A New, Convenient Route to Erbstatin and *N*-Acetyl-1,2-didehydrodopamine

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Erbstatin dimethyl ether (12) was synthesized by Friedel–Crafts reaction of chloro(methyl- or phenylthio)acetonitrile (5a or 5b) with hydroquinone dimethyl ether, followed by reduction to the amine, formylation, and oxidative desulfenylation. By using a similar sequence of reactions, *N*-acetyl-1,2-didehydrodopamine dimethyl ether (13) was prepared from veratrole and 5a, b.

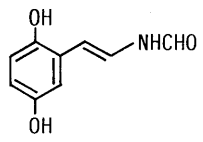
Keywords *N*-acetyl-1,2-didehydrodopamine; alane; β-aminostyrene; α-chlorosulfide; erbstatin; Friedel–Crafts reaction; sulfoxide

N-Acyl-β-aminostyrenes have been the subject of intensive synthetic studies, since they possess a wide spectrum of biological activities. Erbstatin (**1**) is an antibiotic isolated by Umezawa and co-workers in 1986 from the broth of *Streptomyces* sp. (MH435-hF3).[1] This compound has been shown to inhibit the membrane-associated tyrosine kinase activity of the human epidermoid carcinoma (A-431 cells). On the other hand, *N*-acetyl-1,2-didehydrodopamine (**2**) has been suggested to be one of the causative agents of sclerotization of insect cuticle.[2] The present paper describes a new, convenient synthesis of these compounds utilizing the Friedel–Crafts reaction of α-chlorosulfides **5** with arenes[3] as a key step.

Erbstatin dimethyl ether (**12**) was synthesized by the sequence of steps depicted in Chart 2. Thus, treatment of a mixture of hydroquinone dimethyl ether (**3**) and chloro(methylthio)acetonitrile (**5a**) with a stoichiometric amount of titanium (IV) chloride ($TiCl_4$) in dichloromethane (CH_2Cl_2) at 0 °C gave the Friedel–Crafts product **6a** in 71% yield. Similar reaction of **3** with chloro(phenylthio)-acetonitrile (**5b**) was rather sluggish at 0 °C, but afforded at room temperature the desired product **6b** in 78% yield.

Reduction of the nitriles **6a**, **b** to the amines **8a**, **b** proceeded poorly with lithium aluminum hydride ($LiAlH_4$). However, they were reduced smoothly by alane (AlH_3) in diethyl ether at 0 °C. The amines **8a**, **b** were then treated with an excess amount of ethyl formate under reflux to afford the formamides **10a** and **10b** in 84 and 82% yields (from **6a** and **6b**), respectively.

Conversion of **10b** to erbstatin dimethyl ether (**12**), which involves oxidation with sodium metaperiodate ($NaIO_4$) followed by thermolysis of the resultant sulfoxide in refluxing toluene (111 °C), has been reported.[4] Thermolysis of the corresponding methyl sulfoxide derived from **10a** was carried out in refluxing chlorobenzene (132 °C) to afford, in 63% yield, the enamide **12** (mp 85 °C, lit.[4] 87—88 °C). Demethylation of **12** to erbstatin (**1**) with boron tribromide has been described in the literature.[4,5]



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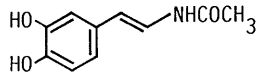

