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2,4-Bis(fluorocarbon)-substituted phenols for high yield Newman–Kwart rearrangement reactions

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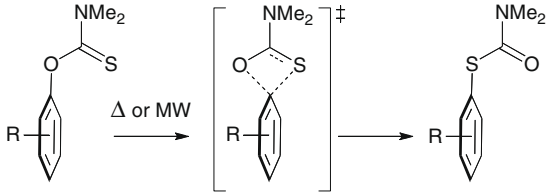
ABSTRACT

The Newman–Kwart thermal rearrangement of two 2,4-disubstituted *O*-arylthiocarbamates, prepared from the corresponding phenols, is reported. Clean conversion to the *S*-arylthiocarbamates in high yields was observed. The rearrangement appears to be facilitated by the presence of electron-withdrawing substituents in the 2- and 4-positions of the aromatic ring.

The synthesis of highly substituted thiophenols has been an active field of research due to their potential uses in several areas of chemistry.[1] Applications include, for example, the preparation of biologically-relevant thiyl radicals with enhanced stability,[2] and the synthesis of sulfur-based ligands for transition metal-sulfur complexes.[3] The bulky substituents on the thiophenols are of key importance to prevent dimerization of the desired thiyl radicals and to prevent the formation of multimetallic assemblies, respectively. As part of our efforts to access chelating sulfur ligands for transition metal chemistry, we seek to develop 2,4-disubstituted thiophenols that provide steric protection around the metal center by means of bulky substituents at the 2-position. Such compounds are ideally suited for metalation at sulfur and the *ortho* C–H bond, allowing the assembly of highly substituted, and potentially chelating thiophenol derivatives.[4]

In this context, one of the most attractive synthetic methodologies is the Newman–Kwart thermal rearrangement (NKR) of *O*-arylthiocarbamates to the corresponding *S*-arylthiocarbamates, which relies on the availability of the corresponding phenols.[1,5] Despite the versatility of this method, in many cases it is limited by the forcing conditions required for the preparation of highly substituted *S*-arylthiocarbamates, particularly when bulky substituents are present in the 2- and 6-positions of the aromatic ring.[6] Although the presence of methyl or *iso*-propyl substituents in the *ortho*-positions has a rate-enhancing effect on NKR due to restricted rotation about the C(*ipso*)-O bond (Scheme 1),[7] the bulkier *tert*-butyl groups effectively depress the rate of rearrangement. For example, the 2-*tert*-butyl group in 2,4-di-*tert*-butyl-6-formylphenyl-*N*,*N*-dimethyl-*O*-thiocarbamate precludes NKR, even at 500 °C.[8] In our experience, the presence of a single sterically encumbering group on the position adjacent to the *ipso*-carbon atom results in a high activation barrier for the rearrangement to occur. Thus, the thermal rearrangement of 2-(1-adamantyl)-4-methylpheyl-*N*,*N*-dimethyl-*O*-thiocarbamate requires heating in excess of 300 °C, and the optimized yield of the *S*-arylthiocarbamate does not exceed 25%.[9]

In the aforementioned cases, as well as in related examples of *O*-arylthiocarbamates with bulky groups in the 2-position, the electron-donating properties of the substituents do not favor the nucleophilic attack of the sulfur atom on the *ipso*-carbon required for the NKR. These limitations have been partially overcome by adapting catalysts that promote the rearrangement at relatively low temperatures,[10] as well as by resorting to microwave irradiation to achieve the required reaction temperatures.[11] As a complementary approach, we decided to prepare phenol derivatives with



Scheme 1. Proposed mechanism for the Newman–Kwart rearrangement.

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a bulky substituent in the 2-position, and with electron-withdrawing properties that may facilitate NKR of the corresponding *O*-thiocarbamates by polar effects, in an analogous fashion to related bis(trifluromethyl)phenyl-substituted binaphthyl derivatives.[12] In addition, the electronic effect of another fluorinated substituent on the 4-position can be assessed by employment of 4-methyl, and 4-trifluoromethyl substituents. Thus, we selected 2-[3,5-bis(trifluoromethyl)phenyl]-4-methylphenol **1** and 2-[3,5-bis(trifluoromethyl)phenyl]-4-trifluoromethylphenol **2** as our target precursors.

