HETEROCYCLES, Vol. 78, No. 6, 2009, pp. 1463 - 1476. © The Japan Institute of Heterocyclic Chemistry
Received, 16th December, 2008, Accepted, 16th February, 2009, Published online, 17th February, 2009
DOI: 10.3987/COM-08-11627

SYNTHESIS OF INDOLYLINDOLINES MEDIATED BY *t*-BuNH$_2$

Oscar R. Suárez-Castillo,[a,*] Myriam Meléndez-Rodríguez,[a] Ana L. Morales-García,[a] Indira C. Cano-Escudero,[a] Yaneth M. A. Contreras-Martínez,[a] Martha S. Morales-Ríos,[b] and Pedro Joseph-Nathan[b]

[a]Área Académica de Química, Universidad Autónoma del Estado de Hidalgo, Mineral de la Reforma, Hidalgo, 42184 México. osuarez@uaeh.edu.mx
[b]Departamento de Química, Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional, Apartado 14-740, México, D. F., 07000 México

Abstract – An improved synthesis of *N*1-carbomethoxylated indolylindolines **2** from 5-substituted indoles **1**, by replacing the previously employed strong acids or toxic metals with *t*-BuNH$_2$/MeOCOCl in CH_2Cl_2/H_2O, is described. The substituent effect of electron donor or acceptor groups was examined, revealing that electron-deficient indoles are less reactive to dimerization than electron-rich indoles, with 5-cyano and 5-nitroindoles leading to no reaction. A dynamic process caused by the restricted rotation of the *N*-CO_2Me bond of **2** was evidenced by ^{1}H NMR measurements.

INTRODUCTION

Due to the potential synthetic applications and biological effects of indole dimers[1] there is a constant need to develop efficient protocols to achieve indole oligomerization. In general, such oligomerizations are effected under harsh reaction conditions in the presence of strong acids or toxic metals and tedious workup procedures are generally required. The acids frequently used are anhydrous HCl,[2a,b] HBr,[2c] NBS/AcOH,[2d] TFA,[2e-h] HCO_2H,[2i] $BF_3{\cdot}Et_2O$,[2c] $ZnCl_2$/AcOH,[2c] Se, Pd-Charcoal[2j] and $POCl_3$.[2k] Indole dimerization to indolylindolines is usually carried out by the acid-induced 3*H*-indolium cation which can react with an unprotonated indole molecule leading to indole dimers and/or 3,3'-(aminophenethylidene)diindoles.[3] To the best of our knowledge only one example is reported for the oligomerization of indoles to give 3,3'-(aminophenethylidene)diindoles under basic conditions,[4] using aqueous Na_2CO_3 or $NaHCO_3$, with acyl chlorides or chloroformates. The latter work punctualized that if nitrogenated bases such as Et_3N or *N*-methylpyrrolidine are used together with acyl chlorides, the only

products obtained are the *N*-acyl protected indoles, as expected. In fact, we already reported our results on the protection of indole derivatives with MeOCOCl in the presence of NaH without dimerization or trimerization reactions.[5] Recently, the $InCl_3$/MeOCOCl/CH_2Cl_2 system has been used as catalyst in the synthesis of indole dimers and trimers.[6] The authors report that in the absence of MeOCOCl, indoles give trimers.

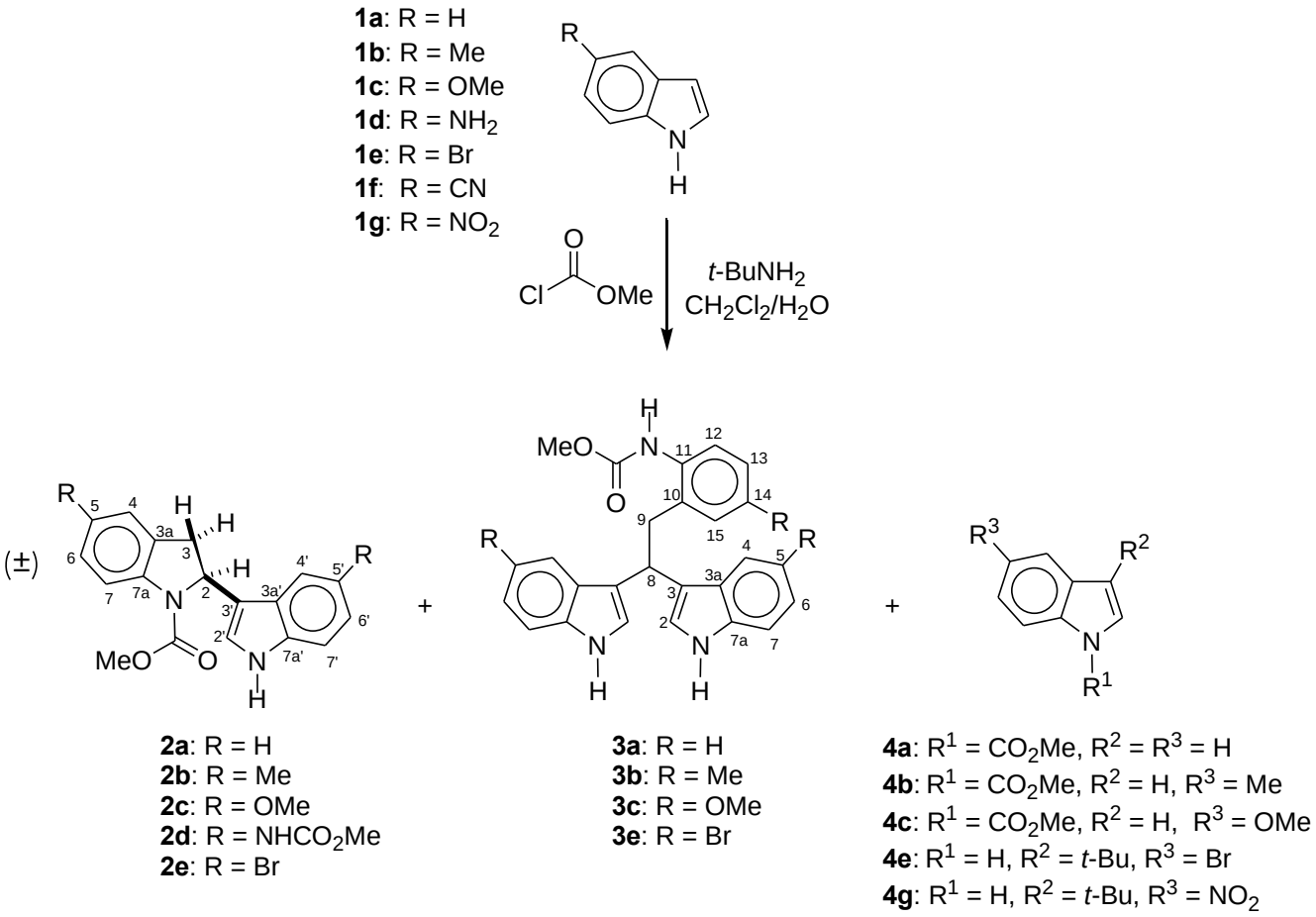
Although there are a number of protocols to dimerize or trimerize indole derivatives, the main drawback of these procedures is the need to use anhydrous conditions. Thus, we report here on the details concerning an alternative simple procedure in which the use of *t*-$BuNH_2$/MeOCOCl represents a valuable protocol for the synthesis of *N*1-carbomethoxylated indolylindolines **2**, together with some amounts of 3,3'-(aminophenethylidene)diindoles **3**, without the need to use anhydrous conditions. Indeed, reactions were carried out in aqueous mixtures to favor products **2**, and this is the first time that dimers **2** and trimers **3** are obtained using a nitrogenated base.

