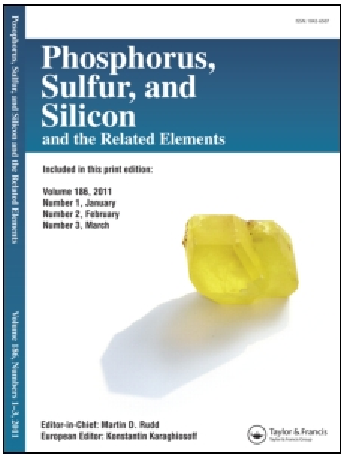

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LIGAND COUPLING AND PSEUDOROTATION IN THE REACTION OF ALKYL 2-PYRIDYL SULFOXIDE WITH GRIGNARD REAGENTS[1]

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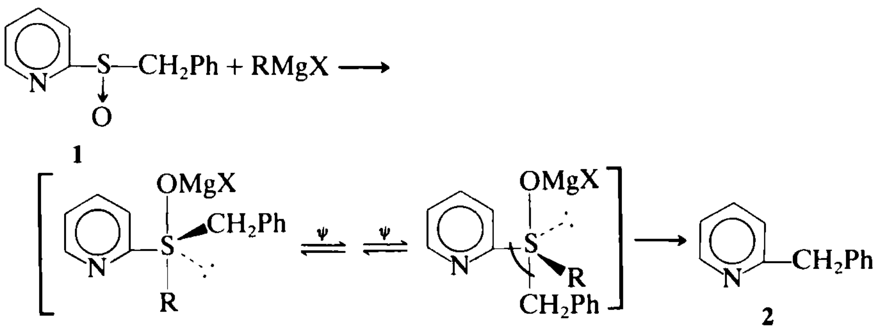
In the reaction of benzyl 2-pyridyl sulfoxide (**1**) with $C_6H_5CH_2MgCl$, the incoming Grignard reagent tends to couple preferentially with 2-pyridyl group at lower temperatures, whereas, at higher temperatures, coupling between benzyl and 2-pyridyl groups with **1** tends to increase due presumably to the relatively more facile pseudorotation[2] at higher temperatures.

In previous papers,[3,4] we have shown that in the reaction of benzyl 2-pyridyl sulfoxide (**1**) with the Grignard reagent 2-benzylpyridine (**2**) was obtained in excellent yield, whereas in the reaction of allyl 2-pyridyl sulfoxide with $C_6H_5CH_2MgCl$, **2** was the sole coupling product obtained also in excellent yield. The former reaction is interesting in that the incipient σ-sulfurane formed is presumed to undergo pseudorotation to place the coupling ligands, i.e., 2-pyridyl and benzyl groups, at equatorial and axial positions, respectively, prior to the final ligand coupling to afford **2**, as shown in Equation 1.



(1)

The alkaline hydrolysis of dialkylarylbenzylphosphonium salts has also been considered to proceed via formation of the incipient phosphorane intermediate, from which a benzyl group is extruded. This means that benzyl group is considered to be a better leaving group and more apicophilic than the aryl group.[5] In these hypervalent intermediates, such as phosphoranes and sulfuranes,

