

Divinyl Sulfide as Synthetic Equivalent of Ethenethiolate and 3-Butenethiolate Anions in Nucleophilic Substitution in Halopyridines and Haloalkanes

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Abstract—The use of divinyl sulfide as synthetic equivalent of ethenethiolate and 3-butenethiolate anions makes it possible to obtain vinylthio(halo)- and 3-butenylthio(halo)pyridines from halopyridines. 2,6-Bromo-(chloro)pyridines react with a mixture of ethenethiolate and 3-butenethiolate ions more readily than does 3,5-dibromopyridine. The reaction yields mainly products of halogen replacement by vinylthio group. The formation of 3-butenethiolate ion in the reaction of divinyl sulfide with sodium in liquid ammonia is governed by the order of mixing of the reactants. Possible ways of generation of 3-butenethiolate ion in the reaction with 1-bromobutane are discussed.

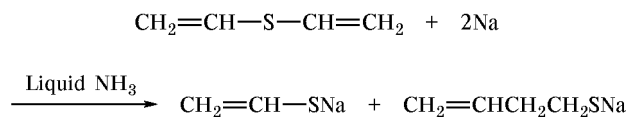
Halopyridines having acceptor and donor substituents exhibit high reactivity in nucleophilic substitution reactions, and they have found application in the synthesis of functional pyridine derivatives [1]. The synthesis, structure, and chemical properties of vinylthiopyridine have been reported [2]. Introduction into pyridine molecule of a butenylthio or vinylthio group, which is capable of being involved in polymerization and copolymerization processes, considerably extends the scope of application of functionalized pyridine derivatives. Prior to our studies, there were no published data on 3-butenylthiopyridines which are new compounds possessing a wide synthetic potential. We showed in [3] that the reaction of 3,5-dibromopyridine with products of cleavage of divinyl sulfide with metallic sodium in liquid ammonia, apart from the expected 3-bromo-5-vinylthiopyridine, gave 3-bromo-5-(3-butenylthio)pyridine. The present work continues our studies on the synthesis of heteroaromatic compounds having vinylthio and 3-butenylthio groups. We examined reactions of 2,6-dichloro-, 2,6-dibromo-, and 3,5-dibromopyridines with products formed by

the action of metallic sodium on divinyl sulfide in liquid ammonia [4], as well as possible ways of generation of one of these products, 3-butenethiolate ion [5] (Scheme 1).

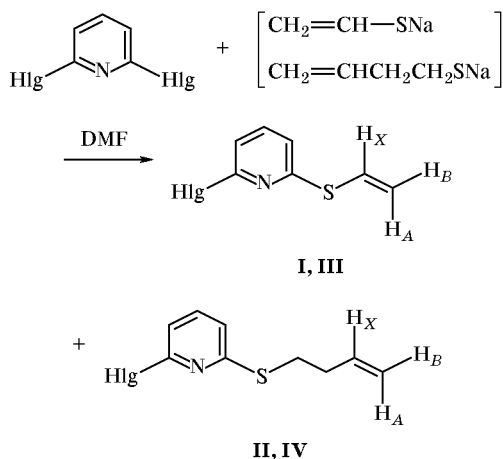
We have found that 2,6-dichloro(bromo)pyridines react at 20, 50, and 80°C in dimethylformamide (DMF) or diethyl ether with products formed by cleavage of divinyl sulfide with sodium in liquid ammonia to give the expected vinylthio derivatives and also 3-butenylthio-substituted compounds (Table 1, Scheme 2). In the reaction with 2,6-dichloropyridine at 20°C in DMF (reaction time 20 h), replacement of one halogen atom occurs to afford 2-chloro-6-vinylthiopyridine (**I**) and 2-(3-butenylthio)-6-chloropyridine (**II**) at a ratio of 2.5:1 (58 and 20%, respectively; see Table 1, run no. 1). When the reaction time was prolonged to 45 h, a small amount of 2,6-bis(vinylthio)pyridine (about 5%, according to the GC-MS data; M^+ 195) was obtained in addition to the monosubstitution products (Table 1, run no. 2).

