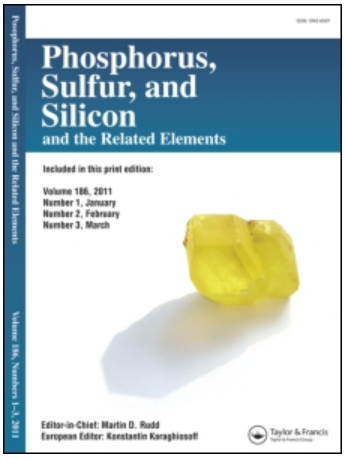

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LIGAND COUPLING REACTIONS OF 2-PYRIDYL, 4-PYRIDYL AND 2-PYRIMIDYL SULFOXIDES WITH GRIGNARD REAGENTS

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Dedicated to Professor John Verkade on the occasion of his 60th birthday

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The ligand coupling reaction was extended to 3- and 4-pyridyl sulfoxides as well as the 2-pyrimidyl moiety with Grignard reagents. It was found that both 4-pyridyl and 2-pyrimidyl sulfoxides nicely underwent the ligand coupling reactions, but 3-pyridyl sulfoxide underwent ligand exchange.

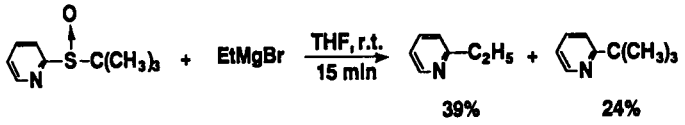
Key words: Sulfoxides, Grignard reagents, ligand coupling reaction.

Many years ago,[1] it was shown that the reaction of the triarylsulfonium ion with any aryl Grignard or organolithium reagent proceeded by what would be now called ligand coupling. Subsequent discovery of a high-yield reaction of benzyl 2-pyridyl sulfoxide with Grignard reagents,[2] led to a serious study of this synthetically useful and mechanistically interesting reaction.

In this paper good ligand couplings of 4-pyridyl and 2-pyrimidyl sulfoxides with aryl or benzyl Grignard reagent are reported. Benzyl 3-pyridyl sulfoxide with phenylmagnesium bromide underwent ligand exchange to afford benzyl phenyl sulfoxide and diphenyl sulfoxide. Some alkyl 2-pyridyl sulfoxides with ethylmagnesium bromide also gave the ligand coupling products. The competitive reactions between heteroaryl substituted sulfoxides and benzyl Grignard reagent were performed and interesting results were found.

RESULTS AND DISCUSSION

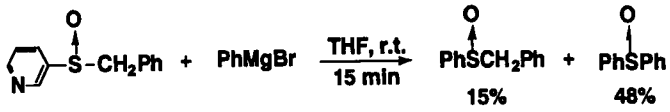
We have had a theory that an electron donating alkyl group which would form a stable carbocation attached to the sulfoxide group is favored for the ligand coupling reaction. Thus, *sec*- and *tert*-alkyl 2-pyridyl sulfoxides were treated with ethylmagnesium bromide, no ligand exchange proceeded but the coupling of alkyl and 2-pyridyl group took place. One representative example is shown below.



Apparently, the theory was right and indeed there was a nice ligand coupling of 2-pyridyl and an alkyl group which gives stable carbocationic species in the reaction of alkyl 2-pyridyl sulfoxide with alkylmagnesium bromide. However, the allyl group seems to couple more favorably with the 2-pyridyl group than the alkyl group. Thus, allyl 2-pyridyl sulfoxide reacts with phenylmagnesium bromide to afford allyl 2-pyridine. As compared to the allyl ligand, benzyl is a far better coupling ligand.

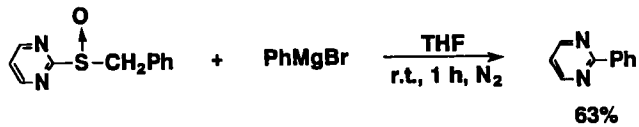
Indeed, the coupling of benzyl 2-pyridyl sulfoxide with any Grignard reagent were the first we looked at as the examples to study the reaction.[3] The reaction of benzyl 4-pyridyl sulfoxide was performed with one equivalent mole of phenylmagnesium bromide and found to be a good example of a ligand coupling reaction and 4-benzylpyridine was obtained in 60% yield as shown below, although the reaction conditions were not optimized.