Preparation of the precursors involved the protection of the hydroxy group of 2-bromo-4-alkylphenols, with alkyl = methyl or trifluoromethyl. Thus, treatment of both phenols with benzyl bromide in acetone, and potassium carbonate as base resulted in the corresponding benzyl ethers in excellent yields. These compounds were subjected to Suzuki–Miyaura coupling conditions with 3,5-bis(trifluoromethyl)phenylboronic acid, and $Pd(PPh_3)_4$ catalyst.[13] A slight excess of the boronic acid (1.6 equiv) consistently resulted in better yields of the desired 2-[3,5-bis(trifluoromethyl)phenyl]-4-alkylphenyl benzyl ethers, albeit accompanied by the formation of the homocoupling product of the boronic acid 3,5,3′,5′-tetrakis(trifluoromethyl)biphenyl.[14] Deprotection of the benzyl phenyl ethers by removal of the benzyl groups was accomplished by hydrogenolysis with Pd/C, which afforded the target precursors 2-[3,5-bis(trifluoromethyl)phenyl]-4-methylphenol **1** and 2-[3,5-bis(trifluoromethyl)phenyl]-4-trifluoromethylphenol **2** in good yields (Scheme 2).[15]

Subsequent treatment of the phenols with *N*,*N*-dimethylthiocarbamoyl chloride and 4-dimethylaminopyridine (DMAP) in refluxing, dry DME resulted in the corresponding *O*-thiocarbamates **3** and **4**. Both compounds are crystalline solids, and were characterized by spectroscopic methods, IR and ^{1}H NMR spectra being particularly indicative of their identities. IR spectra feature characteristic C=S stretching bands at 1543 and 1548 cm^{-1}, while the ^{1}H NMR spectra acquired in $CDCl_3$ display inequivalent NMe_2 signals at δ 3.15 and 3.32 for **3**, and δ 3.16 and 3.32 ppm for **4**.

Analysis of the electron-ionization mass spectra of **3** and **4** reveals the relative ease for the NKR to occur for each compound. In the case of **3**, the molecular ion at $m/z = 407$ is accompanied by the base peak at $m/z = 88$, which was assigned to the $[Me_2N{=}C{=}S]^+$ fragment as the result of carbonyl C–O bond cleavage of the *O*-thiocarbamate. The peak at $m/z = 72$ was assigned to the $[Me_2N{=}C{=}O]^+$ fragment, and would result from C–S bond cleavage of the corresponding *S*-thiocarbamate, indicating that there is a significant amount of rearrangement taking place in the ionization chamber (67% relative intensity).[16] The presence of the additional *para*-CF_3 electron-withdrawing group in **4** appears to facilitate NKR, based on the relative ratios of the fragments observed. Thus, the $[Me_2N{=}C{=}O]^+$ fragment arising from the rearranged product at $m/z = 72$ corresponds to the base peak, while the $[Me_2N{=}C{=}S]^+$ fragment gives rise to a peak with a relative intensity of 92%.

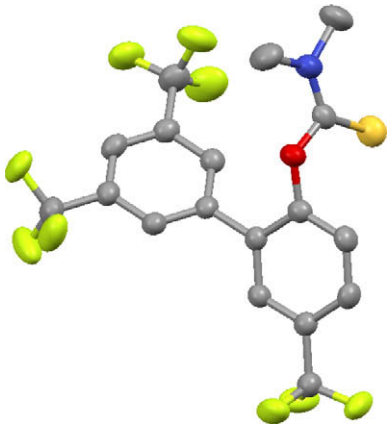
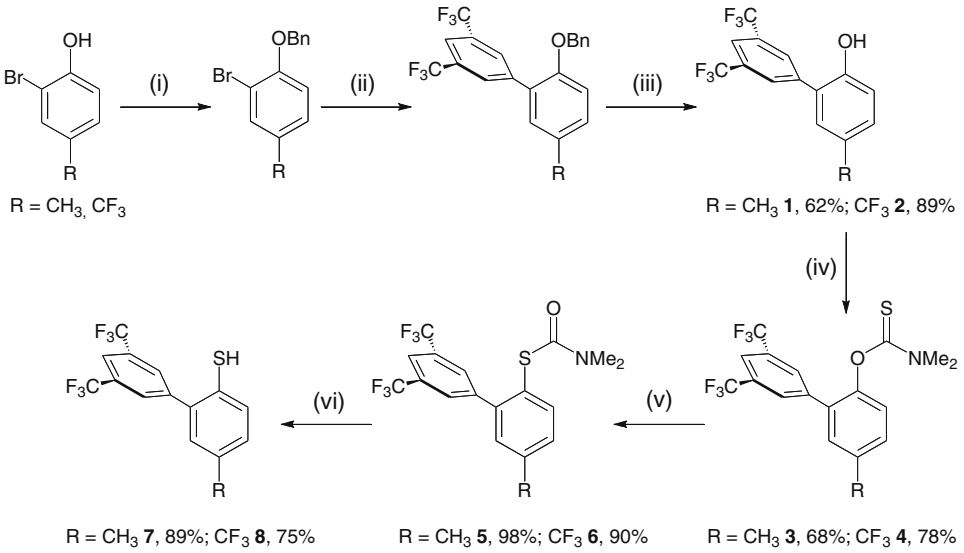


Figure 1. ORTEP diagram of **4** at the 50% probability level; color code: C, gray; N, blue; O, red; S, yellow; F, lemon.

