

A new route to functionally-substituted tetrazines

Mikhail G. Voronkov,^a Irina P. Lebedeva,^b Vladimir I. Rakhlin^a, and Svetlana G. D'yachkova^b

^a *A.E. Favorsky Irkutsk Institute of Chemistry Siberian Branch of the Russian Academy of Sciences, 1 Favorsky St., Irkutsk, 664033 Russian Federation*

^b *Irkutsk State Technical University, 83 Lermontov St., Irkutsk, 664033 Russian Federation*
E-mail: vir@irioch.irk.ru; dsg@irk.ru

The paper is dedicated to the 70th birthday of our friend Professor Vladimir Minkin who has contributed a great deal to organic and physical-organic chemistry
(received 29 Nov 04; accepted 10 Feb 05; published on the web 03 Mar 05)

Abstract

Ethylthio and isopropylthio chloroacetylenes react with dimethylhydrazine in ether at room temperature to form 1,1,4,4-tetramethyl-3,6-bis-[(alkylthio)methyl]-1,4-dihydro-1,2,4,5-tertazinium-1,4-dichlorides in 67 and 80% yield.

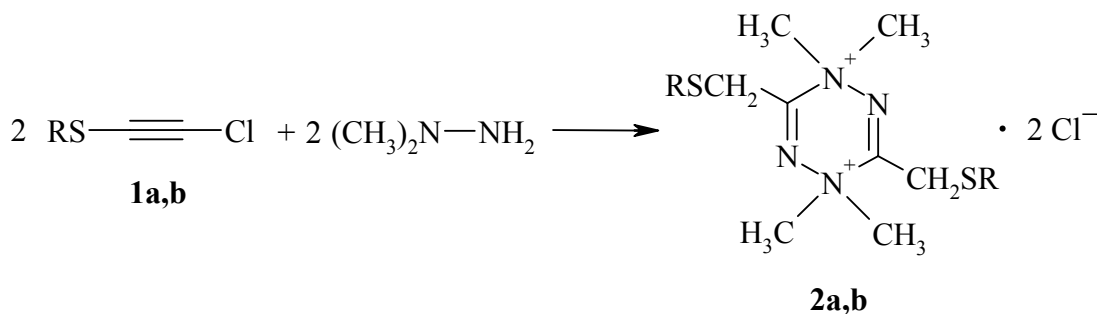
Keywords: (Alkylthio)chloroacetylenes, dimethylhydrazine, tetrazines

Introduction

(Alkylthio)chloroacetylenes react readily with *N*-, *O*- and *S*- mono- and bifunctional nucleophiles¹ to afford substituted polyfunctional unsaturated compounds including heterocyclic ones. For instance, the reactions with alkylenediamines,² 2-hydroxyethylamine³ 2-hydroxy-*N,N*-dimethylamine,⁴ thiosemicarbazones,⁵ proceed by nucleophilic substitution of the acetylenic chlorine forming ynammonium salts which further undergo cyclization. In this way it was possible to obtain imidazole, oxazolone, oxazolidine, oxazine, and thiazole derivatives which, in certain cases, display effective complex-forming properties or high antimicrobial and antitumor activity. The reactions of (alkylthio)chloroacetylenes with nucleophiles open up new routes to new classes of polyfunctional acyclic and heterocyclic compounds and allow investigation of the nucleophilic substitution at *sp*-hybridized carbon atoms.

Results and Discussion

The reaction of (alkylthio)chloroacetylenes **1** with dimethylhydrazine, a large-tonnage product within the chemical industry, is not well understood. Prior to our investigation the literature on the reaction of haloacetylenes with hydrazine and its derivatives was limited to a brief note describing the reaction of bromoethynyl(aryl)ketones with *N,N*-dimethylhydrazine leading to further polymerization and hydrobromination of the intermediate ethynylhydrazines.⁶ The bidentate nucleophilic character of *N,N*-dimethylhydrazine (DMH) and the presence of two C_{sp} atoms in the acetylene **1** makes prediction of the product composition difficult. We have shown that (ethylthio) and (*iso*-propylthio) chloroacetylenes **1a,b** react readily with an equimolar amount of DMH in ether at 20-22°C to afford 1,1,4,4-tetramethyl-3,6-bis-[(alkylthio)methyl]-1,4-dihydro-1,2,4,5-tetrazinium-1,4-dichlorides **2a,b** in 67 and 80% yield, respectively (Scheme 1).

