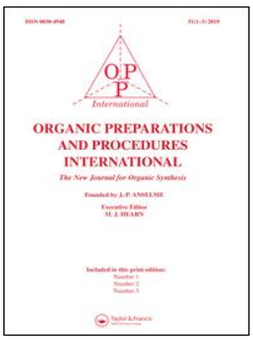

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EXPERIMENTAL PAPER

An Efficient Synthesis of Novel 1,3,5-Triazine-2-selenones from Acyl Isoselenocyanates and 2-Aminobenzimidazole

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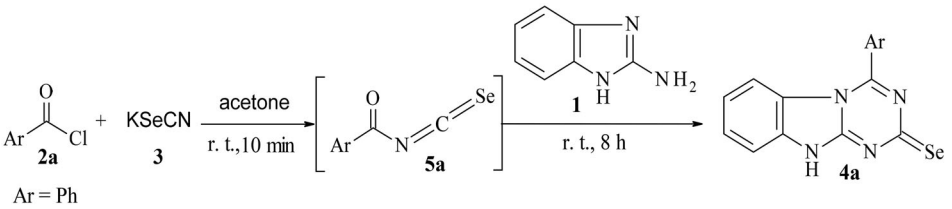
In recent years, increasing attention has been paid to organoselenium compounds because of their diverse pharmaceutical and synthetic applications.[1–11] For example, acyl isoselenocyanates are useful reactive intermediates, and they have been prepared by the reaction of acyl chlorides with KSeCN.[12–14] The acyl isoselenocyanates, however, were never isolated.[15–18] The existence of these intermediates was inferred by their reactions with nucleophiles.[19–21] With this in mind, we now report on the use of such acyl isoselenocyanates, generated *in situ*, to prepare novel 1,3,5-triazine-2-selenones (Scheme 1, compounds **4**). The aim of our work was to prepare and rigorously characterize the new 1,3,5-triazine-2-selenones via this unique synthetic route.

Initially, the reaction among benzoyl chloride, potassium selenocyanate, and 2-aminobenzimidazole was selected as the model reaction for the preparation of compound **4a** (Ar = Ph). A number of solvents were explored for this reaction. The results are summarized in Table 1. Among the solvents tested, acetone was the best. When the reaction was performed in dry acetone at room temperature for 8 h, 4-phenylbenzo[4,5]imidazo[1,2-a][1,3,5]triazine-2-selenone (**4a**) was obtained in 80% yield. In light of this, we used 1 mmol of acyl chloride, 1 mmol of potassium selenocyanate, and 1 mmol of 2-aminobenzimidazole in dry acetone at room temperature for the rest of our reactions.



We thus examined a range of acyl chlorides containing different electron-donating and electron-withdrawing groups. These were used to prepare acyl isoselenocyanates *in situ* to afford the 4-substituted derivatives **4** (Table 2, mean yield 80%). There did not seem to be much dependence of the reaction on the nature of substituents, as yields were uniformly good.

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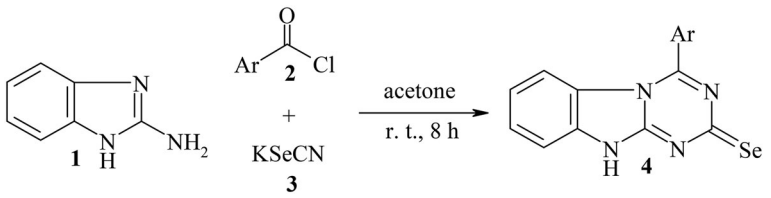


Scheme 1. Synthesis of 1,3,5-triazine-2-selenones **4**.

Table 1. The effect of solvents on the synthesis of **4a** (R = Ph).

Entry	Solvent	Time (h)	**Yield** (%)[a]
1	EtOH	11	65
2	Acetone	8	80
3	DMF	8	53
4	THF	9	58
5	MeCN	10	60

[a]Isolated yield.

Table 2. Yields of compounds **4**[a].

