JOC*Note*

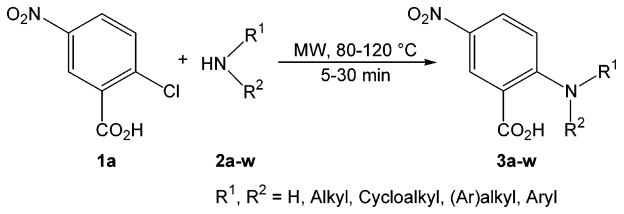
Catalyst-Free Microwave-Assisted Amination of 2-Chloro-5-nitrobenzoic Acid

Younis Baqi and Christa E. Müller*

Pharmaceutical Chemistry I, University of Bonn, An der Immenburg 4, D-53121 Bonn, Germany

christa.mueller@uni-bonn.de

Received April 7, 2007



The synthesis of N-substituted 5-nitroanthranilic acid derivatives **3a-w** was achieved by a new, mild, microwave-assisted, regioselective amination reaction of 5-nitro-2-chlorobenzoic acid (**1a**) with a diverse range of aliphatic and aromatic amines **2a-w** without added solvent or catalyst. Up to >99% isolated yield was obtained within 5−30 min at 80−120 °C. The reaction, which is suitable for upscaling, yielded new compounds that are of considerable interest as useful building blocks and as potential drugs.

N-Substituted anthranilic acid derivatives possess various pharmacological activities, e.g., *N*-arylanthranilic acids, such as mefenamic and flufenamic acid, are therapeutically used as nonsteroidal antiinflammatory drugs (NSAIDs) (Figure 1).[1] Recently, these compounds have been identified as promising lead structures for the development of novel therapeutics for neurodegenerative and amyloid diseases, such as Alzheimer's disease, because of their potency to inhibit plaque formation.[1,2] On the other hand, *N*-aralkylanthranilic acid derivatives, such as 2-benzylamino-5-nitrobenzoic acid (**3t**) and 5-nitro-2-phenethylaminobenzoic acid (**3u**), have been shown to interact with the cystic fibrosis transmembrane conductance regulator (CFTR) causing blockade of the chloride channel and have therefore potential as novel antiarrhythmic drugs.[3]

Furthermore, *N*-arylanthranilic acids are important precursors required for the synthesis of drug molecules, e.g., acridones and acridines, which have been developed as antiherpes agents,[4] anticancer and antimalarial drugs,[5] and the MEK-1 inhibitor 2-(2-chloro-4-iodophenylamino)-*N*-cyclopropylmethoxy-3,4-difluorobenzamine (CI-1040, PD184352),[6] which has been evaluated in clinical trials as a novel anticancer agent (Figure 1).

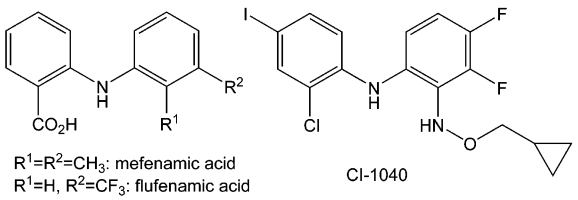


FIGURE 1. Structures of drug molecules derived from N-substituted anthranilic acids.

Because of their importance as drug molecules and building blocks for drugs, interest has grown in the development of methods for the efficient and rapid synthesis of *N*-arylanthranilic acids. The classical and still most widely used strategy for the synthesis of *N*-arylanthranilic acids utilizes the Ullmann coupling reaction,[7] or the related Ullmann−Goldberg coupling reaction,[8] which involve the reaction of a halobenzoic acid with an alkyl- or aryl-amine, or conversely, the coupling of an anthranilic acid derivative with an aryl halide, in the presence of a catalytic amount of copper (the metal, its oxide, or a salt).[9] A carboxylate group adjacent to the amine or to the halogen atom is essential for Ullmann type reactions. They typically require harsh conditions, such as high temperatures and long reaction times (130 °C for up to 24 h).[9a,b] Microwave irradiation has recently been shown to accelerate and improve Ullmann coupling reactions.[10] More recently, the Buchwald−Hartwig amination reaction has gained importance for the preparation of *N*-alkyl- and *N*-arylanthranilic acid derivatives and related compounds, in which aryl chlorides and aliphatic or aromatic amines undergo palladium-catalyzed C−N cross-coupling.[11]

* Corresponding author. Tel.: +49-228-73-2301, Fax.: +49-228-73-2567.

