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A Metal-Free Approach to the Synthesis of Indoline Derivatives by a Phenyliodine(III) Bis(trifluoroacetate)-Mediated Amidohydroxylation Reaction

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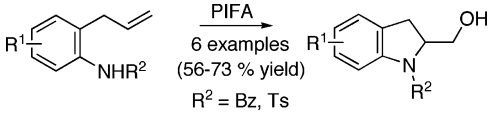

A novel approach to the synthesis of indoline derivatives is presented. The key cyclization step features the phenyliodine-(III) bis(trifluoroacetate)- (PIFA-) mediated formation of a *N*-acylnitrenium ion and its succeeding intramolecular trapping by the olefin fragment. In addition, difunctionalization of the alkene moiety is achieved since the in situ generation of an additional hydroxy group at the terminal position of the original double bond accompanies the intramolecular C−N bond formation.

The pursuit of concise methods for rapid buildup of molecular complexity is a major focus of the synthetic organic chemical community. Strategies that allow multiple transformations in a single-pot process without excessive functionalization of the substrates are especially attractive. In this context, vicinal difunctionalization of alkenes is among the most powerful transformations known in the field of chemical synthesis.[1] These reactions are particularly appealing from the standpoint of green chemistry because they usually display perfect atom economy,[2] and therefore, we envisaged that such conception might be applied to the preparation of 2-substituted indoline derivatives.

Aside from the role of the indole ring as the key substructure in all molecules containing the amino acid tryptophan, the indole and indoline frameworks are embedded in a wide range of natural products and designed compounds with varied biological activities (see Figure 1).[3] On the basis of their promising pharmacological applications, intensive research has been directed to develop new and efficient protocols for the synthesis of both types of heterocycles. However, the employment of substantial quantities of either toxic or expensive metal salts, and the high sensitivity of some of the required complexes to air and moisture, limit the generality of most of the related reported protocols.[4] Thus, the development of a new metal-free strategy for the synthesis of the target heterocycles remains a challenge in synthetic organic chemistry.

As part of our ongoing research work dealing with the development of hypervalent iodine chemistry,[5] we envisaged the synthesis of a series of indoline derivatives by employing the environmentally friendly iodine reagent PIFA [phenyliodine-(III) bis(trifluoroacetate)]. Thus, in this paper we report a straightforward metal-free approach to the olefin amidation reaction mediated by PIFA and its application to the synthesis of the target heterocycles.[6] The essential key step of our approach relies on the ability of the employed iodine reagent to generate *N*-acylnitrenium intermediates[7] and, thus, provide the formation of a novel C−N bond, as well as the introduction of a hydroxy group (in one single step from B to A), in the final product through an olefin amidation process, as depicted in Figure 2.

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(1) For some selected reviews and monographs on alkene vicinal difunctionalization processes, such as dihydroxylation or aminohydroxylation reactions, see (a) Kolb, H. C.; VanNienwenzhe, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483−2547. (b) Johnson, R. A.; Sharpless, K. B. Catalytic Asymmetric Dihydroxylation: Discovery and Development. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley−VCH: New York, 2000; pp 357−398. (c) Bolm, C.; Hildebrand, J. P.; Muniz, K. Recent Advances in Asymmetric Dihydroxylation and Aminohydroxylation. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley−VCH: New York, 2000; pp 399−428. (d) Schlingloff, G.; Sharpless, K. B.; Asymmetric Aminohydroxylation. In *Asymmetric Oxidation Reactions: A Practical Approach in Chemistry*; Katsuki, T., Ed.; Oxford University Press: New York, 2001; pp 104−114.

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(3) 2-Methylindoline derivatives constitute a structural class of heterocycles from which several drugs have emerged, including antineoplastic sulfonamides, 5-hydroxytryptamine receptor antagonists (5-HT3), and muscarine receptor agonists and antagonists. See for example (a) Bermudez, J.; Dabbs, S.; Joiner, K. A.; King, F. D. *J. Med. Chem.* **1990**, *33*, 1929−1932. (b) Adachi, S.; Koike, K.; Takayanagi, I. *Pharmacology* **1996**, *53*, 250−258. (c) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893−930.

