One-Pot Synthesis of Isoindolo[2,1-*a*]quinolin-11-ones by Cyclocondensation of 3-Hydroxy-2-arylisoindol-1-ones with 1,3-Dicarbonyls

Yuehua Zhou, Lingfeng Qian, Wei Zhang*

State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, P. R. of China
Fax +86(931)8625657; E-mail: zhangwei6275@lzu.edu.cn

Received 20 September 2008

Abstract: Isoindolo[2,1-*a*]quinolin-11-ones have been synthesized by one-pot reaction of 3-hydroxy-2-arylisoindol-1-ones with 1,3-dicarbonyls via coupling of *N*-acyliminium ion intermediates with 1,3-dicarbonyls and subsequent intramolecular Friedel–Crafts reactions catalyzed by H_3PO_4–P_2O_5 or H_3PO_4–H_2SO_4.

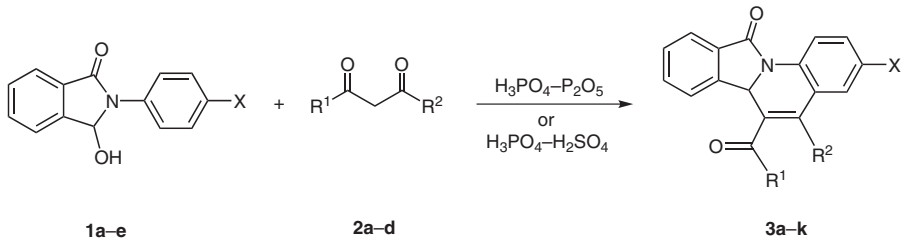
Key words: 2,3-dihydro-3-hydroxy-2-arylisoindol-1-one, 1,3-dicarbonyls, 6a,11-dihydroisoindolo[2,1-*a*]quinolin-11-ones, *N*-acyliminium ions, Friedel–Crafts reaction

Isoindolo[2,1-*a*]quinolines are a class of molecules that possess a wide range of biological activities. For examples, 6-aminomethylisoindolo[2,1-*a*]quinolin-5,11-diones, analogues of berberine alkaloids, show protective effects against N_2-induced hypoxia and are used for prophylactic and therapeutic treatment of senile dementia, angina pectoris, myocardial infarction, and emotional disorder caused by stroke and cerebral infarction;[1a,b] trihydroxyisoindolo[2,1-*a*]quinolin-5,11-diones show inhibitory activities against bacterial DNA-gyrase and human topoisomerase II.[1c] Considering the important pharmacological properties displayed by the isoindolo[2,1-*a*]quinoline core, several synthetic approaches have been developed[2a–2f] and reviewed,[3] for example, N-acylation of 4-(2′-furyl)-4-(*N*-aryl)aminobutenes with maleic anhydride, subsequent intramolecular Diels–Alder reaction with the furan moiety, and dehydration to afford the 5,6,6a,12-tetrahydroisoindolo[2,1-*a*]quinolin-11-one-10-carboxylic acids;[2a,b] the Suzuki–Miyaura coupling of 2-chloroquinoline with 2-formylphenylboronic acid and nucleophilic cyclization to produce 5,6,6a,12-tetrahydroisoindolo[2,1-*a*]quinolin-11-one;[2c] lithium bistrimethylsilylamide (LBTSA)[2d] or sodium hydride[2e] catalyzed intramolecular aldol condensation of 2-(phthalimidin-3-yl)acetophenone and thermal dehydration; one-pot condensation of substituted 2-amino-2-methoxyacetophenones with phthalic anhydrides in refluxing toluene in the presence of triethylamine to give isoindolo[2,1-*a*]quinoline-5,11-diones;[1b] intramolecular Friedel–Crafts reaction of 2-aryl-3-carboxymethyl isoindol-1-ones prepared from the reaction of the 2-aryl-3-hydroxyisoindol-1-ones with 1-methoxy-1-trimethylsilyloxyethene in the presence of titanium(IV) chloride[2f] or from Wittig reaction of *N*-acyliminium ion from 3-hydroxyphenylisoindolones with $Ph_3P{=}CHCO_2Et$[2g,1a] to produce isoindolo[2,1-*a*]quinoline-5,11-diones.

