JOC Note
pubs.acs.org/joc

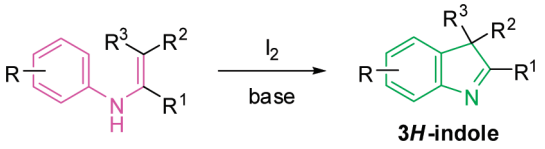
Iodine-Mediated Synthesis of 3*H*-Indoles via Intramolecular Cyclization of Enamines

Zhiheng He, Huanrong Li, and Zhiping Li*

Department of Chemistry, Renmin University of China, Beijing 100872, China

zhipingli@ruc.edu.cn

Received April 23, 2010



The synthesis of 3*H*-indoles was achieved via the iodine-mediated intramolecular cyclization of enamines. A wide variety of 3*H*-indole derivatives bearing multifunctional groups were obtained in good to high yields under transition metal-free reaction conditions.

Indole alkaloids are ubiquitous heterocycles in natural products and play pharmacologically important roles because of the broad spectrum of their biological activities. Many efforts have therefore been made to synthesize the indole skeleton.[1] 3*H*-Indole is one of the most important structural units found in nature[2] and has been utilized as a key scaffold to construct various indoline alkaloids.[3] Although there are a variety of methods to synthesize 1*H*-indole derivatives, the methodologies for the synthesis of 3*H*-indole derivatives are very limited.[4] Therefore, a general and efficient method for the synthesis of 3*H*-indole derivatives is an attractive and formidable challenge in synthetic chemistry.[5]

In the course of our studies on C−H bond oxidation and C−C bond formation,[6] we unexpectedly found that elemental iodine (I_2)[7] could efficiently promote an intramolecular cyclization of enamines.[8,9] The current process presents a novel and efficient method to construct the 3*H*-indole skeleton. Herein we report our efforts on the synthesis and preliminary applications of 3*H*-indoles.

(*Z*)-Ethyl 2-methyl-3-phenyl-3-(phenylamino)acrylate (**1a**) was used as a model substrate for optimization of the reaction conditions (Table 1). An extensive investigation of a range of oxidants, bases, and solvents was carried out. The desired product **2a**, ethyl 3-methyl-2-phenyl-3*H*-indole-3-carboxylate, was obtained in 82% yield when elemental iodine was used as oxidant with K_2CO_3 as base and DMF as solvent (entry 1). A lower yield of **2a** (60%) was formed when IBr was employed instead of I_2 (entry 2). Hypervalent iodine reagents, phenyliodine(III) diacetate (PIDA) and phenyliodine(III) bis(trifluoroacetate) (PIFA), were much less effective for 3*H*-indole formation (entries 3 and 4). Other inorganic bases, such as Na_2CO_3, $NaHCO_3$, and Cs_2CO_3, gave comparable yields of **2a**, while an organic base, 2,6-lutidine, afforded a lower yield of **2a** (Table 1, entries 5−8). Other solvents were inferior to DMF with regard to the yield of the desired 3*H*-indole, for example, CH_3NO_2 (17% yield) and toluene (33% yield) (entries 9 and 10). Product **2a** was not observed in the absence of I_2 or base (entries 11 and 12).

(1) For representative reviews, see: (a) Thansandote, P.; Lautens, M. *Chem.—Eur. J.* **2009**, *15*, 5874. (b) Patil, N. T.; Yamamoto, Y. *Chem. Rev.* **2008**, *108*, 3395. (c) Kruger, K.; Tillack, A.; Beller, M. *Adv. Synth. Catal.* **2008**, *350*, 2153. (d) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (e) Humphrey, G. R.; Kuethe, J. T. *Chem. Rev.* **2006**, *106*, 2875. (f) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (g) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (h) Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893. (i) Hegedus, L. S. *Angew. Chem., Int. Ed.* **1988**, *27*, 1113.

(2) Some selected examples, see: (a) Lim, K.-H.; Hiraku, O.; Komiyama, K.; Koyano, T.; Hayashi, M.; Kam, T.-S. *J. Nat. Prod.* **2007**, *70*, 1302. (b) Kam, T.-S.; Choo, Y.-M. *J. Nat. Prod.* **2004**, *67*, 547. (c) Chaturvedula, U. S. P.; Sprague, S.; Schilling, J. K.; Kingston, D. G. I. *J. Nat. Prod.* **2003**, *66*, 528. (d) Sheludko, Y.; Gerasimenko, I.; Kolshorn, H.; Stockigt, J. *J. Nat. Prod.* **2002**, *65*, 1006. (e) Steele, J. C. P.; Veitch, N. C.; Kite, G. C.; Simmonds, M. S. J.; Warhurst, D. C. *J. Nat. Prod.* **2002**, *65*, 85.

