SYNTHESIS OF 4-, 5-, 6- AND 7-SUBSTITUTED N-TOSYLINDOLES FROM SUBSTITUTED ANILINES

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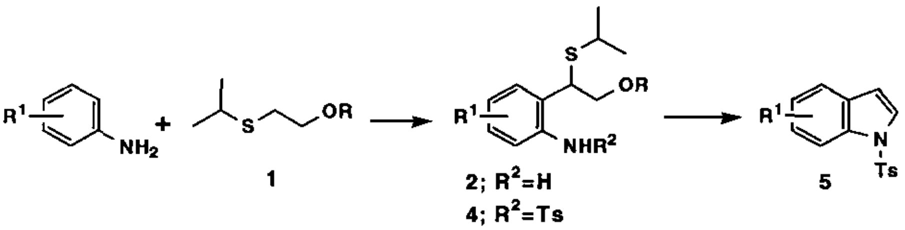
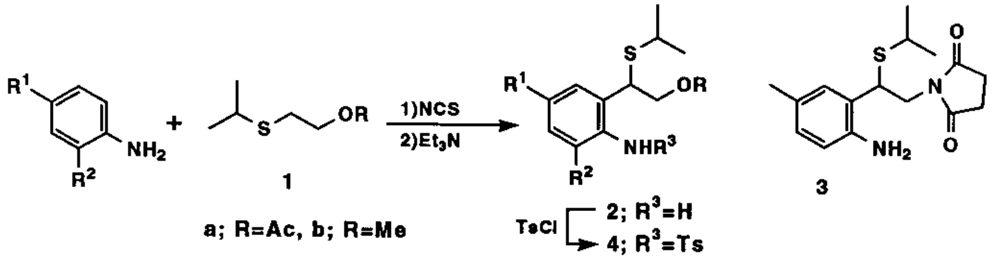
Abstract-4-, 5-, 6-, and 7-Substituted N-tosylindoles are prepared from N-tosylanilides, carrying 2-acetoxy-1-(isopropylthio)ethyl group at the ortho position, which can be prepared from substituted anilines and dialkyl sulfide by [2,3] sigmatropic rearrangement.

In our previous paper,[1] we have described a new method for the synthesis of N-tosylindole from ortho-functionalized N-tosylanilide, which can be prepared from aniline and isopropyl sulfides[2] by [2,3] sigmatropic rearrangement. In this paper we wish to report an application of this methodology to a variety of N-tosylindoles substituted on the benzene nucleus in view of taking insight into the effects of substituents on the functionalization and cyclization.



4- or 6-Substituted ortho-functionalized anilines were obtained by means of ortho-substitution of the corresponding aniline with sulfide (**1a**) or (**1b**) via [2,3] sigmatropic rearrangement of azasulfonium ylides. The addition of N-chlorosuccinimide (NCS) to a mixture of aniline and sulfide (**1a**) or (**1b**) and the subsequent treatment of the reaction mixture with triethylamine afforded **2**. The results are summarized in Table I.



1

a; R=Ac, b; R=Me

2; R^3=H

4; R^3=Ts

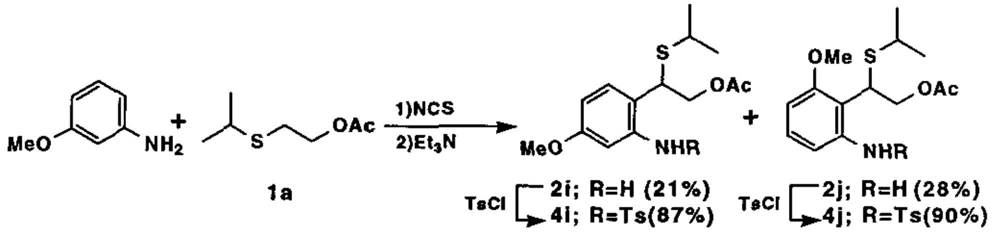
3

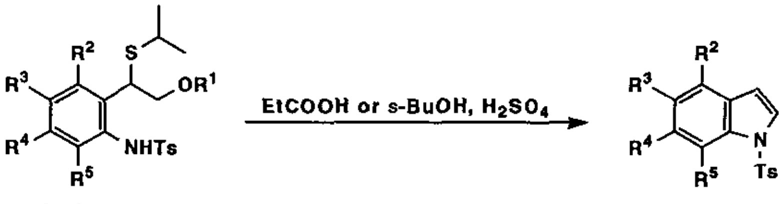
Table I. Preparation of ortho-functionalized anilines (**2**) and ortho-functionalized N-tosylanilides (**4**)

Aniline		Sulfide	yield(%)	
R^1	R^2	R	**2**	**4**[b]
Me	H	Ac	40(**2a**)[a]	85(**4a**)
Me	H	Me	64(**2b**)	85(**4b**)
MeO	H	Me	42(**2c**)	94(**4c**)
Cl	H	Me	45(**2d**)	99(**4d**)
NO_2	H	Me	20(**2e**)	62(**4e**)
H	MeO	Ac	56(**2f**)	82(**4f**)
H	Cl	Me	48(**2g**)	56(**4g**)
H	Me	Me	40(**2h**)	80(**4h**)

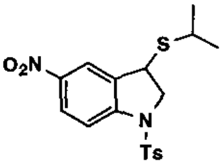
[a] ortho-Functionalized aniline (**3**) is obtained as by-product (24%). [b] Yield of isolated product is on the basis of **2**.