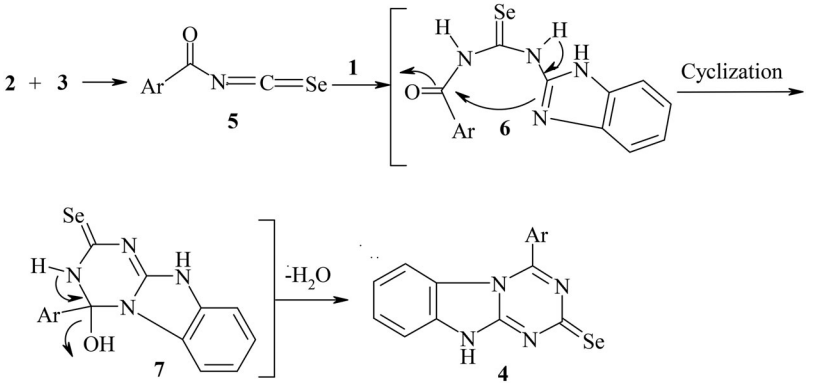
Entry	Ar	Product	**Yield** (%)[b]
1	C_6H_5	**4a**	80
2	4-ClC_6H_4	**4b**	82
3	4-BrC_6H_4	**4c**	81
4	3-$O_2NC_6H_4$	**4d**	78
5	4-$O_2NC_6H_4$	**4e**	85
6	3,5-$O_2NC_6H_3$	**4f**	79
7	4-$CH_3C_6H_4$	**4g**	76
8	4-*t*BuC_6H_4	**4h**	77

[a]Reaction conditions: acyl chloride (**2**, 1 mmol) and KSeCN (**3**, 1 mmol) in acetone (6 mL) were stirred at r.t. 10 min and then 2-aminobenzimidazole (**1**) in acetone (3 mL) was added. Stirring was continued at r.t. for 8 h.
[b]Yields of isolated product.

The structures of compounds **4a-h** were deduced from their elemental analysis and their IR, ^{1}H NMR, and ^{13}C NMR spectra. The mass spectra of compounds **4a–h** are all fairly similar and display molecular ion peaks. For example, the mass spectrum of compound **4a** showed a molecular ion peak at 325, confirming that it is a (1:1:1) adduct. The IR spectrum of compound **4a** exhibited two absorption bands at 1674 cm^{-1} for the C = N and 1259 cm^{-1} for the C = Se groups. The ^{1}H NMR spectrum of compound **4a** exhibited aromatic protons as multiplets at 7.12-8.15 ppm. The ^{13}C NMR spectrum of compound **4a** showed 13 distinct resonances in agreement with the proposed structure.

A plausible mechanism for the formation of selenones **4** is given in Scheme 2. The reaction starts with the formation of acyl isoselenocyanate **5**, followed by the addition of **1** to afford intermediate **6**. Subsequent cyclization of this intermediate generates **7**, which eliminates H_2O to afford product **4**.

In conclusion, trapping acyl isoselenicyanates, generated *in situ* from acyl chlorides and potassium selenocyanate, by 2-aminobenzimidazole affords aryl-substituted benzo[4,5]imidazo[1,2,a][1,3,5]triazine-2-selenone derivatives. The advantages of this



Scheme 2. Proposed mechanism for the synthesis of 1,3,5-triazine-2-selenones.

methodology are its operational simplicity, straightforward workup, substrate availability, and potential diversity. Having explored a unique method for the synthesis of these new compounds and their complete characterization, we hope that our preparative experiments will stimulate further research into this novel category of heterocyclic selenones.

Experimental section

Melting points were determined with an Electrothermal 9100 apparatus and are uncorrected. Elemental analyses 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 MHz, ^{13}C NMR at 125 MHz) in DMSO-d_6 using TMS as an internal standard. Chemical shifts (δ) are given in parts per million (ppm). All of the chemicals used in this study were purchased from Merck and Fluka (Buchs, Switzerland) and were used without further purification.

Safety Notes: Caution! All workers must be thoroughly trained on the use of selenium-containing compounds, and they must wear appropriate personal safety gear. All of the reactions involving selenium-containing compounds must be carried out in a well-ventilated hood.

General procedure for the synthesis of compounds 4

To a stirred solution of potassium selenocyanate (**3**, 0.144 g, 1 mmol) in dry acetone (3 mL), a solution of acyl chloride (**2**, 1 mmol) in dry acetone (3 mL) was added at room temperature. After 10 min, a solution of 2-aminobenzimidazole (**1**, 0.133 g, 1 mmol) in dry acetone (3 mL) was added to the mixture. After completion of the reaction (*ca.* 8 h; as monitored by thin layer chromatography (silica gel; AcOEt/hexane 4/1))

the precipitate which formed was filtered and washed with ether (10 mL) to give the product.

4-Phenylbenzo[4,5]imidazo[1,2,a][1,3,5]triazine-2(10H)-selenone (4a)

Yellow solid. Yield 80%; mp 183-185 °C, IR (KBr) (ν_{max} cm^{-1}): 3310, 1674, 1591, 1518, 1465, 1259 cm^{-1}. ^{1}H NMR (500MHz, DMSO-d_6) δ (ppm): δ 7.12 (t, 1H, J = 8.1Hz), 7.28 (d, 1H, J = 8.5Hz), 7.47 (t, 1H, J = 8.8Hz), 7.52 (t, 2H, J = 8.6Hz), 7.59 (t, 1H, J = 8.5Hz), 7.95 (d, 1H, J = 7.4Hz), 8.14 (d, 2H, J = 7.3Hz), 12.63 (s, 1H, NH). ^{13}C NMR (125MHz, DMSO) δ (ppm): δ 111.3, 113.3, 122.0, 128.3, 128.4, 128.6, 129.2, 132.0, 132.4, 134.4, 152.0, 157.2 and 168.1 (C = Se) ppm. ESI-MS (M+, 325).

