Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters 49 (2008) 867–869
Tetrahedron Letters

A facile synthesis of naturally occurring 5-(3-indolyl)oxazoles

Dalip Kumar *, Swapna Sundaree, Gautam Patel, V. S. Rao

Chemistry Group, Birla Institute of Technology and Science, Pilani 333 031, India

Received 4 July 2007; revised 18 November 2007; accepted 28 November 2007
Available online 4 December 2007

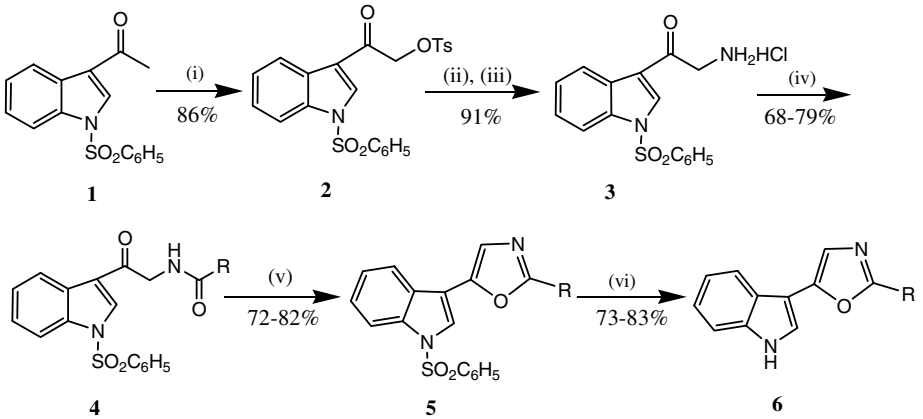
Abstract

A simple and efficient synthesis of naturally occurring 5-(3-indolyl)oxazoles is described. The key steps of this convergent approach are the formation of a 3-tosyloxyacetyl-1-benzenesulfonylindole, a 3-amino-acetyl-1-benzenesulfonylindole hydrochloride and cyclodehydration of an α-acylaminoketone.

Keywords: 5-(3-Indolyl)oxazoles; Hydroxy(tosyloxy)-iodobenzene; α-Acylaminoketones; *p*-Toluenesulfonic-acid

The 5-(3-indolyl)oxazole moiety is an important heterocyclic scaffold of medicinal and therapeutic interest that is found in various natural products such as pimprinine, labradorin 1 and labradorin 2. 5-(3-Indolyl) oxazoles have been isolated from various microorganisms and are known to display interesting biological activities.[1]

α-Tosyloxyketones are very useful precursors for the synthesis of diverse heterocyclic compounds[2] and can be easily prepared from the reaction of enolizable ketones with hydroxy(tosyloxy)iodobenzene.[3] In this Letter, we have demonstrated the utility of hitherto unknown 3-tosyloxyacetylindole in the synthesis of natural and biologically



Scheme 1. Synthesis of 5-(3-indolyl)oxazoles. Reagents and conditions: (i) $C_6H_5I(OH)OTs$, CH_3CN, rt; (ii) HMTA, $CHCl_3$; (iii) HCl, reflux; (iv) RCOCl, Et_3N, 0–5 °C; (v) PTSA, EtOH, reflux; (vi) NaOH, EtOH–H_2O, reflux.

* Corresponding author. Tel.: +91 1596 245073 279; fax: +91 1596 244183.
E-mail address: dalipk@bits-pilani.ac.in (D. Kumar).

0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.11.173

Table 1
Synthesis of 5-(3-indolyl)oxazoles **6**

Entry	R	Yield[a] (%)			Overall yield[b] (%)	Mp (°C)
		4	**5**	**6**		
1	Phenyl	68	82	83	29	216
2	Methyl	79	80	82	32	196[4]
3	Ethyl	79	76	73	27	156[4]
4	*i*-Butyl	74	74	73	24	144[1]
5	Benzyl	75	72	76	25	172

[a] Yield of isolated pure products.
[b] Five steps.

potent 5-(3-indolyl)oxazoles. Many procedures have been developed for the construction of 5-(3-indolyl)oxazoles.[4] However, some of these procedures often utilize toxic and costly reagents, and afford products in only moderate yields. Thus, it is desirable to develop a straightforward and environmentally benign method to synthesize 5-(3-indolyl)oxazoles (Scheme 1).