(3) (a) Somei, M. S.; Yamada, F. Y. *Nat. Prod. Rep.* **2005**, *22*, 73. (b) Austin, J. F.; Kim, S. G.; Sinz, C. J.; Xiao, W. J.; MacMillan, D. W. C. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5482. (c) Witkop, B.; Patrick, J. B. *J. Am. Chem. Soc.* **1951**, *73*, 1558. (d) Rahman, A. U.; Basha, A. *Indole Alkaloids*; Hawood Academic Publishers: Amsterdam, The Netherlands, 1997.

(4) (a) Boyarskikh, V.; Nyong, A.; Rainier, J. D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5374. (b) Trost, B. M.; Quancard, J. *J. Am. Chem. Soc.* **2006**, *128*, 6314. (c) Kimura, M.; Futamata, M.; Mukai, R.; Tamaru, Y. *J. Am. Chem. Soc.* **2005**, *127*, 4592. (d) Hamel, P. *Tetrahedron Lett.* **1997**, *38*, 8473. The electrochemical oxidation: (e) Kobayashi, M.; Sadamune, K.; Mizukami, H.; Uneyama, K. *J. Org. Chem.* **1994**, *59*, 1909.

(5) Fischer indole synthesis presents one of the most powerful synthetic methods to construct 1*H*-indoles as well as a few specific 3*H*-indoles, see: (a) Xu, D.-Q.; Luo, W.-L.; Yang, S.-P.; Wang, B.-T.; Wu, J.; Xu, Z.-Y. *Eur. J. Org. Chem.* **2009**, 1007. (b) Wagaw, S.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 10251. (c) Glish, G. L.; Cooks, R. G. *J. Am. Chem. Soc.* **1978**, *100*, 6720. (d) Illy, H.; Funderburk, L. *J. Org. Chem.* **1968**, *33*, 4283. (e) Deorha, D. S.; Joshi, S. S. *J. Org. Chem.* **1961**, *26*, 3527. (f) Pausacker, K. H.; Schubert, C. I. *Nature* **1949**, *163*, 289. (g) Grgin, D. J. *Monatsh Chem.* **1906**, *27*, 731.

(6) (a) Guo, X.; Yu, R.; Li, H.; Li, Z. *J. Am. Chem. Soc.* **2009**, *131*, 17387. (b) Guo, X.; Pan, S.; Liu, J.; Li, Z. *J. Org. Chem.* **2009**, *74*, 8848. (c) Li, H.; He, Z.; Guo, X.; Li, W.; Zhao, X.; Li, Z. *Org. Lett.* **2009**, *11*, 4176. (d) Li, Z.; Yu, R.; Li, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 7497. (e) Li, Z.; Li, H.; Guo, X.; Cao, L.; Yu, R.; Li, H.; Pan, S. *Org. Lett.* **2008**, *10*, 803. (f) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505.

(7) For representative reviews, see: (a) Togo, H.; Iida, S. *Synlett* **2006**, 2159. (b) French, A. N.; Bissmire, S.; Wirth, T. *Chem. Soc. Rev.* **2004**, *33*, 354.

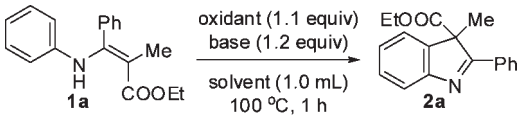
(8) Representative methodologies for the synthesis of indole derivatives via intramolecular oxidative coupling reactions. [Pd]: (a) Wurtz, S.; Rakshit, S.; Neumann, J. J.; Droge, T.; Glorius, F. *Angew. Chem., Int. Ed.* **2008**, *47*, 7230. (b) Shi, Z.; Zhang, C.; Li, S.; Pan, D.; Ding, S.; Cui, Y.; Jiao, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 4572. [Cu]: (c) Bernini, R.; Fabrizi, G.; Sferrazza, A.; Cacchi, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 8078. (d) Perry, A.; Taylar, R. J. K. *Chem. Commun.* **2009**, 3249. (e) Jia, Y.-X.; Kundig, E. P. *Angew. Chem., Int. Ed.* **2009**, *48*, 1636. [I^{III}]: (f) Yu, W.; Du, Y.; Zhao, K. *Org. Lett.* **2009**, *11*, 2417. (g) Du, Y.; Liu, R.; Linn, G.; Zhao, K. *Org. Lett.* **2006**, *8*, 5919.

