Organic Process Research & Development **2007**, *11*, 490–493

# New Practical Synthesis of the Key Intermediate of Candesartan

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**Abstract:**

**The development of a new, practical synthesis of methyl 3-amino-*N*-[(2′-cyanobiphenyl-4-yl)methyl]anthranilate, key intermediate of candesartan, is described, starting from methyl anthranilate. The features of our approach are as follows: (*i*) introduction of the 3-nitro group by acid catalysed rearrangement of the corresponding methyl *N*-nitroanthranilate; (*ii*) introduction of a (2′-cyanobiphenyl-4-yl)methyl side chain by *N*-alkylation of the appropriate *N*-nitroanthranilic acid derivative. In the most efficient procedure methyl *N*,3-dinitroanthranilate was *N*-alkylated with 4′-bromomethyl-biphenyl-2-nitrile. Catalytic reduction of the aromatic nitro group was accompanied with the removal of the *N*-nitro function to afford the required key intermediate in good yield.**

## Introduction

Candesartan cilexetil (**1**), an angiotensin II receptor blocker, has been available for several years for the treatment of hypertension and for use in heart failure.[1] Several methods have been described for the synthesis of compound **1** involving key intermediate **2**[2−4] (Figure 1).

The synthesis of 1,2,3-trisubstituted aromatic compounds is generally cumbersome by conventional methods. The presumable manufacturing synthesis of Takeda[4] started with nitro derivative **3** (available as the minor product by nitration of phthalic anhydride followed by hydrolysis). After selective esterification (**4**) the required amino function was introduced by Curtius reaction resulting carbamate **5**, which is an inconvenient method for scaling-up (Scheme 1). *N*-Alkylation with compound **6** followed by removal of the *tert*-butoxycarbonyl group and subsequent reduction of nitro derivative **7** afforded key intermediate **2**.

The most powerful method for the synthesis of 1,2,3-trisubstituted benzenes is lithiation of benzene derivatives substituted with 1,3-interrelated directing metalation groups (DMGs) at their common site followed by introduction of the new substituent with an appropriate nucleophile.[5] However, lithiation of benzene derivatives substituted with 1,3-related carbon and nitrogen based DMGs (e.g., −$CONR_2$, oxazolino and −NHCOR, −NHCOOR, respectively) followed by reaction with a $N^+$ synthon (electrophilic amination)[6] does not promise a more efficient industrial scale synthesis of the required compound.

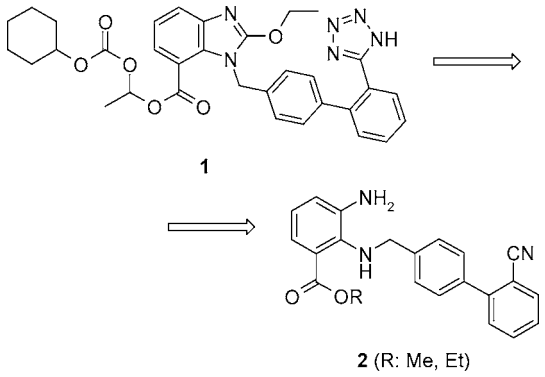
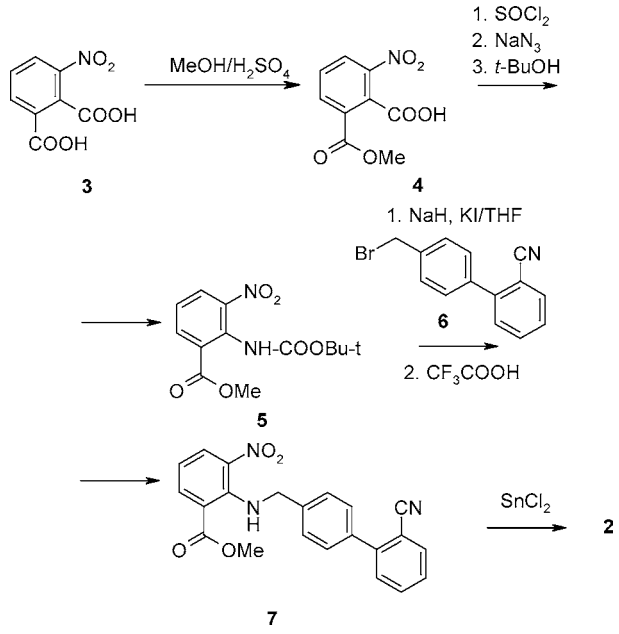



