A NEW SYNTHESIS OF N-TOSYLINDOLE FROM ANILINE VIA ORTHO-SUBSTITUTED N-TOSYLANILIDES

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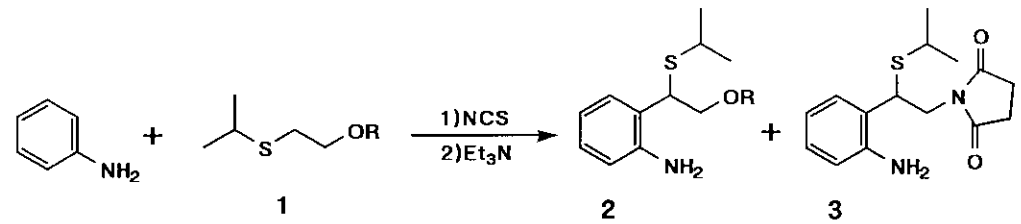
Abstract- A simple and very efficient synthesis of N-tosylindole is described, based on the acid-catalysed cyclization of ortho-alkylated N-tosylanilides, which can be prepared from aniline and dialkyl sulfide by [2,3]sigmatropic rearrangements.

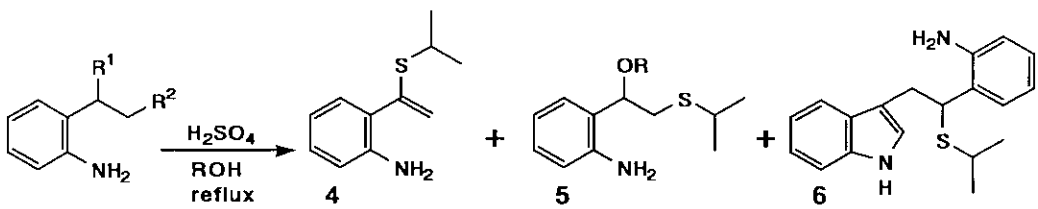
The classical Fischer method is the most frequently used for preparation of substituted indoles.[1] Although anilines are often the precursors of hydrazones used in the Fischer cyclization, more direct methods[2] for conversion of anilines to indoles would be highly desirable. We expected that introduction of a vicinal alkylthio group may facilitate nucleophilic substitution reaction of an acetoxy group by nitrogen nucleophiles[3] *via* an episulfonium ion intermediate under acidic conditions. Therefore we anticipated that another indole synthesis could be realized by the cyclization of 2-[2-acetoxy-1-(alkylthio)ethyl]aniline which was prepared by the selective ortho-alkylation of aniline.[4] In this paper we report a new synthetic method of N-tosylindole *via* ortho-alkylated N-tosylanilide in a single step.

The ortho-alkylation[5] of aniline with sulfide (**1a**) via intramolecular rearrangement of ylides derived from azasulfonium salt gave ortho-alkylated aniline (**2a**) and (**3**) in 49% and 12% yield, respectively, while with sulfide (**1b**) was given **2b** in 61% yield as a single product. It was very interesting that the acetoxy group of **2a** was displaced by a succinimide during the reaction and that the use of an excess of N-chlorosuccinimide (NCS) increased the formation of 3.



