Preparation of 2-Amino-4H-5,6-dihydro-1,3-selenazin-4-ones by Reaction of N,N-Unsubstituted Selenoureas with α,β-Unsaturated Acid Chlorides

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Abstract: 2-Dialkylamino-4H-5,6-dihydro-1,3-selenazin-4-ones were obtained by the reaction of N,N-unsubstituted selenoureas with α,β-unsaturated acid chlorides at room temperature.

Key words: heterocycles, ring closure, selenium, selenourea, 1,3-selenazine

There are many reports concerning the five-membered ring 1,3-selenazoles.1 On the other hand, there are only limited number of literature regarding the six-membered ring 1,3-selenazines.2 To date, few methods have been developed for the synthesis of 1,3-selenazines. One is the [4+2] cycloaddition using the C=Se bond as 2π dienophile intermediates. For instance, reaction of primary selenoamides with α,β-unsaturated ketones or aldehydes gave the corresponding 1,3-selenazines.3 Another method for the synthesis of 1,3-selenazines is achieved by an intramolecular cycloaddition of 2-selenocyanatobenzoyl chloride.4 The 1,3-selenazines showed significant biological effects such as antimicrobial, antitumor activities, selective inhibitory activity against eukaryotic elongation factor 2-kinase, and inhibition of HT-1080 proliferation through the induction of apoptosis cell death.5 Therefore, the preparation of many types of 1,3-selenazines has been desired for the development of potential agents.

We describe here the synthesis of 2-dialkylamino-1,3-selenazin-4-one derivatives by the reaction of N,N-unsubstituted selenoureas with α,β-unsaturated acid chlorides at room temperature.

Optimal conditions for the reaction of 1-selenocarbamoylpiperidine (1d) with acryloyl chloride (2a) were studied. In this reaction, dichloromethane was used as solvent at room temperature without catalysis (Scheme 1). When another solvent such as THF, acetonitrile, or chloroform was used, almost the same yield of the product was obtained. The reactions of 1d with 2a at room temperature in dichloromethane afforded 2-piperidino-4H-5,6-dihydro-1,3-selenazin-4-one (3d) in 99% yield (Table 1, entry 4). The structure of 3d was elucidated by studies of IR, 1H NMR, 13C NMR, 77Se NMR, elemental analysis, and X-ray diffraction. X-ray crystal structure analysis of 3d (Figure 1) showed disorder in the crystal. The torsion angles of C(1)–Se(1)–C(4)–C(3) in 3d was 29.3(14)° and that of C(1)–Se(1)–C(6)–C(5) in 3d was –49.0(11)°. Conformers, generated by flip of both methylene carbons at positions 5 and 6 in 1,3-selenazine skeleton, were confirmed in the crystals. The bond angles of the selenium atom C6–Se1–C1 and C1–Se1–C4 in 3d were 94.0(3)° and 95.1(4)°, which were sharper than the previously reported value of 98.50(8)° for 4-hydroxy-4-methyl-6-phenyl-2-p-tolyl-4H-5,6-dihydro-1,3-selenazine.6

Reactions of N,N-unsubstituted selenoureas 1a–d with 2a gave the corresponding 2-amino-4H-5,6-dihydro-1,3-selenazin-4-ones 3a–d in high yields (Table 1, entries 1–4). Using the optimal reaction conditions, several 2-amino-4H-5,6-dihydro-1,3-selenazin-4-one derivatives 3a–g were prepared from the reaction of corresponding N,N-unsubstituted selenoureas 1a–d with α,β-unsaturated acid chlorides.

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The structures of products 3a–g were determined by comparing the spectral data with those of 3d. Though reaction of N,N-unsubstituted selenoureas 1a–d with 2a gave the products in high yields, the yields of 3d to 3g decreased in turn. Steric factors at the β-position of the carbonyl carbon of α,β-unsaturated acid chlorides 2a–d were thought to disturb the cyclization reaction. As one of the evidence, the noncyclic compound, N-acylselenourea, was recovered in the reaction with cinnamoyl chloride (entry 6). In the case of 3f, NMR spectra was observed for the tautomers of 4H-5,6-dihydro-1,3-selenazin-4-one and 4-hydroxy-6H-1,3-selenazine.

In summary, we have now found that the reaction of N,N-unsubstituted selenoureas (1) with α,β-unsaturated acid chlorides 2 at room temperature affords several types of 2-dialkylamino-4H-5,6-dihydro-1,3-selenazin-4-one de-
rivatives. Earlier reports on the reaction of N,N-unsubstituted selenoureas 1 with α,β-unsaturated ketones and aldehydes have disclosed the formation of the corresponding five-membered ring 1,3-selenazoles.

Selenoureas were synthesized according to previously described procedures. The NMR spectra were obtained from a Jeol ECA500 spectrometer. The 77Se chemical shifts are expressed in ppm deshielded with respect to Me2Se in CDCl3. J(77Se,13C) values are the 77Se satellites of the 1H NMR spectra and proton-decoupled 13C NMR spectra, respectively.

