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A Solvent- and Metal-Free Synthesis of 3-Chacogenyl-indoles Employing DMSO/I_2 as an Eco-friendly Catalytic Oxidation System

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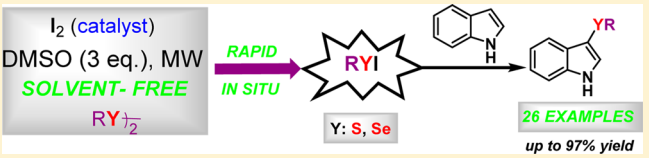
Supporting Information

ABSTRACT: Herein, we describe a solvent- and metal-free method for the synthesis of 3-chalcogenyl-indoles from indoles and diorganyl dichalcogenides using an equivalent amount of DMSO as an oxidant, under catalysis by molecular iodine. This mild and eco-friendly approach allowed the preparation of a wide range of 3-selenyl- and 3-sulfenyl-indoles in good to excellent yields.



The indole core is a ubiquitous heterocycle found in many bioactive natural products, pharmaceuticals, and agrochemicals,[1] and as a consequence has been continuously capturing the interest of chemists worldwide. Recent studies have shown that 3-sulfenylindoles act on specific targets, attracting the attention of a number of researchers[2] due their several potential activities such as inhibitor of tubulin polymerization at submicromolar concentration and cell growth at low nanomolar concentrations,[3] antitumor[4] and antiviral activities.[5]

Analogously, organoselenium compounds are bioactive[6] and have been highlighted because of their ability to mimic natural compounds with biological proprieties, such as antioxidant activity,[7] and potential usefulness as valuable synthetic intermediates.[8] Thus, 3-chalcogenyl-indoles have emerged as a powerful class by virtue of their potent pharmacological activity in the treatment of several diseases.

The methodologies reported for the preparation of 3-chalcogenyl-indoles commonly involve the direct reaction of the indole core with diorganoyl dichalcogenides catalyzed by metals such as iron(III),[9] copper,[10] $VO(acac)_2$,[11] and MgBr.[12]

In addition, the chalcogenylation of indoles has been developed employing quinone-mono-*O*,*S*-acetals,[13] *N*-chalcogenoimides,[14] sulfonylhydrazides,[15] thiols,[9] and arylsulfonyl chlorides[16] as chalcogenylation agents.

Other processes for the preparation of 3-chalcogenyl-indoles involves the electrophilic cyclization of *o*-alkynylanilines[17] or 2-(gem-dibromo(chloro)vinyl)anilines employing organochalcogen electrophilic species as cyclization agents[18] and the use of ionic liquids as a recyclable solvent.[19] Nevertheless, most of these methods have drawbacks such as the use of toxic solvents/metals or long reaction times. In addition, we have described an alternative approach for the synthesis of 3-chalcogenyl indoles by using trichloroisocyanuric acid (TCCA) and dichalcogenides.[20]

Wey and co-workers[21] reported a simple protocol for the synthesis of 3-sulfenyl-indoles in dimethyl carbonate (DMC), employing an equivalent amount of DMSO as stoichiometric oxidant and catalytic quantity of molecular iodine (I_2).

Very recently, a similar system of I_2 and DMSO was also used for the preparation of 3-sulfenyl-indoles by using aryl sodium sulfinates as an organosulfur source, in the presence of diethyl fosfite as an additive and anisole as solvent.[22] In spite of their good features, long reaction times and use of solvent or additives are required and the synthesis of 3-selenyl-indoles by these methods was not explored.

On the other hand, the use of microwave (MW) irradiation in organic transformations, including C−Se and C−S bond formation,[23] can provide higher yields in shorter reaction times.[24] In addition, with the development of sustainable technologies, solvent-free conditions have emerged as a benign alternative for organic synthesis.[25] Besides avoiding problems related to flammability and toxicity, these methodologies decrease significantly the amount of waste generated.

In this regard, the combination of a solvent-free reaction medium with microwave irradiation heating has been used successfully for the synthesis of organochalcogen compounds.[26] However, to date, there are no reports of studies in which this attractive strategy was applied to the synthesis of 3-chalcogenyl-indoles.

Thus, herein we detail the synthesis of 3-chalcogenyl-indoles in the absence of solvents, under microwave irradiation in a very short reaction time and employing molecular iodine as a catalyst (Scheme 1).

Optimization of the reaction conditions was initiated using indole (**1**) and diphenyl diselenide as standard substrates, 5 mol % of catalyst, and 3 equiv of the stoichiometric oxidant (Table 1). Initially, the influence of the reaction time on the

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Scheme 1. Molecular Iodine Catalyzed 3-Chalcogenylation of Indoles under Solvent-Free Conditions

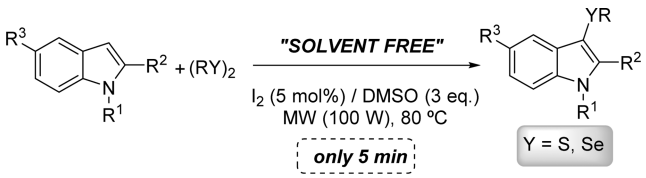
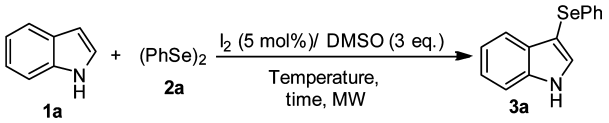


Table 1. Optimization of Microwave Parameters



entry	power (W)	T (°C)	t (min)	yield (%)[a]
1	100	80	1	59
2	100	80	3	70
3	100	80	5	84
4	100	80	7	85
5	100	100	5	84
6	100	60	5	50
7	150	80	5	86
8	50	80	5	79
9	–	80	12 h	75[b]

[a]Isolated yields. [b]Conventional heating.

performance of the transformation was investigated. Carrying out the reaction for 1 min provided the desired product in only 59% yield (entry 1). However, when the time was increased to 3 min, a significant improvement in the yield was observed (entry 2).

