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SHORT COMMUNICATIONS

Facile Replacement of the Halogen Atom in 4-Amino-1-chloronaphthalen-2-ols by S- and N-Centered Nucleophiles

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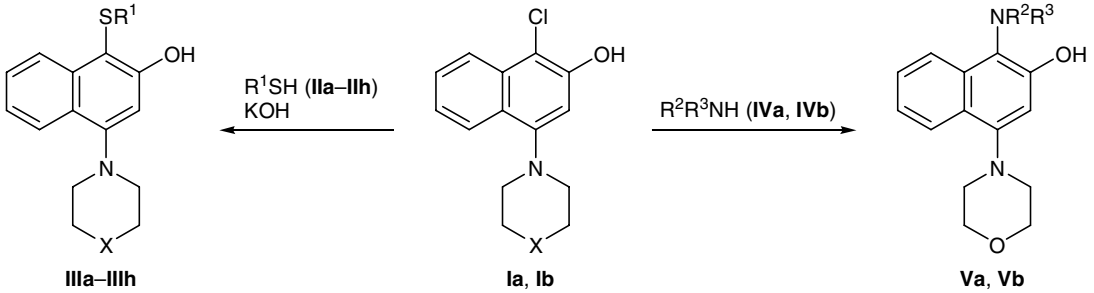
Reactions of halogen derivatives with thiols and amines underlie known methods of synthesis of sulfides and substituted amines. Aromatic halogen derivatives having electron-withdrawing groups react under standard conditions of such processes. Reactions of sulfides and amines with aryl halides having electron-donor substituents require severe conditions: elevated temperature, high pressure, and the presence of strong bases [1–11]. In most cases, sulfides are obtained using such catalysts as copper [1–5] and nickel compounds [6]. Some reactions of thiols and their salts with aryl halides are catalyzed by palladium complexes [7–9]. Thiols and various disulfides are used as sulfur-containing nucleophiles [2, 10, 11]. Sodium sulfide gives rise to symmetric diaryl sulfides [3, 12].

We examined nucleophilic substitution of the halogen atom in 1-chloronaphthalen-2-ol by aromatic and heterocyclic thiols and secondary amines. However, no expected sulfides were detected in the reaction mixtures when equimolar amounts of 1-chloronaphthalen-2-ol and various potassium arenethiolates were heated in different solvents in a wide temperature range. The reactivity of the halogen atom was considerably enhanced via introduction of an electron-donor substituent into the 4-position of 1-chloronaphthalen-2-ol. By heating 4-amino-1-chloronaphthalen-2-ols **Ia** and **Ib** with substituted benzenethiols **IIa**–**IIc** and some heterocyclic thiols **IId**–**IIh** in DMF at 70–80°C in the presence of potassium hydroxide we obtained a series of arylsulfanyl- and hetarylsulfanyl-substituted naphthols **IIIa**–**IIIh**.

Likewise, the reactions of 1-chloro-4-morpholinonaphthalen-2-ol (**Ia**) with excess secondary amine **IVa** and **IVb** at 200–240°C gave 1,4-diaminonaphthalen-2-ols **Va** and **Vb**, respectively. Alkyl ethers derived from 4-amino-1-chloronaphthalen-2-ols failed to react with thiols under analogous conditions. Therefore, we presumed that unusually facile replacement of chlorine in



IIIa–IIIh **Ia, Ib** **Va, Vb**

I, X = O (**a**), NMe (**b**); **II**, **III**, R^1 = Ph (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 1,3-benzothiazol-2-yl (**d**), 1,3-benzoxazol-2-yl (**e**), 4-methyl-4*H*-1,2,4-triazol-3-yl (**f**), 1-phenyl-1*H*-tetrazol-5-yl (**g**), 1*H*-benzimidazol-2-yl (**h**); **III**, X = O (**a**–**f**) NMe (**g**, **h**); **IV**, **V**, R^2R^3N = morpholino (**a**), R^2 = Me, R^3 = Ph (**b**).

4-amino-1-chloronaphthalen-2-ols **Ia** and **Ib** is related to their ability to undergo tautomeric keto–enol transformations.

Initial compounds **Ia** and **Ib** were synthesized according to the procedure described in [13].

