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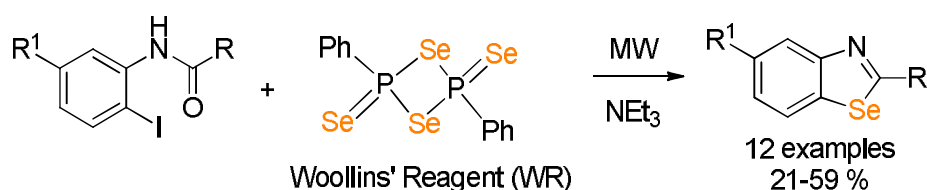
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One-pot preparation of 2-(alkyl)arylbenzoselenazoles from the corresponding *N*-(acetyl)benzoyl-2-iodoanilines *via* a microwave-assisted methodology.

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ABSTRACT

We report here the first example of a one-pot synthesis of 2-(alkyl)arylbenzoselenazoles from *N*-(acetyl)benzoyl-2-iodoanilines. The reaction was carried out in the presence of Woollins' reagent under microwave irradiation and resulted in moderate to good yields.

Keywords:

Woollins' reagent

Benzoselenazole

Microwave irradiation

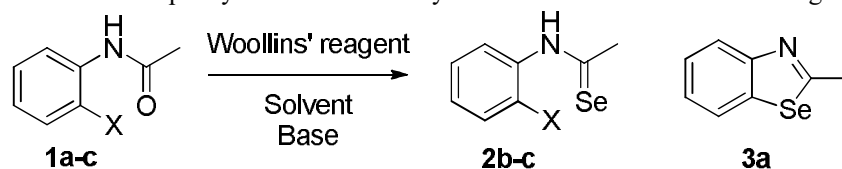
Cyclization

The value of the selenium-containing heterocycles has been demonstrated in medicinal chemistry,¹ offering antiviral,² antihypertensive,³ antifungal⁴ and anticancer⁵ properties. Some 1,3-benzoselenazole derivatives are also useful as precursors of new materials such as cyanine-type dyes.⁶ Compared to their sulfur homologues, selenium compounds exhibit very valuable antioxidant properties.⁷ However, synthetic routes remain poorly explored because of their high cost or low stability in air.

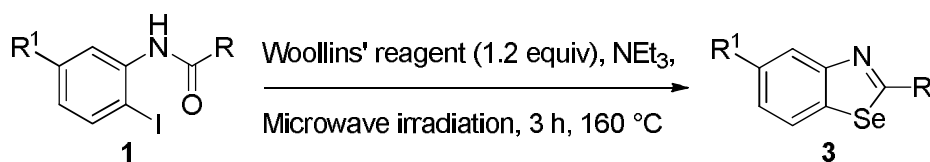
In continuation of our research program on medicinal chemistry⁸ we investigate the synthesis of benzoselenazoles as homologues of benzothiazoles. The few existing synthetic routes it should be notified the condensation of zinc bis(*o*-aminoselenoate) with acid chlorides^{9a} or bis(*o*-aminophenyl) diselenide with aldehydes promoted by sodium metabisulfite.^{9b} Recently an efficient method was developed *via* intermolecular C–Se cross-coupling catalyzed by transition metal giving 2-aminobenzoselenazole from 2-iodo-4-methylphenyl)selenourea.¹⁰ Sashida improved this method *via* a one-pot reaction starting from iodoaniline and isoselenocyanates.¹¹ Kambe reported a copper(I)-catalyzed reaction of 2-bromophenylisocyanide with selenium and heteroatom nucleophiles.¹²

We focused on an existing benzothiazole synthesis *via* an intramolecular nucleophilic aromatic substitution of *o*-halo-thiobenzanilide (INASOB) promoted by base.¹³ We used the well-known Woollins' reagent¹⁴ (WR) to convert the amides into the corresponding selenoamides. We initially explored the reaction of **1a** with 1.2 equiv. of WR under classical heating

procedure (reflux of THF, toluene). Unfortunately, the starting material was entirely recovered without any trace of the expected product (entries 1-2, Table 1). However, this reaction, under reflux of organic base (pyridine), afforded the 2-methylbenzoselenazole **3a** alone with no trace of selenoamide after 16 h (entry 3). Although the yield was low, this encouraging result showed that the selenation/cyclization sequence could be realized under one-pot conditions. With a higher boiling point solvent (mixture of xylenes), a better though still low yield was obtained without any trace of intermediate selenamide **2** (entry 4). With this classical heating procedure, **1a** was still present after reaction and the yield of **3a** remained low, we therefore investigated whether the selenation/cyclization sequence could be promoted under microwave irradiation.¹⁵ Using pyridine as the solvent at 160 °C under microwave irradiation, we monitored the reaction by LCMS. The starting material was completely consumed after 6 h but 2-methylbenzoselenazole **3a** was obtained in moderate yield (entry 5). Variation of the amount of WR (2 equiv) slightly improved the yield to 41% (entry 6). Next, pyridine was replaced by NEt₃ at the same temperature (160 °C). The reaction was finished in 3 h and 2-methylbenzoselenazole **3a** was obtained in higher yield (57%) (entry 7). With other base (2 equiv of Cs₂CO₃ in xylenes),¹³ a low yield (<10%) was observed under microwave irradiation for 3 h (entry 8). Furthermore, cyclization is less efficient with other *N*-acetyl-2-