In general, ortho-substitution products (**2**) were produced in 40-64% yield. When a strong electron withdrawing group (such as nitro group) was placed on the aniline, the yield decreased. This could be explained in terms that the nucleophilicity of the amino group was decreased by the nitro group, therefore the halogen-sulfide complex (chlorosulfonium salt) was hardly attacked by the aniline to give azasulfonium salt.[3] When m-methoxyaniline was treated with sulfide (**1a**)-NCS complex followed by triethylamine, a mixture of 2-substituted 3-methoxyaniline (**2i**) and 2-substituted 5-methoxyaniline (**2j**), which were easily separated by column chromatography, was afforded, in 21% and 28% yields, respectively. It is noteworthy that the more crowded isomer was produced a little predominantly than the other one. The ortho-functionalized anilides (**4**) were prepared from the corresponding anilines (**2**) with p-toluenesulfonyl chloride and pyridine in high yields.

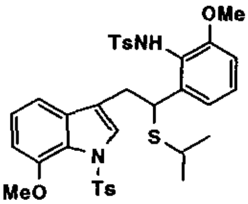




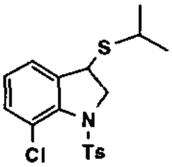
4a-j **5a,c,d-j**



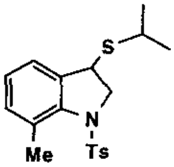
6e



6f



6g

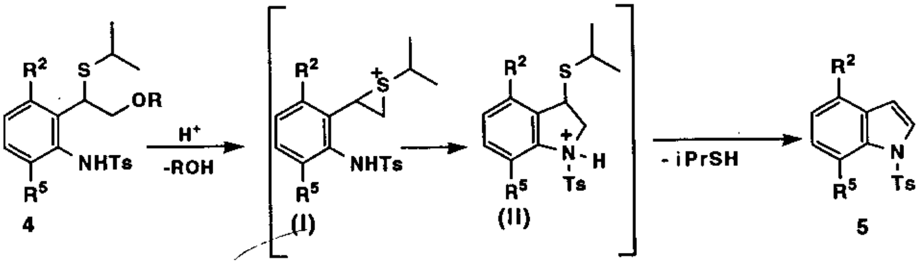


6h

Table II. Cyclization of Substituted N-Tosylanilide (**4**) to Indoles

	R^1	R^2	R^3	R^4	R^5	solvent	time(h)	additive	products(%)
a	Ac	H	Me	H	H	EtCOOH	47	-	92(**5a**)
b	Me	H	Me	H	H	EtCOOH	44	-	95(**5a**)
c	Me	H	MeO	H	H	EtCOOH	46	-	92(**5c**)
d	Me	H	Cl	H	H	EtCOOH	98	-	79(**5d**)
d	Me	H	Cl	H	H	s-BuOH	15	H_2SO_4	51(**5d**)
e	Me	H	NO_2	H	H	EtCOOH	120	-	53(**5e**), 22(**6e**)
f	Ac	H	H	H	MeO	EtCOOH	48	-	60(**5f**), 18(**6f**)
g	Me	H	H	H	Cl	EtCOOH	100	-	14(**5g**)
g	Me	H	H	H	Cl	s-BuOH	14	H_2SO_4	15(**5g**), 28(**6g**)
h	Me	H	H	H	Me	EtCOOH	48	-	52(**5h**), 34(**6h**)
i	Ac	MeO	H	H	H	EtCOOH	30	-	68(**5i**)
j	Ac	H	H	MeO	H	EtCOOH	27	-	91(**5j**)

We then examined the conversion of **4** into N-tosylindoles (**5**) and found that heating of ortho-functionalized N-tosylanilides in propionic acid (or in some cases with sulfuric acid in 2-butanol) at reflux yielded N-tosylindoles mostly in high yield (Table II). The cyclization reaction of methoxy- and methyl-substituted anilides took place in high yields (90%-92%), except **4f** and **4i**, which afforded **5f** and **5i** in 60% and 68% yields, respectively. In the cyclization of **4f**, **6f** which can be assumed as the result of in situ coupling between the postulated reaction intermediate (I) and indole (**5f**) was obtained in 18% yield.



The substituent at 3- (R^2) or 6-position (R^5) might, therefore, hinder proper orientation of the episulfonium ring or the tosylamino group capable of intramolecular nucleophilic substitution. When chloro or nitro group was placed on the aromatic nucleus, N-tosylindoles, e.g. **(5d)**, **(5e)**, and **(5g)**, were obtained in low yields. We examined cyclization with sulfuric acid in 2-butanol, but the yields were modest to low. We believe these results were probably due to the less nucleophilic and less basic character of the amide nitrogen caused by the electronegative substituents.

As substituted N-tosylindoles can be converted to substituted indoles by sodium naphthalenide or alkaline alcoholysis,[5] the above conversion implies a short and efficient synthesis of substituted indoles. This process is of paticular importance in the synthesis of methoxylated indoles, which constitute a portion of numerous indole alkaloids.