RESULTS AND DISCUSSION

With the aim of exploring new applications of cheap and easily manageable *t*-$BuNH_2$ in organic synthesis,[7a,b] as a base of low nucleophilicity when compared to other primary amines of similar basicity due to the steric effect of the *t*-butyl group,[7c] we decided to investigate its use to generate indole dimers **2**. We examined the reactivity profile for a series of indoles **1a-g** with MeOCOCl and *t*-$BuNH_2$ (Scheme) whose results are summarized in Table 1. Control experiments were initially conducted without water, and it was found that the fastest and cleanest reaction was observed using 10 equivalents of amine and 8 equivalents of chloroformiate in CH_2Cl_2 at room temperature, although prolonged reaction times (120 h) were required to give indolylindoline **2a**, trimer **3a** and protected indole **4a**[8] in 50%, 23% and 5% yield, respectively (Table, Entry 1). Pure **2a** showed spectroscopic data (^{1}H NMR, ^{13}C NMR, MS) consistent with those reported in the literature.[6] Compound **3a** was determined to be the corresponding aniline carbamate derivative as supported by ^{1}H and ^{13}C NMR and MS. With the objective of achieving the conversion of **1a** into **2a** or **3a** in shorter reaction times, the number of equivalents of MeOCOCl were increased to 32 and the reaction was carried out under reflux, whereby the reaction time decreased to 74 h and compounds **2a** and **3a** were obtained in 60% and 10% yield, respectively (compare Entries 2 and 3).

It is worth noting that when *t*-$BuNH_2$ and MeOCOCl are added to the solution of **1a** in CH_2Cl_2, a precipitate is formed which is maintained through the reaction. This precipitate was identified by ^{1}H and ^{13}C NMR as *tert*-butyl ammonium chloride (*t*-$BuNH_2 \cdot HCl$). Based on this information, the reaction for the transformation of **1a** into **2a** or **3a** was carried out using water as a co-solvent thus dissolving the precipitate, and under the new reaction conditions the yields and reaction times vary notably. The optimized procedure for the transformation of **1a** into **2a** and **3a** namely in the presence of 15 equivalents

of *t*-$BuNH_2$ and 30 equivalents of MeOCOCl under reflux of CH_2Cl_2/H_2O, occurred in 21 h to give **2a** and **3a** in 79% (Lit. 56%)[6] and 12% yield, respectively, together with traces of **4a** (compare Entries 4 and 5). A plausible mechanism for the formation of dimer **2a** and trimer **3a** from **1a** could involve *tert*-butylimidodicarbamate hydrochloride as the catalytic species, since the reaction occurs when *t*-$BuNHCO_2Me$ in the presence of an excess of MeOCOCl is used.



Scheme

With successful reaction conditions established as in Entry 5, in order to explore the scope and limitations of this reaction, the reactivity profile for a series of readily available 5-substituted indoles **1b-g** was studied, and the results are summarized in Table 1 (Entries 6-11). When 5-methylindole (**1b**) and 5-methoxyindole (**1c**) were reacted under the above optimized reaction conditions, the corresponding indolylindolines **2b** and **2c** were obtained in 67% and 59% yield, respectively (Entries 6 and 7). It should be noted that 5-aminoindole (**1d**) provides only dimer **2d** (Entry 8); however, compared to **1a-c** (Entries 5-7), the reaction was significantly slower, requiring 65 h for the complete consumption of starting **1d**. Interestingly for 5-bromoindole (**1e**) the main product was trimer **3e**, isolated in 48% yield, whereas dimer **2e** was obtained in only 27% yield (Entry 9).

Table 1. Indole oligomerization mediated by *t*-$BuNH_2$/MeOCOCl.

Entry	Starting material	Equiv of *t*-$BuNH_2$	Equiv of MeOCOCl	Reaction conditions	Time (h)	Product (%)		
						2	**3**	**4**
1	**1a**: R = H	10	8	rt	120[a]	**a** (50)	**a** (23)	**a** (5)
2	**1a**	10	32	rt	96[a]	**a** (62)	**a** (11)	**a** (7)
3	**1a**	10	32	reflux	74[a]	**a** (60)	**a** (10)	**a** (4)
4	**1a**	10	30	reflux	30[b]	**a**(70)	**a**(12)	**a**(2)
5	**1a**	15	30	reflux	21[b]	**a** (79)	**a** (12)	**a** (2)
6	**1b**: R = Me	15	30	reflux	27[b]	**b** (67)	**b** (14)	**b** (3)
7	**1c**: R = OMe	15	30	reflux	33[b]	**c** (59)	**c** (8)	**c** (1)
8	**1d**: R = NH_2	15	30	reflux	65[b]	**d** (59)	---	---
9	**1e**: R = Br	15	30	reflux	100[b]	**e** (27)	**e** (48)	**e** (7)
10	**1f**: R = CN	15	30	reflux	100[b,c]	---	---	---
11	**1g**: R = NO_2	15	30	reflux	164[b,c]	---	---	**g** (3)

[a]In absence of water
[b]In presence of water
[c]Starting material was recovered.

Attempts to dimerize indoles **1f** and **1g** carrying stronger electron-withdrawing groups such as –CN or $–NO_2$ failed even after prolonged reaction times (Entries 10 and 11), as starting **1f** or **1g** were recovered. It is also worth noting that in the case of indoles **1e** and **1g**, the C-3 *tert*-butyl derivatives **4e** and **4g** were obtained in trace amounts (Entries 9 and 11). These compounds could be formed by reaction of **1e** and **1g** with the *tert*-butyl cation generated by thermal scission of *tert*-butylimidodicarbamate.[7a,9] Indoles with substituents at C-3 like 3-methylindole did not react under the above reaction conditions.