The reaction with 2,6-dibromopyridine in DMF at 20°C (45 h) gave a mixture of 2-bromo-6-vinylthiopyridine (**III**) and 2-bromo-6-(3-butenylthio)pyridine (**IV**) at a ratio of 2:1 (52 and 23%, respectively) and 2,6-bis(vinylthio)pyridine (~5%) (Table 1, run no. 3). Raising the temperature to 80°C (reaction time 1 h) in order to replace both halogen atoms in 2,6-dibromopyridine resulted in formation of a mixture of 7 com-

Scheme 1.



Scheme 2.

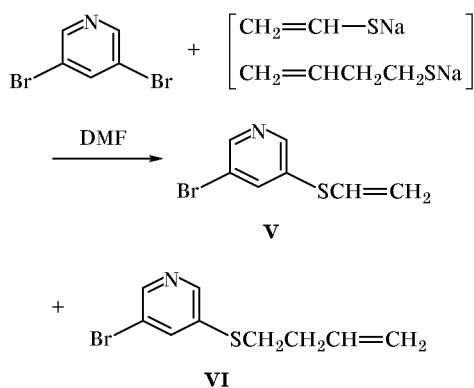


I, II, Hlg = Cl; III, IV, Hlg = Br.

pounds (according to the GC–MS data). Among these, we identified 2-bromo-6-vinylthiopyridine (28%), 2-bromo-6-(3-butenylthio)pyridine (24%), and a small amount of 2-(3-butenylthio)-6-vinylthiopyridine (M^+ 223; Table 1, run no. 4). Increase of the reaction time to 4 h led to formation of a mixture of 2-bromo-6-(3-butenylthio)pyridine and 2-(3-butenylthio)-6-vinylthiopyridine at a ratio of 2:1 (GC–MS data). In this case, no molecular ion peak of 2-bromo-6-vinylthiopyridine was observed in the mass spectrum. Also, an appreciable amount of polymeric products was obtained, which were likely to be formed from readily polymerizable (at elevated temperature) vinylthiopyridines.

Unlike 2,6-dibromo(chloro)pyridines, 3,5-dibromopyridine failed to react in DMF at 20°C with products obtained from divinyl sulfide by the action of sodium in liquid ammonia. The reaction occurred in DMF at 55°C and afforded a mixture of 3-bromo-5-vinylthiopyridine (V) and 3-bromo-5-(3-butenylthio)pyridine

Scheme 3.

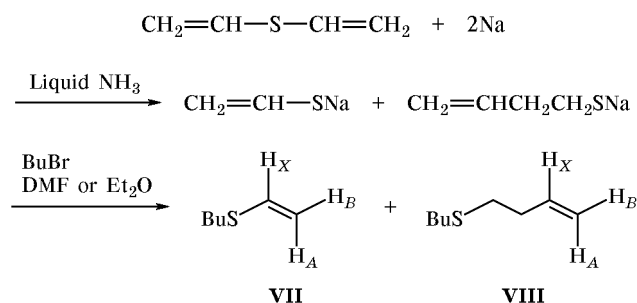


(VI) at a ratio of ~1:1 (33 and 28%, respectively; Table 1, run no. 5; Scheme 3).

It should be emphasized that 3-butenethiolate ion is formed (and is then involved in nucleophilic substitution in dihalopyridines) mainly when sodium is added to a solution of divinyl sulfide in liquid ammonia, i.e., when divinyl sulfide is present in a large excess. Addition of divinyl sulfide to a solution of sodium in liquid ammonia gives rise to very small amounts of 3-butenethiolate ion. Therefore, in such cases either 3-butenylthio derivatives are not formed (Table 1, run no. 7) or their yield decreases to 11% (Table 1, run nos. 8–10).

Possible ways of generation of 3-butenethiolate ion in the reaction of divinyl sulfide with metallic sodium in liquid ammonia were studied in detail using the reaction with 1-bromobutane as an example (Table 2; Scheme 4).