Our synthesis of 5-(3-indolyl)oxazoles (**6**) started from 3-acetyl-1-benzenesulfonylindole (**1**).[5,6] The synthesis of novel 3-tosyloxyacetyl-1-benzenesulfonylindole (**2**) was accomplished by reaction of **1** with hydroxy(tosyloxy)iodobenzene in an excellent yield (86%) at room temperature.[7] The reaction of unprotected 3-acylindole with hydroxy(tosyloxy)iodobenzene led to a complex mixture without any trace of the desired 3-tosyloxyacetylindole. 3-Aminoacetyl-1-benzenesulfonyl indole hydrochloride (**3**) was obtained in very good yield from the reaction of **2** with hexamethylenetetraamine (HMTA) followed by refluxing the reaction mixture in the presence of dilute hydrochloric acid. Compound **3** was acylated with the appropriate acyl chloride in the presence of triethylamine to give acylaminoketones **4**.

Cyclodehydration of acylaminoketones **4** to give 5-(3-indolyl)oxazoles (**5**) was accomplished successfully using *p*-toluenesulfonic acid. Generally, cyclodehydration of acylaminoketones into oxazoles involves harsh reagents such as H_2SO_4, PCl_5, P_2O_5, $SOCl_2$, $POCl_3$, Ac_2O and Ph_3P. Finally, the benzenesulfonyl moiety of 5-(3-indolyl)-oxazoles **5** was removed using dilute sodium hydroxide to afford the 5-(3-indolyl)oxazoles **6** in good yields. Similarly, other analogues of 5-(3-indolyl)oxazoles **6** were prepared and their melting points and spectral data were in excellent agreement with those reported (Table 1).[1,4]

In summary, we have developed a facile and high yielding protocol for the synthesis of 5-(3-indolyl)oxazoles **6** from readily available starting materials. This general protocol can be used to prepare a series of 5-(3-indolyl)oxazole analogues.

Acknowledgement

We thank the University Grants Commission, New Delhi for financial support (Project F. No. 32-216/2006).

