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Rapid and Convenient Synthesis of S-Acetylarenethiols by Non-aqueous Diazotization

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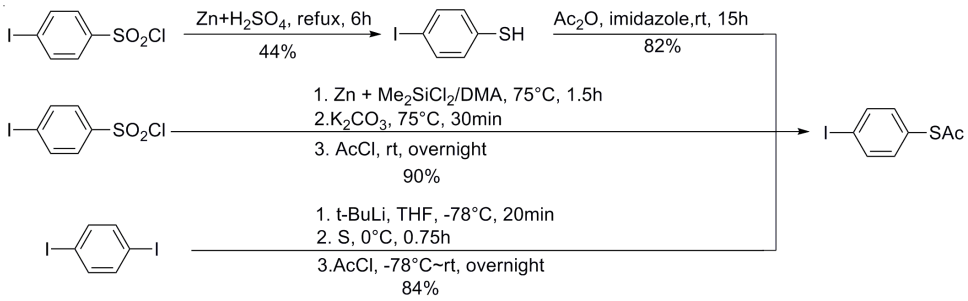
A series of S-acetylarenethiols were synthesized from aromatic amines by a rapid, convenient and efficient method. Arenediazonium tetrafluoroborates were afforded from aromatic amines, isoamyl nitrite and boron trifluoride etherate in non-aqueous diazotization system, then reacted with potassium thioacetate in dimethylsulfoxide to obtain desired products in moderate to good yields and short reaction times. The product S-acetyl-4-iodothiophenol was characterized by single crystal X-ray diffraction. The crystal belongs to monoclinic, space group $P2_1/C$ with unit cell parameters: a = 0.594 20(12) nm, b = 0.542 00(11) nm, c = 2.9618(6) nm, $\alpha = 90.00°$, $\beta = 94.23(3)°$, $\gamma = 90.00°$, $D_x = 1.942$ g/cm^3, Z = 4, F(000) = 528, $\mu = 3.528$ mm^{-1}, R = 0.039 2, wR = 0.099 3, P = $(F_o^2 + 2F_c^2)/3$, S = 1.077, $(\Delta\rho)max = 0.692 \times 10^{30}$ e/m^3, $(\Delta\rho)min = -0.558 \times 10^{30}$ e/m^3. The X-ray crystallographic structure (CCDC-684683) clearly shows that the para atoms I and S lie in the benzene ring plane and no hydrogen bonds were observed.

Key Words: S-acetyl-arenethiols, Aromatic amines, Non-aqueous diazotization, Synthesis, Crystal structure.

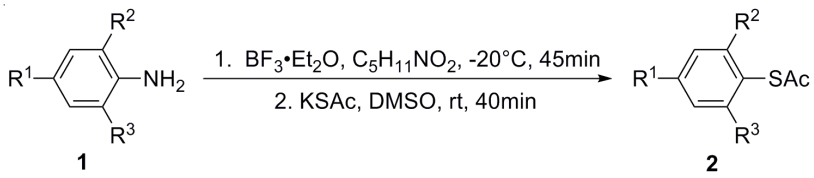
INTRODUCTION

During the past decade, the molecular devices containing thiol groups have attracted much interest in their electron-transport properties through individual molecules since they can form self-assembled monolayers (SAMs)[1-4]. Arenethiols and its S-acetyl derivatives constitute an important class of organic regents which are currently widely used as intermediates to synthesize self-assembled molecular wires and chemical sensors[2-6]. For the S-acetyl protecting group is stable in basic conditions and relatively high temperature, which is widely met for the subsequent aryl coupling reactions and can be deprotected in mild conditions, acetyl protected thiols provide excellent precursors for generating *in situ* the thiols in order to form SAMs[4,7-10]. S-acetyl-arenethiols, especially their halogen substituent derivatives, as an important class of functional intermediate, were prepared by diverse synthetic routes[11-18]. The main synthesis method is arenethiols or disulfides acetylated by reacting with electrophilic reagents such as acetic anhydride or acetyl chloride. However, the arenethiols are not facile and the synthesis routes usually due to more cost, time consuming and afforded relatively lower yields with certain impurities. These main classical routes to synthesize S-acetyl-4-iodothiophenol were shown in **Scheme-I** as examples[11,13,19].