Table 1. One-pot cyclization of *N*-acetyl-2-haloaniline with Woollins' reagent.

Entry	X	Compounds	W. R. (equiv)	Conditions		Yield % ^a
1	I	1a	1.2	THF, 80 °C, 12h		0
2	I	1a	1.2	Toluene, 110 °C, 16 h		0
3	I	1a	1.2	Pyridine, 115 °C, 16 h		< 10 (3a)
4	I	1a	1.2	Xylenes, 140 °C, 16 h		18 (3a)
5	I	1a	1.2	Pyridine, 160 °C, 6 h	MW	27 (3a)
6	I	1a	2.0	Pyridine, 160 °C, 6 h	MW	41 (3a)
7	I	1a	1.2	NEt ₃ , 160 °C, 3 h	MW	57 (3a)
8	I	1a	1.2	Xylenes, CsCO ₃ (2 equiv), 3 h	MW	< 10 (3a)
9	Br	1b	1.2	NEt ₃ , 160 °C, 6 h	MW	35 (2b), 19 (3a)
10	Cl	1c	1.2	NEt ₃ , 160 °C, 3 h	MW	49 (2c), <10 (3a)

^a Isolated yield**Table 2.** Scope of the reaction

Entry	Starting material	R	R ¹	Product	Yield % ^a
1	1a	-CH ₃	-H	3a	57
2	1d	-CH ₂ CH ₂ C ₆ H ₅	-H	3d	53
3	1e	-C ₆ H ₅	-H	3e	59
4	1f	- <i>p</i> MeC ₆ H ₄	-H	3f	50
5	1g	- <i>p</i> ClC ₆ H ₄	-H	3g	49
6	1h	- <i>p</i> CF ₃ C ₆ H ₄	-H	3h	48
7	1i	- <i>p</i> OMeC ₆ H ₄	-H	3i	48
8	1j	-2-furanyl	-H	3j	46
9	1k	-2-thienyl	-H	3k	45
10	1l	-2-pyrrolyl	-H	3l	55
11	1m	-CH ₃	-Br	3m	44
12	1n	-CH ₃	-OCH ₃	3n	21

^a Isolated yield

haloanilines with chlorine or bromine atoms. For example, with *N*-acetyl-2-bromoaniline **1b** and *N*-acetyl-2-chloroaniline **1c**, the reaction gave a mixture of corresponding selenamides **2** and 2-methylbenzoselenazole **3a** (entries 9-10).

To extend the substrate scope of this one-pot selenation/cyclization, various *N*-(acetyl)benzoyl-2-iodoanilines were synthesized¹⁶ and subjected to the microwave protocol. The results obtained under the optimized reaction conditions¹⁷ are listed in Table 2 and show that the reaction is efficient with different alkyl, aryl and heteroaryl derivatives. Different functional groups including electron-withdrawing groups such as chloro and trifluoromethyl and electron-donating groups such as methoxy, furan, thiophene and pyrrole on the benzoyl moiety showed roughly the same efficiency. The electron-withdrawing groups such as carbonyl,^{18a} cyano,^{18b}, amide^{18c} and sulfone^{18d} on the benzoyl moiety were not tested because of their well-known good reactivity with Woollins reagent. The selenation/cyclization process was also applied with electron-withdrawing groups or electron-donating groups such as bromo or methoxy in *para* position of iodo. The corresponding yields are similar for the bromo compound **3m** (entry 11) and lower for the methoxy compound **3n** (entry 12).

In summary, we have developed a novel method of benzoselenazole synthesis with Woollins' reagent under basic conditions and microwave irradiation *via* a one-pot reaction from corresponding *N*-(acetyl)benzoyl-2-iodoanilines. To the best of our knowledge, this work describes for the first time a synthetic pathway in benzoselenazole series under microwave irradiation. Under these experimental conditions, the *N*-acetylchloro or bromoanilines led to selenoamide intermediate as the isolated major product and 2-methylselenazole as the isolated minor product. The scope of the reaction included synthesis of *N*-(acetyl)benzoyl-2-iodoanilines succeeded in moderate to good yields.

