

Ips0 Substitution of 2-Alkylsulfinylpyridine by  
2-Pyridyllithium; A New Preparation of Oligopyridine and  
Their Bromomethyl Derivatives

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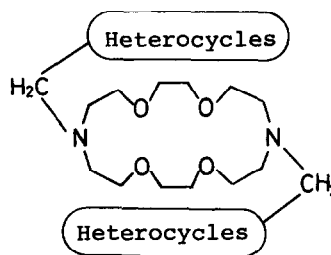
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Summary; Unsymmetrical and symmetrical 2,2'-bipyridines 5 and 6 have been prepared. The methods applied are new and offer efficient syntheses of higher oligopyridines and their bromomethyl derivatives.

Nitrogen heterocycles are capable of coordinating with a various metal ions.<sup>1)</sup> In particular, 2,2'-bipyridine has been used as a potentially useful coordinating ligand for both organic and inorganic complex chemistry.<sup>2)</sup> In recent years a considerable attention has also been focused on higher oligopyridines<sup>3)</sup> including 2,2':6',2"-terpyridine (1) as well as 2,2':6',2":6",2"'-quaterpyridine (2).

Since the chemistry of double armed diaza-18-crown ether (I) having heterocycles on the both aza arms is of our current interest,<sup>4)</sup> bromomethyl substituted oligopyridines and the related heterocycles are necessary for the preparation of I. However there has no report for general and satisfactory method to provide unsymmetrical oligopyridines bearing a various substituents, e.g. bromomethyl, hydroxymethyl, methyl or halide groups.

We now would like to report a general preparation of 2,2'-bipyridine derivatives by the reaction of 2-alkylsulfinylpyridine with 2-pyridyllithium reagent, and also a facile preparation of terminally pyridino substituted oligopyridines including the bromomethyl derivatives.



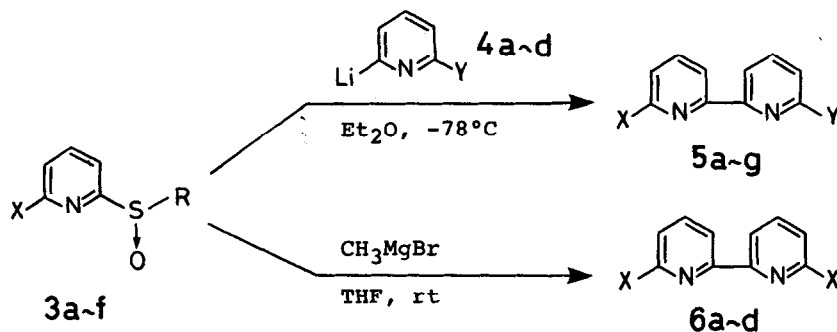


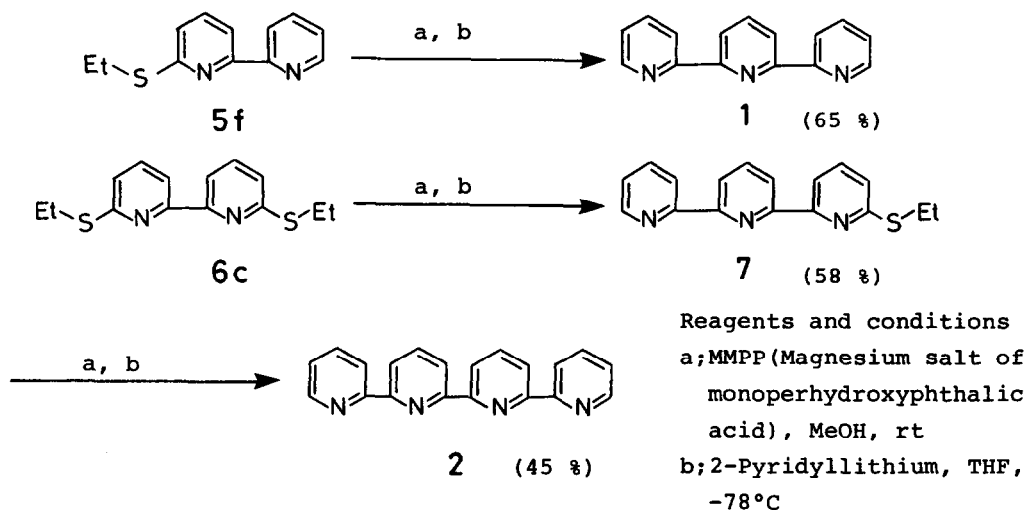
Table Reaction of 3 with 2-Pyridyllithium 4 or Methylmagnesium Bromide