Scheme-I: Various classical routes to synthesize S-acetyl-4-iodothiophenol

Giovanni Petrillo *et al.*[15,16] reported a method to prepare S-aryl thioacetates by reaction of potassium thioacetate with arenediazonium tetrafluoroborates which were obtained by diazotization in hydrochloric acid followed by addition of $NaBF_4$. Arenediazonium tetrafluoroborates can be synthesized from aromatic amines, *t*-butyl nitrite and boron trifluoride etherate in anhydrous media[20]. In this report, this diazotization method is modified using non-aqueous media, which is proved to be a rapid and convenient synthetic approach to S-aryl thioacetates from aromatic amines, as shown in **Scheme-II**.



Scheme-II: Route to non-aqueous diazotization to synthesize S-acetylarenethiols

EXPERIMENTAL

Reagents, solvents and starting materials were purchased from standard sources and purified using literature procedures. Reactions were monitored by silica-gel-coated thin-layer chromatography (TLC). Silica gel (200-300 mesh) was used for column chromatography. All the reactions were performed under nitrogen atmosphere.

General procedure: In a round-bottom flask fitted with an addition funnel and nitrogen inlet was added boron trifluoride etherate 5.1 mL (40.0 mmol, 4 equiv.) which was then chilled in a dry ice-acetone bath (-20 ºC). To the reaction flask was added dropwise over 5 min a solution of the aniline derivative (1 equiv.) in 10 mL dry ether, followed by a solution of isoamyl nitrite 4.7 mL (35 mmol, 3.5 equiv.) in 10 mL dry ether over 0.5 h. The chilled mixture was stirred an additional 10 min and the cold bath was allowed to warm to 5 ºC. To the mixture was added 3 mL cold ether and the mixture was chilled in the ice-bath for 15 min. The solid was collected by filtration, washed with chilled (0-5 ºC) ether and dried to give diazonium salt. After briefly air-drying, the diazonium salt was dissolved in 10 mL of DMSO and

then added dropwise *via* cannula to a solution of potassium thioacetate 1.38 g (12 mmol, 1.2 equiv.) in 20 mL DMSO. The mixture was stirred at room temperature for 40 min, then the mixture was poured into 30 mL of brine solution, extracted with ether (3 × 30 mL) and the organic phase was dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the solid residue was purified by column chromatography (petroleum ether: EtOAc, 8:1) to give the corresponding pure product.

Detection method: Melting points were measured on an X-4 melting-point apparatus and were uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker AV-300 NMR spectrometer. Chemical shifts (δ) are reported relative to TMS as an internal standard. The X-ray crystallographic analysis was performed on a Nonius CAD4 single-crystal diffractometer.

S-Acetyl-thiophenol (2a): Yellow liquid, ^1H NMR ($CDCl_3$): δ 7.40 (s, 5H, Ar-H), 2.40 (s, 3H, S-CH_3). MS (EI): m/z 152 (M^+), 110, 65, 43.

S-Acetyl-2-methyl-thiophenol (2b): Yellow liquid, ^1H NMR ($CDCl_3$): δ 7.39 (d, 1H, *J* = 7.4 Hz, Ar-H), 7.30 (m, 2H, Ar-H), 7.21 (m, 1H, Ar-H), 2.43 (s, 3H, S-CH_3), 2.34 (s, 3H, Ar-CH_3). ^{13}C NMR ($CDCl_3$): δ 193.6, 141.9, 135.8, 130.7, 130.0, 127.4, 126.5, 30.1, 20.6. MS (EI): m/z 166 (M^+), 124, 91, 43.

S-Acetyl-4-fluorothiophenol (2c): Yellow liquid, ^1H NMR ($CDCl_3$): δ 7.38 (m, 2H, *J* = 8.8 Hz, Ar-H), 7.09 (m, 2H, *J* = 8.8 Hz, Ar-H), 2.41 (s, 3H, S-CH_3). MS (EI): m/z 170 (M^+), 155, 128, 108, 83, 43.

S-Acetyl-4-chlorothiophenol (2d): Yellow solid, m.p. 38-40 ºC (lit.[22] m.p. 38-39 ºC). ^1H NMR ($CDCl_3$): δ 7.39 (m, 2H, *J* = 8.8 Hz, Ar-H), 7.33 (m, 2H, *J* = 8.8 Hz, Ar-H), 2.42 (s, 3H, S-CH_3). MS (EI): m/z 186 (M^+), 144, 108, 43.

