Regioselective and Versatile Synthesis of Indoles via Intramolecular Friedel–Crafts Heteroannulation of Enaminones

María del Carmen Cruz,[a,b] Fabiola Jiménez,[a] Francisco Delgado,[a] Joaquín Tamariz*[a]

[a] Departamento de Química Orgánica, Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional. Prol. Carpio y Plan de Ayala, 11340 México, D.F., Mexico

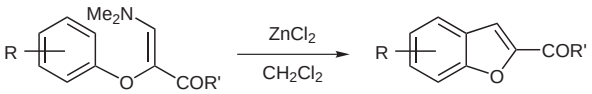
[b] Centro de Investigación en Biotecnología Aplicada, Instituto Politécnico Nacional. Km 15 Carretera Sta. Inés Tecuexcomac, Tepetitla, 90700 Tlaxcala, Mexico
Fax +52(55)53963503; E-mail: jtamariz@woodward.encb.ipn.mx

Received 21 December 2005

Abstract: A new approach is described for the synthesis of substituted indoles **5**, through an intramolecular and regioselective Friedel–Crafts cyclization of enaminones **6a**–**h** catalyzed by Lewis acids. Compounds **6** were prepared from the 2-anilinocarbonyl compounds **7**, by treatment with DMFDMA under thermal or microwave (MW) irradiation conditions. An alternative and shorter one-pot two-step synthesis of indoles **5** was achieved starting from compounds **7** and promoted by MW radiation, including the elusive 2-acetylindoles **5i**–**m**.

Key words: indoles, enaminones, Friedel–Crafts annulations, Lewis acid catalysis, microwaves

Enaminones have proved to be privileged Michael acceptors in the addition of a large variety of nucleophiles.[1] Among the latter, activated aromatic rings have been efficient in adding enaminones through a Friedel–Crafts reaction.[2] Recently, we reported a novel synthesis of 2-methoxycarbonylbenzofurans **1** by an intramolecular Friedel–Crafts cyclization of methyl 2-aryloxy-3-dimethylaminopropenoates **2**, promoted by Lewis acid catalysis (Scheme 1).[3] The efficiency of this key synthetic step depended on the presence of electron-donating groups in the aromatic ring. Moreover, the conjugate addition in the enaminone analogues 3-aryloxy-4-dimethylamino-3-buten-2-ones **3**, which was much faster than in substrates **2**, led to the regioselective formation of 2-acylbenzofurans **4**, which included some natural products of the genus *Calea*.[4]



2, R' = OMe
3, R' = Me

1, R' = OMe
4, R' = Me

Scheme 1

Encouraged by success in the synthesis of benzofurans, we investigated the potential of this methodology in the preparation of other heterocycles. Owing to the importance of indoles[5] because of their widespread presence as natural alkaloids[6] as well as pharmacologically active compounds,[7] versatile synthons,[8] and synthetic targets,[9] we now report that this methodology provides a valuable new route for the synthesis of this crucial framework. Therefore, we decided to prepare 2-acyl- and 2-alkoxycarbonyl-indoles **5** by an intramolecular Friedel–Crafts heteroannulation of enaminones **6** (Scheme 2).

5, R' = Me, OMe, OEt

6, R' = Me, OMe, OEt

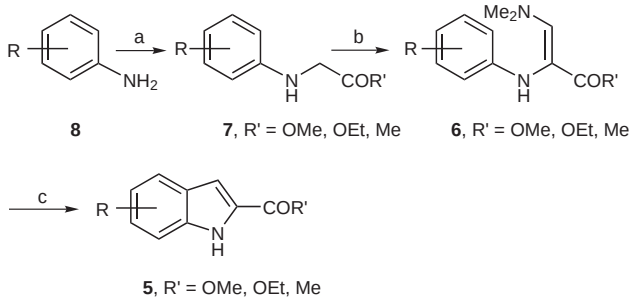
Scheme 2

Although benzofurans **1** and **4** were prepared efficiently,[3,4] the benzene ring of precursors **2** and **3** needed strong electron-donating groups *R* to achieve the cyclization step. In the case of indoles **5**, it was expected that the amino group attached to the benzene ring in the precursor **6** would be a stronger activating group in the heteroannulation process than the oxygen atom in the benzofuran enaminones **2** and **3**, due to the lower electronegativity and higher polarizability of the nitrogen atom. Hence, we evaluated the electron-demand of the aromatic ring required in this process. Consequently, we prepared the series of dimethylaminopropenoates **6b**–**h**, whose aromatic rings are substituted either by weak electron-donating groups such as the methyl group (**6b** and **6c**) or the chlorine atom (**6d** and **6e**), or by a stronger one such as the methoxy groups (**6f**–**h**). The non-activated anilino derivative **6a** was also examined.