References and notes

1. (a) Bhate, D. S.; Hulyalker, R. K.; Menon, S. K. *Experientia* **1960**, *16*, 504; (b) Pettit, G. R.; Knight, J. C.; Herald, D. L.; Davenport, R.; Pettit, R. K.; Tucker, B. E.; Schmidt, J. M. *J. Nat. Prod.* **2002**, *65*, 1793; (c) Joshi, B. S.; Taylor, W. I.; Bhate, D. S.; Karmarkar, S. S. *Tetrahedron* **1963**, *19*, 1437; (d) Koyama, Y.; Yokose, K.; Dolby, L. J. *Agric. Biol. Chem.* **1981**, *45*, 1285; (e) Noltenmeyer, M.; Sheldrick, G. M.; Hoppe, H.-U.; Zeeck, A. *J. Antibiot.* **1982**, *35*, 549; (f) Umehara, K.; Yoshida, K.; Okamoto, M.; Iwami, M.; Tanaka, H.; Kohsaka, M.; Imanaka, H. *J. Antibiot.* **1984**, *37*, 1153; (g) Takahashi, S.; Matsunaga, T.; Hasegawa, C.; Saito, H.; Fujita, D.; Kiuchi, F.; Tsuda, Y. *Chem. Pharm. Bull.* **1998**, *46*, 1527; (h) Nishida, A.; Fuwa, M.; Fujikawa, Y.; Nakahata, E.; Furuno, A.; Nakagawa, M. *Tetrahedron Lett.* **1998**, *39*, 5983; (i) N'Diaye, I.; Guella, G.; Mancini, I.; Pietra, F. *Tetrahedron Lett.* **1996**, *37*, 3049.
2. Koser, G. F. *Adv. Heterocycl. Chem.* **2004**, *86*, 225.
3. Koser, G. F.; Relenyi, A. G.; Kalos, A. N.; Rebrovic, L.; Wettach, R. H. *J. Org. Chem.* **1982**, *47*, 2487.
4. (a) Kelly, T. R.; Fu, Y.; Xie, R. L. *Tetrahedron Lett.* **1999**, *40*, 1857; (b) Doyle, K. J.; Moody, C. J. *Synthesis* **1994**, 1021; (c) Roy, S.; Haque, S.; Gribble, G. W. *Synthesis* **2006**, 3948; (d) Brain, C. T.; Paul, J. M. *Synlett* **1999**, 1642; (e) Nishada, A.; Fuwa, M.; Naruto, S.; Sugano, Y.; Saito, H.; Nakagawa, M. *Tetrahedron Lett.* **2000**, *41*, 4791.
5. Liu, S. F.; Wu, Q.; Schmider, H. L.; Aziz, H.; Hu, N.-X.; Popovic, Z.; Wang, S. *J. Am. Chem. Soc.* **2000**, *122*, 3671.
6. Ketcha, D. M.; Gribble, G. W. *J. Org. Chem.* **1985**, *50*, 5451.
7. 3-Tosyloxyacetyl-1-benzenesulfonylindole (**2**): A mixture of 3-acetyl-1-benzenesulfonylindole **1** (3.0 g, 10.0 mmol) and [hydroxy(tosyloxy)iodo]benzene (4.72 g, 12.0 mmol) was stirred in acetonitrile at room temperature for 8 h. After completion of the reaction, as monitored by TLC, the solvent was distilled off and the residue obtained was crystallized from methanol to afford pure 3-tosyloxyacetyl-1-benzenesulfonylindole **2**: (4.03 g, 86%); mp 138–140 °C; IR (KBr) cm^{-1} = 3147, 2983, 1693, 1597, 1174, 1143, 1087, 873 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3H, CH_3), 5.02 (s, 2H, CH_2), 7.30–7.40 (m, 4H, Ar-H), 7.51–7.55 (m, 2 H, Ar-H), 7.61–7.63 (m, 1H, Ar-H), 7.83 (d, 2H, $J = 8.40$ Hz, Ar-H), 7.94–8.00 (m, 3H, Ar-H), 8.21 (dd, 1H, $J = 1.2$, 8.0 Hz, Ar-H), 8.36 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.74$, 70.70, 113.15, 117.75, 122.98, 125.25, 126.28, 127.33, 127.49, 128.23, 129.85, 130.13, 132.44, 132.82, 134.51, 134.88, 137.40, 145.63, 186.93; MS (EI), m/z $[M+H]^+ = 470.0$; Anal. Calcd for $C_{23}H_{19}NO_6S_2$: C, 58.83; H, 4.08; N, 2.98. Found: C, 59.07; H, 3.74; N, 3.43.
3-Aminoacetyl-1-benzenesulfonylindole hydrochloride (**3**): To a stirred solution of hexamethylenetetramine (1.41 g, 10 mmol) in 10 mL of chloroform was added 3-tosyloxyacetyl-1-benzenesulfonylindole **2** (4.0 g, 8.5 mmol) over a period of 1 h. The solution was stirred under reflux for 3 h and allowed to stand overnight. Upon cooling, the precipitated salt was filtered and dried. The ammonium chloride formed in the reaction was removed by dissolving the crude salt in a warm solution of water, ethanol and 12*N* hydrochloric acid (1:4:1, v/v). Pure **3** precipitated from the above homogeneous solution which was filtered and recrystallized from methanol-dichloromethane (1:2) and dried. (2.71 g, 91%); mp 220 °C (dec.); IR (KBr) cm^{-1} = 3248, 3088, 1681, 1606, 1514, 1211, 1000, 750; ^1H NMR (400 MHz, DMSO-d_6) $\delta = 4.80$ (s, 2H, CH_2), 7.08 (d, 2H, $J = 7.84$ Hz, Ar-H), 7.51–7.55 (m, 2H, Ar-H), 7.36–7.43 (m, 2H, Ar-H), 7.66 (d, 2H, $J = 8.00$ Hz, Ar-H), 7.96 (d, 1H, $J = 5.96$ Hz, Ar-H), 8.14 (d, 2H, $J = 7.80$ Hz, Ar-H), 8.20 (d, 1H, $J = 7.72$ Hz, Ar-H), 8.98 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) $\delta = 58.06$, 112.76, 118.00, 121.96, 125.32, 127.15, 127.98, 129.52, 133.86, 134.63, 135.04, 136.21, 138.28, 144.02, 186.19; MS (EI), m/z $[M]^+ = 314.0$; Anal. Calcd for $C_{16}H_{15}ClN_2O_3S$: C, 54.78; H, 4.31; N, 7.99. Found: C, 54.47; H, 4.22; N, 7.57.
3-(Benzoylamidoacetyl)-1-benzenesulfonylindole (**4**): 3-aminoacetyl-1-benzenesulfonylindole hydrochloride **3** (0.3 g, 0.86 mmol) was dissolved in dichloromethane (5 mL) followed by dropwise addition of

