Pergamon

Tetrahedron Letters 40 (1999) 5565–5568

TETRAHEDRON LETTERS

Concise Synthesis of Pyridyl Sulfides Direct Nucleophilic Displacement of Haloheteroaromatics by Mercaptan Promoted by K-Selectride

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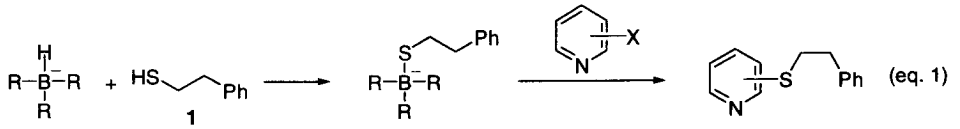
Received 27 April 1999; revised 17 May 1999; accepted 21 May 1999

Abstract: A simple and efficient synthetic method for sulfides from halogenated heteroaromatic compounds is described. An alkylthioborate, generated from K-Selectride and a thiol, rapidly reacted with various haloheteroaromatics under mild conditions.

Nucleophilic substitution of halopyridine with thiolate anion is one of the most convenient methods to prepare pyridyl sulfides. The facileness of the substitution on a pyridine ring compared to a benzene ring has been ascribed to the overall electron deficiency of the former.[1] Furthermore, halogen substituents α and γ to the nitrogen are usually more reactive than β-halogens. The majority of reactions involving loss of halogens are the addition-elimination kind; an addition of a nucleophile to the carbon carrying the halogen followed by elimination of the halide. However, if alkaline metal or ammonium thiolates are employed, the substitution reaction at pyridine requires rather harsh reaction conditions.[2, 3] With the exceptions of halopyridines possessing strong electron-withdrawing groups, the reaction does not take place effectively at room temperature.[4]

In this paper, we wish to report that haloheteroaromatics are converted to the corresponding sulfides at room temperature, when thioborate, prepared from benzeneethanethiol (**1**) and K-Selectride KBH(*sec*-Bu)$_3$, is employed (eq. 1).[5]

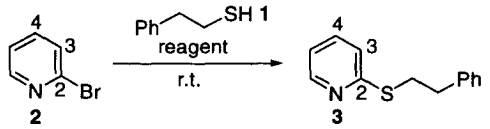


R = *sec*-Bu

This new thioborate reagent had an additional advantage in that it underwent substitution with less reactive 3-halopyridines.[6]

0040-4039/99/$ - see front matter
PII: S0040-4039(99)01038-2

Table 1



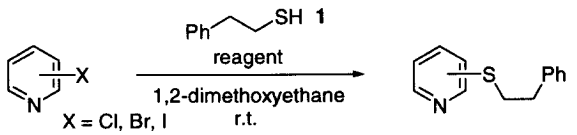
run	reagent	solvent	time / h	yield / %
1	*n*-BuLi	THF	4	2
2	NaH	1,2-dimethoxyethane	4	3
3	NaOMe	1,2-dimethoxyethane	4	3
4	KH	1,2-dimethoxyethane	4	2
5	KO*t*-Bu	1,2-dimethoxyethane	5	12
6	$NaBH_4$	MeOH	12	No Reaction
7	$NaBH_4$	1,2-dimethoxyethane	12	12
8	$NaBH_4$ + NaH	1,2-dimethoxyethane	48	25
9	$NaBH(OMe)_3$	1,2-dimethoxyethane	12	No Reaction
10	$Me_4N\ BH(OAc)_3$	1,2-dimethoxyethane	12	No Reaction
11	L-Selectride	1,2-dimethoxyethane	4	48
12	K-Selectride	1,2-dimethoxyethane	3	51
13	KS-Selectride	1,2-dimethoxyethane	24	24
14	Superhydride	1,2-dimethoxyethane	4	64

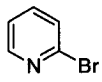
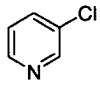
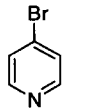
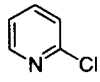
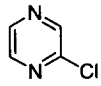
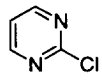
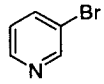
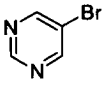
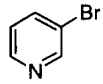
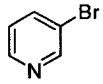
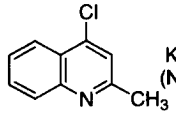
Treatment of 2-bromopyridine (**2**) and alkaline metal 2-phenylethanethiolate ($PhCH_2CH_2S^-\ M^+$) in 1,2-dimethoxyethane at room temperature, when *n*-BuLi, NaH, NaOMe, KH or KO*t*-Bu were employed as the bases, gave very low yields of the pyridyl sulfides (Table 1, runs 1-5).[5, 7] Since the thiolates, prepared in these conditions, smoothly reacted with various alkyl halides to give the corresponding sulfides in good yield, they proved to be cleanly generated. Therefore, the alkali metal thiolates turned out not to be versatile reagents.