Notably, when the reaction was carried out for 5 min at 80 °C and 100 W, product **3a** was accessed in 84% yield (entry 3). However, no significant change in the yield was observed on applying a 7 min reaction time (entry 4).

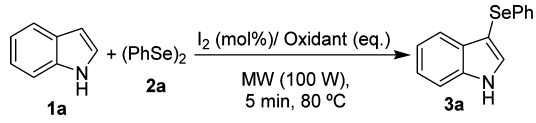
Next, the influence of temperature was investigated. Increasing the temperature from 80 to 100 °C produced no appreciable variation in the yield (entry 5). Nonetheless, a considerable decrease was detected when the reaction was performed at a lower temperature (entry 6). The reaction was also performed employing different levels of irradiation power. Carrying out the reaction at 150 W did not affect the yield (entry 7). However, when the power was decreased to 50 W a significant decreased in the yield was observed (entry 8).

In order to evaluate the influence of the heating methodology the reaction was also performed under conventional heating (entry 9). Under this condition, the desired product **3a** was obtained in 75% yield after 12 h, highlighting the importance of the use of microwaves.

The influence of the catalyst and the stoichiometric oxidant on the reaction system was next explored (Table 2). Carrying out the reaction with 1 mol % of iodine afforded only 22% of 3-selenyl-indole **3a** (entry 1). Increasing the catalyst amount to 2.5 mol % caused an increase to 64% yield (entry 2), which further improved to 84% when 5 mol % of iodine was used (entry 3).

Furthermore, no significant additional changes were observed upon increasing the catalyst load to 10 mol % (entry 4). The requirement of iodine as a catalyst was demonstrated when the reaction was carried out in its absence. In this case, no product was observed (entry 5).

Table 2. Optimization of Reaction Conditions



entry	I_2 (mol %)	oxidant (equiv)	yield (%)
1	1	DMSO (3)	22
2	2.5	DMSO (3)	64
3	5	DMSO (3)	84
4	10	DMSO (3)	86
5	–	DMSO (3)	–
6	5	DMSO (1)	40
7	5	–	15
8[a]	–	DMSO (3)	80
9	5	H_2O_2 (3)	55

[a]Reaction performed using 5 mol % of HI.

With the best catalyst loading in hand, the effect of the amount of the oxidant on the transformation was evaluated. It was observed that decreasing the amount of added DMSO decreased the yields of **3a** to 40% (entry 6), while in its absence the yield dropped to 15% (entry 7). When HI was used instead of I_2 the reaction also worked well, indicating that most likely the HI is one of the intermediates of this reaction (entry 8). The employment of H_2O_2 instead of DMSO resulted in a less efficient transformation (entry 9). Thus, the optimal reaction conditions are shown in entry 3.

With the best result in hand, a library of 3-selenyl-indoles was synthesized in order to evaluate the scope of the protocol (Table 3). The effect of different groups bound to selenium was evaluated at first, reacting **1a** with several diorganoyl diselenides.

The electronic characteristics of the substituent attached to the *para* position of the aromatic ring (electron donor or acceptor) did not affect performance of the transformation, and the corresponding 3-selenyl-indoles were obtained in very high yield. Notably, when a diselenide with a CF_3 group at the *meta* position was employed, the respective product was obtained in 86% yield. Furthermore, steric effects did not significantly affect the reaction, and on using an *ortho*-methoxyphenyl diselenide the corresponding product was delivered in good yield. However, aliphatic diselenides, which are less reactive than their aromatic analogues,[27] were not efficient substrates for this transformation.

Next, the influence of the indole moiety was evaluated, employing heterocycles with different functionalities attached at the 5-position of the ring, including methyl, methoxy, bromo, and ester group. The results indicate that both electron-withdrawing and electron-donating groups are suitable substrates, affording the corresponding products **3h–k** in 72–85% yield.

Substituents at the 1-position of the indole also modulated the performance of the process. For example, the 1-methyl and 1-phenyl derivatives afforded the expected 3-selenyl-indoles **3l,m** in 89 and 78% yield, respectively. However, the reaction failed when electron-withdrawing groups such as the *N*-Boc (**3n**) and *N*-Ts (**3r**) were used (Table 3).

Indoles substituted at 2 position such as 2-methyl and 2-phenyl indoles afforded the corresponding products (**3o,p**) in 88 and 67% yield, respectively. We have also observed that all indoles used as starting materials, including 2-phenylindole with high melting point, were melted in our reaction conditions.

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Table 3. Synthesis of 3-Selanylindoles