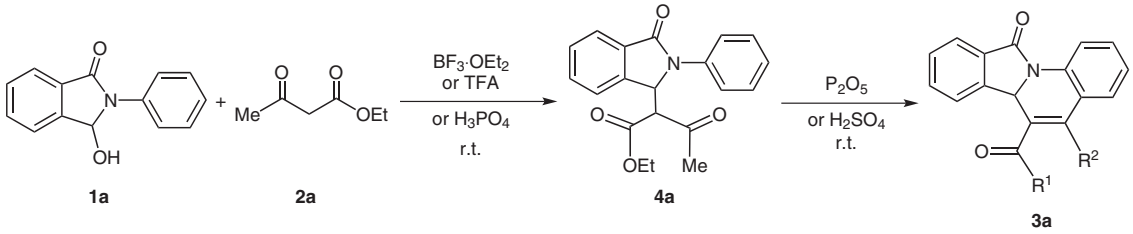
As a part of our research program directed towards the synthesis of polycyclic heterocycles, we recently reported the synthesis of 5-aryl-5,6,6a,12-tetrahydroisoindolo[2,1-*a*]quinolin-11-ones and 5-aryl-3a,9a-dihydropyrrolo[2,1-*a*]quinolin-1-ones by the [4+2] reactions of *N*-acyliminium ions produced from 3-hydroxy-2-arylisoindol-1-ones with styrenes.[4] We report herein a concise and efficient synthesis of 6-ethoxycarbonyl- or 6-acyl-subsituted 6a,11-dihydroisoindolo[2,1-*a*]quinolin-11-ones by a one-pot reaction of 3-hydroxy-2-aryl-isoindol-1-ones and 1,3-dicarbonyls via the coupling of *N*-acyliminium ions produced from 3-hydroxy-2-aryl-isoindol-1-ones with 1,3-dicarbonyls and subsequent intramolecular Friedel–Crafts reactions catalyzed by acids. Although the coupling of *N*-acyliminium ions produced from 5-hydroxypyrrolidin-2-ones and 4-hydroxy[1,3]benzoxazin-2-ones with 1,3-dicarbonyls had been reported,[5] but no similar work has been found in literature for 3-hydroxy-2-arylisoindol-1-ones. Only the condensation of 3-methoxy-2-phenylisoindol-1-ones with acetaldehyde to form 5,6,6a,11-tetrahydro-5-trifluoroacetoxyisoindolo[2,1-*a*]quinolin-11-one was reported recently.[6] Therefore, this is the first report of a one-pot synthesis of 6a,11-dihydroisoindolo[2,1-*a*]quinolin-11-ones from 3-hydroxy-2-arylisoindol-1-ones and 1,3-dicarbonyls (Scheme 1).

N-Acyliminium ions are known as important, reactive species in organic synthesis for the construction of carbon–carbon bonds.[5–7] The reactions of *N*-acyliminium ions generated from 5-ethoxypyrrolidin-2-ones or 5-acetoxypyrrolidin-2-ones with ethyl acetoacetate under the catalysis of $NbCl_5$ or $AlCl_3$ afforded coupling product ethyl 2-(2-oxo-pyrrolidin-2-on-5-yl)acetoacetate in high yields.[5a,b] We found the reaction of *N*-acyliminium ion generated from 3-hydroxy-2-phenylisoindol-1-ones (**1a**) with ethyl acetoacetate (**2a**) could also proceed quickly under the catalysis of $BF_3{\cdot}OEt_2$, TFA, PTSA, or H_3PO_4 to afford the coupling product ethyl 2-(1-oxo-2-arylisoindol-3-yl)acetoacetate (**4**) in high yields, but no further Friedel–Crafts reaction between aryl group and carbonyl group took place. Only when P_2O_5 (method A) or H_2SO_4 (method B) was added to the above solutions, the coupling product ethyl 2-(1-oxo-2-arylisoindol-3-yl)acetoacetate could be converted into the cyclization product 6-ethoxycarbonyl-6a,11-dihydroisoindolo[2,1-*a*]quinolin-11-one (**3a**) smoothly (Scheme 2).

