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A Cross-Coupling Reaction of Methylsulfinylarene

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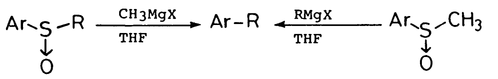
Cross-coupling product 2-(2-pyridyl)quinolines were obtained in the reaction of 2-(methylsulfinyl)-quinolines and 2-(methylsulfinyl)pyridines with methylmagnesium bromide. Attempts of cross coupling in the reaction of other substrates were unsuccessful.

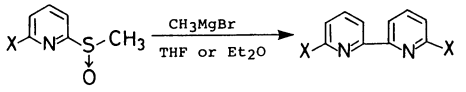
Earlier, we have reported many ligand coupling reactions of sulfoxides with various types of Grignard reagents.[1] This reaction provides a new carbon-carbon bond formation between α and ipso carbons of arylsulfinyl group or ipso carbon and the Grignard reagent with retention of the configuration.[2] In this coupling reaction which is typically described in Scheme 1, R is usually a benzylic, allylic, aromatic, and azaaromatic group,[1,3] otherwise the reaction becomes messy and gives no desired coupling product.



Scheme 1.

When R is methyl or other alkyl group, a dimeric compound is a major product. For example, in the coupling reaction of 2-(methylsulfinyl)pyridine (**1a**) with methylmagnesium bromide, 2,2′-bipyridyl (**2a**) was formed in moderate yields.[4] This is quite a unique reaction because it involves ligand coupling of two azaaromatic groups after initial ligand exchange on the sulfoxide and has promised to be a productive method for preparation of biazaaromatics.[5]

In the extension of these studies, we were interested in cross-coupling reaction between two different azaaromatic sulfoxides, and have found some successful examples. In this article the details are described.



1a,b

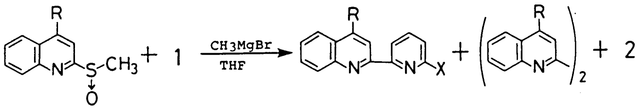
2 a,b

a, X : H
b, X : Cl

Scheme 2.

Results and Discussion

A mixture of 2-(methylsulfinyl)quinoline (**3a**) and **1a** was treated with methylmagnesium bromide in THF at room temperature. The reaction completed in about 15 min and gave 2-(2-pyridyl)quinoline (**4**) in 57% yield. Homo-coupling product 2,2′-biquinolyl (**8a**) and **2a** were also formed in 42 and 23% yields respectively. Results of the other combination of the reactions between **3a**, **b** and **1a**, **b** are summarized in Table 1, in which the cross coupling products **4—7** were obtained in 20 to 57% yield.



3a,b

4~7

8a,b

a, R : H
b, R : CH3

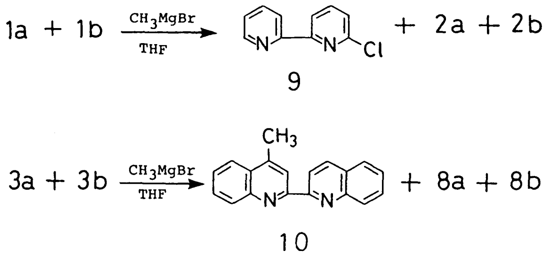
Scheme 3.

Meanwhile, the cross coupling reaction of **1a** and **1b** provides unsymmetric 2,2′-bipyridyl along with symmetric bipyridyls **2a** and **2b**. But somehow the yield of unsymmetric bipyridyl was low, only 16% of 6-chloro-2,2′-bipyridyl (**9**) was obtained. The yields of **2a** and **2b** were 36 and 77% respectively. Reaction of **3a** and **3b** gave three kinds of 2,2′-biquinolyls, thus 4-methyl-2,2′-biquinolyl (**10**), **8a** and **8b**, which were hard to be purified by chromatographic techniques. The product ratios of **10**, **8a**, and **8b** were found to be 6:4:7 approximately determined by ^{1}H NMR spectrum of the mixture.