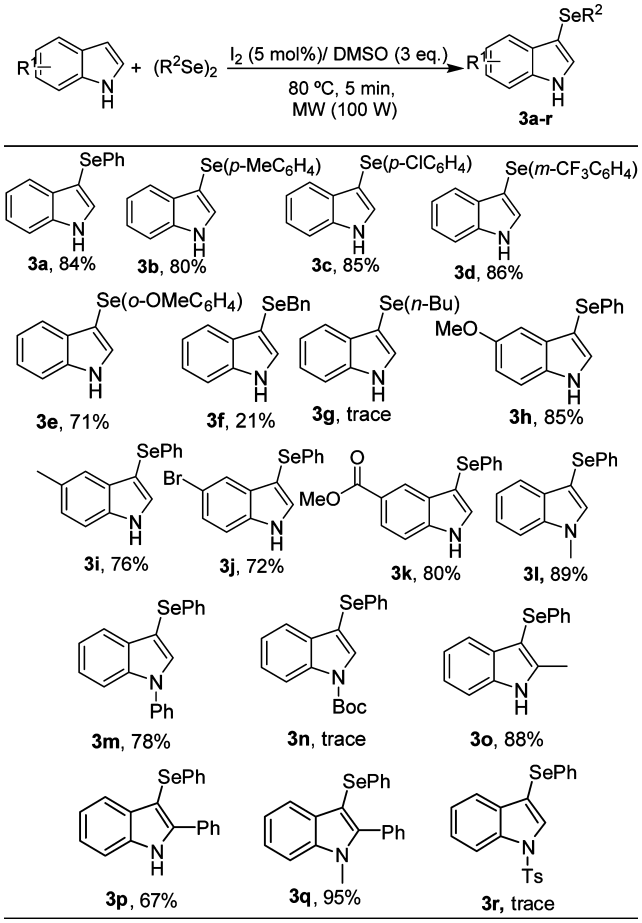
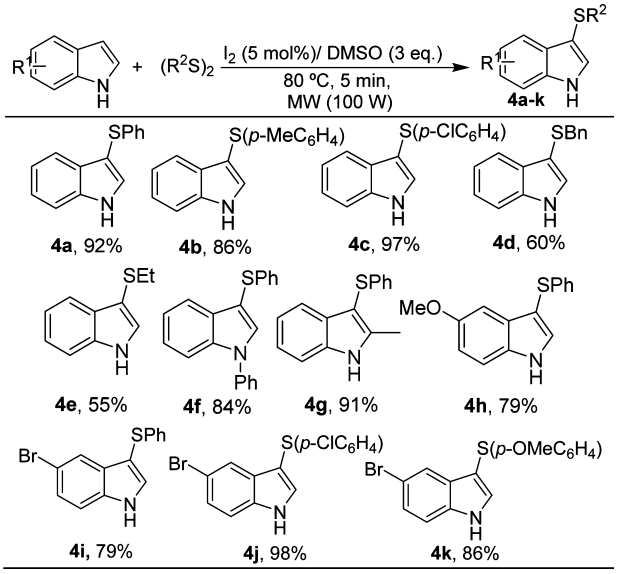
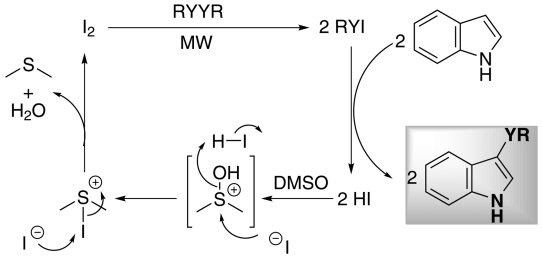


Table 4. Synthesis of 3-Sulfenyl Indoles



Scheme 2. Proposed Reaction Mechanism



Furthermore, the reaction also tolerated a 1,2-disubstituted indole, furnishing the respective product **3q** in very high yield.

The scope of the reaction regarding the preparation of 3-sulfenyl-indoles was explored next. Using diphenyl disulfide as the substrate, the sulfenyl indole **4a** was obtained in 92% yield. Likewise, the use of di-*para*-methyl disulfide afforded **4b** in 86% yield. Notably, the presence of chloro- at the *para* position of the disulfide was beneficial for the reaction, furnishing 97% of the desired product. Moreover, the reaction also worked well with dialkyl disulfides, affording the corresponding products in reasonable yields.

Subsequently, some substituted indoles were reacted with diphenyl disulfide in order to obtain different 3-sulfenyl-indoles. At the same way, high yields were obtained with both 1- and 2-substituted indoles (Table 4, compounds **4f** and **4g**).

In addition, substituents attached at the 5-position did not significantly affect the reaction, furnishing the desired products in good to excellent yields. For example, reaction of 5-bromoindole with di-*p*-chlorophenyl and di-*p*-methoxyphenyl disulfides afforded **4j** and **4k** in 98 and 86% yields, respectively.

On the basis of literature reports,[28,21] a plausible reaction pathway for the synthesis of the sulfenyl/selenyl derivatives is described in Scheme 2. Probably, an electrophilic species of the form RYI (Y = S, Se) is generated when the diorganyl dichalcogenide RYYR is submitted to reaction with I_2. In turn, the reactive RYI intermediate would react with the indole at the 3-position, affording the desired 3-chalcogenyl-indole, with concomitant formation of HI.

The reaction of 2 equiv of HI with DMSO would then regenerate iodine, through the intermediacy of the protonated sulfur species, including iododimethylsulfonium iodide (iodine-dimethyl sulfide adduct),[29] simultaneously releasing water and dimethyl sulfide.

In summary, a rapid, economic, and highly efficient methodology for the preparation of 3-selenyl- and 3-sulfenyl-indoles, a class of compounds of interest for therapeutic applications, has been developed. The new approach afforded the desired products in good to excellent yields in only 5 min, under solvent- and metal-free conditions. Thus, the chemistry described herein represents a feasible eco-friendly synthetic alternative for accessing 3-chalcogenyl indoles.

EXPERIMENTAL SECTION

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 400 and 200 MHz or at 100 and 50 MHz, respectively. Chemical shifts (δ) are reported (ppm) relative to the TMS (^{1}H NMR) and the solvent (^{13}C NMR). APPI-Q-TOFMS measurements were performed with a mass spectrometer equipped with an automatic syringe pump for sample injection. Infrared spectra were recorded on a commercial Fourier transformer spectrometer. The indoles were obtained from commercial sources and used without further purification. All reactions were performed in 10 mL sealed glasses tubes in a commercially available microwave monomode CEM reactor with IR monitoring and a noninvasive pressure transducer. The yields are based on isolated compounds after purification.

