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Studies on Heterocyclic Compounds. XXXIV.[1] Synthesis of 2-Substituted Aminobenzoxazoles with Nickel Peroxide

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Oxidation of N-methyl (or phenyl)-N′-(4-methylpyrid-2-yl)thiourea (Ia, b) with nickel peroxide (Ni-PO) under reflux in benzene or acetonitrile afforded the corresponding ureas (IIa, b).

N-(2-Hydroxy-5-methylphenyl)-N′-methylthiourea (IVa) was synthesized by the reaction of 2-amino-4-methylphenol (III) and methyl isothiocyanate in benzene under reflux. However, the reaction of III and phenyl isothiocyanate in benzene under reflux did not afford the thiourea (IVb) but IVb was obtained in ethanol at room temperature. Ni-PO oxidation of thioureas (IVa—f) in acetonitrile at room temperature afforded 2-substituted aminobenzoxazoles (VIIa—f) in good yields. The reaction mechanisms of Ni-PO and thioureas (Ia, b and IVa—f) are discussed.

Keywords——N-substituted N′-(4-methylpyrid-2-yl)thioureas; N-substituted N′-(4-methylpyrid-2-yl)ureas; N-(2-hydroxyphenyl) N′-substituted thioureas; 2-substituted aminobenzoxazoles; nickel peroxide; oxidative cyclization; 2-mercaptobenzoxazole; isothiocyanates

In the previous paper,[1] we reported the synthesis of 1,2,3-triazolo[1,5-*a*]pyridines by oxidative cyclization of hydrazone derivatives of pyridine-2-carbaldehydes and 2-pyridyl ketones with nickel peroxide (Ni–PO). As a continuation and extension of our studies on oxidative cyclization with Ni–PO, we were interested in the synthesis of heterocyclic compounds with Ni–PO and investigated the oxidation of thioureas bearing 2-pyridyl and *o*-hydroxyphenyl groups.

The starting materials, N-methyl (or phenyl)-N′-(4-methylpyrid-2-yl)thiourea (Ia, b), were synthesized by refluxing 2-amino-4-methylpyridine and methyl (or phenyl) isothiocyanate in xylene or ethanol (Table I). Ia and Ib were stirred under reflux with Ni–PO in benzene or acetonitrile and the structures of products (IIa, b) were determined on the basis of elemental analyses ($C_8H_{11}N_3O$ and $C_{13}H_{13}N_3O$), mass (MS) (*m/z* 165 (M^+) and 227 (M^+)), infrared (IR), and nuclear magnetic resonance (NMR) spectra, and also by comparison with authentic compounds prepared by an alternate method from 2-amino-4-methylpyridine and methyl (or phenyl) isocyanate. The IR spectrum showed the C=O absorption band at 1675 (IIa) and 1685 cm^{-1} (IIb) (Table II). In order to attempt the oxidation of S-methylated derivatives of Ia, b with Ni–PO, Ia, b were treated with methyl iodide and triethylamine in methanol. The reaction afforded the ureas (IIa, b) instead of S-methylated products. This reaction presumably proceeded through the S-methylated intermediate, and the intermediate was hydrolyzed immediately to afford ureas (Chart 1). Konaka *et al.*[2] reported that Ni–PO could generate a hydroxy radical and thus abstract a hydrogen radical from a target molecule. Presumably the formation of IIa, b from Ia, b with Ni–PO proceeded through initial abstraction of a hydrogen radical from the thiourea to afford carbodiimide as an intermediate and then a hydroxy radical attacked the carbodiimide (path A), or the hydroxy radical attacked Ia, b directly and a hydrogen radical was abstracted from the hydroxy group (path B), affording the ureas (Chart 2). Omar *et al.*[3] reported the same mechanism, *i.e.*, that the synthesis of benzimidazoles from N-(2-aminophenyl)-N′-substituted thioureas and dicyclohexylcarbodi-