We then examined the use of the thioborate with the expectations that the thioborate will show better nucleophilicity than the alkaline metal thiolates and that the Lewis acidity of the trialkylborane could activate the halopyridines. Our initial attempts using sodium borohydride were disappointing (runs 6-8). $NaBH(OMe)_3$ and $Me_4NBH(OMe)_3$ were totally ineffective (runs 9 and 10). We were, however, pleased to find that L-Selectride $LiBH(sec\text{-}Bu)_3$ and K-Selectride $KBH(sec\text{-}Bu)_3$ dramatically promoted the substitution reaction, which was completed within several hours at room temperature (entries 11 and 12). Although Superhydride $LiBHEt_3$ also gave satisfactory results (entry 14), it was eventually abandoned due to poor reactivity to 3-halopyridine (*vide infra*).

The new methodology using K-Selectride was then applied to other halogenated heteroaromatic compounds (Table 2).[8, 9]

Table 2



run	heterocycle	reagent	yield / %	run	heterocycle	reagent	yield / %
1		K-Selectride (KO*t*-Bu)	51 (12)	8		K-Selectride (KO*t*-Bu)	63 (0)
2		K-Selectride (NaH)	20 (35)	9		K-Selectride (NaH)	69 (1)
3		K-Selectride (KO*t*-Bu)	34 (5)	10		K-Selectride (NaH)	41 (0)
4		K-Selectride (NaH)	56 (3)	11		KS-Selectride (NaH)	59 (84)
5		K-Selectride (NaH)	58 (0)	12		KS-Selectride (NaH)	10 (0)
6		Superhydride	0				
7		KS-Selectride	0	13		KS-Selectride (NaH)	30 (0)

The reactions with various bases were carried out at room temperature for 4 h.

2-Fluoro, 2-chloro and 2-iodopyridines reacted with the thioborate as well as 2-bromopyridine, and the substitution turned out to be relatively insensitive to the halogens (runs 1 to 4). These are consistent with the nucleophilic aromatic substitution mechanism.[10] The reaction of 3-bromo and 3-chloropyridine also took place smoothly (runs 5 and 8). This is the unique aspect of the present method, since 3-halopyridine is considered to be much less reactive than 2-halo and 4-halopyridines. While K-Selectride was effective for 3-halopyridine, no reaction took place with Superhydride and KS-Selectride (runs 6 and 7). Therefore, moderate size of the alkyl group on the thioborate reagents also appears to be critical at least in this case. 2-Chloropyrazine, 2-chloropyrimidine and 4-chloroquinaldine gave the corresponding substitution products (runs 10, 11 and 13). Less reactive 5-bromopyrimidine also underwent the reaction, although the yield was low (run 12). In some of these reactions, use of KS-Selectride, $KBH[CH(CH_3)CH(CH_3)_2]_3$, gave better results than K-Selectride (runs 11 to 13), although the reason is not clearly understood.[11] It should be emphasized again that use of sodium hydride or potassium *tert*-butoxide gave very low yields of the sulfides for all these substrates with the exceptions of 2-fluoropyridine and 2-chloropyrimidine (runs 2 and 11).

In conclusion, an efficient synthesis of heterocyclic sulfides was accomplished. A detailed mechanistic

study is now in progress.

