HETEROCYCLES, Vol. 81, No. 2, 2010, pp. 433 - 439. © The Japan Institute of Heterocyclic Chemistry
Received, 2nd November, 2009 Accepted, 22nd December, Published online, 25th December, 2009
DOI: 10.3987/COM-09-11867

SYNTHESIS OF 1-(1-ARYLSULFANYLALKYL)INDOLES AND 2,2-BIS[1-(1-ARYLSULFANYLALKYL)INDOL-3-YL]PROPANES BY ACID-CATALYZED REACTIONS OF INDOLES WITH ARYL VINYL SULFIDES

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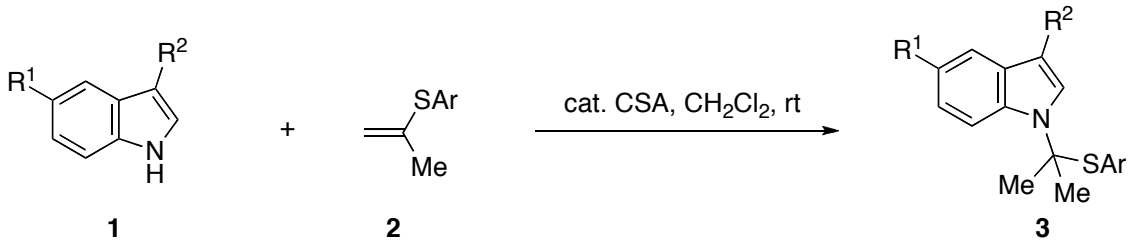
Abstract – We report a facile synthesis of 1-(1-arylsulfanylalkyl)indoles and 2,2-bis[1-(1-arylsulfanylalkyl)indol-3-yl]propanes under mild conditions. Thus, treatment of 3-substituted indoles with aryl vinyl sulfides in dichloromethane at room temperature in the presence of a catalytic amount of (±)-camphor-10-sulfonic acid yields the former indole derivatives in moderate to fair yields. 3-Nonsubstituted indoles can be transformed into the latter indole derivatives in satisfactory yields on treatment with excess aryl vinyl sulfides in the presence of a catalytic amount of the acid under similar conditions.

Indoles are undoubtedly important heterocycles not only in medicinal chemistry but also in synthetic organic chemistry. Recently, we described syntheses of 1-(1-alkoxyalkyl)indoles and 2,2-bis[1-(1-alkoxyalkyl)indol-3-yl]propanes by acid catalyzed reactions of indoles with vinyl ethers.[1] On continuation of this work, we became interested in investigating reactions of indoles with aryl vinyl sulfides under acidic conditions, which would give 1-(1-arylsulfanylalkyl)indoles and 2,2-bis[1-(1-arylsulfanylalkyl)indol-3-yl]propanes, because there have been no reports on the synthesis of these types of indole derivatives and they may be of biological importance. We found that the reactivity of aryl vinyl sulfides to indoles is analogous to that of vinyl ethers and that the expected above indole derivatives could be obtained from 3-substituted indoles and 3-nonsubstituted indoles, respectively. Herein, we report the results of our work, which provide facile synthetic routes to these indole derivatives under mild conditions.

