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Efficient method for the synthesis of new [2-(alkylarylthio)ethyl]pyridines

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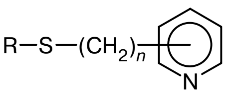
An efficient method for the synthesis of new [2-(alkylarylthio)ethyl]pyridines was developed. The method is based on one-step mono- and polyalkylchlorosulfonation of arenes with complex electrophilic reagents (RX—HSO_3Cl, RX = Bu^{t}Cl, and 1-AdBr).

Key words: [2-(alkylarylthio)ethyl]pyridines, pyridylethylation, one-step mono- and polyalkylchlorosulfonation, complex electrophilic reagents, alkylarenesulfonyl chlorides, aromatic thiols, 2- and 4-vinylpyridines.

Alkyl(aryl)thioalkylpyridines **1** exhibit a variety of biological activities; for example, they have been found to be effective radioprotecting substances,[1] acaricides, fungicides,[2] and antiinflammatory and immunoregulating agents.[3,4]



1

R = Alk, Ar
n = 1, 2

The above compounds are synthesized either by the reactions of the corresponding thiols with vinylpyridines[1,2] or picolyl halides[3] or by the reactions of picolinethiols with halogenated hydrocarbons.[4] The most promising method for preparing [2-(alkylarylthio)ethyl]pyridines (**1**, *n* = 2) is the pyridylethylation of thiols, which affords high yields and can easily be put into large-scale production. However, unlike industrially produced vinylpyridines, arenethiols, especially with one or several branched alkyl groups, are not easily available.

In the present paper, an efficient method for the synthesis of alkylarylthioethylpyridines (**1**, *n* = 2) is reported. The method is similar to that proposed by us for the preparation of alkylarenesulfonyl chlorides and thiols (Scheme 1).

Our method is based on one-step mono- or polyalkylchlorosulfonation of arenes with complex electrophilic RX—HSO_3Cl reagents (RX = Bu^{t}Cl and AdBr) and allows chemo- and regioselective introduction of one or several *tert*-alkyl groups and one chlorosulfonyl group into the starting arenes.[5,6] The resulting arenesulfonyl chlorides are reduced to the corresponding thiophenols by the known method.[7] The properties of compounds **2—4** are given in Experimental.

Exothermic reactions of arenethiols **2—4** with 2- and 4-vinylpyridines in equimolar amounts proceed in benzene or dioxane at 50—60 °C without a catalyst and are high-yielding.

This efficient method allows one to obtain various (alkylarylthio)ethylpyridines from available arenes almost in two steps. The structures of compounds **5—10** were confirmed by ^{1}H NMR and IR data and by elemental analysis.

Experimental

^{1}H NMR spectra were recorded on a Bruker WM-250 instrument. IR spectra were recorded on a Specord M-80 spectrometer (KBr pellets and thin films). The purity of the compounds was checked by TLC using Silufol plates in a light petroleum—ether system (1 : 1 and 3 : 1); spot visualization with I_2.

Arenethiol **2** was prepared as described in Ref. 8. The yield was 72.1%, m.p. 98—99 °C. ^{1}H NMR ($CDCl_3$), δ: 1.78 (br.s, 6 H, Ad); 1.89 (br.s, 6 H, Ad); 2.10 (br.s, 3 H, Ad); 3.38 (s, 1 H, SH); 7.25 (m, 4 H, Ar). Thiophenol **4** was synthesized according to the known procedure.[6] The yield was 13%, m.p. 68—69.5 °C. ^{1}H NMR ($CDCl_3$), δ: 1.30 (s, 9 H, Bu^t); 1.42 (s, 9 H, Bu^t); 2.86 (s, 1 H, SH); 6.62 (s, 1 H, OH); 7.31 (br.s, 1 H, Ar); 7.38 (br.s, 1 H, Ar)].

4-*tert*-Butyl-2,6-dimethylthiophenol (3). *tert*-Butyl chloride (16.3 mL, 0.15 mol) was added at −5 °C for 15 min to a mixture of $FeCl_3$ (7.30 g, 0.045 mol) and *m*-xylene (18.3 mL, 0.15 mol). The reaction mixture was kept at −5 °C for 15 min, then at 20 °C for 1 h, and cooled again to −5 °C. Sulfonyl chloride (30 mL, 0.45 mol) was added with stirring, and keeping was continued at −5 °C for 30 min and at 15 °C for 1 h. The resulting solution was poured into ice, and the organic material was extracted with ether. The organic layer was separated, washed with water, dried with Na_2SO_4, and concentrated *in vacuo* to give 4-*tert*-butyl-2,6-dimethylbenzenesulfonyl chloride (25.66 g). ^{1}H NMR ($CDCl_3$), δ: 1.35 (s, 9 H, Bu^t); 2.78 (s, 6 H, Me); 7.21 (s, 2 H, Ar). The product was not additionally purified, and conc. H_2SO_4 (41 mL) and ice (185 g) were added. A zinc powder (35.22 g, 0.539 mol) was added with stirring at 5 °C over 15 min. The reaction mixture was heated to 80 °C, kept at this temperature for 4.5 h, cooled, and poured into water. The organic material was extracted with benzene, washed