The solid state structure of **4** was determined by X-ray crystallography,[17] featuring a characteristic C=S bond length of 1.650(2) Å. The angle between the phenol (C1–C6), and the *ortho*-aromatic rings (C7–C12) is 50.99° (Fig. 1). In addition, the sulfur atom is in close proximity of the *ipso*-carbon atom at a distance of 2.987(2) Å, which could facilitate the nucleophilic attack required for NKR. An alternative route for the desired thiophenols would require initial preparation of the 2-bromo-4-alkylphenyl-*O*-thiocarbamates, followed by Suzuki–Miyaura coupling. We tested this method with 2-bromo-4-methylpheyl-*N*,*N*-dimethyl-*O*-thiocarbamate, and subsequent thermolysis afforded the corresponding *S*-thiocarbamate in low yield after heating to 270 °C. Considering the moderate steric demand of the bromine atom in



Scheme 2. Preparation of 2,4-disubstituted thiophenols. Reagents and conditions: (i) K_2CO_3, BnBr, acetone; (ii) 3,5-$(CF_3)_2C_6H_3B(OH)_2$, $Pd(PPh_3)_4$, K_2CO_3, DME/H_2O; (iii) H_2, Pd/C, ethyl acetate; (iv) $ClC(S)NMe_2$, DMAP, DME; (v) 260–265 °C, neat; (vi) KOH, MeOH; $NaBH_4$, then 3 N HCl.

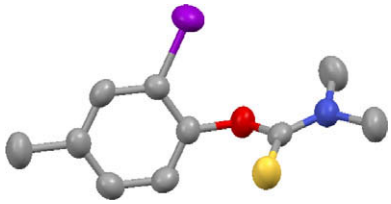


Figure 2. ORTEP diagram of 2-bromo-4-methylpheyl-*N*,*N*-dimethyl-*O*-thiocarbamate at the 50% probability level; color code: Br, purple.

the 2-position, the outcome of the thermolysis can be ascribed to the decreased capacity of the bromine to activate the aromatic ring toward nucleophilic attack. In addition, *O*-thiocarbamates have a tendency to attack the *ortho*-position when a halogen is present as a leaving group,[18] significantly reducing the yield of the Newman–Kwart rearrangement product. Moreover, the solid state structure of 2-bromo-4-methylpheyl-*N*,*N*-dimethyl-*O*-thiocarbamate features a slightly longer distance between the sulfur and the *ipso*-carbon atoms of 2.992(3) Å (Fig. 2).

In contrast to the yields of the rearrangement obtained with 2-bromo-4-methylpheyl-*N*,*N*-dimethyl-*O*-thiocarbamate, thermolysis of **3** and **4** proceeded smoothly at 265 and 260 °C, respectively. Both *O*-thiocarbamates melt below the reaction temperatures employed, avoiding the sublimation problems observed with related compounds.[9] Compounds **5** and **6** were obtained in good yields after purification. IR and ^{1}H NMR spectra are characteristic of *S*-arylthiocarbamates, with C=O stretching bands at 1670 and 1665 cm^{-1}, and one singlet at δ 2.93 ppm corresponding to equivalent NCH_3 groups.

Methanolysis of the *S*-thiocarbamates **5** and **6** under basic conditions in N_2 atmosphere resulted in the corresponding thiophenolates, which upon acidification afforded the desired thiophenols **7** and **8** in good overall yields. The compounds were characterized by spectroscopic methods including ^{1}H NMR, which contain S–H singlets at δ 3.82 and 3.51 ppm. Although both thiophenols are stable toward air oxidation in the solid state, their solutions oxidize rapidly resulting in the disulfides: if the methanolysis of the *S*-thiocarbamates is carried out under aerobic conditions, the disulfides are the only products obtained. Reduction of the disulfides to the thiophenols was readily achieved with $NaBH_4$ in MeOH. The oxidation of **7** in MeOH solution is faster than that of **8**, probably due to the electron-donating ability of the 4-methyl group in the former, compared to the 4-CF_3 group in the latter. The enhanced stability of **8** toward oxidation allowed us to obtain X-ray quality crystals, which are characterized by a dihedral angle of 55.14° between the mean planes of the aromatic rings (Fig. 3). Attempts to crystallize **7** in air resulted in oxidation to the disulfide **7a**, which has a dihedral angle of 64.63° between the aromatic rings, and a S1–S1* bond length of 2.0215(8), which is short compared to similar disulfides (Fig. 4).

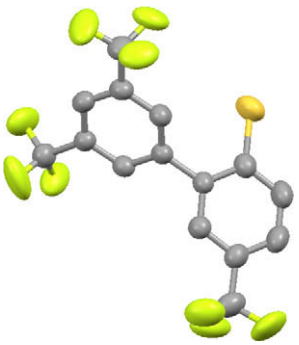


Figure 3. ORTEP diagram of **8** at the 50% probability level.