***Figure 1.*** **Candesartan cilexetil and its key intermediate.**

***Scheme 1***




## Results and Discussions

Here we report a convenient synthesis of key intermediate **2** starting from methyl anthranilate **8** (Scheme 2). Our strategy for the introduction of the second amino substituent was to use the rearrangement of *N*-nitroamine **9**, which is expected to give the 1,2,3-trisubstituted nitro derivative **10** as the major product.

*N*-Nitration of anilines and their rearrangement on treatment with acids to afford *ortho*- and *para*-nitroanilines, with

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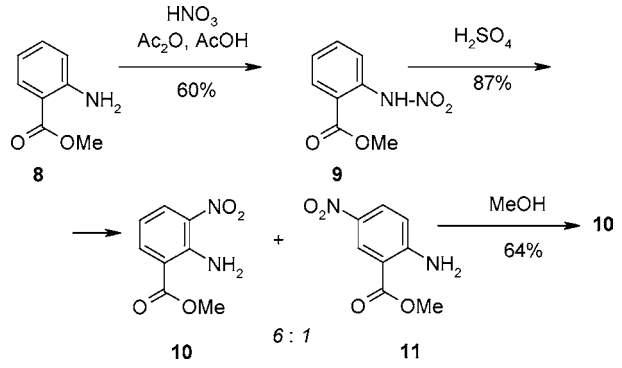
(1) *Drugs of the Future* **1993**, *18* (7), 609.
(2) Naka, T.; Nishikawa, K.; Kato, T. (Takeda Chem. Ind.) EP 459136 (filed 04.12.1991); U.S. Patent 5196444 (filed 23.03.1993).
(3) Naka, T.; Kato, T.; Nishikawa, K. (Takeda Chem. Ind.) EP 720982 (filed 19.04.1991).
(4) Hashimoto, H.; Hanaoka, T.; Kato, M. (Takeda Chem. Ind.) EP 881212 (filed 20.05.1998).
(5) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879.
(6) Greck, Ch.; Genêt, J.-P. *Synlett* **1997**, 741.


