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Efficient synthesis of 3-selanyl- and 3-sulfanylindoles employing trichloroisocyanuric acid and dichalcogenides

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ABSTRACT

3-Arylselanyl- and 3-arylsulfanylindoles were prepared in EtOAc, by the reaction of indole with the diaryl dichalcogenide–trichloroisocyanuric acid (TCCA) reagent system. The products were efficiently and conveniently obtained, at room temperature and in short reaction times.

1. Introduction

Substituted indoles constitute a permanent focus of scientific interest because the indole ring is an important structural unit found in numerous biologically active natural products and pharmaceutical agents[1] and several indole derivatives are known to have therapeutic value.[2]

Some 3-arylthioindoles were shown to act on specific targets, which in recent years have attracted the attention of researchers.[3] For example, compound **1**, is a powerful inhibitor of tubulin polymerization,[4] which inhibits the growth of certain breast cancer cells.[5] On the other hand, compound **2** (MK-886) is an inhibitor of 5-lipoxygenase, which may increase the antitumor activity of celecoxib in human colorectal cancer.[6]

Analogously, organoselenium compounds are bioactive[7] and potentially useful as valuable synthetic intermediates.[8] However, there is a lack of general methods for the preparation of 3-chalcogenylindoles, suitable for the use of indoles as starting material[8b,9] (Fig. 1).

Trichloroisocyanuric acid (TCCA) is a stable and inexpensive solid, frequently found in commercial products for swimming-pool disinfection,[10] which has been widely used in organic synthesis. Recent examples of its application include oxidation[11] and halogenation[12] reactions as well as key steps during total synthesis sequences.[13]

In view of our interest in the development of new methods for the synthesis of organochalcogenium compounds,[14] and considering our recent results on the synthesis of sulfenyl indoles,[15] we decided to explore the synthesis of 3-chalcogenylindoles (**5a**–**n**) by the electrophilic substitution reaction of indoles (**3a**–**d**) with the diaryl dichalcogenide–TCCA reagent system (Scheme 1).

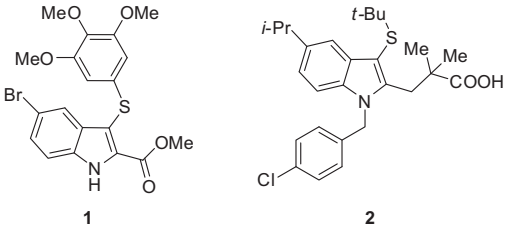
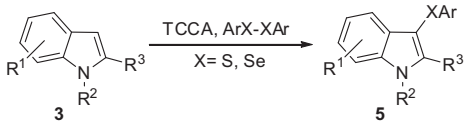


Fig. 1. Some bioactive 3-arylthioindoles.



Scheme 1.

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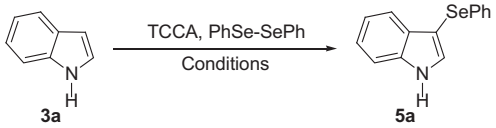
2. Results and discussion

Initially, indole (**3a**) and diphenyl diselenide (**4a**, 1.2 equiv) were chosen as starting materials to establish the optimum reaction conditions, and the effects of the solvent, amount of TCCA, and reaction temperature on the efficiency of the transformation were evaluated (Table 1). MeOH, DCE, EtOAc, and H_2O were tested as potential solvents (entries 1–4), finding that a reasonable yield of **5a** (45%) was obtained in EtOAc, after stirring the reagents with 3.0 equiv TCCA at room temperature for 15 min (entry 4).

