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

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a b s t r a c t

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] 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. Among 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' 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 and 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 selenoamide 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-haloanilines with chlorine or bromine atoms.

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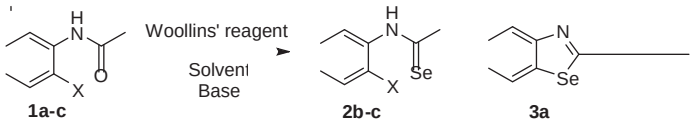
Table 1
One-pot cyclization of N-acetyl-2-haloaniline with Woollins' reagent



Entry	X	Compounds	W.R. (equiv)	Conditions		Yield[a] (%)
1	I	2	1a	1.2	THF, 80 °C, 12 h		0
	I	3	1a	1.2	Toluene, 110 °C, 16 h		0
	I	4	1a	1.2	Pyridine, 115 °C, 16 h		<10 (3a)
	I	5	1a	1.2	Xylenes, 140 °C, 16 h		18 (3a)
	I	6	1a	1.2	Pyridine, 160 °C, 6 h	MW	27 (3a)
	I	7	1a	2.0	Pyridine, 160 °C, 6 h	MW	41 (3a)
	I	8	1a	1.2	NEt_3, 160 °C, 3 h	MW	57 (3a)
	I	9	1a	1.2	Xylenes, $CsCO_3$ (2 equiv), 3 h	MW	<10 (3a)
	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)

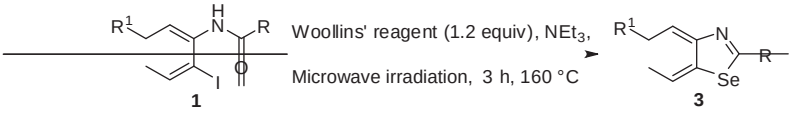
[a] Isolated yield.

For example, with N-acetyl-2-bromoaniline 1b and N-acetyl-2-chloroaniline 1c, the reaction gave a mixture of corresponding selenoamides 2 and 2-methylbenzoselenazole 3a (entries 9 and 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 succeeded in moderate to good yields.

Table 2
Scope of the reaction



Entry	Starting material	R	R^1	Product	Yield[a] (%0)
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	$-pMeC_6H_4$	–H	3f	50
5	1g	$-pClC_6H_4$	–H	3g	49
6	1h	$-pCF_3C_6H_4$	–H	3h	48
7	1i	$-pOMeC_6H_4$	–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.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.07.055.

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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 the 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 is in agreement with that reported in the literature.[9b,c] 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$) d: 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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, $CDCl_3$, d, 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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