1 **2** **3**

a; R=Ac, b; R=Me



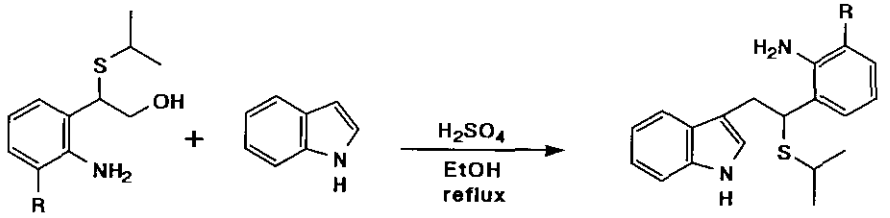
4 **5** **6**

a;R=Me, b;R=Et, c;R=s-Bu

Table I. Reaction of ortho-Alkylaniline with Sulfuric Acid in Alcohol

compd.	R^1	R^2	solvent	time(h)	yield(%)		
					4	**5**	**6**
2a	Me_2CHS	OAc	MeOH	8	-	45(**5a**)	-
2a	Me_2CHS	OAc	EtOH	5	trace	63(**5b**)	trace
2a	Me_2CHS	OAc	EtOH	24	trace	7(**5b**)	31
2a	Me_2CHS	OAc	n-PrOH	5	-	-	35
5a	MeO	Me_2CHS	EtOH	24	-	16(**5b**)	40
2a	Me_2CHS	OAc	i-PrOH	6	-	6	34
2a	Me_2CHS	OAc	s-BuOH	0.5	20	23(**5c**)	14
2a	Me_2CHS	OAc	s-BuOH	2	-	-	45

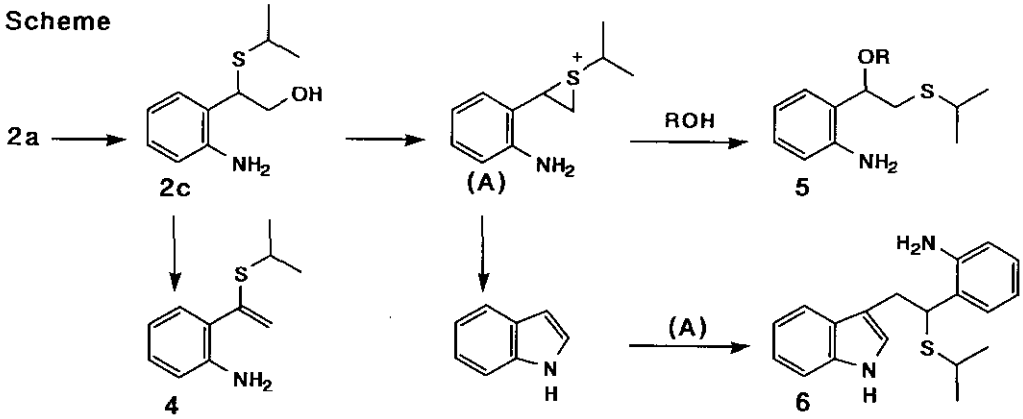
Heating of the ortho-alkylated aniline (**2a**) with sulfuric acid (1.7 M) in alcohol at reflux gave **4**, **5**, and **6**. As shown in Table I, the product distribution was greatly affected by the reaction conditions, i.e. the boiling point and the type of alcohols. Though indole itself was not obtained, the indole derivative (**6**) was given as the main product for prolonged periods.



2c;R=H, 2d;R=NO$_2$ **6;R=H, 7;R=NO$_2$**

The formation of **6** may be accounted for as the result of condensation of **2a** with indole which was produced *in situ* from **2a**, and this assumption is supported by the following experiments. The treatment of a mixture of **2c**[6] and indole with sulfuric acid in ethanol at reflux for 2 h afforded **6** in 67% yield and a similar treatment of a mixture of 2-[2-hydroxy-1-(isopropylthio)]ethyl-6-nitroaniline (**2d**)[7] and indole for 1 h produced indole (**7**) in 62% yield. Possible routes for the formation of **4**, **5**, and **6** are outlined in the Scheme.

Scheme



Acetate (**2a**) undergoes alcoholysis to produce alcohol (**2c**), which then

undergoes protonation followed by dehydration by the assistance of the neighboring isopropylthio group to yield the episulfonium ion (**A**). Then the intramolecular nucleophilic attack of the aromatic amino group affords the immediate precursor of indole, but **A** is susceptible of nucleophilic attack by the indole thus formed to afford the adduct **6**. Episulfonium ion (**A**) has not been isolated, but its presence in the reaction mixture can be accounted for by the formation of solvolysis products (**5a**, **5b**, and **5c**).[8] When the isopropylthio group is located on a benzylic position, substitution reaction proceeds with 1,2-migration of the isopropylthio group to give **5**.[8,9] These pathway for the formation of the products suggest that if the electronegative property of the amino group of the parent aniline is decreased by derivatization, the nucleophilicity of the aromatic amino group under acidic conditions is increased, and indole, which is immediate precursor of **6**, will be isolated.