The preparation of 1-(1-arylsulfanylalkyl)indoles (**3**) from 3-substituted indoles (**1**) and aryl isopropenyl sulfides (**2**) was accomplished under the conditions shown in Scheme 1. 3-Methylindole (**1a**) was commercially available. 3-Ethylindole (**1b**) and 5-methoxy-3-methylindole (**1c**) were prepared by Ito-Saegusa indole synthesis.[2] The three aryl isopropenyl sulfides (**2**) were prepared by reacting the respective aryl isopropyl sulfoxides with a magnesium amide generated from ethylmagnesium bromide and diisopropylamine under the conditions developed by us.[3] 3-Substituted indoles (**1**) were allowed to react with two molar amounts of aryl isopropenyl sulfides (**2**) in dichloromethane containing 0.05 molar amount of (±)-camphor-10-sulfonic acid (CSA) in the presence of Molecular Sieves 3A at room temperature. The reactions proceeded smoothly as expected to afford the desired 1-(1-arylsulfanylalkyl)indoles (**3**) in the yields ranging from 55 to 69%. In all cases the presence of Molecular Sieves was essential for satisfactory production of the desired products; the reactions in the absence of Molecular Sieves resulted in the formation of only traces of the products. This may be attributable to inhibition of the reaction by contaminated water in the reaction mixtures. Aryl isopropenyl sulfides (**2**) seem to be labile to water under the present acidic conditions; they were transformed into 1-arylsulfanylpropan-2-ones before reaction with indoles. Although we have no explanation for the mechanism of this transformation at the present stage, the participation of water in it is evident.



1 **2** **3**

Scheme 1

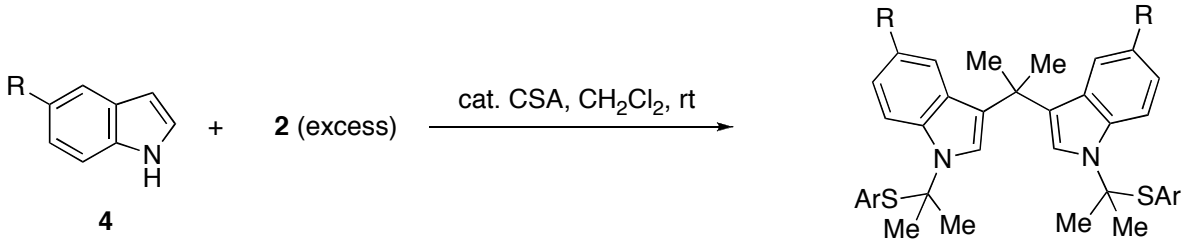
Table 1. Preparation of 1-(1-Arylsulfanylalkyl)indoles (**3**)

Entry	**1**	**2**	**3** (Yield/%)[a]
1	**1a** (R^1 = H, R^2 = Me)	**2a** (Ar = Ph)	**3a** (56)
2	**1a**	**2b** (Ar = *p*-Tol)	**3b** (64)
3	**1a**	**2c** (Ar = 4-$MeOC_6H_5$)	**3c** (69)
4	**1b** (R^1 = H, R^2 = Et)	**2b**	**3d** (64)
5	**1c** (R^1 = OMe, R^2 = Me)	**2a**	**3e** (55)

[a]Isolated yields.

2,2-Bis[1-(1-arylsulfanylalkyl)indol-3-yl]propanes (**5a**) and (**5b**) were obtained by the reaction of indole (**4**; R = H) with four molar amounts of isopropenyl 4-methylphenyl sulfide (**2b**) or isopropenyl

4-methoxyphenyl sulfide (**2c**) in the presence of 0.15 molar amount of (±)-camphor-10-sulfonic acid under conditions similar to those described above for the preparation of **3** in moderate yields, as shown in Scheme 2. Similar treatment of 5-bromoindole (**4**; R = Br) with **2c** also led to the facile formation of the corresponding desired bis(indolyl)propane derivative (**5c**) in moderate yield. However, it was surprising to find that the reaction of indole (**4**; R = H) with isopropenyl phenyl sulfide (**2a**) under the same reaction conditions resulted in an almost quantitative recovery of the starting materials. Probably, indole is not reactive enough toward this sulfide in the present reaction. Elevating the reaction temperature to reflux resulted in the formation of an intractable mixture of products. The bis(indolyl)propane structure of these products was confirmed by FAB-mass spectroscopic analyses as well as ^{1}H and ^{13}C NMR spectra. The use of 0.1 molar amount of the acid gave rather lower yields of the desired products. In each case the absence of Molecular Sieves gave a disappointing result as mentioned above for the preparation of **3.**



5a R = H, Ar = *p*-Tol 41%
5b R = H, Ar = 4-$MeOC_6H_5$ 53%
5c R = Br, Ar = 4-$MeOC_6H_5$ 48%

Scheme 2

In conclusion, we have discovered that acid catalyzed reactions of indoles with aryl isopropenyl sulfides, which provide efficient synthetic routes to 1-(1-arylsulfanylalkyl)indoles and 2,2-bis[1-(1-arylsulfanylalkyl)indol-3-yl]propanes. These methods may find value in preparing these indole derivatives, because the starting materials are readily available and operations are very simples.

