Polish J. Chem., **76**, 953–958 (2002)

The Reactions of 2-(Chloroseleno)benzoyl Chloride with Pyridine and Related Azines

by M. Osajda and J. Młochowski*

Institute of Organic Chemistry, Biochemistry and Biotechnology, Wrocław University of Technology, Wyb. Wyspiańskiego 27, 50-375 Wrocław, Poland

(Received January 25th, 2002; revised manuscript April 9th, 2002)

The reaction of 2-(chloroseleno)benzoyl chloride with pyridine and pyridine-like heterocycles such as pyrimidine, pyrazine, quinoline, phthalazine, phenazine and 1,10-phenanthroline was studied. In the most cases stable 2-(hydroxyseleno)benzoylazinium chlorides were produced depending on the number of the pyridinium-like nitrogen atoms and their situation in the ring system.

Key words: 2-(chloroseleno)benzoyl chloride, pyridine, azines, N-acylation

During last two decades many organoselenium compounds have found applications in organic synthesis, material synthesis, ligand chemistry and biologically relevant processes [1,2]. Some of them exhibited appreciable biological activity as antioxidants, enzyme inhibitors, antitumor agents, cytokine inducers and immunomodulators. Many of these compounds have antibacterial, antifungal, antiviral, antiparasitic and antiradiation properties [3–5].

Apart from common selenium containing aminoacids such as selenocysteine and selenomethionine, another important group of organoselenium compounds of biomedical interest are 2-substituted benzisoselenazol-3(2H)-ones [3]. They are prepared by treatment of 2-(chloroseleno)benzoyl chloride with various compounds having primary amino group such as alkyl and aryl amines [6], aminoacids and their esters [7], carboxyamides and sulfonamides [8]. Most recently the reaction of 2-(chloroseleno)benzoyl chloride was extended on the enolizable ketones [9] an other C-H acids [10]. In all these reactions the evolved hydrogen chloride is bounded by reacted amine (used in an excess) or by the other base added to the reaction mixture, such as triethylamine or pyridine. In some cases it was observed that pyridine itself reacted with 2-(chloroseleno)benzoyl chloride, but the results of this reaction remained ambiguous. It seems to be possible that two electrophilic centers of this dichloride, localized on the carbonyl carbon and selenium, can interact with nucleophilic pyridine nitrogen atom forming pyridinium salts.

Since N-selenopyridinium salts have been hitherto unknown and N-acylpyridinium salts have been generally known as unstable compounds and rarely were isolated [11], it begs a question how pyridine and pyridine-like heterocycles could react with 2-(chloro-

*Author for correspondence. E-mail:Mlochowski@kchf.ch.pwr.wroc.pl

seleno)benzoyl chloride. The results of our investigations presented here explain this problem. Moreover, a series of relatively stable 2-(hydroxyseleno)benzoylazinium salts, obtained in this work, may also be an interesting material for medical biologists, since numerous azinium quaternary salts are known as the biological response modifiers, *e.g.* antimicrobials, antiprotozoals, enzyme inhibitors, inhibitors of serum complement, acetylcholineesterase reactivators, carcinostatics, herbicides and insecticides commercially used as pharmaceuticals, veterinary products and agrochemicals [12–14].