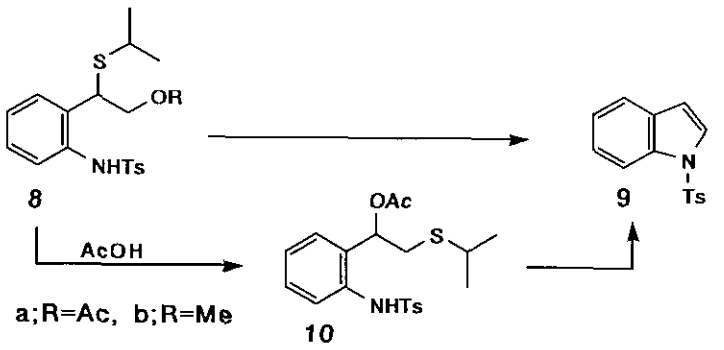


Table II. Cyclization of N-Tosylanilides to N-Tosylindole (**9**)

anilide	solvent	time(h)	additive	yield(%)
8a	s-BuOH	2	H_2SO_4	63
8b	s-BuOH	6	H_2SO_4	67
8a	EtCOOH	35	-	89
8b	EtCOOH	48	-	93
10	EtCOOH	40	-	92

In fact, the reaction of **8a** and **8b** with sulfuric acid in 2-butanol gave N-tosylindole (**9**) in good yields. Finally, we found that the heating of **8a** in propionic acid for a prolonged period afforded **9** exclusively in 89% yield, whereas heating of **8a** for shorter period in acetic acid yielded positional isomer (**10**) in 93% yield, which was again converted to **9** in a high yield upon heating in propionic acid at reflux for 40 h. This result also suggests the episulfonium ion as a transient intermediate in the proceeding reaction.[9] As N-tosylindole can be converted to indole by sodium naphthalenide or alkaline alcoholysis,[10] the above conversions imply a short and very efficient synthesis of indole.

Experimental

Melting points were determined on a Shimadzu MM-2 hot-stage apparatus and are uncorrected. Ir spectra were measured on a Hitachi 260-10 spectrophotometer. ^{1}H-Nmr spectra were recorded on a Jeol JNM-GX400 (400 MHz) spectrophotometer with TMS as an internal standard. Mass spectra were recorded with a Hitachi M-80.

2-[2-Acetoxy-1-(isopropylthio)ethyl]aniline (2a). N-Chlorosuccinimide (NCS) (0.67 g, 5.0 mmol) was added to a mixture of 2-(isopropylthio)ethyl acetate[5] (0.81 g, 5.0 mmol) and aniline (0.455 ml, 5.0 mmol) in dry CH_2Cl_2 (13 ml) at -30°C under nitrogen. After the reaction mixture was stirred for 30 min at -30°C, triethylamine (0.71 ml, 5.0 mmol) was added to the mixture and then the mixture was refluxed for 2 h. The reaction mixture was partitioned between CH_2Cl_2 (13 ml) and ice-water containing 1N-NaOH (15 ml). The organic layer was separated, washed with water (7 ml), dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on a silica gel column with EtOAc-$CHCl_3$ (20:1) to afford **2a** (0.62 g, 49%) and with EtOAc-$CHCl_3$ (5:1) to afford **3** (0.18 g, 12%). **2a**: oil, FD-ms(M/Z), 253 (M^+); ir(film)ν_{max}: 3450, 3350, 1735, and 1620 cm^{-1}; ^{1}H nmr($CDCl_3$)δ: 1.20 and 1.26(6H, each d, J=6.7 Hz), 2.02(3H, s), 2.85(1H, septet, J=6.7 Hz), 4.18(2H, br s), 4.29(1H, t, J=7.5 Hz), 4.45 and 4.55(2H, dABq, J=7.5 and 11

