Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 6633–6636
Tetrahedron Letters

Synthesis of 3,5-difunctionalized 1-methyl-1H-pyrazolo [3,4-*b*]pyridines involving palladium-mediated coupling reactions

G. Lavecchia, S. Berteina-Raboin and G. Guillaumet*

Institut de Chimie Organique et Analytique, UMR CNRS 6005, Université d'Orléans, BP 6759, 45067 Orleans Cedex 2, France

Received 31 March 2004; revised 6 July 2004; accepted 6 July 2004
Available online 23 July 2004

Abstract—Indirect iodination of 2-chloro-nicotinonitrile gave 2-chloro-5-iodonicotinonitrile, which was cyclized with methylhydrazine to lead to 3-amino-5-iodopyrazolo[3,4-*b*]pyridine. Position 3 was then protected by pivaloyl group and the resulting 5-iodo-3-pivaloylaminopyrazolo[3,4-*b*]pyridine was engaged in palladium-promoted coupling reactions with various reagents to give 3-pivaloylamino-5-substituted compounds. Deprotection and iododediazoniation followed by cross-coupling reactions in position 3 afforded novel unsymmetrical 3,5-disubstituted pyrazolo[3,4-*b*]pyridine species.

Indoles and aza-indoles are known to be natural or not[1–8] pharmacophoric moieties represented in many active compounds.

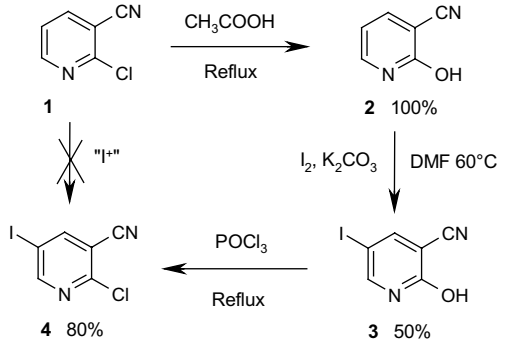
Fused pyrazoles show a wide variety of biological properties.[9–11] However, few publications are devoted to chemistry of pyrazolo[3,4-*b*]pyridines[12,13] as indole or indazole isosteres. Particularly, functionalization of pyrazolo[3,4-*b*]pyridines in position 5 was only recently investigated.[14,15]

Aiming to extend pyrazolo[3,4-*b*]pyridine libraries, we report here a pathway leading to 3,5-disubstituted-pyrazolo[3,4-*b*]pyridines via successive palladium-catalyzed coupling reactions.

The key intermediate 2-chloro-5-iodonicotinonitrile **4** was prepared by indirect iodination of 2-chloronicotinonitrile **1**. Indeed, the latter was completely unreactive toward electrophilic substitution with an 'I^+' equivalent such as *N*-iodosuccinimide.

2-Chloronicotinonitrile **1** was transformed by nonanhydrous acetic acid[16] into 2-hydroxynicotinonitrile **2**. The latter was halogenated in position 5 by iodine and potassium carbonate in DMF. Resulting 2-hydroxy-5-iodonicotinonitrile **3** was refluxed with phosphorus oxychloride to lead 2-chloro-5-iodonicotinonitrile **4** in fair yield (Scheme 1).

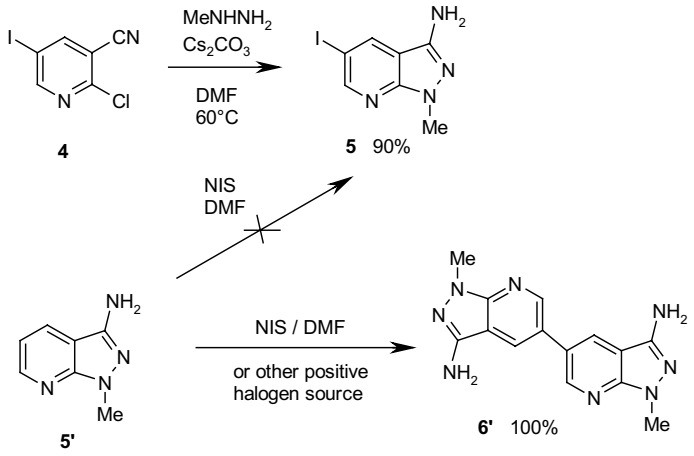
Efficient cyclization of 2-chloronicotinonitrile with various hydrazines using copper iodide and *ortho*-phenantroline as catalyst in the presence of cesium carbonate in DMF was reported earlier.[17] Reaction of 2-chloro-5-iodo nicotinonitrile **4** in these conditions only resulted in degradation. However, cyclization to 3-amino-5-iodopyrazolo[3,4-*b*]pyridine **5** occurred in the absence of catalyst. Direct iodination of known 3-amino-pyrazolo-[3,4-*b*]pyridine[11,17] **5′** only granted dimer **6′** (Scheme 2). This kind of aromatic dimerization or coupling has been already described when reagent like PIFA was used.[18]