(1) (a) Green, N. S.; Palaninathan, S. K.; Sacchettini, J. C.; Kelly, J. W. *J. Am. Chem. Soc.* **2003**, *125*, 13404. (b) Oza, V. B.; Smith, C.; Raman, P.; Koepf, E. K.; Lashuel, H. A.; Petrassi, H. M.; Chiang, K. P.; Powers, E. T.; Sachettinni, J.; Kelly, J. W. *J. Med. Chem.* **2002**, *45*, 321. (c) Klabunde, T.; Petrassi, H. M.; Oza, V. B.; Raman, P.; Kelly, J. W.; Sacchettini, J. C. *Nat. Struct. Biol.* **2000**, *7*, 312.

(2) (a) Oza, V. B.; Petrassi, H. M.; Purkey, H. E.; Kelly, J. W. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1. (b) Baures, P. W.; Oza, V. B.; Peterson, S. A.; Kelly, J. W. *Bioorg. Med. Chem.* **1999**, *7*, 1339.

(3) (a) Schultz, B. D.; Singh, A. K.; Devor, D. C.; Bridges, R. J. *Physiol. Rev.* **1999**, *79*, 109. (b) Walsh, K. B.; Wang, C. *Mol. Pharmacol.* **1998**, *53*, 539.

(4) Goodell, J. R.; Madhok, A. A.; Hiasa, H.; Ferguson, D. M. *Bioorg. Med. Chem.* **2006**, *14*, 5467.

(5) (a) Demeunynck, M.; Charmantray, F.; Martelli, A. *Curr. Pharm. Des.* **2001**, *7*, 1703. (b) Brana, M. F.; Cacho, M.; Gradillas, A.; De Pascual-Teresa, B.; Ramos, A. *Curr. Pharm. Des.* **2001**, *7*, 1745. (c) Girault, S.; Grellier, P.; Berecibar, A.; Maes, L.; Mouray, E.; Lemiere, P.; Debreu, M.-A.; Davioud-Charvet, E.; Sergheraert, C. *J. Med. Chem.* **2000**, *43*, 2646.

(6) Chen, M. H. G.; Magano, J. Preparation of 2-phenylaminobenzoic acids by coupling of 2-halobenzoic acids with anilines in the presence of alkali metal hexamethyldisilazide. (Warner-Lambert Company). WO 2000064856 A1, 2000.

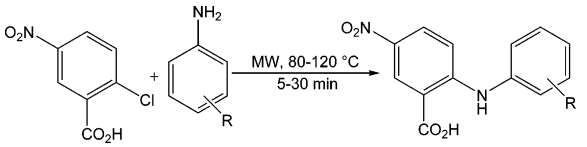
(7) (a) Ullmann, F. *Chem. Ber.* **1903**, *36*, 2382. (b) Ullmann, F. *Chem. Ber.* **1904**, *37*, 853. (c) Ma, D.; Xia, C. *Org. Lett.* **2001**, *3*, 2583. (d) Lindley, J. *Tetrahedron* **1984**, *40*, 143.

(8) (a) For review see: Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400. (b) Goldberg, I. *Chem. Ber.* **1906**, *39*, 1691. (c) Goldberg, A. A.; Kelly, W. *J. Chem. Soc.* **1947**, 595. (d) Goldberg, A. A.; Alan, A.; Kelly, W. *J. Chem. Soc.* **1946**, 102. (e) Goodell, J. R.; Puig-Basagoiti, F.; Forshey, B. M.; Shi, P-Y.; Ferguson, D. M. *J. Med. Chem.* **2006**, *49*, 2127. (f) Okano, K.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2003**, *5*, 4987. (g) Bauman, D. R.; Rudnick, S. I.; Szewczuk, L. M.; Jin, Y.; Gopishetty, S.; Penning, T. M. *Mol. Pharmacol.* **2005**, *67*, 60.

(9) (a) Mei, X.; August, A. T.; Wolf, C. *J. Org. Chem.* **2006**, *71*, 142. (b) Wolf, C.; Liu, S.; Mei, X.; August, A. T.; Casimir, M. D. *J. Org. Chem.* **2006**, *71*, 3270. (c) Yuhong, J.; Varma, R. S. *J. Org. Chem.* **2006**, *71*, 135. (d) Yuhong, J.; Varma, R. S. *Green Chem.* **2004**, *6*, 219. (e) Wu, Y.-J.; He, H.; L'Heureux, A. *Tetrahedron Lett.* **2003**, *44*, 2417. (f) Ma, D.; Cai, Q.; Zhang, H. *Org. Lett.* **2003**, *5*, 2453. (g) Ma, D.; Cai, Q. *Org. Lett.* **2003**, *5*, 3799. (h) Li, F.; Wang, Q.; Ding, Z.; Tao, F. *Org. Lett.* **2003**, *5*, 2169. (i) Kwong, F. Y.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 793. (j) Xu, G.; Wang, Y.-G. *Org. Lett.* **2004**, *6*, 985.