Scheme 4.



As noted above, the yield of 3-butenethiolate ion depends mainly on the order of mixing of the reactants. Addition of sodium to a solution of divinyl sulfide in liquid ammonia leads to formation of both ethenethiolate and 3-butenethiolate ions. Correspondingly, the subsequent reaction with 1-bromobutane gives 45–47% of butyl vinyl sulfide (VII) and 15–25% of butyl 3-butenyl sulfide (VIII) (Table 2, run nos. 1–3). Addition of ammonium chloride to the reaction mixture obtained from divinyl sulfide and metallic sodium in liquid ammonia (NH_4Cl binds sodium amide which favors metalation process) inhibits the formation of 3-butenethiolate ion, and the yield of butyl 3-butenyl sulfide (VIII) is 15% (Table 2, run no. 1). When the reactants are mixed in the reverse order (divinyl sulfide is added to a solution of sodium in liquid ammonia), only traces of 3-butenethiolate are formed (Table 2, run no. 5). The reaction in DMF is faster than in diethyl ether (Table 2, run nos. 2, 3). In the reaction of divinyl sulfide with lithium (instead of sodium), the yield of butyl vinyl sulfide (VII) is lower, and sulfide VIII

Table 1. Reactions of dichloro- and dibromopyridines in DMF with products formed by reaction of divinyl sulfide with metallic sodium in liquid ammonia^a

Run no.	Initial dihalopyridine	Order of mixing of reactants	Temperature, °C	Reaction time, h	Yield, % (product)	Product ratio
1	2,6-Dichloropyridine	A	20	20	20 (II), 58 (I)	1:2.5
2	2,6-Dichloropyridine	A	20	45	19 (II), 54 (I)	1:2.5
3	2,6-Dibromopyridine	A	20	45	23 (IV), 52 (II)	1:2
4	2,6-Dibromopyridine ^c	A	80	1	24 (IV), 28 (III)	1:1
5	3,5-Dibromopyridine	A	55	2	28 (IV), 33 (V)	1:1
6	3,5-Dibromopyridine	A	20	15	28 (IV), 33 (V)	1:1
7	2,6-Dichloropyridine	B	20	20	36 (I)	–
8	2,6-Dichloropyridine	B	20	45	11 (II), 68 (I)	1:5
9	2,6-Dichloropyridine	B	50	4	10 (II), 40 (I)	1:3.5
10	2,6-Dichloropyridine	B	20	15	10 (II), 40 (I)	1:3.5
11	2,6-Dichloropyridine ^c	B	80	5	11 (II), 43 (I)	1:2
12	2,6-Dichloropyridine ^c	B	20	15	11 (II), 43 (I)	1:2

^a Divinyl sulfide–sodium–dihalopyridine molar ratio 4:8:1.

^b A: sodium was added to a solution of divinyl sulfide in liquid ammonia; B: divinyl sulfide was added to a solution of sodium in liquid ammonia.

^c The reaction was carried out in the presence of hydroquinone.

is not formed at all (Table 2, run no. 4). The products were analyzed by NMR spectroscopy and gas chromatography–mass spectrometry.

The mechanism of formation of 3-butenethiolate ion remains a matter of discussion. A possible way is metalation of divinyl sulfide with sodium in liquid ammonia, which is concurrent to the formation of ethenethiolate ion (Scheme 5). Intermediate α -carbanion **A** undergoes rearrangement into 3-butenethiolate ion which then replaces halogen atom in dihalopyridines or 1-bromobutane. According to our

data, metalation of divinyl sulfide and formation of 3-butenethiolate ion occurs mainly when metallic sodium is added to a solution of divinyl sulfide in liquid ammonia.