(4) For palladium-catalyzed synthesis of indolines, see (a) Lira, R.; Wolfe, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 13906−13907. (b) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690−7691. For copper-catalyzed synthesis of indolines, see (c) Sherman, E. S.; Chemler, S. R.; Tan, T. B.; Gerlits, O. *Org. Lett.* **2004**, *6*, 1573−1575. (d) Zabawa, T. P.; Kasi, D.; Chemler, S. R. *J. Am. Chem. Soc.* **2005**, *127*, 11250−11251. Other processes: (e) Nicolaou, K. C.; Roecker, A. J.; Pfefferkorn, J. A.; Cao, G.-Q. *J. Am. Chem. Soc.* **2000**, *122*, 2966−2967. (f) Yin, Y.; Zhao, G. *Heterocycles* **2006**, *68*, 23−31. (g) Gleave, D. M.; Brickner, S. J.; Manninen, P. R.; Allwine, D. A.; Lovasz, K. D.; Rohrer, D. C.; Tucker, J. A.; Zurenko, G. E.; Ford, C. W. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1231−1236. (h) Gleave, D. M.; Brickner, S. J. *J. Org. Chem.* **1996**, *61*, 6470−6474.

(5) For recent reviews on the synthetic applications of polyvalent iodine reagents, see (a) Zhdankin, V. V.; Stang, P. J. *Chem. Rev.* **2002**, *102*, 2523−2284. (b) Stang, P. J. *J. Org. Chem.* **2003**, *68*, 2997−3008. (c) Wirth, T. *Top. Curr. Chem.* **2003**, *224*, 1−264. (d) Tohma, H.; Kita, Y. *Adv. Synth. Catal.* **2004**, *346*, 111−124. (e) Moriarty, R. M. *J. Org. Chem.* **2005**, *70*, 2893−2903. (f) Wirth, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 3656−3665.

(6) For some other contributions by our group on the synthesis of other N-containing heterocycles by employing this PIFA-promoted olefin amidohydroxylation, see (a) Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron* **2004**, *60*, 6533−6539. (b) Serna, S.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *Tetrahedron Lett.* **2003**, *44*, 3483−3486.

(7) The hypervalent iodine reagent PIFA has been reported to generate *N*-acylnitrenium ions from adequately substituted amides. See for example (a) Kikugawa, Y.; Kawase, M. *Chem. Lett.* **1990**, 581−582. (b) Romero, A. G.; Darlington, W. H.; McMillan, M. W. *J. Org. Chem.* **1997**, *62*, 6582−6587. (c) Wardrop, D. J.; Burge, M. S. *Chem. Commun.* **2004**, 1230−1231. (d) Correa, A.; Tellitu, I.; Domínguez, E.; Moreno, I.; SanMartin, R. *J. Org. Chem.* **2005**, *70*, 2256−2264. (e) Correa, A.; Tellitu, I.; Domínguez, E.; SanMartin, R. *J. Org. Chem.* **2006**, *71*, 3501−3505.

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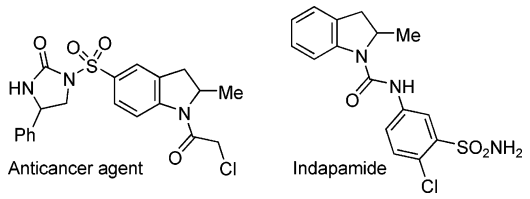


FIGURE 1. Selected examples of 2-substituted indolines of interest.

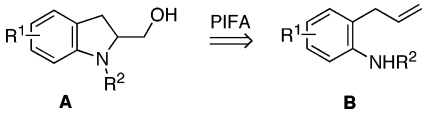
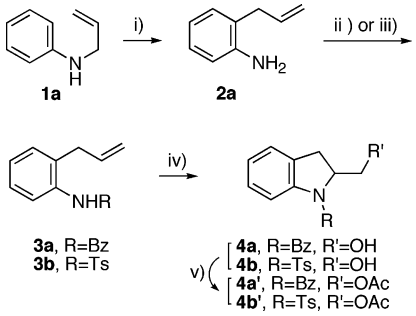


FIGURE 2. Proposed strategy for the synthesis of the indoline skeleton.