Published on Web 04/25/2007
10.1021/op700041z CCC: $37.00 

**Scheme 2**

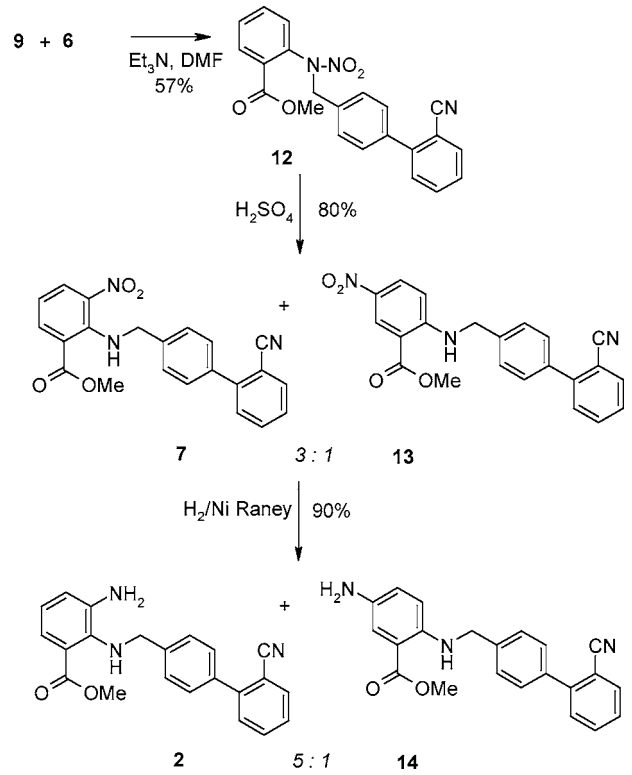



the *ortho* compounds predominating, is well documented in the literature.[7] The method has also been described starting from anthranilic acid.[8] However, it was not reproducible in our hands. We performed *N*-nitration of methyl anthranilate **8** with a mixture of fuming nitric acid, acetic acid, and acetic anhydride at 18−20 °C generating compound **9** in 60% yield. The reaction was reproducible and appropriate for scaleup. Treatment of *N*-nitro derivative **9** with sulfuric acid resulted in a mixture of 3- and 5-nitro derivatives (**10** and **11**) in a ratio of 6:1 (as determined by $^1$H NMR). After recrystallization of the crude mixture from methanol, pure isomer **10** was obtained in 55% yield based on *N*-nitro derivative **9**. As indicated in the literature,[8] 80% aqueous sulfuric acid was used in the rearrangement reaction. The formation of 3,5-dinitro derivative was observed in more concentrated (85−90%) sulfuric acid, presumably as the result of intermolecular processes. When using more diluted sulfuric acid, lower yields were obtained.

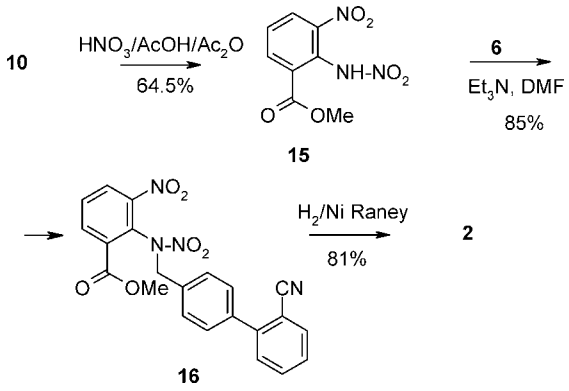
As it was to be expected, the amino group of compound **10** could not be alkylated with biphenylylmethyl bromide **6**. However, *N*-alkylation of the conjugate base of *N*-nitro derivative **9** and subsequent rearrangement might also offer a reasonable route to the required intermediate **7** (Scheme 3). *N*-Alkylation of compound **9** afforded derivative **12** (Scheme 3). Migration of the nitro group induced by acidic treatment of **12** produced a mixture of 3- and 5-nitro derivatives (**7** and **13**) in a ratio of 3:1, a mixture inseparable by crystallization. The primary product obtained after catalytic reduction of the nitro compound mixture was a 5:1 mixture of the hydrochlorides of phenylenediamines **2** and **14**. After tedious conventional separation procedures the desired product **2** was isolated in low (26%) yield.

Nevertheless, the conception to use *N*-nitro compounds for the introduction of the biphenyl side chain could be successfully applied starting from *ortho*-nitroaniline **10** (Scheme 4). It is worth mentioning that attempts to activation of the aniline nitrogen of compound **10** by acylation with ethyl chloroformate, acetic anhydride, and acetyl chloride under conventional conditions resulted in the recovery of the starting compound. *N*-Nitration of **10** afforded *N*,3-dinitro derivative **15**, which was *N*-alkylated with biphenylylmethyl bromide (**6**) to compound **16** in good yield. DSC studies of

**Scheme 3**




**Scheme 4**




both dinitro derivatives **15** and **16** do not indicate any decomposition of the compounds which could give rise to safety problems.

In the next step reduction of the aromatic nitro function by catalytic hydrogenation was accompanied with the removal of the *N*-nitro group providing intermediate **2** in 81% yield, isolated as its hydrochloride.

The studies described above allowed the development of a new manufacturing procedure for the preparation of key intermediate **2** of active pharmaceutical ingredient candesartan cilexetil (**1**).

## Experimental Section

Melting points are uncorrected. Infrared spectra were recorded as KBr pellets. $^1$H NMR spectra were recorded at 200 or 500 MHz. All unspecified reagents were from commercial resources. Methyl anthranilate was acquired from a Fluka catalogue, and 4′-bromomethyl-biphenyl-2-nitrile was synthetized according to the procedure described.[3,4]

(7) Williams, D. L. H. In *The Chemistry of Functional Groups, Supplement F*; Patai, S., Ed.; Wiley: New York, 1982; Part 1, pp 127−153.
(8) Macciotta, E. *Gazz. Chim. Ital*. **1939**, *69*, 330.