Table 1
Optimization of the synthesis of **5a** from indole (**3a**)[a]



Entry no.	Solvent	TCCA (equiv)	MgO (equiv)	Temp (°C)	Time (min)	Yield[b] (%)
1	MeOH	3.0	—	rt	15	10
2	DCE	3.0	—	rt	15	18
3	H_2O	3.0	—	rt	15	—
4	EtOAc	3.0	—	rt	15	45
5	EtOAc	1.2	—	rt	15	56
6	EtOAc	6.0	—	rt	15	32
7	EtOAc	1.2	—	0	15	21
8	EtOAc	1.2	—	60	15	49
9	EtOAc	1.2	0.5	rt	4	63
10	EtOAc	1.2	1.0	rt	5	81
11	EtOAc	1.2	2.0	rt	4	80

[a] The reaction was performed with indole (**3a**, 1.0 mmol) and diphenyl diselenide (**4a**, 0.6 mmol); 1 mol of TCCA is capable of forming 3 mol of ArXCl.
[b] Isolated yield.

In view of the convenience of use of this low toxicity solvent, EtOAc was employed as solvent when the effect of the amount of TCCA in the reaction was evaluated. Under these conditions, it was observed that 1.2 equiv TCCA afforded 56% yield of **5a** (entry 5), while use of larger amounts of this reagent did not improve the yields. Interestingly, however, it was observed that excess of TCCA led to the formation of 3-chloro-1*H*-indole, being this side reaction responsible for the decrease in the yields of the expected chalcogen derivative product (entry 6).

The reaction was also performed at different temperatures, observing that at 60 °C the yields were similar to those obtained at room temperature, while carrying out the transformation at 0 °C resulted in a significant decrease in product yield, even after long reaction times (entry 7).

In general, it was detected that the products were formed in a few minutes after mixing the reagents, and then no further modification was observed, even after a long reaction time or by adding an excess of TCCA or diaryl dichalcogenide.

In search of improved conditions, MgO (1.0 equiv) was tested as an additive, taking into account that metal-oxides have been described as convenient and practical bases that form strong metal–nitrogen bonds and thereby increase the nucleophilicity of the annular carbon centers of the heteroarene.[16] Under these new conditions, 81% of **5a** was obtained (entry 10); however, its yields could not be improved by the use of larger amounts of MgO (entry 11).

Once the optimum reaction conditions were established, the protocol was extended to other indoles (**3a**–**d**) and diaryl dicalchogenides (**4a**–**d**). These afforded 3-chalcogenylindoles in good yields after stirring at room temperature for 3–40 min (Table 2). Interestingly, 5-bromo-1*H*-indole (**3b**) furnished slightly diminished yields of the corresponding indole derivatives (entries 4–6), while *N*-methyl-1*H*-indole (**3c**) comparatively outperformed its congeners (entries 7–9). The beneficial effect of MgO can be observed even for the *N*-methylindole **3c**. In the absence of MgO the yield of compound **5g** was reduced to 55%.

In view of the characteristics of the new method, which uses the odorless diselenides and TCCA as a highly convenient reagent system for the generation of electrophilic arylselenide species, the method was extended to the corresponding sulfur derivatives, employing the same procedure. Luckily, the transformation exhibited similar behavior, since the 3-sulfenylindoles **5j**–**l** were obtained in 72–85% isolated yield (entries 10–12), in very fast reactions.

The transformation also accepted 2-substituted indoles as substrates. The sulfenylation of 2-methylindole, under the established conditions, furnished almost instantaneously the 3-sulfur derivative **5n** in 90% isolated yield, at room temperature. The corresponding reaction with diphenyl diselenide followed a more complex pathway, since a mixture of 3-selanyl-2-methylindole (minor) and 3-chloro-2-methylindole (major) was obtained at room temperature. However, at −78 °C clean formation of the 3-selanyl derivative **5m** was observed (71% isolated yield) after 40 min.

Noteworthy, this widened the scope of the TCCA-based alternative because indole nitrogen protection is not required for accessing the product and there is no significant difference in product yields when comparing those resulting from protected and unprotect indoles (Table 2).

GC–MS monitoring of the reaction revealed the quick formation of PhSeCl and PhSCl, which were consumed during the reaction. Therefore, it can be assumed that this is the actual active electrophilic species in the reaction.