Another possible way is as follows. Cleavage of divinyl sulfide with sodium in liquid ammonia gives vinylsodium which adds to divinyl sulfide [6] to form 3-butenyl vinyl sulfide anion **B**. Protonation of the latter yields 3-butenyl vinyl sulfide which undergoes cleavage at the C–S bond by the action of metallic sodium, affording sodium 3-butenethiolate and vinyl-

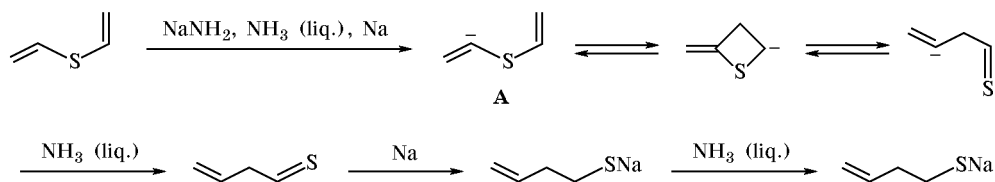
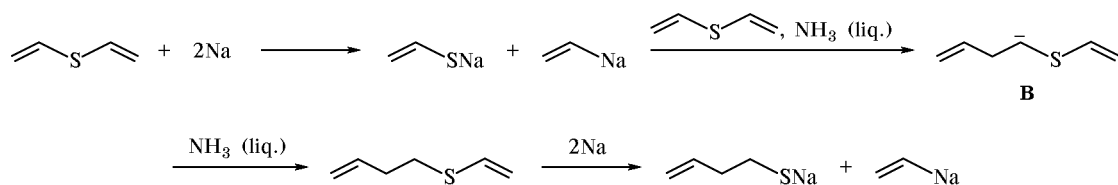
Scheme 5.**Scheme 6.**

Table 2. Reaction of 1-bromobutane with products formed by reaction of divinyl sulfide with metallic sodium in liquid ammonia^a

Run no.	Order of mixing of reactants	Solvent	Temperature, °C	Reaction time, h	Yield, %		Product ratio
					VIII	VII	
1	A ^c	Et ₂ O	20	20	15	45	1:2.6
2	A	DMF	20	4	20	47	1:1.8
3	A	Et ₂ O	20	20	25	47	1:1.5
4	A ^d	Et ₂ O	20	20	—	30	—
5	B	DMF	20	20	Traces	61	—

^a Divinyl sulfide–sodium–1-bromobutane molar ratio 4:8:1.

^b A: sodium was added to a solution of divinyl sulfide in liquid ammonia; B: divinyl sulfide was added to a solution of sodium in liquid ammonia.

^c In the presence of NH₄Cl.

^d Lithium was used instead of sodium.

sodium. The latter is again involved in the addition to divinyl sulfide (Scheme 6). We failed to find conditions for selective formation of 3-butenethiolate ion.

Thus the use of divinyl sulfide as synthetic equivalent of ethenethiolate and 3-butenethiolate ions makes it possible to prepare vinylthio(halo)- and 3-butenylthio(halo)pyridines. 2,6-Dibromo(chloro)pyridines react with ethenethiolate and 3-butenethiolate ions more readily than does 3,5-dibromopyridine. The reaction gives mainly the corresponding vinylthio derivatives.

EXPERIMENTAL

The ¹H NMR spectra were recorded on a Bruker DPX-400 instrument (400 MHz) in CDCl₃ using HMDS as internal reference. Gas chromatographic–mass spectrometric analysis was performed with the aid of an HP 5971A mass-selective detector (electron impact, 70 eV).

A mixture of 3-bromo-5-vinylthiopyridine (V) and 3-bromo-5-(3-butenylthio)pyridine (VI) was obtained as described in [3].

2-Chloro-6-vinylthiopyridine (I) and 2-(3-butenylthio)-6-chloropyridine (II). Metallic sodium, 1.84 g, was added in small portions with stirring to a solution of 3.44 g of divinyl sulfide in 100 ml of liquid ammonia. When the ammonia evaporated, 70 ml of DMF was added, and a solution of 1.48 g of 2,6-dichloropyridine in 10 ml of DMF was added dropwise. The mixture was stirred for 4 h and was left overnight. It was then diluted with 150 ml of water and treated with diethyl ether. The ether extracts were washed with water, dried over MgSO₄, and