Although indolylindoline **2a** is known,[6] its spectroscopic data are ambiguous mainly due to signal broadening, suggesting the presence of conformational isomers arising from slow rotation around the *N*-CO_2Me bond,[10] giving rise to the two mayor *E* and *Z* isomers denoted by the torsion angle C(7a)-N(1)-C=O. The room temperature (293 K) ^{1}H NMR spectra of **2a**, recorded in $CDCl_3$ and $Cl_2CDCDCl_2$ exhibited extensive line broadening of aromatic protons and the *N*-carbomethoxyl group signals (Figure 1, B and C). When the ^{1}H NMR spectrum of **2a** was recorded in DMSO-d_6 line broadening increased but the aromatic proton signals were dispersed (Figure 1, A) allowing unambiguous assignment by means of 1D (homonuclear ^{1}H-^{1}H decoupling, ^{13}C{^{1}H}) and 2D (^{1}H-^{13}C HMQC and HMBC) experiments.

The broadening of the aromatic protons and the *N*-carbomethoxyl group signals in **2a** indicate that rotation around the *N*-CO_2Me bond is the dominant dynamic process.[10] This assumption was confirmed

when the ^{1}H NMR spectrum of **2a** was obtained in $Cl_2CDCDCl_2$ at 100 °C (Figure 1, D), whereby the signals for H7 and the *N*-CO_2Me group became sharpened. The dynamic process was also evidenced by comparison of the ^{1}H NMR spectra of **2a** and 2-(3'-indolyl)indoline **5**,[2i] since the latter exhibited only sharp lines[11] (Figure 1, E).

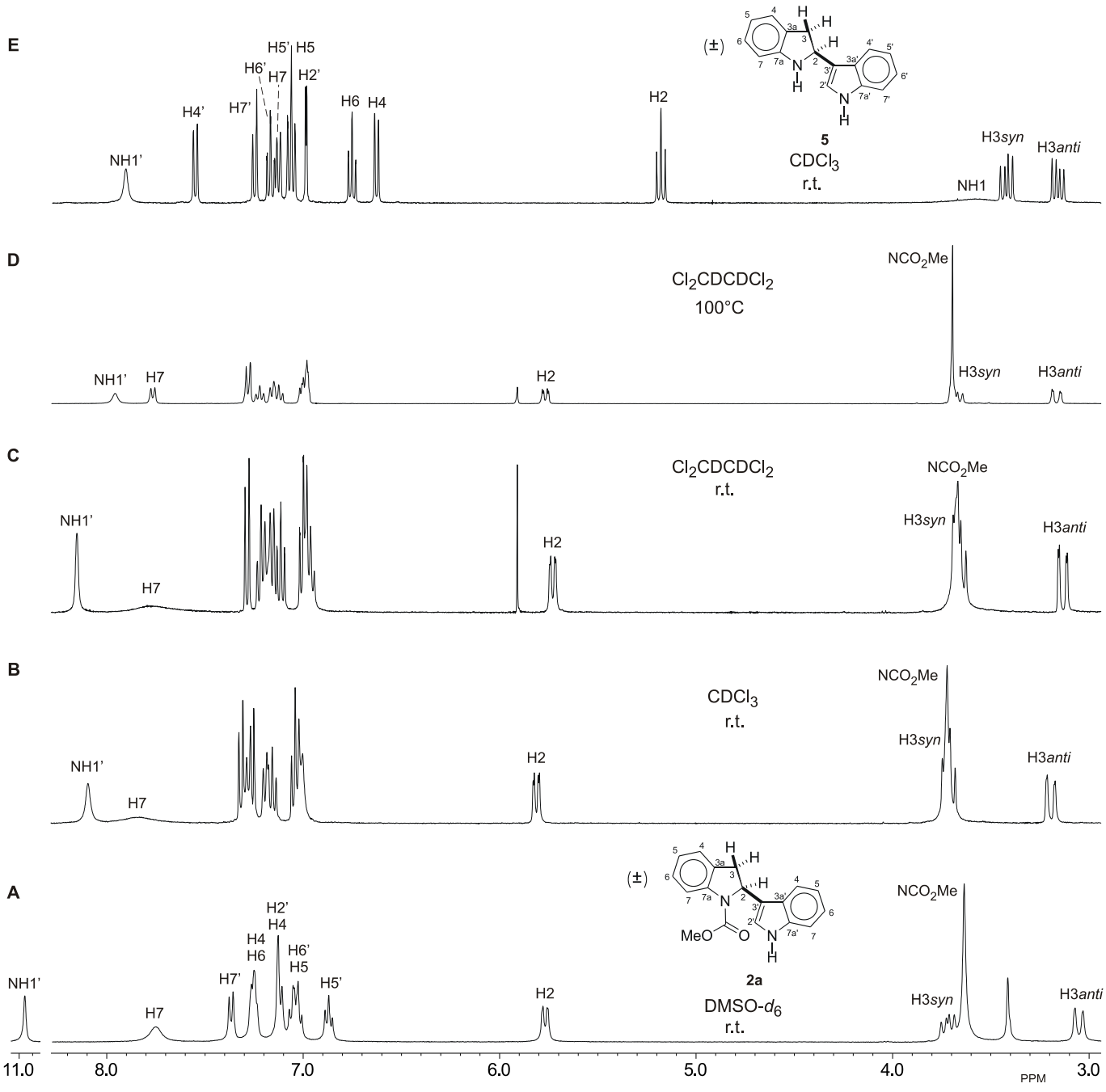


Figure 1. ^{1}H NMR spectra of **2a** (**A**. in DMSO-d_6; **B**. in $CDCl_3$, **C**, **D**. in $Cl_2CDCDCl_2$) and **5** (**E**. in $CDCl_3$).

Furthermore, conformational evaluations of **2a** were carried out by means of systematic and Monte Carlo search protocols within the Spartan 04 program[12] employing the MMFF94 molecular mechanics force field, which afforded four conformers. These four structures were submitted to geometry optimization using DFT calculations at the B3LYP/6-31G(d) level of theory (Figure 2), from where the $^{3}J_{H2,H3syn}$ and $^{3}J_{H2,H3anti}$ values were calculated[13] (Table 2), thus allowing individual assignments of the two H3 signals as is shown in Figure 1.

Compound **2a** gave single crystals suitable for X-ray diffraction analysis, the corresponding structure being shown in Figure 3, where it is evident that the *Z* isomer is preferred in the crystalline state. The sum of bond angles around the carbamate N atom is 360°, suggesting that the geometry of the nitrogen atom is totally planar according to the degree of pyramidalization, defined as 360° - ∑(R-N-R).[14] The five membered ring adopts a preferred enveloped conformation in which C-2 is the flap, as is evidenced from the torsion angles C(2)-C(3)-C(3a)-C(7a) (-13.6°) and C(2)-N(1)-C(7a)-C(3a) (12.4°).