Hz), 6.68(1H, dd, J=1.1 and 7.8 Hz), 6.75(1H, dt, J=1.1 and 7.8 Hz), 7.09 (1H, dt, J=1.1 and 7.8 Hz), 7.49(1H, dt, J=1.1 and 7.8 Hz). Anal. Calcd for $C_{13}H_{19}NO_2S$, C, 61.63, H, 7.56, N, 5.53; Found, C, 61.36, H, 7.77, N, 5.47. **3**: mp 110-111°C; FD-ms(M/Z), 292(M^+); ir(nujol)ν_{max}: 3440, 3360, 1765, 1690, and 1650 cm^{-1}; ^1H nmr($CDCl_3$)δ : 1.15 and 1.17(6H, each d, J=6.7 Hz), 2.67(4H, s), 2.73(1H, septet, J=6.7 Hz), 3.87(1H, dABq, J=6.7 and 14 Hz), 4.00(1H, dABq, J=9.2 and 14 Hz), 4.29(2H, br s), 4.48(1H, dd, J=6.7 and 9.2 Hz), 6.65(1H, dd, J=1.0 and 7.7 Hz), 6.72(1H, dt, J=1.0 and 7.7 Hz), 7.07 (1H, dt, J=1.5 and 7.7 Hz), 7.27(1H, dd, J=1.5 and 7.7 Hz). Anal. Calcd for $C_{15}H_{20}N_2O_2S$, C, 61.61, H, 6.89, N, 9.58; Found, C, 61.43, H, 7.06, N, 9.48.

N-Tosyl-2-[2-acetoxy-1-(isopropylthio)ethyl]anilide (8a). Tosyl chloride (190 mg, 1 mmol) was added to a mixture of **2a** (246 mg, 0.97 mmol) and pyridine (0.16 ml, 2 mmol) in dry CH_2Cl_2 at room temperature for 2 h. The reaction mixture was partitioned between CH_2Cl_2 and water containing 1N-NaOH. The organic layer was separated and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on a silica gel column with $CHCl_3$-AcOEt (50:1) to afford **8a** (343 mg, 87%). **8a**: mp 128-129°C; ir(nujol)ν_{max}: 3150, 1705, and 1600 cm^{-1}; ^1H nmr($CDCl_3$)δ : 1.14 and 1.23(6H, each d, J=6.7 Hz), 2.01(3H, s), 2.39(3H, s), 2.76(1H, septet, J=6.7 Hz), 4.06(1H, m), 4.27(2H, m), 7.15(1H, dt, J= 1.4 and 7.8 Hz), 7.26(4H, m), 7.42(1H, dd, J=1.1 and 8.0 Hz), 7.54(1H, br s), 7.68(2H, d, J=8.3 Hz). Anal. Calcd for $C_{20}H_{25}NO_4S_2$, C,58.94, H, 6.18, N, 3.44; Found, C, 58.73, H, 6.27, N, 3.37.

2-[2-Methoxy-1-(isopropylthio)ethyl]aniline (2b). The compound was prepared from aniline and sulfide (**1b**) in 61% yield by the method used for **2a**. **2b**: oil, ir(film)ν_{max}: 3410, 3330, 1620, 1600, and 1580 cm^{-1}; ^1H nmr ($CDCl_3$)δ : 1.21 and 1.23(6H, each d, J=6.7 Hz), 2.79(1H, septet, J=6.7 Hz), 3.35(3H, s), 3.83(2H, m), 4.24(2H, br s), 4.26(1H, m), 6.66(1H, dd, J=1.2 and 7.7 Hz), 6.75(1H, dt, J=1.2 and 7.7 Hz), 7.07(1H, dt, J=1.5 and 7.7 Hz), 7.17(1H, dd, J=1.5 and 7.7 Hz).

