Nucleophilic Substitution of Halopyridines by Benzenethiolate Anion *via* a Radical Chain Mechanism

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2-Halopyridines **1a-d** reacted with sodium thiophenoxide in DMF at 80° to afford the *ipso*-substitution products. The following relative order of reactivity was observed: 2-iodopyridine (**1a**) ~ 2-bromopyridine (**1b**) ≫ 2-chloropyridine (**1c**) ~ 2-fluoropyridine (**1d**). The reaction of **1b** is inhibited by the electron scavenger azobenzene and by the radical scavenger benzoqoquinone. Furthermore, results of the reaction of 3-bromopyridine (**2b**) serve to rule out pyridyne mechanism. It is reasonable to suggest therefore that the reaction proceeds through the radical chain process containing one electron transfer, that is $S_{RN}1$.

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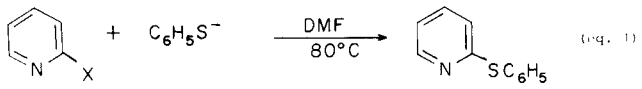
In the course of a synthetic study of chelating reagents containing nitrogen and sulfur atoms, we observed that 2-bromopyridine (**1b**) undergoes smoothly nucleophilic aromatic substitution by benzenethiolate anion in DMF or HMPA in the dark to afford the *ipso*-substitution product, although the anion scarcely attacked 2-chloropyridine (**1c**) [1]. Interestingly, in these reactions, the relative reactivity of 2-halopyridines toward the nucleophile is in contrast to that of general aromatic substitution (S_NAr) [2]. Although experimental conditions slightly differ from ours, earlier report concerning the reaction of 2-halopyridines with thiolate anions implied that the displacement takes place by S_NAr mechanism [3]. Recently Wolfe and Komin observed a similar behavior of halogen atoms in the reaction of halopyridines with ketone enolates in liquid ammonia on irradiation of uv light [4]. This finding was explained by free radical chain mechanism initiated by single electron transfer ($S_{RN}1$) [5,6]. Their reports prompted us to examine the possible participation of thiolate anion to $S_{RN}1$ mechanism. We wish to describe here that benzenethiolate anion as nucleophile can attack halopyridines by free radical mechanism even under thermal conditions.

The reaction was carried out by simply heating a mixture of halopyridine, sodium thiophenoxide, and solvent; the yield of the sulfide was determined by gc analysis. The results are summarized in Table I.



(eq. 1)

1a–d

Whereas **1c** and 2-fluoropyridine (**1d**) were scarcely attacked by benzenthiolate anion, 2-iodopyridine (**1a**) as well as **1b** readily reacted to afford 2-phenylthiopyridine in about 60% yield. Thus, the relative reactivity of 2-halopyridines toward benzenethiolate anion seems to decrease in the order: **1a** ~ **1b** ≫ **1c** ~ **1d**. This result indicates that unlike S_NAr, carbon-halogen bond strength is an important factor in these reactions. Moreover, 3-bromopyridine (**2b**) also undergoes *ipso*-substitution by benzenethiolate anion, and affords no 4-phenylthiopyridine which is expected to be produced by pyridyne mechanism. In addition a solution of **1b** and thiophenoxide in DMF was photoirradiated to afford the substituted product in 31% yield. In these reactions, dipolar aprotic solvents such as DMF and HMPA are the most recommendable solvents.

Table I

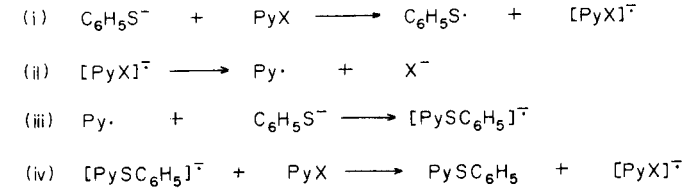
Reaction of Halopyridines with Sodium Thiophenoxide at 80°

Substrate	Solvent [a]	Time (minutes)	Yield (%)
1a	DMF	240	58
1b	DMF	5	11
1b	DMF	30	46
1b	DMF	60	52
1b	DMF	240	52
1b	HMPA	240	65
1b	ethanol	240	trace
1c	DMF	240	5
1d	DMF	240	7
2b	DMF	240	24

[a] Solvent: 30 ml, [Substrate] = 6.33×10^{-3} mole, [Thiophenoxide] = 6.96×10^{-3} mole.