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Chart 1

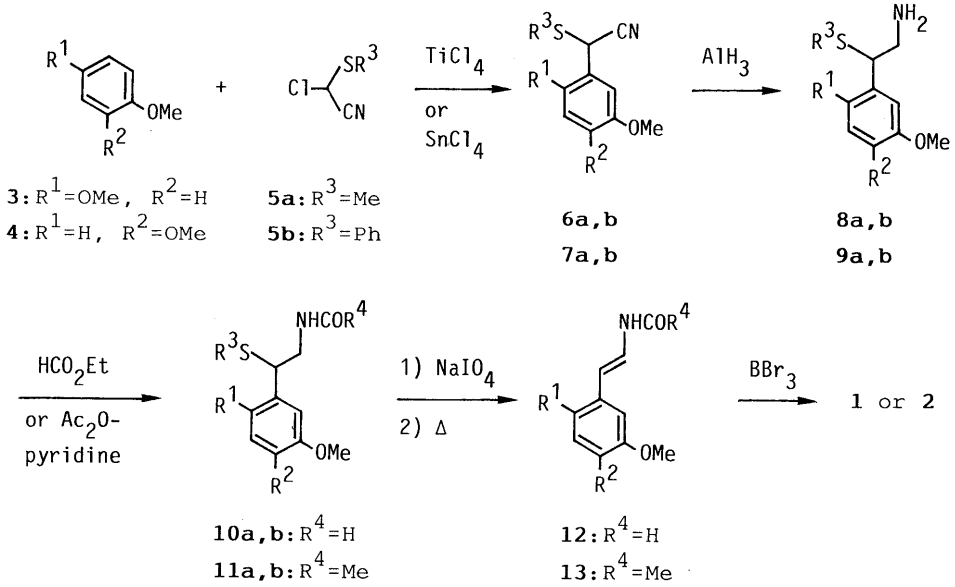

Chart 2

By using essentially the same method as above, *N*-acetyl-1,2-didehydrodopamine dimethyl ether (**13**) was prepared. Thus, the Friedel–Crafts reaction of veratrole (**4**) with α-chlorosulfides **5a**, **b** in the presence of tin (IV) chloride ($SnCl_4$) afforded the desired products **7a**, **b** in 57 and 32% yields, respectively. Reduction of **7a**, **b** with alane followed by acylation of the resultant amines **9a**, **b** with acetic anhydride and pyridine gave the acetamides **11a**, **b** in 74 and 80% yields (from **7a**, **b**), respectively. The amides **11a**, **b** were then oxidized and the resultant sulfoxides were heated in chlorobenzene or toluene to give the enamide **13**. Conversion of **13** to *N*-acetyl-1,2-didehydrodopamine (**2**) has been reported in the literature.[6,7]

In conclusion, the results described herein offer a general procedure for the synthesis of the *N*-acylated β-aminostyrenes such as **1** and **2** starting from common aromatic compounds.

Experimental

All melting points are uncorrected. Infrared (IR) spectra were recorded with a JASCO A-100 spectrophotometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were determined with a JEOL JNM-PMX 60 (60 MHz) spectrometer, and δ values are quoted relative to tetramethylsilane. Column chromatography was performed on Silica gel 60 PF_{254} (Merck) under pressure.

2,5-Dimethoxyphenyl(methylthio)acetonitrile (6a) $TiCl_4$ (0.81 ml, 7.4 mmol) was added to a stirred solution of **3** (1.02 g, 7.4 mmol) and **5a**[3] (0.9 g, 7.4 mmol) in CH_2Cl_2 (15 ml) at 0 °C, and stirring was continued at the same temperature for 1 h. The reaction was quenched by the addition of water, then the mixture was extracted with CH_2Cl_2, and dried ($MgSO_4$). The solvent was evaporated off and the residue was chromatographed on silica gel (hexane–ethyl acetate, 7 : 1) to give **6a** (1.17 g, 71%), mp 42.5—43.0 °C [from petroleum ether (bp 35—60 °C)]. IR ν_{max}^{KBr} cm^{-1}: 2240, 1595, 1500. ^{1}H-NMR ($CDCl_3$) δ: 2.24 (3H, s, SMe), 3.75 (3H, s, OMe), 3.80 (3H, s, OMe), 5.10 (1H, s, CH), 6.8—7.1 (3H, m, arom.). *Anal.* Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 58.84; H, 5.80; N, 6.42.

2,5-Dimethoxyphenyl(phenylthio)acetonitrile (6b) $TiCl_4$ (0.5 ml, 3.6 mmol) was added to a stirred solution of **3** (0.6 g, 4.3 mmol) and **5b**[8] (0.67 g, 3.6 mmol) in CH_2Cl_2 (10 ml) at 0 °C, and the mixture was stirred at room temperature for 1.5 h. Work-up gave **6b** (0.81 g, 78%), mp 61.0—61.5 °C [from petroleum ether (bp 35—60 °C)]. IR ν_{max}^{KBr} cm^{-1}: 2245, 1615, 1500. ^{1}H-NMR ($CDCl_3$) δ: 3.65 (3H, s, OMe), 3.86 (3H, s, OMe), 5.34 (1H, s, CH), 6.6—6.9 (3H, m, arom.), 7.2—7.6 (5H, m, arom.). *Anal.* Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.19. Found: C, 67.33; H, 5.17; N, 4.16.