Scheme 1. Preparation of 2-chloro-5-iodonicotinonitrile.

Keywords: Pyrazolo[3,4-*b*]pyridines.
* Corresponding author. Tel.: +33-023-841-7073; fax: +33-023-841-7078; e-mail: gerald.guillaumet@univ-orleans.fr

0040-4039/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2004.07.022



Scheme 2. Synthesis of 1-methyl-3-amino-5-iodopyrazolo[3,4-*b*]pyridine.

Prior to cross-coupling pivaloylation[19] of **5** was compulsory to ensure cleaner reaction and easier isolation step (Scheme 3).

Compounds **7a**–**d** were prepared from 5-iodo-3-pivaloylaminopyrazolo[3,4-*b*]pyridine **6** following Suzuki,[20] Sonogashira,[21] Heck,[22] or Stille[23] conditions. Deprotection was performed in anhydrous methanol/hydrogen chloride solution[24] to give 1-methyl-3-amino-5-substituted pyrazolo[3,4-*b*]pyridines **8a**–**d** (Scheme 4).

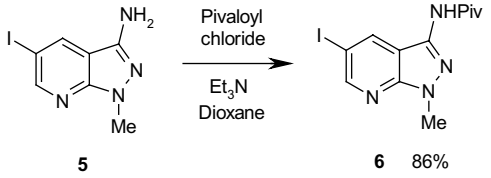
The transformations proceeded under quite mild conditions and reaction times were often short. The experiments led to the expected compounds in good to excellent yields (Table 1).

Treatment of 3-amino-5-substituted pyrazolo[3,4-*b*]pyridines **8a** and **8b** by sodium nitrite[25] in aqueous acidic conditions at 0 °C led to the corresponding diazonium salt, which was decomposed by potassium iodide[26] into 1-methyl-3-iodo-5-substituted pyrazolo[3,4-*b*]pyridines **9a** and **9b** (Scheme 5) in moderate to satisfying yields.

3,5-Difunctionalized compounds **10a**,**b** were prepared from 1-methyl-3-iodo-5-substituted pyrazolo[3,4-*b*]pyridines **9a**,**b** according to Sonogashira[27] and Heck[28] methods (Scheme 6).

Cross-coupling reactions afforded unsymmetrical products in fair yields as shown in Table 2.

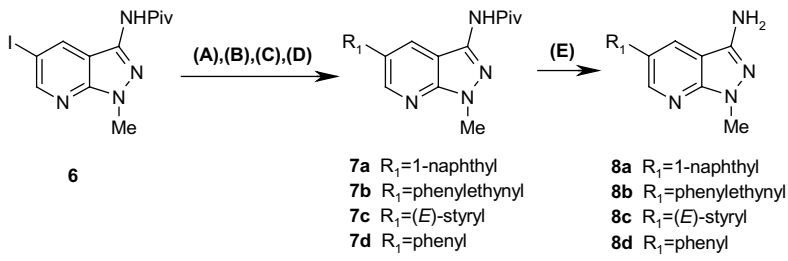
In conclusion, we synthesized various pyrazolo[3,4-*b*]pyridines by the mean of easy and clean reactions. The first step consisted in introduction of iodine in position 5 followed by palladium-mediated cross-coupling reactions. A further derivatization using iododediazoniation in position 3 was performed also by palladium-mediated



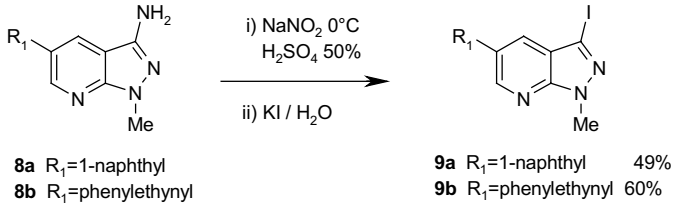
Scheme 3. Pivaloylation of 1-methyl-3-amino-5-iodopyrazolo[3,4-*b*]pyridine.