(9) I_2-mediated 1*H*-indole synthesis: (a) Fischer, D.; Tomeba, H.; Pahadi, N. K.; Patil, N. T.; Huo, Z.; Yamomoto, Y. *J. Am. Chem. Soc.* **2008**, *130*, 15720. (b) Kobayashi, K.; Miyamoto, K.; Yamase, T.; Nakamura, D.; Morikawa, O.; Konishi, H. *Bull. Chem. Soc. Jpn.* **2006**, *79*, 1580. (c) Hessian, K. O.; Flynn, B. L. *Org. Lett.* **2006**, *8*, 243. (d) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (e) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539. (f) Barluenga, J.; Trincado, M.; Rubio, E.; Gonzalez, J. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 2406.

Published on Web 06/04/2010 DOI: 10.1021/jo100796s

The substrate variation was then investigated. To our satisfaction, the reaction shows a wide scope for the structural variation of enamine **1** under the optimized reaction conditions (Table 2). Both electron-donating and electron-withdrawing groups at the para- or ortho-position of *N*-phenyl enamines **1** allowed smooth transformation of **1** into the corresponding products with good yields (entries 1−6). It should be noted that the reaction could be carried out on 2 mmol scale with similar efficacy (entry 2). α-Naphthalenyl enamine was also transformed into the corresponding indole (entry 7). The meta-substituted enamine **1g** afforded two regioisomers with a ratio of 1:2.2, where 4-methyl-substituted product **2g′** was the major product (entry 8). Ethyl- and benzyl-substituted enamines **1h** and **1i** afforded the desired 3*H*-indoles with moderate yields (entries 9 and 10), whereas diester enamines **1j**,**k** gave the corresponding products in good to excellent yields (entries 11−13). Aryl-substituted substrate **1m** also led to **2m** exclusively albeit in a lower conversion (entry 14). Cyanoethyl product **2n** formed in 74% yield; however, a prolonged reaction time was necessary to consume the starting enamine **1n** (entry 15). Benzoyl enamine **1o** was also transformed into the corresponding product **2o** in good yield (entry 16).

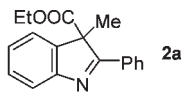
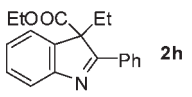
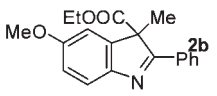
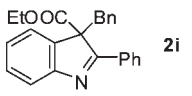
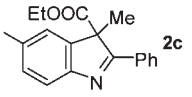
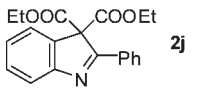
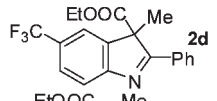
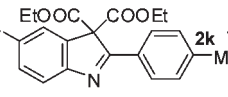
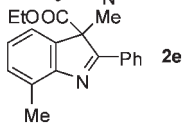
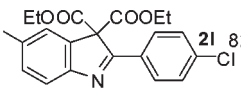
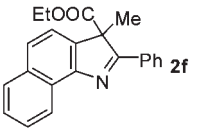
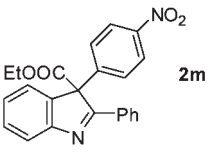
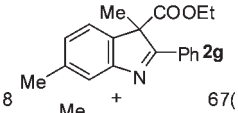
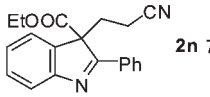
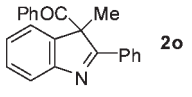
TABLE 1. Optimization of Reaction Conditions[a]



entry	oxidant	base	solvent	yield (%)[b]
1	I_2	K_2CO_3	DMF	82 (76)
2	IBr	K_2CO_3	DMF	60
3	PIDA	K_2CO_3	DMF	5
4	PIFA	K_2CO_3	DMF	N.D.[c]
5	I_2	Na_2CO_3	DMF	78
6	I_2	$NaHCO_3$[d]	DMF	77
7	I_2	Cs_2CO_3	DMF	79
8	I_2	2,6-lutidine	DMF	39
9	I_2	K_2CO_3	CH_3NO_2	17
10	I_2	K_2CO_3	toluene	33
11		K_2CO_3	DMF	N.D.
12	I_2		DMF	N.D.

