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Regioselective synthesis of 3,3-bis(indolyl)propanoic acid derivatives by iron(III)-catalyzed hydroarylation of propynoic acid derivatives with indoles

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ABSTRACT

Intermolecular hydroarylation of propynoic acid and its esters with indoles proceeded efficiently in acetic acid under a catalytic system of $FeCl_3$/3AgOTf and afforded the corresponding 3,3-bis(indol-3yl) propanoic acids and their esters in high yields. In the case of 2-methylindole, 3-indolylacrylic acid and its ethyl ester were obtained in high yields. This iron-catalyzed hydroarylation showed a high regioselectivity at the 3-position of indoles and a high utility for the synthesis of bis(indol-3-yl) compounds, which are important for biological and pharmaceutical fields.

1. Introduction

Indoles and pyrroles are an important class of nitrogen-containing heterocyclic compounds in organic chemistry due to their biological activities and synthetic applications, such as fluorescent dyes, synthetic analogues of natural products and pharmaceuticals.[1] Among them, more specially, numerous bis(indolyl)alkane have been isolated from several terrestrial and marine sources and the range of biological activities possessed by individual members of this series includes coronary dilatory properties, genotoxicity, and antibacterial activity[2] and the discovery of important anti-carcinogenic properties of some bis(indolyl) compounds have brought to the forefront the importance of such bis(indolyl) compounds.[3] Moreover, some substituted bis(indolyl) derivatives have been investigated as the useful tools in biochemical, biomedical, and medical applications in therapeutic and/or diagnostic applications as contrast agent for the identification and visualization of tissues and organs, more specially necrosis diseases, myocardial, and cerebral infarction.[4]

Recently, transition metal-catalyzed functionalization of aromatic C–H bonds has attracted much attention in view of a wide range of useful applications.[5] Hydroarylation of alkynes can formally be regarded as a reaction in which both aryl and hydrogen moieties of an aromatic compound add across a triple bond.[6] Therefore, hydroarylation of alkynes is one of the most effective methods for the direct C–H bond functionalization that provides a convenient, clean, atom-economic, and environmentally benign methodology to aryl-substituted compounds without requiring prefunctionalization of arenes, such as halogenation. The hydroarylation method has so far been applied also to heterocyclic aromatic compounds.[6]

We have applied both palladium- and platinum-catalyzed hydroarylations of propynoic acid derivatives to heteroarenes, such as pyrroles, indoles, and furans.[7] Recently several researchers reported the hydroarylation of alkynes and alkenes with indole derivatives catalyzed by various transition metals, such as palladium,[8] platinum,[8b,9] gold,[2,10] indium,[11] nickel,[12] rhenium,[13] rhodium,[14] metal trifluorosulfonates [$M(OTf)_n$; M=Sc, Zr, In],[15] and heteropoly acid ($H_4[Si(W_3O_{10})_3]$).[16] However, palladium, platinum, gold, and the lanthanide triflate catalysts are rather rare metals, expensive, toxic, and pollutants for environment, which limits their use in large scale synthesis. For this reason, cheaper metal catalysts that secure catalytic activity, low toxicity, and are readily available, are most desirable in the hydroarylation.

Iron is an abundant, inexpensive, readily available, nontoxic, and environmentally friendly transition metal, and shows increasing and promising catalytic ability in many organic syntheses.[17] Until now, however, little attention has been paid to iron as a catalyst for hydroarylation reactions of alkynes and hence the challenge of direct C–H bond functionalization by iron catalytic system continues to be an area of intense interest among academic and

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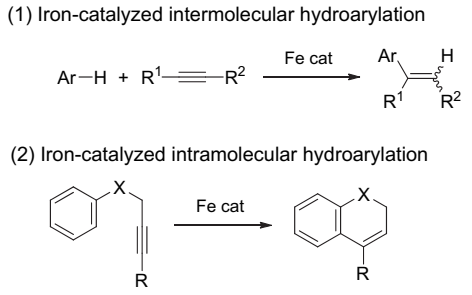
industrial researchers.[18] Recently, intermolecular hydroarylation (Scheme 1, (1)) was reported by Lu and co-workers with iron(III) chloride,[19] and by us using iron(III) chloride treated with silver(I) triflate.[20] Intramolecular hydroarylation of alkynes by an iron catalyst was reported to occur effectively (Scheme 1, (2)).[21] Therefore, such iron-catalyzed hydroarylations would be of particular value for functionalization of indoles because of the biological and pharmaceutical importance of indole derivatives mentioned above.