SYNLETT 2009, No. 5, pp 0843–0847
Advanced online publication: 26.02.2009
DOI: 10.1055/s-0028-1087955; Art ID: W14608ST



Scheme 1 Reactions of 3-hydroxy-2-arylisoindol-1-ones with 1,3-dicarbonyls



Scheme 2 Two-step synthesis of **3a**

After comparison of the experimental results from different catalysts and solvents, H_3PO_4–P_2O_5 or H_3PO_4–H_2SO_4 mixture was selected as a catalyst for the reactions of 3-hydroxy-2-arylisoindol-1-ones (**1a**–**e**) with 1,3-dicarbonyls including ethyl acetoacetate (**2a**), acetoacetone (**2b**), and benzoylacetone (**2c**) as well as monocarbonyl compound cyclohexanone (**2d**).[8] The results of the reactions are summarized in Table 1. All these reactions afforded isoindolo[2,1-*a*]quinolin-11-ones as the main products which were fully characterized by ^{1}H NMR, ^{13}C NMR, and MS and the structure of **3c** was further confirmed by X-ray crystal structure as depicted in Figure 1.[9]

In comparison of the reactions of **1a**–**e** with **2a**, it could be noticed that the reaction rate of **1b** with **2a** was faster than that of **1a** with **2a**, and the yield of product **3b** was higher than that of **3a**; while the reaction rate of **1c** with **2a** was much slower than that of **1a** with **2a**, and the yield of product **3c** was relatively lower. These results could be ascribed to the activating effect of methyl group and the deactivating effect of chlorine atom. But in the case of **1d**, the yield of **3d** was decreased because **1d** could undergo self-condensation in acidic medium. In contrast to **1a**–**d**, no cyclization product was obtained from the reaction of **1e** with **2a** (Scheme 3), only the decarboxylation product **5** was separated from the reaction mixture after prolonged stirring. Obviously, the deactivating effect of nitro group resisted the intramolecular Friedel–Crafts reaction.

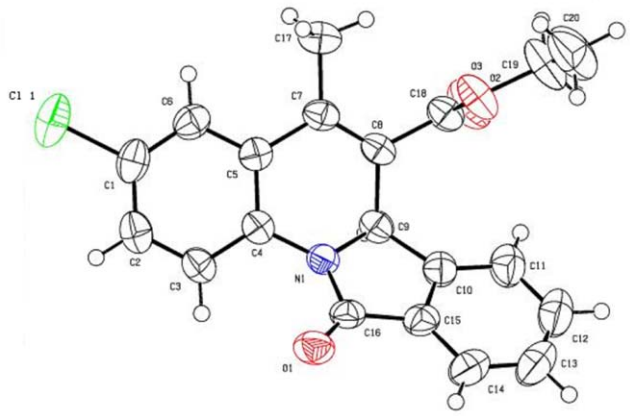
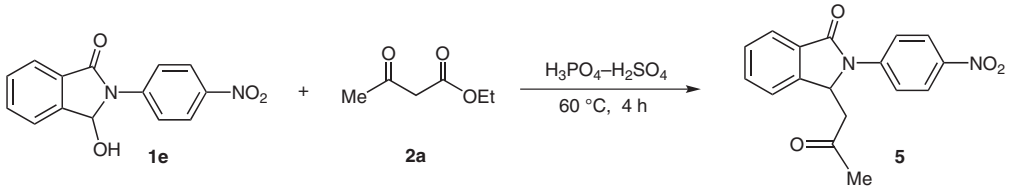


Figure 1 The X-ray crystal structure (ORTEP drawing) of **3c**

Another difference in the reaction outcome was found in the reaction of **1a**,**b** with **2b** under different reaction conditions. The main products produced in H_3PO_4–P_2O_5 medium at room temperature were the normal cyclization products **3e** and **3f**, but in the presence of H_3PO_4–H_2SO_4 at 60 °C deacetylation and reduction products **6a** and **6b** appeared as main products (Scheme 4). We were unable to rationalize the mechanism of their formation.

Besides of the 1,3-dicarbonyls, cyclohexanone (**2d**) could also react with **1a**,**b** under similar conditions to give the isoindolo[2,1-*a*]quinolin-11-ones as shown in Scheme 5.

