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SELECTIVE IPSO-SUBSTITUTION IN PYRIDINE RING AND ITS APPLICATION FOR THE SYNTHESIS OF MACROCYLCES CONTAINING BOTH OXA- AND THIA-BRIDGES

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Summary: Both the sulfinyl and sulfonyl groups directly bound to 2 or 4 position in pyridine were readily displaced by several nucleophiles such as RO^- and RS^-. The facility of the leaving groups is $RSO_2 \simeq RSO > Br \simeq Cl \gg RS$ (R:alkyl or benzyl). The ipso-substitution could be applied for the synthesis of new type of 2,6-disubstituted macrocycles containg both carbon-oxygen and carbon-sulfur bridges in moderate yields.

The nucleophilic substitution on pyridine ring takes place more readily than that of simple benzene system, since the halogen atom in 2 or 4-halopyridines can be substituted readily with several nucleophiles such as thiolates while the corresponding substitution of simple halobenzenes does not take place under the same conditions.
Recently, we have prepared several new sulfur compounds containing pyridine ring and shown that these alkyl 2-pyridyl sulfoxides or 2,6-disulfinylated pyridine derivatives can be used as phase transfer catalysts.[1] However, the general reactivities of these sulfur compounds bound to pyridine ring have not been well investigated at all. In this communication, we report that the new type of ipso-substitution in pyridine ring and its application for the synthesis of macrocyclic compounds containing pyridine ring.

Generally, the preparation of sulfur compounds bound to pyridine ring was carried out by employing the displacement reactions of 2-halo- or 2,6-dihalopyridines with thiolate anions in alcohol.[2] However, when 2,6-dihalopyridines were treated with several thiolates under the phase transfer conditions using quaternary ammonium salts, e.g., tetra-n-butylammonium bromide, and sodium hydroxide as a base in two phase system, the reaction stopped at the mono-substitution stage affording the 2-halo-6-alkylthiopyridines in quantitative yields as shown in Table 1. Furthermore, when one of these products, 2-chloro-6-methylthiopyridine was treated with several nucleophiles such as alkoxides and thiolates in refluxing alcohol, pyridine derivatives bearing two different substituents on 2 or 6 positions, e.g., 2-alkoxy-6-methylthiopyridines were obtained in good yields as shown in Table 2. Moreover, the reaction of 2-chloro-6-methylthiopyridine with several oligoethylene glycols in the presence of sodium hydride as a base in refluxing xylene afforded oligoether bridged methylthiopyridines in good yields as shown in Table 3. These bridged products were readily oxidized to the corresponding sulfone upon treatment with m-chloroperoxybenzoic acid or hydrogen peroxide in quantitative yields as also shown in Table 3. Oxidation of these 2-halo-6-alkylthiopyridine derivatives with m-chloro-

peroxybenzoic acid or hydrogen peroxide also afforded either the corresponding sulfoxides or sulfones in good yields. Furthermore, unexpectedly, when these sulfoxides or sulfones were treated with alkoxides or thiolates, ipso-substitution took place at the position bound to sulfinyl or sulfonyl group and not the position substituted by halogen. When sulfoxides were used as substrates, the major product was the ipso-substitution at the position bound to the sulfinyl group, but reduction was also observed as a side reaction to afford the corresponding sulfides. Meanwhile, when sulfones were used as substrates, the reduction was not observed under the same conditions and only the corresponding displacement products by nucleophiles were obtained in good yields. The results are summarized in Table 4. Therefore, these unusual observations indicate that the leaving abilities of the leaving groups in these ipso-substitution reactions of pyridine fall in the following order;

$$RSO_2 \simeq RSO > Br \simeq Cl \gg RS$$

Recently, a number of macrocyclic polyethers refered as "crown ether" were synthesized[3] and their abilities for the formation of complexes with a number of metals have been examined.[4] Meanwhile,hetero-crown compounds such as polyamines and cyclic polythiaethers, and their complexes with metals have also been studied extensively.[5] Newkome et al.[6] and Vögtle et al.[7] have prepared such macrocyclic compounds containing pyridine ring and tested their roles as ligands for complexing with various cations. However, these types of macrocycles especially, carbon-oxygen bridged 2,6-pyridino macrocycles in which the bridging oxygens are directly attached to the pyridine ring were difficult to prepare in good yields.[8] Therefore, we tried the preparation of new type of 2,6-pyridino macrocycles containing both carbon-oxygen and carbon-sulfur bridges in which both oxygen and sulfur atoms are directly attached to the pyridine ring by using new ipso-substitution.