Table 1. Cross-coupling reactions in position 5 and deprotection of position 3

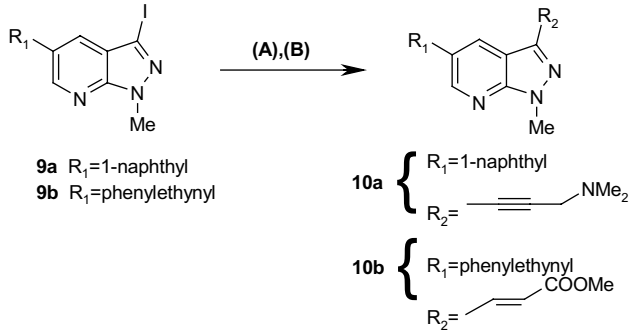
R_1	Path	Coupling yield	Deprotection yield
1-Naphthyl	A	**7a** 90%	**8a** 93%
Phenylethynyl	B	**7b** 75%	**8b** 99%
(*E*)-Styryl	C	**7c** 65%	**8c** 92%
Phenyl	D	**7d** 50%	**8d** 94%



Scheme 4. Conditions and reagents: (A) (naphth-1-yl)-boronic acid, $Pd(PPh_3)_4$, Na_2CO_3, DME, 75 °C, 1 h 30 min; (B) phenylacetylene, $PdCl_2(PPh_3)_2$, CuI, DMF/TEA, rt overnight; (C) styrene, $PdCl_2(dppf)_2$, *n*-Bu_4NI, DMF/TEA/H_2O, 50 °C, 2 h; (D) $Sn(Ph)_4$, $Pd(PPh_3)_4$, toluene, reflux 2 h; (E) MeOH/HCl anhyd reflux overnight.

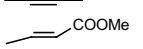


Scheme 5. Preparation of 1-methyl-3-iodo-5-substituted pyrazolo[3,4-*b*]pyridines.



Scheme 6. Conditions and reagents: (A) 3-dimethylamino-prop-1-yne, $PdCl_2(PPh_3)_2$, CuI, DMF/TEA, rt overnight; (B) methyl acrylate, $PdCl_2(dppf)_2$, *n*-Bu_4NI, DMF/TEA/H_2O, 50 °C, 2 h.

Table 2. Synthesis of 1-methyl-3,5-disubstitutedpyrazolo[3,4-*b*]pyridines

R_1	R_2	Path	Coupling yield
1-Naphthyl		A	**10a** 63%
Phenylethynyl		B	**10b** 77%

cross-coupling reactions, affording new dissymmetrical species **10a** and **10b**.

Acknowledgements

The authors gratefully acknowledge Laboratoires SERVIER (Courbevoie, France) for financial support.