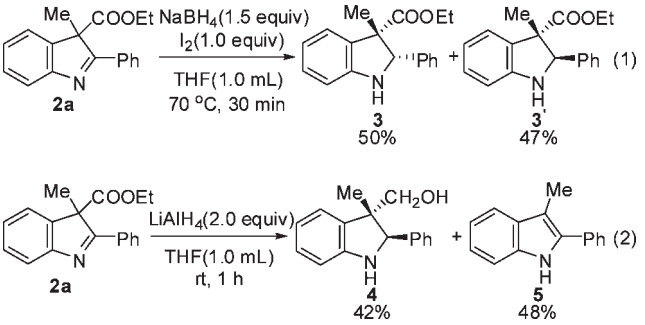
[a]Conditions unless otherwise noted: **1a** (0.25 mmol), oxidant (0.28 mmol), base (0.30 mmol), and solvent (1.0 mL). [b]NMR yields are determined by ^{1}H NMR spectroscopy with mesitylene as an internal standard; isolated yield is given in parentheses. [c]Not detected by TLC. [d]2.4 equiv.

TABLE 2. Synthesis of 3*H*-Indoles[a]

entry	product	yield (%)[b]	entry	product	yield (%)[b]
1		**2a** 76	9		**2h** 69
2[c]		72			
3		**2b** 85	10		**2i** 61
4		**2c** 65	11		**2j** 92
5		**2d** 70	12		**2k** 70
6		**2e** 74	13		**2l** 82
7		**2f** 62	14		**2m** 59
8		**2g** + **2g'** 67(1:2.2)	15		**2n** 74[d]
			16		**2o** 68

[a]Conditions unless otherwise noted: **1** (0.25 mmol), I_2 (0.28 mmol), K_2CO_3 (0.30 mmol), and DMF (1.0 mL), 100 °C, 1 h. [b]Isolated yields. [c]**1a** (2.0 mmol), I_2 (2.2 mmol), K_2CO_3 (2.4 mmol), and DMF (5.0 mL). [d]2 h.

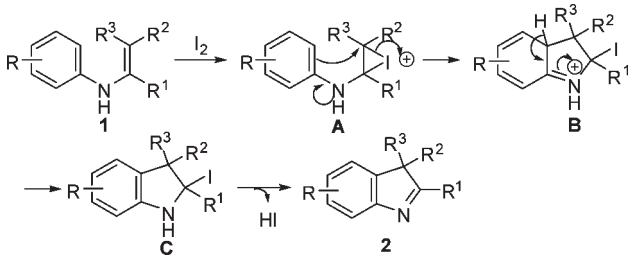
With the synthetic method for 3*H*-indole derivatives in hand, preliminary applications of the obtained 3*H*-indoles **2** were investigated. The C=N double bond of **2a** was reduced by common reducing reagents effectively (eqs 1 and 2). A 1:1 ratio of the diastereomers, **3**[10] and **3′**, was obtained when $NaBH_4$ was used (eq 1). In contrast, both the C=N double bond and the ester group were reduced by $LiAlH_4$ (eq 2). Interestingly, only one isomer **4** was formed together with decarboxylation product **5** when $LiAlH_4$ was used. This result indicated that the ester group of **2a** is first reduced to a hydroxyl group and then acts as a directing group for the reduction of the C=N bond via a chelated transition state. This is supported by the outcome of the reduction of a 1:1 ratio of **3** and **3′** by $LiAlH_4$, which gave a 1:2.1 diastereisomeric mixture of **4**. With regard to the formation of **5**, presumably the carboxylate formed from **2a** under basic condition is susceptible to decarboxylation.



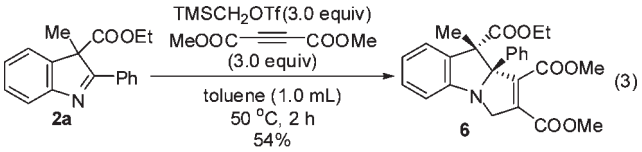
Polycyclic indoline alkaloids are frequently found in natural products and pharmaceuticals; direct cyclization from the 3*H*-indole represents a convenient and powerful method to construct such structures.[11] The cycloadduct **6** was selectively formed when a mixture of 3*H*-indole **2a** and dimethyl but-2-ynedioate was treated with trimethylsilylmethyl

(10) Hodges, J. C.; Wang, W.; Riley, F. *J. Org. Chem.* **2004**, *69*, 2504.
(11) Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B.; Eggleston, D. S.; Baures, P. W. *Synlett* **1990**, *6*, 359.