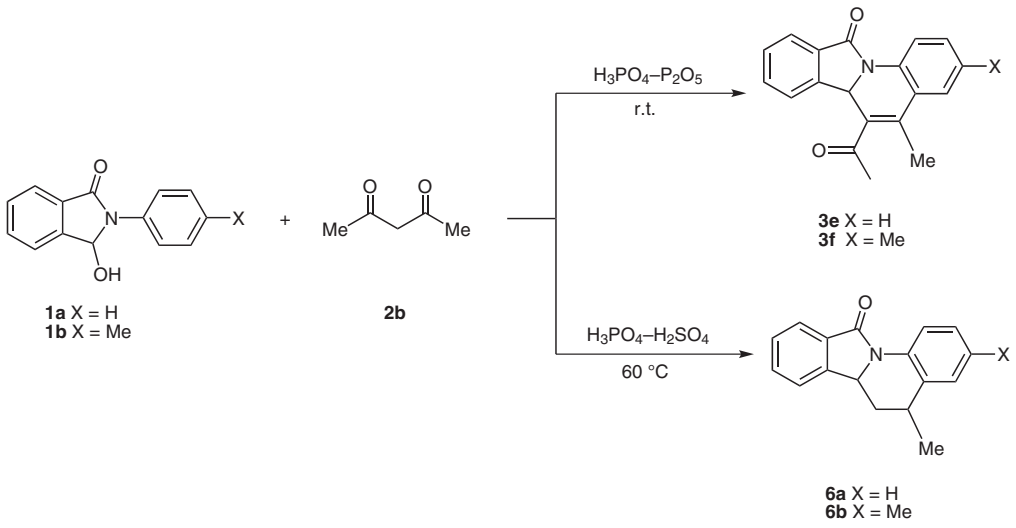


Scheme 3 Reaction of **1e** with **2a** in H_3PO_4–H_2SO_4 under heating

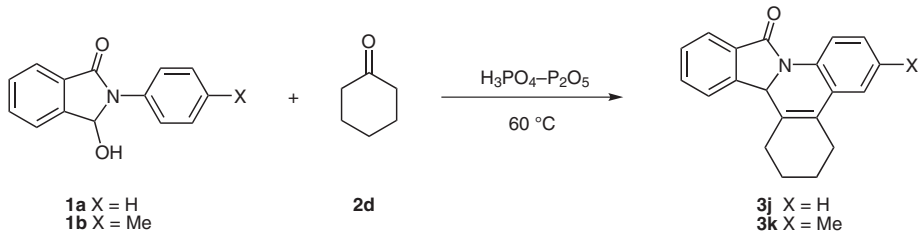
Table 1 The Reactions of 3-Hydroxy-2-arylisoindol-1-ones with 1,3-Dicarbonyls Catalyzed by Acids

Entry	Reactant					Method	Time (h)	Temp (°C)	Product	Yield (%)[c]
		X		R^1	R^2					
1	**1a**	H	**2a**	Me	OEt	A[a]	24	r.t.	**3a**	85
2	**1a**	H	**2a**	Me	OEt	A	12	60	**3a**	78
3	**1a**	H	**2a**	Me	OEt	B[b]	16	r.t.	**3a**	75
4	**1b**	Me	**2a**	Me	OEt	A	8	60	**3b**	93
5	**1c**	Cl	**2a**	Me	OEt	A	32	60	**3c**	76
6	**1d**	MeO	**2a**	Me	OEt	A	12	60	**3d**	45
7	**1e**	NO_2	**2a**	Me	OEt	B	4	60	**5**	90
8	**1a**	H	**2b**	Me	Me	A	34	r.t	**3e**	83
9	**1a**	H	**2b**	Me	Me	A	4	60	**3e** + **6a**	62 + 8
10	**1a**	H	**2b**	Me	Me	B	24	r.t	**3e** + **6a**	28 + 37
11	**1a**	H	**2b**	Me	Me	B	2	60	**6a**	78
12	**1b**	Me	**2b**	Me	Me	A	1.5	60	**3f**	82
13	**1b**	Me	**2b**	Me	Me	B	0.5	60	**6b**	67
14	**1a**	H	**2c**	Ph	Me	A	2	60	**3g**	81
15	**1a**	H	**2c**	Ph	Me	B	1	60	**3g**	75
16	**1b**	Me	**2c**	Ph	Me	A	12	r.t.	**3h**	84
17	**1c**	Cl	**2c**	Ph	Me	A	32	60	**3i**	78
18	**1a**	H	**2d**	cyclohexanone		A	12	60	**3j**	63
19	**1b**	Me	**2d**	cyclohexanone		A	6	60	**3k**	78

[a] H_3PO_4–P_2O_5 as catalyst.
[b] H_3PO_4–H_2SO_4 as catalyst.
[c] Isolation yields based on **1a–e**.