References and notes

1. Moore, P. K.; Wallace, P.; Gaffen, Z.; Hart, S. L.; Babbedge, R. C. *Br. J. Pharmacol.* **1993**, *110*, 219–225.
2. Patel, M.; Rodgers, J. D.; McHugh, R. J.; Johnson, B. L.; Cordova, B. C.; Klabe, R. M.; Bacheler, L. T.; Erickson-Viitanen, S.; Ko, S. S. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 3217–3220.
3. Kharitonov, V. G.; Sharma, V. S.; Magde, D.; Koesling, D. *Biochemistry* **1999**, *38*, 10699–10706.
4. Schumman, P.; Collot, V.; Hommet, Y.; Gsell, W.; Dauphin, F.; Sopkova, J.; MacKenzie, E.; Duval, D.; Boulouard, M.; Rault, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1153–1156.
5. Sanger, G. J.; Nelson, G. R. *Eur. J. Pharmacol.* **1989**, *159*, 113–124.
6. Villa, R.; Orlandi, L.; Berruti, A.; Dogliotti, L.; Zaffaroni, N. *Int. J. Oncol.* **1999**, *14*, 133–138.
7. Mazéas, D.; Guillaumet, G.; Viaud, M.-C. *Heterocycles* **1999**, *50*, 1065–1080.
8. Mérour, J.-Y.; Joseph, B. *Curr. Org. Chem.* **2001**, *4*, 471–506.
9. Elnagdi, M. H.; Al-Awadi, N.; Erian, A. W. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Pergamon: Oxford, 1996; 4, pp 431.
10. Desenko, S. M.; Komykhov, S. A.; Orlov, V. D.; Meier, H. *J. Heterocycl. Chem.* **1998**, *35*, 989–990.
11. Quiroga, J.; Insuashy, B.; Craz, S.; Hernandez, P.; Bolafios, A.; Moreno, R.; Homoza, A.; de Almedias, R. H. *J. Heterocycl. Chem.* **1998**, *35*, 333–338.
12. Kuczynski, L.; Mrozikiewicz, A.; Banaszkiewicz, W.; Poreba, K. *Pol. J. Pharmacol. Pharm.* **1997**, *31*, 217–225.
13. Lynch, B. M.; Khan, M. A.; Teo, H. C.; Pedrotti, F. *Can. J. Chem.* **1988**, *66*, 420–428.
14. Witherington, J.; Bordas, V.; Garland, S. L.; Hickey, D. M. B.; Ife, R. J.; Liddle, J.; Saunders, M.; Smith, D. G.; Ward, R. W. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1577–1580.
15. Haigh, D.; Hickey, D. M. B.; Liddle, J.; Smith, D. G.; Witherington, J.; Ward, R. W. 2002, PCT Int. Appl. WO02/24694 A1.
16. Srivastava, R. P.; Seth, M.; Bhaduri, A. P. *Indian J. Chem.* **1989**, *28*, 65–66.
17. Lavecchia, G.; Berteina-Raboin, S.; Guillaumet, G. *Tetrahedron Lett.* **2004**, *45*, 2389–2392.
18. Faul, M. M.; Sullivan, K. A. *Tetrahedron Lett.* **2001**, *42*, 3271–3273; Anakabe, E.; Carrillo, L.; Badia, D.; Vicario, J. L.; Villegas, M. *Synthesis* **2004**, *7*, 1093–1101.
19. Turner, J. A. *J. Org. Chem.* **1983**, *48*, 3401–3408.
20. See experimental section for Suzuki coupling: Enguehard, C.; Renou, J. L.; Allouchi, H.; Leger, J. M.; Gueiffier, A. *Chem. Pharm. Bull.* **2000**, *48*, 935–940, **Compound 7a**: 1-methyl-3-(2,2-dimethyl-propionamido)-5-(naphth-1-yl)-1H-pyrazolo[3,4-*b*]pyridine: ^{1}H NMR ($CDCl_3$): δ_{ppm} 1.34 (s, 9H, CCH_3); 4.12 (s, 3H, NCH_3); 7.40–7.57 (m, 4H, H_{arom}); 7.77–7.80 (m, 1H, H_{arom}); 7.91–7.94 (m, 2H, H_{arom}); 8.20 (sl, 1H, N*H*); 8.64 (d, 1H, H_4, J = 1.9 Hz); 8.68 (d, 1H, H_6, J = 1.9 Hz); ^{13}C NMR ($CDCl_3$): δ_{ppm} 29.0 (CCH_3); 35.1 (NCH_3); 40.7 (CCH_3); 109.6 (C_{3a}); 126.8; 127.0; 127.4; 127.8; 129.5; 129.6; 129.8; 130.6; 133.6; 135.2; 136.1 (C_4); 138.2; 140.1; 150.1 (C_{7a}); 152.6 (C_6); 177.8 (*C*=O); MS: *m*/*z* = 359 (M + H)$^+$; IR (cm^{-1}): 1685 (C=O).
21. See experimental section for Sonogashira coupling: Arnautu, A.; Collot, V.; Calvo Ros, J.; Alayrac, C.; Witulski, B.; Rault, S. *Tetrahedron Lett.* **2002**, *43*, 2695–2697, **Compound 7b**: 1-methyl-3-(2,2-dimethyl-propionamido)-5-phenylethynyl-1H-pyrazolo[3,4-*b*]pyridine: ^{1}H NMR ($CDCl_3$): δ_{ppm} 1.38 (s, 9H, CCH_3); 4.02 (s, 3H, NCH_3); 7.33–7.38 (m, 3H, H_{arom}); 7.53–7.57 (m, 2H, H_{arom}); 8.16 (sl, 1H, N*H*); 8.62 (d, 1H, H_4, J = 1.8 Hz); 8.78 (d, 1H, H_6, J = 1.8 Hz); ^{13}C NMR ($CDCl_3$): δ_{ppm} 28.0 (CCH_3); 33.9 (NCH_3); 39.7 (CCH_3); 87.3 (C≡*C*Ph); 90.9 (*C*≡CPh); 108.0 (C_{3a}); 113.0 (C_5); 123.4 (C_{arom}); 128.7 (C_{arom}); 128.8

(C_{arom}); 131.9 (C_{arom}); 137.4 (C_4); 139.1 (C_3); 149.7 (C_{7a}); 152.6 (C_6); 176.7 (*C*=O); MS: *m*/*z* = 333 $(M + H)^+$; IR (cm^{-1}): 1665 (C=O).