SCHEME 1. Preparation of Indolines 4a,b[a]



[a] Reagents and conditions: (i) $BF_3{\cdot}OEt_2$, xylene, 180 °C, sealed tube, 2 h (66%); (ii) BzCl, pyridine, CH_2Cl_2, 0 °C → room temperature, overnight (98% for **3a**); (iii) TsCl, pyridine, CH_2Cl_2, 0 °C → room temperature, overnight (90% for **3b**); (iv) PIFA (see Table 1); (v) Ac_2O, pyridine, room temperature (quantitative for **4a**, quantitative for **4b**).

The first issue we had to address in our research was referred to the nature of the N-substituent.[8] Thus, our synthesis started by the preparation of N-protected amides **3a,b** in a two-step sequence, as outlined in Scheme 1. Thus, *o*-allylanilides **3a,b** were efficiently obtained from commercially available *N*-allylaniline (**1a**) by a known aza-Claisen rearrangement[9] followed by a subsequent N-protection process of the so-obtained 2-allylaniline (**2a**).

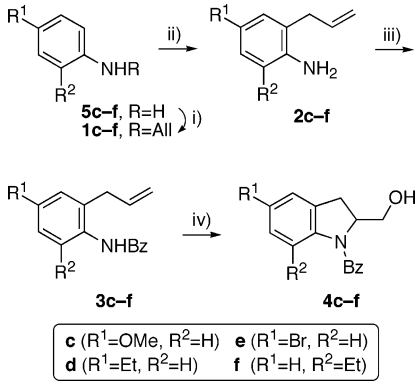
Next, to test the viability of the proposed amidation reaction, we briefly examined the behavior of anilides **3a,b** under the action of PIFA to optimize the experimental conditions (see Table 1). Thus, when amides **3a,b** were treated with PIFA with dichloromethane (entry 1) or acetonitrile (entry 2) as solvents, the projected amidation reaction did not take place, and the starting material was recovered unaltered in both cases. However, when the reaction was carried out in trifluoroethanol (TFEA) at room temperature (entry 3), indoline **4a** was satisfactorily obtained after a 3-h period of time. Nevertheless, under these conditions total conversion did not occur for **3b**, and the corresponding indoline **4b** was obtained in lower yield. In an effort to optimize these results, the olefin amidation reaction was performed at higher temperatures (entry 4), but unfortunately, the yields for both indolines **4a**,**b** slightly decreased. Therefore, it can be pointed out that the optimal reaction conditions for the amidation reaction involve the treatment of substrates **3a,b** with PIFA (1.5 equiv) in trifluoroethanol at room temperature for 3 h (entry 3). Since both indolines **4a,b** were unstable, they were efficiently transformed into the corresponding acetyl derivatives **4a′** and **4b′**, respectively, for a full structural characterization.

TABLE 1. Selected Assays Performed on Anilides 3a,b

entry	solvent	*T*	**4a**[a] (%)	**4b**[a] (%)
1	CH_2Cl_2	rt	0[b]	0[b]
2	CH_3CN	rt	0[b]	0[b]
3	TFEA	rt	71	41[c]
4	TFEA	80 °C	52	20[c]

[a] Isolated yield after purification by flash chromatography. [b] Unreacted starting material was recovered. [c] The reaction reached only 50% conversion.

SCHEME 2. Synthesis of Indolines 4c−f[a]



[a] Reagents and conditions: (i) $BrCH_2CH{=}CH_2$, K_2CO_3, DMF, 80 °C, overnight (69% for **1c**, 64% for **1d**, 67% for **1e**, 59% for **1f**); (ii) $BF_3{\cdot}OEt_2$, xylene, 180 °C, sealed tube, 2 h (72% for **2c**, 77% for **2d**, 66% for **2e**, 58% for **2f**); (iii) BzCl, pyridine, CH_2Cl_2, 0 °C → room temperature, overnight (73% for **4c**, 75% for **4d**, 84% for **4e**, 96% for **4f**); (iv) PIFA, TFEA, room temperature, 3 h (61% for **4c**, 70% for **4d**, 73% for **4e**, 56% for **4f**).

