Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 9093–9095

Synthesis of benzo-γ-carboline alkaloid cryptosanginolentine by reaction of indole-2,3-dicarboxylic anhydrides with anilines

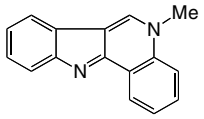
Yasuyoshi Miki,* Makoto Kuromatsu, Hideaki Miyatake and Hiromi Hamamoto

School of Pharmaceutical Sciences, Kinki University, 3-4-1 Kowakae, Higashi-Osaka 577-8502, Japan

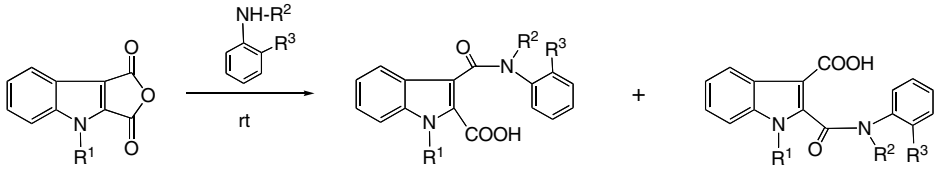
Received 12 September 2007; revised 24 October 2007; accepted 26 October 2007
Available online 30 October 2007

Abstract—1-Benzenesulfonylindole-2,3-dicarboxylic anhydride was reacted with aniline to give the 2-carbamoylindole-3-carboxylic acid as the sole product, but with *N*-methylaniline, the 3-carbamoylindole-2-carboxylic acid was the major product, which could be transformed into the 1-benzenesulfonylbenzo-γ-carbolinone in the presence of $Pd(OCOCF_3)_2$. The reduction of the benzo-γ-carbolinone with $LiAlH_4$ gave the cryptosanginolentine in high yield.

Cryptosanguinolentine (isocryptolepine) (**1**), isolated from the West African plant *Cryptolepis sanguinolentia* in 1996,[1] is a member of the indoloquinoline alkaloids (benzo-γ-alkaloids), which showed antiplasmodial properties. Molina reported the useful synthesis of **1** by Red-Al reduction of the benzo-γ-carbolinone derivative, which was prepared by the cyclization of the azide compound, but some difficulties occurred in the preparation of the benzo-γ-carbolinone derivative by using the azide compound.[2] A similar preparation of **1** by the cyclization of the azide compound was also done by Timári.[3] Maes found a novel synthesis of **1** via a palladium-catalyzed amination–arylation of 4-chloroquinoline with 2-chloroaniline[4] and Mohan showed three synthetic routes of **1** by the Fisher indole synthesis and photochemical intramolecular cyclization of an imine and haloquinoline derivative.[5] Mérour described the excellent synthesis of benzo-γ-carbolinone derivatives by Heck cyclization of *N*-(2-iodophenyl)indole-3-carboxamide prepared from indole-3-carboxylic acid and 2-iodoaniline.[6] The decarboxylative Heck-type cross-coupling reaction of aromatic carboxylic acids with olefins in the presence of a palladium catalyst was reported by Myers.[7] Forgione showed the unexpected intramolecular palladium-catalyzed reaction of



cryptosanginolentine (**1**)



2

a: $R^1 = SO_2Ph$
b: $R^1 = CH_2Ph$

3

a: $R^1 = SO_2Ph$, R^2, $R^3 = H$, **b**: $R^1 = SO_2Ph$, $R^2 = Me$, $R^3 = H$,
c: $R^1 = SO_2Ph$, $R^2 = Me$, $R^3 = I$, **d**: $R^1 = CH_2Ph$, $R^2 = Me$, $R^3 = H$

4

Scheme 1.

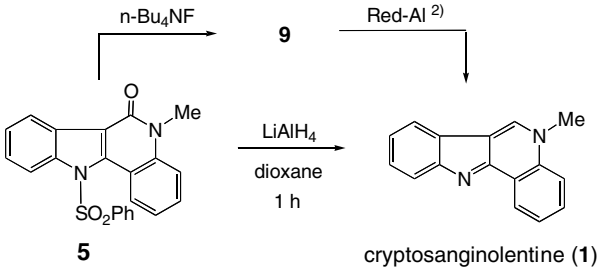
* Corresponding author. E-mail: y_miki@phar.kindai.ac.jp

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.10.130

Table 1.