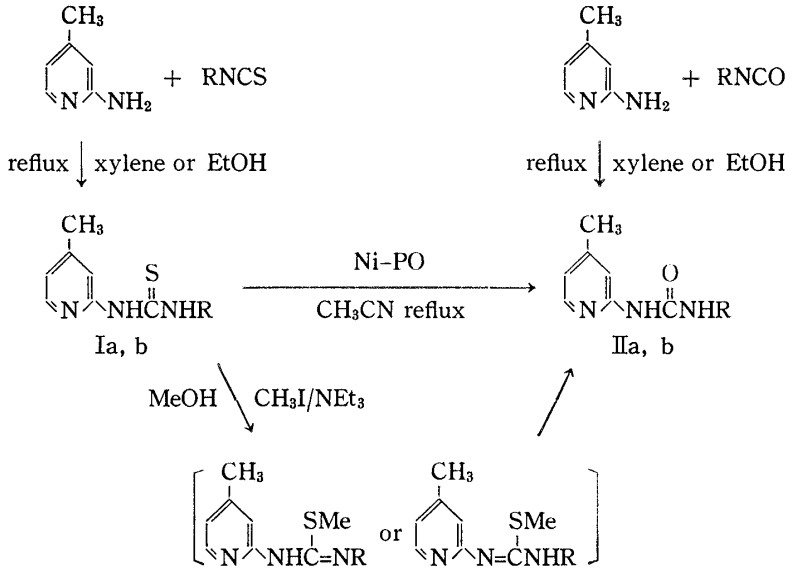

Chart 1

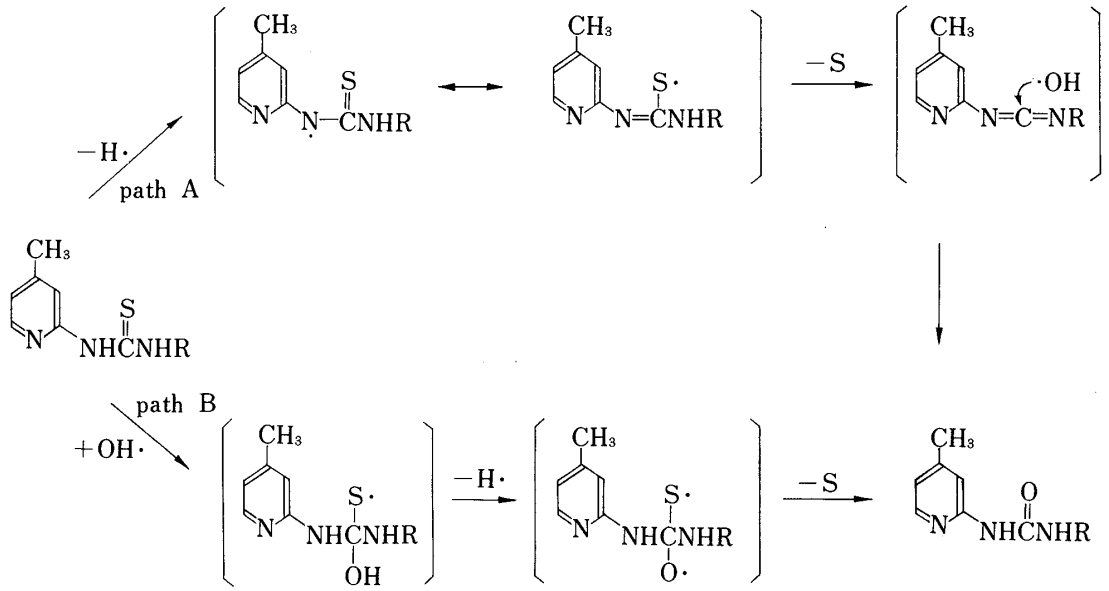

Chart 2

imide (DCC) or $HgCl_2$ proceeded through the carbodiimide as an intermediate. It was considered, from the reaction mechanisms of the formation of II from I with Ni–PO, that heterocyclic compounds could be synthesized by means of intramolecular oxidative cyclization with Ni–PO.