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) spectrometer in $CDCl_3$ with TMS as an internal standard. Mass spectra were recorded with a Hitachi M-80.

General Procedure for the Preparation of ortho-Functionalized Substituted Aniline (2). N-Chlorosuccinimide (0.67 g, 5.0 mmol) was added to a mixture of isopropyl sulfide **(1a)** or **(1b)** (5.0 mmol) and substituted aniline (5.0 mmol) in dry CH_2Cl_2 (13 ml) at -30°C under nitrogen. After the reaction mixture had been stirred for 30 min at -30°C, triethylamine (0.71 ml, 5.0 mmol) was added to the mixture and then the whole mixture was refluxed for 2 h (in the case of nitroaniline required for 12 h). The reaction mixture was partitioned between CH_2Cl_2 (13 ml) and ice-water containing 10%-NaOH (7 ml). The organic layer was separated, washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on a silica gel column with EtOAc-$CHCl_3$ (20:1-3:1) to afford **2**. The spectral data of the compounds are as follows.

2-(2-Acetoxy-1-isopropylthioethyl)-4-methylaniline (2a): oil, EIms(M/Z), 267(M^+) for $C_{14}H_{21}NO_2S$; ir(film) ν_{max}: 3420, 3350 and 1735 cm^{-1}; ^{1}H nmr δ: 1.21 and 1.27(6H, each d, J=6.7 Hz), 2.04(3H, s), 2.23(3H, s), 2.88(1H, septet, J=6.7 Hz), 4.00(2H, br s), 4.27(1H, dd, J=7.2 and 7.7 Hz), 4.45(1H, dABq, J=7.2 and 11.3 Hz), 4.52(1H, dABq, J=7.7 and 11.3 Hz), 6.59(1H, d, J= 8.2 Hz), 6.88-6.96(1H, m), 6.98(1H,d, J=1.5 Hz).

2-(1-Isopropylthio-2-methoxyethyl)-4-methylaniline (2b): oil, ir(film) ν_{max}: 3400, 3330 and 1620 cm^{-1}; ^{1}H nmr δ: 1.22(6H, d, J=6.7 Hz), 2.23(3H, s), 2.83(1H, septet, J=6.7 Hz), 3.35(3H, s), 3.77-4.30(5H, m), 6.57-6.61 (1H, m), 6.87-6.97(2H, m). Anal. Calcd for $C_{13}H_{21}NOS$: C, 65.25; H, 8.84; N, 5.85. Found: C, 65.57; H, 9.12; N, 5.97.

2-(1-Isopropylthio-2-methoxyethyl)-4-methoxyaniline (2c): oil, ir(film) ν_{max}: 3400, 3330 and 1605 cm^{-1}; ^{1}H nmr δ: 1.23(6H, d, J=6.7 Hz), 2.83(1H, septet, J=6.7 Hz), 3.35(3H, s), 3.75(3H, s), 3.78(1H, dABq, J=7.4 and 10 Hz), 3.83(1H, dABq, J=6.7 and 10 Hz), 3.80(2H, br s), 4.25(1H, dd, J=6.7 and 7.4 Hz), 6.63(1H, d, J=8.6 Hz), 6.68(1H, dd, J=2.8 and 8.6 Hz), 6.83 (1H, d, J=2.8 Hz). Anal. Calcd for $C_{13}H_{21}NO_2S$: C, 61.14; H, 8.28; N, 5.48. Found: C, 61.26; H, 8.43; N, 5.52.

2-(1-Isopropylthio-2-methoxyethyl)-4-chloroaniline (2d): oil, FDms(M/Z), 259(M^+) for $C_{12}H_{18}NOClS$; ir(film) ν_{max}: 3340, 1620, 1490 and 820 cm^{-1}; ^{1}H nmr δ: 1.22 and 1.24(6H, d, J=6.6 Hz), 2.81(1H, septet, J=6.6 Hz), 3.35(3H, s), 3.72-3.85(2H, m), 4.16(2H, br s), 4.16-4.21(1H, m), 6.59(1H, d, J=8.3 Hz), 7.03(1H, dd, J=2.3 and 8.3 Hz), 7.18(1H, d, J=2.3 Hz).

2-(1-Isopropylthio-2-methoxyethyl)-4-nitroaniline (2e): oil, EIms(M/Z), 270(M^+) for $C_{12}H_{18}N_2O_3S$; ir(film) ν_{max}: 3440, 3360, 1630, 1500 and 1300 cm^{-1}; ^{1}H nmr δ: 1.23 and 1.24(6H, each d, J=6.6 Hz), 2.79(1H, septet, J=6.6 Hz), 3.37(3H, s), 3.81-3.85(2H, m), 4.20(1H, dd, J=5.9 and 7.6 Hz), 5.08 (2H, br s), 6.65(1H, d, J=8.9 Hz), 8.00(1H, dd, J=2.6 and 8.9 Hz), 8.14(1H, d, J=2.6 Hz).