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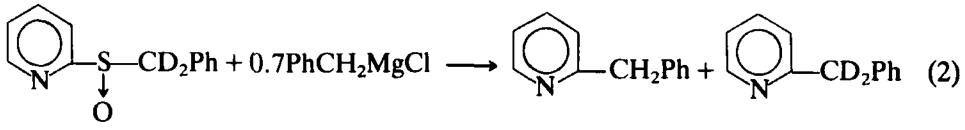
the polar ligand is considered to occupy an axial position while the electron-donating or π-ligands tend to be at an equatorial position. By analogy, in this reaction between **1** with any alkyl Grignard reagent, the 2-pyridyl group, being an aromatic π-system, is considered to be placed at an equatorial position while the benzyl group would occupy an axial position for facile ligand coupling. Since attack of the nucleophile has been considered to take place from an axial position to form the incipient σ-sulfurane, the nucleophilic attack of benzylmagnesium chloride on an alkyl or aryl 2-pyridyl sulfoxide would place the two coupling ligands in the proper positions, i.e., the 2-pyridyl group equatorial and the incoming benzyl group axial, without requiring pseudorotation if attack of the nucleophile takes place from the direction opposite the sulfinyl oxygen atom, namely direction (2), as shown later. Although the benzylic group has been found to be favored for coupling with the 2-pyridyl group in the reaction of benzylic 2-pyridyl sulfoxides with an alkyl or aryl Grignard reagent, in order for the benzyl group to couple with 2-pyridyl within the same molecule, the intermediary σ-sulfurane formed by the nucleophilic attack of the Grignard reagent on the sulfoxide has to undergo pseudorotation to place the benzylic group at axial and the 2-pyridyl group at equatorial positions, respectively.

One way to examine the ease of pseudorotation of the incipient σ-sulfurane formed by the nucleophilic attack of benzylmagnesium chloride on benzylic 2-pyridyl sulfoxide would be to compare the relative amounts of the coupling products, 2-benzylic pyridines, by which the relative ratios of the incoming benzyl group and the original benzylic group of the sulfoxide can be estimated. Thus, we have examined the reactions of benzylic 2-pyridyl sulfoxides with other benzylic Grignard reagents estimating the relative amounts of the coupling products **2** and **2**-d$_2$ in the reaction of D-labeled **1**–d$_2$ with $C_6H_5CH_2MgCl$ and that of **1** with 4-methylphenylmethylmagnesium chloride and found that the relative amounts of the coupling products, **2** to **2**-d$_2$ and the relative amounts of 2-(4-methylphenylmethyl)pyridine and **2** decrease as the temperature of the reaction is raised. This paper describes the results of these experiments and consideration of the plausible direction of the original attacking nucleophile on benzyl 2-pyridyl sulfoxide.

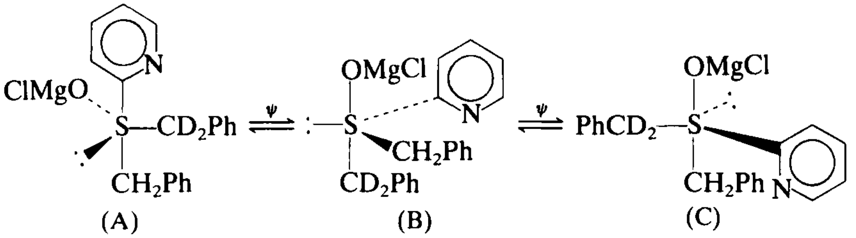
RESULTS AND DISCUSSION

When **1**-d$_2$ was treated with 0.7 equivalent of $C_6H_5CH_2MgCl$ at low temperature, i.e., −68°C, the coupling product was predominantly **2**, as shown in the following Equation 2. This means that the incoming benzyl group can form the sulfurane



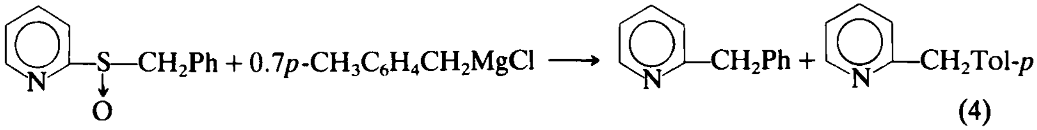
1-d$_2$	−68°C	95%	5%
	r.t.	88%	12%

(C) in which the benzyl and 2-pyridyl groups are placed in the right positions, i.e., axial and equatorial, respectively, for facile ligand coupling without pseudorotation. On the other hand, in order for the benzyl-d_2 and 2-pyridyl groups to couple, the σ-sulfurane (C) has to undergo pseudorotation to structure (B) as shown in the following Equation 3.