22. See experimental section for Heck coupling: Collot, V.; Varlet, D.; Rault, S. *Tetrahedron Lett.* **2000**, *41*, 4363–4366, **Compound 7c**: (*E*)-1-methyl-3-(2,2-dimethyl-propionamido)-5-styryl-1H-pyrazolo[3,4-*b*]pyridine: ^1H NMR ($CDCl_3$): δ_{ppm} 1.39 (s, 9H, CCH_3); 3.99 (s, 3H, NCH_3); 7.11 (d, 1H, C=C*H*, J_{trans} = 16.6 Hz); 7.17 (d, 1H, C*H*=C, J_{trans} = 16.6 Hz); 7.24–7.37 (m, 3H, H_{arom}); 7.48–7.51 (m, 2H, H_{arom}); 8.35 (sl, 1H, N*H*); 8.60 (d, 1H, H_4, *J* = 2.2 Hz); 8.66 (d, 1H, H_6, *J* = 2.2 Hz); ^{13}C NMR ($CDCl_3$): δ_{ppm} 27.6 (C*C*H_3); 33.5 (N*C*H_3); 39.3 (*C*CH_3); 108.4 (C_{3a}); 125.6 (C_5); 126.1 (*C*=C); 126.4 (C_{arom}); 127.6 (C_{arom}); 128.6 (C=*C*); 128.7 (C_{arom}); 130.8 (C_4); 137.1 (C_{arom}); 138.7 (C_3); 148.9 (C_6); 150.1 (C_{7a}); 176.5 (*C*=O); MS: *m*/*z* = 335 $(M + H)^+$; IR (cm^{-1}): 1683 (C=O).
23. See experimental section for Stille coupling: Aboul-Fadl, T.; Löber, S.; Gmeiner, P. *Synthesis* **2000**, *10*, 1727–1732, **Compound 7d**: 1-methyl-3-(2,2-dimethyl-propionamido)-5-phenyl-1H-pyrazolo[3,4-*b*]pyridine: ^1H NMR ($CDCl_3$): δ_{ppm} 1.36 (s, 9H, CCH_3); 4.06 (s, 3H, NCH_3); 7.37–7.50 (m, 3H, H_{arom}); 7.61–7.65 (m, 2H, H_{arom}); 8.19 (sl, 1H, N*H*); 8.74 (s, 2H, H_4 and H_6); ^{13}C NMR ($CDCl_3$): δ_{ppm} 27.7 (C*C*H_3); 33.7 (N*C*H_3); 39.4 (*C*CH_3); 108.4 (C_{3a}); 127.8; 128.0; 129.3; 130.4; 132.5 (C_4); 138.9; 139.1; 149.8 (C_6); 150.6 (C_{7a}); 176.5 (*C*=O); MS: *m*/*z* = 309 $(M + H)^+$; IR (cm^{-1}): 1669 (C=O).
24. Kawana, M.; Nishikawa, M.; Yamasaki, N.; Kuzuhara, H. *J. Chem. Soc., Perkin Trans. 1* **1989**, *9*, 1593–1596.
25. Wright, J. L.; Gregory, T. F.; Kesten, S. R.; Boxer, P. A.; Serpa, K. A.; Meltzer, L. T.; Wise, D. L. *J. Med. Chem.* **2000**, *43*, 3408–3419.
26. *General procedure for the preparation of 1-methyl-3-iodo-5-substitued pyrazolo[3,4-b]pyridines* **9a**,**b**: 3.4 mmol of 1-methyl-3-aminopyrazolo[3,4-*b*]pyridine in 10 mL of sulfuric acid 16 N were cooled to 0 °C then 3.5 mmol of sodium nitrite in 3 mL of water were added slowly at 0 °C. The medium was stirred 1 h at 0 °C then 13.5 mmol of potassium iodide in 10 mL of water were poured all at once. The mixture was heated to room temperature during 1 h then brought to pH = 7/8 using solid sodium carbonate and extracted with dichloromethane. The organic phase was washed with a saturated solution of sodium thiosulfate then dried on $MgSO_4$ and finally evaporated under reduced pressure. The crude was purified on silica gel column chromatography.