Acknowledgments

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- The substrates **1** were prepared from the acyl chlorides in toluene.
- Typical experimental procedure for synthesis of benzoselenazoles: In a 5 mL glass vial equipped with a small magnetic stirring bar, the *N*-(2-iodophenyl)-acetamide **1a** (0.57 mmol, 150 mg), Woollins' reagent (0.34 mmol, 180 mg, 1.2 equiv) were mixed with dry triethylamine (3 mL) under nitrogen atmosphere. The vial was tightly sealed with an aluminum/teflon crimp top. The mixture was then irradiated in a Biotage® Initiator microwave reactor for 3 h at 160 °C. After the reaction was complete, the reaction mixture was evaporated under *vacuum*. The residue was purified by flash chromatography on silica gel using petroleum ether/EtOAc (95:5) as the eluent, yielding **3a** (65 mg, 57%). Analysis for compounds **3a**, **3e**, **3f** and **3i** are in agreement with those reported in the literature.^{9b,9c} Data for the new compounds:
2-(2-Phenylethyl)-1,3-benzoselenazole (**3d**): White solid (87 mg), yield = 53%; mp 114–116 °C; R_f = 0.35 (ethyl acetate/petroleum ether: 5/95); ¹H NMR (200 MHz, CDCl₃, δ, ppm) 7.93 (d, J = 8.2 Hz, 1H), 7.79 (d, J = 7.9 Hz, 1H), 7.38 (t, J = 7.9 Hz, 1H), 7.12–7.27 (m, 6H), 3.39 (t, J = 7.9 Hz, 2H), 3.12 (t, J = 7.9 Hz, 2H); ¹³C NMR (50 MHz, CDCl₃, δ, ppm) 174.5, 152.0, 138.0, 136.3, 126.7, 126.6, 124.6, 124.3, 123.2, 123.0, 122.1, 37.2, 33.8. LC-MS (ESI+): t_R = 4.02 min; m/z [M + H]⁺: 288.15. HRMS for C₁₅H₁₄NSe [M + H]⁺ calcd/found: 288.0291/288.0288.
2-(4-Chlorophenyl)-1,3-benzoselenazole (**3g**): White solid (82 mg), yield = 49%, mp 101 °C; R_f = 0.35 (ethyl acetate/petroleum ether: 5/95); ¹H NMR (200 MHz, CDCl₃, δ, ppm) 8.12 (d, J = 8.1 Hz, 1H), 7.90–8.00 (m, 3H), 7.42–7.55 (m, 3H), 7.33 (dt, J = 7.9, 1.2 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃, δ, ppm) 171.2, 155.5, 138.3, 137.3, 134.6, 129.5, 129.3, 126.7, 125.7, 125.0. HRMS for C₁₃H₉ClNSe [M + H]⁺ calcd/found: 293.9581/293.9584.
2-[4-(Trifluoromethyl)phenyl]-1,3-benzoselenazole (**3h**): White solid (90 mg), yield = 48%, mp 143–145 °C; R_f = 0.35 (ethyl acetate/petroleum ether: 5/95); ¹H NMR (200 MHz, CDCl₃, δ, ppm) 8.01–8.06 (m, 3H), 7.95 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.4 Hz, 2H), 7.37 (dt, J = 8.2 Hz, 1.2 Hz, 1H), 7.32 (dt, J = 8.0 Hz, 1.2 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃, δ, ppm) 170.6, 155.7, 139.3, 138.7, 132.5 (q, J = 32.5 Hz), 128.3, 126.8, 126.2 (q, J = 3.5 Hz), 126.0, 125.4, 125.1, 123.9 (q, J = 27.2 Hz). LC-MS (ESI+): t_R = 4.77 min; m/z [M + H]⁺: 328.05. HRMS for C₁₄H₉F₃NSe [M + H]⁺ calcd/found: 327.9847/327.9850.
2-(Furan-2-yl)-1,3-benzoselenazole (**3j**): White solid (65 mg), yield = 46%, mp 122–124 °C; R_f = 0.46 (ethyl acetate/petroleum ether: 10/90); ¹H NMR (200 MHz, CDCl₃, δ, ppm) 8.11 (d, J = 8.1, 0.6 Hz, 1H), 7.87 (d, J = 7.8, 0.8 Hz, 1H), 7.62 (d, J = 1.3 Hz, 1H), 7.49 (dd, J = 7.7, 1.2 Hz, 1H), 7.26–7.35 (m, 2), 6.61 (dd, J = 3.5, 1.8 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃, δ, ppm) 160.9, 155.1, 151.0, 145.1, 137.4, 126.7, 125.4, 124.9, 124.7, 113.0, 111.4. LC-MS (ESI+): t_R = 3.07 min; m/z [M + H]⁺: 250.18. HRMS C₁₁H₈NOSe [M + H]⁺ calcd/found: 249.9766 / 249.9766.
2-(Thiophen-2-yl)-1,3-benzoselenazole (**3k**): Yellow solid (68 mg), yield = 45%, mp 107–109 °C; R_f = 0.57 (ethyl acetate/petroleum ether: 10/90); ¹H NMR (200 MHz, CDCl₃, δ, ppm) 8.07 (dd, J = 8.1 Hz, 1H), 7.87 (dd, J = 7.8 Hz, 1H), 7.60 (d, J = 3.7 Hz, 1H), 7.42–7.52 (m, 2H), 7.24–7.34 (m, 1H), 7.12 (d, J = 5.1, 1.2 Hz, 1H); ¹³C NMR (50 MHz, CDCl₃) δ: 164.5, 155.1, 140.1, 137.9, 129.9, 129.8, 128.2, 126.7, 125.5, 124.8, 124.6. LC-MS (ESI+): t_R = 3.50 min; m/z [M + H]⁺: 266.06. HRMS C₁₁H₈NSSe [M + H]⁺ calcd/found: 265.9537/265.9536.