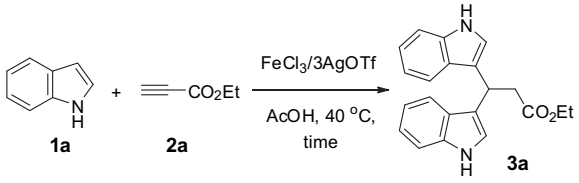


Scheme 1. Iron-catalyzed hydroarylations.

Intrigued by the potential of these successful iron-catalyzed reactions, we investigated the iron-catalyzed reaction between indoles and alkynoic acid derivatives in order to explore further successive development of a highly expedient methodology for the synthesis of bis(indol-3-yl)propanoic acids and their esters. In this paper we report for the first time iron(III)-catalyzed hydroarylation of propynoic acid and its esters with indoles affording the regioselective synthesis of bis(indol-3-yl)alkanoic acid derivatives.

2. Results and discussion

In order to optimize the reaction conditions, we initially investigated the iron-catalyzed reaction between indole (**1a**) and ethyl propynoate (**2a**). In our previous study on iron-catalyzed hydroarylation of arenes,[19] it was found that the catalytic system of $FeCl_3$/3AgOTf is the best one among $FeCl_3$, $FeCl_3 \cdot 6H_2O$, and $FeCl_3 \cdot 6H_2O$/AgOTf. The outline of the reaction is shown in Scheme 2 and the results are given in Table 1. When the reaction of **1a** (2 mmol) and **2a** (1 mmol) in AcOH (1 mL) was conducted in the presence of $FeCl_3$ (0.1 mmol) and AgOTf (0.3 mmol) at 40 °C for 15 h, ethyl 3,3-bis(1*H*-indol-3-yl)propanoate (**3a**) was obtained in 26% yield (entry 1). Since the mono-hydroarylation product was obtained by the hydroarylation reaction with indoles using a palladium catalyst,[7a] it is interesting that the double hydroarylation product was obtained by the reaction of the present iron catalyst. Elongation of the reaction time improved the yield of **3a** (entries 2–4) and the reaction for 36 h gave **3a** in 77% yield (entry 3). Although the reaction temperature was examined from 30 to 50 °C by 5 °C unit, the most sufficient result was obtained at 40 °C. Decreasing the iron catalyst to 5 mol % gave a better result but the reaction with 2.5 mol % of $FeCl_3$ led to a poor yield (entries 5 and 6). The best result was obtained using 1 mmol of **1a** and 1 mmol of **2a** (entry 7). Neither of the reactions in AcOH (1.5 mL) and in a mixed solvent of AcOH and CH_2ClCH_2Cl improved the result (entries 8 and 9). When $FeCl_3$ and AgOTf both did not exist, the reaction did not occur (entry 10). Although the reaction proceeded also with the catalyst of only $FeCl_3$, the activation by AgOTf was required to attain a high yield (entries 11–13).



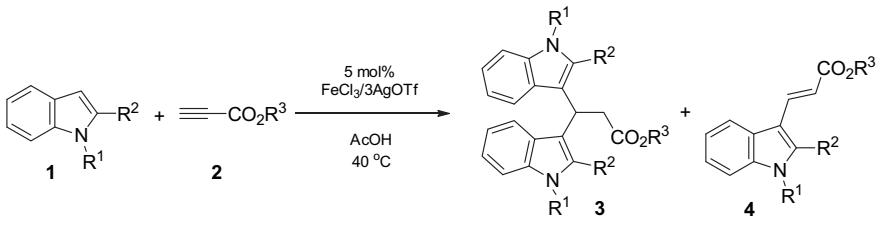
Scheme 2. $FeCl_3$/3AgOTf-catalyzed reaction of **2a** with **1a**.