Treatment of 4-methyl-2-aminophenol (III) with methyl isothiocyanate in benzene under reflux gave the thiourea derivative (IVa) in 80% yield. However, when III was treated with phenyl isothiocyanate in benzene under reflux, a trace amount of thiourea (IVb), 5-methyl-2-mercaptobenzoxazole (VI; 68%), and N,N′-diphenylthiourea (V; 9%) were obtained. IVb was synthesized from III and phenyl isothiocyanate in ethanol at room temperature in 93% yield (Chart 3). VI was obtained as a main product upon refluxing IVb in benzene, ethanol or acetic acid. The starting material was recovered upon refluxing IVa in benzene or ethanol, but a 49% yield of VI was obtained in acetic acid.

Oxidation of IVa—f with Ni–PO in acetonitrile at room temperature afforded 2-substituted aminobenzoxazoles (VIIa—f) in relatively high yields (59—85%) and at the same time sulfur

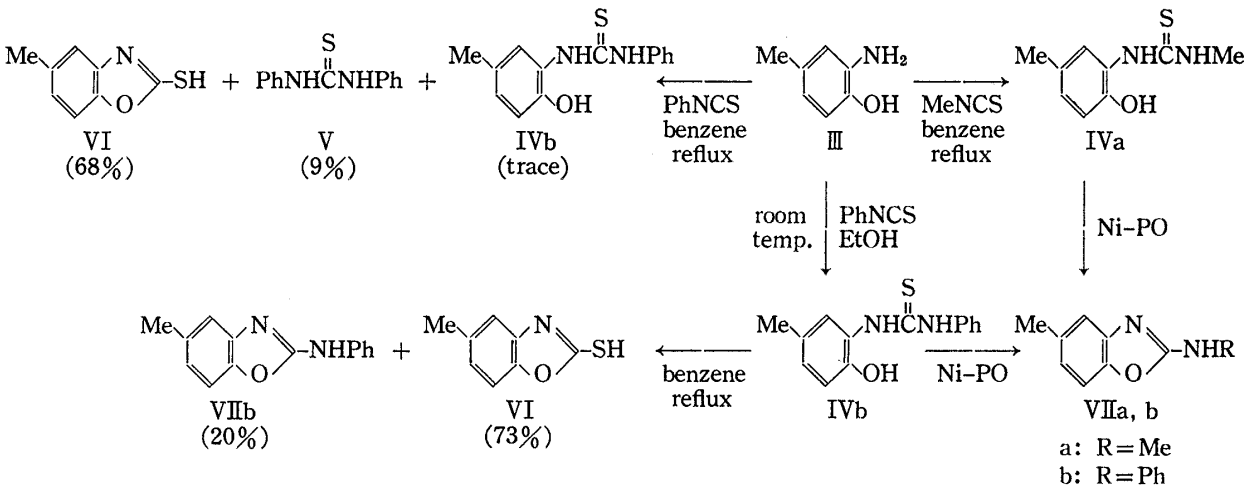

Chart 3

was obtained (mp 100—102°, MS *m/z*; 256 (M^+)). In our previous report on the synthesis of nucleoside analogs,[4] N-glycosylaminoimidazoles were synthesized from the reaction of glycosyl thioureides, which were obtained from diamines and glycosyl isothiocyanates, with methyl iodide and triethylamine in high yields. Treatment of IV with methyl iodide and triethylamine in methanol afforded VII (Table IV).

It can be presumed that the formation mechanism of VII from the reaction of IV and Ni–PO is the same as that of II from I and Ni–PO (Chart 4).