3,4-Dimethoxyphenyl(methylthio)acetonitrile (7a) $SnCl_4$ (770 mg, 2.96 mmol) was added to a solution of **4** (410 mg, 2.96 mmol) and **5a** (360 mg, 2.96 mmol) in CH_2Cl_2 (50 ml) at 0 °C and the mixture was stirred at the same temperature for 1 h. Work-up gave **7a**[3] (377 mg, 57%) as an oil

3,4-Dimethoxyphenyl(phenylthio)acetonitrile (7b) In a manner similar to that described for **7a**, the chloride **5b** (200 mg, 1.09 mmol) was allowed to react with **4** (151 mg, 1.09 mmol) to give **7b** (100 mg, 32%), mp 84 °C [from petroleum ether (bp 35—60 °C)]. IR ν_{max}^{KBr} cm^{-1}: 2245, 1595, 1500. ^{1}H-NMR ($CDCl_3$) δ: 3.80 (3H, s, OMe), 3.86 (3H, s, OMe), 4.93 (1H, s, CH), 6.6—7.0 (3H, m, arom.), 7.2—7.7 (5H, m, arom.). *Anal.* Calcd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30; N, 4.91. Found: C, 67.35; H, 5.30; N, 4.87.

***N*-[2-(2,5-Dimethoxyphenyl)-2-(methylthio)ethyl]formamide (10a)** $AlCl_3$ (120 mg, 0.9 mmol) was added to a stirred suspension of $LiAlH_4$ (34 mg, 0.9 mmol) in dry diethyl ether (2.3 ml) at 0 °C and stirring was continued at the same temperature for 5 min. A solution of **6a** (200 mg, 0.9 mmol) in dry diethyl ether (1.8 ml) was added to the above solution of alane at 0 °C, and the mixture was stirred at the same temperature for 1 h. Water (10 ml) was added to the reaction mixture and the whole was made alkaline with 10% NaOH solution, then extracted with diethyl ether. The extract was dried (NaOH) and the solvent was evaporated off to give the amine **8a** (214 mg, quantitative), which was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (2H, s, NH_2), 1.97 (3H, s, SMe), 3.01 (2H, d, J=7 Hz, NCH_2), 3.75 (6H, s, OMe×2), 4.23 (1H, t, J=7 Hz, CH), 6.7—7.0 (3H, m, arom.). This amine was dissolved in ethyl formate (1 ml) and the mixture was heated under reflux for 2 h. Excess ethyl formate was evaporated off and the residue was chromatographed on silica gel (hexane–ethyl acetate, 1 : 1) to give **10a** (192 mg, 84% from **6a**), mp 64—65 °C (from hexane–ethyl acetate). IR ν_{max}^{KBr} cm^{-1}: 3300, 1655, 1490. ^{1}H-NMR ($CDCl_3$) δ: 2.00 (3H, s, SMe), 3.4—3.9 (2H, m, CH_2), 3.73 (3H, s, OMe), 3.77 (3H, s, OMe), 4.37 (1H, t, J=7 Hz, CH), 6.0—6.7 (1H, br, NH), 6.7—7.0 (3H, m, arom.), 8.03 (1H, br s, CHO). *Anal.* Calcd for $C_{12}H_{17}NO_3S$: C, 56.45; H, 6.71; N, 5.49. Found: C, 56.15; H, 6.67; N, 5.44.

***N*-[2-(2,5-Dimethoxyphenyl)-2-(phenylthio)ethyl]formamide (10b)** Using a procedure similar to that described for **10a**, the nitrile **6b** (290 mg, 1.02 mmol) was reduced by alane and the resultant amine **8b** was formylated with ethyl formate to give **10b** (266 mg, 82% from **6b**), mp 80—81 °C (from hexane–ethyl acetate), lit.[4] 84—86 °C. IR ν_{max}^{KBr} cm^{-1}: 3250, 1655, 1500. ^{1}H-NMR ($CDCl_3$) δ: 3.6—3.9 (2H, m, CH_2), 3.70 (3H, s, OMe), 3.76 (3H, s, OMe), 4.78 (1H, t, J=7 Hz, CH), 5.5—6.2 (1H, br, NH), 6.77 (3H, s, arom.), 7.1—7.5 (5H, m, arom.), 8.05 (1H, br s, CHO).