N-Tosyl-2-(1-isopropylthio-2-methoxyethyl)anilide (8b). The compound was

prepared from **2b** in 86% yield by the method used for **8a**. **8b**: oil, ir (film)ν_{max}: 3250, 1600, 1580, and 1160 cm^{-1}; ^1H nmr($CDCl_3$)δ: 1.07 and 1.09 (6H, each d, J=6.7 Hz), 2.37(3H, s), 2.54(1H, septet, J=6.7 Hz), 3.27(3H, s), 3.45(1H, t, J=9.0 Hz), 3.71(1H, dd, J=4.9 and 9.0 Hz), 4.00(2H, dd, J=4.9 and 9.0 Hz), 7.12(1H, ddd, J=3.1, 7.4, and 7.7 Hz), 7.18-7.26(3H, m), 7.34(1H, dd, J=1.5 and 7.7 Hz), 7.46(1H, dd, J=1.3, and 8.0 Hz), 7.71(2H, d, J=8.4 Hz), 8.26(1H, br s). Anal. Calcd for $C_{19}H_{25}NO_3S_2$, C, 60.12, H, 6.64, N, 3.69; Found, C, 59.76, H, 6.68, N, 3.59.

Reaction of 2a with Sulfuric Acid in Alcohol at Reflux. To a solution of **2a** (253 mg, 1 mmol) in alcohol (8 ml) was added 97% sulfuric acid (0.7 ml) with ice cooling. The mixture was refluxed for 0.5-24 h and then cooled to room temperature. The reaction mixture was partitioned between CH_2Cl_2 and ice-water containing 1N-NaOH (30 ml). The organic layer was separated and washed with water. The organic layer was dried over $MgSO_4$ and concentrated to give an oily residue. The residue was purified by silica gel column chromatography with $CHCl_3$-AcOEt (5:1) as an eluent.

2-(1-Isopropylthio)vinylaniline (4): oil, FD-ms(M/Z), 193(M^+); ir(film) ν_{max}: 3350 and 1620 cm^{-1}; ^1H nmr($CDCl_3$)δ: 1.35(6H, d, J=6.7 Hz), 3.22(1H, septet, J=6.7 Hz), 3.65(2H, br s), 6.63(2H, s), 6.67(1H, dd, J=1.1 and 7.8 Hz), 6.75(1H, dt, J=1.1 and 7.5 Hz), 7.05(1H, dt, J=1.4 and 7.5 Hz), 7.20 (1H, dd, J=1.4 and 7.8 Hz).

2-(2-Isopropylthio-1-methoxyethyl)aniline (5a): oil, FD-ms(M/Z), 418($2M^+$-MeOH); ir(film)ν_{max}: 3450, 3360, and 1620 cm^{-1}; ^1H nmr($CDCl_3$)δ: 1.21 and 1.23(6H, each d, J=6.6 Hz), 2.85(1H, dABq, J=5.6 and 13 Hz), 2.92(1H, septet, J=6.7 Hz), 3.21(1H, dABq, J=8.3 and 13 Hz), 3.29(3H, s), 4.32(1H, dd, J=8.3 and 5.6 Hz), 6.60-6.90(2H, m), 7.00-7.20(2H, m). Anal. Calcd for $C_{12}H_{19}NOS$, C, 63.96, H, 8.50, N, 6.21; Found, C, 63.90, H, 8.85, N, 6.12.

2-[1-Ethoxy-2-(isopropylthio)ethyl]aniline (5b): FD-ms(M/Z), 433($2M^+$-EtO); ir(film)ν_{max}: 3450, 3360, and 1620 cm^{-1}; ^1H nmr($CDCl_3$)δ: 1.12-1.16(9H, m), 2.73-2.82(3H, m), 3.09-3.14(1H, m), 3.32-3.43(3H, m), 4.34(1H, dd, J=5.8 and 8.3 Hz), 6.54(1H, d, J=7.5 Hz), 6.61(1H, dt, J=7.5 Hz), 6.94(1H, d,

J=7.5 Hz), 7.00(1H, t, J=7.5 Hz). Anal. Calcd for $C_{13}H_{21}NOS$, C, 65.22, H, 8.84, N, 5.85; Found, C, 65.17, H, 9.13, N, 5.75.

