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A three-component and one-pot reaction for synthesis of 1-(aroyl)3-{6-[3-(aroyl)selenoureido]pyridine-2-yl}selenourea

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Abstract: A three-component and one-pot reaction between pyridine-2,6-diamine and potassium selenocyanate in the presence of aroyl chlorides to afford the 1-(aroyl)3-{6-[3-(aroyl)selenoureido]pyridine-2-yl}selenourea in excellent yields. It is important to make the selenocyanate derivatives first and then to use this to prepare the selenourea derivatives. The present method carries the advantage that not only is the reaction performed under neutral conditions but also that the substances can be mixed without any activation or modification. Alsothis new protocol offers advantages such as mild reaction conditions, easy work-up, and use of an inexpensive and non-toxic catalyst, high yields of biological active products. To a solution of potassium selenocyanate in acetone was added aroyl chloride in acetone. The reaction mixture was stirred at r.t. for 10 min. Pyridine-2,6-diamine in acetone was added to the mixture. The reaction mixture was then stirred for 12h. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting precipitate was collected by filtration on a Buchner funnel and washed with cold water and recrystallized from EtOH to afford the pure title compounds.

Keywords: KSeCN, Aroyl chlorides, Pyridine-2,6-diamine, MCRs, Selenourea.

Introduction

The current interest in selenium-containing organic compounds stems from their remarkable synthetic and biological functions [1-5]. Although the existence of isoselenocyanates was doubted for a long time, the synthesis of aryl and alkyl derivatives has been achieved in the past decades [6]. Acyl isoselenocyanates are useful building blocks for the synthesis of linear and cyclic selenoorganic compounds [7-12]. The first synthesis of acyl isoselenocyanates, which were generated by the reaction of acyl chlorides and potassium selenocyanate, has been described by Douglas [13]. Recently, a few syntheses of hetrocycles from acyl isoselenocyanates were reported [14-16].

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As a part of studies on the development of new routes in organic synthesis [17-20], I now report an efficient one-pot synthesis of 1-(aroyl)3-{6-[3-(aroyl)selenoureido]pyridine-2-yl}selenourea employing readily available starting materials.

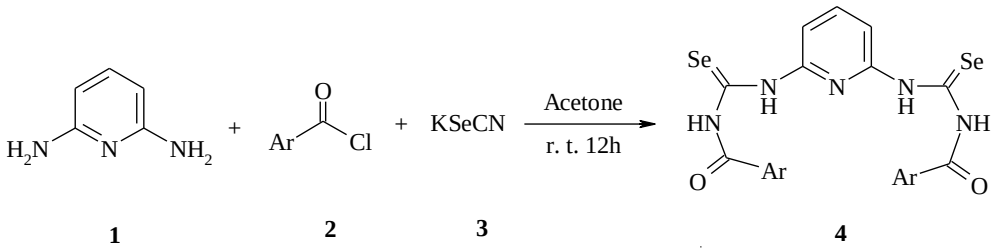
Result and Discussion

Reaction between pyridine-2,6-diamine and potassium selenocyanate in the presence of aroyl chlorides to afford the 1-(aroyl)3-{6-[3-(aroyl)selenoureido]pyridine-2-yl}selenourea in excellent yields (Scheme **1**).

The structures of compounds **4a-f** were deduced from their elemental analyses and their IR, ^{1}H NMR, ^{13}C NMR spectra. The mass spectra of compounds **4a**–**f** are fairly similar and display molecular ion peaks. For example, the mass spectrum of the compound (**4a**)

showed a molecular ion peak at 597 confirming that it is a (1:1:1) adduct of pyridine-2,6-diamine and potassium selenocyanate in the presence of aroyl chlorides. The IR spectrum of compound **4a** also supported the suggested structure. The 500 MHz ^{1}H NMR of **4a** showed shows four singlet signals (δ = 8.51, 10.53, 11.97 and 13.17 ppm) corresponded to the protons of the NH groups which disappear after addition to DMSO solution of **5a** few drops of D_2O. The aromatic protons resonated between 6.75-7.94 ppm.

