A Novel and Short Synthesis of Naturally Occurring 5-(3′-Indolyl)oxazoles

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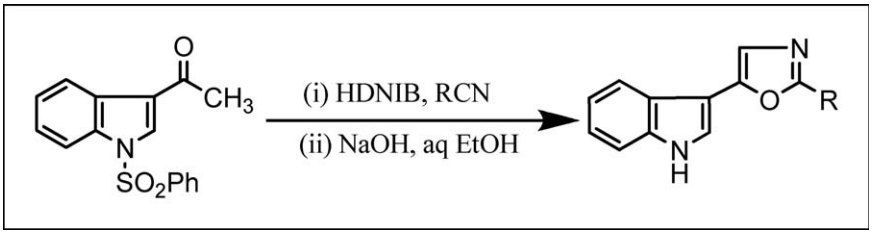

A novel, concise, and convenient synthesis of 5-(3′-indolyl)oxazoles using relatively benign reagent [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benezene has been described. The advantages of this procedure include operational simplicity, good yield, and avoidance of the use of toxic metal.

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INTRODUCTION

The 5-(3′-indolyl)oxazole is a naturally occurring an important heterocyclic motif of immense medicinal and therapeutic potential. Many 5-(3′-indolyl)oxazoles have been isolated from different microorganisms and are known to display interesting biological activities [1]. The 2,5-disubstituted (3′-indolyl)oxazoles, such as pimprinine (2-methyl-5-(3′-indolyl)oxazole); pimprinethine (2-ethyl-5-(3′-indolyl)oxazole), and pimprinaphine (2-benzyl-5-(3′-indolyl)oxazole) were isolated from *Streptoverficillium oliva reticuli*. The pimprinine is known to inhibit monoamine oxidase and showed antiepileptic effects [1a]. Analogs WS-30581 A and B isolated from *Streptoverticillium waksmanii* are shown to display potent inhibitory effects of platelet aggregation [1b]. Recently isolated, the Labradorin 1 (2-isobutyl-5-(3′-indolyl)oxazole) and Labradorin 2 (2-*n*-pentyl-5-(3′-indolyl)oxazole) from *Pseudomonas syringae pv. coronafaciens* are reported to exhibit very good inhibitory activity against various human cancer cells [1c].

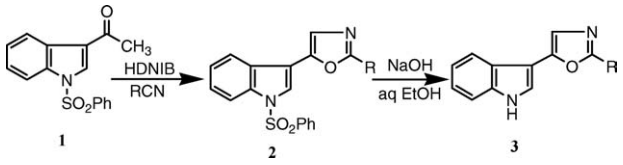
Many procedures are reported for the synthesis of 5-(3′-indolyl)oxazoles, however, straightforward and simple methods are quite limited [2]. Direct synthesis of 5-(3′-indolyl)oxazoles involve rhodium catalyzed reaction of diazoacetylindole with nitriles [2a] and aza-Wittig-type reaction of iminophosphorane derived from 3-azidoacetyl-1-methylindole with isocyanates and acid chlorides [2b]. In general, most of the methods involve multiple synthetic steps, which often require harsh reagents and reaction conditions and afford products in moderate yields. Thus, it is desirable to develop a simple and direct method for the synthesis of 5-(3′-indolyl)oxazoles that can be achieved under milder reaction conditions from readily available starting material.

Hypervalent iodine reagents have found broad utility in organic synthesis due to their low toxicity, ready availability, and ease of handling [3]. The α-[(2,4-dinitrobenzene)sulfonyl]oxyketones are very useful intermediate in organic synthesis, and can be easily prepared from the reaction of enolizable ketone with [hydroxy(2,4-dinitrobenzene-sulfonyloxy)iodo]benzene (PhI(ODNs)OH, HDNIB) [4]. More recently, we have reported a multistep synthesis of 5-(3′-indolyl)oxazoles involving preparation of key intermediate α-aminoketones and cyclization of acylamidoketones using *p*-toluenesulfonic acid [5]. To further improve synthesis of 5-(3′-indolyl)-oxazoles, and to continue our efforts to explore hypervalent iodine reagents in the syntheses of biological important heterocyclic compounds [6], we report herein HDNIB mediated one-pot conversion of 3-acetyl-1-benzenesulfonylindole **1** into naturally occurring 5-(3′-indolyl)oxazoles **3**.

