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PREPARATION OF BIPYRIDYL DERIVATIVES VIA α-LITHIATION OF PYRIDYL PHENYL SULFOXIDES, SUBSTITUTION WITH ELECTROPHILES AND CROSS-COUPLING REACTIONS WITH GRIGNARD REAGENTS

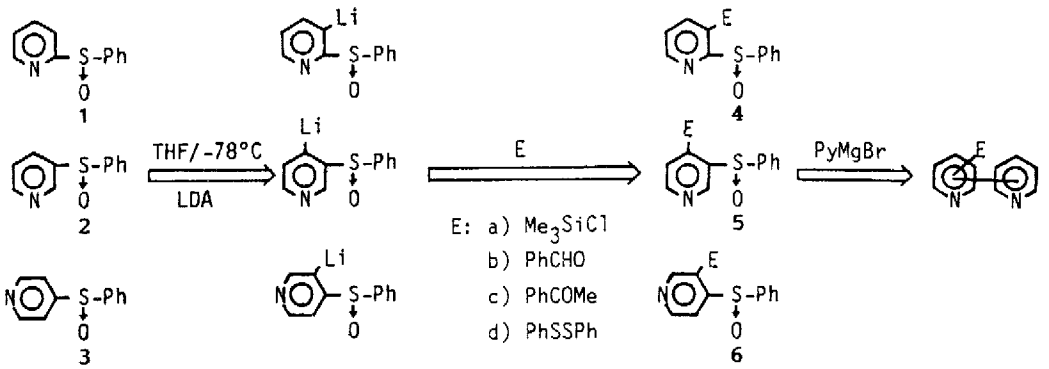
Naomichi Furukawa,* Tadao Shibutani, and Hisashi Fujihara
Department of Chemistry, University of Tsukuba, Tsukuba, Ibaraki 305, Japan

Abstract: Treatment of 2-, 3-, and 4-pyridyl phenyl sulfoxides with lithium diisopropylamide (LDA), subsequently with electrophiles gave the corresponding sulfoxides regioselectively bearing substituents at the α-position in the pyridine ring. These sulfoxides were converted to the substituted bipyridyls in high yields via cross-coupling reactions with pyridyl Grignard reagents (PyMgBr).

Sulfoxides have been known to undergo ligand exchange and/or ligand coupling reactions upon treatment with organolithium or Grignard reagents to provide new organometallic reagents or numerous coupling products.[1] Recently, we reported that pyridyl and quinolyl sulfoxides react with pyridyl Grignard reagents to proceed via initial formation of σ-sulfurane affording unsymmetric bipyridyl derivatives in high yields.[2] Furthermore, we found that lithiation of pyridyl phenyl sulfoxides with LDA takes place only at the α-position to the sulfinyl group in the pyridine ring.[3]

This communication reports facile conversion of pyridyl phenyl sulfoxides to numerous bipyridyl and pyridyl phenyl derivatives via regioselective lithiation, substitution with electrophiles and cross-coupling reactions with Grignard reagents as shown in Scheme 1.

Scheme 1



The lithiation of three isomeric sulfoxides (**1**)-(**3**)[4] was performed by using an equimolar amount of LDA in THF at -78 °C. The lithiation took place only at the α-position of the sulfinyl group in the pyridine ring. The lithio-derivatives generated were treated in situ with electrophiles at 0 °C to afford the sulfoxides bearing α-substituents in the pyridine ring to the sulfinyl group. The lithiation of **2** was observed only at the 4-position and not at the 2-position in the ring. The products obtained were separated by general work-up and purified by column or preparative liquid chromatography. The structures of the products were identified by conventional spectroscopic and elemental analysis. The results are summarized in Table 1.[5]