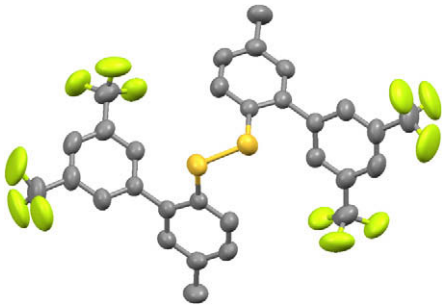


Figure 4. ORTEP diagram of **7a** at the 50% probability level.

The incorporation of fluorinated groups in the 2- and 4-positions of protected phenols activate the corresponding *O*-arylthiocarbamates for NKR to the *S*-arylthiocarbamates, allowing the easy preparation of substituted thiophenols in good yields. Thus, introduction of the bulky 3,5-bis(trifluoromethyl)phenyl group in the 2-position facilitates the intramolecular nucleophilic attack on the *ipso*-carbon, and this effect is further reinforced by the presence of a 4-CF_3 group, relative to 4-methyl. The 4-CF_3 groups renders the corresponding thiophenol more tolerant toward air, since oxidation to the disulfide appears to be disfavored due to the electron-withdrawing nature of the substituent.

Acknowledgments

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Supplementary data

Supplementary data (CCDC 753275 - 753278 contain the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.12.004.

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17. *Crystal data for* **6**: $C_{18}H_{12}F_9NOS$, M = 461.35, monoclinic, space group $P2_1/c$, $a = 9.7837(2)$, $b = 8.6413(2)$, $c = 23.170(4)$ Å, $\beta = 98.613(3)°$, $V = 1936.7(6)$ Å^3, $T = 173(2)$ K, $Z = 4$, $D_c = 1.582$ g cm^{-3}, μ (Mo Kα) = 0.876 mm^{-1}, $F(0\,0\,0) = 928$; 4429 unique reflections and 442 parameters: $R = 0.047$, $R_w = 0.104$, $\Delta\rho_{max} = 0.231$ and $\Delta\rho_{min} = -0.174$ e Å^{-3}. *Crystal data* for 2-bromo-4-methylpheyl-*N*,*N*-dimethyl-*O*-thiocarbamate: $C_{10}H_{12}BrNOS$, M = 274.18, monoclinic, space group $P2_1/n$, $a = 6.925(3)$, $b = 10.528(4)$, $c = 16.424(6)$ Å, $\beta = 99.704(6)°$, $V = 1180.3(8)$ Å^3, $T = 298(2)$ K, $Z = 4$, $D_c = 1.543$ g cm^{-3}, μ (Mo Kα) = 0.876 mm^{-1}, $F(0\,0\,0) = 552$; 2155 unique reflections and 130 parameters: $R = 0.029$, $R_w = 0.066$, $\Delta\rho_{max} = 0.368$ and $\Delta\rho_{min} = -0.200$ e Å^{-3}. *Crystal data* for **10**: $C_{15}H_7F_9S$, M = 390.27, monoclinic, space group $P2_1/c$, $a = 4.663(1)$, $b = 20.444(2)$, $c = 16.100(2)$ Å, $\beta = 94.650(2)°$, $V = 1529.8(3)$ Å^3, $T = 298(2)$ K, $Z = 4$, $D_c = 1.695$ g cm^{-3}, μ (Mo Kα) = 0.876 mm^{-1}, $F(0\,0\,0) = 776$; 2821 unique reflections and 310 parameters: $R = 0.051$, $R_w = 0.133$, $\Delta\rho_{max} = 0.332$ and $\Delta\rho_{min} = -0.200$ e Å^{-3}. *Crystal data* for **9a**: $C_{30}H_{18}F_{12}S_2$, M = 670.56, monoclinic, space group C2/*c*, $a = 28.964(4)$, $b = 4.8156(6)$, $c = 22.098(3)$ Å, $\beta = 108.668(2)°$, $V = 2920.1(7)$ Å^3, $T = 298(2)$ K, $Z = 4$, $D_c = 1.525$ g cm^{-3}, μ (Mo Kα) = 0.876 mm^{-1}, $F(0\,0\,0) = 1352$; 3479 unique reflections and 313 parameters: $R = 0.051$, $R_w = 0.131$, $\Delta\rho_{max} = 0.233$ and $\Delta\rho_{min} = -0.242$ e Å^{-3}. Crystals were mounted in glass capillaries and used for data collection on a Bruker SMART diffractometer equipped with an Apex CCD area detector. Frames were collected by omega scans, and integrated with the Bruker SAINT software package using the appropriate unit cell. The structure was solved with SHELXS-97, and refined by full-matrix least-squares on F^2 with SHELXL-97.[19]
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