Compound 9b: 1-methyl-3-iodo-5-phenylethynyl-1H-pyrazolo[3,4-*b*]pyridine: ^1H NMR ($CDCl_3$): δ_{ppm} 4.16 (s, 3H, CH_3); 7.35–7.38 (m, 3H, H_{arom}); 7.54–7.58 (m, 2H, H_{arom}); 7.93 (d, 1H, H_4, *J* = 1.8 Hz); 8.68 (d, 1H, H_6, *J* = 1.8 Hz); ^{13}C NMR ($CDCl_3$): δ_{ppm} 35.8 (*C*H_3); 86.3 (C≡*C*Ph); 89.5 (C_3); 91.6 (*C*≡CPh); 114.2 (C_5); 120.0 (C_{3a}); 122.7 (C_{arom}); 128.6 (C_{arom}); 128.8 (C_{arom}); 131.7 (C_{arom}); 133.0 (C_4); 150.0 (C_{7a}); 150.7 (C_6); MS: *m*/*z* = 360 $(M + H)^+$.
27. See experimental section of Ref. 20 for Sonogashira coupling. **Compound 10a**: 1-methyl-3-(1-dimethylamino-prop-2-ynyl)-5-(naphth-1-yl)-1H-pyrazolo[3,4-*b*]pyridine: ^1H NMR ($CDCl_3$): δ_{ppm} 2.39 (s, 6H, N(CH_3)$_2$); 3.58 (s, 2H, CH_2N); 4.24 (s, 3H, NNCH_3); 7.45–7.94 (m, 7H, H_{arom}); 8.21 (d, 1H, H_4, *J* = 1.9 Hz); 8.69 (d, 1H, H_6, *J* = 1.9 Hz); ^{13}C NMR ($CDCl_3$): δ_{ppm} 34.5 (N(*C*H_3)$_2$); 44.3 (NN*C*H_3); 48.7 (*C*H_2N); 89.1 (C≡*C*CH_2); 98.0 (*C*≡CCH_2); 117.0 (C_{3a}); 125.4; 125.5; 126.2; 126.7; 127.2; 128.6; 128.7; 130.4; 130.5; 132.1; 132.2; 133.9; 136.5 (C_4); 149.7 (C_{7a}); 151.1 (C_6); MS: *m*/*z* = 341 $(M + H)^+$.
28. See experimental section of Ref. 21 for Heck coupling. **Compound 10b**: methyl(*E*)-3-(1-methyl-5-phenylethynyl-1H-pyrazolo[3,4-*b*]pyridin-3-yl)-acrylate: ^1H NMR ($CDCl_3$): δ_{ppm} 3.85 (s, 3H, NCH_3); 4.18 (s, 3H, OCH_3); 6.73 (d, 1H, C*H*=CHCOOMe, J_{trans} = 16.3 Hz); 7.37–7.40 (m, 3H, H_{arom}); 7.56–7.60 (m, 2H, H_{arom}); 7.90 (d, 1H, CH=*C*HCOOMe, J_{trans} = 16.3 Hz); 8.39 (d, 1H, H_4, *J* = 1.8 Hz); 8.70 (d, 1H, H_6, *J* = 1,8 Hz); ^{13}C NMR ($CDCl_3$): δ_{ppm} 34.6 (N*C*H_3); 52.0 (OCH_3); 86.4 (C≡*C*Ph); 91.9 (*C*≡CPh); 113.8 (C_{3a} or C_5); 114.7 (C_{3a} or C_5); 120.0 (C=CCOOMe); 122.7 (C_{arom}); 128.6 (C_{arom}); 128.8 (C_{arom}); 131.7 (C_4 or C_{arom}); 132.4 (C_4 or C_{arom}); 135.5 (C=*C*COOMe); 139.0 (C_3); 140.5 (C_6); 150.1 (C_{7a}); 151.2 (C_6); 167.2 (*C*=O); MS: *m*/*z* = 318 $(M + H)^+$; IR (cm^{-1}): 1708 (C=O).