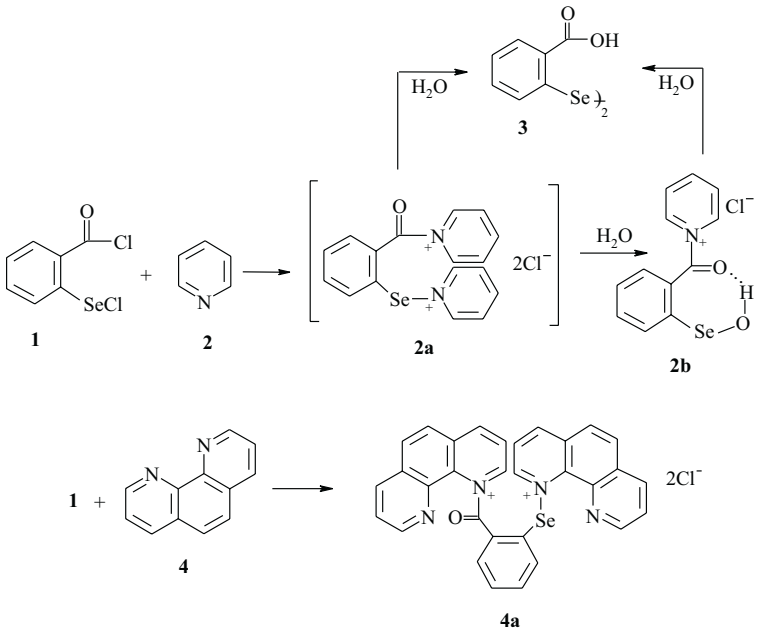
RESULTS AND DISCUSSION

The common method for preparation of quaternary pyridinium salts is based on the reaction of pyridine (or its derivative) with an organic halide, carried out in the solution or without solvent [11]. In our work the solution of pyridine **2** in ethyl acetate was treated with solution of dichloride **1** in the same solvent at room temperature for 12 h. The precipitated solid was filtered off, recrystallized from ethyl acetate and identified as **2b**. In the IR spectrum of pyridinium salt **2b** C=O absorption bands were observed at 1626 and 1668 cm^{-1}, similar to these measured for benzoylpyridinium chloride (1631 and 1687 cm^{-1}) [15]. Moreover, hydroxyselenium group SeOH was easy to recognize in IR spectra by their characteristic O–H stretching absorption in the 2100–2300 and 2300–2750 cm^{-1} regions [16]. For the compound **2b** two strong absorption bands 2100–2200 and 2300–2620 cm^{-1} were observed. It seems possible that the structure **2b** is stabilized by intramolecular hydrogen bond.

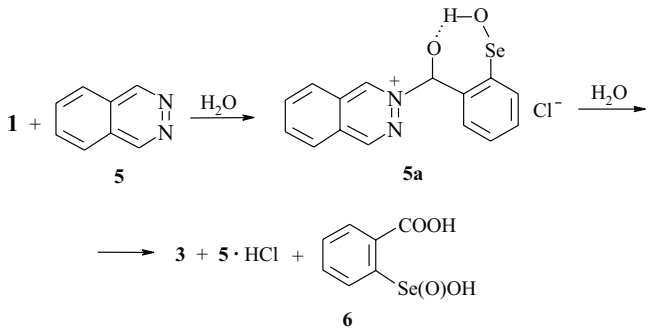
Most probably in the first step of the reaction both electrophilic centers interact with pyridine nitrogen atoms. It results in the tandem N-acylation and N-selenenylation of two pyridine molecules and intermediate **2a** is formed. This assumption is supported by additional experiments. Pyridine was treated separately by benzoyl chloride and phenylselenenyl chloride. In both cases reactions took place, although the product of reaction beetwen pyridine and chloroselenobenzene could not be isolated and was only observed by TLC chromatography. For the slightly more stable benzoylpyridinium chloride IR spectrum was measured. (Although benzylpyridinium chloride was mentioned earlier in [15]; its spectroscopic data have not been reported). Moreover, in an other experiment, when 1,10-phenanthroline (**4**) was treated with dichloride **1**, the stable product of tandem N-selenenylation and N′-acylation was isolated (Scheme 1). The structure of **4** was supported by ^{1}H NMR spectrum and elemental analysis (see Experimental). In the IR spectrum none of absorption bands characteristic for O–H bond were observed. These results support the supposition that the reaction of pyridine (**2**) with dichloride **1** proceeds *via* dual quaternary pyridinium salt **2a**. Water added to the reaction mixture caused hydrolysis of this unstable intermediate to known 2,2′-diselenobis(benzoic acid) **3** [17]. Nevertheless, the traces of water, such as moisture from air or from the solvent, caused only a partial hydrolysis splitting of less stable Se–N bond, and stable compound **2b** was the final product, which could be subsequently hydrolyzed to diselenide **3**. The same

hydrolysis was observed when N-acylpyridinium salt **2b** was stored in normal conditions. It was observed more detaily for N-phthalazinium chloride **5a** (Scheme 2), which stored in normal conditions (in closed flask on air) for two month completely decomposed to diselenide **3**, 2-carboxybenzeneseleninic acid (**7**) [16] and phthalazine hydrochloride (**5a**·HCl)). The same compound **5a** stored in the strictly anhydrous conditions remained unchanged.