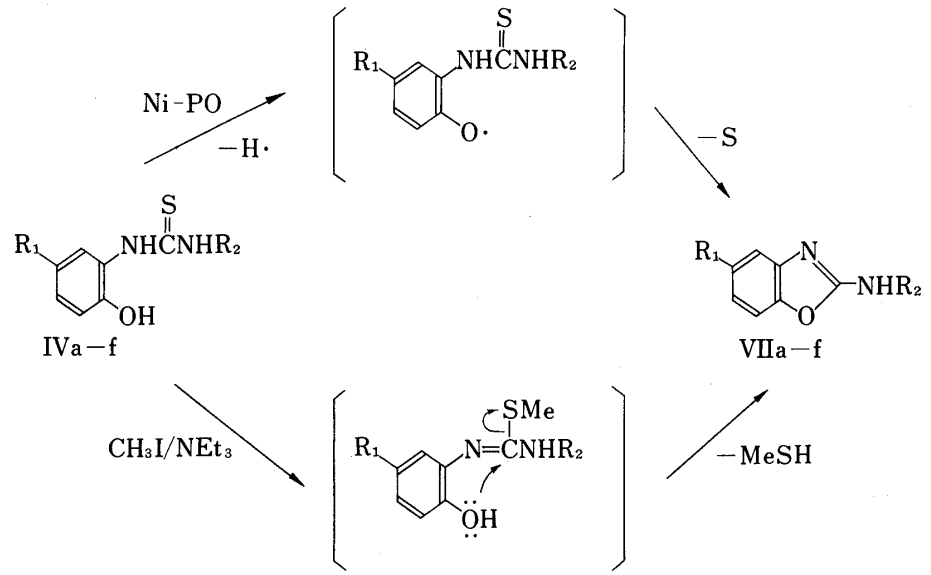

Chart 4

Ni–PO oxidation is a very convenient and economical method, because the work-up procedure is very simple and the oxidant can be stored for several years at room temperature without decrease of activity. The Ni–PO reagent can be renewed with alkaline hypochlorite solution after oxidation reactions. Thus, Ni–PO is an excellent agent for the preparation of 2-substituted aminobenzoxazoles by oxidative cyclization of the thioureas.

Experimental

All melting points were determined in a capillary tube and are uncorrected. IR spectra were determined on a JASCO model IRA-2 spectrometer and NMR spectra with a Varian T-60 using tetramethylsilane as an

internal standard (s, singlet; br, broad; d, doublet; m, multiplet; ar, aromatic). Mass spectra were recorded with a JEOL 01S spectrometer; in all cases direct sample insertion was carried out into the ion source at an ionizing energy of 70 eV.

Nickel Peroxide——Solid nickel peroxide was prepared by the treatment of an aqueous solution of nickel sulfate with sodium hypochlorite in alkaline solution. The available-oxygen content in Ni-PO was determined by iodometry as described in a previous report.[5] It contained (after being washed and dried at room temperature) about 3.4 mg-atom active oxygen per gram Ni-PO.

N-Methyl (or Phenyl)-N′-(4-methylpyrid-2-yl)thiourea (Ia, b)——2-Amino-4-methylpyridine (1.8 g), methyl isothiocyanate (1.2 g) and xylene (22 ml) were refluxed for 2 hr. After cooling to room temperature,

Table I. N-Methyl (or Phenyl)-N′-(4-methylpyrid-2-yl)thioureas

Comp. No.	Yield (%)	mp (°C)	MS m/z (M^+)	IR ν_{max}^{KBr} cm^{-1}	NMR δ (DMSO-d_6)	Formula	*Anal.* (%) Calcd. (Found) C	H	N
Ia	94	168—170	181	3170, 2970 1605, 1520	2.30 (3H, s, $-CH_3$) 3.12 (3H, d, $J=5$ Hz, $-NHCH_3$) 6.80—7.07 (2H, m, 3, 4-H) 8.10 (1H, d, $J=5$ Hz, 6-H) 10.38 (1H, br-s, NH) 11.55 (1H, br-s, NH)	$C_8H_{11}N_3S$	53.01 (53.19	6.12 6.10	23.18 23.15)
Ib	64	157—159	243	3200, 2950 1610, 1565 1530	2.30 (3H, s, $-CH_3$) 6.87—7.87 (7H, m, ar-H) 8.18 (1H, d, $J=5$ Hz, 6-H) 10.47 (1H, br-s, NH) 13.97 (1H, br-s, NH)	$C_{13}H_{13}N_3S$	64.17 (64.00	5.39 5.38	17.27 17.39)