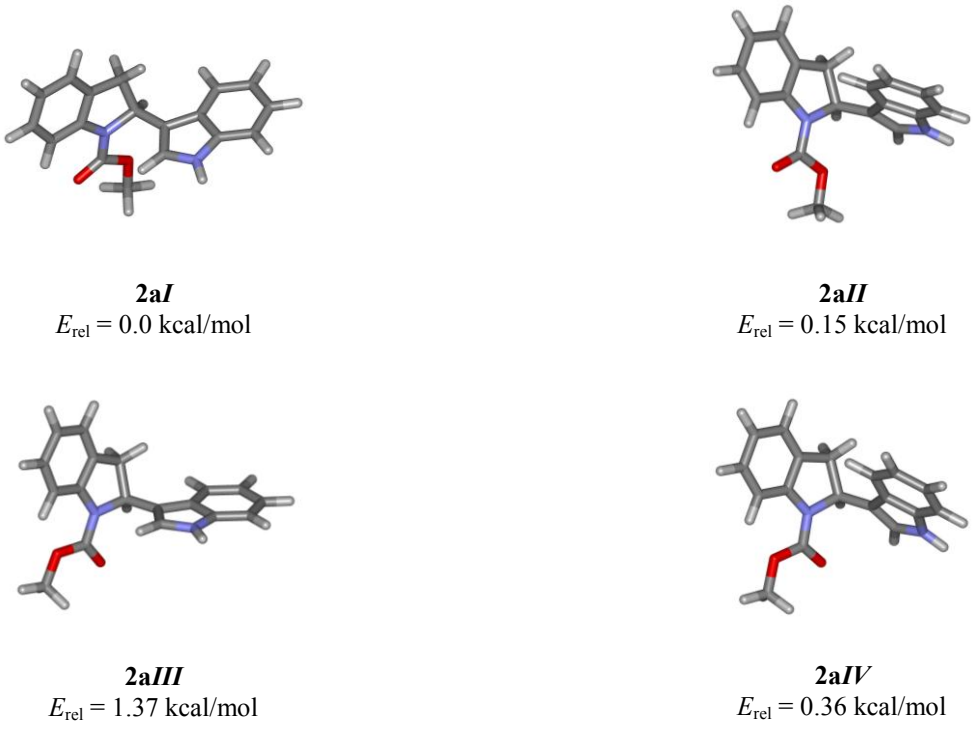


Figure 2. Optimized geometries and relative energy difference (E_{rel}/kcal mol^{-1}) for conformers **2a*I-IV*** obtained at the DFT [B3LYP/6-31G(d)] level of theory.

Table 2. Calculated and experimental coupling constant values *J*(Hz) for **2a**.

Conformer	Dihedral(°)		*J*(Hz)[a]	
	H2-C2-C3-H3*syn*	H2-C2-C3-H3*anti*	$J_{H2\text{-}H3syn}$	$J_{H2\text{-}H3anti}$
2a*I*	18.3	101.1	9.1	2.0
2a*II*	4.0	114.5	9.8	3.7
2a*III*	18.2	101.4	9.1	2.0
2a*IV*	8.3	110.4	9.7	3.1
			9.5[b]	2.8[b]
X-ray structure	12.6	-108.5	9.5	2.9
			10.4[c]	1.7[c]

[a]Calculated using PCMODEL.[13]
[b]Weighted average.
[c]From the ^{1}H NMR of **2a** obtained in DMSO-d_6.

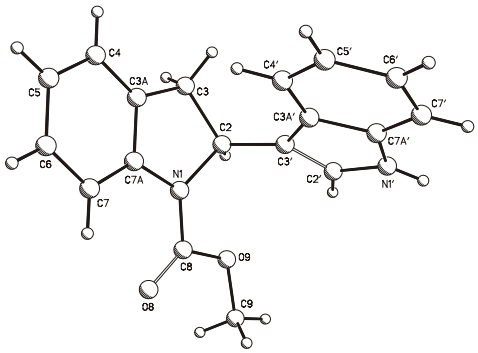


Figure 3. X-Ray diffraction structure of **2a**.

In conclusion, we have developed a simple protocol for the oligomerization of indoles **1** into the corresponding selectively protected dimers **2** and trimers **3**. The procedure employs operationally facile reaction conditions in yields ranging from fair to good, providing advantages over those previously reported. The method can be applied to indoles with substituent groups other than deactivating functionalities at the C-5 position on the indole ring.

EXPERIMENTAL

All commercial grade reagents were used without further purification. Analytical thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} coated aluminum sheets (0.25 mm thickness) with a fluorescent indicator. Visualization was accomplished with UV light (254 nm). Flash chromatography was performed using silica gel 60 (230–400 mesh). Melting points were determined on a

Büchi B-540 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer 2000 FT-IR spectrophotometer. The ^{1}H and ^{13}C NMR spectra were recorded on JEOL Eclipse+ 400 and Varian Mercury spectrometers working at 400, 300 and 100, 75.4 MHz for ^{1}H and ^{13}C, respectively, using $CDCl_3$ or DMSO-d_6 as the solvent and TMS as the internal reference unless indicated otherwise. For complete data assignments, 2D HMQC and HMBC NMR spectra were used. Chemical shifts are reported as follows: chemical shift from TMS, integration, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; br = broad; m = multiplet), coupling constants (Hz) and assignment. NMR data are reported in parts per million downfield from tetramethylsilane. GC/MS analyses were conducted on a Varian CP 3800 GC equipped with a selective mass Varian Saturn 2000 detector and a 30 m, 0.25 mm i.d., 0.25 mm CP-SIL capillary column, using helium as carrier gas (1 mL/min), programmed from 70 °C to 250 °C at a rate of 30 °C/min, with the injector temperature at 200 °C. Relative percentage amounts were calculated from total ion chromatograms by the computer. MS analyses were obtained in the electron impact (EI) mode at an ionizing voltage of 70 eV on a Hewlett Packard 5989-A spectrometer. High-resolution (HR) mass spectra were measured at the UCR Mass Spectrometry Facility, University of California, Riverside, CA. Microanalytical determinations were performed on a Perkin Elmer 2400 Series PCII apparatus.

General procedure for the preparation of indolylindolines 2a-e and trimers 3a-d.