Having established the optimal protocol for the projected process, the scope of the presented transformation was expanded to prepare a short family of indoline derivatives **4a**−**f**. For this purpose, and selecting the benzoyl group over the tosyl group as the optimal substituent for the amino group, a series of benzamides **3c**−**f** were easily prepared following the synthetic sequence depicted below in good overall yields and starting from the commercially available anilines **5c**−**f** (see Scheme 2).

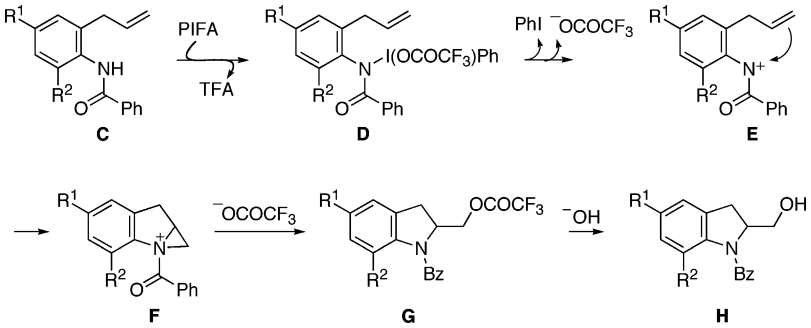
When substrates **3c**−**f** were submitted to the action of the hypervalent iodine reagent PIFA, the proposed amidohydroxylation reaction proved to be suitable for the projected transformation and, hence, they rendered successfully the corresponding indoline derivatives **4c**−**f**.[10] In general, the cyclization reaction of benzamides bearing substituents in the para position with respect to the amino group, independently of their electronic nature, proceeded in higher yields than when substituents were placed in the orthq position. This result may be attributed to an unfavorable steric hindrance developed in intermediate **D**, a species that results from the mechanistic proposal shown below.

(8) Unless a nitrenium ion is stabilized by a proper neighboring group, such as an aryl or alkoxy group, its existence as a reaction intermediate is quite fleeting. Thus, the selection of an adequate N-substituent is of key importance. For some reviews on nitrenium intermediates, see (a) Falvey, D. E. In *Reactive Intermediate Chemistry* Moss, R. A.; Platz, M. S.; Jones, M., Jr., Eds.; Wiley−Interscience: New York, 2004; pp 594−650. (b) Shubin, V. G.; Borodkin, G. I. *Russ. J. Org. Chem.* **2005**, *41*, 473−504.

(9) (a) Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1993**, *58*, 5095−5100. (b) Anderson, W. K.; Lai, G. *Synthesis* **1995**, 1287−1290.

(10) Due to its labile nature, indoline **4c** had also to be acetylated for a full structural identification.

SCHEME 3. Proposed Mechanism for the Olefin Amidohydroxylation of Benzamides of Type C



The described transformation can be rationalized as depicted in Scheme 3. Thus, the *N*-acylnitrenium ion **E** generated by the action of PIFA on **C** through the formation of **D** can be intramolecularly trapped by the olefin moiety by a 5-*exo*-trig cyclization mode. The so-obtained primary carbocationic species created, preferably stabilized as the aziridinium ion **F,** can be subsequently opened by the nucleophilic attack of a free trifluoroacetate group delivered from the employed iodine reagent. The resulting nonisolated ester **G** is hydrolyzed during the basic workup of the reaction to afford the final indoline derivatives **H**.

In summary, the PIFA-mediated amidohydroxylation reaction has proven to be an efficient and rapid method for the synthesis of indoline derivatives. Besides, unlike other metal-based approach to the target heterocycles, the proposed strategy allows not only the formation of a new C−N bond but also the introduction of a hydroxy group in the final product, which facilitates the construction of more complex molecules by further structural modifications. Finally, it must be pointed out that the presented protocol avoids the use of toxic and expensive metals by using the easy-to-handle hypervalent iodine reagent PIFA.