Table II. N-Methyl (or Phenyl)-N′-(4-methylpyrid-2-yl)ureas

Comp. No.	Yield (%) Ni-PO	CH_3I/NEt_3	RNCO	mp (°C)	MS m/z (M^+)	IR ν_{max}^{KBr} cm^{-1}
IIa	59	58	94	185—186	165	3230, 3030, 1675, 1610
IIb	36	30	85	174—176	227	3200, 3000, 1685, 1600

Comp. No.	NMR δ (DMSO-d_6)	Formula	*Anal.* (%) Calcd (Found) C	H	N
IIa	2.27 (3H, s, $-CH_3$) 2.75 (3H, d, $J=5$ Hz, NH–CH_3) 6.75 (1H, d, $J=5$ Hz, 5-H) 7.08 (1H, s, 3-H) 8.02 (1H, d, $J=5$ Hz, 6-H) 8.23 and 9.05 (each 1H, br-s, NH)	$C_8H_{11}N_3O$	58.16 (58.10	6.71 6.58	25.44 25.71)
IIb	2.33 (3H, s, $-CH_3$) 6.73—7.70 (7H, m, ar-H) 8.08 (1H, d, $J=5$ Hz, 6-H) 9.32 and 10.63 (each 1H, br-s, NH)	$C_{13}H_{13}N_3O$	68.70 (68.46	5.77 5.69	18.49 18.30)

the precipitates were collected and recrystallized from EtOH to give 1.67 g (94%) of Ia, mp 168—170°. Ib was synthesized by the same procedure but with EtOH as the solvent and phenyl isothiocyanate in place of methyl isothiocyanate; yield 64% and mp 157—159°. The results are summarized in Table I.

General Procedure for the Oxidation of Ia, b——Ni-PO (4.11 g) was added to a solution of I (0.01 mol) in benzene (100 ml) or CH_3CN (100 ml), with stirring on a magnetic stirrer, and the heterogeneous solution was stirred under reflux for 5 hr. The reaction mixture was filtered through a glass filter (G-4), and washed repeatedly. The combined filtrate was concentrated under reduced pressure to remove the solvent and the residue was recrystallized from EtOH. The results are summarized in Table II.

N-Methyl (or Phenyl)-N′-(4-methylpyrid-2-yl)urea (IIa, b)——(i) 2-Amino-4-methylpyridine (0.1 mol) was added to a solution of methyl (or phenyl) isocyanate (0.1 mol) in xylene (50 ml), and the mixture was stirred for 1 hr at room temperature. The precipitates were collected and recrystallized from EtOH.

(ii) I (5 mmol) was dissolved in MeOH (40 ml) and CH_3I (20 mmol) was added. The mixture was stirred for 30 min at room temperature. Next NEt_3 (20 mmol) was added and the whole was stirred overnight. The reaction mixture was refluxed for 3 hr then concentrated under reduced pressure. The residue was dissolved in $CHCl_3$ and the solution was washed with H_2O, dried over Na_2SO_4 and concentrated. The residual semi solid was crystallized from acetone or EtOH. The results are summarized in Table II.

Preparation of N-(2-Hydroxyphenyl)-N′-methyl(or phenyl)thiourea Derivatives (IVa—f)——Unless otherwise stated, thioureas (IVa—f) listed in Table III were obtained by the general method described below for the preparation of IVa and IVb.

N-(2-Hydroxy-5-methylphenyl)-N′-methylthiourea (IVa)——2-Amino-4-methylphenol (6.435 g), MeNCS (3.82 g) and benzene (45 ml) were refluxed for 1 hr. The reaction mixture was filtered and the collected precipitates were recrystallized from MeOH to give 8.22 g (80%) of IVa as colorless prisms.