The ^{13}C-NMR spectrum of compound **4a** showed 9 distinct resonances in agreement with the proposed structure. A tentative mechanism for this transformation is proposed in (Scheme 2). It is conceivable that the reaction starts with formation of aroyl isoselenocyanate **5**, followed by addition of pyridine-2,6-diamine **1** to generate **6** or **4**.

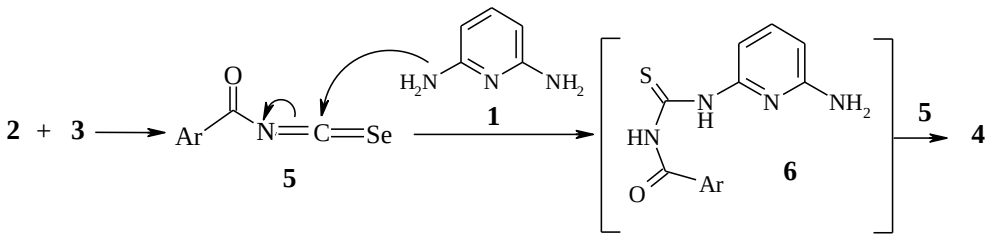


1 **2** **3** **4**

4	Ar	%Yield	m.p.(°C)
a	4-ClC_6H_4	88	271-273
b	C_6H_5	82	245-247
c	4-BrC_6H_4	85	258-260
d	3-O_2N C_6H_4	90	282-284
e	4-O_2N C_6H_4	91	294-296
f	2-CH_3 C_6H_4	81	230-232

**Yields refer to the pure isolated prodoucts*

Scheme 1: Yields of a series of 1-(aroyl)3-{6-[3-(aroyl)selenoureido] pyridine-2-yl}selenourea (**4**) prepared from pyridine-2,6-diamine (**1**), aroyl chlorides (**2**) and potassium selenocyanate (**3**)



Scheme 2: Suggested mechanism for formation of compound **4**

Conclusions

In conclusion here we reported a three-component reaction between pyridine-2,6-diamine and potassium selenocyanate in the presence of aroyl chlorides and afforded high yields of products. The present method carries the advantage that not only is the reaction performed under neutral conditions but also that the substances can be mixed without any activation or modification.

Experimental

Melting points were determined with an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses for C and H were performed using a Heraeus CHN-O-Rapid analyzer. Mass spectra were

recorded on a FINNIGAN-MAT 8430 mass spectrometer operating at an ionization potential of 70 eV. IR spectra were recorded on a Shimadzu IR-470 spectrometer. NMR spectra were obtained on a Brucker DRX 500 Avance spectrometer (^{1}H NMR at 500 Hz, ^{13}C NMR at 125 Hz) in DMSO-d_6 using TMS as an internal standard. Chemical shifts (δ) are given in ppm. All of the chemicals used in this study were purchased from Merck and Fluka (Buchs, Switzerland) and were used without further purification.

Caution! All of the reactions involving selenium-containing compounds should be carried out in a wellventilated hood.

General procedure for preparation of compounds **4a-f**:

To a solution of potassium selenocyanate (2 mmol) in dry acetone (3 cm^3) was added aroyl chloride (2 mmol) in dry acetone (3 cm^3). The reaction mixture was stirred at r.t. for 10 min. Pyridine-2,6-diamine (1 mmol) in acetone (4 cm^3) was added to the mixture. The reaction mixture was then stirred for 12 h. The progress of the reaction was monitored by TLC. After completion of the reaction, the resulting precipitate was collected by filtration on a Buchner funnel and washed with cold water (20 cm^3) and recrystallized from EtOH to afford the pure title compounds.