EXPERIMENTAL

All melting points were obtained on a Laboratory Devices MEL-TEMP II melting apparatus and are uncorrected. IR spectra were determined with a Shimadzu FTIR-8300 spectrophotometer. The ^{1}H NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 500 MHz or a JEOL LA400 FT NMR spectrometer operating at 400 MHz. The ^{13}C NMR spectra were determined in $CDCl_3$ using TMS as an internal reference with a JEOL ECP500 FT NMR spectrometer operating at 125 MHz or a JEOL LA400 FT NMR spectrometer operating at 100 MHz. Low-resolution MS spectra (EI, 70 eV or FAB) and a high-resolution MS

spectrum (EI, 70 eV) were measured by a JEOL JMS AX505 HA spectrometer. TLC was carried out on a Merck Kieselgel 60 PF_{254}. Column chromatography was performed using Merck Kieselgel 60 (0.063–0.200 mm). All of the organic solvents used in this study were dried over appropriate drying agents and distilled prior to use.

Starting Materials. Vinyl sulfides **2a** and **2b** were prepared according to the procedure reported previously by us.[3] All other chemicals used in this study were commercially available.

1-Ethyl-2-isocyano-5-methoxybenzene. This compound was prepared by treating 1-isocyano-2-lithiomethyl-4-methoxybenzene with iodomethane according to the procedure reported by Ito *et al*.[2] in 63% yield; a pale-yellow liquid; bp 88 °C (bath temp)/1.1 mmHg; IR (neat) 2120, 1607 cm^{-1}; ^1H NMR (500 MHz) δ 1.27 (3H, t, *J* = 7.3 Hz), 2.76 (2H, q, *J* = 7.3 Hz), 3.82 (3H, s), 6.71 (1H, dd, *J* = 8.7, 2.8 Hz), 6.77 (1H, d, *J* = 2.8 Hz), 7.28 (1H, d, *J* = 8.7 Hz). HR-MS Calcd for $C_{10}H_{11}NO$: M, 161.0841. Found: *m*/*z* 161.0857.

5-Methoxy-3-methylindole. This compound was prepared by treating the above isocyanide with lithium 2,2,6,6-tetramethylpiperidide according to the procedure reported by Ito *et al*.[2] in 54% yield; mp 64–66 °C (hexane) (lit.,[4] mp 66 °C). The spectral (IR and ^1H NMR) data for this compound were identical to those reported previously.[5]

Isopropenyl 4-Methoxyphenyl Sulfide (2c).[6] This compound was prepared by treating isopropyl 4-methoxyphenyl sulfoxide,[7] prepared by a successive treatment of 4-methoxybenzenethiol with sodium hydride and 2-iodopropane and the subsequent $NaIO_4$ oxidation of the resulting isopropyl 4-methoxyphenyl sulfide,[8] with a magnesium amide, generated from *i*-Pr_2NH and EtMgBr, under conditions reported previously by us[1] in 66% yield; a pale-yellow oil; R_f 0.37 (1:5 CH_2Cl_2–hexane); IR (neat) 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.95 (3H, d, *J* = 1.5 Hz), 3.82 (3H, s), 4.63 (1H, s), 4.98 (1H, q, *J* = 1.5 Hz), 6.89 (2H, d, *J* = 8.7 Hz), 7.40 (2H, d, *J* = 8.7 Hz).