Scheme 1

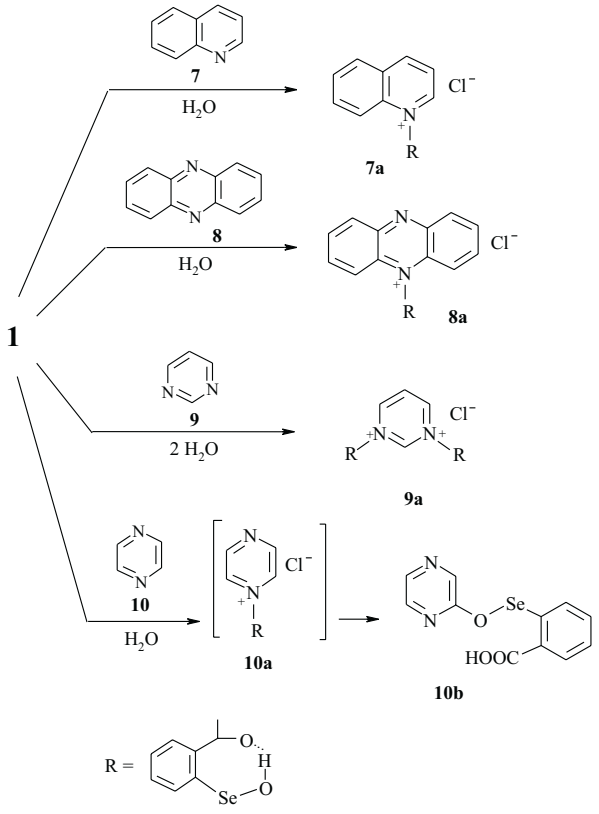


Scheme 2



Quinoline **7** reacted with dichloride **1** in a similar way as pyridine giving quinolinium salt **7a**, while reactions of other azines (**4**, **5**, **7–10**) gave different products, depending on the situation of nitrogen atoms in the heterocyclic ring. 1,10-Phenanthroline afforded **5a**, while phthalazine **8** was acylated like pyridine, but only on the one nitrogen atom. The mono N-acylation was also observed for phenazine **8**, while another diazine – pyrimidine **9** was acylated on nitrogen atoms (Scheme 3). This can be explained in the terms of deactivation of the second nitrogen atom, present in α or γ position, by resonance interaction of positive charged N-acylated nitrogen. Similar effects for N-oxidation and N-alkylation of other diazines were observed earlier [18]. Surprisingly, when pyrazine **10** reacted with dichloride 1,2-[(2-carboxy-phenyl)selenoxy]pyrazine (**10b**) was produced, instead of expected product of N-acylation **10a**. The compound **10a** seems to be an intermediate, which undergoes subsequent nucleophilic oxyselenenylation on the highly electrophilic α-carbon atom in the positively charged pyrazinium ring. The ^{1}H NMR and IR spectra and elemental analysis of **10a** confirmed the proposed structure. The singlet 8.64 ppm of the

Scheme 3



four pyrazine protons is changed to the one-proton singlet 8.89 ppm and two-protons doublet 8.70 ppm. Moreover, the broad singlet of carboxylic OH proton is present at 13.50 ppm. In the IR spectrum characteristic absorption bands for COOH group (3428, 3224–2850 cm^{-1}), C=O group (1682 cm^{-1}) and C–O bond (1263 cm^{-1}) are present.