However, when benzyl 3-pyridyl sulfoxide was treated with one equivalent amount of phenylmagnesium bromide, there was no ligand coupling product, 3-benzylpyridine but ligand exchange products, shown below, were found among the product. Benzyl phenyl sulfoxide is undoubtedly formed as the primary ligand exchange prod-

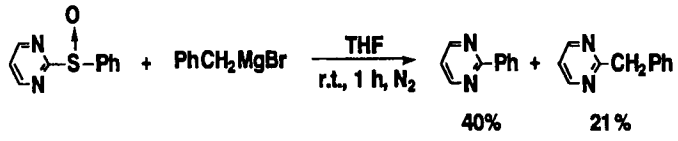


uct which would receive the nucleophilic attack of another mole of phenyl ligand to afford diphenyl sulfoxide, the secondary ligand exchange product. This means that 3-pyridyl group is a better leaving group than benzyl group which in turn is a better leaving group than phenyl group as in the alkaline hydrolysis to involve a hypervalent intermediate.[4]

The 2-pyrimidyl group has been found to be a good ligand coupling ligand. Interestingly when benzyl 2-pyrimidyl sulfoxide was treated with benzylmagnesium bromide, 2-phenylpyrimidine was obtained in 63% yield while when benzyl 2-py-

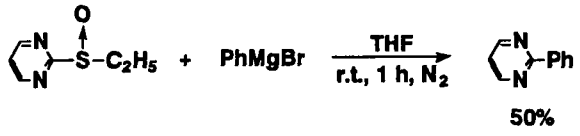


rimidine was treated with benzylmagnesium bromide in THF, 2-phenylpyrimidine was obtained in 40% yield but 2-benzyl pyrimidine was formed in 21% yield, ap-



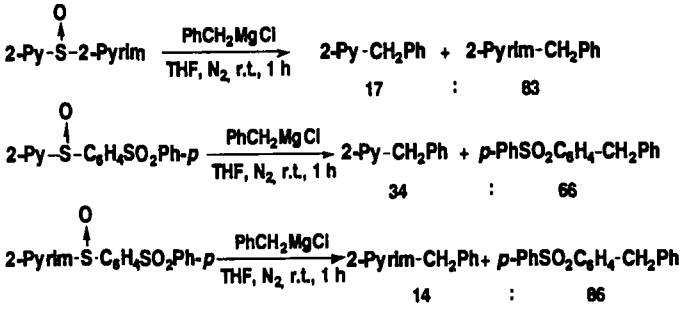
parently as pointed out earlier by Holmes[4] phenyl is a better coupling ligand than the benzyl group.

There is another example of ligand coupling, namely ethyl pyrimidyl sulfoxide with phenylmagnesium bromide as shown below. None of the reactions were optimized, however it shows that the 2-pyrimidyl group is a good coupling ligand and



indeed the substituted pyrimidine can couple with other substituted 2-pyrimidine sulfoxides with alkylmagnesium or phenyl bromides to afford interesting anti-fungicides.[5] Probably, the 2-pyrimidyl group is electron-withdrawing enough to stabilize the incipient σ-sulfuran formed by the nucleophilic attack of the benzyl group or phenyl group and the sulfurane thus formed would be so long lived that pseudorotation takes place to place a 2-pyrimidyl group at an equatorial coordinate ready for the coupling.

The following three competitive reactions are interesting in that the ligand coupling is quite sensitive to the stereo-electronic environment. Not only the electronic effect, but the bulky phenylsulfonylphenyl group tends to couple with benzyl group.



EXPERIMENTAL

General

All the melting points were uncorrected and taken on a Yanaco micro melting-point apparatus. IR spectra were obtained an a JASCO mode IRA-1 spectromater. 1H-NMR and 13C-NMR spectra were taken on HITACHI R-24B, HITACHI R-90H FT-NMR and JEOL FX-100 spectrometer at ionization potentional of 70 ev at the University laboratory. GLC and HPLC analyses were performed on Yanaco model G-180 gas chromatography with a glass column (1 m × 3 mm i.d.) packed with 10% PEG-20H on chromatography equipped with a Zelbax-ODS column using Shimazu SPD-6A UV monitor. All the reactions were monitored by chromatography, namely, TLC (Wacogel B-O), GLC and HPLC. Silica gel used for column chromatography was Wacogel HPLC C-200, ca. 200 mesh. Alumina used for column chromatography was Waco activated aluminum oxide about 200 mesh.