Table 1
Optimization of reaction conditions[a]

Entry	**1a** (mmol)	**2a** (mmol)	$FeCl_3$ (mmol)	AgOTf (mmol)	Time (h)	Yield (%)[b]
1	2	1	0.1	0.3	15	26
2	2	1	0.1	0.3	24	44
3	2	1	0.1	0.3	36	77
4	2	1	0.1	0.3	48	68
5	2	1	0.05	0.15	36	80
6	2	1	0.025	0.075	36	46
7	1	1	0.05	0.15	36	86
8[c]	1	1	0.05	0.15	36	74
9[d]	1	1	0.05	0.15	36	51
10	1	1	0	0	15	—
11	1	1	0.05	0	36	35
12	2	1	0.1	0	36	38
13	1	1	0.3	0	36	47

[a] Reaction conditions: **1a**, **2a**, $FeCl_3$, AgOTf, and AcOH (1 mL) at 40 °C.
[b] Isolated yield based on the least amount of the substrate.
[c] AcOH (1.5 mL) was used.
[d] A mixture of AcOH (0.5 mL) and CH_2ClCH_2Cl (0.5 mL) was used.

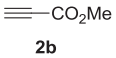
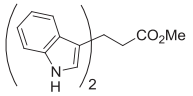
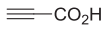
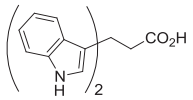
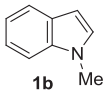
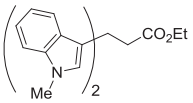
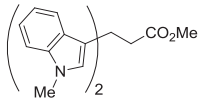
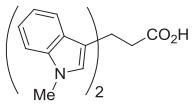
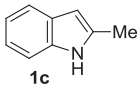
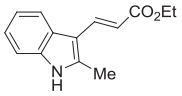
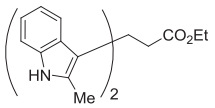
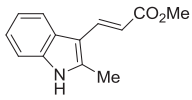
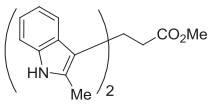
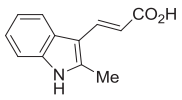
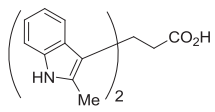
With the optimized conditions in hand, we examined the scope of the iron-catalyzed hydroarylation of propynoic acid derivatives **2** with indoles **1**. The outline of the hydroarylation reaction is drawn on Scheme 3. The results are given in Table 2.



Scheme 3. Iron-catalyzed hydroarylation of **2** with **1**.

When the reaction of methyl propynoate (**2b**) with **1a** was carried out under the same optimized conditions, the double hydroarylation product **3b** was obtained in 99% yield (entry 1). Moreover, the reaction of propynoic acid (**2c**) afforded the double hydroarylation product **3c** in 96% yield (entry 2). Similarly, the reaction of *N*-methylindole (**1b**) with propynoic acid derivatives **2a**, **2b**, and **2c** yielded the corresponding double hydroarylation products **3d**, **3e**, and **3f** in 62, 80, and 75% yields, respectively (entries 3–5).

