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

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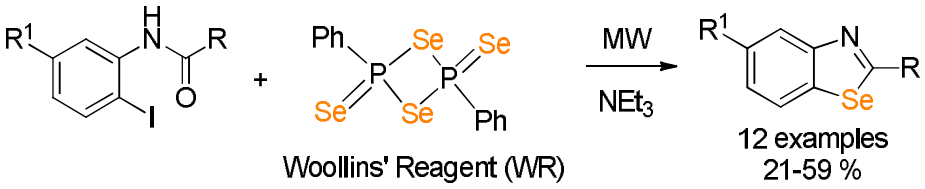

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ABSTRACT

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.

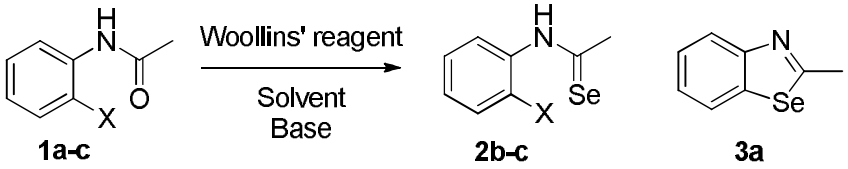
The value of the selenium-containing heterocycles has been demonstrated in medicinal chemistry,[1] offering antiviral,[2] antihypertensive,[3] antifungal[4] and anticancer[5] properties. Some 1,3-benzoselenazole derivatives are also useful as precursors of new materials such as cyanine-type dyes.[6] 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 chemistry[8] 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 *i*ntramolecular *n*ucleophilic *a*romatic *s*ubstitution of *o*-halo-thio*b*enzanilide (INASOB) promoted by base.[13] We used the well-known Woollins' reagent[14] (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 NEt_3 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 Cs_2CO_3 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-

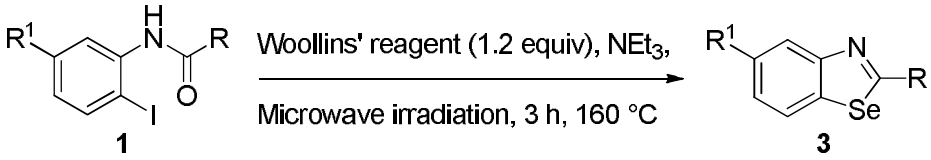
Table 1. One-pot cyclization of *N*-acetyl-2-haloaniline with Woollins' reagent.



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**	$-CH_2CH_2C_6H_5$	-H	**3d**	53
3	**1e**	$-C_6H_5$	-H	**3e**	59
4	**1f**	$-p$MeC$_6$H$_4$	-H	**3f**	50
5	**1g**	$-p$ClC$_6$H$_4$	-H	**3g**	49
6	**1h**	$-p$CF$_3$C$_6$H$_4$	-H	**3h**	48
7	**1i**	$-p$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 synthesized[16] and subjected to the microwave protocol. The results obtained under the optimized reaction conditions[17] 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.

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15. For an example of efficient thionation under microwave irradiation see: Varma, R. S.; Kumar, D. *Org. Lett*. **1999**, *1*, 697–700.
16. The substrates **1** were prepared from the acyl chlorides in toluene.
17. 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); ^{1}H NMR (200 MHz, $CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$, 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 $C_{15}H_{14}NSe$ $[M + H]^+$ 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); ^{1}H NMR (200 MHz, $CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$, δ, ppm) 171.2, 155.5, 138.3, 137.3, 134.6, 129.5, 129.3, 126.7, 125.7, 125.0. HRMS for $C_{13}H_9ClNSe$ $[M + H]^+$ 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); ^{1}H NMR (200 MHz, $CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$, 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* = 272.6 Hz). LC-MS (ESI+): t_R= 4.77 min; m/z $[M + H]^+$: 328.05. HRMS for $C_{14}H_9F_3NSe$ $[M + H]^+$ 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); ^{1}H NMR (200 MHz, $CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$, 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 $C_{11}H_8NOSe$ $[M + H]^+$ 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); ^{1}H NMR (200 MHz, $CDCl_3$, 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); ^{13}C NMR (50 MHz, $CDCl_3$) 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 $C_{11}H_8NSSe$ $[M + H]^+$ calcd/found: 265.9537/265.9536.

2-(1H-pyrrol-2-yl)-1,3-benzoselenazole (**3l**): White solid (78 mg), yield = 55%; mp 148-150 °C; R_f = 0.31 (ethyl acetate/petroleum ether: 10/90); ^{1}H 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 $[M + H]^+$: 249.22. HRMS $C_{11}H_9N_2Se$ $[M + H]^+$ 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); ^{1}H 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 $[M + H]^+$: 275.92. HRMS C_8H_7BrNSe $[M + H]^+$ 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); ^{1}H 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 $[M + H]^+$: 228.19. HRMS $C_9H_{10}NOSe$ $[M + H]^+$ 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.