- 2-(1*H*-pyrrol-2-yl)-1,3-benzoselenazole (**3i**): White solid (78 mg), yield = 55%; mp 148-150 °C; R_f = 0.31 (ethyl acetate/petroleum ether: 10/90); ^1H NMR (200 MHz, CDCl_3 , δ , ppm) 10.09 (s, 1H), 7.95 (d, J = 8.2 Hz, 1H), 7.91 (d, J = 8.2 Hz, 1H), 7.48 (dt, J = 6.8, 1.1 Hz, 1H), 7.20-7.25 (m, 1H), 7.00-7.05 (m, 1H), 6.80-6.85 (m, 1H), 6.30-6.35 (m, 1H); ^{13}C NMR (50 MHz, CDCl_3 , δ , ppm) 163.8, 155.0, 136.7, 128.9, 126.5, 124.9, 124.7, 123.3, 122.7, 114.4, 110.9. LC-MS (ESI+): t_R = 3.02 min; m/z [$\text{M} + \text{H}$] $^+$: 249.22. HRMS $\text{C}_{11}\text{H}_9\text{N}_2\text{Se}$ [$\text{M} + \text{H}$] $^+$ calcd/found: 248.9926/248.9925.
- 5-Bromo-2-methyl-benzoselenazole (**3m**): White solid (70 mg), yield = 44%; mp 148-150 °C; R_f = 0.25 (ethyl acetate/petroleum ether: 10/90); ^1H NMR (200 MHz, CDCl_3 , δ , ppm) 8.11 (d, J = 1.8 Hz, 1H), 7.70 (d, J = 8.4 Hz, 1H), 7.39 (dd, J = 8.6, 1.8 Hz, 1H), 2.87 (s, 3H); ^{13}C NMR (50 MHz, CDCl_3 , δ , ppm) 173.6, 155.6, 137.7, 128.0, 126.8, 125.8, 119.7, 23.8. LC-MS (ESI+): t_R = 2.96 min; m/z [$\text{M} + \text{H}$] $^+$: 275.92. HRMS $\text{C}_8\text{H}_7\text{BrNSe}$ [$\text{M} + \text{H}$] $^+$ calcd / found: 275.8919/275.8918.
- 5-Methoxy-2-methyl-benzoselenazole (**3n**): Orange solid (25 mg), yield = 21%; mp 88-90 °C; R_f = 0.23 (ethyl acetate/petroleum ether: 10/90); ^1H NMR (200 MHz, CDCl_3 , δ , ppm) 7.68 (d, J = 8.5 Hz, 1H), 7.51 (d, J = 2.4 Hz, 1H), 6.92 (dd, J = 9.3, 2.1 Hz, 1H), 3.86 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (50 MHz, CDCl_3 , δ , ppm) 171.3, 157.0, 128.0, 123.0, 114.5, 112.6, 105.2, 53.7, 27.8. LC-MS (ESI+): t_R = 2.34 min; m/z [$\text{M} + \text{H}$] $^+$: 228.19. HRMS $\text{C}_9\text{H}_{10}\text{NOSe}$ [$\text{M} + \text{H}$] $^+$ calcd / found: 227.9928/227.9923.
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Supplementary Material

Supplementary data associated with this article can be found, in the online version.