1-Chloro-4-morpholinonaphthalen-2-ol (Ia). Naphthalen-2-ol, 42.6 g (0.295 mol), was dissolved in 300 ml of toluene on heating. The brown solution was cooled until the dissolved substance began to crystallize, and 44.2 g (0.623 mol) of chlorine was immediately passed through the solution at a rate of 2–3 g× min^{-1}. The mixture was purged with argon to remove excess chlorine and liberated hydrogen chloride, and 36.4 g (0.36 mol) of triethylamine and 25.7 g (0.295 mol) of morpholine were added dropwise in succession, maintaining the temperature below 15°C. The mixture was kept for 1.5 h at that temperature, and triethylamine hydrochloride was filtered off. The filtrate was washed with water (4×150 ml) and dried over anhydrous Na_2SO_4, the solvent was distilled off, and the residue was recrystallized from petroleum ether. Yield 45 g (57.8%), mp 164–165°C; published data [10]: mp 163–165°C. ^{1}H NMR spectrum, δ, ppm: 3.0 t (CH_2NCH_2), 3.87 t (CH_2OCH_2), 6.88 s (3-H), 7.25 d.t and 7.5 d.t (6-H, 7-H), 8.0 m (5-H, 8-H), 9.93 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 150.8, 148.9, 132.3, 126.8, 123.7, 123.4, 122.8, 122.3, 107.9, 66.5, 53.1.

1-Chloro-4-(4-methylpiperazin-1-yl)naphthalen-2-ol (Ib) was synthesized in a similar way. Yield 68.4 g (59.5%), mp 226–227°C. ^{1}H NMR spectrum, δ, ppm: 2.33 s (CH_3), 2.7 t (CH_2NCH_2), 3.15 t (CH_2NCH_2), 6.9 s (3-H), 7.25 d.t and 7.45 d.t (6-H, 7-H), 8.0 m (5-H, 8-H), 9.9 s (OH). Mass spectrum, *m/z* (I_{rel}, %): 276 (100), 261 (13), 219 (10), 204 (40), 191 (30), 170 (14), 149 (21), 114 (19), 70 (45), 57 (8), 43 (45). Found, %: C 65.55; H 7.18; N 9.48. $C_{16}H_{21}ClN_2O$. Calculated, %: C 65.63; H 7.23; N 9.57.

4-Morpholino-1-phenylsulfanylnaphthalen-2-ol (IIIa). Naphthol **Ia**, 1.58 g (6 mmol), was dissolved in 20 ml of DMF, a solution of 0.66 g (6 mmol) of benzenethiol (**IIa**) and 0.34 g (6 mmol) of KOH in 10 ml of methanol was added, and the mixture was heated at 70°C allowing the solvent to escape over a period of 1.5–2 h. The residue was cooled and treated with 150 ml of water, and the precipitate was filtered off, washed with water, dried, and recrystallized from methanol. Yield 1.05 g (52%), mp 126–127°C. ^{1}H NMR spectrum, δ, ppm: 3.1 t (CH_2NCH_2), 3.9 t (CH_2OCH_2), 7.15 m (3-H, 6-H, 7-H, 2′-H, 3′-H, 4′-H, 5′-H, 6′-H), 8.1 d.d and 8.3 d.d (5-H, 8-H), 9.78 s (OH). Mass spectrum, *m/z* (I_{rel}, %): 337 (100), 304 (8), 276 (25), 260 (5), 246 (20), 232 (19), 221 (8), 202 (12), 174 (25), 145 (17), 128 (12), 115 (13), 77 (26), 51 (17), 45 (10), 39 (8). Found, %: C 71.64; H 5.99; N 4.30. $C_{20}H_{19}NO_2S$. Calculated, %: C 71.19; H 5.68; N 4.15.