2-(2-Acetoxy-1-isopropylthioethyl)-6-methoxyaniline (2f): oil, ir(film)

ν_{max}: 3430, 3360, 1730 and 1620 cm^{-1}; ^{1}H nmr δ: 1.20 and 1.26(6H, each d J=6.7 Hz), 2.02(3H, s), 2.85(1H, septet, J=6.7Hz), 3.85(3H, s), 4.15(2H, br s), 4.32(1H, t, J=7.5 Hz), 4.45 and 4.46(1H, dABq, J=7.5 and 11.4 Hz), 4.53 and 4.56(1H, dABq, J=7.5 and 11.4 Hz), 6.70-6.84(3H, m). Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.33; H, 7.46; N, 4.94. Found: C, 59.46; H, 7.69; N, 4.85.

2-(1-Isopropylthio-2-methoxyethyl)-6-chloroaniline (2g): oil, EIms(M/Z), 259(M$^+$) for $C_{12}H_{18}NOClS$; ir(film) ν_{max}: 3430, 3330, 1615, 1590 and 820 cm^{-1}; ^{1}H nmr δ: 1.21 and 1.23(6H, each d, J=6.6 Hz), 2.78(1H, septet, J=6.6 Hz), 3.34(3H, s), 3.76-3.85(2H, m), 4.26(1H, dd, J=6.6 and 7.3 Hz), 4.71 (2H, br s), 6.67(1H, t, J=7.9 Hz), 7.10(1H, d, J=7.9 Hz), 7.20(1H, d, J=7.9 Hz).

2-(1-Isopropylthio-2-methoxyethyl)-6-methylaniline (2h): oil, EIms(M/Z), 239(M$^+$) for $C_{13}H_{21}NOS$; ir(film) ν_{max}: 3420, 3300, 1610 and 1570 cm^{-1}; ^{1}H nmr δ: 1.21 and 1.23(6H, each d, J=6.6 Hz), 2.17(3H, s), 2.80(1H, septet, J=6.6 Hz), 3.35(3H, s), 3.83(1H, dd, J=6.9 and 12 Hz), 3.86(1H, dd, J=6.9 and 12 Hz), 4.22(2H, br s), 4.27(1H, t, J=6.9 Hz), 6.67(1H, t, J=7.6 Hz), 6.99(1H, t, J=7.6 Hz), 7.05(1H, d, J=7.6 Hz).

2-(2-Acetoxy-1-isopropylthioethyl)-3-methoxyaniline (2i): oil, ir(film) ν_{max}: 3400, 1735, 1620 and 1585 cm^{-1}; ^{1}H nmr δ: 1.26(6H, d, J=6.7 Hz), 2.01(3H, s), 2.76(1H, m), 3.78(3H, s), 4.44(2H, m), 4.55(1H, br s), 4.61 (1H, dd, J=6.7 and 11.0 Hz), 5.21(1H, br s), 6.27-6.32(2H, m), 7.01(1H, dd, J=7.9 and 8.0 Hz). Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.33; H, 7.46; N, 4.94. Found: C, 59.10; H, 7.43; N, 5.08.

2-(2-Acetoxy-1-isopropylthioethyl)-5-methoxyaniline (2j): oil, ir(film) ν_{max}: 3430, 3360 and 1730 cm^{-1}; ^{1}H nmr δ: 1.19 and 1.26(6H, each d, J=6.7 Hz), 2.03(3H, s), 2.84(1H, septet, J=6.7 Hz), 3.74(3H, s), 4.25(1H, m), 4.26(2H, br s), 4.42(1H, dABq, J=7.2 and 11.3 Hz), 4.51(1H, dABq, J=7.7 and 11.3 Hz), 6.24(1H, d, J=2.6 Hz), 6.31(1H, dd, J=2.6 and 8.5 Hz), 7.07(1H, d J=8.5 Hz). Anal. Calcd for $C_{14}H_{21}NO_3S$: C, 59.33; H, 7.46; N, 4.94. Found: C, 59.07; H, 7.55; N, 5.03.

2-(1-Isopropylthio-2-N-succinimidoethyl)-4-methylaniline (3): mp 113-114°C; ir(nujol) ν_{max}: 3450, 3360, 1770, 1690, 1505, 1410 and 1170 cm^{-1}; ^{1}H nmr δ: 1.16 and 1.17(6H, each d, J=6.6 Hz), 2.22(3H, s), 2.68(4H, s), 2.73(1H, septet, J=6.6 Hz), 3.83(1H, dABq, J=6.6 and 13.5 Hz), 4.02(1H, dABq, J=9.2 and 13.5 Hz), 4.13(2H, br s), 4.45(1H, dd, J=6.6 and 9.2 Hz), 6.57(1H, d, J=7.9 Hz), 6.89(1H, d, J=7.9 Hz), 7.08(1H, s). Anal. Calcd for $C_{16}H_{22}N_2O_2S$: C, 62.71; H, 7.24; N, 9.14. Found: C, 62.57; H, 7.42; N, 9.10.

General Procedure for the Preparation of ortho-Functionalized Substituted N-Tosylanilide (4). Tosyl chloride (190 mg, 1 mmol) was added to a mixture of **2** (1 mmol) and pyridine (0.16 ml, 2 mmol) in dry CH_2Cl_2 (4 ml) at room temperature for 2 h (in the case of **4g** refluxed for 18 h). The reaction mixture was partitioned between CH_2Cl_2 and ice-water containing 10%-NaOH. The organic layer was separated, washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on a silica gel column with EtOAc-$CHCl_3$ (20:1-3:1) to afford **4**. The spectral data of the compounds are as follows.

