Tetrahedron Letters, Vol.22, No.44, pp 4409 - 4412, 1981
Printed in Great Britain

0040-4039/81/444409-04$02.00/0

ORGANIC SULFUR COMPOUNDS CONTAINING HETEROCYCLES. II: METHYL 2-PYRIDYL SULFOXIDE AS PHASE TRANSFER CATALYST.

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Summary: Methyl 2-pyridyl sulfoxide was found to be an excellent phase transfer catalyst which promotes simple S_N2 type displacement reactions of alkyl halides with some nucleophiles.

Recently, phase transfer catalyzed reactions(PTC Reaction) have been widely applied for organic syntheses.1) As to the catalysts used for PTC reactions, quaternary ammonium or phosphonium salts and crown ethers or cryptates have commonly been used. Besides these typical phase transfer catalysts, such neutral compounds as tert-amines2) and tert-amine-oxides3) are known to function as effective catalysts. Meanwhile, DMSO has been known to enhance the rates of such reactions as substitution and elimination.4) Similarly, we found recently that dimethyl and thiane sulfoximines have strong affinities toward several alkali or alkali earth metal salts, and enhance the rates of both S_N2 and E2 reactions.5) In search of other and possibly better sulfur compounds which may be used as chelating reagents for metal ion, solvents or phase transfer catalysts, we have prepared several organic sulfur compounds bound to pyridine.6) Mikolajczyk et al.7) reported earlier that a few sulfoxides i.e., α-phosphoryl sulfoxides, could be used as phase transfer catalysts to promote alkylation of active methylene compounds, but did not catalyze ordinary nucleophilic substitution reactions.

We now wish to report that a simple sulfoxide bound to pyridine i.e., methyl 2-pyridyl sulfoxide (1) can be used as a phase transfer catalyst which can promote several nucleophilic substitution reactions of alkyl halides with some anionic nucleophiles which proceed with inversion of configuration.

Nucleophilic Substitution of Benzyl Bromide with Nucleophiles

The Finkelstein reaction of benzyl bromide with lithium chloride and the S_N2 reaction of benzyl bromide with sodium cyanide were carried out either in benzene or in a mixture of benzene-water(liquid-solid or liquid-liquid system), in the presence or absence of the catalyst (1).

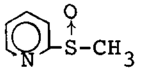
In a typical run, 0.12-4.8 mmol of (1) was added onto a heterogeneous mixture of 1.0 mmol of benzyl bromide and 1.2 mmol of lithium chloride in either 4 ml of benzene or 4 ml(1:1) of benzene-water mixture. The whole mixture was stirred vigorously at 70°C for 4 to 22 hrs. The yield of benzyl chloride formed in the reaction was determined by GLC, while the rate of the reaction was estimated by following the amount of benzyl chloride formed by GLC. The results thus obtained under various conditions are listed in Table 1 and Fig. 1.

Table 1

Reactions of benzyl bromide with lithium chloride

$$C_6H_5CH_2Br + LiCl \xrightarrow[70°C]{(1)} C_6H_5CH_2Cl + LiBr$$

	(1)(eq. vol)	Solvent	Time(h)	Yield(%)
a)	0.0	C_6H_6	22	0
b)	0.5	"	"	7
c)	1.0	"	"	26
d)	2.0	"	8	50
e)	4.0	"	4	70
f)	0.1	C_6H_6-H_2O	22	40
g)	0.5	"	"	35



(1)

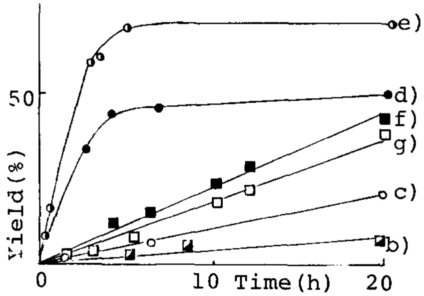


Fig. 1 Plots of yield of benzyl chloride vs. time

The reaction did not proceed at all in the absence of (1). As shown in Fig.1, the higher the concentration of (1), the higher was the yield of benzyl chloride formed, while the shorter was the reaction time to complete. For example, the reaction was completed within four hours when the mole ratio of sulfoxide (1) to the substrate was four. Even with one tenth or a half equivalent of (1), the reaction was found to be initiated substantially in benzene solution. Meanwhile, both the rate of reaction and the yield of benzyl chloride increased in benzene-water(liquid-liquid) solution, suggesting that selection of solvent composition is quite important for the substitution reaction. The reaction of benzyl bromide with sodium cyanide was also carried out in either benzene or benzene-water. The results shown in Table 2 indicate clearly that reaction proceeded smoothly in the presence of (1) in both benzene and benzene-water mixture. Both the rate of the reaction and yield of benzyl cyanide increased as the amount of (1) increased, while no reaction took place without the catalyst.