**Methyl *N*-Nitroanthranilate (9).** Methyl anthranilate (177.4 g; 152.0 mL; 1.17 mol) was dissolved in a mixture of acetic acid (1000 mL) and fuming nitric acid (304.0 g, 200 mL; 4.83 mol) at 20 °C. To the solution acetic anhydride (216.0 g; 200 mL; 2.12 mol) was added at 18−20 °C, and the mixture was stirred at room temperature for 20 min. It was poured into ice−water (2000 g). The crystalline product was filtered and washed with water to give **9** (138.0 g; 60%) as light gray crystals, mp 65−67 °C.

Anal. Calcd for $C_8H_8N_2O_4$ (196.16): C, 48.98; H, 4.11; N, 14.28%. Found: C, 48.86; H, 4.28; N, 14.30%. IR (KBr, $cm^{-1}$) 3133 (NH), 1692 (C═O), 1568, 1257 ($NO_2$); $^1$H NMR ($CDCl_3$) $\delta$ 13,29 (1H, s); 8.19 (1H, dd, $J$ = 8.4 Hz, $J$ = 1.1 Hz); 8.09 (1H, dd, $J$ = 8.0 Hz, $J$ = 1.9 Hz); 7.67 (1H, dt, $J$ = 8.4 Hz, $J$ = 1.9 Hz); 7.28 (1H, dt, $J$ = 8.0 Hz, $J$ = 1.1 Hz); 3.97 (3H, s).

**Methyl 3-Nitroanthranilate (10).** Methyl *N*-nitroanthranilate (**9**, 138.0 g; 0.7 mol) was added to a solution of sulfuric acid (80%, 690 mL) at 0 °C, and the mixture was stirred for 30 min at this temperature. It was poured into crushed ice (690 g), and the crystalline product was filtered and washed with water to give a mixture of **10** and **11** (121.0 g; 87.5%) in a ratio of 6:1, as determined by $^1$H NMR measurements on the basis of the intensity ratio of signals corresponding to the aromatic protons of the isomers.

$^1$H NMR (DMSO-$d_6$) for the 3-nitro derivative: $\delta$ 8.35 (1H, dd, $J$ = 8.4 Hz, $J$ = 1.1 Hz); 8.23 (1H, dd, $J$ = 8.0 Hz, $J$ = 1.4 Hz); 6.75 (1H, t, $J$ = 8.4 Hz); 3.86 (3H, s) and for the 5-nitro derivative: $\delta$ 8.60 (1H, d, $J$ = 2.6 Hz); 8.10 (1H, dd, $J$ = 9.2 Hz, $J$ = 1.4 Hz); 6.90 (1H, d, $J$ = 9.5 Hz); 3.86 (3H, s).

The crude product was recrystallized from methanol resulting in **10** (76.0 g; 55%, based on **9**) as yellow crystals, mp 94−95 °C. Anal. Calcd for $C_8H_8N_2O_4$ (196.16): C, 48.98; H, 4.11; N, 14.28%. Found: C, 49.10; H, 4.12; N, 14.09%. IR (KBr, $cm^{-1}$) 3455, 3320 ($NH_2$), 1703 (C═O), 1620, 1353 ($NO_2$); $^1$H NMR ($CDCl_3$) $\delta$ 8.47 (2H, bs); 8.37 (1H, dd, $J$ = 8.4 Hz, $J$ = 1.4 Hz); 8.23 (1H, dd, $J$ = 8.4 Hz, $J$ = 1.4 Hz); 6.65 (1H, t, $J$ = 8.4 Hz); 3.92 (3H, s).

