 9-iodo-α-pinene (VIII)[4] gave coupled sulfide (IX) in 79% yield. (Purified by silica gel column chromatography), then the reduction of IX with 4 equiv of $CuCl_2$, 8 equivs of $LiAlH_4$ and lithium methoxide was carried out in tetrahydrofuran under refluxing for 1 hr. The reduction product was obtained in 91% yield, and it was found that it contained two compenents in 55:45 ratio by glpc examination. Each component was separated by glpc, and it was found that the major product was the desired α-cis-bergamotene (VII) [Nmr spectrum ($CDCl_3$) showed the charasteristic peaks at 8.84 ((1H, d, =7Hz), 8.23 (3H, s), 8.42 (3H, s), 8.34 (3H, s), 8.31 (3H, d, =2Hz), 4.99 (1H, broad t, =7Hz), which are identical with the datum of Gibson's report[3b]) Mass spectrum showed the parent peak at m/e 204, and the base peak at m/e 93.] and the minor product was its isomer (X) [Nmr spectrum ($CDCl_3$) showed four peaks of methyl group at 9.08 (s), 9.02 (s), 8.78 (s) and 8.32 (d), and the peak of three olefinic protons at 4.70-4.85 (m). Mass spectrum showed the parent peak at m/e 204, and the fragment peak at 161 ($M^+-CH(CH_3)_2$)].



(VIII) (IX)

(VII) (X)

The ratio of VII:X = 55:45

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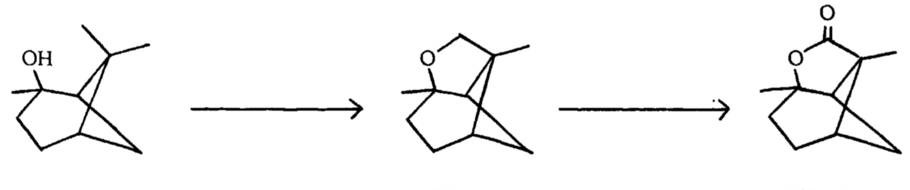
   b. T. W. Gibson and W. F. Erman has synthesized α-cis-bergamotene; J. Amer. Chem. Soc., 91, 4771 (1969).

4) The synthesis of 9-iodo-α-pinene (VIII) was carried out according to the method of Gibson and Erman[3b]. The lactone (XIII), which is the key intermediate of the synthesis of VIII, was obtained in very low yield by Gibson's method. The XIII was synthesized in good yield from the alcohol (XI) by the following procedure; 1.5 equiv of iodine was added to the n-pentane solution of the alcohol (XI) and 3 equiv of yellow mercuric oxide and the irradiation of the reaction mixture with a tungsten lamp afforded the ether (XII) in 65% yield. The lactone (XIII) was obtained in 73% by the oxidation of the ether (XII) with 20 equiv of chromium trioxide-pyridine complex in methylene chloride under refluxing[5].



XI XII XIII

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(Received February 8, 1972)