Scheme 4 Reactions of **1a**,**b** with **2b** under two different conditions

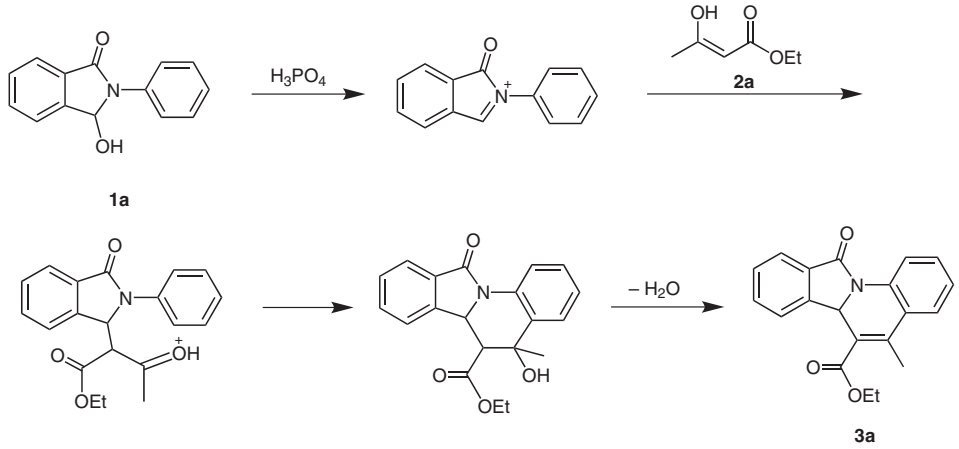


1a X = H
1b X = Me

2d

3j X = H
3k X = Me

Scheme 5 Reactions of **1a**,**b** with cyclohexanone (**2d**)



Scheme 6 Plausible mechanism for the formation of **3a**

According to the above results, a plausible mechanism for the formation of isoindolo[2,1-*a*]quinolin-11-ones was proposed (Scheme 6). The reaction was initiated by the formation of an *N*-acyliminium intermediate which was then attached by the nuclephilic 1,3-dicarbonyl compounds. Subsequent intramolecular Friedel–Crafts reaction between the protected aniline with the ketone afforded the isoindolo[2,1-*a*]quinolin-11-one derivative.

In summary, an efficient methodology for the synthesis of isoindolo[2,1-*a*]quinolin-11-ones has been developed. To our best knowledge, this is the first report for the synthesis of these compounds via a one-pot, two-step reaction of *N*-acyliminium ions with 1,3-dicarbonyls under the catalysis of H_3PO_4–P_2O_5 or H_3PO_4–H_2SO_4. Further investigations of synthetic application of this strategy were under way.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

Acknowledgment

We thank the National Natural Science Foundation of China (20872056) for financial support.

References and Notes

(1) (a) Ishihara, Y.; Kiyota, Y.; Goto, G. *Chem. Pharm. Bull.* **1990**, *38*, 3024. (b) Sui, Z.; Altom, J.; Nguyen, V. N.; Fernandez, J.; Bernstein, J. I.; Hiliard, J. J.; Barrett, J. F.; Podlogar, B. L.; Ohemeng, K. A. *Bioorg. Med. Chem.* **1998**, *6*, 735. (c) Goto, G.; Ishihara, Y. JP 02042078, **1990**; Application: JP 88-193656 19880802.

(2) (a) Kouznetsov, V. V.; Cruz, U. M.; Zubkov, F. I.; Nikitina, E. V. *Synthesis* **2007**, 375. (b) Zubkov, F. I.; Boltukhina, E. V.; Turchin, K. F.; Borisov, R. S.; Varlamov, A. V. *Tetrahedron* **2005**, *61*, 4099. (c) Mamane, V.; Fort, Y. *Tetrahedron Lett.* **2006**, *47*, 2337. (d) Hamersak, Z.; Litvic, M.; Sepac, D.; Lesac, A.; Raza, Z.; Sunjic, V. *Synthesis* **2002**, 2174. (e) Kim, G.; Keum, G. *Heterocycles* **1997**, *45*, 1979. (f) Epsztajn, J.; Jozwiak, A.; Koluda, P.; Sadokierska, I.; Wilkowska, I. D. *Tetrahedron* **2000**, *56*, 4837. (g) Epsztajn, J.; Grzelak, R.; Jozwiak, A. *Synthesis* **1996**, 1212. (h) Kumar, P.; Dinesh, C. U.; Pandey, B. *Tetrahedron Lett.* **1994**, *35*, 9229.

(3) Bonnett, R.; North, S. A. *Adv. Heterocycl. Chem.* **1981**, *29*, 341.

(4) (a) Zhang, W.; Zhen, A.; Liu, Z.; Yang, L.; Liu, Z. L. *Tetrahedron Lett.* **2005**, *46*, 5691. (b) Zhang, W.; Huang, L.; Wang, J. *Synthesis* **2006**, 2053.