N-Tosyl-2-(2-acetoxy-1-isopropylthioethyl)-4-methylanilide (4a): mp 98-100°C; ir(nujol) ν_{max}: 3150, 1700, 1600 and 1160 cm^{-1}; ^{1}H nmr δ: 1.15 and 1.22(6H, each d, J=6.7 Hz), 2.02(3H, s), 2.29(3H, s), 2.39(3H, s), 2.76(1H, septet, J=6.7 Hz), 4.06(1H, m), 4.24(2H, m), 7.01(1H, dd, J=1.5 and 8.2 Hz), 7.09(1H, d, J=1.5 Hz), 7.21-7.25(3H, m), 7.47(1H, br s), 7.65(2H,d, J= 8.2 Hz). Anal. Calcd for $C_{21}H_{27}NO_4S_2$: C, 59.82; H, 6.45; N, 3.32. Found: C, 59.94; H, 6.57; N, 3.30.

N-Tosyl-2-(1-isopropylthio-2-methoxyethyl)-4-methylanilide (4b): oil, ir (film) ν_{max}: 3250, 1605 and 1160 cm^{-1}; ^{1}H nmr δ: 1.08 and 1.10(6H, each d, J=6.7 Hz), 2.28(3H, s), 2.37(3H, s), 2.56(1H, septet, J=6.7 Hz), 3.26(3H, s), 3.42(1H, dABq, J=8.7 and 9.2 Hz), 3.68(1H, dABq, J=5.1 and 9.2 Hz), 3.95(1H, dd, J=5.1 and 8.7 Hz), 7.00(1H, dd, J=1.8 and 8.2 Hz), 7.13(1H, d, J=1.8 Hz), 7.25(2H, d, J=8.2 Hz), 7.30(1H, d, J=8.2 Hz), 7.69(2H, d, J=8.2 Hz), 8.00(1H, br s). Anal. Calcd for $C_{20}H_{27}NO_3S_2$: C, 61.03; H, 6.91; N, 3.55. Found: C, 60.92; H, 7.08; N, 3.51.

N-Tosyl-2-(1-isopropylthio-2-methoxyethyl)-4-methoxyanilide (4c): oil, ir (film) ν_{max}: 3250, 1600 and 1580 cm^{-1}; ^{1}H nmr δ: 1.08 and 1.09(6H, each d, J= 6.7 Hz), 2.38(3H, s), 2.56(1H, septet, J=6.7 Hz), 3.25(3H, s), 3.37(1H, m), 3.67(1H, m), 3.77(3H, s), 3.97(1H, m), 6.73(1H, d, J=3.1 and 8.7 Hz), 6.99(1H, d, J=3.1 Hz), 7.23(1H, d J=8.7 Hz), 7.26(2H, d J=8.5 Hz), 7.64(1H, br s), 7.65(2H, d, J=8.5 Hz). Anal. Calcd for $C_{20}H_{27}NO_4S_2$: C, 58.65; H, 6.64; N, 3.42. Found: C, 58.52; H, 6.70; N, 3.35.

N-Tosyl-2-(1-isopropylthio-2-methoxyethyl)-4-chloroanilide (4d): mp 77-79 °C; ir(KBr) ν_{max}: 3380, 1600, 1475, 1170 and 820 cm^{-1}; ^{1}H nmr δ: 1.05 and 1.07(6H, each d, J=6.6 Hz), 2.43(3H,s), 2.50(1H, septet, J=6.6 Hz), 3.28 (3H, s), 3.37(1H,dd, J=8.9 and 9.2 Hz), 3.71(1H, dd, J=4.6 and 8.9 Hz), 3.90(1H, dd,J=4.6 and 9.2 Hz),7.17(1H, dd, J=2.6 and 8.6 Hz), 7.25(2H, d, J=8.9 Hz),7.38(1H, d, J=2.6 Hz), 7.42(1H, d, J=8.6 Hz), 7.69(2H, d, J=8.9 Hz), 8.18(1H, br s). Anal. Calcd for $C_{19}H_{24}NO_3S_2Cl$: C, 55.12; H, 5.84; N, 3.38. Found: C, 55.14; H, 5.85; N, 3.34.

N-Tosyl-2-(1-isopropylthio-2-methoxyethyl)-4-nitroanilide (4e): mp 86-88°C; ir(KBr) ν_{max}: 3100, 1580, 1530, 1340, 1270 and 1165 cm^{-1}; ^{1}H nmr δ: 1.06 and 1.12(6H, each d, J=6.6 Hz), 2.39(3H,s), 2.56(1H, septet, J=6.6 Hz), 3.37(3H, s), 3.59(1H,dd, J=8.6 and 9.2 Hz), 3.83(1H, dd, J=4.0 and 9.2 Hz), 4.06(1H, dd, J=4.0 and 9.2 Hz), 7.28(2H, d, J=8.3 Hz), 7.70(1H, d, J= 8.9 Hz), 7.79(2H, d, J=8.3 Hz),8.07(1H, dd, J=2.6 and 8.9 Hz), 8.23(1H, d, J=2.6 Hz), 9.11(1H, br s). Hz), Anal. Calcd for $C_{19}H_{24}N_2O_5S_2$: C, 53.75; H, 5.69; N, 6.59. Found: C, 53.72; H, 5.68; N, 6.51.