To a solution of the appropriate indole **1a** (0.5 g, 4.30 mmol), **1b** (0.15 g, 1.14 mmol), **1c** (0.5 g, 3.40 mmol), **1d** (0.15 g, 1.10 mmol), **1e** (0.15 g, 0.80 mmol), **1f** (0.15 g, 1.1 mmol) **1g** (0.5 g, 3.10 mmol) in CH_2Cl_2/H_2O (4.5-15/4.5-15 mL) were added 15 equiv of *t*-$BuNH_2$. The solution was cooled to 5 °C and treated dropwise, over 15 min, with 30 equiv of $ClCO_2Me$. After addition was complete, the mixture was stirred under reflux during 21 h for **1a**, 27 h for **1b**, 33 h for **1c**, 65 h for **1d**, 100 h for **1e**, 100 h for **1f**, and 164 h for **1g**. After cooling to rt the organic phase was washed with a saturated aqueous solution of NH_4Cl (2 x 20 mL), saturated aqueous solution of $NaHCO_3$ (2 x 20 mL), brine (2 x 20 mL) dried over Na_2SO_4, filtrated and concentrated in vacum. The resultant crude products were purified by flash column chromatography with EtOAc/hexane 1:9.

***N*-Methoxycarbonyl-2-(3'-indolyl)indoline (2a).**

Prepared from **1a** as a white powder (0.493 g, 79.0%); mp 172-173 °C (CH_2Cl_2). Although **2a** is known,[4] its spectroscopic data are ambiguous. Thus, NMR data follow: ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.95 (1H, brs, N-H), 7.74 (1H, brs, H-7), 7.36 (1H, d, *J* = 8.1 Hz, H7'), 7.24 (1H, d, *J* = 6.5 Hz, H-4), 7.23 (1H, t, *J* = 6.5 Hz, H-6), 7.12 (1H, s, H-2'), 7.11 (1H, d, *J* = 7.7 Hz, H-4'), 7.04 (1H, t, *J* = 7.7 Hz, H-6'), 7.02 (1H, t, *J* = 7.6 Hz, H-5), 6.86 (1H, t, *J* = 7.4 Hz, H-5'), 5.76 (1H, dd, *J* = 10.2, 1.7 Hz, H-2), 3.71 (1H, dd, *J* = 16.3, 10.4 Hz, H-3*syn*), 3.63 (3H, s, Me), 3.04 (1H, dd, *J* = 16.3, 1.7 Hz, H-3*anti*); ^{13}C NMR (DMSO-d_6, δ 100 MHz) δ 153.1 (C=O), 142.0 (C-7a), 136.7 (C-7a'), 130.7 (C-3a), 127.4 (C-6), 124.9

(C-4), 124.5 (C-3a'), 122.8 (C-5), 122.6 (C-2'), 121.1 (C-6'), 118.7 (C-5'), 118.6 (C-4'), 116.7 (C-3'), 114.4 (C-7), 111.8 (C-7'), 56.2 (C-2), 52.3 (Me), 36.2 (C3); *Anal*. Calcd for $C_{18}H_{16}N_2O_2$: C 73.95; H 5.52; N 9.58. Found: C 73.81; H 5.52; N 9.30.

_N_-Methoxycarbonyl-2-[2,2-bis-(1*H*-indol-3-yl)ethyl]phenylamine (3a).

Prepared from **1a** as a brown powder (69 mg, 12.0%); mp 170-172 °C (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.70 (2H, brd, N-H), 8.91 (1H, brs, N*H*-CO_2Me), 7.50 (2H, d, *J* = 8.1 Hz, H-4), 7.26 (2H, d, *J* = 8.0 Hz, H-7), 7.21 (1H, d, *J* = 7.7 Hz, H-12), 7.14 (2H, d, *J* = 2.2 Hz, H-2), 7.04 (1H, t, *J* = 7.6 Hz, H-13), 6.99 (1H, d, *J* = 7.5 Hz, H-15), 6.98 (2H, t, *J* = 7.8 Hz, H-6), 6.86 (1H, t, *J* = 7.4 Hz, H-14), 6.85 (2H, t, *J* = 7.5 Hz, H-5), 4.77 (1H, t, *J* = 7.7 Hz, H-8), 3.65 (3H, s, Me), 3.48 (2H, d, *J* = 7.7 Hz, H-9); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.3 (C=O), 136.4 (C-7a), 136.1 (C-11), 136.0 (C-10), 129.9 (C-15), 126.6 (C-3a), 126.1 (C-12), 126.0 (C-13), 124.9 (C-14), 122.2 (C-2), 120.6 (C-6), 119.0 (C-4), 118.3 (C-3), 117.9 (C-5), 111.3 (C-7), 51.7 (Me), 36.8 (C-9), 33.3 (C-8); IR (CsI) ν_{max} 3442, 3061, 3042, 2954, 1678, 1598, 1544, 1430 cm^{-1}; EIMS *m/z* 409 [M+]$^+$ (8), 292 (13), 245 (100), 218 (13), 117 (9). FABHRMS *m/z* 409.1785 (calcd for $C_{26}H_{23}N_3O_2$, 409.1790).

_N_-Methoxycarbonylindole (4a).

Prepared from **1a** as a pale yellow oil (0.017 g, 2.0%).[8]

_N_-Methoxycarbonyl-2-(5'-methyl-3'-indolyl)-5-methylindoline (2b).

Prepared from **1b** as a white powder (0.122 g, 67.0%); mp 136-139 °C (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.76 (1H, s, N-H), 7.60 (1H, brs, H-7), 7.23 (1H, d, *J* = 8.4 Hz, H-7'), 7.03 (1H, brd, *J* = 8.1 Hz, H-6), 7.02 (1H, s, H-4), 6.97 (1H, d, *J* = 2.9 Hz, H-2'), 6.96 (1H, d, *J* = 1.8 Hz, H-4'), 6.88 (1H, dd, *J* = 8.4, 1.4 Hz, H-6'), 5.71 (1H, dd, *J* = 10.1, 2.4 Hz, H-2), 3.63 (1H, dd, *J* = 16.8, 10.6 Hz, H-3*syn*), 3.61 (3H, s, NCO_2Me), 2.94 (1H, dd, *J* = 16.1, 1.8 Hz, H-3*anti*), 2.25 (6H, s, C5-*Me*, C5'-*Me*); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 153.2 (C=O), 139.8 (C-7a), 135.1 (C-7a'), 131.9 (C-5), 130.9 (C-3a), 127.7 (C-6), 127.1 (C-5'), 125.7 (C-4), 125.0 (C-3a'), 122.9 (C-6'), 122.3 (C-2'), 118.5 (C-4'), 116.5 (C-3'), 114.3 (C-7), 111.6 (C-7'), 56.4 (C-2), 52.3 (NCO_2Me), 36.4 (C-3), 21.5 (C5'-*Me*), 20.7 (C5-*Me*); IR (CsI) ν_{max} 3339, 3019, 2952, 2857, 1686, 1596, 1449 cm^{-1}; EIMS *m/z* 321 [M+1]$^+$ (20.9), 320 [M]$^+$ (100), 262 (21), 190 (5), 130 (4). *Anal.* Calcd for $C_{20}H_{20}N_2O_2$: C 74.98; H 6.29; N 8.74. Found: C 74.82; H 6.34; N 8.48.