General Procedure for Solvent-Free Iodine-Catalyzed 3-Chalcogenylation of Indoles. A mixture of indole (0.5 mmol), dichalcogenide (0.25 mmol), iodine (5 mol %), and DMSO (3 equiv) were added in a glass tube, which was sealed and placed in a CEM

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Discover microwave apparatus. A maximum irradiation power of 100 W and a temperature of 80 °C were applied for 5 min. When the reaction was finished, it was dissolved in EtOAc (20 mL) and washed with 15 mL of an aqueous solution of 10% $Na_2S_2O_4$, and the crude product was purified by column chromatography over silica gel using a mixture of hexane/EtOAc as the eluent.

*3-(Phenylselenyl)-1H-indole (**3a**).* 0.1142g, Yield: 84%; white solid; mp 134−137 °C (lit.[20] 135.4−137.0 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.34 (br s, 1H), 7.63 (d, J = 7.9, 1H), 7.43−7.38 (m, 2H), 7.25−7.20 (m, 4H), 7.15−7.08 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.4, 133.8, 131.2, 129.9, 128.9, 128.6, 125.6, 122.9, 120.8, 120.4, 111.3, 98.1.

*3-(p-Tolylselenyl)-1H-indole (**3b**).* 0.144g, Yield: 80%; white solid; mp 104−106 °C (lit.[20] 104−106); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.34 (br s, 1H), 7.71−6.98 (m, 9H), 2.28 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 136.5, 135.4, 131.0, 129.9, 129.8; 129.7, 129.0, 122.8, 120.7, 120.2, 111.3, 98.4, 20.8.

*3-(4-Chlorophenylselenyl)-1H-indole (**3c**).* 0.1300g, Yield: 85%; white solid; mp 117.0−120.0 °C (lit.[20] 116−120); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.38 (br s, 1H), 7.58 (d, J = 7.7 Hz, 1H), 7,43−7.38 (m, 2H), 7.29−7.03 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 136.4, 133.4, 132.0, 131.6, 131., 130.0, 129.0, 123.1, 121.0, 120.2, 111.4, 97.9.

*3-((3-(Trifluoromethyl)phenyl)selenyl)-1H-indole (**3d**).* 0.1462g, Yield: 86%; yellow solid; mp 75.8−77.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.33 (br s, 1H), 7.59 (d, J = 8.21, 1H), 7.53 (s, 1H), 7.39−7.36 (m, 2H), 7.31−7.23 (m, 3H), 7.19−7.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) = 136.3, 135.2, 131.7, 131.5, 131.1 (q, J = 32 Hz), 129.5, 129.1, 124.5 (q, J = 4.4 Hz), 123.8 (q, J = 272.0 Hz), 123.1, 122.3 (q, J = 4.4 Hz), 121.0, 120.0, 111.5, 97.1; HRMS (APPI+) m/z calculated for $C_{15}H_{10}F_3NSe$ $[M]^+$ 340.9926, found 340.9930.

*3-((2-Methoxyphenyl)selenyl)-1H-indole (**3e**).* 0.1071g, Yield: 71%; black solid; mp 117.5−118.3 °C; ^{1}H NMR (400 MHz, $CDCl_3$) = 8.43 (br s, 1 H), 7.60 (d, J = 8.21, 1H), 7;40−7.38 (m, 2H), 7.26−7.22 (m, 1H), 7.17−7.13 (m, 1H), 7.08−7.04 (m, 1H), 6.79 (d, J = 8.21, 1H), 6−66−6.58 (m, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) = 155.9, 136.5, 131.9, 130.1, 128.0, 126.2, 123.1, 122.8, 121.5, 120.7, 120.3, 111.4, 109.9, 95.7, 55.8; IR (film) 3446, 3010, 1587, 1490, 1320, 1036, 752; HRMS (APPI+) m/z calculated for $C_{15}H_{14}NOSe$ $[M + H]^+$ 304.0236, found 304.0234.

*3-(Benzylselenyl)-1H-indole (**3f**).* 0.0300g, Yield: 21%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.09 (br s, 1H), 7.58 (d, J =, 8.31 Hz, 1 H), 7.27−7.05 (m, 8H), 6.95−6.88 (m, 1H), 3.76 (s, 2H); ^{13}C NMR ($CDCl_3$, 50 MHz, $CDCl_3$) δ = 138.6, 136.1, 130.6, 130.1, 128.7, 128.1, 126.4, 122.5, 120.4, 120.1, 111.2, 98.8, 32.1; HRMS (APPI+) m/z calculated for $C_{15}H_{14}NSe$ $[M + H]^+$ 288.0286, found 288.0288.

*5-Methoxy-3-(phenylselenyl)-1H-indole (**3h**).* 0.1282g, Yield: 85%; yellow viscous liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.31 (br s, 1H), 7.34 (d, J = 2.34 Hz, 1H), 7.25−7.20 (m, 3H), 7.13−7.06 (m, 4H), 6.89 (dd, J^1 = 2.74 Hz, J^2 = 6.25 Hz, 1H), 3.76 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ = 155.0, 133.8, 131.9, 131.3, 130.7, 128.9, 128.4, 125.5, 113.3, 112.2, 101.5, 97.4, 55.7; IR (film) 3450, 300, 1598, 1580, 1505, 1310, 1043, 516 cm^{-1}; HRMS (APPI+) m/z calculated for $C_{15}H_{13}NOSe$ $[M]^+$ 303.0157, found 303.0159.