benzoyl chloride (0.120 g, 0.86 mmol) at 0–5 °C. Triethylamine (0.173 g, 1.72 mmol) was added to the above reaction mixture and the solution became clear. After completion of the reaction as confirmed by TLC, the mixture was taken into water and the organic phase was extracted with dichloromethane and dried over anhydrous sodium sulfate. The solvent was removed under vacuum to afford an oily liquid which upon trituration with diisopropyl ether gave **4** as a white solid (0.24 g, 68%); mp 132 °C; IR (KBr) $cm^{-1} = 3305$, 3105, 2922, 1788, 1687, 1444, 1190, 1150, 750; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 4.89$ (s, 2H, CH_2), 7.10–7.72 (m, 5H, Ar-H), 7.83–8.20 (m, 9H, Ar-H), 8.45 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 47.24$, 113.26, 118.72, 122.73, 125.16, 126.16, 127.18, 128.64, 129.73, 131.81, 132.13, 133.81, 133.90, 134.75, 134.80, 134.87, 137.37, 167.47, 189.87; MS (EI), m/z $[M+H]^+ = 419.1$; Anal. Calcd for $C_{23}H_{18}N_2O_4S$: C, 66.01; H, 4.34; N, 6.69. Found: C, 65.96; H, 3.85; N, 6.67.

5-(1-Benzenesulfonylindol-3-yl)-2-phenyloxazole (**5**): 3-(Benzoylamidoacetyl)-1-benzene-sulfonyl indole **4** (0.21 g, 0.50 mmol) and *p*-toluenesulfonic acid (0.086 g, 0.50 mmol) were refluxed in 8 mL of ethanol. After completion of the reaction, ethanol was distilled off and the residue was taken into water and extracted with dichloromethane. The organic phase was washed with dilute sodium bicarbonate solution and dried over anhydrous sodium sulfate. Finally, removal of dichloromethane under vacuum yielded **5** as a light brown solid (0.164 g, 82%); mp 156 °C; IR (KBr) $cm^{-1} = 3145$, 1625, 1446, 1176, 979, 688; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.26$–7.59 (m, 9H, Ar-H), 7.83 (dd, 1H, $J = 1.2$, 8.0 Hz, Ar-H), 7.95–7.97 (m, 2H, Ar-H), 7.99 (s, 1H, Ar-H), 8.06 (dd, 1H, $J = 1.2$, 7.6 Hz, Ar-H), 8.13–8.15 (m, 2 H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 103.86$, 111.63, 119.20, 119.94, 120.20, 121.87, 122.35, 123.47, 123.52, 125.26, 127.15, 128.24, 129.26, 129.73, 133.90, 134.63, 136.27, 145.00, 158.42; MS (EI), m/z $[M+H]^+ = 401.0$; Anal. Calcd for $C_{23}H_{16}N_2O_3S$: C, 68.98; H, 4.03; N, 7.00. Found: C, 68.66; H, 3.90; N, 6.79.

5-(Indol-3-yl)-2-phenyloxazole (**6**): A stirred solution of **5** (0.130 g, 0.32 mmol), sodium hydroxide (0.038 g, 0.96 mmol), ethanol (10 mL) and water (3 mL) was refluxed for 2 h. The ethanol was evaporated under vacuum, and the aqueous solution was extracted with dichloromethane. The organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum to afford **6** as a white solid (0.07 g, 83%); mp 216 °C; IR (KBr) $cm^{-1} = 3460$, 3169, 1633, 1454, 1126, 750; ^1H NMR (400 MHz, DMSO-d_6): $\delta = 7.19$–7.26 (m, 2H, Ar-H), 7.42–7.52 (m, 4 H, Ar-H), 7.58 (s, 1H, Ar-H), 7.67 (d, 1H, $J = 2.8$ Hz, Ar-H), 7.87–7.89 (m, 1H, Ar-H), 8.09–8.11 (m, 2H, Ar-H), 11.03 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 103.86$, 111.63, 119.00, 119.91, 120.16. 121.87, 122.43, 123.47, 125.26, 127.15, 128.27, 129.26, 136.15, 147.97, 158.38. MS (EI), m/z $[M+H]^+ = 261.1$; Anal. Calcd for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 77.18; H, 4.53; N, 10.64.