The transformation seems to be general, since reacting indoles and TCCA (0.4 mmol; 1.2 equiv) in EtOAc, gave the corresponding 3-chloroindoles in unoptimized 47% yield. This compound is unstable and usually generated and used in situ.[17] Under the same conditions, 5-bromoindole furnished the corresponding 3-chloroindole in 92% isolated yield. This procedure can be an alternative for the preparation of 3-chloroindoles, which usually employs corrosive and less convenient sources of chlorine, such as Cl_2 and SO_2Cl_2.[17,18]

The use of excess diaryl disulfides was also tested, resulting in the known formation of 2,3-disubstituted disulfenyl indoles such as **5o** (Scheme 2). Employing diphenyl sulfide (1.0 equiv) and TCCA (0.8 equiv) in EtOAc, in the presence of MgO (1.0 equiv), 56% of **5o** was obtained after 5 h. TLC and GC–MS monitoring of the transformation confirmed the formation of 3-(phenylthio)-1*H*-indole (**5j**) as an intermediate. Therefore, **5j** was employed as substrate under similar conditions, affording an improved 90% yield of **5o** after 4.5 h. Unfortunately, however, under the same conditions, a similar reaction with the corresponding selenium derivative was unsuccessful.

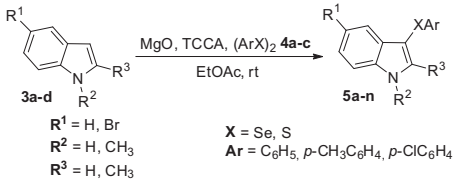
The mechanism of the C-3 substitution and the bis sulfenylation at C-2 and C-3 was studied in detail and seems to be following the mechanism shown in Scheme 2.[19] The C-3 position of the indole nucleus is very nucleophilic, allowing a nucleophilic substitution to take place in the presence of the chalcogenyl halide, to form the corresponding 3-arylchalcogenyl indole (Scheme 2).

In the case of sulfur derivatives, and in the presence of excess arylsulfenyl chloride, this is followed by a second sulfenylation at the 3-position, which leads to a 3,3-substituted indolinium intermediate. Subsequent migration of an arenesulfenyl moiety to the C-2 position, yields the 2,3-bis(phenylthio)-1*H*-indole product. Removal of the HCl formed during the reaction seems to be the key role of MgO, the presence of which leads to greatly improved yields.

3. Conclusion

In conclusion, we have developed a convenient method for the preparation of 3-selenyl- and 3-sulfenylindoles from the