Table III. N-(2-Hydroxyphenyl) -N′-methyl(or phenyl)thiourea Derivatives

Comp. No.	R_1	R_2	Yield (%)	mp (°C)	MS m/z (M^+)	Formula	*Anal.* (%) Calcd (Found) C	H	N
IVa	Me	Me	80	173—174	196	$C_9H_{12}N_2OS$	55.07 (54.94	6.16 6.14	14.27 14.43)
IVb	Me	Ph	93	144—146	258	$C_{14}H_{14}N_2OS$	65.09 (64.86	5.46 5.42	10.84 10.84)
IVc	H	Me	52	135—136	182	$C_8H_{10}N_2OS$	52.73 (52.97	5.53 5.53	15.37 15.51)
IVd	H	Ph	80	138—140	244	$C_{13}H_{12}N_2OS$	63.91 (63.98	4.59 4.88	11.47 11.49)
IVe	Cl	Me	64	160—162	216	$C_8H_9ClN_2OS$	44.34 (44.61	4.19 4.23	12.93 13.19)
IVf	Cl	Ph	84	127—130	278	$C_{13}H_{11}ClN_2OS$	56.01 (55.94	3.98 3.83	10.05 10.07)

Comp. No.	IR ν_{max}^{KBr} cm^{-1}	NMR δ(DMSO-d_6)
IVa	3400, 3290, 3000, 1540	2.20 (3H, s, $-CH_3$), 2.90 (3H, d, $J=4$ Hz, N–CH_3), 6.78 (2H, s, ar-H), 7.47 (1H, s, ar-H), 7.63 (1H, br-s, NH), 8.67 and 9.27 (each 1H, s, NH and OH)
IVb	3360, 3150, 3000, 1590	2.23 (3H, s, $-CH_3$), 6.80—7.80 (8H, m, ar-H), 9.02, 9.50 and 9.55 (each 1H, br-s, NH×2 and OH)
IVc	3350, 3150, 1600, 1570	2.95 (3H, d, $J=5$ Hz, $-CH_3$), 6.60—7.20 (3H, m, ar-H), 7.50—7.90 (2H, m, ar-H and NH), 8.75 and 9.55 (each 1H, s, NH and OH)
IVd	3330, 3150, 2950, 1600	6.60—8.10 (9H, m, ar-H), 9.00, 9.72 and 9.87 (each 1H, s, OH and NH×2)
IVe	3400, 3280, 2900, 1590	2.98 (3H, d, $J=4$ Hz, $-CH_3$), 6.70—7.10 (2H, m, ar-H), 7.90—8.30 (2H, m, ar-H and NH), 8.87 and 10.00 (each 1H, s, NH and OH)
IVf	3340, 3200, 2980, 1590	6.70—7.70 (8H, m, ar-H), 8.25, 9.07 and 10.10 (each 1H, s, OH and NH×2)

N-(2-Hydroxy-5-methylphenyl)-N′-phenylthiourea (IVb)——2-Amino-4-methylphenol (1.23 g), PhNCS (1.35 g) and EtOH (50 ml) were stirred for 1 hr at room temperature and left overnight. The precipitates were collected and washed thoroughly with a mixture of H_2O and EtOH (1: 1) to give IVb as white crystals.

Refluxing of 2-Amino-4-methylphenol and PhNCS in Benzene——2-Amino-4-methylphenol (1.23 g), PhNCS (1.35 g) and benzene (25 ml) were refluxed for 1 hr then cooled to room temperature. White needles were precipitated and collected by filtration to afford VI, 1.12 g (68%), mp 223—225°. MS *m/z*: 165 (M^+). *Anal.* Calcd for C_8H_7NOS: C, 58.16; H, 4.27; N, 8.48. Found: C, 58.21; H, 4.16; N, 8.47. IR ν_{max}^{KBr} cm^{-1}: 3300, 1470, 1450. NMR ($CDCl_3$) δ: 2.40 (3H, s, $-CH_3$), 6.90—7.10 (3H, m, ar-H), 7.43 (1H, s, –SH). The filtrate was concentrated to *ca.* 3 ml to give V as white needles, 21.4 mg (9%), mp 137—139°. MS *m/z*: 228 (M^+). *Anal.* Calcd for $C_{13}H_{12}N_2S$: C, 68.39; H, 5.30; N, 12.27. Found: C, 68.67; H, 5.32; N, 12.01. IR ν_{max}^{KBr} cm^{-1}: 3200, 1600, 1550. NMR ($CDCl_3$) δ: 7.00—7.70 (10H, m, ar-H), 9.77 (2H, s, –NH–×2). The mother liquor of V gave IVb (trace) and its structure was determined by comparison with an authentic sample that was prepared from 2-amino-4-methylphenol and PhNCS.