EXPERIMENTAL

All reagents and solvents were purchased from Aldrich or Fluka. 2-(Chloroselenobenzoyl) chloride (**1**) was obtained according to [4]. Melting points were determined with a Digital Melting Point Apparatus Electrothermal IA 9100. ^{1}H NMR spectra were recorded in DMSO-d_6 on a Bruker DRX 300 spectrometers 300 MHz. Chemical shifts δ are reported in ppm relative to TMS. IR spectra were measured on a Perkin-Elmer 2000 FT spectrometer.

Reaction of 2-(chloroselenium)benzoyl chloride with azines 2–4, 5, 7–9, 11. General procedure: A solution of chloride **1** (0.51 g, 2 mmol) in ethyl acetate (15 ml) was added dropwise at room temperature over a period of 30 min to a stirred solution of pyridine (**2**), 1,10-phenanthroline (**4**), quinoline (**5**), phthalazine (**6**), phenazine (**8**), pyrimidine (**9**) and pyrazine (**11**) (4 mmol) in ethyl acetate (45 ml) and the reaction was continued 12 h (for **2**, **4**, **5**, **10**) and 72 h (for **7**, **8**, **9**). After the reaction was finished, the solid was filtered off from the filtrate, ethyl acetate was evaporated *in vacuo* and the crude product was recrystallized from ethyl acetate.

N-[2-(Hydroxyseleno)benzoyl]pyridinium chloride (2b): Yellow powder. Yield 0.21 g (33%), m.p. 135°C. IR (KBr): 3052 cm^{-1} (OH...O); 2100–2200, 2310–2620 cm^{-1} (Se–OH); 1626 cm^{-1} (CO) . ^{1}H NMR: 7.34 (t, 1H, J = 7.4 Hz, ArH); 7.59 (t, 1H, J = 7.4 Hz, ArH); 7.76 (d, 1H, J = 4.0 Hz, ArH); 8.05 (t, 2H, J = 6.7 Hz, ArH); 8.18 (d, 1H, J = 4.0 Hz, ArH); 8.57 (t, 1H, J = 7.8 Hz, ArH); 8.92 (d, 2H, J = 2.6 Hz, ArH); 13.00 (s, 1H, OH). Anal. Calcd for $C_{12}H_{10}NO_2SeCl$: (314.50); C, 45.79; H, 3.18; Cl, 11.79. Found: C, 46.50; H, 3.50; Cl, 12.06.

Hydrolysis of compounds 2a and 2b: The hydrolyzed compound **2b** (0.63 g, 2 mmol) or the reaction mixture containing **2a** was poured into water (30 ml), the mixture was stirred for 24 h and formed solid was filtered off. 2,2′-Diselenobisbenzoic acid **3** thus obtained were dried *in vacuo* and recrystallized from dioxane. White powder, yield (from **2b**) 0.57 g (90%), m.p. 295°C, ref. [17] 296–297°C.

Synthesis of benzoylpyridinium chloride: A solution of benzoyl chloride (0.28 g, 2 mmol) in ethyl acetate (5 ml) was added dropwise at room temperature over a period of 10 min to a stirred solution of pyridine (0.32 g, 4 mmol) in the same solvent (10 ml) and the reaction was continued for 10 min. After the reaction finished, the solid of benzoylpyridinium chloride was filtered off in anhydrous condition and IR spectrum was measured immediately. IR (KBr) 1687, 1631 cm^{-1} (CO).

N,N′-Bis(1,10-phenanthrolinium)2-selenobenzoyl dichloride (4a): Yellow powder. Yield: 0.14 g (27%), m.p. 127–130°C. IR (KBr): 1635 cm^{-1} (CO). ^{1}H NMR: 7.30 (t, 1H, J = 7.4 Hz, ArH); 7.55 (t, 1H, J = 7.4 Hz, ArH); 7.72 (d, 1H, J = 5.1 Hz, ArH); 8.15–8.22 (m, 5H, ArH); 8.31 (s, 4H, ArH); 9.04 (d, 4H, J = 4.1Hz, Ar-H); 9.29 (d, 4H, J = 2.8 Hz, Ar-H). Anal. Calcd for $C_{18}H_{14}N_2O_2Se_2Cl_2$ (614.00); C, 60.00; H, 3.26; Cl, 11.56; N, 11.56. Found: C, 59.93; H, 3.90; Cl, 11.45; N, 11.45.