Run	Sulfinylpyridine		Reagent		Product		
	X	R	Y	Yield	%		
1	3a	H	$\text{CH}_3$	4a	H	5a	70
2	3a	H	$\text{CH}_3$	4b	Br	5b	71
3	3a	H	$\text{CH}_3$	4c	$\text{CH}_3$	5c	60
4	3a	H	$\text{CH}_3$	4d	$\text{CH}_2\text{OTBS}$	5d	55
5	3b	$\text{CH}_3$	Et	4a	H	5c	60
6	3b	$\text{CH}_3$	Et	4b	Br	5e	57
7	3c	SEt	Et	4a	H	5f	85
8	3d	$\text{CH}_2\text{OTHP}$	Et	4b	Br	5g	71
9	3e	$\text{CH}_2\text{OTBS}$	Et	4b	H	5d	73
10	3f	Cl	Et	—	$\text{CH}_3\text{MgBr}$	6a	66
11	3b	$\text{CH}_3$	Et	—	$\text{CH}_3\text{MgBr}$	6b	53
12	3c	SEt	Et	—	$\text{CH}_3\text{MgBr}$	6c	60
13	3d	$\text{CH}_2\text{OTHP}$	Et	—	$\text{CH}_3\text{MgBr}$	6d	69

Generation of 2-pyridyllithium 4 (prepared by halogen-metal exchange of the corresponding 2-bromopyridine with *n*-butyllithium in ether or THF at  $-78^\circ\text{C}$ ) and subsequent treatment with 2-alkylsulfinylpyridine 3 gave unsymmetrical 2-(2-pyridyl)pyridine 5. The results are shown in Table. The yields are generally moderate to high (run 1-9). A variety of substituents can be introduced into the pyridine ring in either pyridyllithium reagent 4 or 2-alkylsulfinylpyridine 3 in this reaction, e.g. the substituents such as bromo, methyl, ethylthio, and protected hydroxymethyl groups. However lower yields, less than 7 %, were obtained in the reaction of 2-fluoro and 2-bromopyridine with 4. The results show that the reaction is not a simple nucleophilic substitution on pyridine ring but seems to be a specific

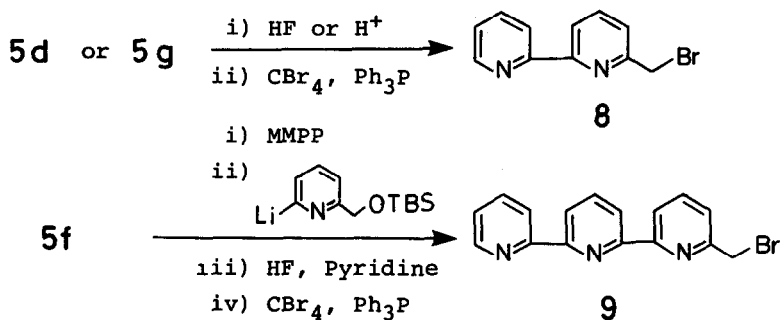
reaction of 3 and with 2-pyridyllithium reagent.<sup>5)</sup> We consider the reaction would proceed through  $\sigma$ -sulfurane intermediate, namely called ligand coupling proposed earlier by S. Oae.<sup>6)</sup> Meanwhile a new ligand coupling reaction to prepare symmetrical 2,2'-bipyridine has been found in 1984<sup>7)</sup> by treating 2-pyridyl sulfoxide with an alkyl Grignard reagent. This reaction involves a simple treatment of 3 with alkylmagnesium bromide in ether or THF. Some additional results are shown in Table (run 10-13).

These two kinds of reactions of 2-alkylsulfinylpyridine 3 would not only serve unsymmetrical and symmetrical 2,2'-bipyridines, 5 or 6, but also offer a flexible and productive preparation of functionalized oligopyridines. Indeed higher oligopyridine, 1 and 2 and the bromomethyl derivatives 8 and 9 have been synthesized by these reactions.



The unsymmetrical 2,2'-bipyridine 5f was oxidized by MMPP to the resulting sulfoxide which was then subjected to the reaction with 2-pyridyllithium to afford terpyridine 1 in 65 % yield, while the symmetrical 2,2'-bipyridyl 6c was monooxidized and subsequent treatment with 2-pyridyllithium afforded ethylthioterpyridine 7 in 58 % yield. Repeating the same two steps gave quaterpyridine 2<sup>8)</sup> in 45 % yield.

In order to combine these oligopyridyl groups with amino groups in aza crown ethers, introduction of bromomethyl group at 6 position of 2,2'-bipyridine and 2,2':6',2''-terpyridine is desired. Thus, the protecting group of 5d and 5g were removed respectively by the standard procedures (HF in pyridine and HCl in methanol) and the hydroxymethyl group formed was brominated by carbon tetrabromide with triphenylphosphine to give 6-bromomethyl-2,2'-bipyridine 8 in 87 % yield.



Synthesis of bromomethylterpyridine **9** was achieved from **5f** by four steps in 45 % yield described in the scheme.

These bromomethyl derivatives **8** and **9** were found to serve as functional double armed diaza-18-crown ethers, of which preparation and properties against metal cations will be reported in due course.

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- 8, mp. 215-217°C, lit. 217-8°C, J. Haginiwa and Y. Higuchi, *Yakugaku Zasshi*, **93**, 144 (1973), 400 MHz nmr in  $CDCl_3$   $\delta$  =7.35(2H, ddd, J=7.3, 4.8, 1.1), 7.88(2H, td, J=8.1, 1.8), 8.00(2H, t, J=7.9), 8.48(2H, dd, J=8.1, 1.1), 8.66(2H, dt, J=8.1, 1.1), 8.67(2H, dd, J=7.9, 1.1), 8.72(2H, ddd, J=4.8, 1.6, 0.9).

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