Table 1. α-Lithiation of Pyridyl Sulfoxides and Substitution with Electrophiles

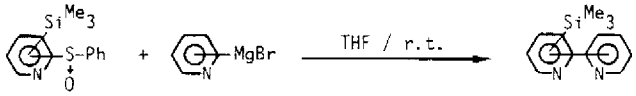
Sulfoxide	E	Product		Yield (%)
2-PySOPh (**1**)	Me_3SiCl	2-(3-Me_3Si)PySOPh	(**4a**)	85
2-PySOPh (**1**)	PhCHO	2-[3-PhH(OH)C]PySOPh	(**4b**)	87
2-PySOPh (**1**)	PhCOMe	2-[3-PhMe(OH)C]PySOPh	(**4c**)	90
2-PySOPh (**1**)	PhSSPh	2-(3-PhS)PySPh [6]	(**4d**)	50
3-PySOPh (**2**)	Me_3SiCl	3-(4-Me_3Si)PySOPh	(**5a**)	80
3-PySOPh (**2**)	PhCHO	3-[4-PhH(OH)C]PySOPh	(**5b**)	81
4-PySOPh (**3**)	Me_3SiCl	4-(3-Me_3Si)PySOPh	(**6a**)	81
4-PySOPh (**3**)	PhCHO	4-[3-PhH(OH)C]PySOPh	(**6b**)	67

As shown in Table 1, several substituted pyridyl phenyl sulfoxides (**4**)-(**6**) were obtained in good yields, except in the reaction of lithiated sulfoxide (**1**) with diphenyl disulfide.[6]

Various substituted pyridyl sulfoxides (**4**)-(**6**) obtained were subjected to ligand coupling with Grignard reagents. In general reactions of pyridyl sulfoxides with common Grignard reagents, both 3- and 4-pyridyl derivatives give the corresponding ligand exchange products, while 2-derivatives used to give the ligand coupling products.[1-2] Meanwhile, all the isomeric pyridyl sulfoxides always afford the corresponding ligand coupling products upon reaction with pyridyl Grignard reagents as described previously.[2] In the present reactions with freshly prepared pyridyl Grignard reagents, the sulfoxides (**4**)-(**6**) afforded the ligand coupling products, namely the unsymmetrically substituted bipyridyl derivatives.

All the silylated sulfoxides (**4a-6a**) gave the corresponding silylated bipyridyls in high yields except the reaction of **5a** with 3-PyMgBr which was unreactive under the present condition. The results are shown in Table 2. These results demonstrate that the present reactions provide a simple and convenient procedure for synthesis of silylated bipyridyls.

Table 2



Sulfoxide	PyMgBr	Product	Yield (%)
4a	2-PyMgBr	2-(3-Me_3Si)Py-Py-2	78
4a	3-PyMgBr	2-(3-Me_3Si)Py-Py-3	69
4a	4-PyMgBr	2-(3-Me_3Si)Py-Py-4	76
5a	2-PyMgBr	3-(4-Me_3Si)Py-Py-2	34
5a	3-PyMgBr	no reaction	
6a	2-PyMgBr	4-(3-Me_3Si)Py-Py-2	86
6a	3-PyMgBr	4-(3-Me_3Si)Py-Py-3	55

On the other hand, the reactions of sulfoxides bearing α-hydroxymethyl group (**4b,c and 6b**) gave different products and reaction modes depending on the position of the sulfinyl group attached in the pyridine ring and also the Grignard reagents employed. Sulfoxide **4b** reacts readily with Grignard reagents to result in the formation of ligand coupling products which depend on the nature of the Grignard reagents used in the reactions. Namely, upon treatment with excess EtMgBr, 3-[2-(phenyl)]pyridyl(phenyl)methanol was obtained in 83% yield, while with 2-PyMgBr, 3-[2-(2-pyridyl)]pyridyl(phenyl)methanol was obtained in 78% yield as shown in the following Scheme 2. In the reactions of 3- and 4-pyridyl sulfoxides, EtMgBr or other alkyl Grignard reagent gives the ligand substitution products. However, the reactions are sluggish to afford mixtures of unidentified products presumably generated by the reaction of free hydoxymethyl groups.[3] However, after conversion to the corresponding ethers upon treatment with alkylating agents, the ethers of 2- and 4-pyridyl derivatives were found to react smoothly with pyridyl Grignard reagents to afford bipyridyls in excellent yields except 3-pyridyl derivatives which were found to be unreactive. These results are summarised in Scheme 2 and Table 3.