1-(4-Chlorophenylsulfanyl)-4-morpholinonaphthalen-2-ol (IIIb) was synthesized in a similar way from 1.58 g (6 mmol) of compound **Ia** and 0.94 g (6 mmol) of 4-chlorobenzenethiol (**IIb**); the product was recrystallized from toluene. Yield 1.2 g (50%), mp 123–125°C. ^{1}H NMR spectrum, δ, ppm: 3.1 t (CH_2NCH_2), 3.9 t (CH_2OCH_2), 7.4 m (3-H, 6-H, 7-H, 2′-H, 3′-H, 5′-H, 6′-H), 8.0 d.d and 8.2 d.d (5-H, 8-H), 9.83 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 149.7, 131.9, 127.3, 124.6, 123.5, 123.2, 108.5, 107.3, 77.5, 76.9, 76.3, 67.0, 53.3. Mass spectrum, *m/z* (I_{rel}, %): 371 (100), 310 (30), 280 (25), 260 (10), 232 (22), 211 (13), 186 (16), 174 (40), 154 (7), 145 (30), 139 (43), 128 (20), 115 (23), 102 (15), 86 (7), 69 (10), 57 (15), 45 (16). Found, %: C 64.83; H 5.04; N 3.81. $C_{20}H_{18}ClNO_2S$. Calculated, %: C 64.60; H 4.88; N 3.77.

1-(4-Methylphenylsulfanyl)-4-morpholinonaphthalen-2-ol (IIIc) was synthesized in a similar way from 1.58 g (6 mmol) of naphthol **Ia** and 0.74 g (6 mmol) of 4-methylbenzenethiol (**IIc**); the product was recrystallized from methanol. Yield 1.1 g (52%), mp 116–118°C. ^{1}H NMR spectrum, δ, ppm: 2.2 s (CH_3), 3.1 t (CH_2NCH_2), 3.9 t (CH_2OCH_2), 6.9, 7.3 m (3-H, 6-H, 7-H, 2′-H, 3′-H, 5′-H, 6′-H), 8.0 d.d and 8.2 d.d (5-H, 8-H), 9.83 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 158.5, 152.4, 136.7, 134.6, 133.6, 129.1, 127.0, 125.8, 124.8, 123.8, 123.7, 107.2, 102.7, 66.4, 52.9, 20.4. Mass spectrum, *m/z* (I_{rel}, %): 351 (100), 318 (5), 290 (34), 260 (30), 232 (33), 221 (8), 202 (15), 174 (40), 145 (33), 128 (23), 115 (26), 102 (15), 91 (60), 65 (48), 45 (23), 39 (26). Found, %: C 72.02; H 6.25; N 4.17. $C_{21}H_{21}NO_2S$. Calculated, %: C 71.77; H 6.02; N 3.99.

1-(1,3-Benzothiazol-2-ylsulfanyl)-4-morpholinonaphthalen-2-ol (IIId) was synthesized in a similar way from 1.58 g (6 mmol) of naphthol **Ia** and 1 g (6 mmol) of 1,3-benzothiazole-2-thiol (**IId**); the product was recrystallized from propan-2-ol. Yield 1.7 g (72%), mp 209–210°C. ^{1}H NMR spectrum, δ, ppm: 3.1 t (CH_2NCH_2), 3.95 t (CH_2OCH_2), 6.93 s (3-H), 7.45 m (6-H, 7-H, 4′-H, 5′-H, 6′-H, 7′-H), 8.1 d.d and 8.3 d.d (5-H, 8-H), 9.83 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 159.6, 154.2, 136.5, 127.9, 125.9, 124.2, 123.9, 123.7, 122.8, 121.2, 120.9, 107.1, 66.4, 53.0. Mass spectrum, *m/z* (I_{rel}, %): 394 (42), 361 (17), 334

(73), 303 (12), 232 (40), 119 (14), 174 (28), 167 (100), 154 (23), 145 (63), 128 (45), 108 (43), 90 (40), 77 (25), 63 (63), 57 (22), 45 (60), 39 (48). Found, %: C 64.07; H 4.44; N 7.20. $C_{21}H_{18}N_2O_2S_2$. Calculated, %: C 63.93; H 4.60; N 7.10.