Starting from anilines **8a**–**h**, the preparation of the series of compounds **6a**–**h** was achieved in a two-step synthetic sequence, via the corresponding α-anilino esters **7a**–**h** (Scheme 3). Thus, in the first step, the reaction of anilines **8a**–**e** with methyl bromoacetate (**9**) took place smoothly in the presence of K_2CO_3 in refluxing acetone for 12 hours, to give compounds **7a**–**e** in high yields (83–86%).[10] Ethyl esters **7f**–**h** were obtained in similar yields (78–81%) by reacting the respective anilines **8f**–**h** with ethyl bromoacetate (**10**). This methodology was successfully extended to the preparation of α-anilinoacetones **7i**–**o**, carrying out the reaction between anilines **8a**,**b**,**d**–**h** and α-chloroacetone (**11**) to furnish the desired products **7i**–**o**, respec-

SYNLETT 2006, No. 5, pp 0749–0755
Advanced online publication: 09.03.2006
DOI: 10.1055/s-2006-933135; Art ID: S12505ST

tively, in good yields (68–86%). In the second step, compounds **7a**–**h** were treated with *N*,*N*-dimethylformamide dimethyl acetal (DMFDMA) under thermal conditions, to provide dimethylaminopropenoates **6a**–**h** in good yields (Table 1, entries 1–8).[11] Interestingly, it was found that microwave (MW) radiation could promote the same transformation with shorter reaction times, although the yields were slightly lower (Table 1, entries 9–16). In all these products, the *Z*-configuration was found for the stereochemistry of the double bond, as revealed by NOE experiments (an enhancement of the aromatic signals was observed when the broad singlet attributed to the *N*,*N*-dimethyl groups was irradiated). The *E*-isomer was not observed from the ^{1}H NMR analysis of the crude mixtures. The same stereoselectivity was found in the formation of benzofuran precursors **2** and **3**.[3,4] A more efficient resonance of the enaminone system in the *Z*- than in the *E*-isomer might account for this preference.



Scheme 3 *Reagents and conditions*: a) XCH_2COR' (**9**, X = Br, R′ = OMe; **10**, X = Br, R′ = OEt; **11**, X = Cl, R = Me), K_2CO_3, acetone, 60 °C, 12 h; b) DMFDMA, 90 °C, 2–5 h, or DMFDMA, MW (600 W), 100 °C, 10 min; c) $AlCl_3$, CH_2Cl_2, 20 °C, 24 h, or $ZnCl_2$, CH_2Cl_2, 20 °C, 24 h.

Unlike enaminones **3**, which were prepared in high yields and found to be stable under the purification process (column chromatography over silica gel), anilino compounds **6i**–**o** were found to be unstable during this process. Enaminones **6k**–**m** were isolated in low yields, and characterized by spectroscopy (Table 1, entries 19–21), while the remaining compounds of the series were only identified by ^{1}H NMR of the crude mixtures. For this reason, we decided to use compounds **6i**–**o** in the cyclization reaction without previous purification (vide infra).

The heteroannulation of dimethylaminopropenoates **6a**–**h** to give the corresponding indoles **5a**–**h** was assisted by Lewis acid catalysis. The choice of the catalyst depended on the substituents in the aromatic ring of the starting materials. For derivatives **6a**–**e**, the best catalyst was $AlCl_3$, while $ZnCl_2$ was more efficient for the precursors **6f**–**h**, which contain methoxy groups in the benzene ring (Table 2, entries 1–8). Although the unsubstituted analogue **6a** provided the corresponding indole **5a** in a low yield under more severe reaction conditions, it is worth noting that for derivatives **6b**–**e**, whose aromatic ring is substituted by fairly strong activating groups, the cyclization proceeded satisfactorily to give indoles **5b**–**e** (Table 2, entries 2–5).[12] This is in contrast with similar analogues in the benzofuran series, whose corresponding aminopropenoates **2** and **3** were not reactive enough to give the heterocyclic framework.[3,4]

Therefore, and in agreement with the initial hypothesis, it appears that the electron-donating effect of the nitrogen atom on the aromatic ring in precursors **6a**–**e** contributes significantly to the reactivity of the cyclization process to provide indoles **5**. This is evident when we compare the reaction efficiency observed for the *para*-isomers **6c** and **6e** (Table 2, entries 2 and 4). Even though the methyl group, or the chlorine atom, does not directly activate the ring-closure at the proper position, the cyclization proceeds in fairly good yield. As opposed to the activation of the aryl ring, the double bond might be deactivated by a resonance effect from the lone pairs of the anilino nitrogen atom. The X-ray diffraction of compound **6a** shows that the anilino group is completely out of the plane of the π_{CC} of the double bond (Figure 1).[13] Consequently, the deactivating resonance effect between the lone pairs of the nitrogen atom and the π_{CC} of the double bond could be inhibited by a conformational restriction, and by a favorable delocalization of the electronic density of the nitrogen atom through the aryl ring. A similar behavior has been observed for many analogous captodative olefins we have studied.[14]

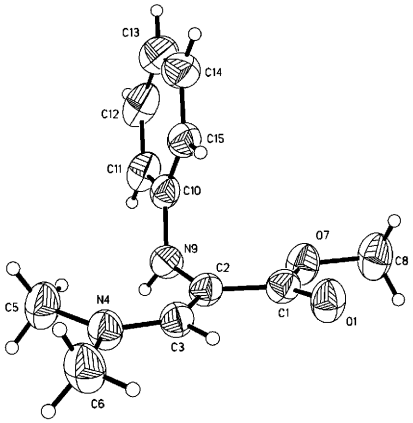


Figure 1 X-ray structure of **6a** (ellipsoids with 30% probability).