N-[2-(Hydroxyseleno)benzoyl]phthalazinium chloride (5a): Yellow powder. Yield: 0.23 g (31%), m.p. 155°C. IR (KBr): 3428, 3060 cm^{-1} (OH...O); 2360–2620, 2100–2200 cm^{-1} (OH); 1659 cm^{-1} (CO). ^{1}H NMR: 7.35 (t, 1H, J = 7.4 Hz, ArH); 7.60 (t, 1H, J = 7.4 Hz, ArH); 7.77 (d, 1H, J = 4.0 Hz, ArH); 8.15 (d, 1H, J = 4.0 Hz, ArH); 8.36–8.39 (m, 2H, ArH); 8.50–8.54 (m, 2H, ArH); 10.18 (s, 2H, ArH); 10.50–12.00 (bs, 1H, OH). Anal. Calcd for $C_{15}H_{11}N_2O_2SeCl$: (365.50); C, 49.24; H, 3.00; Cl, 9.71. Found: C, 49.11; H, 2.84; Cl, 10.00.

2-Carboxybenzeneseleninic acid (6): White powder, m.p. 132°C, ref. [16] 132°C.

N-[2-(Hydroxyseleno)benzoyl]quinolinium chloride (7a): Pale yellow powder. Yield: 0.23 g (32%), m.p. 121°C. IR (KBr): 3399, 3066 cm^{-1} (OH...O); 2300–2750, 2100–2200 cm^{-1} (OH); 1618, 1664 cm^{-1} (CO). ^{1}H NMR: 7.35 (t, 1H, J = 7.4 Hz, ArH); 7.60 (t, 1H, J = 7.4 Hz, ArH); 7.77 (d, 1H, J = 3.8 Hz, ArH); 7.97 (d, 2H, J = 3.8 Hz, ArH); 8.06–8.13 (m, 3H, ArH, OH); 8.17 (d, 1H, J = 3.9 Hz, ArH); 8.38 (d,

3H, J = 4.0 Hz, ArH). Anal. Calcd for $C_{16}H_{12}NO_2SeCl$: (364.50); C, 52.67; H, 3.29; Cl, 9.74. Found: C, 52.83; H, 3.60; Cl, 9.73.

N-[2-(Hydroxyseleno)benzoyl]phenazinium chloride (8a): Yellow needles.Yield: 0.24 g (28%), m.p. 260–263°C. IR (KBr): 3400, 3057 cm^{-1} (OH...O); 2150–2400, 1800–2000 cm^{-1} (OH); 1629 cm^{-1} (CO). ^1H NMR: 7.42 (t, 1H, J = 7.2 Hz, ArH); 7.70 (t, 1H, J = 7.2 Hz, ArH); 7.88 (d, 1H, J = 4.0 Hz, ArH); 7.98–8.01 (m, 4H, ArH); 8.14 (d, 1H, J = 4.0 Hz, ArH); 8.27–8.30 (m, 4H, ArH); 8.57 (s, 1H, ArH). Anal. Calcd for $C_{19}H_{13}N_2O_2SeCl$: (415.50); C, 54.87; H, 3.13; N, 6.74; Cl, 8.54. Found: C, 54.74; H, 3.00; N, 6.70; Cl, 8.72.