(5) (a) Kleber, C.; Andrade, Z.; Matos, R. A. F. *Synlett* **2003**, 1189. (b) Kraus, G. A.; Neuenschwander, K. *Tetrahedron Lett.* **1980**, *21*, 3841.

(6) Lübbers, T.; Angehrn, P.; Gmünder, H.; Herzig, S. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4708.

(7) (a) Maryanoff, B. E.; Zhang, H. C.; Cohen, J. H.; Turchi, I. J.; Maryanoff, C. A. *Chem. Rev.* **2004**, *104*, 1431. (b) Speckamp, W. N.; Hiemstra, H. *Tetrahedron* **1985**, *41*, 4367.

(8) **Typical Experimental Procedure**
Method A
To a stirred mixture of 3-hydroxy-2-phenylisoindol-1-one (**1a**, 1.0 mmol), ethyl acetoacetate (**2b**, 1.2 mmol) and H_3PO_4 (2 mL), P_2O_5 (2 g) was added at one portion at r.t. After the solid was dissolved completely the mixture was stirred at r.t. or heated at 60 °C for 6–24 h (TLC control). The

reaction was quenched by crashed ice and the solution was extracted with CH_2Cl_2 (2 × 10 mL).The organic phase was washed with sat. aq $NaHCO_3$ (10 mL) and H_2O, respectively and dried with anhyd Na_2SO_4, concentrated at reduced pressure to furnish the crude products **3a** which was purified by silica gel column chromatography using EtOAc–hexane (1:9) as eluents and further purified by recrystallization from EtOH.

Method B

The procedure is similar to method A, only P_2O_5 was replaced by H_2SO_4 (2 mL, 98%) which was added dropwise into the mixture of **1a** (1.0 mmol), **2a** (1.2 mmol), and H_3PO_4 (2 mL).

Selected Spectroscopic Data

Compound **3a**: colorless needles; mp 124–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.5 Hz, CH_3), 2.21 (s, 3 H, CH_3), 4.35 (q, 2 H, *J* = 7.5 Hz, OCH_2), 5.92 (s, 1 H, H-6a), 7.23 (t, 1 H, *J* = 7 8 Hz), 7.42–7.60 (m, 5 H), 7.96 (d, 1 H, *J* = 7.2 Hz H-10), 8.05 (d, 1 H, *J* = 7 8 Hz H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 15.6 (CH_3), 58.7 (OCH_2), 61.0 (C-6a), 122.0 (CH), 123.7 (CH), 124.3 (CH), 125.0 (CH), 125.2 (CH), 126.8 (C), 127.5 (C), 128.9 (CH), 129.7(CH), 132.0 (C), 132.5 (CH), 133.7 (C), 134.7 (C), 140.7 (C), 166.5 (CO), 166.9 (CO). MS (EI): *m/z* (%) = 319 (18) [M$^+$], 304 (8), 290 (30), 274 (4), 262 (6), 246 (99), 86 (100). Anal. Calcd (%) for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N 4.39 Found: C, 75.13; H, 5.45; N 4.25.

Compound **3c**: colorless needles; mp 151–153 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.33 (t, 3 H, *J* = 7.2 Hz, CH_3), 2.17 (s, 3 H, CH_3), 4.35 (q, 2 H, *J* = 7.5 Hz, OCH_2), 5.90 (s, 1 H, H-6a), 7.39 (dd, 1 H, *J* = 7.5, 1.5 Hz), 7.42 (d, 1 H, *J* = 1.5 Hz, H-4), 7.52–7.60 (m, 3 H), 7.94 (d, 1 H, *J* = 7.5 Hz, H-1), 8.00 (d, 1 H, *J* = 8.1 Hz, H-10). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (CH_3), 15.6 (CH_3), 58.5 (OCH_2), 61.2 (C-6a), 123.1 (CH), 123.7 (CH), 124.4 (CH), 125.2 (CH), 128.0 (C), 129.0 (CH), 129.4 (CH), 130.4 (C), 131.7 (C), 132.5 (C), 132.7 (CH), 133.1 (C), 140.5 (C), 166.5 (CO), 166.7 (CO). MS (EI): *m/z* (%) = 355 (8) [M + 2$^+$], 353 (25 [M$^+$], 340 (20), 338 (62), 326 (31), 324 (87), 310 (28), 296 (5), 282 (29), 280 (100). Anal. Calcd (%) for $C_{20}H_{18}ClNO_3$: C, 67.90; H, 4.56; N, 3.96 Found: C, 67.83; H, 4.63; N, 4.07.