In contrast with the efficient cyclization of 3-dimethylaminopropenoates **6b**–**h** to 2-alkoxycarbonylindoles **5b**–**h**, the preparation of 2-acetylindoles **5i**–**o** was particularly difficult, due to the partial or total decomposition of the reaction mixtures of the in situ preparation of 4-dimethylamino-3-buten-2-ones **6i**–**o** when they were treated with the Lewis acid ($ZnCl_2$). Thus, under these conditions, only indole **5k** was obtained in a low yield (28%).

As with benzofurans, we investigated the preparation of indoles **5** by a one-step tandem reaction, starting from the α-anilino acetic esters **7** with DMFDMA under thermal conditions, followed by a Lewis acid-catalyzed cyclization promoted by MW radiation (Scheme 4). Unlike with benzofurans, where the use of MW radiation provided low yields of the heterocycles, in the case of the indoles the

Table 1 Preparation of Enaminones **6** from Compounds **7**[a]

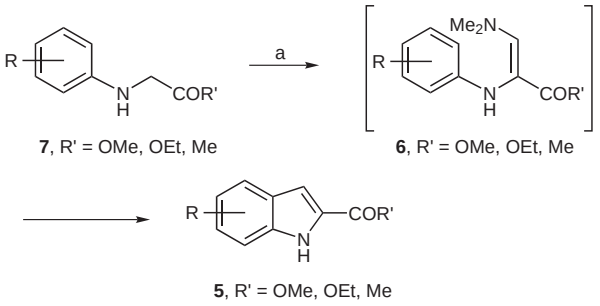
Entry	**7** [R]	R′	Conditions	Temp (°C)	Time	**6**	Yield (%)[b]
1	**7a** [H]	OMe	Thermal	90	5 h	**6a**	75
2	**7b** [3-Me]	OMe	Thermal	90	5 h	**6b**	79
3	**7c** [4-Me]	OMe	Thermal	90	5 h	**6c**	80
4	**7d** [3-Cl]	OMe	Thermal	90	5 h	**6d**	76
5	**7e** [4-Cl]	OMe	Thermal	90	5 h	**6e**	72
6	**7f** [3-OMe]	OEt	Thermal	90	5 h	**6f**	70
7	**7g** [3,4-$(OMe)_2$]	OEt	Thermal	90	5 h	**6g**	72
8	**7h** [3,5-$(OMe)_2$]	OEt	Thermal	90	5 h	**6h**	71
9	**7a** [H]	OMe	MW[c]	100	10 min	**6a**	74
10	**7b** [3-Me]	OMe	MW[c]	100	10 min	**6b**	75
11	**7c** [4-Me]	OMe	MW[c]	100	10 min	**6c**	72
12	**7d** [3-Cl]	OMe	MW[c]	100	10 min	**6d**	68
13	**7e** [4-Cl]	OMe	MW[c]	100	10 min	**6e**	70
14	**7f** [3-OMe]	OEt	MW[c]	100	10 min	**6f**	65
15	**7g** [3,4-$(OMe)_2$]	OEt	MW[c]	100	10 min	**6g**	66
16	**7h** [3,5-$(OMe)_2$]	OEt	MW[c]	100	10 min	**6h**	62
17	**7i** [H]	Me	Thermal	90	2 h	**6i**	[d]
18	**7j** [3-Me]	Me	Thermal	90	2 h	**6j**	[d]
19	**7k** [3-Cl]	Me	Thermal	90	2 h	**6k**	28
20	**7l** [4-Cl]	Me	Thermal	90	2 h	**6l**	40
21	**7m** [3-OMe]	Me	Thermal	90	2 h	**6m**	22
22	**7n** [3,4-$(OMe)_2$]	Me	Thermal	90	2 h	**6n**	[d]
23	**7o** [3,5-$(OMe)_2$]	Me	Thermal	90	2 h	**6o**	[d]

[a] In the presence of 1.5 mol equiv of DMFDMA for anilinoacetates **7a**–**h**, and 1.1 mol equiv for anilinoketones **7i**–**o**.
[b] After column chromatography and recrystallization.
[c] 600 W.
[d] Decomposition.

process was much more efficient, providing indoles **5b**,**d**,**f**–**h** in fairly good yields (Table 2, entries 9–13). In addition to the fact that the yields were slightly higher than the overall yields for the two-step process (i.e., acetic esters **7** to the isolated dimethylaminopropenoates **6**, then to the indoles **5**; Table 1 and Table 2), the reaction time was significantly reduced. Interestingly, the methyl ester of indole **5g** has been previously used as an intermediate in the total synthesis of natural β-carboline reharmine.[15]

This one-pot two-step reaction procedure was also investigated to prepare the elusive indoles **5i**–**m** (Scheme 4). Thus, when a mixture of the respective compound **7j** or **7k** and DMFDMA (1.1 mol equiv) was heated to 90 °C for five hours, followed by addition of anhydrous $AlCl_3$ (3.0 mol equiv) in acetonitrile (20 mL), the desired indoles **5i** and **5j** were obtained in moderate yields (Table 2, entries 14 and 15). Under these conditions, the preparation of indoles **5k**–**m** was unsuccessful. It was found that by using $ZnCl_2$ in CH_2Cl_2 (20 mL) and carrying out the reaction at room temperature for 24 hours, the heterocycles were furnished in moderate yields (Table 2, entries 16–18). We tried, albeit unsuccessfully, to improve the reaction by using MW radiation as done with the methoxycarbonyl indoles.