**Methyl *N*-[(2′-Cyanobiphenyl-4-yl)methyl]-*N*-nitroanthranilate (12).** To a solution of methyl *N*-nitroanthranilate (**9**, 19.6 g; 0.10 mol) and triethylamine (11.1 g; 15.3 mL; 0.11 mol) in DMF (80 mL) was added a solution of 4′-bromomethyl-biphenyl-2-nitrile (27.2 g; 0.10 mol) at 20−25 °C, and the reaction mixture was stirred at room temperature for 6 h. After cooling to 0−5 °C it was diluted with water (200 mL), the solvents were decanted, and the thick oily residue was triturated with methanol (60 mL) to give a crystalline product. It was filtered and recrystallized from ethanol to give **12** (18.7 g; 48.3%) as colorless crystals, mp 96−97 °C. Anal. Calcd for $C_{22}H_{17}N_3O_4$ (387.40): C, 68.21; H, 4.41; N, 10.85%. Found: C, 67.93; H, 4.42; N, 10.59%. IR (KBr, $cm^{-1}$) 2228 (CN), 1724 (C═O), 1533, 1289 ($NO_2$); $^1$H NMR ($CDCl_3$) $\delta$ 8.17 (1H, dd, $J$ = 7.3, $J$ = 1.8 Hz), 7.77 (1H, dt, $J$ = 7.7 Hz, $J$ = 1.4 Hz), 7.70−7.41 (9H, m), 7.19 (1H, dd, $J$ = 7.1 Hz, $J$ = 2.1 Hz), 5.84 (1H, d, $J$ = 15.6 Hz), 4.71 (1H, d, $J$ = 15.6 Hz), 3.90 (3H, s). $^{13}$C NMR ($CDCl_3$): $\delta$ 164.9, 144.7, 139.2, 138.1, 135.3, 133.8, 133.7, 132.9, 132.3, 130.0, 129.9, 129.9, 129.1, 129.0, 127.7, 126.8, 118.5, 111.2, 57.5, 52.1.

**Mixture of Methyl 3- and 5-Nitro-*N*-[(2′-cyanobiphenyl-4-yl)methyl]anthranilate (7 and 13).** Methyl *N*-[(2′-cyanobiphenyl-4-yl)methyl]- *N*-nitroanthranilate (**12**, 22.6 g; 58 mmol) was added to a solution of 80% sulfuric acid (95 mL) at 0 °C, and the mixture was stirred at this temperature for 30 min. It was poured into crushed ice (200 g), and the reddish solid product was filtered, washed with water and refluxed in methanol (220 mL) for 1 h. After cooling the mixture was stirred at 0−5 °C for 1 h. The crystalline product was filtered to give a mixture of **7** and **13** (18.2 g; 80%) in a ratio of 3:1 as yellow crystals. The ratio of compounds **7** and **13** was determined by $^1$H NMR measurements on the basis of the intensity ratio of signals corresponding to the aromatic protons of the isomers.

Signals assigned to compound **7**: $^1$H NMR (DMSO-$d_6$) $\delta$ 8.65 (1H, t, $J$ = 5.5 Hz), 8.10 (1H, dd, $J$ = 8.1, $J$ = 1.8 Hz), 7.95 (1H, d, $J$ = 7.7 Hz), 7.78 (1H, dt, $J$ = 7.7, $J$ = 1.4 Hz), 7.68−7.50 (5H, m), 7.46 (2H, d, $J$ = 8.1, Hz), 6.87 (1H, t, $J$ = 8.0 Hz), 4.26 (2H, d, $J$ = 5.1 Hz), 3.84 (3H, s).

Signals assigned to **13**: $^1$NMR (DMSO-$d_6$) $\delta$ 9.09 (1H, t, $J$ = 5.5 Hz), 8.68 (1H, d, $J$ = 2.5 Hz), 8.20 (1H, dd, $J$ = 9.5 Hz, $J$ = 2.5 Hz), 8.10 (1H, m), 7.68−7.50 (5H, m), 7.46 (2H, d, $J$ = 8.1, Hz), 6.94 (1H, d, $J$ = 9.5 Hz), 4.76 (2H, d, $J$ = 5.8 Hz), 3.91 (3H, s).