These results seem to be explained by $S_{RN}1$ mechanism proposed by Bunnett [5] shown in Scheme 1, where PyX is an appropriate halopyridine.

Scheme 1



In step (i), one electron transfer from benzenethiolate anion to halopyridine to afford benzenethiyl radical and radical anion. Most aromatic $S_{RN}1$ reactions require stimulation by photons, solvated electrons, or electrons from cathode [6,7]. However, more recently, dark reaction of halobenzenes with pinacolone enolate ion was found to proceed by $S_{RN}1$ [8]. Further, Rico *et al.* showed that benzenethiolate anion is capable of one electron transfer to perhaloalkanes in DMF at −40° [9]. Therefore, on our study, step (i) seems to be a possible pathway. The next process that scission of the radical anion give to a pyridyl radical and halide ion is well known [4]. In $S_{RN}1$ mechanism, this step is rate determining. The order of relative reactivity of 2-halopyridines mentioned above is considered to support this step. The pyridiyl radical produced combines with benzenethiolate anion (step iii). The evidence of this step is not obtained, but Bunnett established this process in the case of phenyl radical [5]. Step (iv) may be plausible since halopyridines are more acceptable electron than halobenzenes [10].

Table II

Effect of Additives in the Reacton of 2-Bromopyridine with Sodium Thiophenoxide in DMF at 80° for 4 Hours

Additives [a]	Yield of 2-phenylthiopyridine
none	52
p-dinitrobenzene	9
benzoquinone	5
azobenzene	10

[a] 0.1 *M* Additive was used.

In order to confirm this hypothesis that the reaction of benzenethiolate anion with 2-halopyridines in DMF proceeds in $S_{RN}1$ mechanism, we performed inhibition experiments. The results are shown in Table II. The addition of 0.1 *M* benzoquinone as radical scavenger reduces the amount of substitution product from 52% to 5%. This result is a good indication of a radical chain process. Similar result was obtained in the case of HMPA as solvent. Moreover, azobenzene which is well known as an excellent electron acceptor [10] suppressed the formation of substitution. From these results, it seems likely that formation of phenylthiopyridine proceeds by radical chain process containing one electron transfer, that is $S_{RN}1$. The study of mechanistic detail, and synthetic scope and limitation of these reactions is in progress.

General Methods.

Gas chromatographic (gc) analysis and separation were accomplished on a Hitachi 063 instrument using a column of 20% Carbowax 20M on Celite 545 support at 210°. Yields of products were determined by the usual method with diphenyl sulfide as an internal standard. The ^1H nmr spectra were determined on a Hitachi R-600 spectrometer at 60 MHz with tetramethylsilane as an internal reference.

Materials.

Compound **1b** was prepared in 78% yield from 2-aminopyridine at 84-85°/25 Torr (lit [11] 91-92°/25 Torr). Compound **1c** was prepared in 24% yield by the procedure of Baker and McEvoy, bp 67-70°/5 Torr (lit [12] 93-95°/13 Torr). DMF and HMPA were purified by distillation. Other chemicals were commercially available, and they were used after ordinary purification.

Dark Reactions.

In a typical run, a DMF solution (40 ml) of sodium thiophenoxide (3.96 g, 30 mmoles) and **1b** (2.37 g, 15 mmoles) were placed in 100 ml of a three necked flask with nitrogen inlet tube and reflux condenser. Under nitrogen atmosphere, the reaction mixture was stirred magnetically at 80° for a given time. After evaporation of the solvent, the residue was dissolved in 100 ml of water and the aqueous mixture was extracted three times with 30 ml of chloroform; the organic layer was washed with a 2% hydrochloric acid solution, followed by washing with water, and dried over sodium sulfate. The organic layer obtained after filtration was separated by column chromatography (silica gel; petroleum ether) to give 2-phenylthiopyridine in 52% yield.

Photostimulated Reaction.

A solution of DMF, 2-bromopyridine and thiophenoxide was charged in a test tube, which was degassed and sealed under vacuum. The tube was irradiated by a RIKO 100 W high pressure mercury lamp at 5 cm distance for a given time at room temperature. Subsequent work up was identical with that described in the procedure of dark reaction.

Inhibited Dark Reaction of **1b** with Thiophenoxide.

The procedure of dark reaction was modified by adding 10 mol% of benzoquinone or azobenzene to the DMF solution.

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