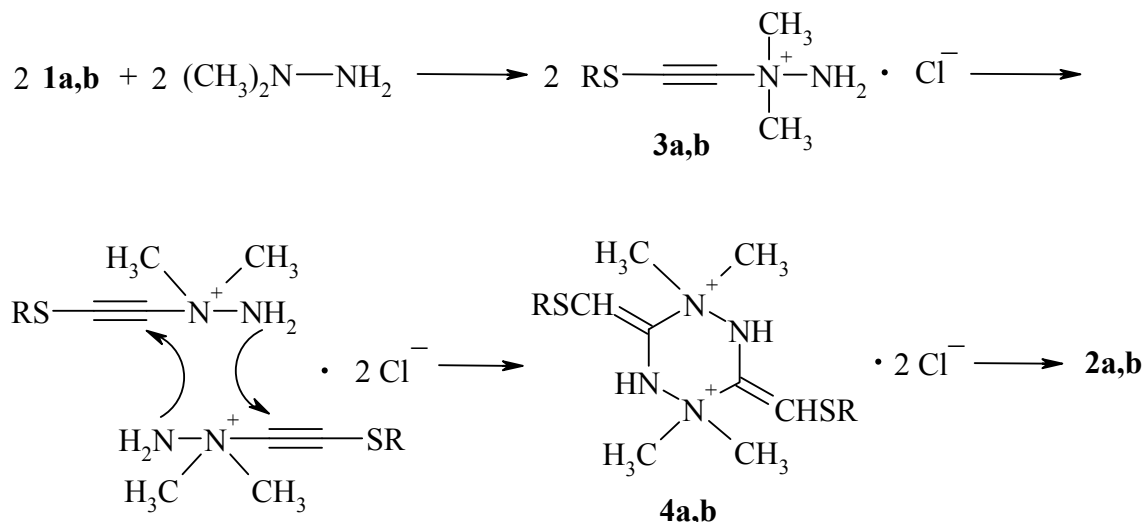


R = Et (a), *i*-Pr (b).

Scheme 1

Compounds **2a,b** are white crystalline substances soluble in water, DMSO and ethanol. In the ¹³C NMR spectra of **2a,b** there are signals of carbon atoms of alkylthio-, $\text{CH}_3\text{-N}^+$ and exocyclic alkylthiomethylene (SCH_2) groups, as well as a signal at 128 ppm, which was assigned to two magnetically equivalent carbon atoms ($\text{C}=\text{N}$) in the tetrazine cycle^{6,7} Apart from the alkylthio proton signals, the ¹H NMR spectra of compounds **2a,b** show two singlet signals at ~2.7 and 3.6 ppm corresponding to SCH_2 - and $\text{CH}_3\text{-N}$ - group protons, respectively. In the IR spectra of the dichlorides **2a,b** display absorption bands at 1600 cm^{-1} from the $\text{C}=\text{N}$ stretching vibrations. Their ionic character was confirmed by mercurimetric titration which indicated the presence of two chloride-ions per mole of compound.

Formation of tetrazines **2a,b** in the reaction under consideration (Scheme 1) can be rationalized by Scheme 2 including the nucleophilic attack of the tertiary nitrogen atom of dimethylhydrazine at the C_{sp} carbon atom of chloroacetylenes **1a,b** leading to substitution of the halogen atom and formation of ethynylammonium salts **3a,b**. The latter dimerize into alkylthiomethylidene tetrazines **4a,b** which after prototropic isomerization give tetrazinium-1,4-dichlorides **2a,b**.



Scheme 2

Thus, the reaction of (ethylthio) and (*iso*-propylthio) chloroacetylenes with *N,N*-dimethylhydrazine allows the elaboration of a new synthetic approach to functionally substituted tetrazines. The representatives of this class of compounds have for long time attracted the attention of research chemists due to their high and diverse biological activity.⁸

Experimental Section

General Procedures. IR Spectra were recorded on a Specord IR-75 spectrometer in microlayer. ¹H and ¹³C NMR spectra were run on a Bruker DPX-400 (400 MHz for ¹H and 100 MHz for ¹³C) in DMSO, TMS as internal standard.

GLC analysis was carried out on a Tsvet-500 chromatograph, glass columns 3m x 4mm, sorbent Inerton-super 0.125-0.150 mm impregnated with 10% PMS-1000, katharometer, helium as gas carrier.