***N*-[2-(3,4-Dimethoxyphenyl)-2-(methylthio)ethyl]acetamide (11a)** Using a procedure similar to that described for **8a**, the nitrile **7a** (200 mg, 0.9 mmol) was reduced by alane to give the amine **9a**, which was used in the next step without further purification. ^{1}H-NMR ($CDCl_3$) δ: 1.7—2.1 (2H, br, NH_2), 1.92 (3H, s, OMe), 2.6—3.1 (2H, m, CH_2), 3.52 (1H, t, J=7 Hz, CH), 3.84 (6H, s, OMe×2), 6.5—7.1 (3H, m, arom.). This amine was dissolved in a mixture of acetic anhydride (0.5 ml) and pyridine (1 ml), and the mixture was allowed to stand overnight at room temperature. CH_2Cl_2 (15 ml) was added to the reaction mixture, and the whole was washed with 10% HCl, saturated $NaHCO_3$ solution, and water. The organic layer was dried ($MgSO_4$), the solvent was evaporated off, and the residue was chromatographed on silica gel (benzene–ethyl acetate, 5 : 1) to give **11a** (179 mg, 74% from **7a**), mp 99 °C (from benzene–ethyl acetate). IR ν_{max}^{KBr} cm^{-1}: 3360, 1660, 1590, 1510. ^{1}H-NMR ($CDCl_3$) δ: 1.93 (3H, s, COMe or SMe), 1.96 (3H, s, SMe or COMe), 3.3—4.0 (3H, m, $CHCH_2$), 3.86 (6H, s, OMe×2), 5.7—6.2 (1H, br, NH), 6.7—6.9 (3H, m, arom.). *Anal.* Calcd for $C_{13}H_{19}NO_4S$: C, 57.96; H, 7.11; N, 5.20. Found: C, 57.66; H, 7.14; N, 5.55.

***N*-[2-(3,4-Dimethoxyphenyl)-2-(phenylthio)ethyl]acetamide (11b)** According to the same procedure as that described for **11a**, the nitrile **7b** (100 mg, 0.35 mmol) was reduced by alane, and the resultant amine **9b** was treated with acetic anhydride and pyridine to give **11b** (93 mg, 80% from **7b**), mp 89 °C (from hexane–ethyl acetate). IR ν_{max}^{KBr} cm^{-1}: 3350, 1665, 1515. ^{1}H-NMR ($CDCl_3$) δ: 1.83 (3H, s, COMe), 3.5—3.8 (2H, m, CH_2), 3.77 (3H, s, OMe), 3.80 (3H, s, OMe), 4.32 (1H, dd, J=8, 6.5 Hz, CH), 5.75—6.25 (1H, br, NH), 6.73 (3H, s, arom.), 7.0—7.5 (5H, m, arom.). *Anal.* Calcd for $C_{18}H_{21}NO_3S$: C, 65.23; H, 6.39; N, 4.23. Found: C, 64.93; H, 6.50; N, 4.46.

***(E)*-*N*-[2-(2,5-Dimethoxyphenyl)ethenyl]formamide (12)** A solution of $NaIO_4$ (161 mg, 0.75 mmol) in water (3.4 ml) was added dropwise to a solution of **10a** (192 mg, 0.75 mmol) in methanol (2.3 ml), and the mixture was stirred at room temperature for 15 h. Water (10 ml) was added to the reaction mixture and the whole was extracted with CH_2Cl_2. The extract was dried ($MgSO_4$) and the solvent was evaporated off to give *N*-[2-(2,5-dimethoxyphenyl)-3-(methylsulfinyl)ethyl]formamide (202 mg, quantitative). This sulfoxide, without further purification, was dissolved in chlorobenzene (5 ml) and the mixture was heated under reflux for 4 h. The solvent was removed *in vacuo* and the residue was chromatographed on silica gel (benzene–ethyl acetate, 5 : 1) to give **12** (105 mg, 63% from **10a**), mp 85 °C (from ethyl acetate), lit.[4] 87—88 °C. IR ν_{max}^{KBr} cm^{-1}: 3280, 1670, 1520. ^{1}H-NMR (CD_3COCD_3) δ: 3.74 (3H, s, OMe), 3.77 (3H, s, OMe), 6.50 (1H, d, J=15 Hz, ArCH=C), 6.7—7.1 (3H, m, arom.), 7.65 (1H, dd, J=15, 10 Hz, NCH=C), 8.23 (1H, br s, CHO), 8.9—9.6 (1H, br, NH).