Experimental Section

Typical Procedure for the Synthesis of Indolines 4a−f: Synthesis of 2-Acetoxymethyl-*N*-benzoylindoline (4a′). A solution of PIFA (5.16 g, 12.00 mmol) in 120 mL of trifluoroethanol (TFEA) was slowly added at room temperature to a solution of benzamide **3a** (1.58 g, 6.66 mmol) in 66 mL of the same solvent. The mixture was stirred at room temperature until total consumption of the starting material was observed (TLC, 3 h). Then, a solution of Na_2CO_3 (aqueous 10%, 50 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was evaporated at reduced pressure. The resulting residue was purified by column chromatography (hexanes/EtOAc 1:1) to afford indoline **4a** (71%) as a colorless oil. Due to its labile nature, indoline **4a** was subsequently acetylated for a full structural identification. For this purpose, Ac_2O (0.5 mL, 5.54 mmol) was added at room temperature to a solution of indoline **4a** (700 mg, 2.77 mmol) in pyridine (10 mL), and the mixture was stirred overnight. Then, the mixture was diluted with CH_2Cl_2 (30 mL) and washed with a saturated solution of $CuSO_4$ (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and filtered, and the solvent was evaporated at reduced pressure. The resulting residue was purified by column chromatography (CH_2Cl_2) to afford quantitatively indoline **4a′** as a yellowish oil: ^{1}H NMR ($CDCl_3$) δ 2.12 (s, 3H), 3.04−3.25 (m, 2H), 4.33−4.35 (m, 2H), 4.78−4.83 (m, 1H), 7.10−7.11 (m, 2H), 7.28−7.47 (m, 5H), 8.18 (d, J = 7.7 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 20.6 (CH_3), 37.8 (CH_2), 65.6 (CH_2), 80.1 (CH), 124.9 (CH), 127.5 (CH), 127.9 (CH), 128.2 (CH), 128.6 (CH), 128.9 (CH), 130.4 (CH), 132.1 (C), 134.9 (C), 143.0 (C), 150.9 (C), 170.4 (C); IR (film) 1710; MS (EI) *m*/*z* (%) 295 (M^+, 74), 235 (76), 193 (87), 165 (62), 105 (100), 90 (65); HRMS calcd for $C_{18}H_{17}NO_3$ 295.1208, found 295.1201.

2-Acetoxymethyl-*N*-tosylindoline (4b′). According to the general procedure, indoline **4b** was obtained from amide **3b** (100 mg, 0.35 mmol) in 41% yield (50% conversion) as a yellowish oil after purification by column chromatography (hexanes/EtOAc 1:1). Due to its labile nature, indoline **4b** was quantitatively transformed into the corresponding acetyl derivative **4b′** as expressed above, and its spectral data were in total concordance with those described in the literature.[4b]

2-Acetoxymethyl-*N*-benzoyl-5-methoxyindoline (4c′). According to the general procedure, indoline **4c** was obtained from amide **3c** (100 mg, 0.37 mmol) in 61% yield as a colorless oil after purification by column chromatography (hexanes/EtOAc 1:1). Due to its labile nature, indoline **4c** was quantitatively transformed into the corresponding oily acetyl derivative **4c′** by following the typical procedure: ^{1}H NMR ($CDCl_3$) δ 2.11 (s, 3H), 3.01−3.24 (m, 2H), 3.81 (s, 3H), 4.33−4.35 (m, 2H), 4.76−4.80 (m, 1H), 6.66−6.83 (m, 2H), 7.34−7.43 (m, 4H), 8.08−8.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 20.8 (CH_3), 38.4 (CH_2), 55.4 (CH_3), 65.8 (CH_2), 78.8 (CH), 112.4 (CH), 114.1 (CH), 127.9 (CH), 128.1 (CH), 130.2 (CH), 130.8 (CH), 133.5 (C), 135.2 (C), 136.4 (C), 149.6 (C), 156.9 (C), 170.7 (C); IR (film) 1740; MS (EI) *m*/*z* (%) 325 (M^+, 68), 252 (30), 160 (47), 105 (100); HRMS calcd for $C_{19}H_{19}NO_4$ 325.1314, found 325.1325.