S-Acetyl-4-bromothiophenol (2e): Yellow solid, m.p. 51-53 ºC (lit.[23] m.p. 51-52 ºC). ^1H NMR ($CDCl_3$): δ 7.54 (d, 2H, *J* = 8.5 Hz, Ar-H), 7.27 (d, 2H, *J* = 8.5 Hz, Ar-H), 2.42 (s, 3H, S-CH_3). MS (EI): m/z 231 (M^+), 230, 188, 108, 43.

S-Acetyl-4-iodothiophenol (2f): White solid, m.p. 53-55 ºC (lit.[13] mp 54-55 ºC). ^1H NMR ($CDCl_3$): δ 7.74 (d, 2H, *J* = 6.7 Hz, Ar-H), 7.13 (d, 2H, *J* = 6.7 Hz, Ar-H), 2.42 (s, 3H, S-CH_3).

S-Acetyl-2-methyl-4-iodothiophenol (2g): Yellow solid, m.p. 47-49 ºC. ^1H NMR ($CDCl_3$): δ 7.68 (d, 1H, *J* = 1.6 Hz, Ar-H), 7.55 (dd, 1H, *J* = 1.6, 8.2 Hz, Ar-H), 7.09 (d, 1H, *J* = 8.2 Hz, Ar-H), 2.42 (s, 3H, S-CH_3), 2.29 (s, 3H, Ar-CH_3). ^{13}C NMR ($CDCl_3$): δ 192.8, 144.0, 139.6, 137.2, 135.7, 127.4, 96.6, 30.1, 20.3. MS (EI): m/z 292 (M^+), 250, 123, 89, 78, 43.

S-Acetyl-2,6-dimethyl-4-iodothiophenol (2h): Yellow solid, m.p. 80-82 ºC. ^1H NMR ($CDCl_3$): δ 7.51 (s, 2H, Ar-H), 2.43 (s, 3H, S-CH_3), 2.29 (s, 3H, Ar-CH_3). ^{13}C NMR ($CDCl_3$): δ 192.4, 144.5, 137.1, 127.4, 96.8, 30.2, 21.1. MS (EI): m/z 306 (M^+), 264, 137, 91, 77, 43.

S-Acetyl-2-ethyl-4-iodothiophenol (2i): Yellow solid, m.p. 52-54 ºC. ^1H NMR ($CDCl_3$): δ 7.66 (d, 1H, *J* = 1.9 Hz, Ar-H), 7.55 (dd, 1H, *J* = 1.9, 8.2 Hz, Ar-H), 7.08 (d, 1H, *J* = 8.2 Hz, Ar-H), 2.64 (q, 2H, *J* = 7.6 Hz, Ar-CH_2), 2.41 (s, 3H, S-CH_3),

1.14 (t, 3H, *J* = 7.6 Hz, C-CH_3). ^{13}C NMR ($CDCl_3$): δ 193.2, 149.4, 138.1, 137.7, 135.7, 126.6, 96.9, 30.2, 27.1, 14.8. MS (EI): m/z 306 (M^+), 264, 249, 231, 135, 91, 77, 43.

S-Acetyl-2-methyl-6-ethyl-4-iodothiophenol (2j): Yellow solid, m.p. 67-69 ºC. ^{1}H NMR ($CDCl_3$): δ 7.52 (s, 1H, Ar-H), 7.49 (s, 1H, Ar-H), 2.67 (q, 2H, *J* = 7.6 Hz, Ar-CH_2), 2.42 (s, 3H, S-CH_3), 2.28 (s, 3H, Ar-CH_3), 1.13 (t, 3H, *J* = 7.6 Hz, C-CH_3). ^{13}C NMR ($CDCl_3$): δ 192.7, 150.1, 137.1, 135.8, 126.7, 97.2, 30.2, 27.8, 21.1, 15.0. MS (EI): m/z 320 (M^+), 278, 245, 193, 151, 115, 91, 77, 43.