The annulation reaction for enaminones **6b** and **6d**, whose aryl rings are substituted in the *meta*-position, was not completely regioselective, because a mixture of the corresponding indoles **5b** and **5d** and their isomers **12a** and **12b**



Scheme 4 *Reagents and conditions*: for indoles **5b** and **5d**: a) i) DMFDMA, 90 °C, 5 h; ii) $AlCl_3$, toluene, MW (600 W), 120 °C, 10 min. For indoles **5f**–**h**: a) i) DMFDMA, 90 °C, 5 h; ii) $ZnCl_2$, toluene, MW (600 W), 120 °C, 10 min. For indoles **5i** and **5j**: a) i) DMFDMA, 90 °C, 5 h; ii) $AlCl_3$, CH_3CN, 20 °C, 24 h. For indoles **5k**–**m**: a) i) DMFDMA, 90 °C, 5 h; ii) $ZnCl_2$, CH_2Cl_2, 20 °C, 24 h.

were isolated (Scheme 5). A slightly lower regioselectivity was also found in the process of the intermediates 4-dimethylamino-3-buten-2-ones **6j** and **6k** (formed in situ from aniline ketones **7j** and **7k**, respectively), which provided a mixture of the corresponding indoles **5i** and **5j** and their *ortho*-isomers **12c** and **12d** (Scheme 5). This is in contrast with the highly regioselective cyclization of enaminones **6f** and **6g** (also for the alternative route from precursors **7f** and **7g**), which furnished the expected indoles **5f** and **5g** exclusively. A similar behavior was shown for the transformation of anilinoketones **7m** and **7n** into their corresponding indoles **5k** and **5l**, in which the *ortho*-isomers **12** were not detected by ^1H NMR in the crude mixtures. This was rather surprising, since the anilino rings of enaminones **6f** and **6g** are much more activated with the presence of methoxy groups, and, consequently, a lower regioselectivity might be predicted. A steric repulsion may be involved between the *meta*-methoxy group of the aryl ring and the bulky dimethylamino group attached to the reaction center during the *ortho* approach to give isomers **12**. The methoxy group in the *meta*-position in precursors **6f** and **6g** is relatively bulkier than the methyl group in **6b** and even more so than the chlorine atom in **6d**. The lower proportion of the *ortho*-regioisomer **12c** with respect to isomer **12d** might be in agreement with such steric control.

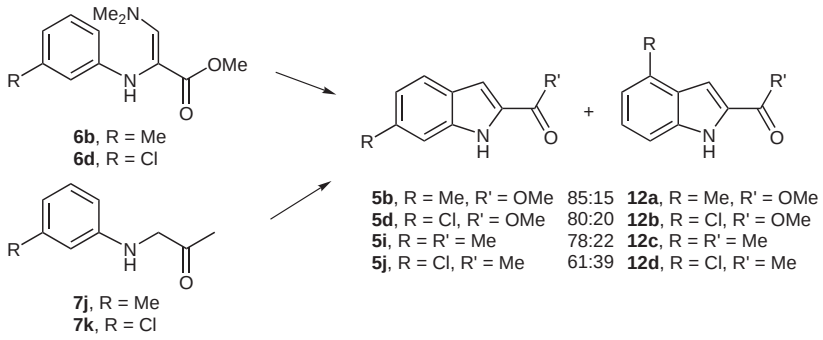
In summary, a new synthesis of indoles has been developed, by taking advantage of the enaminones that undergo conjugate nucleophilic addition. This regioselective methodology provided functionalized indoles **5** that were not only limited to the methoxy groups, as we previously observed in the preparation of benzofurans. It was also established that the amino group that bonds to the aromatic ring significantly facilitates the heteroannulation of enaminones **6**. An alternative method was also described by using MW radiation to promote the cascade process: the in situ formation of intermediates **6** from the anilino compounds **7** in the presence of DMFDMA, and their intramolecular cyclization to indoles **5**. This shortened the synthetic pathway and the reaction times, and improved the overall yields.

Acknowledgement

We are grateful to Dr. Hugo A. Jiménez-Vázquez for assisting with the X-ray data collection. We thank Fernando Labarrios for his help in spectrometric measurements. J.T. gratefully acknowledges Coordinación General de Posgrado e Investigación del Instituto Politécnico Nacional (Grants 20030147. 20040123, and 20050151), and CONACYT (Grant 43508-Q) for financial support. C.C. and F.J. thank CONACYT for graduate scholarships, and the Ludwig K. Hellweg Foundation for a partial scholarship. J.T. and F.D. are fellows of the EDI-IPN and COFAA-IPN programs.