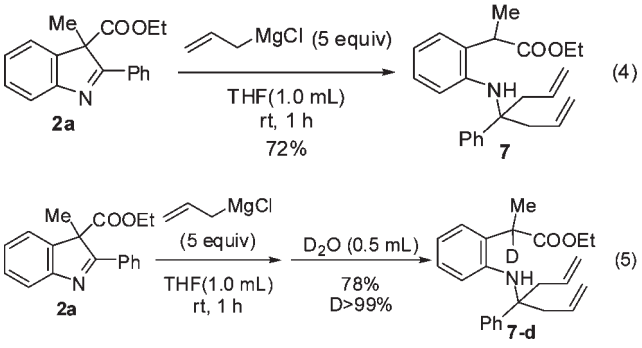
SCHEME 1. An Initially Proposed Pathway for the Formation of 2



triflate in toluene (eq 3). The structure of **6** was confirmed by NOE analysis.

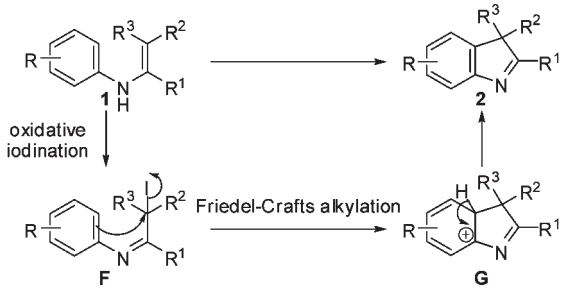


Interestingly, the reaction of **2a** with allylmagnesium chloride afforded ring-opening product **7** (eq 4).[12] When the reaction mixture was quenched by deuterated water, **7d** was obtained exclusively (eq 5). Presumably an addition−elimination reaction occurs with addition of the first equivalent of reagent to give an equilibrium between the expected addition product and an ester enolate and imine formed from cleavage of the C2−C3 bond. Attack of a second equivalent of allylmagnesium chloride on the imine and quenching of the enolate with D_2O would generate **7d**.

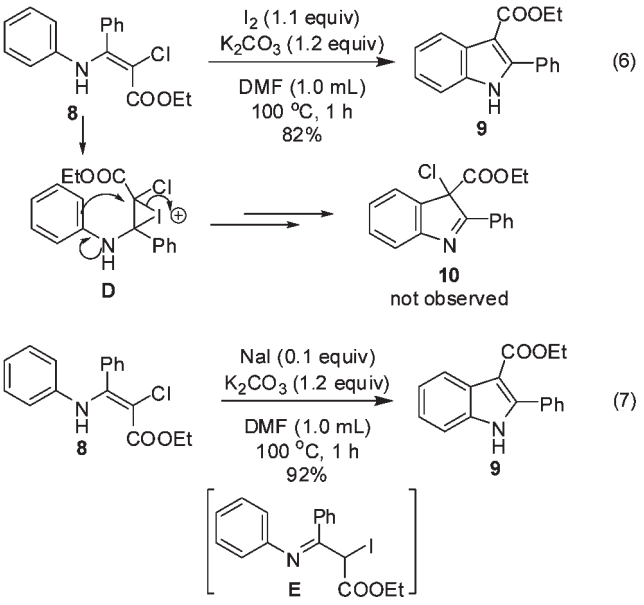


The initial mechanistic proposal for the formation of **2** was based on a general iodocyclization pathway (Scheme 1).[13] Iodocyclization of the enamine C=C double bond forms a three-membered iodonium intermediate **A**, followed by an intramolecular electrophilic aromatic substitution to give **C**, followed by removal of HI under basic condition to give 3*H*-indole **2**. However, when chloro-substituted enamine **8** was employed in the reaction, des-chlorine indole product **9** was formed under the standard reaction conditions (eq 6). The expected product **10** was not observed. To investigate the

SCHEME 2. A Proposed Mechanism for the Formation of 3*H*-Indole 2



role of I_2 in this reaction, a catalytic amount of NaI instead of stoichiometric I_2 was used and **9** was obtained with a 92% yield (eq 7). These results suggested that an iodide intermediate **E**, presumably formed by nucleophilic displacement of Cl by I from the tautomer of **8**, is involved in the present transformation. Moreover, the application of a catalytic amount NaI in eq 7 also indicated that a three-membered iodonium intermediate **A** or **D** is not involved in the formation of the indole ring.