1,1,4,4-Tetramethyl-3,6-bis-[(ethylthio)methyl]-1,4-dihydro-1,2,4,5-tetrazinium-1,4-

dichloride (2a). To a solution of 2.50 g (0.042 mol) DMH and 100 ml of dry ether a solution of 5.06 g (0.042 mol) of acetylene **1a** in 20 ml of dry ether was added drop wise on stirring for 30 min. The reaction proceeded exothermally. The reaction temperature was kept at 20-22°C using external cooling. After the addition of the acetylene solution, the reaction mixture was stirred at 20-22° for further 8 h. Then, the precipitate was filtered off, washed with dry diethyl ether (3×10 ml) and dried in vacuum. 5.10 g (67%) of compound **2a** was obtained as a white crystalline substance, m.p. 77-79°C. **Anal.** calcd. for C₁₂H₂₆Cl₂N₄S₂, %: C 39.88; H 7.20; Cl 19.67; N 15.51; S 17.73. Found, %: C, 39.57; H, 7.28; Cl, 19.81; N, 15.60; S, 17.53. IR (KBr), cm⁻¹: 3056, 2988, 2924 [ν(C-H)], 2800-2600 [ν(ammonium band)], 1626 [ν(C=N)]. ¹H NMR, δ,

ppm: 1.25 t (6H, CH₃), 2.74 s (4H, SCH₂), 2.96 q (4H, CH₂S), 3.59 s (12H, CH₃N⁺). ¹³C NMR, δ_C, ppm: 16.15 (CH₃), 27.16 (CH₂S), 39.50 (SCH₂), 59.95 (CH₃N⁺), 128.66 (C=N).

1,1,4,4-Tetramethyl- 3,6-bis-[(iso-propylthio)methyl] -1,4-dihydro-1,2,4,5-tetrazinium-1,4-dichloride (2b). Obtained by the above described procedure from 2.05 g (0.034 mol) of DMH and 4.60 g (0.034 mol) of acetylene **1b**. Yield of **2b** 5.30 g (80%). M.p.. 80-81°C. **Anal.** calcd. for C₁₄H₃₀Cl₂N₄S₂, %: C 43.18; H 7.71; Cl 18.25; N 14.39; S 16.45. Found, %: C, 43.32; H, 7.52; Cl, 18.39; N, 14.60; S, 16.53. IR (KBr), cm⁻¹: 3076, 2988, 2920 [ν(C-H)], 2800-2600 [ν(ammonium band)], 1632 [ν(C=N)]. ¹H NMR, δ, ppm: 1.36 d(12H, CH₃), 2.74 s(4H, CH₂S), 3.54 q (2H,CH), 3.60 s (12H, CH₃N⁺). ¹³C NMR, δ_C, ppm: 23.65 (CH₂S), 23.82 (CH₃), 37.74 (CH), 57.38 (CH₃N⁺), 127.23 (C=N).

Acknowledgements

The work has been performed with financial support of the Presidium of the Siberian Branch of the Russian Academy of Sciences, Integration Project No. 114 and the Fund of the President of the Russian Federation (Science Schools), Grant 1129.2003.3

References

1. Mirskova, A.N.; Sereckina, S.G. (D'yachkova S.G.); Voronkov, M.G. *Sulfur Rep.* **1989**, *9*, 75.
2. Mirskova, A.N.; Sereckina, S.G.; Kalikhman, I. D., Voronkov, M.G.; Bannikova, O.B. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, *4*, 906.
3. Mirskova, A.N.; Sereckina, S.G.; Kukharev, B. F.; Bannikova, O.B. *Zh. Org. Khim.* **1990**, *26*, 1, 201.
4. Mirskova, A.N.; Sereckina, S.G.; Voronkov, M.G.; Kalikhman, I. D.; Bannikova, O.B. *Zh. Org. Khim.* **1985**, *21*, 3, 503.
5. D'yachkova, S.G.; Nikitina, E. A.; Larina, L. I.; Ushakov, P. E.; Gusarova, N. K.; Sinegovskaya, L.M.; Trofimov, B.A. *Synthesis* **2002**, *7*, 916.
6. Elokhina, V. N.; Nachmanovich, A. S.; Larina, L. I.; Shishkin, O. V.; Baumer, B. H.; Loparev, V. A. *Izv. Rus. Akad. Nauk, Ser. Khim.* **1999**, *8*, 1536.
7. Levy, G. C.; Nelson, G. L. *Carbon-13 Nuclear Magnetic Resonance for Organic Chemists*; John Wiley & Sons: New York, 1972.
8. Wilson, C. O.; Gisvold, O.; Doerge, R. F. *Textbook of Medicinal and Pharmaceutical Chemistry*; Pitman: London, 1966; p 237.