References and Notes

(1) (a) Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277. (b) Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1996**, *67*, 207. (c) Elassar, A.-Z. A.; El-Khair, A. A. *Tetrahedron* **2003**, *59*, 8463.
(2) (a) Selic, L.; Grdadolnik, S. G.; Stanovnik, B. *Helv. Chim. Acta* **1997**, *80*, 2418. (b) Smodis, J.; Stanovnik, B. *Tetrahedron* **1998**, *54*, 9799. (c) Stanovnik, B.; Svete, J. *Synlett* **2000**, 1077.
(3) Cruz, M. C.; Tamariz, J. *Tetrahedron Lett.* **2004**, *45*, 2377.
(4) Cruz, M. C.; Tamariz, J. *Tetrahedron* **2005**, *61*, 10061.
(5) (a) Gribble, G. W. *Pyrroles and their Benzo Derivatives: Applications*, In *Comprehensive Heterocyclic Chemistry*, Vol. 2; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, **1996**, 207–257. (b) Sundberg, R. J. *Indoles*; Academic Press: St. Louis, **1996**. (c) Joule, J. A. *Indoles*, In *Science of Synthesis*, Vol. 10; Thomas, E. J., Ed.; Thieme: Stuttgart, **2000**, Chap. 13.



Scheme 5

Table 2 Preparation of Indoles **5a**–**m** from Compounds **6** and **7**[a]

Entry	**6** [R]	R′	Conditions	Solvent	Temp (°C)	Temp	**5**	Yield (%)[b]
1	**6a** [H]	OMe	$AlCl_3$	Toluene	80	96 h	**5a**	14
2	**6b** [3-Me]	OMe	$AlCl_3$	CH_2Cl_2	20	24 h	**5b**	76
3	**6c** [4-Me]	OMe	$AlCl_3$	CH_2Cl_2	20	24 h	**5c**	65
4	**6d** [3-Cl]	OMe	$AlCl_3$	CH_2Cl_2	20	24 h	**5d**	72
5	**6e** [4-Cl]	OMe	$AlCl_3$	CH_2Cl_2	20	24 h	**5e**	61
6	**6f** [3-OMe]	OEt	$ZnCl_2$	CH_2Cl_2	20	24 h	**5f**	68
7	**6g** [3,4-$(OMe)_2$]	OEt	$ZnCl_2$	CH_2Cl_2	20	24 h	**5g**	71
8	**6h** [3,5-$(OMe)_2$]	OEt	$ZnCl_2$	CH_2Cl_2	20	24 h	**5h**	65
9	**7b** [3-Me]	OMe	MW[c]	Toluene	120	10 min	**5b**	68
10	**7d** [3-Cl]	OMe	MW[c]	Toluene	120	10 min	**5d**	61
11	**7f** [3-OMe]	OEt	MW[d]	Toluene	120	10 min	**5f**	60
12	**7g** [3,4-$(OMe)_2$]	OEt	MW[d]	Toluene	120	10 min	**5g**	59
13	**7h** [3,5-$(OMe)_2$]	OEt	MW[d]	Toluene	120	10 min	**5h**	63
14	**7j** [3-Me]	Me	$AlCl_3$[e]	[e]	[e]	[e]	**5i**	32[f]
15	**7k** [3-Cl]	Me	$AlCl_3$[e]	[e]	[e]	[e]	**5j**	27[g]
16	**7m** [3-OMe]	Me	$ZnCl_2$[h]	[h]	[h]	[h]	**5k**	29
17	**7n** [3,4-$(OMe)_2$]	Me	$ZnCl_2$[h]	[h]	[h]	[h]	**5l**	32
18	**7o** [3,5-$(OMe)_2$]	Me	$ZnCl_2$[h]	[h]	[h]	[h]	**5m**	34

[a] In the presence of 3.0 mol equiv of Lewis acid. For the reactions starting from compounds **7b**,**d**,**f**–**h**, 1.5 mol equiv of DMFDMA were used, while for **7i**–**m**, 1.1 mol equiv of DMFDMA were used.
[b] After column chromatography or recrystallization.
[c] i) DMFDMA, 90 °C, 5 h; ii) $AlCl_3$, toluene, MW (600 W), 120 °C, 10 min.
[d] i) DMFDMA, 90 °C, 5 h; ii) $ZnCl_2$, toluene, MW (600 W), 120 °C, 10 min.
[e] i) DMFDMA, 90 °C, 5 h; ii) $AlCl_3$, MeCN, 20 °C, 24 h.
[f] An inseparable mixture of **5i**/**12a** (78:22), as shown by ^{1}H NMR and GCMS.
[g] An inseparable mixture of **5j**/**12b** (61:39), as shown by ^{1}H NMR and GCMS.
[h] i) DMFDMA, 90 °C, 5 h; ii) $ZnCl_2$, CH_2Cl_2, 20 °C, 24 h.

(6) (a) Saxton, J. E. *The Monoterpenoid Indole Alkaloids*, In *Indoles*, Part 4; Wiley-Interscience: New York, **1983**. (b) Abreu, P.; Pereira, A. *Heterocycles* **1998**, *48*, 885. (c) Faulkner, D. J. *Nat. Prod. Rep.* **1999**, *16*, 155. (d) Lousnasmaa, M.; Tolvanen, A. *Nat. Prod. Rep.* **2000**, *17*, 175. (e) Steele, J. C. P.; Veitch, N. C.; Kite, G. C.; Simmonds, M. S. J.; Warhurst, D. C. *J. Nat. Prod.* **2002**, *65*, 85. (f) Grougnet, R.; Magiatis, P.; Fokialakis, N.; Mitaku, S.; Skaltsounis, A.-L.; Tillequin, F.; Sévenet, T.; Litaudon, M. *J. Nat. Prod.* **2005**, *68*, 1083.