_N_-Methoxycarbonyl-2-[2,2-bis-(1*H*-5-methylindol-3-yl)ethyl]-4-methylphenylamine (3b).

Prepared from **1b** as a pale yellow oil (24 mg, 14.0%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (2H, s, N-H), 7.18 (2H, d, *J* = 8.0 Hz, H-7), 7.17 (2H, s, H-4), 7.05 (1H, brs, H-15), 6.95 (2H, dd, *J* = 8.4, 1.1 Hz, H-6),

6.96 (1H, d, *J* = 8.4 Hz, H-12), 6.92 (1H, dd, *J* = 8.5, 1.9 Hz, H-13), 6.88 (2H, d, *J* = 2.2 Hz, H-2), 5.75 (1H, brs, N*H*-CO_2Me), 4.63 (1H, t, *J* = 7.3 Hz, H-8), 3.55 (3H, s, NCO_2Me), 3.41 (2H, d, *J* = 7.7 Hz, H-9), 2.34 (6H, s, C5-*Me*), 2.25 (3H, s, C14-*Me*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 155.2 (C=O), 135.1 (C-7a), 134.5 (C-14), 133.5 (C-11), 132.9 (C-10), 131.1 (C-15), 128.6 (C-5), 127.5 (C-13), 127.0 (C-3a), 123.7 (C-6), 123.5 (C-12), 122.3 (C-2), 119.3 (C-4), 118.7 (C-3), 111.0 (C-7), 52.2 (NCO_2Me), 37.6 (C-9), 36.4 (C-8), 21.6 (C5-*Me*), 21.1 (C14-*Me*); IR (CsI) ν_{max} 3407, 3121, 3014, 2920, 1713, 1614, 1516 cm^{-1}; EIMS *m/z* 451 [M]$^+$ (1), 274 (25), 273 (100), 86 (26), 49 (57). FABHRMS *m/z* 451.2253 (calcd for $C_{29}H_{29}N_3O_2$, 451.2260).

_N_-Methoxycarbonyl-5-methylindole (4b).

Prepared from **1b** as a yellow powder (6 mg, 3.0%); mp 53-55 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.03 (1H, brd, *J* = 7.0 Hz, H-7), 7.53 (1H, d, *J* = 3.3 Hz, H-2), 7.33 (1H, d, *J* = 0.8 Hz, H-4), 7.13 (1H, d, *J* = 8.4 Hz, H-6), 6.50 (1H, d, *J* = 3.7 Hz, H-3), 4.00 (3H, s, NCO_2Me), 2.42 (3H, s, C5-*Me*); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 151.7 (C=O), 133.5 (C-7a), 132.6 (C-5), 130.8 (C-3a), 125.9 (C-6), 125.6 (C-2), 121.0 (C-4), 114.8 (C-7), 108.0 (C-3), 53.8 (NCO_2*Me*), 21.4 (C5-*Me*); IR (CsI) ν_{max} 3023, 3153, 2955, 1732, 1585, 1468 cm^{-1}; EIMS *m/z* 190 [M+1]$^+$ (15), 189 [M]$^+$ (100), 174 (3), 144 (46), 130 (22). FABHRMS *m/z* 189.0785 (calcd for $C_{11}H_{11}N_1O_2$, 189.0790).

_N_-Methoxycarbonyl-2-(5'-methoxy-3'-indolyl)-5-methoxyindoline (2c).

Prepared from **1c** as a white powder (0.352 g, 59.0%); mp 190-192 °C (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.78 (1H, s, N-H), 7.63 (1H, brs, H-7), 7.23 (1H, d, *J* = 8.4 Hz, H-7'), 7.09 (1H, d, *J* = 2.6 Hz, H-2'), 6.92 (1H, d, *J* = 2.2 Hz, H-4), 6.81 (1H, dd, *J* = 8.6, 2.4 Hz, H-6), 6.68 (1H, dd, *J* = 8.6, 2.4 Hz, H-6'), 6.48 (1H, d, *J* = 2.6 Hz, H-4'), 5.69 (1H, dd, *J* = 10.0, 2.0 Hz, H-2), 3.71 (3H, s, C5-O*Me*), 3.66 (1H, dd, *J* = 16.5, 5.5 Hz, H-3*syn*), 3.62 (3H, brs, NCO_2Me), 3.50 (3H, s, C5'-O*Me*), 2.98 (1H, brdd, *J* = 16.4, 1.4 Hz, H-3*anti*); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 155.7 (C-5), 153.1 (C-5', C=O), 135.7 (C-7a), 132.7 (C-3a), 131.8 (C-7a'), 124.8 (C-3a'), 123.6 (C-2'), 116.7 (C-3'), 115.1 (C-7), 112.5 (C-7'), 112.4 (C-6), 111.3 (C-6'), 111.0 (C-4), 100.8 (C-4'), 56.7 (C-2), 55.5 (C5-O*Me*), 55.0 (C5'-O*Me*), 52.3 (NCO_2*Me*), 36.3 (C-3); IR (KBr) ν_{max} 3446, 2956, 1675, 1597, 1542 cm^{-1}; EIMS *m/z* 353 [M+1]$^+$ (21), 352 [M]$^+$ (100), 293 (21), 147 (27). *Anal.* Calcd for $C_{20}H_{20}N_2O_4$: C 68.17; H 5.72; N 7.95. Found: C 68.11; H 5.76; N 7.89.

_N_-Methoxycarbonyl-2-[2,2-bis-(1*H*-5-methoxyindol-3-yl)ethyl]-4-methoxyphenylamine (3c).