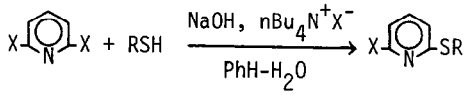
The synthesis of 2,6-pyridino macrocycles in which the bridging oxygen and sulfur directly attached to pyridine ring was carried out as shown in the following Scheme 1, starting with 2,6-dichloropyridine via formation of oligoether-bridged methylthiopyridines. Three new macrocycles (I)-(III) were isolated in total yields 20%, 21%, 19%, respectively.
The spectral data and elemental analyses are as follows.

Macrocycle (I) : Mp 86-87°C, Nmr($CDCl_3$) 2.03(4H, quint, J=8Hz, CCH_2C), 2.67(4H, t, J=8Hz, CH_2S), 3.22(4H, t, J=8Hz, CH_2Spyr), 3.90(4H, t, J=6Hz, β-CH_2O), 4.58(4H, t, J=6Hz, α-CH_2O), 6.44(2H, d, J=8Hz, β-pyrH), 6.79(2H, d, J=8Hz, β-pyrH), 7.38(2H, t, J=8Hz, γ-pyrH), M^+=438, Anal. Found: C 54.59 H 6.13 N 6.09, Calcd. for $C_{20}H_{26}N_2O_3S_3$: C 54.76 H 5.97 N 6.38%.

Macrocycle (II) : Mp 66-67°C, Nmr($CDCl_3$) 1.99(4H, quint, J=8Hz, CCH_2C), 2.64(4H, t, J=8Hz CH_2S), 3.23(4H, t, J=8Hz, CH_2Spyr), 3.71(4H, t, J=6Hz, γ-CH_2O), 3.84(4H, t, J=6Hz, β-CH_2O), 4.51(4H, t, J=6Hz, α-CH_2O), 6.43(2H, d, J=8Hz, β-pyrH), 6.76(2H, d, J=8Hz, β-pyrH). 7.36(2H, t, J=8Hz, γ-pyrH), M^+=482, Anal. Found: C 54.61 H 6.32 N 5.68, Calcd. for $C_{22}H_{30}N_2O_4S_3$: C 54.74 H 6.26 N 5.80%.

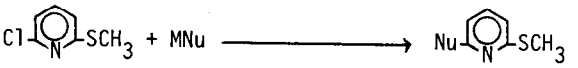
Macrocycle (III) : Mp 42.0-43.5°C, Nmr($CDCl_3$) 1.99(4H, quint, J=8Hz, CCH_2C), 2.65(4H, t, J=8Hz, CH_2S), 3.24(4H, t, J=8Hz, CH_2PSpyr), 3.68(8Hz, s, γ,δ-CH_2O), 3.85(4H, t, J=6Hz, β-CH_2O), 4.52(4H, t, J=6Hz, α-CH_2O), 6.44(2H, d, J=8Hz, β-pyrH), 6.76(2H, d, J=8Hz, β-pyrH), 7.36(2H, t, J=8Hz, α-pyrH), M^+=526, Anal. Found: C 54.54 H 6.52 N 5.20, Calcd. for $C_{24}H_{34}N_2O_5S_3$: C 54.72 H 6.50 N 5.31%.