Entry	2	R^1	R^2	R^3	Solvent	Time (h)	Yield (%)	
							3	4
1	**a**	SO_2Ph	H	I	CH_2Cl_2	0.5	—	99
2	**a**	SO_2Ph	Me	H	CH_2Cl_2	0.5	39	60
3	**a**	SO_2Ph	Me	H	CH_3CN	0.5	73	22
4	**a**	SO_2Ph	Me	I	CH_3CN	72	77	9
5	**b**	Ch_2Ph	Me	H	CH_3CN	1	78	5

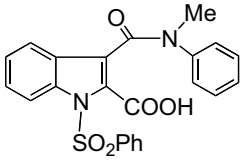
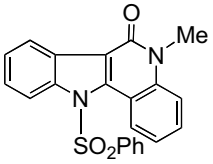
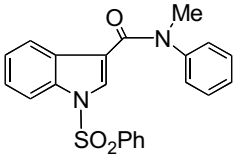
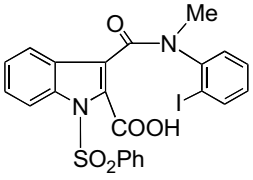
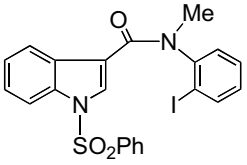
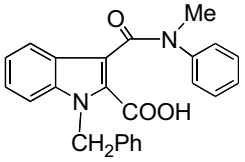
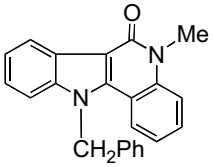
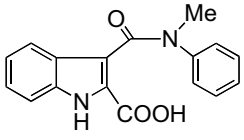
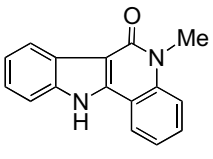
heteroaromatic carboxylic acids with bromobenzene.[8] However, there is no report of the intramolecular decarboxylative Heck-type reaction of indolecarboxylic acids and the synthesis of benzocarboline derivatives. Recently, we have shown that the indole-2,3-dicarboxylic anhydride (**2**) is a useful synthon in the synthesis of olivacine[9] and caulersin.[10] In this Letter, we report the efficacy of anhydrides **2** and its application to the simple and useful synthesis of cryptosanginolentine (**1**) by applying Myers method.[7]



Scheme 2.

The reaction of 1-(benzenesulfonyl)indole-2,3-dicarboxylic anhydride (**2a**) with 2-iodoaniline at room temperature gave the 2-carbamoylindole-3-carboxylic acid (**4a**) in 99% yield as the sole product, but the corresponding

Table 2.

Entry	3		Products		
1	 **3b**	$Pd(OCOCF_3)_2$ (20 mol %) Ag_2CO_3 (3 equiv) 5%DMSO in DMF 80 °C 1 h	 **5** (45%)	+	 **6** (24%)
2	 **3c**	" 80 °C 8 h	**5** (13%)	+	 **7** (37%)
3	 **3d**	" 100 °C 10 h	 **8** (20%)		
4	 **3e**	" X 140 °C 4 h	 **9**		
5	**3b**	" 50 °C 48 h	**5** (71%)	+	**6** (12%)

3-carbamoylindole-2-carboxylic acid (**3a**) was not isolated (entry 1). The treatment of **2a** with *N*-methylaniline in CH_2Cl_2 afforded a mixture of the indole-2-carboxylic acid (**3b**) and indole-3-carboxylic acid (**4b**) in 39% and 60% yields, respectively, but in acetonitrile, **3b** was isolated in 73% yield as the major product along with **4b** (22%) (entries 2 and 3). Compound **2a** was also reacted with *N*-methyl-2-iodoaniline at room temperature for 72 h to provide a mixture of the indole-2-carboxylic acid (**3c**) and indole-3-carboxylic acid (**4c**) in 77% and 9% yields, respectively (entry 4). The reaction of 1-benzylindole-2,3-dicarboxylic anhydride (**2b**) with *N*-methylaniline in acetonitrile gave the corresponding indole-2-carboxylic acid (**3d**) in 78% yield as the major product (Scheme 1, Table 1, entry 5).

The decarboxylative Heck-type cyclization of 1-benzenesulfonylindole-2-carboxylic acid (**3b**) was performed by treatment with $Pd(OCOCF_3)_2$ (20 mmol %)[7] and Ag_2CO_3 in DMSO and DMF at 80 °C to give a mixture of the 11-benzenesulfonyl-5-methylindolo[3,2-*c*]quinoline (**5**)[11] and decarboxylation product (**6**) in 45% and 24% yields, respectively, but from the 2-iodo derivative (**3c**), **5** was isolated in a low yield (13%) along with the decarboxylation product (**7**) (37%) (entries 1 and 2). However, several efforts ($Pd(PPh_3)_4$ or $Pd(OAc)_2$, Ag_2O, AgO, or Cs_2CO_3) were made to obtain the cyclization product (**8**) and (**9**) from the 1-benzylindole compound (**3d**) and NH compound (**3e**), but the results were less than satisfactory (entries 3 and 4). Finally, **5** was obtained in fairly good yield (71%) at 50 °C for 48 h (entry 5, Table 2). The 11-benzenesulfonyl-5-methylindolo[3,2-*c*]quinoline (**5**) could be converted to cryptosanguinolentine (**1**)[12] by treatment with tetrabutylammomium fluoride (rt, 6 h in THF, 80%) followed by treatment with Red-Al (110 °C, 32 h in toluene, 53%),[2] but the reduction of **5** with $LiAlH_4$ in hot dioxane produced **1** in 98% yield (Scheme 2).