(7) (a) Bunker, A. M.; Edmunds, J. J.; Berryman, K. A.; Walker, D. M.; Flynn, M. A.; Welch, K. M.; Doherty, A. M. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1061. (b) Sechi, M.; Derudas, M.; Dallachio, R.; Dessi, A.; Bacchi, A.; Sannia, L.; Carta, F.; Palomba, M.; Ragab, O.; Chan, C.; Shoemaker, R.; Sei, S.; Dayam, R.; Neamati, N. *J. Med. Chem.* **2004**, *47*, 5298. (c) Heinrich, T.; Böttcher, H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2681. (d) Riendeau, D.; Aspiotis, R.; Ethier, D.; Gareau, Y.; Grimm, E. L.; Guay, J.; Guiral, S.; Juteau, H.; Mancini, J. A.; Méthot, N.; Rubin, J.; Friesen, R. W. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3352. (e) Yates, A. S.; Doughty, S. W.; Kendall, D. A.; Kellam, B. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3758.

(8) (a) Black, D. St. C. *Pyrroles and their Benzo Derivatives: Reactivity*, In *Comprehensive Heterocyclic Chemistry*, Vol. 2; Katritzky, A. R.; Rees, C. W.; Scriven, E. F. V., Eds.; Elsevier: Oxford, **1996**, 39–117. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318. (c) Zhang, H.; Larock, R. C. *Org. Lett.* **2002**, *4*, 3035. (d) Wynne, J. H.; Stalick, W. M. *J. Org. Chem.* **2003**, *68*, 4845. (e) Agnusdei, M.; Bandini, M.; Melloni, A.; Umani-Ronchi, A. *J. Org. Chem.* **2003**, *68*, 7126. (f) Duval, E.; Cuny, G. D. *Tetrahedron Lett.* **2004**, *45*, 5411.

(9) For recent examples, see: (a) Gribble, G. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1045. (b) Scott, T. L.; Söderberg, B. C. G. *Tetrahedron Lett.* **2002**, *43*, 1621. (c) Witulski, B.; Alayrac, C.; Tevzadze-Saeftel, L. *Angew. Chem. Int. Ed.* **2003**, *42*, 4257. (d) Walkington, A.; Gray, M.; Hossner, F.; Kitteringham, J.; Voyle, M. *Synth. Commun.* **2003**, *33*,

2229. (e) Yue, D.; Larock, R. C. *Org. Lett.* **2004**, *6*, 1037. (f) Shen, M.; Li, G.; Lu, B. Z.; Hossain, A.; Roschangar, F.; Farina, V.; Senanayake, C. H. *Org. Lett.* **2004**, *6*, 4129. (g) Nazaré, M.; Schneider, C.; Lindenschmidt, A.; Will, D. W. *Angew. Chem. Int. Ed.* **2004**, *43*, 4526. (h) Siu, J.; Baxendale, I. R.; Ley, S. V. *Org. Biomol. Chem.* **2004**, *2*, 160. (i) Amjad, M.; Knight, D. W. *Tetrahedron Lett.* **2004**, *45*, 539. (j) Ackermann, L.; Born, R. *Tetrahedron Lett.* **2004**, *45*, 9541. (k) Arcadi, A.; Bianchi, G.; Marinelli, F. *Synthesis* **2004**, 610. (l) Hiroya, K.; Itoh, S.; Sakamoto, T. *J. Org. Chem.* **2004**, *69*, 1126. (m) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2005**, *105*, 2873. (n) Barluenga, J.; Vázquez-Villa, H.; Ballesteros, A.; González, J. M. *Adv. Synth. Catal.* **2005**, *347*, 526. (o) Söderberg, B. C. G.; Hubbard, J. W.; Rector, S. R.; O'Neil, S. N. *Tetrahedron* **2005**, *61*, 3637. (p) Ackermann, L. *Org. Lett.* **2005**, *7*, 439. (q) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Parisi, L. M. *J. Org. Chem.* **2005**, *70*, 6213.

(10) **Typical Procedure for Preparation of 7b.**
Under an N_2 atmosphere, a mixture of **8b** (1.0 g, 9.33 mmol) and anhyd K_2CO_3 (1.93 g, 14.0 mmol) in dry acetone (10 mL) was heated to 60 °C for 1 h. Methyl bromoacetate (**9**, 1.57 g, 10.26 mmol) was added dropwise and the mixture was stirred at 60 °C for 12 h. The mixture was filtered and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (20 g/g of sample, hexane–EtOAc, 95:5), to give 1.44 g (86%) of **7b** as a brownish solid.
R_f = 0.45 (hexane–EtOAc, 8:2); mp 44–45 °C (hexane–EtOAc, 8:2) [lit.[16] 40 °C]. IR (KBr): 3393, 1741, 1608, 1513, 1439, 1213, 1180, 772 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.33 (s, 3 H, CH_3Ar), 3.81 (s, 3 H, CO_2Me), 3.93 (s, 2 H, CH_2N), 4.24 (br s, 1 H, NH), 6.43–6.49 (m, 2 H, H-2, H-6), 6.63 (br d, *J* = 7.5 Hz, 1 H, H-4), 7.13 (t, *J* = 7.5 Hz, 1 H, H-5). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.4 (CH_3Ar), 45.4 (CH_2N), 51.9 (CO_2CH_3), 109.8 (C-6), 113.6 (C-2), 118.9 (C-4), 129.0 (C-5), 138.8 (C-3), 146.8 (C-1), 171.5 (CO_2Me). MS (70 eV): *m/z* (%) = 179 (65) [M^+], 136 (7), 122 (34), 121 (100), 93 (3), 63 (5).