Table 2
Iron-catalyzed reaction of **2** with **1**[a]

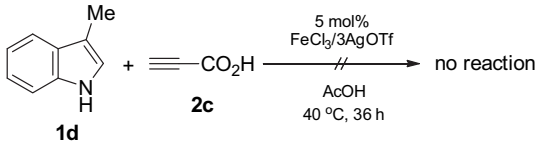
Entry	1	2	Time (h)	Product	Yield (%)
1	 **1a**	 **2b**	36	 **3b**	99
2	**1a**	 **2c**	36	 **3c**	96
3	 **1b**	**2a**	36	 **3d**	62
4	**1b**	**2b**	36	 **3e**	80
5	**1b**	**2c**	36	 **3f**	75
6	 **1c**	**2a**	36	 **4a**	98 (*E*/*Z*=98:2)[b]
7	**1c**	**2a**	60	4a	65
				 **3g**	30
8	**1c**	**2a**	96	**3g**	70
9	**1c**	**2b**	18	 **4b**	75
10	**1c**	**2b**	36	 **3h**	99
11	**1c**	**2c**	18	 **4c**	82
12	**1c**	**2c**	24	 **3i**	95

[a] Reaction conditions: $FeCl_3$ (0.05 mmol), AgOTf (0.15 mmol), **1** (1 mmol), **2** (1 mmol), and AcOH (1 mL) at 40 °C.
[b] The product ratio was determined by ^1H NMR.

Here, it was noticed that 2-methylindole (**1c**) showed a different behavior from other indoles **1a** and **1b**. The reaction of **2a** with **1c** for 36 h gave mono-hydroarylation product, ethyl 3-(2-methyl-1*H*-indol-3-yl)acrylate (**4a**) in 98% yield, containing a 98:2 mixture of *E* and *Z* isomers (entry 6). The reaction for 60 h resulted in a mixture of **4a** and double hydroarylation product **3g** (entry 7). Furthermore, when the reaction time was extended in 96 h, only double hydroarylation product **3g** was formed in 70% yield (entry 8). The reaction of isolated acrylate **4a** with indole **1c** under the same conditions for 24 h bisindolylpropanoate **3g** in 98% yield. The above results indicate that the reaction of **2a** with **1c** is slightly slow compared with other cases. The presence of methyl group at the 2-position of indole intensifies both electronic and steric effects on the reaction at the 3-position. In the case of the reaction of **2a** with **1c**, the steric effect surpasses from the electronic effect, but in other two reactions of **2b** and **2c** with **1c**, the electronic effect is more favorable than the steric effect because of smaller groups of hydrogen and methyl. Similarly, the reaction of **2b** and **2c** for 18 h afforded methyl (*E*)-3-(2-methyl-1*H*-indol-3-yl)acrylate (**4b**) and (*E*)-3-(2-methyl-1*H*-indol-3-yl)acrylic acid (**4c**) in 75 and 82% yields, respectively (entries 9 and 11). Furthermore, the reaction of **2b** and **2c** in longer time yielded the double hydroarylation products **3h** and **3i** in 99 and 95% yields, respectively (entries 10 and 12).

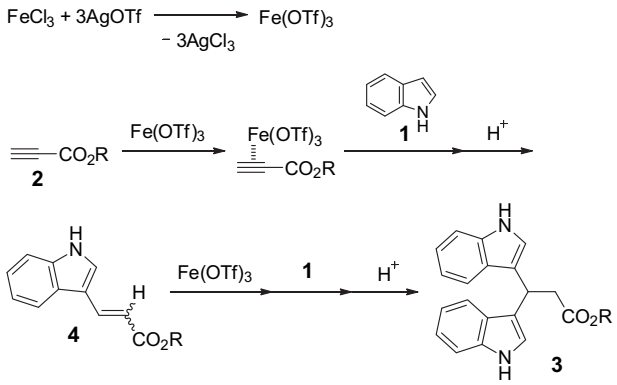
When the reaction of **2c** with 3-methylindole (**1d**) was conducted under the same conditions, no products were formed (Scheme 4) and the starting materials remained unchanged. This

result confirms that under the present conditions only the 3-position of the indole molecule is effective for the present iron-catalyzed hydroarylation reaction. Therefore, this hydroarylation reaction shows a high regioselectivity and is suitable for the synthesis of functionalized indoles at the 3-position.