RESULTS AND DISCUSSION

A series of S-acetylarenethiols were synthesized from corresponding aromatic amines *via* non-aqueous diazotization and reacting with potassium thioacetate within 2 h. Here the non-aqueous diazotization of aromatic amines with boron trifluoride etherate and isoamyl nitrite in anhydrous solvent ether within an ice-acetone bath was employed to produce arenediazonium tetrafluoroborates in high yield. Excess boron trifluoride employed as the conveniently handled etherate complex and the arenediazonium tetrafluoroborates precipitated from the reaction solution[17,21]. The anhydrous tetrafluoroborate salt was obtained following simple filtration. Arenediazonium salts are well-known versatile electrophilic intermediates for the preparation of aromatic derivatives *via* ionic or radical pathways, reacting with potassium thioacetate in DMSO solution resulted in the smooth formation of S-acetylarenethiols. Compared with aqueous diazotization, the non-aqueous method was more efficient and afforded higher yields[15,16]. Various aromatic amines afforded the corresponding S-acetylarenethiols products in various yields under similar reaction conditions within 2 h. The results are listed in Table-1.

The molecular structure of S-acetyl-4-iodothiophenol (**2f**) was also identified by X-ray crystallography diffraction method (Fig. 1). The crystal belongs to monoclinic, space group $P2_1/C$ with unit cell parameters: a = 0.594 20(12) nm, b = 0.542 00(11) nm, c = 2.9618(6) nm, α = 90.00°, β = 94.23(3)°, γ = 90.00°, D_x = 1.942 g/cm^3, Z = 4, F(000) = 528, μ = 3.528 mm^{-1}, R = 0.039 2, wR = 0.099 3, P = $(F_o^2 + 2F_c^2)/3$,

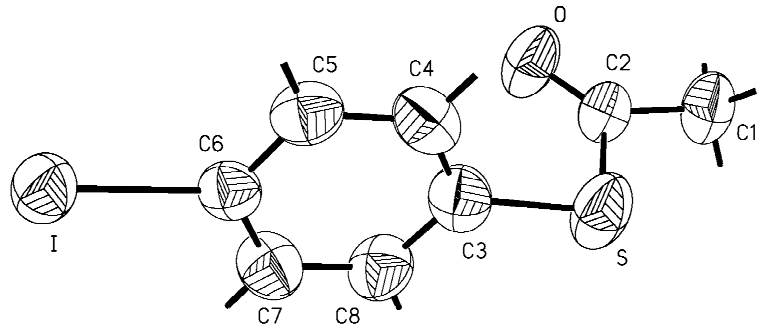
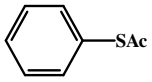
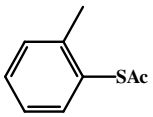
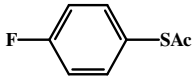
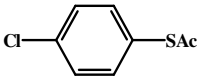
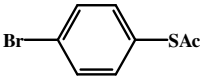
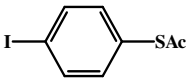
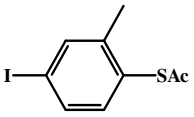
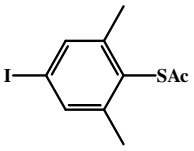
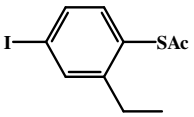
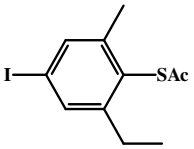


Fig. 1. Molecular structure of **2f**

TABLE-1
SYNTHESIS OF S-ACETYLARENETHIOLS FROM AROMATIC AMINES

Product No.	R^1	R^2	R^3	Product	GC Yield* (%)	Isolated Yield** (%)
2a	H	H	H		80.6	69.2
2b	H	CH_3	H		81.6	71.8
2c	F	H	H		62.2	52.0
2d	Cl	H	H		88.0	73.7
2e	Br	H	H		76.1	60.4
2f	I	H	H		71.0	52.3
2g	I	CH_3	H		64.2	49.8
2h	I	CH_3	CH_3		42.7	35.6
2i	I	H	C_2H_5		53.5	42.1
2j	I	CH_3	C_2H_5		60.0	51.5

*Yields based on gas chromatography. **Isolated yields by silica column chromatography.

S = 1.077, $(\Delta\rho)max = 0.692 \times 10^{30}$ e/m^3, $(\Delta\rho)min = -0.558 \times 10^{30}$ e/m^3. The X-ray crystallographic structure (deposition number CCDC-684683) clearly shows that the para atoms I and S lie in the benzene ring plane and no hydrogen bonds were observed.

Conclusion

Various S-acetylarenethiols were synthesized from corresponding aromatic amines *via* non-aqueous diazotization and reacting with potassium thioacetate within 2 h. This modified method has proved rapid, convenient and efficient. Desired S-acetylarenethiols were obtained in moderate to good yields and less reaction times.

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