N-Tosyl-2-(2-acetoxy-1-isopropylthioethyl)-6-methoxyanilide (4f): mp 86-88 °C; ir(nujol) ν_{max}: 3230, 1740, 1600 and 1590 cm^{-1}; ^{1}H nmr δ: 1.27 and 1.31(6H, each d, J= 6.7 Hz), 2.10(3H, s), 2.38(3H, s), 2.98(1H, septet, J= 6.7 Hz), 3.15(3H, s), 4.47(1H, dABq, J=5.9 and 11 Hz), 4.61(1H, dABq, J=7.2 and 11 Hz), 5.12(1H, dd, J=5.9 and 7.2 Hz), 6.28(1H, br s), 6.51(1H, dd, J= 2.1 and 7.7 Hz), 7.15-7.21(4H, m), 7.48(2H, d J=8.2 Hz). Anal. Calcd for $C_{21}H_{27}NO_5S_2$: C, 57.63; H, 6.21; N, 3.20. Found: C, 57.65; H, 6.30; N, 3.17.

N-Tosyl-2-(1-isopropylthio-2-methoxyethyl)-6-chloroanilide (4g): oil; ir (film) ν_{max}: 3230, 1600, 1445, 1340, 1170 and 820 cm^{-1}; ^{1}H nmr δ: 1.21 and 1.30(6H, each d, J=6.6 Hz), 2.42(3H,s), 2.88(1H, septet, J=6.6 Hz), 3.39 (3H, s), 3.73(1H,dd, J=7.0 and 9.6 Hz), 3.85(1H, dd, J=6.0 and 9.6 Hz), 4.99(1H, dd,J=6.0 and 7.0 Hz),6.80(1H, br s), 7.16(1H, dd, J=2.3 and 7.9 Hz), 7.18-7.27(1H, m),7.23(2H, d, J=8.3 Hz), 7.62(1H, dd, J=2.3 and 7.3 Hz), 7.63(2H, d, J=8.3 Hz). Anal. Calcd for $C_{19}H_{24}NO_3S_2Cl$: C, 55.12; H, 5.84; N, 3.38. Found: C, 54.90; H, 5.88; N, 3.23.

N-Tosyl-2-(1-isopropylthio-2-methoxyethyl)-6-methylanilide (4h): mp 111-112 °C; ir(KBr) ν_{max}: 3245, 1595, 1320 and 1155 cm^{-1}; ^{1}H nmr δ: 1.20(6H, d, J= 6.6 Hz), 2.07(3H,s), 2.42(3H, s), 2.80(1H, septet, J=6.6 Hz), 3.29(3H, s), 3.49(1H,dd, J=8.6 and 9.2 Hz), 3.76(1H, dd, J=5.6 and 9.2 Hz), 4.37(1H, dd,J=5.6 and 8.6 Hz), 7.09(1H, d, J=7.9 Hz), 7.18(1H, t, J=7.9 Hz),7.27 (2H, d, J=8.3 Hz), 7.36(1H, d, J=7.9 Hz), 7.69(2H, d, J=8.3 Hz). Anal. Calcd for $C_{20}H_{27}NO_3S_2$: C, 61.03; H, 6.91; N, 3.55. Found: C, 61.10; H, 6.95; N, 3.51.

N-Tosyl-2-(2-acetoxy-1-isopropylthioethyl)-3-methoxyanilide (4i): mp 130-131°C; ir(nujol) ν_{max}: 3350, 1740, 1610 and 1140 cm^{-1}; ^{1}H nmr δ: 1.16 and 1.34(6H, each d, J= 6.7 Hz), 2.03(3H, s), 2.32(3H, s), 3.40(1H, septet, J= 6.7 Hz), 3.78(3H, s), 4.05-4.15(1H, m), 4.20-4.24(2H, m), 6.90-7.30(5H, m), 7.60(2H, d, J=8.2 Hz), 7.78(1H, br s). Anal. Calcd for $C_{21}H_{27}NO_5S_2 \cdot 1/4H_2O$: C, 57.05; H, 6.26; N, 3.16. Found: C, 57.04; H, 6.00; N, 2.79.

N-Tosyl-2-(2-acetoxy-1-isopropylthioethyl)-5-methoxyanilide (4j): oil, ir(film) ν_{max}: 3250, 1740, 1610 and 1580 cm^{-1}; ^{1}H nmr δ: 1.12 and 1.21(6H, each d, J= 6.7 Hz), 2.01(3H, s), 2.39(3H, s), 2.71(1H, septet, J=6.7 Hz), 3.75(3H, s), 3.95-4.00(1H, m), 4.20-4.24(2H, m), 6.65(1H, dd, J=2.6 and 8.7 Hz), 7.04(1H, d, J=2.6 Hz), 7.15(1H, d, J=8.7 Hz), 7.25(2H, d, J=8.2 Hz), 7.60(2H, d J=8.2 Hz), 7.94(1H, br s). Anal. Calcd for $C_{21}H_{27}NO_5S_2$: C, 57.63; H, 6.22; N, 3.20. Found: C, 57.50; H, 6.33; N, 3.24.

