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PREPARATION OF PYRIDYL GRIGNARD REAGENTS AND CROSS COUPLING REACTIONS WITH SULFOXIDES BEARING AZAHETEROCYCLES

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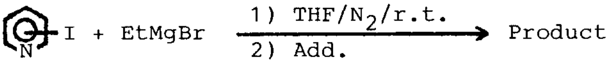
Abstract: Pyridyl Grignard reagents were prepared from the corresponding iodopyridine and EtMgBr. New cross coupling reactions of the Grignard reagents with azaheterocycles took place on the sulfinyl sulfur atom to afford biazaheteroaryls.

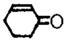
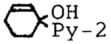
Earlier, pyridyl Grignard reagents have been prepared by the Grignard exchange reactions of the corresponding halides with alkyl1) or aryl Grignard reagents.2) The procedures, however, can be applied only smoothly in the preparation of 3-pyridyl Grignard reagent. Both 2- and 4-chloro (or 2- and 4-bromo)pyridines are innert to aryl Grignard reagents or the reactions with alkyl halides in the presence of Mg and subsequently with carbonyl compounds result in low yields of the desired products. Recently we found that alkyl and aryl pyridyl sulfoxides reacted with several Grignard reagents to afford the corresponding 3-,4-pyridyl and 4-quinolyl Grignard reagents.3) However, this process is unable to provide 2-pyridyl derivative. In order to search for a reproducible and general procedure for preparation of azaheteroaromatic Grignard reagents, we reinvestigated the Grignard exchange reactions of pyridyl halides with numerous Grignard reagents. Then, we found that iodopyridines (2-,3-,and 4-) and EtMgBr were suitable combination for preparation of any pyridyl Grignard reagents. This communication reports the preparation of pyridyl Grignard reagents together with several reactions with carbonyl compounds. New cross-coupling reactions of the Grignard reagents with sulfoxides bearing azaheterocycles are also presented.

A typical procedure for generation of 2-pyridylmagnesiumbromide (2-PyMgBr) (**1**) and reactions with electrophiles are shown as follows. Freshly prepared 2-iodopyridine4) (150 mg, 0.732 mmol) was dissolved in THF (7 ml) under N_2-atmosphere at room temperature. To this solution was added EtMgBr (1.76 ml of 0.5 M THF solution, 1.2 equivalents) at room temperature and the

Table 1



$\text{Py-I} + \text{EtMgBr} \xrightarrow[\text{2) Add.}]{\text{1) THF/N}_2\text{/r.t.}} \text{Product}$

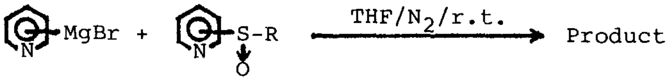
Py-I	Add.	Time(h)	Product	Yield(%)
2-Py-I	PhCHO	3	2-PyPhCHOH	91
2-Py-I	PhMeCHCHO	10	PhMeCH-CH(OH)Py-2	76
2-Py-I	PhCH=CHCHO	10	PhCH=CHCH(OH)Py-2	89
2-Py-I	PhCOMe	3	2-PyPhMeCOH	46
2-Py-I		3		72
2-Py-I	PhCH=CHCOPh	3	PhCH=CHC(OH)PhPy-2	30
			2-PyPhCH-CH_2COPh	64
2-Py-I	$PhCO_2Et$	3	$(2\text{-Py})_2$PhCOH	22
3-Py-I	PhCHO	6	3-PyPhCHOH	81
3-Py-I	PhCH=CHCOPh	3	3-PyPhCH-CH_2COPh	79
4-Py-I	PhCHO	6	4-PyPhCHOH	85
4-Py-I	PhCH=CHCOPh	6	PhCH=CHC(OH)PhPy-4	4
			4-PyPhCH-CH_2COPh	79

solution was stirred for 25 min. Then benzaldehyde (101 mg, 1.3 times excess to iodopyridine) was added. This solution was stirred for 3 h. After the usual work-up procedure, the product was identifed to be 2-pyridyl phenyl methanol in 91% yield: mp 74-75 °C (lit.$^{5)}$ 73 °C). Both 3- and 4-pyridyl Grignard reagents (3-PyMgBr, 4-PyMgBr) were prepared similarly and treated with several carbonyl compounds. The results are summarized in Table 1.

Reactions of **1** with sulfoxides bearing azaheterocycles.$^{6)}$ The Grignard reagent **1** was prepared from 150 mg of 2-iodopyridine in THF. Phenyl 2-pyridyl sulfoxide (134 mg, 0.659 mmol) in 2 ml of THF was treated similarly with **1** as described above. 2,2'-Bipyridyl(77 mg) was obtained in 75% yield: mp 72-73 °C (lit.$^{7)}$ 73 °C). The reactions of other pyridyl Grignard reagents with the sulfoxides bearing azaheteroaromatics are summarized in Table 2.