Table 1. Cross-Coupling Reaction of **3** and **1**

Starting		Sulfoxide R	Sulfoxide X	Cross-coupling product (yield/%)		Homo-coupling product (yield/%)			
3a	**1a**	H	H	**4**[a)]	(57)	**8a**[b)]	(42)	**2a**[c)]	(23)
3a	**1b**	H	Cl	**5**	(20)	**8a**	(42)	**2b**[d)]	(11)
3b	**1a**	CH_3	H	**6**[e)]	(54)	**8b**[f)]	(42)	**2a**	(42)
3b	**1b**	CH_3	Cl	**7**	(36)	**8b**	(61)	**2b**	(41)

a) Ref. 6. b) Ref. 7. c) Ref. 8. d) Ref. 9. e) Ref. 10. f) Ref . 11.



Scheme 4.

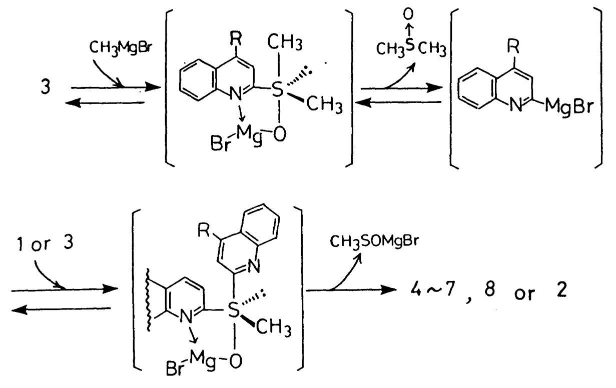
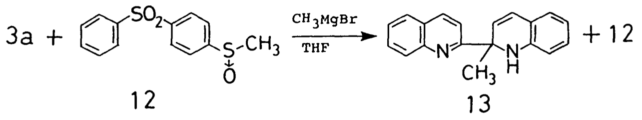


Chart 1.

The mechanism of the reaction has been examined carefully in the cases of 2-(alkylsulfinyl)pyridines and proposed by Oae et al.[4] According to the mechanism, an initial attack of the methylmagenesium bromide on the sulfur atom of **3** forms a σ-sulfurane intermediate followed by dispropotionation to release dimethyl sulfoxide and 2-quinolylmagnesium bromide, which subsequently reacts with another sulfoxide **1** or **3** to promote a normal ligand coupling, and finally affording the cross coupling product **4**—**7** as well as the homo-coupling products **8** and **2**.

The coupling reaction of **3a** with 2-(*t*-butylsulfinyl)-pyridine (**11**) also gave the desired cross couling product **4** in 22% yield along with **8a** in 8% yield but none of **2a** was detected in the reaction mixture.[13] The rest of the starting sulfoxide **11** was recovered in 71% yield. The result would be due to the steric hindrance of the *t*-butylsulfinyl group, thus the rate of formation of the intermediary σ-sulfurane derived from 2-quinolylmagnesium bromide and **11** is anticipated to be considerably slow. The cross coupling reaction obviously competes with the usual ligand coupling reaction as well as other side reactions involving simple ligand exchange or disulfide formation. Thus the reaction is not simple. In fact, no cross couling was observed between **3a** and 1-methylsulfinyl-4-(phenylsulfonyl)benzene (**12**). The major product was 2-methyl-1,2-dihydro-2,2′-biquinolyl (**13**) along with 90% recovery of the other sulfoxide **12**. The compound **13** is known to be produced by treatment of two equivalents of methylmagnesium bromide and **3a**.[5]



Scheme 5.

Reactions of **3a** with other substrates, 2-(methylsulfinyl)pyrimidine, methylsulfinylbenzene, and their *t*-butylsulfinyl derivatives gave almost similar results in which no cross coupling product was detected among the reaction mixtures. In the reaction of **1a** and **12**, the dimeric compound **2a** was obtained in 89% yield and the sulfoxide **12** was recovered quantitatively.