Anal. Calcd. for $C_{15}H_{10}N_4Se$: C, 55.40; H, 3.10; N, 17.23. Found: C, 55.71; H, 3.18; N, 17.31.

4-(4-Chlorophenyl)benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2(10H)-selenone (4b)

Yellow solid. Yield 82%; mp 197-199 °C, IR (KBr) (ν_{max} cm^{-1}): 3320, 1670, 1583, 1511, 1456, 1258 cm^{-1}. ^{1}H NMR (500MHz, DMSO-d_6) δ (ppm): δ 7.15 (t, 1H, J = 8.7Hz), 7.20 (d, 1H, J = 8.6Hz), 7.44 (d, 1H, J = 8.4Hz), 7.56 (t, 1H, J = 8.3Hz), 7.93 (d, 2H, J = 8.2Hz), 8.14 (d, 2H, J = 8.4Hz), 12.53 (s, 1H, NH). ^{13}C NMR (125MHz, DMSO) δ (ppm): δ 111.1, 112.5, 122.6, 128.1, 128.5, 129.8, 130.0, 130.9, 137.5, 150.5, 152.8, 157.0 and 166.3 (C = Se) ppm. ESI-MS (M+, 359).

Anal. Calcd. for $C_{15}H_9ClN_4Se$: C, 50.09; H, 2.52; N, 15.58. Found: C, 50.11; H, 2.55; N, 15.61.

4-(4-Bromophenyl)benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2(10H)-selenone (4c)

Yellow solid. Yield 81%; mp 210-212 °C, IR (KBr) (ν_{max} cm^{-1}): 3310, 1659, 1580, 1490, 1453, 1266 cm^{-1}. ^{1}H NMR (500MHz, DMSO-d_6) δ (ppm): δ 7.16 (t, 1H, J = 8.4Hz), 7.21 (d, 1H, J = 8.8Hz), 7.44 (d, 1H, J = 8.2Hz), 7.71 (t, 1H, J = 7.6Hz), 7.85 (d, 2H, J = 8.1Hz), 8.07 (d, 2H, J = 8.2Hz), 12.63 (s, 1H, NH). ^{13}C NMR (125MHz, DMSO) δ (ppm): δ 111.3, 112.7, 121.9, 125.5, 130.0, 130.5, 131.2, 131.7, 134.8, 150.2, 152.5, 156.0 and 166.6 (C = Se) ppm. ESI-MS (M+, 404).

Anal. Calcd. for $C_{15}H_9BrN_4Se$: C, 44.58; H, 2.24; N, 13.86. Found: C, 44.85; H, 2.31; N, 13.98.

4-(3-Nitrophenyl)benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2(10H)-selenone (4d)

Yellow solid. Yield 78%; mp 198-200 °C, IR (KBr) (ν_{max} cm^{-1}): 3305, 1676, 1600, 1514, 1465, 1261 cm^{-1}. ^{1}H NMR (500MHz, DMSO-d_6) δ (ppm): δ 7.13 (t, 1H, J = 7.3Hz), 7.20 (d, 1H, J = 7.3Hz), 7.44 (d, 1H, J = 7.4Hz), 7.72 (t, 1H, J = 8.8Hz), 7.78 (t, 1H, J = 8.8Hz), 8.32 (d, 1H, J = 7.6Hz), 8.36 (d, 1H, J = 7.3Hz), 8.68 (s, 1H, CH), 12.56 (s, 1H, NH). ^{13}C NMR (125MHz, DMSO) δ (ppm): δ 111.0, 111.8, 121.8, 122.3, 123.3, 125.3, 129.6, 131.4, 134.4, 135.1, 137.2, 147.5, 152.6, 156.2 and 167.7 (C = Se) ppm. ESI-MS (M+, 370).

Anal. Calcd. for $C_{15}H_9N_5O_2Se$: C, 48.66; H, 2.45; N, 18.92. Found: C, 49.02; H, 2.60; N, 18.98.