Typical Procedure for the Preparation of 1-(Arylsulfanylalkyl)indoles (3). 3-Methyl-1-[1-methyl-1-(phenylsulfanyl)ethyl]indole (3a). To a stirred solution of 3-methylindole (**1**) (0.13 g, 1.0 mmol) and isopropenyl phenyl sulfide (**2a**) (0.30 g, 2.0 mmol) in CH_2Cl_2 (3 mL) containing MS 3A (1.3 g) at rt was added (±)-camphor-10-sulfonic acid (11 mg, 0.050 mmol); the mixture was stirred for 2 h. After removal of molecular sieves by filtration, saturated aqueous $NaHCO_3$ (10 mL) and CH_2Cl_2 (7 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 twice (5 mL each). The combined extracts were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave a residue, which was purified by preparative TLC on silica gel to afford **3a** (0.16 g, 56%); a pale-yellow oil; R_f 0.67 (1:5 THF–hexane); IR (neat) 3051, 1611 cm^{-1}; ^1H NMR (500 MHz) δ 1.98 (6H, s), 2.22 (3H, s), 6.66 (1H, s), 6.77 (2H, d, *J* = 7.8 Hz), 7.07 (2H, dd, *J* = 7.8, 7.3 Hz), 7.18 (1H, dd, *J* = 7.8, 6.9 Hz), 7.21 (1H, t, *J* = 7.3 Hz), 7.27 (1H, dd, *J* = 7.8, 6.9 Hz), 7.58 (1H, d, *J* = 7.8 Hz), 8.07 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (125 MHz) δ 9.46, 30.15, 67.80, 109.68, 115.23, 118.90, 119.07, 121.00,

123.68, 128.34, 128.70, 130.67, 131.66, 135.40, 135.90; MS *m/z* 281 (M^+, 2.8), 172 (100). Anal. Calcd for $C_{18}H_{19}NS$: C, 76.82; H, 6.81; N, 4.98. Found: C, 76.71; H, 6.93; N, 4.93.

3-Methyl-1-[1-methyl-1-(4-methylphenylsulfanyl)ethyl]indole (3b): pale-yellow crystals; mp 81–84 °C (hexane); IR (KBr) 3051, 1611 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.97 (6H, s), 2.22 (3H, d, *J* = 1.1 Hz), 2.25 (3H, s), 6.66 (1H, s), 6.67 (2H, d, *J* = 8.4 Hz), 6.87 (2H, d, *J* = 8.4 Hz), 7.16 (1H, dd, *J* = 8.1, 7.0 Hz), 7.25 (1H, dd, *J* = 8.1, 7.0 Hz), 7.57 (1H, d, *J* = 8.1 Hz), 8.07 (1H, d, *J* = 8.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 9.47, 21.15, 30.06, 67.65, 109.55, 115.28, 118.86, 119.00, 120.93, 123.72, 128.12, 129.16, 130.65, 135.40, 135.90, 138.83; MS *m/z* 295 (M^+, 2.8), 172 (100). $C_{19}H_{21}NS$: C, 77.24; H, 7.16; N, 4.74. Found: C, 76.94; H, 7.40; N, 4.58.

1-[1-(4-Methoxylphenylsulfanyl)-1-methylethyl]-3-methylindole (3c): colorless crystals; mp 80–83 °C (hexane–CH_2Cl_2); IR (KBr) 3050, 1611 cm^{-1}; ^1H NMR (400 MHz) δ 1.96 (6H, s), 2.21 (3H, s), 3.72 (3H, s), 6.59 (2H, d, *J* = 9.3 Hz), 6.64 (1H, s), 6.69 (2H, d, *J* = 9.3 Hz), 7.17 (1H, ddd, *J* = 7.8, 7.3, 1.0 Hz), 7.26 (1H, ddd, *J* = 7.8, 7.3, 1.0 Hz), 7.57 (1H, d, *J* = 7.8 Hz), 8.06 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (100 MHz) δ 9.46, 29.91, 55.13, 67.67, 109.50, 113.86, 115.29, 118.84, 118.98, 120.92, 122.43, 123.75, 130.62, 135.40, 137.57, 160.23; MS *m/z* 311 (M^+, 3.0), 172 (100). $C_{19}H_{21}NOS$: C, 73.27; H, 6.80; N, 4.50. Found: C, 73.13; H, 6.87; N, 4.41.