(3)

As the temperature increased to room temperature, the ratio of **2** and **2**-d_2 decreased. This suggests that pseudorotation becomes more facile at higher temperatures. This effect of temperature on the product composition was also observed in the reaction of **1** with 4-methylphenylmethylmagnesium chloride. We found again that the incoming benzylic group underwent coupling preferentially at room temperature. However, when the temperature of the reaction was raised to 50°C, the rate of pseudorotation seemed to become quite competitive with that of ligand coupling and the formation of **2** increased substantially as shown in the following Equation 4.



(4)

1	r.t.	22%	78%
	50°C	60	40

These observations suggest that both ligand coupling and pseudorotation within these σ-sulfuranes proceed nearly with the same ease at a particular temperature but at different rates at other temperatures.

Although ligand coupling and pseudorotation within the sulfurane has been discussed, it would be pertinent to consider even briefly the most favorable attacking direction of the Grignard reagent on the sulfinyl sulfur atom to form the favorable σ-sulfurane at the initial step.

Four possible directions of attack are illustrated schematically for **1**-d_2 as shown in the following Figure 1.

If the Grignard reagent attacks from direction (1), the resulting sulfurane should be (A), which upon pseudorotation may be converted to structure (B),

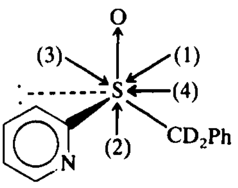
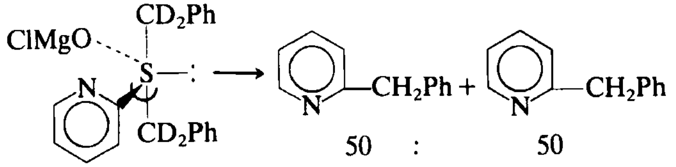


FIGURE 1 Four attacking directions of Grignard reagent for benzyl-d_2 2-pyridyl sulfoxides.

which is favorable for the coupling of benzyl-d_2 and 2-pyridyl groups contrary to our observation as shown in Equation 3. In order for the unlabeled benzyl group to couple with the 2-pyridyl group, the sulfurane (A) has to undergo a number of pseudorotations to assume structure (C) prior to coupling. Thus, attack from the direction (1) may not be favorable. When the Grignard reagent attacks from direction (3), two benzyl groups will occupy equivalent axial positions in the resulting σ-sulfurane (D) and hence the coupling product should be composed of a one-to-one mixture of **2** and **2**-d_2 derivatives. This is inconsistent with the experimental results. Therefore, the formation of a σ-sulfurane from direction (3), shown in the following Equation 5, may be ruled out.



(D)

(5)

Attack from direction (4) will put the lone pair at an axial position to form a σ-sulfurane, which would be highly unstable, since lone pairs, negatively charged ligands and π-systems are always oriented at the equatorial position.[5] Attack of $C_6H_5CH_2MgCl$ from direction (2) alone is considered to be favored, since it will form σ-sulfurane (C) directly in which both benzyl and 2-pyridyl groups are oriented conveniently for facile ligand coupling, as described earlier. Thus, the most plausible direction of nucleophilicic attack would be direction (2) to generate σ-sulfurane (C).

In the reaction of ipso-^{14}C-labeled diphenyl-*N*-*p*-tosylsulfilimine with unlabeled C_6H_5MgBr in refluxing THF, the coupling products, biphenyl and diphenyl sulfide, obtained in 60% and 70% yields, respectively, were found to have $\frac{1}{3}$ and $\frac{2}{3}$ or the original ^{14}C of the starting sulfilimine at their ipso positions,[6] as mentioned in our previous paper.[3]