RESULTS AND DISCUSSION

The reaction of 3-acetyl-1-benzenesulfonylindole **1** with 2-(pyridin-3-yl)acetonitrile in presence of HDNIB at 100°C produced pure 5-(1′-benzenesulfonylindol-3′-yl)-2-(3′-pyridinylmethyl)oxazole (**2a**) in 63% yield (Scheme 1). The benzenesulfonyl moiety of oxazole **2a** was removed by treatment with sodium hydroxide to obtain pure 2-(3′-pyridinylmethyl)-5-(3′-indolyl)oxazole **3a** in quantitative yield. Similarly, analogs 5-(3′-indolyl)oxazoles **2b–h** were obtained and removal of benzenesulfonyl group led to the corresponding 5-(3′-indolyl) oxazoles **3b–h** (Table 1). The spectral data of 5-(3′-indolyl)]oxazoles **3a–h** are in agreement with the proposed structures.

Scheme 1



In the reaction of 3-acetyl-1-benzenesulfonylindole **1** with HDNIB in 2-(pyridin-3-yl)acetonitrile, two additional spots on TLC were initially observed, probably corresponding to the 3-α-(2,4-dinitrobenzenesulfonyloxy)-acetylindole and **2a**, which upon further heating converted exclusively to a single spot, that is, **2a**. The 3-acetyl-1-benzenesulfonylindole **1** reacted equally well with benzonitrile, alkylnitriles, and heteroaryl nitriles to afford corresponding oxazoles **2**. Attempts to isolate probable intermediate 3-α-(2,4-dinitrobenzenesulfonyloxy)acetyl indole could not be successful because of its instability. It is, however, to be noted that the reaction of 3-acetylindole with HDNIB in acetonitrile generated a complex mixture.

It is proposed that initial nucleophilic addition of enol **I** on HDNIB forms species **II**, which subsequently loses iodobenzene and water to afford intermediate 3-[α-(2,4-dinitrobenzenesulfonyloxy)]acetyl indole **III** (Scheme 2). The nucleophilic displacement of ODNs in **III** by nitrile, results in the formation of species **IV**, which finally cyclizes to oxazole **2**. Apparently, ODNs being a better leaving group may be responsible for the efficient cyclization, but reaction fails to proceed with the intermediacy of 3-[α-(tosyloxy)]acetylindole obtained from the reaction of 3-acetyl-1-benzenesulfony-lindole **1** with [hydroxy(tosyloxy)iodo]benzene.

CONCLUSIONS

We have introduced a novel, short, and efficient protocol for the preparation of naturally occurring 5-(3′-indolyl)-oxazoles from readily available 3-acetylindole **1** using metal free [hydroxy(2,4-dinitrobenzenesulfonyloxy)iodo]benezene. This protocol should be complementary to other approaches in the synthesis of 5-(3′-indolyl)oxazoles described.

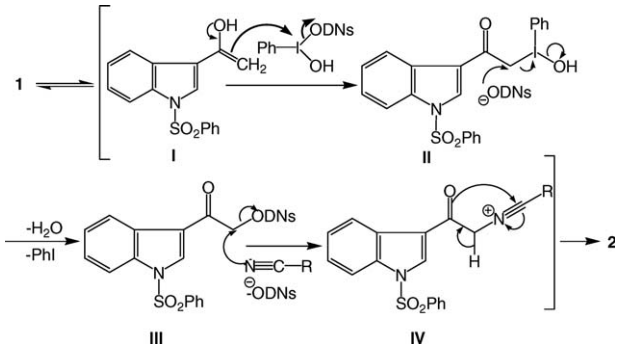
Table 1

Synthesis of 5-(3′-indolyl)oxazoles **2** and **3**.