10.1021/jo070731i CCC: $37.00
Published on Web 06/22/2007

SCHEME 1. Microwave-Assisted Synthesis of *N*-Arylanthranilic Acid Derivatives

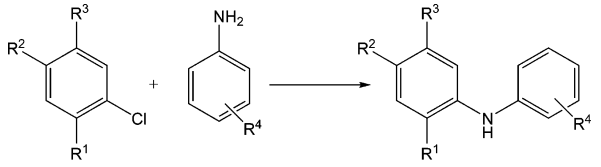


Our medicinal chemistry projects directed toward the development of nucleotide (P2) receptor antagonists[12] required gram amounts of a variety of 5-amino-N-substituted anthranilic acid derivatives as building blocks. The N-substituted 5-nitroanthranilic acids were selected as suitable precursors which can easily be converted to the required aniline derivatives by reduction of the nitro function. In the present study we report on a new, regioselective synthetic procedure providing convenient access to a wide range of *N*-aryl- and *N*-alkyl-5-nitroanthranilic acid derivatives. The coupling of 2-chloro-5-nitrobenzoic acid with amines proceeds smoothly and neatly upon microwave irradiation without added solvent or catalyst (see Scheme 1, Tables 1 and 2).

Previous reports on the synthesis of N-substituted 5-nitroanthranilic acid derivatives employed (a) micellar catalysis (cetyltrimethylammonium bromide) in water for the preparation of **3a** from 2-fluoro-5-nitrobenzoic acid and aniline,[13] or (b) strong base (LiHMDS) for the reaction of 2-fluoro-5-nitrobenzoic acid with *p*-fluoroaniline yielding **3b**,[6] or (c) bronze as a catalyst in the presence of bases for the reaction of 2-chloro-5-nitrobenzoic acid with anilines in 1-pentanol yielding **3f**[14] and **3g**[14] (for structures of compounds see Table 1). Furthermore, the synthesis of 2-benzylamino-5-nitrobenzoic acid (**3t**) has been described by a three-step procedure starting from 2-fluoro-5-nitrobenzoic acid involving acid protection.[15] All of the described reactions did not appear to be generally applicable and suffered from further drawbacks, such as reaction at −78 °C and application of strong base,[6] long reaction times,[6,14,15] need for chromatographic purification,[6] need for protecting the carboxylic acid function,[15] or moderate yields.[14]

Initially, we attempted to obtain the target compounds **3** by microwave-assisted Ullmann−Goldberg coupling reaction of 2-amino-5-nitrobenzoic acid with bromo- or chlorobenzene, but no product was obtained under various conditions.[16,17] Subsequently, the amino and halogen functionalities of the starting compounds were exchanged, and 2-chloro-5-nitrobenzoic acid (**1a**) was reacted with aniline (**2a**) and aniline derivatives. We discovered that the reaction proceeded rapidly and smoothly upon microwave irradiation, even in the absence of solvent and catalyst. Optimized reaction conditions were found to be as follows: excess of amine (6 equiv), 80−120 °C, 5−30 min (see Scheme 1, Tables 1 and 2). The new amination procedure was then applied to a number of aryl- and alkylamines including primary and secondary amines. Different substituents were present on the mono- or disubstituted aniline derivatives

TABLE 1. Synthesized *N*-Arylanthranilic Acid Derivatives[a]