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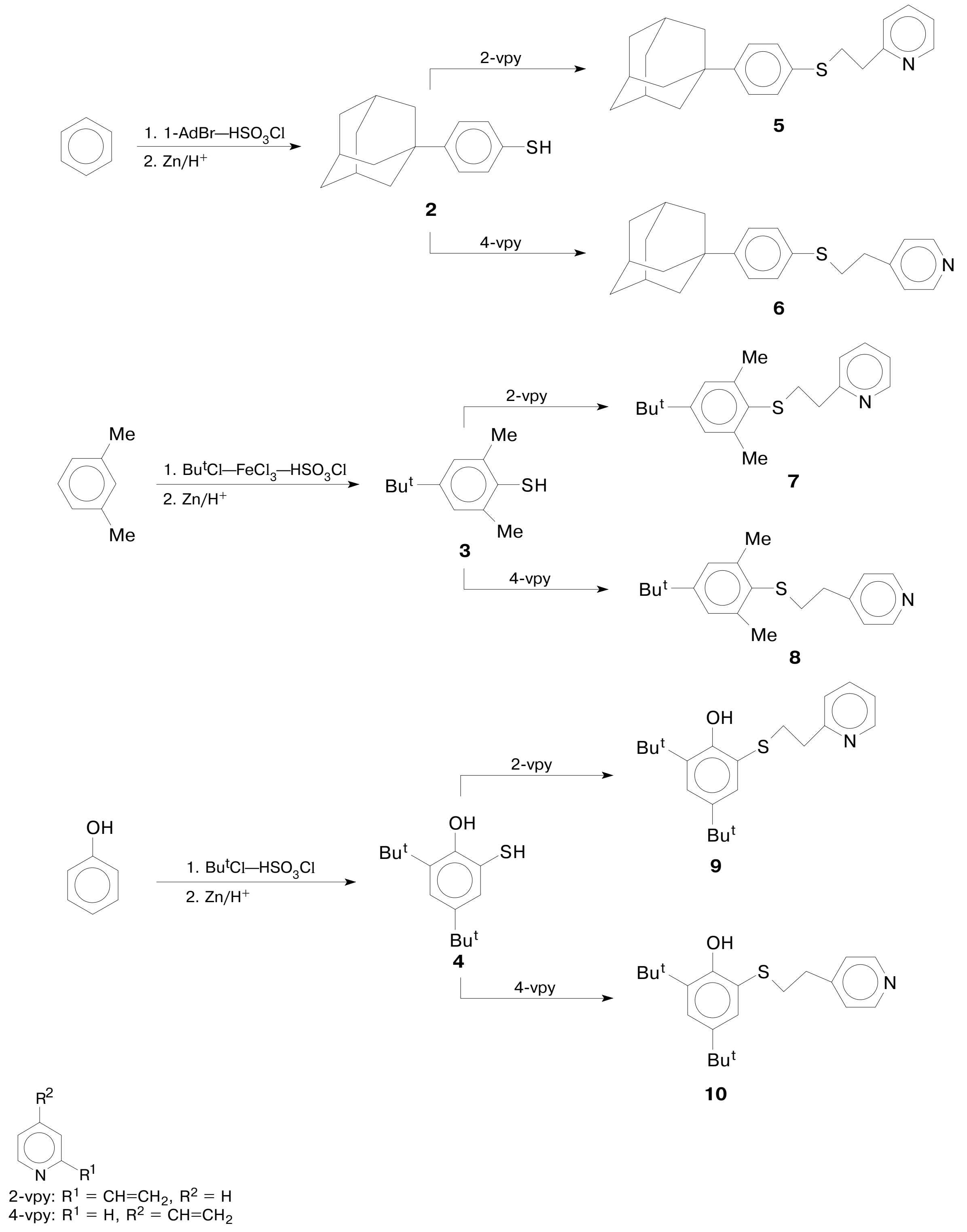
Scheme 1