1-(1,3-Benzoxazol-2-ylsulfanyl)-4-morpholinonaphthalen-2-ol (IIIe) was synthesized in a similar way from 1.58 g (6 mmol) of naphthol **Ia** and 0.91 g (6 mmol) of 1,3-benzoxazole-2-thiol (**IIe**); the product was recrystallized from propan-2-ol. Yield 1.6 g (70.5%), mp 226–227°C. ^{1}H NMR spectrum, δ, ppm: 3.1 t (CH_2NCH_2), 3.91 t (CH_2OCH_2), 6.92 s (3-H), 7.3 m (6-H, 7-H, 4′-H, 5′-H, 6′-H, 7′-H), 8.1 d.d and 8.3 d.d (5-H, 8-H), 10.4 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 159.0, 153.5, 141.7, 136.7, 127.5, 124.2, 124.1, 123.7, 123.6, 122.5, 118.1, 109.8, 107.3, 66.5, 53.0. Mass spectrum, *m*/*z* (I_{rel}, %): 378 (43), 318 (100), 287 (12), 260 (15), 232 (57), 185 (24), 174 (33), 145 (55), 128 (35), 115 (40), 91 (30), 63 (47), 45 (32), 39 (40). Found, %: C 66.83; H 4.63; N 7.43. $C_{21}H_{18}N_2O_3S$. Calculated, %: C 66.65; H 4.79; N 7.40.

1-(4-Methyl-4*H*-1,2,4-triazol-3-ylsulfanyl)-4-morpholinonaphthalen-2-ol (IIIf) was synthesized in a similar way from 1.58 g (6 mmol) of naphthol **Ia** and 0.69 g (6 mmol) of 4-methyl-4*H*-1,2,4-triazole-3-thiol (**IIf**); the product was recrystallized from DMF–isobutyl alcohol. Yield 1.2 g (60%), mp 250–253°C. ^{1}H NMR spectrum, δ, ppm: 3.1 t (CH_2NCH_2), 3.65 s (CH_3), 3.9 t (CH_2OCH_2), 6.85 s (3-H), 7.3 d.t and 7.5 d.t (6-H, 7-H), 8.0 d.d and 8.5 d.d (5-H, 8-H), 8.35 s (3′-H), 10.2 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 157.7, 152.5, 148.5, 145.5, 136.3, 127.0, 124.8, 123.7, 123.6, 122.2, 107.1, 100.5, 66.3, 52.9, 30.1. Mass spectrum, *m*/*z* (I_{rel}, %): 342 (100), 282 (10), 267 (15), 243 (5), 227 (10), 200 (12), 170 (10), 145 (17), 128 (12), 115 (20). Found, %: C 59.94; H 5.61; N 16.57. $C_{17}H_{18}N_4O_2S$. Calculated, %: C 59.63; H 5.30; N 16.36.

4-(4-Methylpiperazin-1-yl)-1-(1-phenyl-1*H*-tetrazol-5-ylsulfanyl)naphthalen-2-ol (IIIg) was synthesized in a similar way from 1.66 g (6 mmol) of naphthol **Ib** and 1.07 g (6 mmol) of 1-phenyl-1*H*-tetrazole-5-thiol (**IIg**); the product was recrystallized from ethanol. Yield 1.83 g (73%), mp 211–212°C. ^{1}H NMR spectrum, δ, ppm: 2.35 s (CH_3), 2.7 t (CH_2NCH_2), 3.15 t (CH_2NCH_2), 6.8 s (3-H), 7.25 d.t and 7.4 d.t (6-H, 7-H), 7.65 m (C_6H_5), 8.0 d.d and 8.1 d.d (5-H, 8-H), 10.2 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 158.7, 153.6, 136.2, 133.4, 129.8, 129.3, 127.2, 124.0, 123.8, 122.1, 107.1, 96.5, 54.8, 52.1, 45.6. Mass spectrum, *m*/*z* (I_{rel}, %): 273 (40), 245 (70), 161 (15), 147 (15), 147 (30), 128 (32), 118 (42), 98 (20), 91 (33), 77 (44), 70 (100), 56 (26), 43 (95). Found, %: C 63.37; H 5.88; N 19.26. $C_{23}H_{26}N_6OS$. Calculated, %: C 63.57; H 6.03; N 19.34.