1-(4-Chlorobenzoyl)3-{6-[3-(4-chlorobenzoyl) selenoureido] pyridine-2-yl}selenourea (**4a**, $C_{21}H_{15}Cl_2N_5O_2Se_2$):

Yellow powder; Yield: 88%, m.p. 271-273^o C; IR (KBr) (ν_{max} cm^{-1}): 3345, 1686, 1621, 1582 and 1268; ^{1}H NMR: δ 6.75 (2H, d, ^3J = 7.5 Hz, CH), 7.41 (1H, t, ^3J = 7.5 Hz, CH), 7.76 (4H, d, ^3J = 7.5 Hz, CH), 7.94 (4H, d, ^3J = 7.5 Hz, CH), 8.51, 10.53, 11.97 and 13.17 (4 H, 4s, 4NH) ppm.; ^{13}C NMR: δ 112.9, 128.7, 129.6, 133.3, 136.1, 140,3 and 150.2 (7C aromatic), 169.3 (C=O), 194.7 (C=Se) ppm.; MS (m/z, %): 597 (8).; Anal. Calcd. for $C_{21}H_{15}Cl_2N_5O_2Se_2$: C, 42.16; H, 2.53; N, 11.71. Found: C, 42.25; H, 2.56; N, 11.86%.

1-(Benzoyl)3-{6-[3-(benzoyl)selenoureido]pyridine-2-yl}selenourea (**4b**, $C_{21}H_{17}N_5O_2Se_2$):

Yellow powder; Yield: 82%, m.p. 245-247^o C; IR (KBr) (ν_{max} cm^{-1}): 3340, 1694, 1635, 1541 and 1263; ^{1}H NMR: δ 7.35 (2H, d, ^3J = 7.5 Hz, CH), 7.48 (1H, t, ^3J = 7.5 Hz, CH), 7.69 (2H, t, ^3J = 7.5 Hz, CH), 7.72 (4H, t, ^3J = 7.5, CH), 8.24 (4H, d, ^3J = 7.5, CH), 8.67, 11.06, 11.82 and 13.16 (4H, 4s, 4NH) ppm.; ^{13}C NMR: δ 113.3, 128.9, 129.5, 132.9, 134.7, 140,4 and 150.2 (7C aromatic), 170.0 (C=O), 194.0 (C=Se) ppm.; MS (m/z, %): 529 (4). ; Anal. Calcd. for $C_{21}H_{17}N_5O_2Se_2$: C, 47.65; H, 3.24; N, 13.23. Found: C, 47.50; H, 3.36; N, 13.07%.

1-(4-Bromobenzoyl)3-{6-[3-(4-romobenzoyl)selenoureido]pyridine-2-yl}selenourea (**4c**, $C_{21}H_{15}Br_2N_5O_2Se_2$):

Yellow powder; Yield: 85%, m.p. 258-260^o C, IR (KBr) (ν_{max} cm^{-1}): 3355, 1675, 1623, 1581 and 1268. ^{1}H NMR: δ 7.05 (2H, d, ^3J = 7.5 Hz, CH), 7.46 (1H, t, ^3J = 7.5 Hz, CH), 7.69 (4H, d, ^3J = 7.5 Hz, CH), 7.91 (4H, d, ^3J = 7.5 Hz, CH), 8.63, 10.70, 11.95 and 13.11 (4H, 4s, 4NH) ppm.; ^{13}C NMR: δ 113.2, 127.2, 130.9, 132.4, 135.9 140,3 and 150.1 (7C aromatic), 169.3 (C=O), 194.5 (C=Se) ppm.; MS (m/z, %): 687 (5). ; Anal. Calcd. for $C_{21}H_{15}Br_2N_5O_2Se_2$: C, 36.71; H, 2.20; N, 10.19. Found: C, 36.82; H, 2.04; N, 10.30%.