Compound **3f**: colorless needles; 141–143 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.09 (s, 3 H, CH_3), 2.16 (s, 3 H, CH_3), 2.39 (s, 3 H, C*H*$_3$), 5.80 (s, 1 H, H-6a), 7.23 (s, 1 H, H-4), 7.26 (t, 1 H, *J* = 6.0 Hz), 7.41 (d, 1 H, *J* = 7.2 Hz, H-2), 7.50–7.59 (m, 3 H), 7.95 (d, 2 H, *J* = 8.7 Hz, H-1, H-10). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.6 (CH_3), 21.2 (CH_3), 32.8 (CH_3), 58.5 (C-6a), 121.5 (CH), 123.7 (CH), 124.3 (CH), 125.2 (CH), 127.2 (C), 128.9 (CH), 129.1 (C), 130.1 (CH), 132.1 (C), 132.2 (C), 132.4 (CH), 134.5 (C), 134.8 (C), 140.1 (C), 166.1 (CO), 204.6 (CO). MS (EI): *m/z* (%) = 303 (16) [M$^+$], 302 (10), 288 (36), 260 (62), 246 (18), 230 (5), 217 (13), 43 (100). Anal. Calcd (%) for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62 Found: C, 79.12; H, 5.74; N, 4.55.

Compound **3g**: colorless needles; 156–158 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.94 (s, 3 H, CH_3), 6.06 (s, 1 H, H-6a), 7.22–7.54 (m, 9 H), 7.80 (d, 2 H, *J* = 7.8 Hz, H-2¢), 7.90 (d, 1 H, *J* = 6.9 Hz, H-10), 8. 16 (d, 1 H, *J* = 7.5 Hz, H-1). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.4 (CH_3), 59.2 (C-6a), 121.7 (CH), 124.0 (2 CH), 124.8 (CH), 125.0 (CH), 127.6 (C), 128.7 (CH), 128.9 (2 CH), 129.2 (2 CH), 129.6 (CH), 131.3 (C), 131.7 (C), 131.9 (C), 132.3 (CH), 134.1 (CH), 134.7 (C), 136.8 (C), 140.1 (C), 166.5 (CO), 196.9 (CO). MS: *m/z* (%) = 351 (37) [M$^+$], 350 (14), 336 (25), 246 (79), 105 (100), 77 (89). Anal. Calcd (%) for $C_{24}H_{17}NO_2$: C, 82.03; H, 4.88; N, 3.99 Found: C, 81.94; H, 4.84; N, 4.07.

Compound **3j**: colorless needles; 131–132 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.49–1.75 (m, 2 H), 1.81–1.85 (m, 2 H), 2.16–2.31 (m, 2 H), 2.54–2.62 (m, 2 H), 5.40 (s, 1 H, NC*H*), 7.22 (t, 1 H, *J* = 8.7 Hz), 7.30–7.35 (m, 2 H), 7.49–7.61 (m, 2 H), 7.67 (d, 1 H, *J* = 7.8 Hz), 7.95 (d, 1 H, *J* = 6.5 Hz), 8.05 (d, 1 H, *J* = 6.9 Hz). ^{13}C NMR (75 MHz $CDCl_3$): δ = 22.0 (CH_2), 22.2 (CH_2), 22.4 (CH_2), 27.5 (CH_2), 60.8 (NCH), 121.3 (CH), 122.7 (CH), 124.0 (CH), 124.7 (CH), 127.3 (CH), 127.6 (C), 128.4 (CH), 129.2 (C), 130.4 (C), 131.5 (CH), 132.4 (C), 133.6 (C), 141.2 (C), 165.6 (NCO). MS (EI): *m/z* (%) = 287 (86) [M$^+$], 286 (67), 270 (4), 258 (100), 232 (10), 216 (11). Anal. Calcd (%) for $C_{20}H_{17}NO$: C, 83.60; H, 5.96; N, 4.87 Found: C, 83.67; H, 6.02; N, 4.74.