In this reaction too, the ligand coupling appears to have taken place faster than the pseudorotation within the σ-sulfurane formed by the nucleophilic attack of the Grignard reagent on the intermediary triphenylsulfonium salt. If the pseudorotation would be faster than the coupling, the resulting products should both have $\frac{1}{2}$ of the ^{14}C in their ipso positions. This was found not to be the case when triphenylsulfonium salt was treated with ^{14}C-labeled phenyllithium in diethyl ether at −78°C.[7] In this case, the ipso carbon atoms in both diphenyl sulfide and biphenyl were completely scrambled. In this reaction, however, there is a possiblity of very fast ligand exchange between triphenylsulfonium salt and phenyllithium prior to coupling of two phenyl groups, since phenyllithium is considered to be more nucleophilic toward the hard sulfonium sulfur atom, and it is possible that the pseudorotation has nothing to do with the scrambling of the ipso-^{14}C label; eg, S_N2-type ligand exchange is responsible. When one compares the values of free energy of activation of both pseudorotation and ligand exchange for σ-sulfuranes bearing polar heteroatom ligands, the value for pseudorotation appears to be somewhat smaller, i.e., 7.4 kcal (31.4 kJ)/mol to

13.5 kcal (56.6 kJ)/mol for Martin's sulfurane,[8] and 10.3 kcal (43.7 kJ)/mol for SF_4,[9] than that of ligand exchange, e.g., 20 kcal (84 kJ)/mol for a typical acid-catalyzed oxygen exchange,[10] which involves two axial polar oxygen-atom ligands. Unfortunately, there has been no measured kinetic value for ligand exchange and pseudorotation, not to mention ligand coupling for the σ-sulfurane in which two carbon ligands are involved. However, in view of their markedly unstable nature, both ligand coupling and pseudorotation within these σ-sulfuranes would be quite facile. In order to confirm this, further experiments are now underway in these laboratories.

EXPERIMENTAL

General. The nmr spectra were obtained on a Hitachi R-600 FT-NMR spectrometer in $CDCl_3$ or CCl_4 using TMS as an internal standard. All the reactions were monitored by TLC (Merck, Kieselgel 60-GF_{254}, aluminum oxide 60-GF_{254}), GLPC(HITACHI 163, using a 5% silicon GE-30 on 60–80 mesh or 2% silicon OV-1 chromosorb W on 80–100 mesh in column). Silica gel used for column chromatography was Merck Kieselgel 60. Alumina used for column chromatography was Wako activated aluminum oxide, about 200 mesh. Mass spectra were taken with a HITACHI RMU-6MG mass spectrometer.

Materials. All reagents were obtained from Wako Pure Chemical Industries Ltd., or Aldrich Chemical Co. The reagents using as reaction solvents were further purified by general methods. Preparation of **1** and **1**-d_2 were described in our previous paper.[4]

Reaction of Benzyl 2-Pyridyl Sulfoxide with Grignard Reagent. A typical procedure is as follows. To a solution of **1**-d_2 (200 mg, 0.91 mmol) in 8 ml THF, $C_6H_5CH_2MgCl$ (0.64 ml, 0.64 mmol) in 1.0 mmol/ml THF solution was added with stirring under N_2 at 25°C. After the solution was stirred for 15 min, water was added to the solution and the solution was neutralized with dil. HCl solution and extracted three times with CH_2Cl_2. The combined CH_2Cl_2 layer was dried over anhyd. Na_2SO_4 and the solvent was evaporated. The residue was separated through activated alumina column chromatography using hexane as eluent. First fraction contained a mixture of $(C_6H_5CH_2S)_2$, $C_6H_5CH_2SSCD_2C_6H_5$ and $(C_6H_5CD_2S)_2$. By changing eluent from hexane to benzene, a mixture of **2** and **2**-d_2 of 76 mg was obtained. The ratio of **2** and **2**-d_2 determined by ^{1}H-nmr on the basis of the proton at the 6-pyridyl position was about 88:12. Other sulfoxides reacted with Grignard reagent in the same way as shown in Equation 4.

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