Experimental

Melting points were determined with Yanaco micromelting point apparatus and were uncorrected. ^{1}H NMR spectra were run on JEOL-GX400 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Chemical shifts are given as σ value. Infrared spectra were obtained with JASCO IR-A spectrometer. Low- and high-resolution mass spectra were taken on JEOL-JMS 303HF spectrometer with a direct inlet method at 70 eV. Only strong and/or structurally important peaks are reported here for IR and MS. Column chromatography was carried out on silica gel (Wako gel 200). THF for the reactions was dried over sodium benzophenone ketyl and freshly distilled just before use. Methylmagnesium bromide was purchased from Kanto Chemical Co. as THF solution.

Typical Procedure of the Cross-Coupling Reaction. To a mixture of sulfoxide (1 mmol) and another sulfoxide (1 mmol) in THF (5 ml) was dropped methylmagnesium bromide (2 ml, 1M solution in THF) at room temperature during a min under Argon atmosphare. The reaction mixture was stirred for 15 min at the same temperature. It was quenched with aq. ammonium chloride (2 ml) and extracted with chloroform (60 ml). The extract was washed with water (4 ml×2) and brine (4 ml), dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica gel. Characteristic properties of the products are the following.

4: Colorless crystals, mp 98—99 °C (EtOH) (lit,[6] 99 °C); ^{1}H NMR δ=7.36 (1H, td, J=6.4, 1.8 Hz), 7.56 (1H, td, J=7.1, 1.5 Hz), 7.74 (1H, dt, J=7.9, 1.5 Hz), 7.85 (1H, d, J=8.5 Hz), 7.88 (1H, td, J=7.3, 1.9 Hz), 8.19 (1H, d, J=8.7 Hz), 8.29 (1H, d, J=8.2 Hz), 8.56 (1H, d, J=8.2 Hz), 8.66 (1H, dd, J=8.1, 1.1 Hz), 8.75 (1H, ddd, J=4.7, 1.9, 1.1 Hz).

8a: Colorless crystals, mp 193—194 °C (EtOH) (lit,[7] 193—196 °C; ^{1}H NMR δ=7.58 (2H, ddd, J=7.5, 5.0, 1.1 Hz), 7.76 (2H, td, J=8.0, 1.1 Hz), 7.89 (2H, d, J=8.0 Hz), 8.23 (2H, d, J=8.1 Hz), 8.33 (2H, d, J=8.1 Hz), 8.85 (2H, d, J=8.1 Hz).

2a: Colorless crystals, mp 70—73 °C (EtOH) (lit,[8] 69.7 °C); ^{1}H NMR δ=7.31 (2H, ddd, J=7.5, 5.0, 1.3 Hz), 7.82 (2H, td, J=7.7, 1.8 Hz), 8.39 (2H, d, J=8.1 Hz), 8.69 (2H, dd, J=5.0, 0.3 Hz).

5: Colorless crystals, mp 156—158 °C (EtOH); ^{1}H NMR δ=7.57 (1H, td, J=8.1, 1.5 Hz), 7.75 (1H, td, J=8.0, 1.5 Hz), 7.76 (1H, t, J=7.9 Hz), 7.82 (1H, d, J=8.1 Hz), 8.16 (1H, d, J=8.4 Hz), 8.28 (1H, d, J=8.4 Hz), 8.34 (1H, dd, J=7.7, 0.7 Hz), 8.55 (1H, d, J=8.7 Hz), 8.62 (1H, dd, J=7.9, 0.8 Hz); IR($CHCl_3$) 2930, 2850, 1600, 1570, 1550, 1410, 1150, 1140 cm^{-1}; MS m/z(rel intensity) 240, 242 (M$^+$, 67 and 23), 205 (65), 128 (26), 28 (base); Found: C, 69.67; H, 3.78; N, 11.77%. Calcd for $C_{14}H_9N_2Cl$: C, 69.86; H, 3.77; N, 11.64%.