Compound **5**: colorless needles; 172–174 °C. ^{1}H NMR (300 MHz $CDCl_3$): δ = 2.20 (s, 3 H, CH_3), 2.73 (dd, 1 H, *J* = 18.6, 9.6 Hz, C*H*H), 3.15 (dd, 1 H, *J* = 18.0, 2.4 Hz, CH*H*), 5.83 (dd, 1 H, *J* = 9.6, 2.4 Hz CH), 7.49 (d, 1 H, *J* = 7.5 Hz, C-5), 7.64 (t, 1 H, *J* = 7.2 Hz, ArH), 7.55 (t, 1 H, *J* = 7.2 Hz, ArH), 7.88 (d, 2 H, *J* = 8.7 Hz, H-2′), 7.92 (d, 1 H, *J* = 7.8 Hz, H-7), 8.30 (d, 2 H, *J* = 9.0 Hz, H-3′). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.7 (CH_3), 46.2 (CH_2), 55.7 (C-3), 121.2 (2 C), 122.8 (CH), 124.5 (CH), 124.9 (2 C), 129.1 (CH), 130.1 (C), 133.3 (CH), 142.6 (C), 143.8 (C), 144.8 (C), 167.1 (NCO), 205.6 (CO). MS (EI): *m/z* (%) = 310 (11) [M$^+$], 293 (10), 281 (7), 267 (27), 253 (44), 234 (18), 43 (100). Anal. Calcd (%) for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03 Found: C, 65.75; H, 4.62; N, 9.02.

Compound **6b**: mixture of *cis*- and *trans*-isomers (30:70). ^{1}H NMR (300 MHz, $CDCl_3$): δ (*trans*-isomer) = 1.48 (d, 3 H, *J* = 7.8 Hz, CH_3), 1.78 (dt, 1 H, *J* = 9.3, 3.3 Hz, CH*H*), 2.30 (dd, 1 H, *J* = 12.9, 1.2 Hz, C*H*H), 2.33 (s, 3 H, CH_3), 3.18 (t, 1 H, *J* = 6.6 Hz, CH), 4.78 (d, 1 H, *J* = 12.3, Hz NCH), 7.06 (s, 1 H, H-4), 7.11 (d, 1 H, *J* = 8.4 Hz, H-2), 7.48–7.51 (m, 2 H), 7.57 (d, 1 H, *J* = 7.5 Hz), 7.92 (d, 1 H, *J* = 8.4 Hz), 8.46 (d 1 H, *J* = 8.1 Hz); δ (*cis*-isomer) = 1.42 (d 3 H, *J* = 6.9 Hz, CH_3), 2.35 (s 3 H, CH_3), 2.60 (dt 1 H, *J* = 13 5, 1 2 Hz, CH*H*), 3 21 (t 3 H, *J* = 6 9 Hz, CH_3), 4 70 (dd 1 H, *J* = 12 3, 2.4 Hz, NCH), 7.11 (d, 1 H, *J* = 8.4 Hz, H-2), 7.18 (s, 1 H, H-4), 7.48–7.51 (m, 2 H), 7.59 (d, 1 H, *J* = 6.9 Hz), 7.92 (d, 1 H, *J* = 8.4 Hz), 8.44 (d, 1 H, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ (*trans*-isomer) = 21.0, 24.5, 30.8, 34.8, 54.2 (NCH), 120.1 (CH), 121.7 (CH), 124.1 (CH), 127.6 (CH), 128.3 (CH), 129.6 (CH), 131.0 (C), 131.8 (CH), 132.8 (C), 133.4 (C), 144.6 (C), 165.9 (NCO); δ (*cis*-isomer) = 20.9, 21.1, 31.4, 37.5, 58.7, 120.0 (CH), 121.7 (CH), 124.1 (CH), 127.6 (CH), 128.4 (CH), 129.6 (CH), 131.0 (C), 131.8 (CH), 132.9 (C), 133.4 (C), 144.6 (C), 165.9 (NCO). MS (EI): *m/z* = 263 (87) [M$^+$], 248 (100), 232 (16), 220 (17), 115 (25), 77 (38).

(9) (9) **Crystal Data for Compound 3c**

Formula: $C_{20}H_{16}ClNO_3$; *M*r = 353.79 monoclinic; *a* = 9.3133(17) Å, *b* = 7.3351(14) Å, *c* = 24.716(5) Å, *β* = 96.800(3)°; space group P2(1)/n; *V* = 1676.6(5) Å^3; colorless plates *ρ* = 1.402 g cm^{-3}, *T* = 296(2) K, space group P2(1)/c *Z* = 4, *μ*(Mo Ka) = 0.71073 mm^{-1}, c_{max} = 25.82°, 3217 reflections collected 2045 unique (R_{int} = 0.1585) which was used in all calculations. Final *wR* (*F*2) = 0.0830 (all data); CCDC No: 695063