IPSO-SUBSTITUTION REACTIONS OF 2- AND 4-SULFONYLPYRIDINES WITH GRIGNARD REAGENTS

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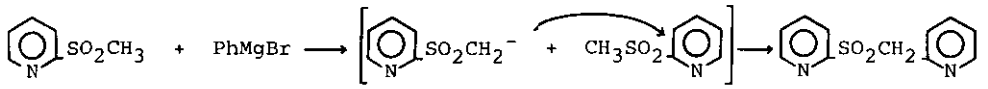
Abstract - The reactions of 2-sulfonylpyridines with Grignard reagents proceeded via an ionic path to give only the corresponding ipso-substitution products, while 4-sulfonylpyridines afforded mainly a mixture of both the substitution and coupling products on treatment with Grignard reagents.

It was reported that both sulfinyl- and sulfonylpyridines(2- and 4-substituted derivatives) react with various nucleophiles to give the corresponding ipso-substitution products.[1] Recently, 2- and 4-(benzylsulfinyl)pyridines or the related sulfoxides bearing heterocycles were found to react with Grignard reagents or butyl lithium to afford the ligand coupling products, e.g., 2-benzylpyridine in high yield.[2] Meanwhile, a few reports on the reactions of the sulfones having heteroaromatics with carbon nucleophiles have been presented, for example, 4-methylsulfonylquinoline reacts with sulfur ylide to give the corresponding ipso-substitution product.[3] In this communication, we report the ipso-substitution of 2- and 4-sulfonylpyridines with Grignard reagents together with the proposed mechanisms for the reactions.

The sulfones **1** and **2** employed in this study were prepared according to the known procedure starting from the corresponding halogenopyridines.[1]

When sulfone **1a** was treated with an equimolar amount of phenylmagnesium bromide, the product obtained was not 2-phenylpyridine but 2-(2-pyridylmethylsulfonyl)pyridine **3** in 65% yield together with the recovered **1a**. The product **3** was also obtained upon treatment of **1a** with t-BuOK in 40% yield together with 2-t-butoxypyridine. The result suggests that the proton attached to the methylsulfonyl group should be removed preferentially by the Grignard reagent, and

then the sulfonyl carbanion **4** once formed attacks the 2-position of the starting sulfone **1a** to afford the product **3** as shown below.

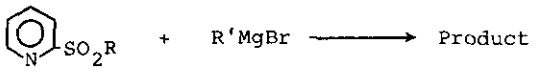


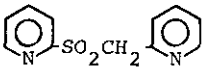
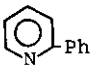
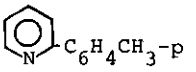
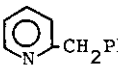
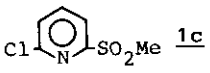
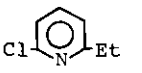
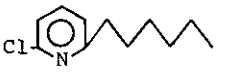
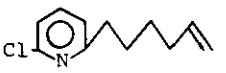
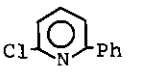
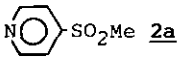
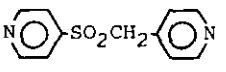
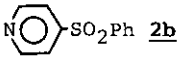
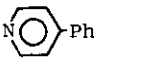
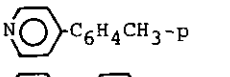
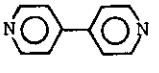
1a **4** **3**

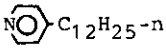
On the other hand, 2-phenyl derivative **1b** was found to react with various Grignard reagents at room temperature to afford the corresponding ipso-substitution products in moderate to high yields. However, the reactions of 4-sulfonylpyridines **2a** and **2b** with Grignard reagents gave a mixture of several products except in the reaction of **2b** with PhMgBr. These results are summarized in Table 1.

From these results shown in Table, the following informations for the reactions are obtained. In the reaction of 2-sulfonylpyridine, the sulfonyl group was substituted by the Grignard reagent and carbon-carbon bond formation took place at the 2-position. Furthermore, treatment of 2-chloro-6-methylsulfonylpyridine **1c** with Grignard reagents, the attacking site was found to be the carbon atom attached to the sulfonyl group and not to the chlorine atom. This more preferential for substitution of the sulfonyl group than the chlorine atom has been observed in the ipso-substitution reactions of **1a** or **1b** with various nucleophiles.[1] The problem on the exclusive replacement of the sulfonyl group by the nucleophiles between these two groups in the pyridine has been still unresolved. From the reaction of **1b** with p-tolylmagnesium bromide the product isolated was 2-(p-tolyl)pyridine as a sole product and 2-phenylpyridine was not detected at all. Therefore, the reaction of 2-sulfonylpyridine with Grignard reagent proceeds via an ipso-substitution on the 2-carbon atom of the pyridine ring and this result rules out the process involving the intial attack by the Grignard reagent on the sulfonyl sulfur atom as was observed in the reaction with 2-sulfinylpyridine. Furthermore, when one treated either **1b** or **1c** with 5-hexenylmagnesium bromide, one obtained only the corresponding 2-(5-hexenyl)pyridine **2b** or **2c** in high yield without containing the 2-(cyclopentylmethyl)pyridine which should be obtained if the reaction proceeded via an initial single electron tranfer (SET) from the Grignard reagent to the substrate. Although an SET process has been reported in many reactions of heterocycles with organometallic reagents[4] and also in the reaction of the styrene

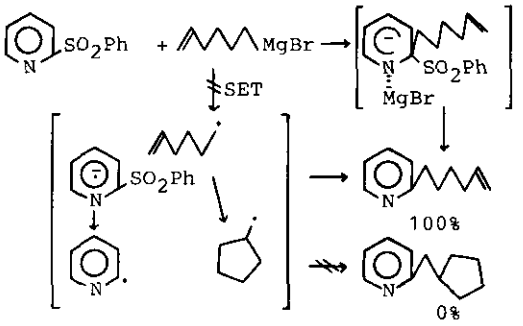
Table 1. The Reactions of Sulfonylpyridines with Grignard Reagents



R	R'	Time(min)	Product & yield(%)		Recovered(%)
2-SO_2Me **1a**	Ph	60		65	25
2-SO_2Ph **1b**	Ph	60		53	39
"	-$C_6H_4CH_3$-p	60		72	21
"	$PhCH_2$[a]	60		57	35
"		30		95	-
"		30		99	-
 **1c**	Et	15		79	-
"		30		44	27
"		30		51	-
"	Ph	120		25	-
 **2a**	Ph	60		13	32
 **2b**	Ph	240		51	10
"	$C_6H_4CH_3$-p	240		25	35
"	$C_{12}H_{25}$-n[b]	240		54	17
"	Et	240	"	28	-
"	 [c]	240	"	23	20

a) $PhCH_2MgCl$ b)  c) 

derivative bearing the phenylsulfonyl group with Grignard reagent,[5] the present results indicate clearly that at least in the ipso-substitutions of 2-sulfonylpyridines with Grignard reagents, an ionic mechanism is the rational process and an SET mechanism can be ruled out as shown in the following Scheme 1.



- **Scheme 1** -

On the contrary the reactions of 4-sulfonylpyridines with Grignard reagents are rather sluggish and are unable to be explained by a simple mechanism. As a summary, the reaction of 2-sulfonylpyridines with Grignard reagents is a convenient procedure to introduce a carbon residue in the 2-position of the pyridine ring.

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