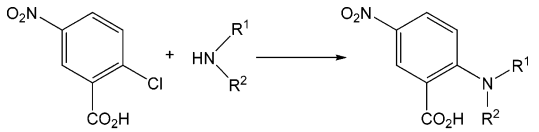
1 2a-q 3a-q

1a: R^1=CO_2H, R^2=NO_2,R^3=H
1b: R^1=CO_2H, R^2=H, R^3=H
1c: R^1=H, R^2=NO_2, R^3=H
1d: R^1=H, R^2=NO_2, R^3=CO_2H

entry	R^1	R^2	R^3	R^4	*T* (°C)	reaction time (min)	products **3** (yield [%])[b]
1	CO_2H	NO_2	H	H	100	10	**3a** (80)
2	CO_2H	NO_2	H	4-F	120	10	**3b** (80)
3	CO_2H	NO_2	H	2-Cl	120	30	**3c** (50)
4	CO_2H	NO_2	H	3-Cl	120	30	**3d** (60)
5	CO_2H	NO_2	H	3-Br	120	15	**3e** (30)
6	CO_2H	NO_2	H	2-OCH_3	120	15	**3f** (67)
7	CO_2H	NO_2	H	3-OCH_3	110	10	**3g** (75)
8	CO_2H	NO_2	H	2-CH_2CH_3	120	20	**3h** (58)
9	CO_2H	NO_2	H	3-CH_2CH_3	80	5	**3i** (76)
10	CO_2H	NO_2	H	4-CH_2CH_3	100	10	**3j** (75)
11	CO_2H	NO_2	H	2-OCH_2CH_3	120	15	**3k** (78)
12	CO_2H	NO_2	H	4-OCH_2CH_3	100	5	**3l** (58)
13	CO_2H	NO_2	H	2,3-*di*-CH_3	120	30	**3m** (70)
14	CO_2H	NO_2	H	2,4-*di*-CH_3	100	10	**3n** (70)
15	CO_2H	NO_2	H	2,5-*di*-CH_3	120	20	**3o** (70)
16	CO_2H	NO_2	H	3,5-*di*-CH_3	120	10	**3p** (85)
17	CO_2H	NO_2	H	2-CH_3, 4-Cl	120	30	**3q** (78)
18	CO_2H	H	H	H	200	180	**3x** (0)
19	H	NO_2	H	H	200	180	**3y** (0)
20	H	NO_2	CO_2H	H	200	180	**3z** (0)

[a] Reaction mixtures were irradiated for 5−30 min without added solvent or catalyst at 80−120 °C. [b] Isolated yields (purity of products ≥95% as determined by HPLC-UV (254 nm)-ESI-MS) calculated based on starting compound **1a**.

TABLE 2. Synthesized *N*-(Ar)alkylanthranilic Acid Derivatives Using Primary and Secondary Amines[a]



1a 2r-w 3r-w

R^1, R^2 = H, Alkyl, Cycloalkyl, (Ar)alkyl

entry	amine	*T* (°C)	reaction time (min)	products **3** (yield [%])[b]
1	cyclopentylamine (**2r**)	120	5	**3r** (>99)
2	cyclohexylamine (**2s**)	120	5	**3s** (>99)
3	benzylamine (**2t**)	120	10	**3t** (60)
4	phenethylamine (**2u**)	120	10	**3u** (50)
5	dipropylamine (**2v**)	100	5	**3v** (>99)
6	pyrrolidine (**2w**)	80	5	**3w** (>99)

[a] Reaction mixtures were irradiated for 5−10 min without added solvent or catalyst at 80−120 °C. [b] Isolated yields (purity of products ≥97% as determined by HPLC-UV (254 nm)-ESI-MS) calculated based on starting compound **1a**.

(10) (a) Baqi, Y.; Müller, C. E. *Org. Lett.* **2007**, *9*, 1271. (b) Kappe, C. O. *Angew. Chem., Int. Ed.* **2004**, *43*, 6250. (c) Vera-Luque, P.; Alajarin, R.; Alvarez-Builla, J.; Vaquero, J. J. *Org. Lett.* **2006**, *8*, 415. (d) Martin, A. M.; Pellon, R. F.; Mesa, M.; Docampo, M. L.; Gomez, V. *J. Chem. Res.* **2005**, *9*, 561.

(11) (a) Huang, X.; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653. (b) Rivas, F. M.; Riaz, U.; Giessert, A.; Smulik, J. A.; Diver, S. T. *Org. Lett.* **2001**, *3*, 2673. (c) Chakraborti, D.; Colis, L.; Schneider, R.; Basu, A. K. *Org. Lett*. **2003**, *5*, 2861. (d) Suo, Z.; Drobizhev, M.; Spangler, C. W.; Christensson, N.; Rebane, A. *Org. Lett.* **2005**, *7*, 4807. (e) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. *Aldrichim. Acta* **2006**, *39*, 97.

(12) Müller, C. E. *Curr. Pharm. Des.* **2002**, *8*, 2353.

(13) Broxton, T. J.; Marcou, V. *J. Org. Chem.* **1991**, *56*, 1041.

(14) Csuk, R.; Barthel, A.; Raschke, C. *Tetrahedron* **2004**, *60*, 5737.