2-[1-(1-Methylpropoxy)-2-(isopropylthio)ethyl]aniline (5c): oil, FD-ms (M/Z), 461($2M^+$-BuO); ir(film)ν_{max}: 3450, 3350, and 1620 cm^{-1}; ^1H nmr($CDCl_3$) δ: 0.80-1.5 (12H, m), 2.60-3.62(5H, m), 3.86(2H, br s), 4.41-4.57(1H, m), 6.58-6.95(2H, m), 7.00-7.20(2H, m).

N-Tosylanilide of 5c: oil, ir(film)ν_{max}: 3220, 1595, 1585, and 1160 cm^{-1}; ^1H nmr($CDCl_3$)δ: 0.82 and 0.92(3H, each t, J=7.4 Hz), 1.05 and 1.17(3H, each d, J=6.4 Hz), 1.13, 1.14, 1.15, and 1.16(6H each d, J=6.7 Hz), 1.40-1.70 (2H, m), 2.37(3H, s), 2.60-2.75(3H, m), 3.25-3.45(1H, m), 4.40-4.50(1H, m), 6.95-7.15(2H, m), 7.15-7.35(3H, m), 7.58(1H, d, J=8.2 Hz), 7.70-7.80(2H, m), 8.78 and 8.88(1H, each br s). Anal. Calcd for $C_{22}H_{31}NO_3S_2$, C, 62.65, H, 7.41, N, 3.32; Found, C, 62.25, H, 7.50, N, 3.23.

3-[2-(2-Aminophenyl)-2-(isopropylthio)ethyl]indole (6): mp 116-117°C; FD-ms (M/Z), 310(M^+); ir(nujol)ν_{max}: 3400, 3230, and 1620 cm^{-1}; ^1H nmr($CDCl_3$)δ: 1.26 and 1.27(6H, each d, J=6.7 Hz), 2.87(1H, septet, J=6.7 Hz), 3.29 and 3.35(1H, dABq, J=7.5 and 13 Hz), 3.65(2H, br s), 4.48(1H, t, J=7.5 Hz), 6.65(1H, dd, J=1.4 and 7.8 Hz), 6.81(1H, dt, J=1.4 and 7.8 Hz), 6.97(1H, d, J=2.5 Hz), 7.06(1H, m), 7.07(1H, dt, J=1.4 and 7.8 Hz), 7.28(1H, dd, J=1.4 and 7.8 Hz), 7.33(1H, d, J=8.1 Hz), 7.50(1H, d, J=8.1 Hz), 8.09(1H, br s). Anal. Calcd for $C_{19}H_{22}N_2S$, C, 73.49, H, 7.14, N, 9.02; Found, C, 73.33, H, 7.21, N, 8.96.

Reaction of ortho-Alkylated Aniline and Indole in Ethanol at Reflux. To a mixture of ortho-alkylaniline (1 mmol) and indole (128 mg, 1.1 mmol) in ethanol (8 ml) was added 97% sulfuric acid (0.7 ml). The mixture was refluxed for 1-2 h and then cooled to room temperature. The organic layer was separated and washed with water. The organic layer was dried over $MgSO_4$ and concentrated to give residue. The residue was purified by silica gel column chromatography with $CHCl_3$-AcOEt (5:1) as an eluent.