Prepared from **1c** as a pale yellow oil (46 mg, 8.0%); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 10.56 (2H, brs, N-H), 8.75 (1H, brs, N*H*-CO_2Me), 7.17 (1H, d, *J* = 8.8 Hz, H-7), 7.13 (1H, d, *J* = 1.9 Hz, H-2), 7.06 (1H, brd, *J* = 7.7 Hz, H-12), 7.00 (1H, d, *J* = 2.2 Hz, H-4), 6.66 (1H, dd, *J* = 8.8, 2.2 Hz, H-6), 6.60 (1H, dd, *J*

= 8.6, 2.8 Hz, H-13), 6.50 (1H, d, *J* = 2.9 Hz, H-15), 4.67 (1H, t, *J* = 7.5 Hz, H-8), 3.68 (6H, s, 2C5-O*Me*), 3.61 (3H, s, NCO_2*Me*), 3.41 (3H, s, C14-O*Me*), 3.39 (2H, d, *J* = 7.5 Hz, H-9); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 156.5 (C-14), 155.8 (C=O), 152.6 (C-5), 138.2 (C-10), 131.6 (C-7a), 129.0 (C-11), 127.8 (C-12), 127.1 (C-3a), 123.1 (C-2), 118.2 (C-3), 115.4 (C-15), 111.8 (C-7), 111.3 (C-13), 110.5 (C-6), 101.4 (C-4), 55.4 (C5-O*Me*), 54.7 (C14-O*Me*), 51.6 (NCO_2*Me*), 37.1 (C-9), 33.1 (C-8); IR (KBr) ν_{max} 3418, 2918, 2849, 1706, 1485 cm^{-1}; EIMS *m/z* 499 $[M]^+$ (7), 353 (13), 352 (53), 305 (100), 147 (39). FABHRMS *m/z* 499.2111 (calcd for $C_{29}H_{29}N_3O_5$, 499.2107).

***N*-Methoxycarbonyl-5-methoxyindole (4c).**[8]

Prepared from **1c** as a yellow powder (9 mg, 1.0%); mp 77-78 °C (EtOAc/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.05 (1H, s, H-7), 7.57 (1H, d, *J* = 3.0 Hz, H-2), 7.03 (1H, d, *J* = 2.5 Hz, H-4), 6.94 (1H, dd, *J* = 8.8, 2.5 Hz, H-6), 6.53 (1H, d, *J* = 4.1 Hz, H-3), 4.02 (3H, s, NCO_2Me), 3.85 (3H, s, C5-OMe); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 156.2 (C-5), 151.6 (C=O), 131.4 (C-3a), 130.1 (C-7a), 126.3 (C-2), 115.9 (C-7), 113.4 (C-6), 108.2 (C-3), 103.7 (C-4), 55.8 (C5-O*Me*), 53.9 (NCO_2*Me*); IR (CsI) ν_{max} 3001, 2956, 2834, 1736, 1588, 1474 cm^{-1}; EIMS *m/z* 206 $[M+1]^+$ (13), 205 $[M]^+$ (100), 190 (41), 174 (1), 146 (28), 131 (5), 118 (37), 59 (3).

***N*-Methoxycarbonyl-2-(5'-amino-3'-indolyl)-5-aminoindoline (2d).**

Prepared from **1d** as a white powder (0.146 g, 59.0%); mp 197-200 °C (EtOAc/hexane); ^{1}H NMR (DMSO-d_6, 400 MHz, at 70 °C) δ 10.62 (1H, s, N-H'), 9.26 (2H, s, NH), 8.99 (2H, s, NH), 7.60 (1H, d, *J* = 8.4 Hz, H-7), 7.44 (1H, brs, H-4'), 7.34 (1H, brs, H-4), 7.27 (1H, dd, *J* = 8.6, 2.0 Hz, H-6), 7.26 (1H, d, *J* = 8.4 Hz, H-7'), 7.09 (1H, dd, *J* = 8.5, 1.6 Hz, H-6'), 6.97 (1H, d, *J* = 2.2 Hz, H-2'), 5.72 (1H, dd, *J* = 9.7, 2.3 Hz, H-2), 3.68 (1H, dd, *J* = 16.5, 9.9 Hz, H-3*syn*), 3.66 (3H, s, OMe), 3.64 (3H, s, OMe), 3.63 (3H, s, OMe), 3.00 (1H, dd, *J* = 16.3, 2.0 Hz, H-3*anti*); ^{13}C NMR (DMSO-d_6, 100 MHz, at 70 °C) δ 154.6, 154.3, 153.1 (3C=O), 137.1, 134.3, 133.3, 131.0, 130.6, 124.8, 122.6, 120.7, 119.4, 117.8, 116.7, 116.0, 115.6, 114.4, 111.4, 109.8, 56.1 (C-2), 52.1 (OMe), 51.4 (OMe), 51.3 (OMe), 36.4 (C-3); IR (CsI) ν_{max} 3537, 2953, 2923, 1703, 1551 cm^{-1}; EIMS *m/z* 438 $[M]^+$ (13), 406 (51), 374 (100), 315 (23), 190 (15), 158 (34). *Anal.* Calcd for $C_{22}H_{22}N_4O_6$: C 60.27; H 5.06; N 12.78. Found: C 60.21; H 5.05; N 12.48.

***N*-Methoxycarbonyl-2-(5'-bromo-3'-indolyl)-5-bromoindoline (2e).**

Prepared from **1e** as a pale yellow oil (46 mg, 27.0%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (1H, brs, N-H), 7.70 (1H, brs, H-7), 7.49 (1H, brs, H-4'), 7.37 (1H, dd, *J* = 8.6, 2.0 Hz, H-6), 7.30 (1H, brs, H-4), 7.27 (1H, dd, *J* = 8.5, 1.9 Hz, H-6'), 7.21 (1H, d, *J* = 6.7 Hz, H-7'), 6.99 (1H, brs, H-2'), 5.76 (1H, dd, *J* = 10.3, 2.4 Hz, H-2), 3.72 (3H, brs, Me), 3.69 (1H, dd, *J* = 16.4, 10.1 Hz, H-3*syn*), 3.10 (1H, dd, *J* = 16.5, 2.4 Hz, H-3*anti*); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.9 (C=O), 141.5 (C-7a), 135.1 (C-7a'), 132.7 (C-3a), 130.6

(C-6), 127.9 (C-4), 127.0 (C-3a'), 125.2 (C-6'), 122.6 (C-2'), 121.7 (C-4'), 118.0 (C-3'), 118.0 (C-7), 115.4 (C-5), 113.1 (C-5'), 112.8 (C-7'), 56.1 (C-2), 52.9 (Me), 36.2 (C-3); IR (CsI) ν_{max} 3336, 3076, 2955, 1705, 1567, 1478 cm^{-1}; EIMS *m/z* 451 $[M+1]^+$ (20), 450 $[M]^+$ (100), 449 (47), 310 (15), 114 (2). FABHRMS *m/z* 447.9418 (calcd for $C_{18}H_{14}N_2O_2Br_2$, 447.9422).

_N_-Methoxycarbonyl-2-[2,2-bis-(1*H*-5-bromoindol-3-yl)ethyl]-4-bromophenylamine (3e).