evaporated under reduced pressure. The residue, 1.4 g, was an amber viscous liquid containing (according to the ¹H NMR data) 2-chloro-6-vinylthiopyridine (I) and 2-(3-butenylthio)-6-chloropyridine (II) at a ratio of 2.5:1 (58 and 20%, respectively). We failed to separate this mixture by chromatography on aluminum oxide using various eluent systems. ¹H NMR spectrum of I, δ, ppm: 5.48 d (1H, H_B), 5.58 d (1H, H_A), 7.07 d.d (1H, H_X), ³J_{BX} = 9.6, ³J_{AX} = 17.1 Hz; 6.99 d (1H, 3-H, pyridine), 7.04 d (1H, 5-H, pyridine), 7.42 t (1H, 4-H, pyridine). ¹H NMR spectrum of II, δ, ppm: 2.45 m (2H, CH₂=CHCH₂CH₂S), 3.20 t (2H, SCH₂), 5.02 d.q (1H, H_B), 5.08 d.q (1H, H_A), 5.83 m (1H, H_X), ²J_{AB} = 1.6, ³J_{BX} = 10.2, ³J_{AX} = 17.1, ⁴J(CH₂H_X) = 1.6 Hz; 6.92 d (1H, 3-H, pyridine), 7.03 d (1H, 5-H, pyridine), 7.35 t (1H, 4-H, pyridine). Mass spectrum, M⁺: m/z 171 (I), 199 (II).

2-Bromo-6-vinylthiopyridine (III) and 2-bromo-6-(3-butenylthio)pyridine (IV) were synthesized by a similar procedure. We failed to separate the products. ¹H NMR spectrum of III, δ, ppm: 5.48 d (1H, H_B), 5.54 d (1H, H_A), 7.17 d.d (1H, H_X), ³J_{BX} = 9.8, ³J_{AX} = 17.2 Hz; 7.06 d (1H, 3-H, pyridine), 7.09 d (1H, 5-H, pyridine), 7.32 t (1H, 4-H, pyridine). ¹H NMR spectrum of IV, δ, ppm: 2.44 m (2H, CH₂=CHCH₂CH₂S), 3.18 t (2H, SCH₂); 5.04 d.q (1H, H_B), 5.10 d.q (1H, H_A), 5.84 m (1H, H_X), ²J_{AB} = 1.6, ³J_{BX} = 10.2, ³J_{AX} = 17.1, ⁴J(CH₂H_X) = 1.6 Hz; 6.88 d (1H, 3-H, pyridine), 7.07 d (1H, 5-H, pyridine), 7.26 t (1H, 4-H, pyridine). Mass spectrum, M⁺: m/z 217 (III), 245 (IV).

Butyl vinyl sulfide (VII) and butyl 3-butenyl sulfide (VIII) were obtained as described above for

compounds **I** and **II**. We failed to separate products **VII** and **VIII**. ^1H NMR spectrum of **VII**, δ , ppm: 0.91 t (3H, CH_3), 1.42 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{H}_2\text{S}$), 1.61 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{S}$), 2.67 t (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{S}$); 5.07 d (1H, H_A), 5.14 d (1H, H_B), 6.33 d.d (1H, H_X), $^3J_{BX} = 10.0$, $^3J_{AX} = 16.8$ Hz. ^1H NMR spectrum of **VIII**, δ , ppm: 0.88 t (3H, CH_3), 1.40 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{S}$), 1.59 m (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{S}$), 2.53 t (2H, $\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2\text{S}$), 2.31 q (2H, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$), 2.50 t (2H, $\text{CH}_2=\text{CHCH}_2\text{CH}_2$); 4.99 d.q (1H, H_B), 5.05 d.q (1H, H_A), 5.81 m (1H, H_X), $^2J_{AB} = 1.6$, $^3J_{BX} = 10.0$, $^3J_{AX} = 16.8$, $^4J(\text{CH}_2\text{H}_X) = 1.6$ Hz. Mass spectrum, $M^{+\cdot}$: m/z 116 (**VII**), 144 (**VIII**).

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