(11) **Typical Procedure for Preparation of 6b.**
A mixture of **7b** (0.20 g, 1.12 mmol) and DMFDMA (0.20 g, 1.68 mmol) was heated to 90 °C for 5 h, under an N_2 atmosphere. The crude mixture was evaporated under vacuum and the residue was purified by column chromatography over silica gel (20 g/g of sample, hexane–EtOAc, 8:2), to give 0.21 g (79%) of **6b** as an orange solid.
R_f = 0.25 (hexane–EtOAc, 8:2); mp 65–72 °C (decomp., hexane–EtOAc, 8:2). IR (KBr): 3318, 3025, 1735, 1645, 1607, 1488, 1435, 1227, 777 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.26 (s, 3 H, CH_3Ar), 3.02 [s, 6 H, $N(CH_3)_2$], 3.61 (s, 3 H, CO_2CH_3), 4.62 (br s, 1 H, NH), 6.40–6.47 (m, 2 H, ArH), 6.54 (br d, *J* = 7.8 Hz, 1 H, H-4), 7.04 (dd, *J* = 7.8, 7.2 Hz, 1 H, H-5), 7.39 (s, 1 H, HC=). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.5 (CH_3Ar), 41.6 [$N(CH_3)_2$], 51.1 (CO_2CH_3), 98.6 (NC=), 110.4 (C-6), 114.1 (C-2), 118.9 (C-4), 128.8 (C-5), 138.7 (C-3), 146.3 (HC=), 149.1 (C-1), 169.6 (CO_2CH_3). MS (70 eV): *m/z* (%) = 234 (4) [M^+], 203 (3), 132 (6), 118 (14), 91 (36), 83 (18), 65 (16), 57 (66), 42 (100). Anal. Calcd for $C_{13}H_{18}N_2O_2$: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.47; H, 7.64; N, 11.74.
NMR spectral data of representative examples.
Compound **6a**: ^1H NMR (300 MHz, $CDCl_3$): δ = 3.01 [s, 6 H, $N(CH_3)_2$], 3.62 (s, 3 H, CO_2CH_3), 4.66 (br s, 1 H, NH), 6.62 (br d, *J* = 7.5 Hz, 2 H, H-2), 6.72 (t, *J* = 7.5 Hz, 1 H, H-4), 7.15 (br t, *J* = 7.5 Hz, 1 H, H-3), 7.40 (s, 1 H, HC=). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 41.6 [$N(CH_3)_2$], 51.1 (CO_2CH_3), 98.6 (NC=), 113.4 (C-2), 117.9 (C-4), 129.0 (C-3), 146.3 (HC=), 149.1 (C-1), 169.6 (CO_2CH_3).
Compound **6c**: ^1H NMR (300 MHz, $CDCl_3$): δ = 2.22 (s, 3 H, CH_3Ar), 3.01 [s, 6 H, $N(CH_3)_2$], 3.60 (s, 3 H, CO_2CH_3), 4.52 (br s, 1 H, NH), 6.51–6.57 (m, 2 H, H-2), 6.93–7.00 (m, 2 H, H-3), 7.36 (s, 1 H, HC=). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 20.3 (CH_3Ar), 41.6 [$N(CH_3)_2$], 51.1 (CO_2CH_3), 99.1 (NC=), 113.4 (C-2), 127.1 (C-4), 129.5 (C-3), 146.1 (HC=), 146.8 (C-1), 169.6 (CO_2CH_3).
Compound **6h**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2O), 3.03 [s, 6 H, $N(CH_3)_2$], 3.73 (s, 6 H, OMe), 4.10 (q, *J* = 7.2 Hz, 2 H, CH_3CH_2O), 4.70 (br s, 1 H, NH), 5.84 (d, *J* = 2.1 Hz, 2 H, H-2, H-6), 5.89 (t, *J* = 2.1 Hz, 1 H, H-4), 7.36 (s, 1 H, HC=). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.6 (CH_3CH_2O), 41.8 [$N(CH_3)_2$], 55.05 (OMe), 55.08 (OMe), 59.7 ($CO_2CH_2CH_3$), 90.3 (C-4), 92.4 (C-2, C-6), 98.8 (NC=), 146.0 (HC=), 151.5 (C-1), 161.5 (C-3, C-5), 169.0 (CO_2Et).