Scheme 2

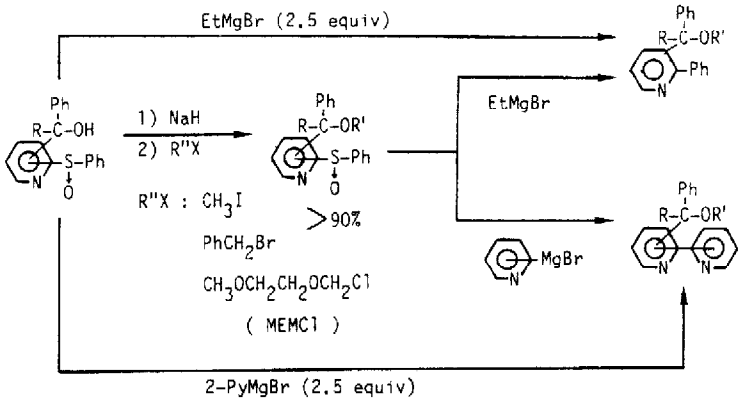


Table 3. Cross-Coupling Reaction of Substituted Pyridyl Sulfoxides

R	R'	PySOPh	R"MgBr	Product	yield (%)
H	H	2-PySOPh	EtMgBr [b]	2-[3-PhH(OH)C]Py-Ph	83
H	H	2-PySOPh	2-PyMgBr [b]	2-[3-PhH(OH)C]Py-Py-2	78
H	Me	2-PySOPh	EtMgBr	2-[3-PhH(OMe)C]Py-Ph	80
H	MEM [a]	2-PySOPh	EtMgBr	2-[3-PhH(OMEM)C]Py-Ph	83
H	$PhCH_2$	2-PySOPh	EtMgBr	2-[3-PhH(OCH_2Ph)C]Py-Ph	78
Me	Me	2-PySOPh	EtMgBr	2-[3-PhMe(OMe)C]Py-Ph	79
H	Me	2-PySOPh	2-PyMgBr	2-[3-PhH(OMe)C]Py-Py-2	79
H	MEM [a]	2-PySOPh	2-PyMgBr	2-[3-PhH(OMEM)C]Py-Py-2	62
H	$PhCH_2$	2-PySOPh	2-PyMgBr	2-[3-PhH(OCH_2Ph)C]Py-Py-2	77
Me	Me	2-PySOPh	2-PyMgBr	2-[3-PhMe(OMe)C]Py-Py-2	75
H	Me	2-PySOPh	3-PyMgBr	2-[3-PhH(OMe)C]Py-Py-3	80
Me	Me	2-PySOPh	3-PyMgBr	2-[3-PhMe(OMe)C]Py-Py-3	67
H	Me	2-PySOPh	4-PyMgBr	2-[3-PhH(OMe)C]Py-Py-4	82
H	Me	4-PySOPh	2-PyMgBr	4-[3-PhH(OMe)C]Py-Py-2	74
H	Me	4-PySOPh	3-PyMgBr	4-[3-PhH(OMe)C]Py-Py-3	68
H	Me	4-PySOPh	4-PyMgBr	4-[3-PhH(OMe)C]Py-Py-4	45

a) MEM: $CH_3OCH_2CH_2OCH_2$. b) 2.5 equiv.

Therefore, present procedures are quite useful for convenient synthesis of numerous biheteroaryl or heteroarylphenyl derivatives. Further studies on these reactions are progress in these laboratories.

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References and Notes

1) S. Oae, T. Kawai, N. Furukawa and F. Iwasaki, J. Chem. Soc., Perkin-2, 405 (1987); N. Furukawa, T. Shibutani, and H. Fujihara, Tetrahedron Lett., **27**, 3899 (1986); T. Satoh, K. Iwamoto, and K. Yamakawa, Bull. Chem. Soc. Jpn., **61**, 2109 (1988); P. G. Theobald and W. H. Okamura, Tetrahedron Lett., **28**, 6565 (1987).

2) N. Furukawa, T. Shibutani, and H. Fujihara, Tetrahedron Lett., **28**, 5845 (1987).

3) The details will be reported elsewhere.

4) N. Furukawa, F. Takahashi, T. Kawai, K. Kishimoto, S. Ogawa, and S. Oae, Phosphorus and Sulfur, **16**, 167 (1983).

5) The products listed in Table 1-3 were identified their structures by examining their ^{1}H-nmr, ir, and mass spectrum. Elemental analyses were within experimental errors.

6) This compound was obtained via an initial 3-sulfenylation subsequently ipso-substitution of the 2-sulfinyl group by PhS^-. Ipso substitutions were reported: G. B. Barlin and W. V. Brown, J. Chem. Soc.(B) 568, 648, 953 (1967); N. Furukawa, S. Ogawa, T. Kawai, and S. Oae, J. Chem. Soc., Perkin-1, 1833 (1984).

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