2b: Colorless crystals, mp 216—219 °C (benzene : hexane, 1 : 1) (lit,[9] 218—219 °C); ^{1}H NMR δ=7.36 (2H, d, J=8.1 Hz), 7.78 (2H, t, δ=7.7 Hz), 8.35 (2H, dd, J=7.7, 0.7 Hz).

6: Colorless crystals, mp 64—66 °C (petr. ether) (lit,[10] 69—70 °C); ^{1}H NMR δ=2.78 (3H, s), 7.32 (1H, ddd, J=7.3, 4.8, 1.1 Hz), 7.56 (1H, td, J=8.4, 1.4 Hz), 7.72 (1H, td, J=7.7, 1.2 Hz), 7.86 (1H, td, J=7.7, 1.8 Hz), 8.01 (1H, d, J=8.4 Hz), 8.17 (1H, dd, J=8.4, 0.7 Hz), 8.39 (1H, s), 8.63 (1H, dd, J=7.0, 1.0 Hz), 8.73 (1H, dm, J=4.0 Hz).

8b: Colorless crystals, mp 279—280 °C (chloroform) (lit,[11] 280 °C); ^{1}H NMR δ=2.85 (6H, s), 7.60 (2H, td, J=8.0, 1.1 Hz), 7.76 (2H, td, J=7.7, 1.0 Hz), 8.06 (2H, d, J=8.4 Hz), 8.25 (2H, d, J=8.4 Hz), 8.67 (2H, s).

7: Colorless crystals, mp 110—112 °C (EtOH); ^{1}H NMR δ=2.80 (3H, s), 7.38 (1H, d, J=7.0 Hz), 7.58 (1H, td, J=7.3, 0.9 Hz), 7.73 (1H, td, J=7.3, 1.5 Hz), 7.82 (1H, t, J=7.7 Hz), 8.03 (1H, dd, J=8.4, 0.7 Hz), 8.15 (1H, d, J=8.4 Hz), 8.39 (1H, s), 8.60 (1H, dd, J=7.7, 0.7 Hz); IR($CHCl_3$) 2960, 2940, 1600, 1585, 1570, 1550, 1440, 1420, 1360, 1160, 1140 cm^{-1}; MS m/z (rel intensity) 254, 256 (M$^+$, base and 31), 219 (65), 112 (14); Found: C, 70.62; H, 4.50; N, 10.69%. Calcd for $C_{15}H_{11}N_2Cl$: C, 70.72; H, 4.32; N, 10.99%.

9: Colorless crystals, mp 59—60 °C (petr. ether) (lit,[12] 60—62 °C); ^{1}H NMR δ=7.33 (1H, td, J=6.2, 1.1 Hz), 7.34 (1H, dd, J=8.0, 0.7 Hz), 7.77 (1H, t, J=7.7 Hz), 7.82 (1H, td, J=7.9, 1.7 Hz), 8.35 (1H, d, J=7.7 Hz), 8.41 (1H, d, J=7.7 Hz), 8.67 (1H, dm, J=4.4 Hz).

10: ^{1}H NMR δ=2.85 (3H, s), 7.58 (1H, t, J=8.0 Hz), 7.60 (1H, t, J=8.0 Hz), 7.75 (1H, t, J=8.4 Hz), 7.76 (1H, t, J=8.4 Hz), 7.88 (1H, d, J=8.0 Hz), 8.06 (1H, d, J=8.4 Hz), 8.22 (1H, d, J=8.4 Hz), 8.23 (1H, d, J=8.4 Hz), 8.32 (1H, d, J=8.8 Hz), 8.68 (1H, s), 8.85 (1H, d, J=8.8 Hz).

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13) The compound **3a** is at least 10^3 times more reactive than **1a** in the homolytic dimerization reaction, the details see in Ref. 5.