1-(1*H*-Benzimidazol-2-ylsulfanyl)-4-(4-methylpiperazino)naphthalen-2-ol (IIIh) was synthesized in a similar way from 1.66 g (6 mmol) of naphthol **Ib** and 0.9 g (6 mmol) of 1*H*-benzimidazole-2-thiol (**IIh**); the product was recrystallized from DMF. Yield 1.45 g (62%), mp 216–217°C. ^{1}H NMR spectrum, δ, ppm: 2.35 s (CH_3), 2.65 t (CH_2NCH_2), 3.15 t (CH_2NCH_2), 6.9 s (3-H), 7.3 m (6-H, 7-H, 4′-H, 5′-H, 6′-H, 7′-H), 8.05 d.d and 8.3 d.d (5-H, 8-H), 11.8 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 158.7, 152.8, 150.1, 136.6, 126.9, 124.4, 123.8, 123.6, 121.9, 120.6, 107.6, 99.3, 54.6, 51.9, 45.5. Mass spectrum, *m*/*z* (I_{rel}, %): 390 (60), 330 (75), 286 (30), 259 (25), 245 (15), 231 (20), 184 (15), 170 (32), 150 (55), 128 (26), 115 (38), 70 (65), 57 (22), 43 (100). Found, %: C 67.69; H 6.33; N 13.62. $C_{23}H_{26}N_4OS$. Calculated, %: C 67.95; H 6.45; N 13.78.

1,4-Dimorpholinonaphthalen-2-ol (Va). A mixture of 1.5 g (5.7 mmol) of naphthol **Ia** and 20 ml of morpholine was heated for 4 h at 200°C in a sealed tube. After cooling, the mixture was poured into 150 ml of water, and the precipitate was filtered off and recrystallized from methanol. Yield 1.1 g (62%), mp 205–206°C. ^{13}C NMR spectrum, δ_C, ppm: 151.4, 132.6, 126.0, 124.5, 124.4, 123.8, 122.1, 121.9, 105.4, 68.2, 67.0, 53.3, 50.7. Mass spectrum, *m*/*z* (I_{rel}, %): 314 (100), 256 (53), 255 (44), 227 (8), 198 (21), 183 (5) 169 (26), 155 (12), 99 (11), 84 (8), 71 (6), 42 (8). Found, %: C 68.53; H 6.97; N 8.71. $C_{18}H_{22}N_2O_3$. Calculated, %: C 68.77; H 7.05; N 8.91.

1-Methyl(phenyl)amino-4-morpholinonaphthalen-2-ol (Vb). A mixture of 1.5 g (5.7 mmol) of naphthol **Ia** and 15 ml of *N*-methylaniline was heated for 4 h at 240°C in a sealed tube. The mixture was subjected to steam distillation to remove excess *N*-methylaniline, and the precipitate was filtered off and recrystallized from methanol. Yield 0.7 g (37%), mp 128–130°C. ^{1}H NMR spectrum, δ, ppm: 3.1 t (CH_2NCH_2), 3.3 s (CH_3), 3.9 t (CH_2OCH_2), 6.8 s (3-H), 7.3 m (6-H, 7-H, C_6H_5), 8.1 d.d and 8.3 d.d (5-H, 8-H), 9.2 s (OH). ^{13}C NMR spectrum, δ_C, ppm: 152.1, 149.2, 149.1, 133.2, 128.4, 126.2, 123.8, 123.6, 122.3, 121.9, 120.8, 115.5, 111.6, 108.1, 66.5, 53.1, 38.0. Mass spectrum, *m*/*z* (I_{rel}, %): 334 (50), 291 (50), 276 (11), 261 (5), 233 (25), 218 (10), 204 (15), 178 (5), 167 (43), 137 (17), 130 (35), 116 (38), 115 (33), 102 (25), 91 (15), 77 (100), 51 (44), 39 (15). Found,

%: C 75.31; H 6.54; N 8.25. $C_{21}H_{22}N_2O_2$. Calculated, %: C 75.42; H 6.63; N 8.38.

The melting point were measured on a Boetius melting point apparatus. The ^1H and ^{13}C NMR spectra were recorded on a Bruker AMX 400 spectrometer (400 MHz for ^1H) from solutions in DMSO-d_6 or $CDCl_3$ (compound **Va**); the chemical shifts were determined relative to the solvent signals. The mass spectra (electron impact, 70 eV) were obtained on a Kratos MS 890 mass spectrometer with direct sample admission into the ion source heated to 200°C. The progress of reactions was monitored by TLC on Silufol UV-254 plates; spots were visualized under UV light. All solvents used in this work were preliminarily purified and dehydrated according to standard procedures.

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