Scheme 4. Reaction of **2c** with **1d** under the catalytic conditions of $FeCl_3$/3AgOTf.

Although there have been several reports on iron(III)-catalyzed hydroarylation of alkynes, the detail reaction mechanism is still not well understood. A possible pathway for the formation of 3,3-bis(indolyl)propanoates **3** is proposed in Scheme 5. First, during the catalyst preparation, $FeCl_3$ reacts with AgOTf in AcOH to produce a highly cationic $Fe(OTf)_3$. The production of $Fe(OTf)_3$ was suggested by the precipitation of white solid AgCl, and by UV measurement, as shown in Fig. 1. Then the resulting $Fe(OTf)_3$ interacts with propynoate **2** to generate an electron-deficient complex, which undergoes electrophilic aromatic substitution with indole **1**, followed by protonation to give indolylacrylate **4** along with elimination of $Fe(OTf)_3$. Since the inodolylacrylate **4** is electron-rich, it readily undergoes the second hydroarylation reaction to give bis(indolyl)propanoate **3**.



Scheme 5. A proposed pathway for formation of 3,3-bis(indolyl)propanoates **3**.

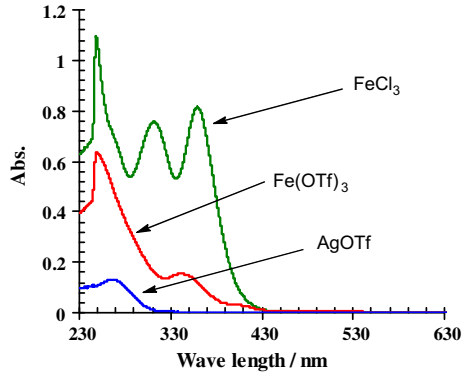


Fig. 1. UV spectra for $FeCl_3$ (8.0×10^{-3} M), $Fe(OTf)_3$ (4.0×10^{-4} M), and AgOTf (2.4×10^{-2} M) in AcOH.

3. Conclusions

In summary, we have demonstrated that the catalytic system of $FeCl_3$/3AgOTf in AcOH media can efficiently cause the double hydroarylation reaction of electron deficient propynoic acid derivatives **2** with indoles **1**. The hydroarylation reaction occurs regioselectivly at the 3-position of indoles **1** to give 3,3-bis(indol-3-yl)propanoates **3** in high yields. The present reaction is a useful tool for 3,3-bis(indol-3-yl)propanoates, which have potent applications for biochemical, biomedical, and pharmaceutical applications because it contains a simple procedure and high yields of the product.

4. Experimental

4.1. General

All solvents and starting materials were used during the research work as received without further purification unless otherwise indicated. $FeCl_3$ and AgOTf were purchased from Aldrich. ^1H and ^{13}C NMR were recorded on a JEOL JNMR-AL 300 FT-NMR spectrometer (TMS as an internal standard). UV spectra were taken on a Shimadzu UV-2450 spectrometer. Melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. Elemental analysis was performed by the Service Center of the Elemental Analysis of Organic Compounds, Faculty of Science, Kyushu University, Fukuoka, Japan. High resolution mass spectra were measured by the Analytical Center, Institute for Materials Chemistry and Engineering, Kyushu University. Column chromatographic separation was carried out using Silica Gel 60, spherical (Kanto Chemical Co.).