Prepared from **1e** as a pale yellow oil (80 mg, 48.0%); ^1H NMR ($CDCl_3$, 300 MHz) δ 8.19 (2H, s, N-H), 7.43 (2H, s, H-4), 7.29 (1H, s, H-12), 7.25 (1H, d, *J* = 1.2 Hz, H-15), 7.25 (1H, dd, *J* = 6.7, 2.3 Hz, H-13), 7.20 (2H, dd, *J* = 8.7, 1.8 Hz, H-6), 7.16 (2H, d, *J* = 8.5 Hz, H-7), 6.92 (2H, d, *J* = 2.3 Hz, H-2), 5.76 (1H, s, N*H*-CO_2Me), 4.51 (1H, t, *J* = 7.5 Hz, H-8), 3.57 (3H, s, Me), 3.35 (2H, d, *J* = 7.5 Hz, H-9); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.5 (C=O), 135.2 (C-7a), 134.9 (C-14), 134.3 (C-10), 133.1 (C-15), 130.1 (C-13), 127.9 (C-3a), 125.0 (C-6), 124.6 (C-12), 123.0 (C-2), 121.7 (C-4), 117.7 (C-11), 117.4 (C-3), 112.8 (C-7), 112.8 (C-5), 52.4 (Me), 36.6 (C-9), 36.1 (C-8); IR (CsI) ν_{max} 3427, 3365, 3123, 2871, 1716, 598 cm^{-1}; EIME *m/z* 647 $[M+1]^+$ (2), 646 $[M]^+$ (1), 404 (55), 402 (100), 400 (51). FABHRMS *m/z* 644.9095 (calcd for $C_{26}H_{20}N_3O_2Br_3$, 644.9085).

3-*tert*-Butyl-5-bromoindole (4e).

Prepared from **1e** as a pale yellow oil (14 mg, 7.0%); IR ^1H NMR ($CDCl_3$, 400 MHz) δ 7.93 (1H, d, *J* = 0.8 Hz, H-4), 7.91 (1H, brs, N-H), 7.25 (1H, dd, *J* = 8.5, 1.6 Hz, H-6), 7.22 (1H, d, *J* = 8.4 Hz, H-7), 6.94 (1H, d, *J* = 2.6 Hz, H-2), 1.43 (9H, s, 3Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.9 (C-7a), 127.8 (C-3a), 126.7 (C-3), 124.4 (C-6), 123.9 (C-4), 120.7 (C-2), 112.8 (C-7), 112.2 (C-5), 31.7 (C-8), 30.9 (3Me); IR (CsI) ν_{max} 3391, 2963, 2905, 1459, 1435, 1413 cm^{-1}; EIME *m/z* 253 $[M+1]^+$ (19), 252 $[M]^+$ (6), 238 (100), 236 (96), 157 (56), 115 (3), 57 (2). FABHRMS *m/z* 251.0309 (calcd for $C_{12}H_{14}N_1Br_1$, 251.0310).

3-*tert*-Butyl-5-nitroindole (4g).

Prepared from **1g** as a pale yellow oil (20 mg, 3.0%); ^1H NMR ($CDCl_3$, 400 MHz) δ 8.79 (1H, d, *J* = 1.8 Hz, H-4), 8.43 (1H, brs, N-H), 8.09 (1H, dd, *J* = 8.8, 2.2 Hz, H-6), 7.39 (1H, d, *J* = 9.1 Hz, H-7), 7.10 (1H, d, *J* = 2.2 Hz, H-2), 1.48 (9H, s, 3Me); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 141.1 (C-5), 140.4 (C-7a), 129.6 (C-3), 125.4 (C-3a), 122.5 (C-2), 118.6 (C-4), 117.4 (C-6), 111.3 (C-7), 31.8 (C-8), 31.0 (3Me); IR (CsI) ν_{max} 3354, 3093, 2900, 1620, 1542 cm^{-1}; EIME *m/z* 219 $[M+1]^+$ (3), 218 $[M]^+$ (11), 204 (12), 203 (100), 157 (18). FABHRMS *m/z* 218.1058 (calcd for $C_{12}H_{14}N_2O_2$, 218.1055).

Preparation of *t*-BuNHCO$_2$Me and *t*-BuNH$_2$·HCl.

A sample of $ClCO_2Me$ (128 mmol, 9.9 mL) was added dropwise to cooled (ice-water bath) *t*-$BuNH_2$ (64 mmol, 6.7 mL) and the mixture was stirred at room temperature for 30 min. The solid formed was

filtrated and washed with $CHCl_3$ (2 x 5 mL) affording *t*-$BuNH_2$·HCl (2.37 g, 34%) as a white solid; mp 303-305 °C. The filtrated was evaporated under reduced pressure to give pure *t*-$BuNHCO_2Me$ as a pale yellow oil; ^{1}H NMR for *t*-$BuNH_2$·HCl (DMSO-d_6, 400 MHz) δ 8.26 (3H, s, RNH_3), 1.29 (9H, s, 3Me); ^{13}C NMR for *t*-$BuNH_2$·HCl (DMSO-d_6, 100 MHz) δ 51.1 (*C*[Me]$_3$), 27.1 (3Me); IR (CsI) ν_{max} 2895, 2961 cm^{-1}; EIMS *m/z* 74 $[M]^+$ (11), 58 (100), 57 (8); ^{1}H NMR for *t*-$BuNHCO_2Me$ ($CDCl_3$, 400 MHz) δ 4.81 (1H, s, N-H), 3.47 (3H, s, OMe), 1.19 (9H, s, 3Me); ^{13}C NMR for *t*-$BuNHCO_2Me$ ($CDCl_3$, 100 MHz) δ 155.4 (NCO_2Me), 51.2 (NCO_2Me), 50.1 (*C*[Me]$_3$), 28.9 (3Me).

X-Ray diffraction analysis of 2a. Single crystals of **2a** were grown by slow crystallization from methylene chloride. The X-ray data were collected on a Bruker-Nonius CAD4 diffractometer equipped with Cu-K_α radiation (λ = 1.54184 Å). The data were collected in the ω-2θ scan mode. Unit cell refinements were done using the CAD4 Express v 2.0 software. The structure was solved by direct methods using the SIR02[15] program included in the WinGX v 1.64.05 crystallographic software package.[16] For the structural refinement, the non-hydrogen atoms were treated anisotropically, and the hydrogen atoms, included in the structure factor calculation, were refined isotropically. Compound **2a** crystallized as colorless blocks in the monoclinic space group $P2_1/a$ with cell dimensions a = 7.736(4) Å, b = 24.096(3) Å, c = 7.989(5) Å, β = 101.71(5)° and was refined to final R indices (all data) R (%) = 4.8, Rw (%) = 13.4. Data collection and refinement parameters, atom coordinates, bond lengths and bond angles have been deposited with the Cambridge Crystallographic Data Centre. The CCDC deposition number is 715888.

ACKNOWLEDGEMENTS

This research was supported in part by CONACYT (Mexico) grant 2002-C01-40641/A-1 and UAEH-PAI 2006-30B.

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