4-(4-Nitrophenyl)benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2(10H)-selenone (4e)

Yellow solid. Yield 85%; mp 215-217 °C, IR (KBr) (ν_{max} cm^{-1}): 3385, 1676, 1596, 1542, 1471, 1262 cm^{-1}. ^1H NMR (500MHz, DMSO-d_6) δ (ppm): δ 7.04 (t, 1H, J = 8.1Hz), 7.24 (d, 1H, J = 8.6Hz), 7.42 (d, 1H, J = 8.9Hz), 7.67 (t, 1H, J = 8.3Hz), 8.18 (d, 2H, J = 7.3Hz), 8.24 (d, 2H, J = 8.3Hz), 12.49 (s, 1H, NH). ^{13}C NMR (125MHz, DMSO) δ (ppm): δ 110.9, 111.0, 120.8, 122.9, 128.4, 129.4, 130.1, 133.7, 142.3, 148.6, 153.4, 156.1 and 168.4 (C = Se) ppm. ESI-MS (M+, 370).

Anal. Calcd. for $C_{15}H_9N_5O_2Se$: C, 48.66; H, 2.45; N, 18.92. Found: C, 48.95; H, 2.50; N, 18.96.

4-(3,5-Dinitrophenyl)benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2(10H)-selenone (4f)

Yellow solid. Yield 79%; mp 220-222 °C, IR (KBr) (ν_{max} cm^{-1}): 3300, 1686, 1600, 1532, 1454, 1259 cm^{-1}. ^1H NMR (500MHz, DMSO-d_6) δ (ppm): δ 7.12 (t, 1H, J = 7.0Hz), 7.32 (d, 1H, J = 7.0Hz), 8.01 (d, 1H, J = 7.0Hz), 8.67 (t, 1H, J = 7.9Hz), 8.85 (s, 1H, CH), 8.96 (s, 2H, 2CH), 12.41 (s, 1H, NH). ^{13}C NMR (125MHz, DMSO) δ (ppm): δ 111.0, 119.3, 120.6, 121.8, 127.5, 128.4, 131.3, 131.4, 141.7, 147.6, 152.6, 156.4, and 166.4 (C = Se) ppm. ESI-MS (M+, 415).

Anal. Calcd. for $C_{15}H_8N_6O_4Se$: C, 43.39; H, 1.94; N, 20.24. Found: C, 44.03; H, 2.01; N, 20.29.

4-(p-Tolyl)benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2(10H)-selenone (4g)

Yellow solid. Yield 76%; mp 195-197 °C, IR (KBr) (ν_{max} cm^{-1}): 3340, 1672, 1596, 1572, 1459, 1257 cm^{-1}. ^1H NMR (500MHz, DMSO-d_6) δ (ppm): δ 2.38 (s, 3H, CH3), 7.12 (t, 1H, J = 8.6Hz), 7.28 (d, 1H, J = 8.8Hz), 7.34 (d, 1H, J = 8.0Hz), 7.46 (t, 1H, J = 8.6Hz), 7.82 (d, 2H, J = 7.6Hz), 8.03 (d, 2H, J = 7.8Hz), 12.32 (s, 1H, NH). ^{13}C NMR (125MHz, DMSO) δ (ppm): δ 20.9 (CH_3), 111.1, 113.3, 122.7, 128.1, 128.7, 128.9, 129.1, 129.6, 142.8, 147.4, 150.4, 155.8 and 167.1 (C = Se) ppm. ESI-MS (M+, 339).

Anal. Calcd. for $C_{16}H_{12}N_4Se$: C, 56.65; H, 3.57; N, 16.51. Found: C, 56.70; H, 3.59; N, 16.63.

4-(4-(tert-Butyl)phenyl)benzo[4,5]imidazo[1,2-a][1,3,5]triazine-2(10H)-selenone (4h)

Yellow solid. Yield 77%; mp 193-195 °C, IR (KBr) (ν_{max} cm^{-1}): 3345, 1661, 1623, 1566, 1451, 1258 cm^{-1}. ^1H NMR (500MHz, DMSO-d_6) δ (ppm): δ 1.32 (s, 9H, 3CH3), 7.12 (t, 1H, J = 8.8Hz), 7.20 (d, 1H, J = 8.8Hz), 7.35 (d, 1H, J = 8.0Hz), 7.54 (t, 1H, J = 8.3Hz), 7.86 (d, 2H, J = 8.2Hz), 8.07 (d, 2H, J = 7.8Hz), 12.48 (s, 1H, NH). ^{13}C NMR (125MHz, DMSO) δ (ppm): δ 30.5 ($3CH_3$), 34.4 (C), 110.9, 111.9, 121.0, 122.5, 124.8,

124.9, 127.7, 128.8, 129.6, 150.2, 152.9, 155.8 and 166.9 (C = Se) ppm. ESI-MS (M+, 381).

Anal. Calcd. for $C_{19}H_{18}N_4Se$: C, 59.84; H, 4.76; N, 14.69. Found: C, 59.90; H, 4.99; N, 14.75.

Acknowledgments

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