*5-Methyl-3-(phenylselenyl)-1H-indole (**3i**).* 0.1085g, Yield: 76%; black solid; mp =132.7−133.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.16 (br s, 1H), 7.41−7.42 (m, 1H), 7.32 (d, J = 2.34 Hz, 1H), 7.25−7.18 (m, 3H), 7.12−7.04 (m, 4H), 2.40 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 134.6, 134.0, 131.4, 130.3, 130.2, 128.9, 128.4, 125.5, 124.7, 119.8, 111.0, 97.2, 21.4; IR (film) 3442, 3100, 1570, 772, 521 cm^{-1}; HRMS (APPI+) m/z calculated for $C_{15}H_{13}NSe$ $[M]^+$ 287.0208, found 287.0216.

*5-Bromo-3-(phenylselenyl)-1H-indole (**3j**).* 0.1263g, Yield: 72%; white solid; mp 107−110 °C (lit.[20] 108.1−109.4 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.39 (br s, 1H), 7.75 (s, 1H), 7.39 (d, J = 2.2 Hz, 1H), 7.33−7.09 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 135.0, 133.3, 132.4, 131.8, 129.0, 128.7, 125.9, 125.8, 122.9, 114.3, 112.8, 97.8.

*Methyl 3-(phenylselenyl)-1H-indole-5-carboxylate (**3k**).* 0.132g, Yield: 80%; white solid; mp 164.6−165.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.71 (br s, 1H), 8.40 (m, 1H), 7.98 (d, J = 8.60 Hz, 1H), 7.55 (d, J = 2.34 Hz, 1H), 7.46 (*d*, J = 8.60 Hz, 1H), 7.26−7.22 (m, 3H), 7.16−7.10 (m, 2H), 3.90 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz, $CDCl_3$) δ = 167.8, 139.00, 133.4, 132.6, 129.7, 129.0, 128.8, 125.8, 124.4, 123.2, 123.1, 111.2, 100.0, 51.9; HRMS (APPI+) m/z calculated for $C_{16}H_{14}NO_2Se$ $[M + H]^+$ 332.0185, found 332.0186.

*1-Methyl-3-(phenylselenyl)-1H-indole (**3l**).* 0.1272g, Yield: 89%; white solid; mp 65−68 °C (lit.[20] 67 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.69 (d, J= 7.03, 1H), 7.42−7.13 (m, 8H), 3.85 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ =137.6, 135.8, 134.3; 130.5, 129.0, 128.7, 125.6, 122.5; 120.5, 109.7, 96.0, 33.1.

*1-Phenyl-3-(phenylselenyl)-1H-indole (**3m**).* 0.1355g, Yield: 78%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.69−7.65 (m, 1H), 7.59−7.49 (m, 6H), 7.42−7.26 (m, 4H), 7.23−7.08 (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 138.8, 136.5, 134.3, 133.4, 131.1, 129.6, 128.9, 128.8, 126.9, 125.6, 124.23, 123.1, 121.2, 120.7, 110.7, 99.17; HRMS (APPI+) m/z calculated for $C_{20}H_{15}NSe$ $[M]^+$ 349.0365, found 349.0372.

*2-Methyl-3-(phenylselenyl)-1H-indole (**3o**).* 0.1258g, Yield: 88%; white solid; mp 97−98 °C (lit.[20] 98 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.22 (br s, 1H), 7.54 (d, J = 7.6 Hz, 1H), 7.33−7.06 (m, 8H), 2.51 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 140.8, 135.7, 133.9, 131.1, 128.9, 128.2, 125.3, 122.0, 120.5, 119.7, 110.4, 96.74; 13.1.

*2-Phenyl-3-(phenylselenyl)-1H-indole (**3p**).*[17a] 0.1166g, Yield: 67%; yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.57 (br s, 1H), 7.67−7.63 (m, 3H), 7.38−7.30 (m, 3H), 7.24−7.02 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 142.0, 136.0, 134.0, 131.9, 131.8, 129.00, 128.5, 128.4, 128.1, 125.3, 123.1, 121.0, 120.7, 111.02, 95.5.

*1-Methyl-2-phenyl-3-(phenylselenyl)-1H-indole (**3q**).* 0.1719g, Yield: 95%; yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 7.55 (d, J = 7.82 Hz, 1H), 7.31−7.15 (m, 7H), 7.08−6.89 (m, 6H), 3.53 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 145.7, 137.6, 134.5, 131.1, 130.7, 130.5, 128.8, 128.6, 128.2, 128.0, 125.1, 122.6, 120.8, 120.5, 109.7, 96.2, 31.6; HRMS (APPI+) m/z calculated for $C_{21}H_{17}NSe$ $[M]^+$ 363.0522, found 363.0520.

*3-(Phenylsulfenyl)-1H-indole (**4a**).* 0.1035g, Yield: 92%; white solid; mp 150−151 °C (lit.[20] 150.1−151.0 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.38 (br s, 1H), 7.61 (d, J = 8.3 Hz, 1H), 7.48−7.41 (m, 2H), 7.30−7.19 (m, 2H), 7.15−7.05 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$) δ = 134.2, 131.7, 126.3, 124.9, 124.5, 121.9, 120.9, 119.3, 117.3, 116.2, 108.8, 100.7.