Reactions of Octyl Bromide with Several Nucleophiles

Both 1- and 2- octyl bromides were also found to react with several nucleophiles such as sodium cyanide, potassium phenolate, potassium thiophenolate in xylene(liquid-solid two phase system) in the presence of four

Table 2

Reactions of benzyl bromide with sodium cyanide

$$C_6H_5CH_2Br \quad + \quad NaCN \xrightarrow[\text{Solv.}]{(\underline{1})} C_6H_5CH_2CN \quad + \quad NaBr$$

($\underline{1}$) (eq. vol)	Solvent	Temp.(°C)	Time(h)	Yield(%)
0.0	C_6H_6	70	24	0
2.0	"	"	10	50
4.0	"	"	2	60
0.1	C_6H_6-H_2O	"	30	40
0.1	H_2O	100	1	94

Table 3

Reactions of octyl bromide with several nucleophiles

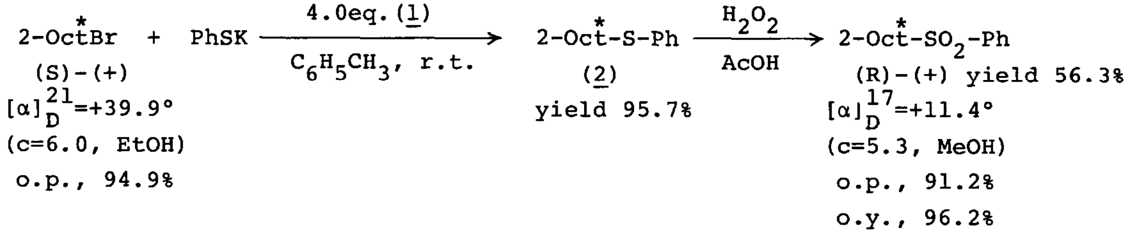
$$RX \quad + \quad MY \xrightarrow[C_6H_5CH_3]{4.0\text{eq. }(\underline{1})} RY \quad + \quad MX$$

RX	MY	Temp.(°C)	Time(h)	Product	Yield(%)
1-OctBr	NaCN	100	36	1-OctCN	quant.
"	KSCN	"	19	1-OctSCN	"
"	PhOK	70	30	1-OctOPh	"
"	PhSK	r.t.	2min.	1-OctSPh	"
2-OctBr	PhSK	"	36.5	2-OctSPh	80

equivalents of the sulfoxide ($\underline{1}$), as shown in Table 3.

The reaction, however, did not proceed at all without the sulfoxide ($\underline{1}$). In the reaction of 1-octyl bromide with potassium thiophenolate, 1-octyl sulfide was obtained quantitatively within only 2 minutes, whereas the reaction of 2-octyl bromide with thiophenolate ion took a much longer time under the same reaction condition.

One interesting observation we made is on the reaction between optically active 2-octyl bromide(o.p., 94.8%) with potassium thiophenolate in the presence of four equivalents of ($\underline{1}$). The sulfide ($\underline{2}$), isolated in 95.7% yield, was converted to the corresponding sulfone for measurement of optical rotation, which indicated clearly that the substitution reaction proceeded with more than 96% inversion of configuration. Therefore, this reaction is a typical S_N2 type substitution on carbon and the possible involvement of the Menshutkin type process, between pyridyl sulfoxide and 2-octyl bromide to form the pyridinium salt as an intermediate in the initial step, can be ruled out.[8)]



$$\underset{\substack{(S)-(+)\\ [\alpha]_D^{21}=+39.9^\circ\\ (c=6.0,\ EtOH)\\ o.p.,\ 94.9\%}}{\text{2-Oc}\overset{*}{\text{t}}\text{Br}} + \text{PhSK} \xrightarrow[C_6H_5CH_3,\ r.t.]{4.0eq.(\underline{1})} \underset{\substack{(\underline{2})\\ \text{yield } 95.7\%}}{\text{2-Oc}\overset{*}{\text{t}}\text{-S-Ph}} \xrightarrow[AcOH]{H_2O_2} \underset{\substack{(R)-(+)\ \text{yield } 56.3\%\\ [\alpha]_D^{17}=+11.4^\circ\\ (c=5.3,\ MeOH)\\ o.p.,\ 91.2\%\\ o.y.,\ 96.2\%}}{\text{2-Oc}\overset{*}{\text{t}}\text{-SO}_2\text{-Ph}}$$

All these observations reveal that even such a simple molecule as (1) can be used as an excellent phase transfer catalyst as quaternary ammonium salts and crown ethers. One advantage of the sulfoxide (1) is that it can be readily prepared and recovered quantitatively by shaking the reaction mixture with aqueous HCl solution after the reaction. Several other sulfoxides have been found to work as phase transfer catalysts and the results will be published in the subsequent papers.

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(Received in Japan 18 July 1981)