1,3-Di[2-(hydroxyseleno)benzoyl]pyrimidinium dichloride (9a): Violet tiny crystals. Yield: 0.14 g (27%), m.p. 127–130°C. IR (KBr): 3444, 3062 cm^{-1} (OH...O); 2150–2600, 1800–2000 cm^{-1} (OH); 1619 cm^{-1} (CO). ^1H NMR: 7.43 (t, 2H, J = 7.5 Hz, ArH); 7.62 (t, 1H, J = 5.0 Hz, ArH); 7.71 (t, 2H, J = 7.5 Hz, ArH); 7.90 (d, 2H, J = 4.0 Hz, ArH); 8.11 (d, 2H, J = 4.0 Hz, ArH); 8.26 (s, 2H, OH); 8.88 (d, 1H, J = 2.5 Hz, ArH); 9.26 (s, 1H, Ar-H). Anal. Calcd for $C_{18}H_{14}N_2O_2Se_2Cl_2$: (519.00); C, 41.62; H, 2.69; Cl, 13.68. Found: C, 41.30; H, 2.60; Cl, 13.12.

2-[(2-Carboxyphenyl)selenoxy]pyrazine (10a): Yellow powder. Yield: 0.20 g (36%), m.p. 170°C. IR (KBr): 3428, 3224–2850 cm^{-1} (COOH); 1682 cm^{-1} (CO); 1263 cm^{-1} (C-O). ^1H NMR: 7.12 (d, 1H, J = 3.9 Hz, ArH); 7.32–7.42 (m, 2H, ArH); 8.00 (d, 1H, J = 3.9 Hz, ArH); 8.70 (d, 2H, J = 10.2 Hz, ArH); 8.88 (s, 1H, ArH); 13.50 (s, 1H, OH). Anal. Calcd for $C_{11}H_8N_2O_3Se$: (294.90); C, 44.75; H, 2.71; N,9.49. Found: C, 45.16; H, 3.04; N, 9.54.

Acknowledgments

The work was supported by the Polish State Committee for Scientific Research (Grant No 3T09A 097 17).

REFERENCES

1. Paulmier C., *Selenium Reagents and Intermediates in Organic Synthesis*, Pergamon Press, Oxford, 1986.
2. Tiecco M., *Topics in Curr. Chem*., **208**, 7 (2000).
3. Mugesh G., du Mont W.-W. and Sies H., *Chem. Rev.*, **101**, 2125 (2001).
4. Bień M., Błaszczyk B., Kalinowska K., Młochowski J. and Inglot A.D., *Arch. Immunol. Ther. Exp*., **47**, 185 (1999).
5. Osajda M., Kloc K., Młochowski J., Piasecki E. and Rybka K., *Polish J. Chem*., **75**, 823 (2001).
6. Młochowski J., Kloc K., Syper L., Inglot A.D. and Piasecki E., *Liebigs Ann. Chem*., 1293 (1993).
7. Młochowski J., Gryglewski R., Inglot A.D., Jakubowski A., Juchniewicz L. and Kloc K., *Liebigs Ann. Chem*., 1751 (1996).
8. Mhizha S. and Młochowski J., *Synth. Commun*., **27**, 283 (1997).
9. Kloc K. and Młochowski J., *Tetrahedron Lett*., **42**, 4899 (2001).
10. Kloc K., Osajda M. and Młochowski J., *Chem. Lett*., 826 (2001).
11. Scriven E.F.V., *Comprehensive Heterocyclic Chemistry*, ed. by Katritzky A.R and Rees C.W., Pergamon, Oxford 1984, Vol. 2, p. 165.
12. Yates F.S., *ibid*, Vol. 2, p. 511.
13. Landquist J.K., *ibid*, Vol. 1, p. 143.
14. Banks B.J., Walshe N.D. and Witty M.J., *ibid*, Vol. 1, p. 201.
15. Kirij N.V., Pasenok S.V., Naumann D. and Tyrra W., *J. Fluoride Chem*., **69**, 219 (1994).
16. Kloc K., Młochowski J. and Syper L., *Liebigs Ann. Chem*., 811 (1989).
17. Palus J., Młochowski J. and Juchniewicz L., *Polish J. Chem*., **72**, 1931 (1998).
18. Kloc K., Młochowski J. and Szulc Z., *Can. J. Chem*., **57**, 1506 (1979).