**Methyl 3-Amino-*N*-[(2′-cyanobiphenyl-4-yl)methyl]anthranilate (2) and Methyl 5-Amino-*N*-[(2′-cyanobiphenyl-4-yl)methyl]anthranilate (14) by the Reduction of a Mixture of Methyl 3- and 5-Nitro-*N*-[(2′-cyanobiphenyl-4-yl)methyl]anthranilate (7 and 13).** The 3:1 mixture of methyl 3- and 5-nitro-*N*-[(2′-cyanobiphenyl-4-yl)methyl]-anthranilate (**7** and **13**; 34.9 g, 0.09 mol) in THF (177 mL) was hydrogenated in the presence of Raney nickel (∼10 g) at room temperature, under 10 bar. The reaction mixture was filtered and concentrated. The oily residue was dissolved in ethyl acetate (150 mL), and concd aqueous hydrochloric acid (7.6 mL; 0.09 mol) was added to the stirred solution at 0 °C. It was stirred for an additional 3 h at this temperature, and the crystalline product was filtered to give a 5:1 mixture of the hydrochlorides of **2** and **14** (32.0 g, 90%), as determined by $^1$H NMR measurements on the basis of the intensity ratio of signals corresponding to the aromatic protons of the isomers. The mixture of the hydrochlorides was suspended in a mixture of ethyl acetate (250 mL) and water (250 mL) and stirred at room temperature for 3 h. The crystalline product was filtered to give the hydrochloride of **14** (3.60 g; 10%), mp 220−223 °C (50% aqueous ethanol). Anal. Calcd for hydrochloride-monohydrate $C_{22}H_{22}ClN_3O_3$ (411.89): C, 64.15; H, 5.38; Cl, 8.61; N, 10.20%. Found: C, 63.89; H, 5.48; Cl, 8.69; N, 10.23%. IR (KBr, $cm^{-1}$) 3565, 3346, 2857, 2622 ($NH_2$), 2221 (CN), 1685 (C═O), 1520, 1442, 1239, 1210 ($NO_2$); $^1$H NMR (DMSO-$d_6$) $\delta$ 9.98 (2H, bs), 8.29 (1H, bs); 7.94 (1H, d, $J$ = 7.7 Hz); 7.86 (1H, d, $J$ = 2.5 Hz); 7.79 (1H, t, $J$ = 7.7 Hz); 7.62 (2H, t, $J$ = 7.7 Hz); 7.58 (2H, d, $J$ = 7.7 Hz); 7.49 (2H, d, $J$ = 8.0 Hz); 7.37 (1H, dd, $J$ = 9.1 Hz, $J$ = 2.5 Hz); 6.85 (1H, d, $J$ = 9.1 Hz); 4.62 (2H, d, $J$ = 3.3 Hz); 3.87 (3H, s).

The filtrate was evaporated to dryness. The solid residue was dissolved in a mixture of water (250 mL), ethyl acetate (250 mL), and aqueous ammonium hydroxide solution (25%, 25 mL). The organic layer was separated, washed with water (50 mL), dried, and evaporated. The dark solid residue was recrystallized from isopropyl ether (800 mL) to give **2** (8.4 g, 26.1%) as yellow crystals, mp 106−110 °C [lit[3] 110−111 °C]. Anal. Calcd for $C_{22}H_{19}N_3O_2$ (357.42): C, 73.93; H, 5.36; N, 11.76%. Found: C, 73.77; H, 5.40; N, 11.83%. IR (KBr, $cm^{-1}$) 3396, 3331 ($NH_2$), 2221 (CN), 1692 (C═O); $^1$NMR (DMSO-$d_6$) $\delta$ 7.76 (1H, dd, $J$ = 7.7 Hz, $J$ = 1.4 Hz); 7.64 (1H, td, $J$ = 7.7 Hz, $J$ = 1.4 Hz); 7.56−7.42 (6H, m); 7.40−7.33 (1H, m), 6.94−6.87 (2H, m); 6.40 (1H, bs); 4.23 (2H, s); 3.97 (2H, bs); 3.81 (3H, s).

**Methyl *N*,3-Dinitroanthranilate (15).** This compound was prepared analogously to **9**, starting from **10** (11.8 g; 0.06 mol). The resulting light gray crystalline product (**15**, 9.3 g; 64.5%), can be used in the next reaction step without further purification. A small sample was recrystallized from a mixture of ethyl acetate/methanol to give yellow crystals, mp 64−66 °C. Anal. Calcd for $C_8H_7N_3O_6$ (241.16): C, 39.84; H, 2.93; N, 17.42%. Found: C, 39.60; H, 2.95; N, 17.19%. IR (KBr): 3200 (NH), 1699 (C═O), 1602, 1538, 1359, 1318 ($NO_2$) $cm^{-1}$; $^1$H NMR ($CDCl_3$) $\delta$ 12.60 (1H, bs); 8.36 (1H, dd, $J$ = 7.9 Hz, $J$ = 1.5 Hz); 8.26 (1H, dd, $J$ = 8.2 Hz, $J$ = 1.5 Hz); 7.61 (1H, t, $J$ = 8.2 Hz; $J$ = 7.9 Hz); 4.03 (3H, s).