Table 2
Synthesis of 3-chalcogenylindoles **5**



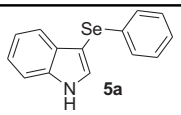
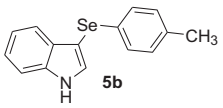
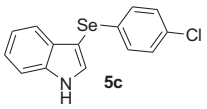
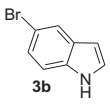
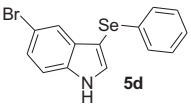
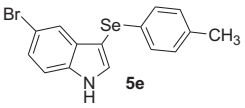
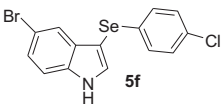
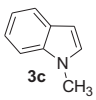
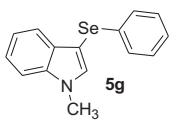
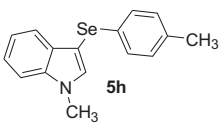
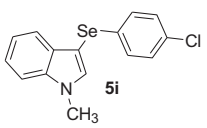
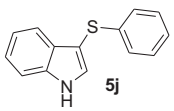
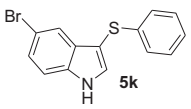
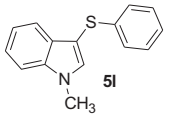
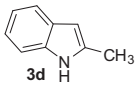
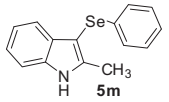
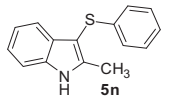
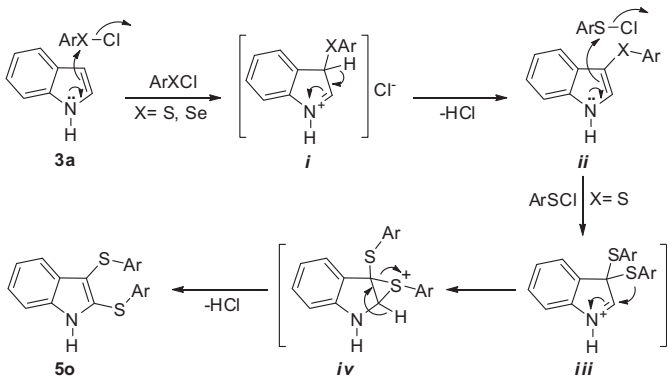
Entry no.	Indole (**3**)	X, Ar	Product (**5**)	Time (min)	Yield[a] (%)
1	 **3a**	Se, C_6H_5 **4a**	 **5a**	5	81
2	**3a**	Se, *p*-$C_6H_4CH_3$ **4b**	 **5b**	3	81
3	**3a**	Se, *p*-C_6H_4Cl **4c**	 **5c**	7	74
4	 **3b**	**4a**	 **5d**	5	80
5	**3b**	**4b**	 **5e**	10	77
6	**3b**	**4c**	 **5f**	9	69
7	 **3c**	**4a**	 **5g**	7	84
8	**3c**	**4b**	 **5h**	12	82
9	**3c**	**4c**	 **5i**	17	79
10	**3a**	S, C_6H_5 **4d**	 **5j**	5	75
11	**3b**	**4d**	 **5k**	5	72

Table 2 (*continued*)

Entry no.	Indole (**3**)	X, Ar	Product (**5**)	Time (min)	Yield[a] (%)
12	**3c**	**4d**	 **5l**	5	85
13	 **3d**	**4a**	 **5m**	40	71[b]
14	**3d**	**4d**	 **5n**	4	90

[a] Yields of pure products isolated by column chromatography (hexanes/EtOAc) and identified by GC–MS, ^{1}H and ^{13}C NMR.
[b] Reaction performed at −78 °C.



Scheme 2.

corresponding indoles and diaryl dichalcogenides by means of a TCCA mediated reaction in the presence of MgO. No additional Lewis acid is necessary. The method is simple, fast, general, and highly convenient, providing an easy access to a wide range of potentially valuable 3-chalcogenylindoles in a few minutes at room temperature.

4. Experimental section

4.1. General

Solvents were purified and dried according to usual techniques before use.[20] All reagents were used as obtained from commercial sources. The ^{1}H (400 and 200 MHz) and ^{13}C (100 and 50 MHz) NMR spectra were recorded on Bruker DPX 400 and DPX 200 instruments, using $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in parts per million downfield from internal tetramethylsilane or $CHCl_3$, and J values are given in hertz. Infrared spectra were recorded on a Shimadzu IRPrestige-21 spectrometer. Melting point (mp) determinations were performed by using an MQAPF-301 instrument and are informed uncorrected. The mass spectra were obtained in a Shimadzu GCMS-QP2010 Plus gas chromatograph coupled to a mass detector. The molecular ion and its fragments are described as the relations between their atomic mass and corresponding charge (m/z), together with their percent relative abundance (%). The reactions were monitored by thin layer chromatography (TLC) carried out on Whatman-AL SIL G/UV plates. Column chromatography was carried out using Merck silica gel 60 (230–400 mesh).

4.2. General synthesis procedure

TCCA (0.4 mmol, 1.2 equiv) was added to a solution of the diaryl dichalcogenide (0.6 mmol) in EtOAc (5 mL), and the solution was stirred at room temperature until colorless. Then, a mixture of indole (1.0 mmol) and MgO (1.0 mmol) in EtOAc was added and the reaction mixture was stirred at room temperature for the specified time. Then, a saturated solution of NH_4Cl (20 mL) and EtOAc (3–10 mL) were added and the organic phase was separated and successively washed with water (20 mL) and brine (20 mL). The extract was dried over anhydrous $MgSO_4$, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexanes/EtOAc 95:5) to afford the pure products (**5a**–**o**).