Acknowledgments

This work was supported by 'High-Tech Research Center Project' for Private Universities and matching fund subsidy from MEXT (2007) and Kinki University.

References and notes

1. Sharaf, M. H. M.; Schiff, P. L.; Tackie, A. N.; Phoebe, C. H.; Martin, G. E. *J. Heterocycl. Chem.* **1996**, *33*, 239–243.
2. Fresneda, P. M.; Molina, P. M.; Delgado *Tetrahedron Lett.* **1999**, *40*, 7275–7278; Fresneda, P. M.; Molina, P. M.; Delgado *Tetrahedron* **2001**, *57*, 6197–6702.
3. Timári, G.; Soós, T.; Hajós, G. *Synlett* **1997**, 1067–1068.
4. Jonckers, T. H. H.; Maes, B. U. W.; Lemière, G. L. F.; Rombouts, G.; Pieters, L.; Haemers, A.; Dommisse, R. A. *Synlett* **2003**, 615–618.
5. Dhanabal, T.; Sangeetha, R.; Mohan, P. S. *Tetrahedron* **2006**, *62*, 6258–6263; Dhanabal, T.; Sangeetha, R.; Mohan, P. S. *Tetrahedron Lett.* **2005**, *46*, 4509–4510; Kumar, R. N.; Suresh, T.; Mohan, P. S. *Tetrahedron Lett.* **2002**, *43*, 3327–3328.
6. Mouladdib, A.; Joseph, B.; Hasnaoui, A.; Mérour, J. *Synthesis* **2000**, 549–556.
7. Tanaka, D.; Romeril, S. P.; Myers, A. G. *J. Am. Chem. Soc.* **2005**, *127*, 10323–10333; Tanaka, D.; Myers, G. *Org. Lett.* **2004**, *6*, 433–436; Myers, A. G.; Tanaka, D.; Mannion, M. R. *J. Am. Chem. Soc.* **2002**, *124*, 11250–11251.
8. Forgione, P.; Brochu, M.-C.; St-Onge, M.; Thesen, K. H.; Bailey, M. D.; Bilodeau, F. *J. Am. Chem. Soc.* **2006**, *128*, 11350–11351.
9. Miki, Y.; Tsuzaki, Y.; Hibino, H.; Aoki, Y. *Synlett* **2004**, 2206–2208.
10. Miki, Y.; Aoki, Y.; Miyatake, H.; Minematsu, T.; Hibino, H. *Tetrahedron Lett.* **2006**, *47*, 5215–5218.
11. 11-Benzenesulfonyl-5-methylindolo[3,2-*c*]-quinoline (**5**): mp 212–214 °C (MeOH). IR (Nujol) cm^{-1}: 1645. ^1H NMR ($CDCl_3$) δ: 3.84 (3H, s, Me), 7.08–7.18 (2H, m, arom), 7.20–7.28 (2H, m, arom), 7.30–7.56 (5H, m, arom), 7.65 (1H, ddd, $J = 8.5$, 8.0, 2.0 Hz, arom), 8.24–8.35 (2H, m, arom), 8.82 (1H, dd, $J = 8.0$, 2.0 Hz, arom). HRMS (EI) *m/z*: calcd for $C_{23}H_{18}O_5N_2S$, 388.0881; found, 388.0872. Anal. Calcd for $C_{23}H_{18}O_5N_2S$: C, 68.02; H, 4.15; N, 7.21. Found: C, 68.15; H, 4.12; N, 7.33.
12. Cryptosanguinolentine: mp 134–135 °C (CH_3CN) (lit.,[3] 132–133 °C). IR (Nujol) cm^{-1}: 1636, 1612, 1596, 1455, 1225, 746, 736. ^1H NMR (DMSO-d_6) δ: 4.32 (3H, s, Me), 7.29 (H, br t, $J = 7.5$ Hz, H-8), 7.47 (1H, dt, $J = 7.5$, 1.0 Hz, H-9), 7.77 (1H, br t, $J = 8.0$ Hz, H-2), 7.80 (1H, br d, $J = 7.5$ Hz, H-10), 7.90 (1H, dt, $J = 8.0$, 1.0 Hz, H-3), 8.13 (1H, br d, $J = 8.0$ Hz, H-4), 8.16 (1H, br d, $J = 7.5$ Hz, H-7), 8.78 (1H, dd, $J = 8.0$, 1.0 Hz, H-1), 9.51 (1H, s, H-6). ^{13}C NMR (DMSO-d_6) δ: 151.49, 150.74, 139.63, 135.78, 130.16, 126.21, 126.05, 124.95, 124.21, 120.72, 120.16, 119.99, 118.14, 117.47, 115.77, 42.81. HRMS *m/z* (M^+) calcd for $C_{16}H_{12}N_2$, 232.1000; found, 232.0986.