4.2. UV measurement of $FeCl_3$/3AgOTf catalyst

At first $FeCl_3$ (0.4 mmol) was dissolved in AcOH (0.5 mL) with stirring at 20 °C for 5 min and a red color solution was obtained. At the same time, AgOTf (1.2 mmol) was dissolved in AcOH (0.5 mL) with stirring at 20 °C for 5 min and then a colorless solution was obtained. A 0.1 mL solution from each solution was separately diluted with AcOH in a 10 mL volumetric bottle, and then each sample of $FeCl_3$ (8.0×10^{-3} M) and AgOTf (2.4×10^{-2} M) in AcOH was used for the measurement of UV spectra individually, with respect to the blank sample of AcOH. Next, the original solution of $FeCl_3$ was added dropwise to the original solution of AgOTf. A white precipitate of AgCl occurred instantly and this precipitation increased with the addition of the $FeCl_3$ solution to the AgOTf solution. After the completion of the addition, the sample was allowed to stir at the same temperature for more 5 min, and then the solid AgCl was filtered out from the deep orange color solution. A 0.1 mL solution of this sample was diluted with AcOH in a 10 mL volumetric bottle and then this diluted solution (4.0×10^{-4} M) was used for the measurement of UV spectrum with respect to the blank sample of AcOH. The generation of $Fe(OTf)_3$ was confirmed by white precipitation of AgCl and UV spectra (Fig. 1).

4.3. General procedure for the $FeCl_3$/3Ag(OTf)$_3$-catalyzed hydroarylation of propynoates 2 with indoles 1 in AcOH

To a test tube, $FeCl_3$ (0.05 mmol), AgOTf (0.15 mmol), and AcOH (1.0 mL) were added, capped with a Septum rubber, and stirred for 10 min at room temperature. To the mixture was added indole **1** (1.0 mmol) and propynoate **2** (1.0 mmol) and then the mixture was stirred at 40 °C for 36 h. The reaction mixture was poured into 20 mL of water, neutralized with $NaHCO_3$, and extracted with dichloromethane (20 mL×3). The combined organic extract was

washed with aqueous saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the crude product, which was purified by silica gel column chromatography (dichloromethane/hexane) to obtain the spectroscopic ally pure product.

In the case of the reaction of propynoic acid (**2c**), after the reaction the reaction mixture was poured into 20 mL of water, neutralized with $NaHCO_3$, and extracted with ether (20 mL×3). The combined ethereal layer was washed with aqueous 2 M NaOH solution (10 mL×3). The combined alkaline aqueous solution was acidified by dropwise addition of concentrated HCl and again extracted with dichloromethane (20 mL×3). The combined dichloromethane extract was washed with aqueous saturated NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give the product.

*4.3.1. Ethyl 3,3-bis(1H-indol-3-yl)propanoate (**3a**)*[22]. The product was obtained as an off-white solid, mp 101–102 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.07 (t, J=7.2 Hz, 3H), 3.15 (d, J=7.8 Hz, 2H), 4.00 (q, J=7.2 Hz, 2H), 5.08 (t, J=7.8 Hz, 1H), 6.81 (d, J=2.1 Hz, 2H), 6.99–7.04 (m, 2H), 7.09–7.14 (m, 2H), 7.22 (d, J=8.1 Hz, 2H), 7.56 (d, J=7.8 Hz, 2H), 7.83 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.0, 30.7, 41.1, 60.4, 111.1, 118.4, 119.1, 119.4, 121.7, 121.8, 126.5, 136.4, 172.7.

*4.3.2. Methyl 3,3-bis(1H-indol-3-yl)propanoate (**3b**).* The product was obtained as a light brown solid, mp 52–54 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.20 (d, J=7.8 Hz, 2H), 3.58 (s, 3H), 5.12 (t, J=7.8 Hz, 1H), 7.00–7.06 (m, 4H), 7.13–7.16 (m, 2H), 7.32–7.35 (m, 2H), 7.56–7.59 (m, 2H), 7.93 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.9, 40.9, 51.6, 111.1, 118.8, 119.3, 119.5, 121.7, 122.0, 126.7, 136.6, 172.9. HRMS (FAB) calcd for $C_{20}H_{18}N_2O_2$ 318.1368, found 318.1366.