*3-(p-Tolylsulfenyl)-1H-indole (**4b**).* 0.1027g, Yield: 86%; yellow solid; mp 123.9−125.8 °C; (lit.[21] 125−126 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.17 (br s, 1H), 7.60 (d, J = 7.82 Hz, 1H), 7.33−7.31 (m, 2H), 7.23−7.19 (m, 1H), 7.14−7.11 (m, 1H), 6.97 (dd, J^1 = 21.49, J^2 = 8.21, 4H), 2.21 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.3, 135.4, 134.6, 130.5, 129.4, 128.9, 126.1, 122.8, 120.7, 119.5, 111.6, 103.0, 20.8.

*3-((4-Chlorophenyl)sulfenyl)-1H-indole (**4c**).* 0.1259g, Yield: 97%; yellow solid; mp 134−135 °C; (lit.[21] 127.5−128.3 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.36 (br s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.28−7.24 (m, 1H), 7.18−7.14 (m, 1H), 7.10 (d, J = 8.4 Hz, 2H), 7.01 (d, J = 8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.6, 135.0, 131.8, 130.9, 128.8, 126.1, 125.8, 125.0, 122.2, 114.9, 113.0, 102.6.

*3-(Benzylsulfenyl)-1H-indole (**4d**).* 0.0717g, Yield: 60%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.00 (br s, 1H), 7.63 (d, J = 8.21, 1H), 7.27−6.88 (m, 9H), 3.77 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 138.9, 136.1, 129.8, 129.10, 128.9, 128.1, 126.7, 122.5, 120.4, 119.2, 111.4, 104.9, 40.9; HRMS (APPI+) m/z calculated for $C_{15}H_{14}NS$ $[M + H]^+$ 240.0841, found 240.0846.

*3-(Ethylsulfenyl)-1H-indole (**4e**).* 0.0487g, Yield: 55%; yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.19 (br s, 1H), 7.78 (d, J = 8.21 Hz, 1H), 7.30−7.17 (m, 4H), 2.79 (q, J = 7.42 Hz, 2H), 1.17 (t, J = 7.42 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 136.1, 129.5, 129.3, 122.5, 120.2, 119.2, 111.4, 105.2, 30.2, 15.1; IR (film) 3420, 2275, 1496, 790 cm $^{-1}$; HRMS (APPI+) m/z calculated for $C_{10}H_{12}NS$ $[M + H]^+$ 178.0685, found 178.0684.

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*1-Phenyl-3-(phenylsulfenyl)-1H-indole (**4f**).* 0.1264g, Yield: 84%; yellow oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 7.66−7.62 (m, 1H), 7.53−7.43 (m, 6H), 7.35−7.00 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz, $CDCl_3$) 139.0, 138.9, 136.8, 133.7, 130.3, 129.7, 128.7, 127.1, 126.2, 124.9, 124.4, 123.3, 121.3, 120.0, 110.9, 104.2; HRMS (APPI+) m/z calculated for $C_{20}H_{16}NS$ $[M + H]^+$ 302.0998, found 302.0996.

*2-Methyl-3-(phenylsulfenyl)-1H-indole (**4g**).* 0.1087g, Yield: 91%; white solid; mp 109−111 °C (lit.[20] 110.9−111.2 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.20 (br s, 1H), 7.53 (d, J = 7.4 Hz, 1 H), 7.31 (d, J = 7.3 Hz, 1H), 7.22−7.00 (m, 7H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 141.1, 139.2, 135.3, 130.2, 128.6, 125.3, 124.4, 122.1, 120.6, 118.9, 110.6, 99.1, 12.1.

*5-Methoxy-3-(phenylsulfenyl)-1H-indole (**4h**).*[21] 0.1007g, Yield: 79%; yellow viscous oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (br s, 1H), d (7.41, J = 2.74 Hz, 1H), 7.30−7.28 (m, 1H), 7.18−7.14 (m, 3H), 7.10−7.03 (m, 4H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ = 155.0, 139.3, 131.3, 129.9, 128.7, 125.6, 124.7, 113.5, 112.4, 104.9, 102.0, 100.7, 54.7.

*5-Bromo-3-(phenylsulfenyl)-1H-indole (**4i**).* 0.1200g, Yield: 79%; white solid; mp 120−122 °C (lit.[20] 120.9−123.1 °C); ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.42 (br s, 1H), 7.74 (s, 1H), 7.47−7.03 (m, 8H), ^{13}C ($CDCl_3$, 50 MHz) δ = 138.6, 135.0, 131.8, 130.9, 128.7, 126.1, 125.8, 125.0, 122.1, 114.4, 113.0, 102.6.

*5-Bromo-3-((4-chlorophenyl)sulfenyl)-1H-indole (**4j**).*[14a] 0.1657g, Yield: 98%; white solid; mp 143−144; ^{1}H NMR (200 MHz, $CDCl_3$) δ = 8.41 (br s, 1H), 7.63 (s, 1H), 7.43−6.88 (m, 7H), ^{13}C NMR ($CDCl_3$, 50 MHz) δ = 137.2, 135.1, 131.9, 130.8, 130.6, 128.9, 127.1, 126.2, 122.0, 114.6, 113.1, 102.3.

*5-Bromo-3-((4-methoxyphenyl)sulfenyl)-1H-indole (**4k**).*[14a] 0.1436g, Yield: 86%; white solid; mp 99−100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ = 8.40 (br s, 1H), 7.75 (s, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.34−7.24 (m, 2H), 7.13−7.08 (m, 2H), 6.76−6.72 (m, 2H), 3.73 (s, 3H). NMR ($CDCl_3$, 100 MHz) δ = 157.8, 135.0, 131.1, 130.8, 128.9, 128.6, 125.9, 122.1, 114.5, 114.2, 113.0, 104.5, 55.3.