2-Dimethylamino-4H-5,6-dihydro-1,3-selenazin-4-one (3a); Typical Procedure

Acryloyl chloride (2a; 0.05 mL, 0.6 mmol) was added to stirred solution of N,N-dimethylselenoureia (1a; 75 mg, 0.5 mmol) in anhyd CH2Cl2 (10 mL) under argon. The mixture was stirred for 1 h at r.t. The mixture was diluted with CH2Cl2 (20 mL) and washed with aq sat. Na2CO3 (2 × 30 mL). The organic layer was separated, dried (Na2SO4) and evaporated to dryness. The residue was purified by flash chromatography on silica gel with acetone–hexane (2:1) as eluent to give 3a (95 mg, 93%) as a white solid; mp 37–39 °C (hexane–acetone).

IR (KBr): 2947, 1634, 1531 cm–1.

1H NMR (500 MHz, CDCl3); δ = 2.66 (2 H, t, J = 6.8 Hz, CH2), 3.20 (2 H, t, J = 6.8 Hz, CH2), 3.17 (2 H, s, CH2), 3.27 (2 H, s, CH2).

13C NMR (125 MHz, CDCl3); δ = 30.4, 39.2, 164.7, 177.6.

77Se NMR (95 MHz, CDCl3); δ = 295.6.


2-Piperidino-4H-5,6-dihydro-1,3-selenazin-4-one (3d); Typical Procedure

1H NMR (500 MHz, CDCl3); δ = 1.57–1.76 (6 H, m, CH2), 2.67 (2 H, t, J = 6.6 Hz, CH2), 3.20 (2 H, t, J = 6.6 Hz, CH2).

13C NMR (125 MHz, CDCl3); δ = 29.8 Hz), 3.42–3.64 (2 H, br, CH2), 3.82–4.03 (2 H, br, CH2).

11C NMR (125 MHz, CDCl3); δ = 18.8 [1J(77Se,13C) = 55.2 Hz], 24.1, 25.2, 25.9, 30.7, 47.2, 49.7, 162.6 [1J(77Se,13C) = 138.0 Hz], 178.0.

77Se NMR (95 MHz, CDCl3); δ = 293.3.

Anal. Calcd for C19H23N4O4Se; C, 44.09; H, 5.76; N, 11.43. Found: C, 43.84; H, 5.93; N, 11.11.

X-ray Crystallographic Data

3d: C19H23N4O4Se. Crystal system monoclinic, space group P21/c, a = 10.526(6) Å, b = 8.701(4) Å, c = 11.823(6) Å, β = 109.37(6)°, Z = 4, μ = 1.594 g/cm3, limiting indices –13 ≤ h ≤ 13, –7 ≤ k ≤ 11, –15 ≤ l ≤ 14, reflections collected 8030, independent reflections 2337, goodness-of-fit on F2 1.152, final R indices [I > 2σ (I)] R1 = 0.0487, wR2 = 0.0803, R indices (all data) R1 = 0.0629, wR2 = 0.0845. Selected bond lengths [Å] and angles [°] for 3d: C–Se(1)–C(1) 1.924(3), C(1)–C(2) 1.465(8), C(1)–N(1) 1.394(4), C(1)–C(5) 1.304(4), C(1)–N(2) 1.337(4), C(1)–C(6) 1.913(12), C(2)–C(5) 1.530(19), C(2)–C(3) 1.581(10), C(6)–C(1)–C(2) 91.0(4), C(6)–C(1)–C(4) 20.3(3), C(1)–C(2)–C(3) 114.9(3), C(1)–C(2)–C(4) 94.0(3), C(1)–C(2)–Se(1) 125.3(2), C(3)–C(2)–C(4) 117.4(4), C(1)–C(2)–C(5) 122.0(4), C(3)–C(2)–C(5) 32.1(4), C(4)–C(3)–C(2) 112.0(2), C(3)–C(4)–Se(1) 114.1(9), C(6)–C(5)–C(2) 112.2(10), C(5)–C(6)–Se(1) 109.5(9).
IR (KBr): 2938, 1650, 1524 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 1.56 (6 H, s, CH₃), 1.59–1.75 (6 H, m, CH₂), 2.55 (2 H, s, CH₂), 3.41–3.53 (2 H, br, CH₂), 3.91–4.03 (2 H, br, CH₂).

¹³C NMR (125 MHz, CDCl₃): δ = 24.1, 25.2, 25.8, 43.1 [¹J (²⁷Se,¹³C) = 55.2 Hz], 47.3, 49.7, 164.5 [¹J (²⁷Se,¹³C) = 140.4 Hz], 179.0.

⁷⁷Se NMR (95 MHz, CDCl₃): δ = 469.0.

Anal. Calcd for C₁₁H₁₈N₂OSe: C, 48.35; H, 6.64; N, 10.25. Found: C, 48.25; H, 6.68; N, 9.89.

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References


(6) Crystal structure data for 3d: Crystallographic data for the structural information have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, CCDC No. 645675. Copies of this information can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(1223)336033 or e-mail: deposit@ccdc.cam.ac.uk].