*4.3.3. 3,3-Bis(1H-indol-3-yl)propanoic acid (**3c**).* The product was obtained as a colorless solid, mp 171–172 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 3.21 (d, J=7.8 Hz, 2H), 5.10 (t, J=7.8 Hz, 1H), 6.88–6.93 (m, 2H), 7.00–7.05 (m, 2H), 7.24 (d, J=2.4 Hz, 2H), 7.34 (d, J=8.1 Hz, 2H), 7.55 (d, J=8.1 Hz, 2H), 9.99 (br s, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 31.8, 41.4, 112.1, 119.2, 119.3, 120.0, 122.0, 122.9, 127.1, 138.0, 173.6. Anal. Calcd for $C_{19}H_{16}N_2O_2$ requires C, 74.98; H, 5.30; N, 9.20, found C, 74.91; H, 5.32; N, 9.24.

*4.3.4. Ethyl 3,3-bis(1-methyl-1H-indol-3-yl)propanoate (**3d**)*[23]. The product was obtained as an off-white solid, mp 113–115 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.10 (t, J=7.2 Hz, 3H), 3.15 (d, J=7.5 Hz, 2H), 3.70 (s, 6H), 4.02 (q, J=7.2 Hz, 2H), 5.11 (t, J=7.5 Hz, 1H), 6.86 (s, 2H), 7.01–7.06 (m, 2H), 7.16–7.21 (m, 2H), 7.26 (d, J=8.1 Hz, 2H), 7.60 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.6, 30.7, 32.7, 41.6, 60.2, 109.1, 117.4, 118.6, 119.6, 121.4, 126.4, 127.1, 137.3, 172.5.

*4.3.5. Methyl 3,3-bis(1-methyl-1H-indol-3-yl)propanoate (**3e**).* The product was obtained as a brownish white solid, mp 118–120 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.17 (d, J=7.8 Hz, 2H), 3.58 (s, 3H), 3.70 (s, 6H), 5.11 (t, J=7.8 Hz, 1H), 6.85 (s, 2H), 7.02–7.06 (m, 2H), 7.16–7.28 (m, 4H), 7.59 (d, J=8.1 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 30.6, 32.7, 41.3, 51.6, 109.1, 117.4, 118.7, 119.6, 121.5, 126.4, 127.0, 137.3, 172.9. Anal. Calcd for $C_{22}H_{22}N_2O_2$ requires C, 76.28; H, 6.40; N, 8.09, found C, 76.08; H, 6.36; N, 7.99.

*4.3.6. 3,3-Bis(1-methyl-1H-indol-3-yl)propanoic acid (**3f**).* The product was obtained as an off-white solid. ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 3.17 (d, J=7.5 Hz, 2H), 3.75 (s, 6H), 5.06 (t, J=7.5 Hz, 1H), 6.91–6.96 (m, 2H), 7.07–7.11 (m, 4H), 7.30 (d, J=8.1 Hz, 2H), 7.55 (d, J=7.8 Hz, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 31.4, 32.7, 41.6, 110.1, 118.4, 119.2, 120.1, 122.0, 127.2, 128.1, 138.3, 173.4. HRMS (FAB) calcd for $C_{21}H_{20}N_2O_2$ 332.1525, found 332.1529.

*4.3.7. Ethyl 3,3-bis(2-methyl-1H-indol-3-yl)propanoate (**3g**).* The product was obtained as a colorless solid, mp 178.5–179.5 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.08 (t, J=7.2 Hz, 3H), 2.37 (s, 6H), 3.46 (d, J=7.8 Hz, 2H), 3.99 (q, J=7.2 Hz, 2H), 5.07 (t, J=7.8 Hz, 1H), 6.95–7.07 (m, 4H), 7.21 (d, J=7.8 Hz, 2H), 7.62 (d, J=7.5 Hz, 2H), 7.67 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 14.0, 31.1, 39.7, 60.2, 110.2, 113.6, 119.1, 120.6, 128.1, 131.0, 135.2, 172.8 (two peaks overlapped). Anal. Calcd for $C_{23}H_{24}N_2O_2$ requires C, 76.64; H, 6.71; N, 7.77, found C, 76.44; H, 6.72; N, 7.84.