■ ASSOCIATED CONTENT

Supporting Information

All synthesized compounds were characterized by ^{1}H NMR and ^{13}C NMR; unknown compounds were also characterized by infrared and high resolution mass spectra. This material is available free of charge via the Internet at http://pubs.acs.org/.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Sundberg, R. J. *Indoles*; Academic Press: New York, 1997. (b) Joule, J. A. *Indole and its Derivatives in Science of Synthesis: Howben−Weyl Methods of Molecular Transformations*; Thomas, E. J., Ed.; George Thieme: Stuttgart, 2001; Vol. *10*, Chapter 10.13. (c) Saxton, J. E. In *The Alkaloids*; Cordell, G. A., Ed.; Academic Press: New York, 1998. (d) Bandini, M.; Eichholzer, A. *Angew. Chem, Int. Ed.* **2009**, *48*, 9608−9644.

(2) (a) La Regina, G.; Gatti, V.; Famiglini, V.; Piscitelli, F.; Silvestri, R. *ACS Comb. Sci.* **2012**, *14*, 258−262. (b) Zhou, N.; Zeller, W.; Krohn, M.; Anderson, H.; Zhang, J.; Onua, E.; Kiselyov, A. S.; Ramirez, J.; Halldorsdottir, G.; Andrésson, P.; Gurney, M. E.; Singh, J. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 123−126.

(3) La Regina, G.; Bai, R.; Rensen, W. M.; Di Cesare, E.; Coluccia, A.; Piscitelli, F.; Famiglini, V.; Regio, A.; Nalli, M.; Pelliccia, S.; Da Pozzo, E.; Costa, B.; Granata, I.; Porta, A.; Maresca, B.; Soriani, A.; Iannitto, M. L.; Santoni, A.; Li, J.; Cona, M. M.; Chen, F.; Ni, Y.; Brancale, A.; Dondio, G.; Vultaggio, S.; Varasi, M.; Mercurio, C.; Martini, C.; Hamel, E.; Lavia, P.; Novellino, E.; Silvestri, R. *J. Med. Chem.* **2013**, *56*, 123−149.

(4) Cianchi, F.; Cortesini, C.; Magnelli, L.; Fanti, E.; Papucci, L.; Schiavone, N.; Messerini, L.; Vannacci, A.; Capaccioli, S.; Perna, F.; Lulli, M.; Fabbroni, V.; Perigli, G.; Bechi, P.; Masini, E. *Mol. Cancer Ther.* **2006**, *5*, 2716−2726.

(5) Nuth, M.; Guan, H.; Zhukovskaya, N.; Saw, Y. L.; Ricciardi, R. P. *J. Med. Chem.* **2013**, *56*, 3235−3246.

(6) (a) Nogueira, C. W.; Zeni, G.; Rocha, J. B. T. *Chem. Rev.* **2004**, *104*, 6255−6285. (b) Alberto, E. E.; Nascimento, V.; Braga, A. L. *J. Braz. Chem. Soc.* **2010**, *21*, 2032−2041. (c) Nogueira, C. W.; Rocha, J. B. T. *J. Braz. Chem. Soc.* **2010**, *21*, 2055−2071.

(7) (a) Nascimento, V.; Alberto, E. E.; Tondo, D. W.; Dambrowski, D.; Detty, M. R.; Nome, F.; Braga, A. L. *J. Am. Chem. Soc.* **2012**, *134*, 138−141. (b) Sarma, B. K.; Mugesh, G. *J. Am. Chem. Soc.* **2005**, *127*, 11477−11485. (c) Roy, G.; Nethaji, M.; Mugesh, G. *J. Am. Chem. Soc.* **2004**, *126*, 2712−2713.

(8) (a) Back, T. G. *Organoselenium Chemistry—A Practical Approach*; Oxford University Press: Oxford, U.K., 1999. (b) Guo, Y. J.; Tang, R. Y.; Li, J. H.; Zhong, P.; Zhang, X. G. *Adv. Synth. Catal.* **2009**, *351*, 2615−2618. (c) Sanz, R.; Guilarte, V.; Castroviejo, M. P. *Synlett* **2008**, 3006−3010. (d) Barraja, P.; Diana, P.; Carbone, A.; Cirrincione, G. *Tetrahedron* **2008**, *64*, 11625−11631. Baig, N. B. R.; Chandrakala, R. N.; Sudhir, V. S.; Chandrasekaran, S. *J. Org. Chem.* **2010**, *75*, 2910−2921.

(9) (a) Yadav, J. S.; Subba Reddy, B. V.; Jayasudhan Reddy, Y. *Tetrahedron Lett.* **2007**, *48*, 7034−7037. (b) Yadav, J. S.; Subba Reddy, B. V.; Reddy, Y. J.; Praneeth, K. *Synthesis* **2009**, 1520−1524.

(10) (a) Li, Z.; Hong, J. Q.; Zhou, X. J. *Tetrahedron* **2011**, *67*, 3690−3697. (b) Ge, W.; Wei, Y. *Synthesis* **2012**, *44*, 934−940.

(11) Maeda, Y.; Koyabu, M.; Nishimuraand, T.; Uemura, S. *J. Org. Chem.* **2004**, *69*, 7688−7693.

(12) Tudge, M.; Tamiya, M.; Savarin, C.; Humphrey, G. R. *Org. Lett.* **2006**, *8*, 565−568.

(13) Matsugi, M.; Murata, K.; Gotanda, K.; Nambu, H.; Anilkumar, G.; Matsumoto, K.; Kita, Y. *J. Org. Chem.* **2001**, *66*, 2434−2441.