*4.2.1. 3-(Phenylselanyl)-1H-indole (**5a**).* White solid; mp 134–137 °C (lit.[9c] 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=136.37, 133.77, 131.18, 129.94, 128.92, 128.66, 125.58, 122.91, 120.83, 120.34, 111.34, 98.16; MS (EI): m/z 273 (M^+, 19), 193 (100), 116 (6), 77 (9).

*4.2.2. 3-(p-Tolylselanyl)-1H-indole (**5b**).* White solid; mp 104–106 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.17 (s, 1H), 7.62 (d, J=7.6, 1H), 7.32–7.12 (m, 7H), 6.90 (d, J=7.6, 1H), 2.19 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=136.48, 135.55, 133.35, 130.82, 130.45, 129.74, 129.37, 122.83, 120.76, 120.40, 111.29, 98.99, 20.80; MS (EI): m/z 287 (M^+, 16), 207 (100), 192 (3), 178 (4), 165 (4), 116 (6), 89 (17), 77 (5).

*4.2.3. 3-(4-Chlorophenylselanyl)-1H-indole (**5c**).* White solid; mp 116–120 °C; ^{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=136.58, 132.09, 131.80, 130.27, 129.87, 129.03, 123.15, 121.07, 120.30, 111.41, 98.42; MS (EI): m/z 309 [M^{+2}] (7), 307 (M^+, 15), 227 (100), 191 (6), 116 (8), 77 (6).

*4.2.4. 5-Bromo-3-(phenylselanyl)-1H-indole (**5d**).* White solid; mp 107–110 °C (lit.[9c] 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, 1H), 7.33–7.09 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=134.99, 133.29, 132.37, 131.82, 129.04,

128.69, 125.90, 125.82, 122.88, 114.32, 112.85, 97.83; MS (EI): *m*/*z* 351 (M^+, 44), 271 (100), 196 (5), 115 (13), 77 (14).

*4.2.5. 5-Bromo-3-(p-tolylselanyl)-1H-indole (**5e**).* White solid; mp 119–123 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.41 (br s, 1H), 7.76 (s, 1H), 7.41 (d, *J*=2.3, 1H), 7.30–7.12 (m, 4H), 6.95 (d, *J*=8.0, 2H) 2.36 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=135.78, 134.99, 132.11, 131.84, 129.85, 129.28, 129.16, 125.84, 122.94, 114.26, 112.80, 98.40, 20.89; HRMS calcd for $C_{15}H_{12}BrNSe$ 364.9318, found 364.9321.

*4.2.6. 5-Bromo-3-(4-chlorophenylselanyl)-1H-indole (**5f**).* White solid; mp 118–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ=8.48 (br s, 1H), 7.72 (d, *J*=1.7, 1H), 7.42 (d, *J*=2.5, 1H), 7.33–7.25 (m, 2H), 7.12–7.06 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ=135.00, 132.40, 131.80, 131.55, 131.54, 129.99, 129.07, 126.04, 122.70, 114.44, 114.44, 112.94; MS (EI): *m*/*z* 386 [$(M+1)^+$, 33], 385 (M^+, 35), 307 (100), 271 (5), 196 (4), 192 (5), 116 (4), 75 (15).

*4.2.7. 1-Methyl-3-(phenylselanyl)-1H-indole (**5g**).* White solid; mp 65–68 °C (lit.[9b] 67 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.62 (d, *J*=7.8, 1H), 7.35–7.06 (m, 9H), 3.80–3.73 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=137.62, 135.46, 134.20, 130.83, 129.34, 128.86, 125.55, 122.44, 120.52, 120.41, 109.45, 96.44, 32.95; MS (EI): *m*/*z* 287 (M^+, 20), 207 (100), 130 (13), 77 (7).