**Methyl *N*-[(2′-Cyanobiphenyl-4-yl)methyl]-*N*,3-dinitroanthranilate (16).** To a suspension of methyl *N*,3-dinitroanthranilate (**15**, 20.3 g; 84 mmol) and 4′-bromomethylbiphenyl-2-nitrile (22.9 g; 84 mmol) in THF (60 mL) was added triethylamine (9.4 g; 12.8 mL; 92.4 mmol). The reaction mixture was refluxed for 6 h, diluted with water (120 mL), and stirred at 0−5 °C for 1 h. The crystalline product was filtered and recrystallized from ethanol (95%) to give **16** (23.0 g; 63.5%) as yellow crystals, mp 150−151 °C. Anal. Calcd for $C_{22}H_{16}N_4O_6$ (432.40): C, 61.11; H, 3.73; N, 12.96%. Found: C, 60.92; H, 3.75; N, 12.84%. IR (KBr, $cm^{-1}$) 2220 (CN), 1731 (C═O), 1600, 1531, 1358, 1293 ($NO_2$); $^1$H NMR ($CDCl_3$) $\delta$ 8.28 (1H, dd, $J$ = 8.0 Hz, $J$ = 1.8 Hz); 8.14 (1H, dd, $J$ = 8.0 Hz, $J$ = 1.8 Hz); 7.78−7.59 (3H, m); 7.50−7.39 (4H, m); 7.29−7.22 (2H, m); 5.34 (1H, d, $J$ = 13.9 Hz); 5.21 (1H, d, $J$ = 13.9 Hz); 3.84 (3H, s).

**Methyl 3-Amino-*N*-[(2′-cyanobiphenyl-4-yl)methyl]anthranilate Hydrochloride (2·HCl).** A solution of methyl *N*-[(2′-cyanobiphenyl-4-yl)methyl]-*N*,3-dinitroanthranilate (**16**, 4.3 g; 10 mmol) in THF (60 mL) was hydrogenated at 50 °C, under 10 bar of hydrogen in the presence of Raney nickel (∼4.5 g). The reaction mixture was filtered and evaporated. The red oily residue was dissolved in ethyl acetate (5 mL), and concd aqueous hydrochloric acid solution (0.8 mL; 10 mmol) was added at 0 °C under vigorous stirring. It was stirred for an additional 3 h at this temperature and filtered to give the hydrochloric salt of **2** (3.2 g, 81%) as colorless crystals, mp 172−173 °C (acetonitrile). Anal. Calcd for $C_{22}H_{20}ClN_3O_2$ (393.88): C, 67.09; H, 5.12; Cl, 9.00; N, 10.67%. Found: C, 66.81; H, 5.20; Cl, 9.10; N, 10.67%. IR (KBr, $cm^{-1}$) 3292, 3181 ($NH_2$), 2218 (CN), 1682 (C═O); $^1$H NMR (DMSO-$d_6$) $\delta$ 7.96 (1H, d, $J$ = 7.7 Hz); 7.81 (1H, td, $J$ = 7.7 Hz; $J$ = 1.4 Hz); 7.62 (2H, d, $J$ = 7.7 Hz), 7.57 (4H, d, $J$ = 1.8 Hz); 7.48 (2H, t, $J$ = 8.2 Hz); 7.15 (1H, t, $J$ = 7.7 Hz); 4.46 (2H, s); 3.77 (3H, s).

**Note Added after ASAP Publication:** In the version published on the Internet April 25, 2007, the file for the Supporting Information was missing from the Internet. The file is present for the version published April 27, 2007.

## Supporting Information Available

DSC results for compounds **15** and **16**; $^1$H NMR and IR spectra for compounds **9**, **10**, **12**, **14**·HCl, **2**, **15**, **16**, and **2**·HCl; and$^1$H NMR spectra for the mixtures **10/11**, **7:13**, and **2**·HCl/**14**·HCl, respectively. This information is available free of charge via the Internet at http://pubs.acs.org.

Received for review February 16, 2007.

OP700041Z