*4.3.8. Methyl 3,3-bis(2-methyl-1H-indol-3-yl)propanoate (**3h**).* The product was obtained as a white solid, mp 176–178 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.35 (s, 6H), 3.48 (d, J=7.8 Hz, 2H), 3.55 (s, 3H), 6.95–7.07 (m, 4H), 7.20 (d, J=7.2 Hz, 2H), 7.61 (d, J=7.5 Hz, 2H), 7.64 (br s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.6, 31.1, 39.5, 51.5, 110.2, 113.5, 119.1, 119.2, 120.6, 128.0, 131.0, 135.2, 173.2. Anal. Calcd for $C_{22}H_{22}N_2O_2$ requires C, 76.28; H, 6.40; N, 8.09, found C, 75.97; H, 6.31; N, 7.92.

*4.3.9. 3,3-Bis(2-methyl-1H-indol-3-yl)propanoic acid (**3i**).* The product was obtained as a brown solid, mp 218–219 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 2.44 (s, 6H), 3.46 (d, J=7.8 Hz, 2H), 5.10 (t, J=7.8 Hz, 1H), 6.8–6.95 (m, 4H), 7.21 (d, J=7.5 Hz, 2H), 7.59 (d, J=7.5 Hz, 2H), 9.75 (br s, 2H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 11.3, 30.6, 38.7, 109.8, 112.7, 117.8, 118.27, 119.3, 127.7, 130.7, 135.2, 172.5. Anal. Calcd for $C_{21}H_{20}N_2O_2$ requires C, 75.88; H, 6.06; N, 8.43, found C, 75.69; H, 6.11; N, 8.42.

*4.3.10. Ethyl (E)-3-(2-methyl-1H-indol-3-yl)acrylate (**4a**)*[24]. The product was obtained as a white solid, mp 182–184 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (t, J=7.2 Hz, 3H), 2.57 (s, 3H), 4.28 (q, J=7.2 Hz, 2H), 6.43 (d, J=15.9 Hz, 1H), 7.19–7.24 (m, 2H), 7.30–7.33 (m, 1H), 7.85–7.88 (m, 1H), 7.95 (d, J=15.9 Hz, 1H), 8.22 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.4, 14.5, 60.0, 109.8, 110.8, 112.4, 120.1, 121.4, 122.5, 126.4, 135.7, 137.4, 139.7, 168.6.

*4.3.11. Methyl (E)-3-(2-methyl-1H-indol-3-yl)acrylate (**4b**).* The product was obtained as a colorless solid, mp 151–153 °C (CH_2Cl_2/hexane). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.56 (s, 3H), 3.81 (s, 3H), 6.43 (d, J=15.8 Hz, 1H), 7.17–7.33 (m, 3H), 7.83–7.86 (m, 1H), 7.96 (d, J=15.8 Hz, 1H), 8.34 (br s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.3, 51.3, 109.7, 110.8, 111.8, 120.0, 121.4, 122.5, 126.4, 135.7, 137.7, 140.0, 169.1. Anal. Calcd for $C_{13}H_{13}NO_2$ requires C, 72.54; H, 6.09; N, 6.51, found C, 72.43; H, 6.06; N, 6.48.

*4.3.12. (E)-3-(2-methyl-1H-indol-3-yl)acrylic acid (**4c**)*[25]. The product was obtained as a colorless solid, mp 182–183 °C (EtOAc/hexane). ^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 2.59 (s, 3H), 6.35 (d, J=15.9 Hz, 1H), 7.13–7.20 (m, 2H), 7.34–7.41 (m, 1H), 7.83–7.86 (m, 1H), 7.96 (d, J=15.9 Hz, 1H), 10.70 (br s, 1H); ^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 12.0, 109.6, 111.9, 112.1, 120.4, 121.8, 122.8, 127.4, 137.3, 138.7, 142.0, 169.1.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2011.08.051. These data include MOL files and InChIKeys of the most important compounds described in this article.

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