***N*-Benzoyl-5-ethyl-2-hydroxymethylindoline (4d).** According to the general procedure, indoline **4d** was obtained from amide **3d** (100 mg, 0.39 mmol) in 70% yield as a white solid after purification by column chromatography (hexanes/EtOAc 1:1) followed by crystallization from hexanes: mp 99−100 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 1.28 (t, J = 7.7, 3H), 2.35 (br s, 1H), 2.64 (q, J = 7.7 Hz, 2H), 3.00−3.19 (m, 2H), 3.82−3.85 (m, 2H), 4.59−4.61 (m, 1H), 6.92−7.26 (m, 2H), 7.34−7.43 (m, 4H), 8.10−8.12 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.5 (CH_3), 28.2 (CH_2), 37.9 (CH_2), 65.3 (CH_2), 82.5 (CH), 124.6 (CH), 126.7 (CH), 127.9 (CH), 128.3 (CH), 129.0 (CH), 130.3 (CH), 132.6 (C), 135.3 (C), 140.7 (C), 141.2 (C), 150.7 (C); IR (KBr) 3364−3390, 1645; MS (EI) *m*/*z* (%) 281 (M^+, 100), 250 (95), 222 (83), 206 (93), 193 (54), 158 (98), 146 (85), 105 (99); HRMS calcd for $C_{18}H_{19}NO_2$ 281.1416, found 281.1417.

***N*-Benzoyl-5-bromo-2-hydroxymethylindoline (4e).** According to the general procedure, indoline **4e** was obtained from amide **3e** (100 mg, 0.32 mmol) in 73% yield as a white solid after purification by column chromatography (hexanes/EtOAc 1:1) followed by crystallization from hexanes: mp 111−112 °C (hexanes); ^{1}H NMR ($CDCl_3$) δ 2.60−3.09 (m, 2H), 3.09 (br s, 1H), 3.58−4.21 (m, 2H), 5.09−5.15 (m, 1H), 6.55 (d, J = 8.3 Hz, 2H), 7.12−7.42 (m, 2H), 7.55−7.60 (m, 2H), 8.02−8.06 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 31.9 (CH_2), 62.3 (CH_2), 74.8 (CH), 122.7 (CH), 125.3 (CH), 129.2 (CH), 129.5 (CH), 130.5 (CH), 130.8 (CH), 133.6 (C), 136.3 (C), 141.2 (C), 144.6 (C), 166.7 (C); IR (KBr) 3367−3390, 1708; MS (EI)

m/*z* (%) 351 ($M^+ + 20$, 5), 349 ($M^+ + 18$, 4), 227 (24), 186 (24), 105 (100), 77 (75); HRMS calcd for $C_{16}H_{14}BrNO_2$ 331.0208, found 331.0218.

***N*-Benzoyl-7-ethyl-2-hydroxymethylindoline (4f).** According to the general procedure, indoline **4f** was obtained from amide **3f** (100 mg, 0.39 mmol) in 56% yield as a colorless oil after purification by column chromatography (hexanes/EtOAc 1:1): ^{1}H NMR ($CDCl_3$) δ 1.30 (t, $J = 7.7$ Hz, 3H), 2.14 (br s, 1H,), 2.94−3.86 (m, 4H), 3.84−3.86 (m, 2H), 4.74−4.80 (m, 1H), 6.87−7.22 (m, 3H), 7.43−7.52 (m, 3H), 8.16−8.20 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 15.2 (CH_3), 25.7 (CH_2), 37.5 (CH_2), 65.5 (CH_2), 84.6 (CH), 124.9 (CH), 126.3 (CH), 127.6 (CH), 128.1 (CH), 128.3 (CH), 130.4 (CH), 132.6 (C), 135.7 (C), 140.9 (C), 142.0 (C), 150.1 (C); IR (film) 3367−3390, 1649; MS (EI) *m*/*z* (%) 281 (M^+, 13), 264 (23), 249 (32), 222 (17), 176 (42), 158 (86), 105 (100); HRMS calcd for $C_{18}H_{19}NO_2$ 281.1416, found 281.1417.

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Note Added after ASAP Publication. There was a typographical error in the title of the version published ASAP September 6, 2006; the corrected version was published ASAP September 8, 2006.

Supporting Information Available: Experimental details for amides **3a**−**f** and ^{1}H NMR and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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