1-(3-Nitrobenzoyl)3-{6-[3-(3-nitrobenzoyl)selenoureido]pyridine-2-yl}selenourea (**4d**, $C_{21}H_{15}N_7O_6Se_2$):

Yellow powder; Yield: 90%, m.p. 282-284^o C; IR (KBr) (ν_{max} cm^{-1}): 3324, 1682, 1613, 1561, 1513, 1346 and 1270; ^{1}H NMR: δ 7.68 (2H, d, ^3J = 7.5 Hz, CH), 7.92 (1H, t, ^3J = 7.5 Hz, CH), 7.96 (2H, d, ^3J = 7.5 Hz, CH), 8.16 (2H, s, CH), 8.58 (2H, t, ^3J = 7.5 Hz, CH), 8.75 (2H, d, ^3J = 7.5 Hz, CH), 10.95, 11.21, 12.16 and 13.08 (4H, 4s, 4NH) ppm.; ^{13}C NMR: δ 112.2, 126.9, 127.8, 130.4, 130.5, 134.8, 140,6, 147.7 and 148.0 (9C aromatic), 168.7 (C=O), 195.1 (C=Se) ppm.; MS (m/z, %): 619 (7).; Anal. Calcd. for $C_{21}H_{15}N_7O_6Se_2$: C, 40.73; H, 2.44; N, 15.83. Found: C, 40.84; H, 2.58; N, 15.92%.

1-(4-Nitrobenzoyl)3-{6-[3-(4-nitrobenzoyl)selenoureido]pyridine-2-yl}selenourea (**4e**, $C_{21}H_{15}N_7O_6Se_2$):

Yellow powder; Yield: 91%, m.p. 294-296^o C; IR (KBr) (ν_{max} cm^{-1}): 3315, 1686, 1610, 1566, 1509, 1343 and 1272; ^{1}H NMR: δ 7.73 (2H, d, ^3J = 7.5 Hz, CH), 7.92 (1H, t, ^3J = 7.5 Hz, CH), 7.53 (4H, d, ^3J = 7.5 Hz, CH), 8.20 (4H, d, ^3J = 7.5 Hz, CH), 10.92, 11.35, 12.27 and 13.08 (4H, 4s, 4NH) ppm.; ^{13}C NMR: δ 112.3, 122.9, 127.7, 133.1, 140.3, 149.1 and 150.7 (7C aromatic), 169.6 (C=O), 194.9 (C=Se) ppm.; MS (m/z, %): 619 (10).; Anal. Calcd. for $C_{21}H_{15}N_7O_6Se_2$: C, 40.73; H, 2.44; N, 15.83. Found: C, 40.86; H, 2.56; N, 15.95%.

1-(2-Methylbenzoyl)3-{6-[3-(4-methylbenzoyl)selenoureido]pyridine-2-yl}selenourea (**4f**, $C_{23}H_{21}N_5O_2Se_2$):

Yellow powder; Yield: 81%, m.p. 230-232^{o} C; IR (KBr) (ν_{max} cm^{-1}): 3293, 1676, 1607, 1552 and 1261; ^{1}H: δ 2.34 (6H, s, 2CH$_3$), 7.22 (2H, d, ^{3}J = 7.5 Hz, CH), 7.40 (1H, t, ^{3}J = 7.5 Hz, CH), 7.73 (2H, d, ^{3}J = 7.5 Hz, CH), 7.76 (2H, t, ^{3}J = 7.5 Hz, CH), 7.85 (2H, t, ^{3}J = 7.5 Hz, CH), 8.04 (2H, d, ^{3}J = 7.5 Hz, CH), 8.72, 10.90, 11.83 and 13.06 (4H, 4s, 4NH)ppm.; ^{13}C NMR: δ 19.9 (CH$_3$), 113.6, 126.0, 128.7, 131.1, 131.6, 134.3, 136.7, 140.5 and 150.3 (9C aromatic), 169.2 (C=O), 193.9 (C=Se) ppm.; MS (m/z, %): 557 (4).; Anal. Calcd. for $C_{23}H_{21}N_5O_2Se_2$: C, 49.56; H, 3.80; N, 12.56. Found: C, 49.67; H, 3.71; N, 12.43%.

Acknowledgements

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