*4.2.8. 1-Methyl-3-(p-tolylselanyl)-1H-indole (**5h**).* White solid; mp 123–125 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.62 (d, *J*=7.9, 1H), 7.36–6.87 (m, 8H), 3.80 (s, 3H), 2.23 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=137.59, 135.41, 135.23, 130.84, 130.23, 129.68, 129.31, 122.37, 120.56, 120.33, 109.40, 96.98, 32.84, 20.81; HRMS calcd for $C_{16}H_{15}NSe$ 301.0370, found 301.0364.

*4.2.9. 3-(4-Chlorophenylselanyl)-1-methyl-1H-indole (**5i**).* White solid; mp 110–114 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.58 (d, *J*=7.7, 1H), 7.38–7.03 (m, 8H), 3.82 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=137.48, 135.58, 132.46, 131.45, 130.41, 129.85, 128.92, 122.55, 120.54, 120.26, 109.60, 91.73, 33.04; MS (EI): *m*/*z* 323 (M^+, 9), 321 (3), 241 (100), 191 (2), 130 (15), 77 (6).

*4.2.10. 3-(Phenylthio)-1H-indole (**5j**).* White solid; mp 150–151 °C (lit.[9c] 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; MS (EI): *m*/*z* 225 (M^+, 100), 193 (21), 148 (12), 121 (11), 77 (19).

*4.2.11. 5-Bromo-3-(phenylthio)-1H-indole (**5k**).* White solid; mp 120–122 °C (lit.[9c] 120.9–123.1 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.42 (br s, 1H), 7.74 (t, *J*=1.8, 1H), 7.47 (d, *J*=2.5, 1H), 7.33–7.03 (m, 7H); MS (EI): *m*/*z* 305 [M+2] (16), 303 (23), 302 (100), 223 (99) 120 (20), 77 (12).

*4.2.12. 1-Methyl-3-(phenylthio)-1H-indole (**5l**).* White solid; mp 85–87 °C (lit.[18] 84.9–87.2 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ=7.59 (s, 1H), 7.35–7.20 (m, 3H), 7.17–7.03 (m, 6H), 3.74 (s, 3H), ^{13}C NMR (50 MHz, $CDCl_3$): δ=134.6, 132.6, 130.3, 125.5, 124.4, 121.7, 120.7, 118.8, 116.9, 116.2, 107.0, 98.4, 36.4; MS (EI): *m*/*z* 239 (M^+, 100), 223 (19), 162 (11), 119 (11), 77 (17).

*4.2.13. 2-Methyl-3-(phenylselanyl)-1H-indole (**5m**).* White solid; mp 97–98 °C (lit.[9a] 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, 13.1.

*4.2.14. 2-Methyl-3-(phenylthio)-1H-indole (**5n**).* White solid; mp 109–111 °C (lit.[9c] 110.9–111.2 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.20 (br s, 1H), 7.53 (d, *J*=7.4 Hz, 1H), 7.31 (d, *J*=7.3 Hz, 1H), 7.22–7.00 (m, 7H), 2.47 (s, 3H); ^{13}C NMR (50 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.

*4.2.15. 2,3-Bis(phenylthio)-1H-indole (**5o**).* White solid, mp 97–99 °C (lit.[21] 97–99 °C); ^{1}H NMR (200 MHz, $CDCl_3$): δ=8.26 (br s, 1H), 7.57 (d, *J*=7.9, 1H), 7.28–7.17 (m, 7H), 7.11–7.08 (m, 5H), 7.06–7.0 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=138.0, 136.9, 134.3, 133.6, 130.0, 129.8, 129.3, 128.6, 127.2, 126.7, 125.1, 123.8, 121.2, 119.9, 111.0, 109.4; MS (EI): *m*/*z* 333 (M^+, 54), 224 (100), 152 (4), 121 (9), 77 (12).

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