Materials

All reagents were obtained from Waco Pure Chemical Industries Ltd., Tokyo Kasei Co., or Aldrich Chemical Co. The reagents used and solvents were further purified by general procedures.

Starting Materials

All the sulfoxides were prepared from the corresponding sulfoxides, which were obtained by the reactions of aryl halide with sodium thiolates (ArSNa) in HMPA. A typical experimental procedure is as follows.

General Procedure for Sulfide Preparation

To a stirred solution of CH_3ONa (2.3 g, 43.0 mmole) in 20 ml HMPA under nitrogen atmosphere at room temperature, a solution of 2-mercaptopyrimidine (4.8 g, 43.0 mmole) in 100 ml HMPA was added slowly. After stirring for 30 min, benzyl chloride (5.4 g, 43.0 mmole) was added to the solution and stirred for 19 hours. Then this mixture was quietly poured into a saturated brine and extracted three times with diethyl ether. The combined mixture of organic layers was washed three times with brine and water, respectively and dried over anhydrous sodium sulfate. After the solvent was removed on the rotary evaporator, the remaining residue was separated through silica gel column chromatography using benzene as an eluent. Benzyl 2-pyrimidine sulfide of 8.4 g (41.5 mmole) was obtained in 97% yield.

General Procedure for Sulfoxide Preparation

To a stirred solution of benzyl 2-pyrimidyl sulfoxide (4.0 g, 19.8 mmole) in 50 ml $CHCl_3$, a solution of *m*-chloroperbenzoic acid (4.0 g, 22.4 mmple) in 60 ml $CHCl_3$ was added using a funnel at $-10°C$. After three hours, the reaction mixture was returned to room temperature and in order to remove unreacted *m*-chloroperbenzoic acid, saturated aqueous sodium thiosulfate was added to the solution. Furthermore the combined organic layer was neutralized with 1 N sodium bicarbonate and washed three times with water and dried over anhydrous sodium sulfate. After the solvent was removed by evaporation, the residue was separated by silica gel column chromatography using benzene: ethyl acetate = 4:1 as the eluent. Benzyl 2-pyrimidyl sulfoxide of 4.10 g (18.8 mmole) was obtained in 88% yield.

Reaction of Sulfoxides with Grignard Reagents

A typical experimental procedure is as follows. To a solution of benzyl 2-pyrimidyl sulfoxide (300 mg, 1.38 mmole) in 4 ml THF, PhMgBr (1.38 ml, 1.38 mmole) in 1.0 mmole/ml THF solution was added with stirring under nitrogen atmosphere at room temperature. Stirring was continued for one hour. Then 5 ml of water was added to the reaction mixture and the solution was neutralized with dilute HCl solution and extracted three times with chloroform. The combined chroloform layer was washed three times with water and dried over anhydrous sodium sulfate. After the solvent was removed by evaporation, the residue was separated by silica gel column chromatography using chloroform as an eluent. Thus, 2-phenylpyrimidine (136 mg, 0.87 mmole) was obtained (63% yield). All the sulfoxides reacted with the Grignard reagents in the same way. Reaction products were identified by comparing the spectra with those of authentic samples, using spectrometry.

2-Benzylpyrimidine: pale yellow oil; ^1H NMR ($CDCl_3$) = 4.27 (s, 2H, CH_2), 7.00 (t, J = 5 Hz, 1H), 7.10–7.69 (m, 5H), 8.59 (d, J = 5 Hz, 2H); IR (neat) 1500 cm^{-1}; MS m/z 170 (M^+, 36), 169 (100). 2-Phenylpyrimidine: pale yellow oil; ^1H NMR ($CDCl_3$) = 7.12 (t, J = 5 Hz, 1H), 7.29–7.78 (m, 3H), 8.28–8.68 (m, 2H), 8.78 (d, J = 5 Hz, 1H); IR (neat) 1570 cm^{-1}; MS m/z 156 (M^+, 100), 103 (85), 76 (11), 51 (10).

All the other coupling reactions follow the same pattern and the characteristics of their properties are described in the respective paragraphs in the equations, and references in Reference 3d.

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