Refluxing of IVb in Benzene——A solution of IVb (258 mg) in benzene (13 ml) was refluxed for 9 hr. The reaction mixture was left overnight and the precipitates were collected by filtration to give VI, 109.7 mg. The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography (SiO_2–benzene) to give VI, 21.2 mg (total 109.7 mg, 73%) and VIIb, 43.4 mg (20%).

Refluxing of IVa in AcOH——A solution of IVa (980 mg) in AcOH (10 ml) was refluxed for 1 hr and the precipitates were collected by filtration to give VI, 403.3 mg (49%). H_2O was added to the filtrate and white needles were precipitated. The precipitates were recrystallized from EtOH to give IVa (130 mg).

Preparation of 2-Substituted Aminobenzoxazoles (VIIa—f) by Oxidative Cyclization with Ni-PO——Unless otherwise stated, VIIa—f listed in Table IV were obtained by the general method described below for the preparation of VIIb.

Table IV. Synthesis of 2-Substituted Aminobenzoles

Comp. No.	R_1	R_2	Yield (%) Ni-PO	Yield (%) CH_3I/NEt_3	mp (°C)[a]	MS *m/z*(M^+)	Formula	*Anal.* (%) Calcd (Found) C	H	N
VIIa	Me	Me	59	41	134—135	162	$C_9H_{10}N_2O$	66.65 (66.53	6.22 6.19	17.27 17.43)
VIIb	Me	Ph	85	38	205—207	224	$C_{14}H_{12}N_2O$	74.99 (74.87	5.38 5.37	12.49 12.49)
VIIc	H	Me	65	33	105—107	148	$C_8H_8N_2O$	64.85 (64.91	5.44 5.32	18.91 19.02)
VIId	H	Ph	82	45	172—174	210	$C_{13}H_{10}N_2O$	74.27 (74.40	4.79 4.77	13.33 13.49)
VIIe	Cl	Me	61	40	145—147	182	$C_8H_7ClN_2O$	52.62 (52.39	3.86 3.82	15.34 15.34)
VIIf	Cl	Ph	80	35	199—200	244	$C_{13}H_9ClN_2O$	63.81 (64.05	3.71 3.72	15.34 15.48)

a) Lit. mp: VIIc 108—109.5°,[b] VIId 170°,[c] VIIe 150.5—151°,[d] VIIf 199°.[c]
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Oxidation of IVb with Ni-PO——Ni-PO (683 mg, 2 mg-atom O*) was added to a solution of IVb (516 mg, 2 mmol) in CH_3CN (50 ml), with stirring, and the heterogeneous solution was stirred at room temperature for 5 hr. The reaction mixture was filtered through a glass filter (G-4), and washed repeatedly with hot CH_3CN. The combined filtrate was concentrated under reduced pressure. The residue was subjected to column chromatography (SiO_2–benzene) to give sulfur (44.8 mg) and VIIb. VIIb was recrystallized from $CHCl_3$ and petroleum ether to give pale yellow needles, 381.7 mg (85%), mp 205—207°. MS *m/z*: 224 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3400, 1660, 1640, 1600. NMR ($CDCl_3$) δ: 2.43 (3H, s, $-CH_3$), 6.75—7.85 (8H, m, ar-H), 8.03 (1H, s, –NH–).

VIIa: MS *m/z*: 162 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3350, 1670, 1640, 1590. NMR ($CDCl_3$) δ: 2.32 (3H, s, $-CH_3$), 2.92 (3H, d, J=4 Hz, $-CH_3$), 6.60—7.30 (3H, m, ar-H), 7.67 (1H, br-s, –NH–).

References and Notes

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