(12) **Typical Procedure for Preparation of 5b.**
Anhyd $AlCl_3$ (0.057 g, 0.43 mmol) was added to a solution of **6b** (0.10 g, 0.43 mmol) in dry CH_2Cl_2 (100 mL) at r.t. The mixture was stirred at r.t. for 24 h and filtered. The filtrate was washed with H_2O (3 × 25 mL), the organic layer was dried (Na_2SO_4), and the solvent was removed under vacuum. The residue was purified by column chromatography over silica gel (10 g, hexane–EtOAc, 95:5), to give 0.061 g (76%) of **5b** as a white solid.
R_f = 0.33 (hexane–EtOAc, 8:2); mp 97–98 °C (hexane–EtOAc, 7:3) [lit.[17] 128–129 °C]. IR (KBr): 3324, 1697, 1527, 1441, 1333, 1262, 1211, 764 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.47 (s, 3 H, CH_3Ar), 3.94 (s, 3 H, CO_2Me), 6.99 (dd, *J* = 8.1, 0.9 Hz, 1 H, H-5), 7.18 (dd, *J* = 2.1, 0.9 Hz, 1 H, H-3), 7.20 (br s, 1 H, H-7), 7.56 (d, *J* = 8.1 Hz, 1 H, H-4), 8.85 (br s, 1 H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 22.0 (CH_3Ar), 51.9 (CO_2CH_3), 108.8 (C-3), 111.5 (C-7), 122.2 (C-4), 123.0 (C-5), 125.3 (ArC), 126.5 (ArC), 135.7 (ArC), 157.3 (C-7a), 162.5 (CO_2CH_3). MS (70 eV): *m/z* (%) = 189 (24) [M^+], 175 (17), 157 (87), 129 (91), 103 (80), 102 (100), 77 (69), 51 (69).
NMR spectral data of representative examples.
Compound **5a**: ^1H NMR (300 MHz, $CDCl_3$): δ = 3.95 (s, 3 H, CO_2CH_3), 7.16 (ddd, *J* = 8.1, 6.8, 1.0 Hz, 2 H, H-5), 7.23 (dd, *J* = 2.3, 1.0 Hz, 1 H, H-3), 7.33 (ddd, *J* = 8.4, 6.8, 1.0 Hz, 1 H, H-6), 7.58 (ddd, *J* = 8.4, 1.0, 0.9 Hz, 1 H, H-7), 7.70 (dd, *J* = 8.1, 0.9 Hz, 1 H, H-4), 8.98 (br s, 1 H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 52.0 (CO_2CH_3), 108.8 (C-3), 111.9 (C-7), 120.8 (C-5), 122.6 (C-4), 125.4 (C-6), 127.1 (C-2), 127.4 (C-3a), 136.8 (C-7a), 162.4 (CO_2CH_3).
Compound **5c**: ^1H NMR (300 MHz, $CDCl_3$): δ = 2.43 (s, 3 H, CH_3Ar), 3.94 (s, 3 H, CO_2CH_3), 7.14 (br s, 1 H, H-3), 7.15 (dd, *J* = 8.4, 1.5 Hz, 1 H, H-6), 7.31 (br d, *J* = 8.4 Hz, 1 H, H-7), 7.45 (br s, 1 H, H-4), 9.11 (br s, 1 H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 21.4 (CH_3Ar), 51.9 (CO_2CH_3), 108.2 (C-3), 111.6 (C-7), 121.8 (C-4), 127.0 (C-2), 127.4 (C-6), 127.7 (C-5), 130.1 (C-3a), 135.3 (C-7a), 162.6 (CO_2CH_3).
Compound **5h**: ^1H NMR (300 MHz, $CDCl_3$): δ = 1.39 (t, *J* = 7.0 Hz, 3 H, CH_3CH_2O), 3.83 (s, 3 H, OMe), 3.90 (s, 3 H, OMe), 4.38 (q, *J* = 7.0 Hz, 2 H, CH_3CH_2O), 6.18 (d, *J* = 1.5 Hz, 2 H, H-2, H-5), 6.43 (dd, *J* = 1.5, 0.9 Hz, 1 H, H-7), 7.27 (dd, *J* = 2.3, 0.9 Hz, 1 H, H-3), 9.10 (br s, 1 H, NH). ^{13}C NMR (75.4 MHz, $CDCl_3$): δ = 14.4 (CH_3CH_2O), 55.3 (OMe), 55.5 (OMe), 60.7 ($CO_2CH_2CH_3$), 86.1 (C-7), 92.6 (C-5), 106.7 (C-3), 113.7 (C-3a), 124.8 (C-2), 138.6 (C-7a), 155.0 (C-4), 160.1 (C-6), 162.1 (CO_2Et).

(13) CCDC-292937 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44(1223)336033; or deposit@ccdc.cam.ac.uk.

(14) (a) Jiménez-Vázquez, H. A.; Ochoa, M. E.; Zepeda, G.; Modelli, A.; Jones, D.; Mendoza, J. A.; Tamariz, J. *J. Phys. Chem. A* **1997**, *101*, 10082. (b) Herrera, R.; Jiménez-Vázquez, H. A.; Modelli, A.; Jones, D.; Söderberg, B. C.; Tamariz, J. *Eur. J. Org. Chem.* **2001**, 4657. (c) Mendoza, J. A.; Jiménez-Vázquez, H. A.; Herrera, R.; Liu, J.; Tamariz, J. *Rev. Soc. Quím. Méx.* **2003**, *47*, 108.

(15) Reddy, M. S.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 5413.

(16) Ellis, F.; Naylor, A.; Wallis, C. J.; Waterhouse, I. EP 388,165, **1990**; *Chem. Abstr*. **1991**, *114*, 81891.

(17) Knittel, D. *Synthesis* **1985**, 186.