Furthermore, a series of competition experiments were performed to address the influences of the electronic properties of enamines in the present transformation.[14] The results showed that the reaction rate of *N*-phenyl enamines **1** with electron-donating groups at the para-position is faster than those with electron-withdrawing groups, which agrees with the Friedel−Crafts aromatic alkylation. On the basis of these results and the literature,[15] a tentative mechanism of the formation of 3*H*-indole **2** is proposed (Scheme 2). The oxidative iodination generates an iodide intermediate **F**. Consequently, the intermediate **G** is formed via an intramolecular Friedel−Crafts aromatic alkylation reaction, followed by rearomatization to give 3*H*-indole **2**.

(12) (a) Rodriguez, J. G.; Urrutia, A.; de Diego, J. E.; Martinez-Alcazar, M. P.; Fonseca, I. *J. Org. Chem.* **1998**, *63*, 4332. (b) Eberson, L.; Greci, L. *J. Org. Chem.* **1984**, *49*, 2135.

(13) Selected reviews: (a) Ranganathan, S.; Muraleedharan, K. M.; Vaish, N. K.; Jayaraman, N. *Tetrahedron* **2004**, *60*, 5273. (b) Kitagawa, O.; Taguchi, T. *Synlett* **1999**, 1191. (c) Robin, S.; Rousseau, G. *Tetrahedron* **1998**, *54*, 13681. (d) Dowle, M. D.; Davies, D. I. *Chem. Soc. Rev.* **1979**, *8*, 171.

(14) The details are provided in the Supporting Information.

(15) For a representative review, see: Stavber, S.; Jereb, M.; Zupan, M. *Synthesis* **2008**, 1487.

In summary, we have demonstrated a general and efficient method for the synthesis of 3*H*-indoles. A detailed mechanistic evaluation and the utilization of elemental iodine for the synthesis of other heterocycles would further highlight the advantages of the present methodology.

Experimental Section

General Procedure for Products 2. To a mixture of *N*-aryl enaminecarboxylate **1** (0.25 mmol), iodine (1.1 equiv), and K_2CO_3 (1.2 equiv) was added 1.0 mL of *N*,*N*-dimethylformamide (DMF) under nitrogen at room temperature. The reaction temperature was raised to 100 °C for 1 h. The temperature of the reaction was reduced to room temperature. The resulting reaction solution was quenched with 20 mL of aqueous ammonia (5%) and extracted with 3 × 20 mL of ethyl acetate. The extract was washed with 2 × 20 mL of brine and dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue was purified by flash column chromatography on silica gel with ethyl acetate/petroleum ether as an eluent to give the desired product **2a**. ^{1}H NMR (ppm) δ 7.99−7.97 (m, 2H), 7.72 (d, J = 7.6 Hz, 1H), 7.48−7.46 (m, 3H), 7.40 (t, J = 7.2 Hz, 2H), 7.25 (t, J = 7.6 Hz, 2H), 4.16−4.08 (m, 1H), 4.02−3.96 (m, 1H), 1.71 (s, 3H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (ppm) δ 178.0, 171.6, 154.9, 141.8, 132.0, 131.1, 129.0, 128.8, 128.4, 126.3, 121.3, 121.2, 62.1, 61.8, 21.0, 13.7; ATR-FTIR (cm^{-1}) 3055, 2990, 1647, 1593, 1572, 1491, 1258, 1173, 1140, 1038, 777, 758, 696; MS (EI) m/z (%) 279 (M^+), 234, 220, 206, 130, 128, 105, 86, 84 (100), 47, 35, 29; HRMS (ESI) calcd for $C_{18}H_{18}NO_2$ ($M^+ + H$) 280.1332, found 280.1328.

Acknowledgment. We thank the NSFC (20832002) for financial support. H.L. thanks RUC (2009030026) for financial support. We also thank Prof. Zhenfeng Xi at Peking University and Prof. Matthew Todd at the University of Sydney for helpful discussion.

Supporting Information Available: Representative experimental procedure, characterization of all new compounds, and ^{1}H NMR and ^{13}C NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.