with dilute hydrochloric acid and with water, dried with $CaCl_2$, and concentrated *in vacuo*. The resulting dark cherry liquid (15.74 g) was distilled to give thiol **3** (10.70 g, 36.7%), b.p. 75—80 °C (2 Torr), m.p. 43—44 °C (Ref. 9: b.p. 126 °C (10 Torr), m.p. 44—46 °C). Found (%): C, 74.34; H, 9.40; S, 16.47. $C_{12}H_{18}S$. Calculated (%): C, 74.16; H, 9.34; S, 16.50. IR (KBr), ν/cm^{-1}: 2952 (Me); 2864 (Me); 2562 (SH); 1448 (Ar); 1392 (Bu^t); 1376 (Me); 1232 (Bu^t). ^{1}H NMR ($CDCl_3$), δ: 1.31 (s, 9 H, Bu^t); 2.40 (s, 6 H, Me); 3.14 (s, 1 H, SH); 7.09 (s, 2 H, Ar).

2-{2-[4-(Adamant-1-yl)phenylthio]ethyl}pyridine (5). A solution of 4-(adamant-1-yl)thiophenol (2.88 g, 11.78 mmol) in 5 mL of benzene was added in one portion to 2-vinylpyridine (1.24 g, 11.78 mmol) in 0.5 mL of benzene. The reaction mixture was heated at 60 °C for 3 h, cooled, and concentrated *in vacuo*. The residue was purified by low-temperature recrystallization from ether—light petroleum (1 : 4) to give compound **5** (3.35 g, 81.3%), n_D^{20} 1.5979. IR (thin film), ν/cm^{-1}: 2906 (Ad); 2856 (CH_2); 1592 (Ar); 1568 (Py); 1474 (CH_2); 1450 (Ad); 1346 (Ad); 1098 (Ad). ^1H NMR ($CDCl_3$), δ: 1.78 (br.s, 6 H, Ad); 1.90 (br.s, 6 H, Ad); 2.10 (br.s, 3 H, Ad); 3.11 (t, 2 H, CH_2, ^3J = 16.0 Hz); 3.33 (t, 2 H, CH_2, ^3J = 16.0 Hz); 7.12—7.37 (6 H, Ar, Py); 7.60 (t, 1 H, Py, ^3J = 16.0 Hz); 8.53 (d, 1 H, Py, ^3J = 5.3 Hz). Found (%): C, 78.77; H, 7.75; S, 9.23; N, 3.94. $C_{23}H_{27}NS$. Calculated (%): C, 79.03; H, 7.79; S, 9.17; N, 4.01.

4-{2-[4-(Adamant-1-yl)phenylthio]ethyl}pyridine (6) was obtained by analogy with compound **5** from 4-vinylpyridine (1.39 g, 13.2 mmol) and 4-(adamant-1-yl)thiophenol (3.22 g, 13.2 mmol). The yield of sulfide **6** was 3.48 g (75.5%), m.p. 44—46 °C (from ether). IR (thin film), ν/cm^{-1}: 2902 (Ad); 2854 (CH_2); 1600 (Ar); 1562 (Py); 1472 (CH_2); 1448 (Ad); 1345 (Ad); 1102 (Ad). ^1H NMR ($CDCl_3$), δ: 1.78 (br.s, 6 H, Ad); 1.90 (br.s, 6 H, Ad); 2.10 (br.s, 3 H, Ad); 2.91 (t, 2 H, CH_2, ^3J = 17.3 Hz); 3.17 (t, 2 H, CH_2, ^3J = 17.3 Hz); 7.11 (d, 2 H, Py, ^3J = 6.5 Hz); 7.25—7.35 (4 H, Ar, Py); 8.51 (d, 2 H, Py, ^3J = 6.5 Hz). Found (%): C, 78.81; H, 7.79; S, 8.93; N, 3.81. $C_{23}H_{27}NS$. Calculated (%): C, 79.03; H, 7.79; S, 9.17; N, 4.01.

2-[2-(4-*tert*-Butyl-2,6-dimethylphenylthio)ethyl]pyridine (7) was obtained by analogy with compound **5** from 2-vinylpyridine (4.21 g, 40 mmol) and 4-*tert*-butyl-2,6-dimethylthiophenol (7.77 g, 40 mmol). The yield of sulfide **7** was 7.05 g (59%), m.p. 46—48 °C (from ether). IR (KBr), ν/cm^{-1}: 2956 (Me); 2862 (CH_2); 1592 (Ar); 1570 (Py); 1474 (CH_2); 1232 (Bu^t). ^1H NMR (DMSO-d_6), δ: 1.26 (s, 9 H, Bu^t); 2.45 (s, 6 H, Me); 2.90 (t, 2 H, CH_2, ^3J = 16.8 Hz); 3.02 (t, 2 H, CH_2, ^3J = 16.8 Hz); 7.13 (s, 2 H, Ar); 7.16—7.26 (2 H, Py); 7.68 (t, 1 H, Py, ^3J = 12.7 Hz); 8.45 (d, 1 H, Py, ^3J = 4.2 Hz). Found (%): C, 76.31; H, 8.45; S, 10.60; N, 4.71. $C_{19}H_{25}NS$. Calculated (%): C, 76.20; H, 8.41; S, 10.71; N, 4.68.