(14) (a) Silveira, C. C.; Mendes, S. R.; Wolf, L.; Martins, G. M. *Tetrahedron Lett.* **2010**, *51*, 2014−2016. (b) Zhao, X.; Yu, Z.; Xu, T.; Wu, P.; Yu, H. Y. *Org. Lett.* **2007**, *9*, 5263−5266. (c) Marcantoni, E.; Cipolletti, R.; Marsili, L.; Menichetti, S.; Properzi, R.; Viglianisi, C. *Eur. J. Org. Chem.* **2013**, 132−140.

(15) Yang, F. L.; Tian, S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 4929−4932.

(16) Wu, Q.; Zhao, D.; Qin, X.; Lan, J.; You, J. *Chem. Commun.* **2011**, *47*, 9188−9190.

(17) (a) Chen, Y.; Cho, C.; Shi, F.; Larock, R. C. *J. Org. Chem.* **2009**, *74*, 6802−6811. (b) Chen, Y.; C. Cho, C.; Larock, R. C. *Org. Lett.* **2009**, *11*, 173−176. (c) Li, Z.; Hong, L.; Liu, R.; Shen, J.; Zhou, X. *Tetrahedron Lett.* **2011**, *52*, 1343−1347. (d) Perança, A.; Godoi, B.; Menezes, P. H.; Zeni, G. *Synlett* **2013**, *24*, 1125−1132.

(18) Liu, J.; Li, P.; Chen, W.; Wang, L. *Chem. Commun.* **2012**, *48*, 10052−10054.

(19) Zimmermann, E.; Thurow, S.; Freitas, C.; Mendes, S. R.; Perin, G.; Alves, D.; Jacob, R.; Lenardão, E. J. *Molecules* **2013**, *18*, 4081−4090.

(20) Silveira, C. C.; Mendes, S. R.; Wolf, L.; Martins, G. M.; von Mühlen, L. *Tetrahedron* **2012**, *68*, 10464−10469.

(21) Ge, Y.; Wei, Y. *Green Chem.* **2012**, *14*, 2066−2070.

(22) Xiao, F.; Xie, H.; Liu, S.; Deng, G. J. *Adv. Synth. Catal.* **2014**, *356*, 364−368. This work was published during the evaluation process of this manuscript.

(23) (a) Ju, Y.; Kumar, D.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 6697−6700. (b) Wu, Q.; Zhao, D.; Qin, X.; Lan, J.; You, J. *Chem. Commun.* **2011**, *47*, 9188−9190. (c) Görmer, K.; Waldmann, H.; Triola, G. *J. Org. Chem.* **2010**, *75*, 1811−1813. (d) Botteselle, G. V.; Godoi, M.; Galetto, F. Z.; Bettanin, L.; Singh, D.; Rodrigues, O. E. D.; Braga, A. L. *J. Mol. Catal. A* **2012**, *365*, 186−193. (e) Azeredo, J. B.; Godoi, M.; Schwab, R. S.; Botteselle, G. V.; Braga, A. L. *Eur. J. Org. Chem.* **2013**, 5188−5194.

(24) (a) Herrero, M. A.; Kremsner, J. M.; Kappe, C. O. *J. Org. Chem.* **2008**, *73*, 36−47. (b) Strauss, C. R.; Rooney, D. W. *Green Chem.* **2010**, *12*, 1340−1345. (c) Najeebullah, M.; Knight, D. W.; Munawar, M. A.; Yaseenx, A.; Vincenzo, F. *Tetrahedron* **2010**, *66*, 6761−6764. (d) Barros, M. T.; Petrova, K. T.; Correia-da-Silva, P.; Potewar, T. M. *Green Chem.* **2011**, *13*, 1897−1906. (e) Nadagouda, M. N.; Speth, T. F.; Varma, R. S. *Acc. Chem. Res.* **2011**, *44*, 469−478. (f) Braga, A. L.; Paixão, M. W.; Westermann, B.; Schneider, P. H.; Wessjohann, L. A. *J. Org. Chem.* **2008**, *73*, 2879−2882. (g) Dallinger, D.; Kappe, C. O. *Chem. Rev.* **2007**, *107*, 2563−2591. (h) Obermayer, D.; Gutmann, B.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2009**, *48*, 8321−8324. (i) Lidström, P.; Tierney, J.; Wathey, B.; Westman, J. *Tetrahedron* **2001**, *57*, 9225−9283. (j) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250−6284.

(25) (a) Varma, R. S. *Green Chem.* **1999**, *1*, 43−55. (b) Tanaka, K.; Toda, F. *Chem. Rev.* **2000**, *100*, 1025−1074.

(26) (a) Godoi, M.; Ricardo, E. W.; Botteselle, G. V.; Galetto, F. Z.; Azeredo, J. B.; Braga, A. L. *Green Chem.* **2012**, *14*, 456−460. (b) Perin, G.; Jacob, R. G.; Dutra, L. G.; Azambuja, F.; Santos, G. F. F.; Lenardão, E. J. *Tetrahedron Lett.* **2006**, *47*, 935−938. (c) Perin, G.; Mendes, S. R.; Silva, M. S.; Lenardão, E. J.; Jacob, R. G.; Santos, P. C. *Synth. Commun.* **2006**, *36*, 2587−2595.

(27) Ananikov, V. P.; Gayduk, K. A.; Beletskaya, I. P.; Khrustalev, V. N.; Antipin, M. Y. *Chem.—Eur. J.* **2008**, *14*, 2420−2434.

(28) Hiller, F. W.; Krueger, J. H. *Inorg. Chem.* **1967**, *6*, 528−533.

(29) (a) Tamres, M.; Bhat, S. N. *J. Am. Chem. Soc.* **1972**, *94*, 2577−2578. (b) Lo, S. J.; Tamres, M. *Can. J. Chem.* **1983**, *61*, 1933−1940.