General Procedure for the Preparation of Substituted N-Tosylindole 5.

ortho-Functionalized substituted N-tosylanilide (**4**) (1 mmol) was dissolved in propionic acid (8 ml) and refluxed for 27-120 h. The solvent was evaporated and the residue was partitioned between CH_2Cl_2 and water containing 10% NaOH. The organic layer was separated, washed with water, dried over $MgSO_4$, filtered and concentrated. The residue was chromatographed on a silica gel column with $CHCl_3$ to afford substituted N-tosylindole (5). The spectral data of the compounds as follows.

N-Tosyl-5-methylindole (5a): mp 67-68°C; ir(nujol) ν_{max}: 1595 and 1170 cm^{-1}; ^1H nmr δ: 2.30(3H, s), 2.38(3H, s), 6.56(1H, d, J=3.6 Hz), 7.11(1H, d, J=8.5 Hz), 7.18(2H, d, J=8.0 Hz), 7.29(1H, s), 7.50(1H, d, J=3.6 Hz), 7.73(2H, d, J=8.0 Hz), 7.86(1H, d, J=8.5 Hz). Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.29; N, 4.90. Found: C, 67.24; H, 5.31; N, 4.84.

N-Tosyl-5-methoxylindole (5c): mp 92.5-93.5°C; ir(nujol) ν_{max}: 1610, 1595, 1590 and 1170 cm^{-1}; ^1H nmr δ: 2.32(3H, s), 3.79(3H, s), 6.57(1H, dd, J=0.8 and 3.6 Hz), 6.91(1H, dd, J=2.6 and 9.0 Hz), 6.95(1H, d, J=2.6 Hz), 7.18 (2H, d, J=8.7 Hz), 7.51(1H, d, J=3.6 Hz), 7.72(2H, d, J=8.7 Hz), 7.87(1H, dd, J=0.8 and 9.0 Hz). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.76; H, 5.01; N, 4.64. Found: C, 63.63; H, 4.98; N, 4.48.

N-Tosyl-5-chlorolindole (5d): mp 85-86°C; ir(KBr) ν_{max}: 1600, 1445, 1370, 1170 and 820 cm^{-1}; ^1H nmr δ: 2.32(3H, s), 6.57(1H, d, J=3.6 Hz), 7.19-7.27 (3H, m), 6.95(1H, d, J=2.6 Hz), 7.47(1H, d, J=2.0 Hz), 7.57(1H, d, J=3.6 Hz), 7.73(2H, d, J=8.3 Hz), 7.92(1H, d, J=8.9 Hz). Anal. Calcd for $C_{15}H_{12}NO_2ClS$: C, 58.91; H, 3.95; N, 4.58. Found: C, 58.83; H, 3.94; N, 4.47.

N-Tosyl-5-nitroindole (5e): mp 158-159°C; ir(KBr) ν_{max}: 1620, 1600 ,1520, 1375, 1350 and 1170 cm^{-1}; ^1H nmr δ: 2.36(3H, s), 6.81(1H, d, J=3.6 Hz), 7.28(2H, d, J=8.3 Hz), 7.74(1H, d, J=3.6 Hz), 7.80(2H, d, J=8.3 Hz), 8.08 (1H, d, J=9.2 Hz), 8.20(1H, d, J=9.2 Hz), 8.46(1H, s). Anal. Calcd for $C_{15}H_{12}N_2O_4S$: C, 56.95; H, 3.82; N, 8.85. Found: C, 56.86; H, 3.79; N, 8.74.

N-Tosyl-3-(isopropylthio)-5-nitro-2,3-dihydroindole (6e): oil, EIms(M/Z), 392(M^+) for $C_{18}H_{20}N_2O_4S_2$; ir(film) ν_{max}: 1600, 1375, 1350 and 1170 cm^{-1}; ^1H nmr δ: 1.23 and 1.28(6H, each d, J=6.6 Hz), 2.40(3H, s), 2.98(1H, septet, J=6.6 Hz), 3.99(1H, dd, J=3.3 and 8.9 Hz), 4.34-4.45(2H, m), 7.30

(2H, d, J=8.3 Hz), 7.69(1H, d, J=8.9 Hz), 7.74(2H, d, J=8.3 Hz), 8.09(1H, d, J=2.3 Hz), 8.15(1H, dd, J=2.3 and 8.9 Hz).

N-Tosyl-7-methoxylindole (5f): mp 50-52°C; ir(nujol) ν_{max}: 1610, 1580 and 1170 cm^{-1}; ^{1}H nmr δ: 2.37(3H, s), 3.67(3H, s), 6.62(1H, d, J=3.6 Hz), 6.67 (1H, d, J=7.8 Hz), 7.10(1H, t, J=7.8 Hz), 7.15(1H, d, J=7.8 Hz), 7.24(2H, d, J=8.3 Hz), 7.72(2H, d, J=8.3 Hz), 7.82(1H, d, J=3.6 Hz). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.76; H, 5.01; N, 4.64. Found: C, 63.66; H, 5.07; N, 4.55.