3-Ethyl-1-[1-methyl-1-(4-methylphenylsulfanyl)ethyl]indole (3d): a yellow oil; R_f 0.46 (1:19 Et_2O–hexane); IR (neat) 3050, 1609 cm^{-1}; ^1H NMR (500 MHz) δ 1.21 (3H, t, *J* = 7.3 Hz), 1.98 (6H, s), 2.25 (3H, s), 2.67 (2H, q, *J* = 7.3 Hz), 6.62 (2H, d, *J* = 8.2 Hz), 6.63 (1H, s), 6.86 (2H, d, *J* = 8.2 Hz), 7.16 (1H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.26 (1H, ddd, *J* = 7.8, 7.3, 0.9 Hz), 7.61 (1H, d, *J* = 7.8 Hz), 8.06 (1H, d, *J* = 7.8 Hz); ^{13}C NMR (125 MHz) δ 14.78, 18.13, 21.16, 30.07, 67.74, 115.41, 116.60, 118.95, 118.97, 120.92, 122.75, 128.14, 129.12, 129.82, 135.54, 135.91, 138.82; MS *m/z* 309 (M^+, 3.3), 186 (100). $C_{20}H_{23}NS$: C, 77.62; H, 7.49; N, 4.53. Found: C, 77.71; H, 7.51; N, 4.30.

5-Methoxy-3-methyl-1-[1-methyl-1-(phenylsulfanyl)ethyl]indole (3e): colorless needles; mp 98–100 °C (hexane); IR (KBr) 3050, 1616 cm^{-1}; ^1H NMR (500 MHz) δ 1.96 (6H, s), 2.18 (3H, d, *J* = 0.9 Hz), 3.91 (3H, s), 6.63 (1H, s), 6.77 (2H, dd, *J* = 7.8, 1.4 Hz), 6.92 (1H, dd, *J* = 9.2, 1.8 Hz), 7.00 (1H, d, *J* = 1.8 Hz), 7.07 (2H, dd, *J* = 7.8, 7.3 Hz), 7.22 (1H, tt, *J* = 7.3, 1.4 Hz), 7.96 (1H, d, *J* = 9.2 Hz); ^{13}C NMR (125 MHz) δ 9.62, 30.23, 55.85, 67.86, 100.88, 109.31, 110.91, 116.01, 124.50, 128.43, 128.78, 130.71, 131.23, 131.79, 136.00, 153.78; MS *m/z* 311 (M^+, 2.9), 202 (100). $C_{19}H_{21}NOS$: C, 73.27; H, 6.80; N, 4.50. Found: C, 73.26; H, 6.76; N, 4.25.

Typical Procedure for the Preparation of 2,2-Bis[1-(1-arylsulfanylalkyl)indol-3-yl]propanes (5). 1-[1-Methyl-1-(4-methylphenylsulfanyl)ethyl]-3-(1-methyl-1-{[1-methyl-1-(4-methylphenylsulfanyl)ethyl]indol-3-yl}ethyl)indole (5a). To a stirred solution of indole (**4**; R = H) (0.12 g, 1.0 mmol) and isopropenyl *p*-tolyl sulfide (**2b**) (0.66 g, 4.0 mmol) in CH_2Cl_2 (3 mL) containing MS 3A (1.3 g) at rt was added (±)-camphor-10-sulfonic acid (33 mg, 0.15 mmol). After the mixture was stirred for 2