(15) South, M. S.; Case, B. L.; Dice, T. A.; Franklin, G. W.; Hayes, M. J.; Jones, D. E.; Lindmark, R. J.; Zeng, Q.; Parlow, J. J. *Comb. Chem. High Throughput Screen.* **2000**, *3*, 139.

(16) Martin, A.; Mesa, M.; Docampo, M.; Gomez, V.; Pellon, R. *Synth. Commun.* **2006**, *36*, 271.

employed, including deactivating groups such as halogen (F, Cl, Br) or activating groups such as alkyl (CH_3, C_2H_5) or alkoxy (OCH_3, OC_2H_5), in order to investigate the scope of the reaction (Tables 1 and 2).

Importantly, the new amination procedure proceeds with notable chemo- and regioselectivity because only the chloride adjacent to the carboxylic acid group and in the para-position to the nitro group is replaced (see Table 1, entries 2−5 and 17). Moreover the new protocol is suitable for the synthesis of sterically hindered *N*-arylanthranilic acids as shown by the reaction of ortho-substituted anilines (Table 1, entries 3, 6, 8, 11, 13−15 and 17). The new amination procedure can also be applied to arylalkylamines such as benzylamine and phenethylamine to synthesize 2-benzylamino-5-nitrobenzoic acid and 5-nitro-2-phenethylaminobenzoic acid (Table 2, entries 3 and 4). Reaction of aliphatic primary and secondary amines (cyclopentylamine, cyclohexylamine, dipropylamine, pyrrolidine) even requires milder conditions and proceeds faster resulting in quantitative yields within only 5 min (Table 2, entries 1, 2, 5 and 6).

The workup of this very clean reaction involves only a simple extraction step (water/sodium hydroxide−dichloromethane) in order to remove unreacted amine (organic phase), followed by precipitation of the product from the water phase by the addition of hydrochloric acid, and filtration of the precipitate, which is subsequently washed with water. Using this simple purification protocol the desired products are obtained in high purity (≥95%) as determined by LC-MS. Structures were confirmed by ^{1}H and ^{13}C NMR analyses (see Supporting Information). Products were mostly obtained in good to excellent yields (typically 60 to >99% isolated). Only in few cases, yields were somewhat lower, e.g., 2-chloroaniline derivative **3c** (50%), 3-bromoaniline derivative **3e** (30%), and phenethylamine derivative **3u** (50%). Reasons for somewhat reduced yields were presumably electronic and steric effects (**3c**), instability of the starting compound (**3e**), and failure to quantitatively isolate the product (**3u**).

In further experiments, we investigated the importance of the electron-withdrawing nitro function as well as the carboxylic acid group on the chlorobenzene derivative **1a**. *o*-Chlorobenzoic acid (**1b**) lacking the nitro group in the para-postion was not reactive under the applied conditions (up to 250 W, 200 °C, 3 h). Also, *p*-nitrochlorobenzene (**1c**) lacking the carboxylate group in the ortho-position did not react with aniline, even under harsh reaction conditions (up to 250 W, 200 °C, 3 h). When the carboxylate group was in the meta-position with respect to the chlorine atom (5-chloro-2-nitrobenzoic acid (**1d**)) the reaction was also not successful indicating that both, a carboxylate group in the ortho-position and an electron-withdrawing nitro function in the para-position of the chlorobenzene derivative, are required for the reaction to proceed. On the other hand, no restrictions were observed for the amine reaction partner. The described substitution reaction is likely to proceed via an S_NAr addition−elimination mechanism.

The results show that the new amination protocol provides a new convenient access to a wide range of N-substituted 5-nitroanthranilic acid derivatives. The reaction tolerates various functionalities as demonstrated by reacting a diverse range of aliphatic primary and secondary amines, and aromatic amine derivatives, including sterically hindered ones and anilines bearing electron-withdrawing substituents on the benzene ring. It proceeds with notable regioselectivity, which is probably because of the accelerating effect of the adjacent carboxylate group in the presence of the nitro group in the para-position with regard to the chlorine atom in starting compound **1a**. The reaction proceeds fast, clean, and under mild conditions. No strong bases are required, allowing the presence of base-labile groups and avoiding side-reactions. Carboxylic acid groups do not need to be protected. The procedure is insensitive to air and moisture and does not require an inert atmosphere. It can easily be upscaled to multigram quantities and provides a practical approach for the preparation of the target compounds which represent an important class of drug molecules and which are in addition valuable intermediate products for the synthesis of pharmacologically active compounds. In a simple reduction step the nitro group may be reduced, yielding the corresponding amines as useful building blocks. The described catalyst-free amination reaction, which does not require the addition of solvent, provides a less expensive, operationally simple alternative to palladium-catalyzed Buchwald−Hartwig cross-coupling reactions and is also superior to copper-catalyzed Ullmann−Goldberg reactions for the preparation of 2-aryl- and 2-(ar)-alkylamino-5-nitrobenzoic acid derivatives.