References and Notes

1. Boulton, A. J.; Bradsher, C. K.; Fowler, F. W.; Johnson, C. D.; Jones, G.; Lowe, P. A.; McKillop, A.; Scriven, E. F. V.; Uff, B. C.; Yates, F. S. *Comprehensive Heterocyclic Chemistry*, Katritzky, A. R.; Rees, C. W., Ed. Pergamon Press: Oxford, 1984; vol. 2.
2. Bradsher, C. K.; McDonald, J. W. *J. Org. Chem.* **1962**, *27*, 4482.
3. Memoli succeeded in introducing sodium *tert*-butyl thiolate at the 3-position of 3-bromo-2-cyanopyridine in refluxing condition, see: Memoli, K.A. *Tetrahedron Lett.* **1996**, *37*, 3617.
4. Dunn *et al.* reported that halogen atom *ortho* to an electron withdrawing group was displaced by sulfur nucleophiles, see: Dunn, A. D.; Norrie, R. *J. Heterocyclic Chem.* **1987**, *24*, 85.
5. Yoon, N. M.; Choi, J.; Ahn, J. H. *J. Org. Chem.* **1994**, *59*, 3490.
6. Reaction using Ph–SH, $PhCH_2SH$ and $PhCH_2$–S–S–CH_2Ph also produced the substituted products. Other thiols were not examined.
7. For an efficient method for preparation of thiolate, see: Yin, J.; Pidgeon, C. *Tetrahedron Lett.* **1997**, *38*, 5953 and references cited therein.
8. Reaction was carried out as follows: Under a nitrogen atmosphere, to a stirred solution of 2-bromopyridine (**2**) (175 mg, 1.11 mmol) and benzeneethanethiol (**1**) (300 mg, 2.12 mmol) in 1,2-dimethoxyethane (4 mL) was added K-Selectride (1N in THF, 3.5 mL) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with aqueous NaOH (1 N) and the products were extracted with EtOAc. The combined organic extracts were washed (brine), dried (Na_2SO_4) and concentrated in vacuo. The residue was purified by PTLC (hexane / EtOAc = 9 / 1) to give **3** (122 mg) in 51 % yield.
9. **2-(Phenylethylthio)-pyridine** (**3**) ^{1}H-NMR ($CDCl_3$) δ 3.01 (t, 2H, J = 8.0 Hz), 3.42 (t, 2H, J = 8.0 Hz), 6.94-6.98 (m, 1H), 7.41-7.37 (m, 6H), 7.42-7.53 (m, 1H), 8.43-8.45 (m, 1H), HRMS *m/z* 215.0767 (215.0769 calcd for $C_{13}H_{13}NS$, M^+); **3-(phenylethylthio)-pyridine** ^{1}H-NMR ($CDCl_3$) δ 2.92 (t, 2H, J = 8.2 Hz), 3.17 (t, 2H, J = 8.2 Hz), 7.13-7.32 (m, 6H), 7.60-7.66 (m, 1H), 8.42 (dd, 1H, J_1 = 4.8, J_2 = 1.2 Hz), 8.58 (d, 1H, J = 2.3 Hz), HRMS *m/z* 215.0771 (215.0769 calcd for $C_{13}H_{13}NS$, M^+); **4-(phenylethylthio)-pyridine** ^{1}H-NMR ($CDCl_3$) δ 2.99 (t, 2H, J = 8.2 Hz), 3.21 (t, 2H, J = 8.2 Hz), 7.10 (dd, 2H, J_1 = 4.8, J_2 = 1.7 Hz), 7.21-7.27 (m, 3H), 7.30-7.35 (m, 2H), 8.38 (dd, 2H, J_1 = 4.8, J_2 = 1.7 Hz), HRMS *m/z* 215.0763 (215.0769 calcd for $C_{13}H_{13}NS$, M^+); **2-(phenylethylthio)-pyrazine** ^{1}H-NMR ($CDCl_3$) δ 3.01 (t, 2H, J = 8.0 Hz), 3.43 (t, 2H, J = 8.0 Hz), 7.20-7.36 (m, 5H), 8.19 (d, 1H, J = 1.5 Hz), 8.39 (dd, 1H, J_1 = 2.7, J_2 = 1.5 Hz), 8.43 (d, 1H, J = 1.5 Hz), HRMS *m/z* 216.0707 (216.0722 calcd for $C_{12}H_{12}N_2S$, M^+); **2-(phenylethylthio)-pyrimidine** ^{1}H-NMR ($CDCl_3$) δ 3.02-3.08 (m, 2H), 3.36-3.42 (m, 2H), 6.94 (dd, 1H, J_1 = J_2 = 4.8 Hz), 7.20-7.34 (m, 5H), 8.50-8.53 (m, 2H), HRMS *m/z* 216.0716 (216.0722 calcd for $C_{12}H_{12}N_2S$, M^+); **5-(phenylethylthio)-pyrimidine** ^{1}H-NMR ($CDCl_3$) δ 2.95 (t, 2H, J = 8.0 Hz), 3.19-3.25 (m, 2H), 7.17-7.35 (m, 5H), 8.66 (s, 2H), 9.02 (s, 1H), HRMS *m/z* 216.0741 (216.0722 calcd for $C_{12}H_{12}N_2S$, M^+); **4-(phenylethylthio)-quinaldine** ^{1}H-NMR ($CDCl_3$) δ 2.69 (s, 3H), 3.09 (t, 2H, J = 8.2 Hz), 3.35 (t, 2H, J = 8.2 Hz), 7.07 (s, 1H), 7.24-7.29 (m, 3H), 7.30-7.37 (m, 2H), 7.48 (ddd, 1H, J_1 = 8.4, J_2 = 6.9, J_3 = 1.2 Hz), 7.67 (ddd, 1H, J_1 = 8.4, J_2 = 6.9, J_3 = 1.2 Hz), 7.99 (d, 1H, J = 8.4 Hz), 8.08 (dd, 1H, J_1 = 8.4, J_2 = 1.2 Hz), HRMS *m/z* 279.1085 (279.1082 calcd for $C_{18}H_{17}NS$, M^+).
10. (a) Bunnett, J. F.; Garbisch, Jr. E. W.; Pruitt, K. M. *J. Am. Chem. Soc.* **1957**, *79*, 385. (b) Bartoli, G.; Todesco, P. E. *Acc. Chem. Res.* **1977**, *10*, 125.
11. Heteroaromatics substituted with both a thiol and a *sec*-butyl group were isolated when K-Selectride was used. But the substituted positions were not determined.