h, it was worked up and purified in a manner similar to that described for the preparation **3a** to afford **5a** (0.13 g, 41%); a white solid; mp 75–78 ˚C (pentane); IR (KBr) 3046, 1611 cm^{-1}; ^1H NMR (500 MHz) δ 1.69 (6H, s), 1.99 (12H, s), 2.31 (6H, s), 6.70 (4H, d, *J* = 8.2 Hz), 6.74 (2H, s), 6.89 (2H, dd, *J* = 7.8, 7.3 Hz), 6.94 (4H, d, *J* = 8.2 Hz), 7.16 (2H, dd, *J* = 8.2, 7.3 Hz), 7.24 (2H, d, *J* = 7.8 Hz), 8.09 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (125 MHz) δ 21.27, 30.14, 30.18, 34.65, 67.79, 115.39, 118.49, 120.37, 121.27, 122.58, 122.88, 128.24, 128.74, 129.27, 135.93, 136.20, 138.87; FAB-MS *m/z* 603.3 [$(M+1)^+$, 100]. Anal. $C_{39}H_{42}N_2S_2$: C, 77.69; H, 7.02; N, 4.65. Found: C, 77.61; H, 7.02; N, 4.69.

1-[1-(4-Methoxyphenylsulfanyl)-1-methylethyl]-3-(1-{[1-(4-methoxyphenylsulfanyl)-1-methylethyl]indol-3-yl}-1-methylethyl)indole (5b): a white solid; mp 84–87 ˚C (MeOH–Et_2O); IR (KBr) 3046, 1591 cm^{-1}; ^1H NMR (400 MHz) δ 1.54 (6H, s), 1.98 (12H, s), 3.76 (6H, s), 6.65 (4H, d, *J* = 8.8 Hz), 6.70 (2H, s), 6.73 (4H, d, *J* = 8.8 Hz), 6.89 (2H, ddd, *J* = 8.2, 7.3, 1.1 Hz), 7.15 (2H, ddd, *J* = 8.2, 7.3, 1.4 Hz), 7.23 (2H, d, *J* = 8.2 Hz), 8.07 (2H, d, *J* = 8.2 Hz); ^{13}C NMR (125 MHz) δ 30.02, 30.16, 34.65, 55.23, 67.78, 113.98, 115.39, 118.47, 120.37, 121.27, 122.51, 122.55, 122.80, 128.69, 136.18, 137.60, 160.31; FAB-MS *m/z* 635.3 [$(M+1)^+$, 100]. Anal. $C_{39}H_{42}N_2O_2S_2$: C, 73.78; H, 6.67; N, 4.41. Found: C, 73.50; H, 6.64; N, 4.32.

5-Bromo-1-[1-(4-methoxyphenylsulfanyl)-1-methylethyl]-3-(1-{5-bromo-1-[1-(4-methoxyphenylsulfanyl)-1-methylethyl]indol-3-yl}-1-methylethyl)indole (5c): a white solid; mp 149–151 ˚C (MeOH–Et_2O); IR (KBr) 3072, 1591 cm^{-1}; ^1H NMR (400 MHz) δ 1.62 (6H, s), 1.98 (12H, s), 3.73 (6H, s), 6.64 (4H, d, *J* = 8.8 Hz), 6.73 (4H, d, *J* = 8.8 Hz), 6.74 (2H, s), 7.20 (2H, dd, *J* = 8.8, 1.9 Hz), 7.31 (2H, d, *J* = 1.9 Hz), 7.94 (2H, d, *J* = 8.8 Hz); ^{13}C NMR (125 MHz) δ 30.07, 30.23, 34.40, 55.25, 67.89, 112.38, 114.08, 116.77, 122.17, 122.21, 123.29, 123.40, 123.67, 120.17, 134.92, 137.50, 160.42; FAB-MS *m/z* 791.1 [$(M+1)^+$, 100]. Anal. $C_{39}H_{40}Br_2N_2O_2S_2$: C, 59.09; H, 5.09; N, 3.53. Found: C, 58.87; H, 5.16; N, 3.37.

ACKNOWLEDGEMENTS

Determination of the mass spectra and performance of combustion analyses by Mrs. Miyuki Tanmatsu of this University are gratefully acknowledged.

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