3-[2-(2-Amino-3-nitrophenyl)-2-(isopropylthio)ethyl]indole (7): mp 158-159 °C; ir(nujol)ν_{max}: 3500, 3380, 1620, and 1240 cm^{-1}; ^1H nmr($CDCl_3$)δ: 1.27

(6H, d, J=6.7 Hz), 2.90(1H, septet, J=6.7 Hz), 3.31(2H, m), 4.47(1H, dd, J= 6.4 and 8.3 Hz), 6.27(2H, br s), 6.75(1H, dd, J=7.8 and 8.6 Hz), 6.99(1H, d, J=2.2 Hz), 7.09(1H, m), 7.22(1H, m), 7.38(1H, d, J=8.0 Hz), 7.46(1H, d, J=7.8 Hz), 7.53(1H, d, J=7.2 Hz), 8.09(1H, dd, J=1.4 and 8.6 Hz), 8.14(1H, br s). Anal. Calcd for $C_{19}H_{21}N_3O_2S$, C, 64.20, H, 5.95, N, 11.82; Found, C, 63.93, H, 5.94, N, 11.67.

Reaction of ortho-Alkylated-N-Tosylanilide in Propionic Acid at Reflux. ortho-Alkyl-N-tosylanilide (1 mmol) was dissolved in propionic acid (8 ml) and refluxed for 35-48 h. The solvent was evaporated and residue was partitioned between CH_2Cl_2 and water containing 1N-NaOH. The organic layer was separated and washed with water. The organic layer was dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on a silica gel column with $CHCl_3$ to afford N-tosylindole. **9**: oil, FD-ms (M/Z), 271(M^+); ir(film)ν_{max}: 1600 and 1370 cm^{-1}; ^1H nmr($CDCl_3$)δ: 2.32(3H, s), 6.64(1H, dd, J=0.8 and 3.9 Hz), 7.19-7.25(3H, m), 7.30(1H, dd, J=7.2 and 8.3 Hz), 7.51(1H, dd, J=0.8 and 7.8 Hz), 7.56(1H, d, J=3.9 Hz), 7.76 (2H, d, J=8.3 Hz), 7.98(1H, ddd, J=0.8, 1.7, and 8.3 Hz).

N-Tosyl-2-[1-acetoxy-2-(isopropylthio)ethyl]anilide (10). The compound was prepared from **8a** or **8b** in 93% yield by refluxing in acetic acid for 8 h by a similar method used for **9**. **10**: oil, FD-ms(M/Z), 408(M^++1); ir(film)ν_{max}: 3250, 1740, 1600, and 1235 cm^{-1}; ^1H nmr($CDCl_3$)δ: 1.23(6H, d, J=6.7 Hz), 2.02(3H, s), 2.23(1H, dABq, J=5.1 and 14 Hz), 2.84(1H, septet, J=6.7 Hz), 2.98(1H, dABq, J=8.8 and 14 Hz), 5.44(1H, dd, J=5.1 and 8.8 Hz), 7.21-7.32 (5H, m), 7.46(1H, d, J=8.2 Hz), 7.63(2H, d, J=8.5 Hz), 7.97(1H, br s). Anal. Calcd for $C_{20}H_{25}NO_4S_2$, C, 58.94, H, 6.18, N, 3.44; Found, C, 58.85, H, 6.27, N, 3.41.

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6. Aniline (**2c**) was prepared from hydrolysis of **2a** in aqueous methanol with 1N-NaOH or in methanol 1N-HCl in quantitative yield.
7. Acetate of **2d** was prepared from ortho-nitroaniline and sulfide (**1a**) in 39% yield by the method used for **2a**. Reaction product was isolated in the form **2d** after hydrolysis. **2d**: oil, ir(film)ν_{max}: 3450, 3330, 1615, 1510, and 1250 cm^{-1}; ^1H nmr($CDCl_3$)δ: 1.22 and 1.27(6H, each d, J= 6.7 Hz), 2.74(1H, br s), 2.83(1H, septet, J=6.7 Hz), 3.99-4.10(2H, m), 4.15-4.18(1H, m), 6.71(1H, dd, J=7.2 and 8.6 Hz), 6.86(2H, br s), 7.51 (1H, dd, J=1.4 and 7.2 Hz), 8.10(1H, dd, J=1.4 and 8.6 Hz).
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