Table 1



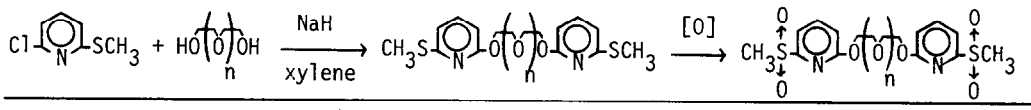
X	R	Temp.	Time(h)	Yield(%)
Cl	CH_3	reflux	6	98
Br	"	"	6	97
Cl	C_2H_5	"	16	89
Cl	n-C_4H_9	"	16	82
Cl	$C_6H_5CH_2$	"	11	82

Table 2



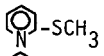
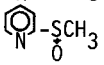
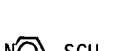
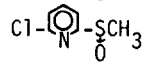
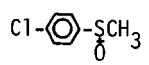
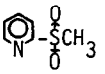
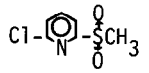
MNu	Solvent	Temp.	Time(h)	Yield(%)
CH_3ONa	CH_3OH	reflux	20	quant.
C_2H_5ONa	C_2H_5OH	"	13	70
CH_3SNa	C_2H_5OH	"	11	83
C_2H_5SNa	C_2H_5OH	"	13	76

Table 3

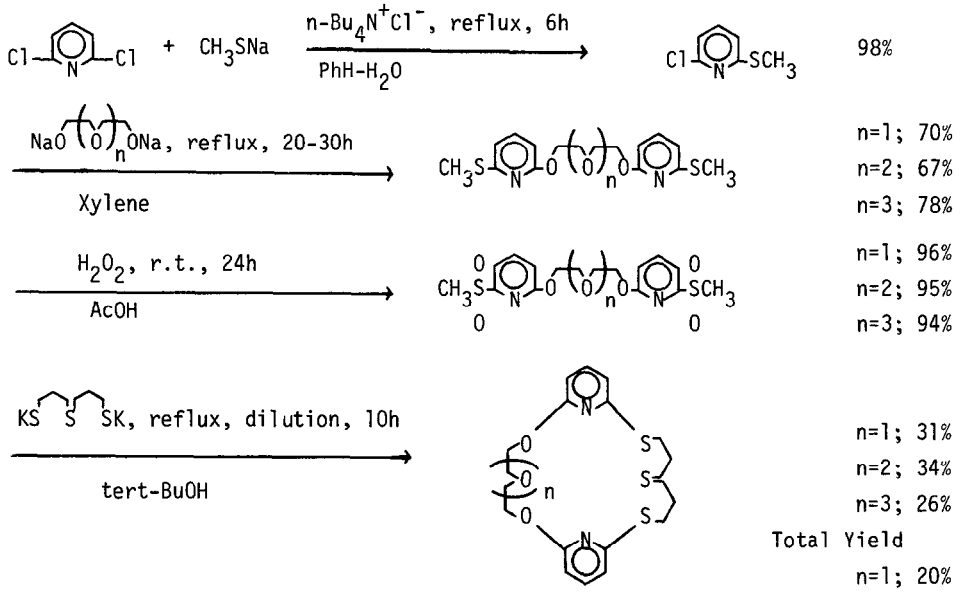


n	Temp.	Time(h)	Yield(%)	[O]	Solvent	Temp.	Time(h)	Yield(%)
0	reflux	30	75	H_2O_2	AcOH	r.t.	24	95
1	"	24	70	mCPBA	$CHCl_3$	"	12	96
				H_2O_2	AcOH	"	24	96
2	"	30	67	H_2O_2	AcOH	"	24	95
3	"	20	78	H_2O_2	AcOH	"	24	94

Table 4

Substrate	Nucleophile	Solvent	Temp.(°C)	Time(h)	Yield(%) Displacement	Yield(%) Reduction
	C_2H_5ONa	C_2H_5OH	reflux	5	no reaction	
	C_2H_5ONa	C_2H_5OH	reflux	2	73	8
	C_2H_5SNa	C_2H_5OH	50	5	74	18
	PhSK	tert-BuOH	reflux	5	47	7
	PhOK	tert-BuOH	reflux	18	no reaction	
	C_2H_5ONa	C_2H_5OH	reflux	3	63	21
	C_2H_5ONa	C_2H_5OH	50	1	74	13
	C_2H_5SNa	C_2H_5OH	r.t.	1.5	68	20
	C_2H_5ONa	C_2H_5OH	reflux	14	no reaction	
	C_2H_5ONa	C_2H_5OH	reflux	1.5	79	0
	C_2H_5ONa	C_2H_5OH	50	1	84	0
	C_2H_5SNa	C_2H_5OH	r.t.	1.5	90	0

Scheme 1



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