4-[2-(4-*tert*-Butyl-2,6-dimethylphenylthio)ethyl]pyridine (8) was obtained by analogy with compound **5** from 4-vinylpyridine (1.56 g, 14.9 mmol) and 4-*tert*-butyl-2,6-dimethylthiophenol (2.90 g, 14.9 mmol). The yield of sulfide **8** was 2.73 g (61.2%), m.p. 83—84 °C (from ether). IR (KBr), ν/cm^{-1}: 2956 (Me); 2862 (CH_2); 1602 (Ar); 1562 (Py); 1480 (CH_2); 1232 (Bu^t).^1H NMR ($CDCl_3$), δ: 1.32 (s, 9 H, Bu^t); 2.52 (s, 6 H, Me); 2.81—2.95 (m, 4 H, CH_2); 7.10 (d, 2 H, Py, ^3J = 4.2 Hz); 7.12 (s, 2 H, Ar); 8.50 (d, 2 H, Py, ^3J = 4.2 Hz). Found (%): C, 76.33; H, 8.35; S, 10.45; N, 4.71. $C_{19}H_{25}NS$. Calculated (%): C, 76.20; H, 8.41; S, 10.71; N, 4.68.

2-[2-(3,5-Di-*tert*-butyl-2-hydroxyphenylthio)ethyl]pyridine (9) was obtained by analogy with compound **5** from 2-vinylpyridine (1.05 g, 10 mmol) and 3,5-di-*tert*-butyl-2-hydroxythiophenol (2.38 g, 10 mmol). The yield of compound **9** was 2.29 g (67%), m.p. 44—46 °C (from MeOH). IR (KBr), ν/cm^{-1}: 3280 (OH); 1600 (Ar); 1568 (Py); 1480 (CH_2); 1240 (Bu^t). ^1H NMR (DMSO-d_6), δ: 1.26 (s, 9 H, Bu^t); 1.38 (s, 9 H, Bu^t); 2.93 (t, 2 H, CH_2, ^3J = 16.8 Hz); 3.09 (t, 2 H, CH_2, ^3J = 16.8 Hz); 7.19—7.30 (4 H, Ar, Py); 7.73 (t, 1 H, Py, ^3J = 16.8 Hz); 8.51 (d, 1 H, Py, ^3J = 4.6 Hz); 8.70 (s, 1 H, OH). Found (%): C, 73.52; H, 8.51; S, 9.58; N, 4.11. $C_{21}H_{29}NS$. Calculated (%): C, 73.42; H, 8.51; S, 9.33; N, 4.08.

4-[2-(3,5-Di-*tert*-butyl-2-hydroxyphenylthio)ethyl]pyridine (10) was obtained by analogy with compound **5** from 4-vinylpyridine (0.87 g, 8.25 mmol) and 3,5-di-*tert*-butyl-2-hydroxythiophenol (1.97 g, 8.25 mmol). The yield of sulfide **10** was 2.00 g (71%), m.p. 71—73 °C (ether—light petroleum, 1 : 3). IR (KBr), ν/cm^{-1}: 3240 (OH); 1604 (Ar); 1564 (Py); 1440 (CH_2); 1248 (Bu^t). ^1H NMR ($CDCl_3$), δ: 1.31 (s, 9 H, Bu^t); 1.43 (s, 9 H, Bu^t); 2.85 (t, 2 H, CH_2, ^3J = 16.8 Hz); 2.99 (t, 2 H, CH_2, ^3J = 16.8 Hz); 6.98 (s, 1 H, OH); 7.10 (d, 2 H, Py, ^3J = 5.5 Hz); 7.33 (s, 2 H, Ar); 8.52 (d, 2 H, Py, ^3J = 5.5 Hz). Found (%): C, 73.64; H, 8.45; S, 9.43; N, 3.86. $C_{21}H_{29}NS$. Calculated (%): C, 73.42; H, 8.51; S, 9.33; N, 4.08.

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