N-Tosyl-3-[2-(2-tosylamino-6-methoxyphenyl)-2-isopropylthioethyl]-7-methoxyindole (6f): oil, FDms(M/Z), 678(M$^+$) for $C_{35}H_{38}N_2O_6S_3$; ir(film) ν_{max}: 3230, 1600 and 1170 cm^{-1}; ^{1}H nmr δ: 1.26 and 1.31(6H, each d, J=6.6 Hz), 2.38(3H, s), 2.40(3H, s), 3.11(3H, s), 3.12-3.20(1H, m), 3.29-3.34(2H, m), 3.64(3H, s), 5.52(1H, m), 6.29(1H, br s), 6.44(1H, dd, J=1.1 and 7.2 Hz), 6.65(1H, d, J=8.0 Hz), 6.80(1H, d, J=7.8 Hz), 7.06(1H, d, J=8.0 Hz), 7.07(2H, d, J=8.3 Hz), 7.20-7.26(4H, m), 7.57(2H, d, J=8.3 Hz), 7.73(2H, d, J=8.3 Hz), 7.77(1H, d, J=3.6 Hz).

N-Tosyl-7-chloroindole (5g): oil, ir(film) ν_{max}: 1595, 1570, 1360, 1170 and 790 cm^{-1}; ^{1}H nmr δ: 2.38(3H, s), 6.70(1H, d, J=3.6 Hz), 7.11(1H, t, J=7.6 Hz), 7.20(1H, dd, J=1.3 and 7.6 Hz), 7.26(2H, d, J=8.3 Hz), 7.46(1H, dd, J= 1.3 and 7.6 Hz), 7.69(2H, d, J=8.3 Hz), 7.90(1H, d, J=3.6 Hz). Anal. Calcd for $C_{15}H_{12}NO_2ClS$: C, 58.91; H, 3.95; N, 4.58. Found: C, 58.69; H, 4.30; N, 4.30.

N-Tosyl-3-isopropylthio-5-chloro-2,3-dihydroindole (6g): oil, EIms(M/Z), 381(M$^+$) for $C_{18}H_{20}NO_2ClS_2$; ir(film) ν_{max}: 1600, 1460, 1360 and 790 cm^{-1}; ^{1}H nmr δ: 1.22, 1.27 and 1.32(12H, each d, J=6.6 Hz), 2.41(3H, s), 2.90(1H, septet, J=6.6 Hz), 3.00(1H, septet, J=6.6 Hz), 3.12(2H, d, J=7.6 Hz), 5.01 (1H, t, J=7.6 Hz), 6.60(1H, br s), 7.16(1H, dd, J=2.0 and 8.3 Hz), 7.18-7.28(1H, m), 7.23(2H, d, J=8.3 Hz), 7.56-7.63(1H, m), 7.62(2H, d, J=8.3 Hz).

N-Tosyl-7-methylindole (5h): mp 50-52°C; ir(KBr) ν_{max}: 1600, 1370, 1190 and 790 cm^{-1}; ^{1}H nmr δ: 2.35(3H, s), 2.54(3H, s), 6.68(1H, d, J=3.6 Hz), 7.00(1H, d, J=7.3 Hz), 7.11(1H, t, J=7.6 Hz), 7.21(2H, d, J=7.9 Hz), 7.38

(1H, d, J=7.6 Hz), 7.53(2H, d, J=7.9 Hz), 7.78(1H, d, J=3.6 Hz). Anal. Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.29; N, 4.90. Found: C, 67.30; H, 5.30; N, 4.83.

N-Tosyl-4-methoxyindole (5i): mp 127-128°C; ir(nujol) ν_{max}: 1605, 1590, 1165 and 1125 cm^{-1}; ^1H nmr δ: 2.32(3H, s), 3.88(3H, s), 6.63(1H, d, J=8.0 Hz), 6.76(1H, d, J=3.9 Hz), 7.20(1H, dd, J=8.0 and 8.5 Hz), 7.23(2H, d, J=8.2 Hz), 7.46(1H, d, J=3.9 Hz), 7.59(2H, d, J=8.2 Hz), 7.74(1H, d, J=8.5 Hz). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.76; H, 5.01; N, 4.64. Found: C, 63.41; H, 4.98; N, 4.48.

N-Tosyl-6-methoxyindole (5j): mp 125-126°C; ir(nujol) ν_{max}: 1610, 1600, 1590 and 1175 cm^{-1}; ^1H nmr δ: 2.33(3H, s), 3.87(3H, s), 6.57(1H, d, J=3.6 Hz), 6.85(1H, dd, J=2.3 and 8.7 Hz), 7.21(2H, d, J=8.5 Hz), 7.37(1H, d, J=8.7 Hz), 7.44(1H, d, J=3.6 Hz), 7.52(1H, d, J=8.7 Hz), 7.74(2H, d, J=8.5 Hz). Anal. Calcd for $C_{16}H_{15}NO_3S$: C, 63.76; H, 5.01; N, 4.64. Found: C, 63.41; H, 4.98; N, 4.48.

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