Inspection of the results shown in the Tables reveals the following aspects on the utilization of pyridyl Grignard reagents for organic synthesis. Since three iodopyridines can readily be prepared $^{8)}$ and are stable to be stored at room temperature in comparison with thermally unstable properties of the corresponding chloro and bromo derivatives, our procedure is a reproducible process for preparations of any PyMgBr particularly of 2-PyMgBr which affords the alcohols in good yields upon treatment with aldehydes and ketones. When the Grignard reagents were treated with

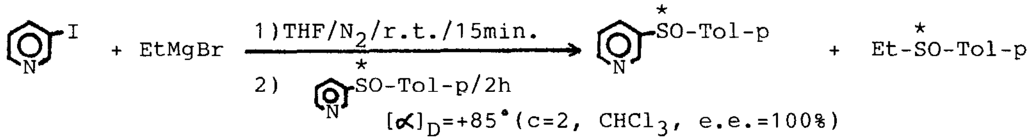
Table 2



Run	Grignard reagent	Sulfoxide	Time(h)	Product	Yield(%)
1	2-PyMgBr	2-Py-SO-Ph	3	2-Py-Py-2	75
2	2-PyMgBr	2-(6-Cl)Py-SO-Me	3	2-(6-Cl)Py-Py-2	43
3	2-PyMgBr	3-Py-SO-Ph	3	2-Py-Py-2	23
				3-Py-Py-2	37
4	2-PyMgBr	4-Py-SO-Ph	3	4-Py-Py-2	58
5	2-PyMgBr	2-Qu-SO-Et	3	2-Qu-Py-2	62
6	3-PyMgBr	2-Py-SO-Ph	3	2-Py-Py-3	63
7	3-PyMgBr	3-Py-SO-Ph	4	no reaction	
8	3-PyMgBr	4-Py-SO-Ph	3	4-Py-Py-3	25
				4-Py-Py-4	14
9	3-PyMgBr	2-Qu-SO-Et	3	2-Qu-Py-3	62
10	4-PyMgBr	2-Py-SO-Ph	10	2-Py-Py-4	63
11	4-PyMgBr	3-Py-SO-Tol-p	10	3-Py-Py-4	13
				4-Py-Py-4	25
12	4-PyMgBr	4-Py-SO-Tol-p	10	4-Py-Py-4	50
13	4-PyMgBr	2-Qu-SO-Et	10	2-Qu-Py-4	56

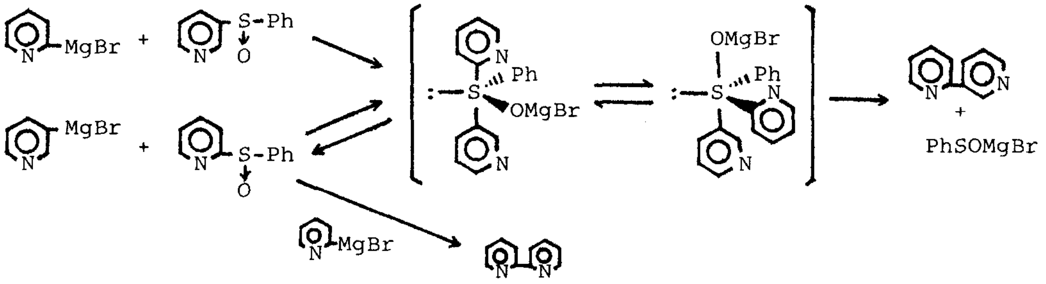
2-Qu- =

sulfoxides bearing azaheteroaromatics, numerous cross coupling products involving not only a symmetric bisazaaryls but also unsymmetric derivatives were obtained in moderate yields. The mechanism for the formation of bipyridyls would be rationally explained in terms of an initial attack of the Grignard reagent on the sulfinyl sulfur atom to afford the sulfurane as an intermediate from which the two azaheteroaryl groups couple selectively while the phenyl group on the sulfoxide does not participate in the reaction. Among various combination of the azaheteroaromatics, 3-PyMgBr apparently does not react at all upon treatment with 3-pyridyl phenyl sulfoxide. Meanwhile, as shown in runs 3 and 11, if one used 2-PyMgBr and 4-PyMgBr with 3-pyridyl sulfoxide as a coupling partner, both the symmetric and unsymmetric bipyridyls were obtained. In the case of run 7, however, when one treated the optically active sulfoxide [3)] with 3-PyMgBr, optical activity of the sulfoxide after recovered was decreased to about 60%. Furthermore, by adding an excess of EtMgBr, both 3-pyridyl p-tolyl sulfoxide and ethyl p-tolyl sulfoxide were obtained but their optical activities were reduced as shown in the following scheme. Thus, this result indicates that the Grignard exchange does take place on the sulfinyl sulfur atom even in this reaction.



mol ratio			Yield(%)	e.e.(%)
3-Py-I	EtMgBr	3-Py-$\overset{*}{\text{S}}$O-Tol-p	3-Py-$\overset{*}{\text{S}}$O-Tol-p	Et-$\overset{*}{\text{S}}$O-Tol-p
1 :	1 :	1	84% $[\alpha]_D$=+51° (e.e.=60%)	0%
1 :	1.4 :	1	49% $[\alpha]_D$=+45° (e.e.=53%)	35% $[\alpha]_D$=−162° (e.e.=87%)

In comparison with the reactivity in the three pyridyl Grignard reagents, the 3-derivative should be most stable and therefore, the reaction between 2-PyMgBr with 3-pyridyl phenyl sulfoxide gives a sulfurane which either via pseudo rotation to afford finally the 2,3-coupling product or to give 2-pyridyl phenyl sulfoxide and 3-pyridyl Grignard reagent with an equilibrium process. 2-Pyridyl phenyl sulfoxide should be more reactive to the 2-PyMgBr than 3-PyMgBr and hence the reaction gives finally the symmetrical coupling products as shown in the scheme.



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6) 2-Thienyl Grignard reagent gives 2-pyridyl or 2-quinolyl thiophene in 66 and 68% yields respectively upon treatment with 2-pyridyl phenyl or 2-quinolyl ethyl sulfoxide.
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