In conclusion, we have developed a convenient, fast, mild, and efficient methodology for the synthesis of N-substituted 5-nitroanthranilic acid derivatives without addition of catalysts or solvents. The method has been used to synthesize several new compounds (Table 1, entries 5, 8−11, 15−17, and Table 2, entry 5), that have, to the best of our knowledge, not been described in the literature. In addition we have synthesized and characterized several compounds (Table 1, entries 3, 4, 12−14, and Table 2, entries 1, 2, 4, 6) for which neither synthetic procedures, nor spectral data, have previously been described. Because of its simplicity, cost-effectiveness and general applicability with respect to the amine component, it may find broad academic as well as industrial application.

Experimental Section

Typical Microwave-Amination Procedure. To an 80 mL microwave reaction vessel equipped with a magnetic stirring bar were added 2-chloro-5-nitrobenzoic acid (2.520 g, 12.5 mmol) and 3,5-dimethylaniline (8.8 mL, 75 mmol) to obtain a homogeneous mixture. The vessel was sealed, and the mixture was irradiated in a microwave oven (CEM Focused Microwave type Discover) for 10 min at 100 °C. Then the reaction mixture was cooled to rt, and the product was subsequently purified using the following procedure: the contents of the vial were dissolved in ca. 300 mL of dichloromethane, and the organic solution was extracted with diluted 0.1 M aq sodium hydroxide solution (ca. 500 mL). The extraction procedure was repeated until the aqueous layer became light yellow (three to four times). Then the aqueous layer was collected and acidified using concentrated aq hydrochloric acid (37%) until pH ≤ 3 and the desired product precipitated in the acidic medium. The precipitated solid was filtered off and dried in an oven at 100 °C, and 2-(3,5-dimethylphenylamino)-5-nitrobenzoic acid (**3p**, 3.04 g, 10.63 mmol, 85% yield) was obtained as a yellow solid, mp 278−279 °C. ^{1}H NMR (500 MHz, DMSO-d_6): δ = 2.48 (s,

(17) Typical Procedure. To an 80 mL microwave reaction vial equipped with a magnetic stirring bar were added 2-amino-5-nitrobenzoic acid (2.275 g, 12.5 mmol), 1 equiv of the halobenzene, and 2 equiv of K_2CO_3 dissolved in an appropriate amount of water, and a mixture of finely powdered copper (Cu(0)) and cupper(II) sulfate ($CuSO_4$). The mixture was irradiated in the microwave oven at 150 °C for up to 2 h.

6H, $2CH_3$), 6.88 (br, 1H), 6.93 (br, 2H), 7.11 (d, 1H, $J = 9.5$ Hz), 8.13 (dd, 1H, $J = 2.9$ Hz, $J = 9.5$ Hz), 8.70 (d, 1H, $J = 2.9$ Hz), 10.47 (br, 1H, NH), 13.5 (br, 1H, COOH). ^{13}C NMR (126 MHz, DMSO-d_6): $\delta = 20.9$, 111.7, 113.3, 121.5, 127.3, 128.5, 129.2, 136.5, 138.2, 139.2, 152.5, 168.8. LC-MS (*m*/*z*): 287 $[M]^+$, 304 $[M + NH_4^+]^+$, 285 $[M]^-$, 241 $[M - COO^-]^-$. Anal. Calcd for $C_{15}H_{14}N_2O_4 \cdot 0.5H_2O$: C, 61.00; H, 5.12; N, 9.49. Found: C, 61.18; H, 4.86; N, 9.44. Purity by HPLC-UV (254 nm)-ESI-MS: 99%.

Acknowledgment. Y.B. thanks the Deutscher Akademischer Austauschdienst (DAAD) for a Ph.D. Fellowship. Support by the Deutsche Forschungsgemeinschaft (DFG, GRK804) is gratefully acknowledged.

Supporting Information Available: Experimental procedures and analytical data for all compounds (**3a**−**w**). This material is available free of charge via the Internet at http://pubs.acs.org.

JO070731I