***(E)*-*N*-[2-(3,4-Dimethoxyphenyl)ethenyl]acetamide (13)** a) Using a standard method, the sulfide **11a** (170 mg, 0.63 mmol) was oxidized with $NaIO_4$ to give *N*-[2-(3,4-dimethoxyphenyl)-2-(methylsulfinyl)ethyl]acetamide, which was used in the next step without further purification. This sulfoxide was dissolved in chlorobenzene (10 ml) containing a small amount of $NaHCO_3$, and the mixture was heated under reflux for 8 h. Inorganic material was filtered off, the filtrate was concentrated *in vacuo*, and the residue was chromatographed on silica gel (benzene–ethyl acetate, 1 : 1) to give **13** (113 mg, 81% from **11a**), mp 180—182 °C (from ethyl acetate), lit.[6] 176—178 °C. IR ν_{max}^{KBr} cm^{-1}: 3250, 1650, 1605, 1510. ^{1}H-NMR ($CDCl_3$) δ: 2.10 (3H, s, COMe), 3.88 (6H, s, OMe×2), 6.00 (1H, d, J=14 Hz, ArCH=C), 6.7—6.9 (3H, m, arom.), 7.35 (1H, dd, J=14, 10 Hz, NCH=C), 7.4—7.8 (1H, br, NH).

b) Using a standard method, the sulfide **11b** (93 mg, 0.28 mmol) was oxidized with $NaIO_4$ to give *N*-[2-(3,4-dimethoxyphenyl)-2-(phenylsulfinyl)-ethyl]acetamide, which was used in the next step without further purification. A solution of the sulfoxide in toluene (3 ml) was heated under reflux for 7 h, the solvent was removed *in vacuo*, and the residue was chromatographed on silica gel (benzene–ethyl acetate, 1 : 1) to give **13** (75 mg,

quantitative from **11b**), mp 176—177 °C (from ethyl acetate), lit.[6] 176—178 °C.

References and Notes

1) H. Umezawa, M. Imoto, T. Sawa, K. Isshiki, N. Matsuda, T. Uchida, H. Iinuma, M. Hamada, and T. Takeuchi, *J. Antibiot.*, **39**, 170 (1986).
2) S. O. Andersen and P. Roepstorff, *Insect Biochem.*, **12**, 269 (1982); S. O. Andersen, "Comprehensive Insect Physiology, Biochemistry and Pharmacology," ed. by G. A. Kerkut and L. I. Gilbert, Pergamon Press, Oxford, 1985, p. 59.
3) Y. Tamura, H. D. Choi, M. Mizutani, Y. Ueda, and H. Ishibashi, *Chem. Pharm. Bull.*, **30**, 3574 (1982).
4) W. K. Anderson, T. T. Dabrah, and D. M. Houston, *J. Org. Chem.*, **52**, 2945 (1987).
5) For other syntheses of erbstatin, see D. G. Haugauer, *Tetrahedron Lett.*, **27**, 5799 (1986); R. L. Dow and M. J. Flynn, *ibid.*, **28**, 2217 (1987); K. Isshiki, M. Imoto, T. Takeuchi, H. Umezawa, T. Tsuchida, T. Yoshioka, and K. Tatsuta, *J. Antibiot.*, **40**, 1207 (1987); M. N. Deshmukh and S. V. Joshi, *Synth. Commun.*, **18**, 1483 (1988); J. Kleinschroth and J. Hartenstein, *Synthesis*, **1988**, 970.
6) B. Ramamurthy and M. Sugumaran, *Synthesis*, **1987**, 523.
7) For other synthesis of *N*-acetyl-1,2-didehydrodopamine, see H. Dali and M. Sugumaran, *Org. Prep. Proced. Int.*, **20**, 191 (1988).
8) H. Ishibashi, M. Okada, K. Sato, M. Ikeda, K. Ishiyama, and Y. Tamura, *Chem. Pharm. Bull.*, **33**, 90 (1985).