Entry	R	Yield (%)[a] (**2a–h**)	Overall Yield (%)[b] (**3a–h**)
a	3-Pyridinylmethyl	63	60
b	C_6H_5	65	61
c	CH_3	66	60
d	$CH_3CH_2CH_2$	65	60
e	$(CH_3)_2CHCH_2$	65	59
f	$C_6H_5CH_2$	71	65
g	$CH_3CH_2CH_2CH_2$	70	66
h	3-Pyridinyl	65	61

[a] Isolated yields.
[b] Combined isolated yields of both the steps.

Scheme 2



EXPERIMENTAL

Melting points were recorded on EZ-Melt automated melting point apparatus (Stanford Research Systems, USA) and are uncorrected. IR spectra were recorded on Jasco IR-Report-100 using KBr pellet. ^{1}H and ^{13}C NMR spectra were recorded on Bruker Avance II (400 MHz) and Bruker (200 MHz) spectrophotometer using $CDCl_3$ and DMSO as solvent. Mass spectra were taken on a Agilent Mass spectrometer using FAB mode. All the reagents and solvents were commercially purchased and further purified according to the standard procedures.

General procedure for the preparation of 2-substituted-5-(1′-benzenesulfonylindol-3′-yl)oxazoles (2a–h). A mixture of 3-acetyl-1-benzenesulfonylindole **1** [7] (0.150 g, 0.501 mmol), HDNIB (0.281 g, 0.602 mmol) and appropriate nitrile (2.51 mmol) were heated at 100°C for 18 h. After completion of the reaction, the crude reaction mixture was percolated through a silica-gel column using ethyl acetate-hexane elution system.

5-(1′-Benzenesulfonylindol-3′-yl)-2-(3′-pyridinylmethyl)oxazole (2a) m.p. 185°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.40 (s, 2H, CH_2), 7.25–7.55 (m, 10H, Ar-H), 7.90–8.04 (m, 5H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.73, 113.63, 113.67, 118.06, 121.09, 123.78, 124.43, 125.02, 126.84, 127.20, 128.40, 128.80, 129.09, 129.28, 133.89, 135.37, 137.67, 137.99, 148.09, 170.43; HRMS for $C_{23}H_{17}N_{3a}O_3S$, calcd. $(M)^+$: 415.0991; found: 415.1201 $(M)^+$.

5-(1′-Benzenesulfonylindol-3′-yl)-2-phenyloxazole (2b). m.p. 153–156°C (Lit. [5] m.p. 156°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, 2H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 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) for $C_{23}H_{16}N_2O_3S$, calcd. $(M + H)^+$: 401.0; found: 401.0 $(M + H)^+$.

5-(1′-Benzenesulfonylindol-3′-yl)-2-methyloxazole (2c). m.p. 145°C (Lit. [5] m.p. 143°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.32 (s, 3H, CH_3), 7.18 (s, 1H, Ar-H), 7.26–7.49 (m, 5H, Ar-H), 7.50 (m, 2H, Ar-H), 7.54 (s, 1H, Ar-H), 7.75–7.82 (m, 2H, Ar-H); MS(EI) for $C_{18}H_{14}N_2O_3S$, calcd. $(M + H)^+$: 339.1; found: 339.1 $(M + H)^+$.

5-(1′-Benzenesulfonylindol-3′-yl)-2-propyloxazole (2d). m.p. 135°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.05 (t, 3H, *J* = 6.9 Hz, CH_3), 1.88 (m, 2H, CH_2), 2.82 (t, 2H, *J* = 7.1 Hz, CH_2), 7.14 (s, 1H, Ar-H), 7.48–7.53 (5H, m, Ar-H), 7.61 (s, 1H, Ar-H), 7. 69 (m, 2H, Ar-H), 7.83 (m, 2H, Ar-H); HRMS for $C_{20}H_{18}N_2O_3S$, calcd. $(M + H)^+$: 367.1116; found: 367.1162 $(M + H)^+$.

5-(1′-Benzenesulfonylindol-3′-yl)-2-(i-butyl)oxazole (2e). m.p. 182–184°C (Lit. [5] m.p. 185°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 1.13 (d, 6H, *J* = 6.6 Hz, $2CH_3$), 2.26 (m, 1H, CH), 2.70 (d, 2H, *J* = 7.6 Hz, CH_2), 7.17 (s, 1H, Ar-H), 7.26–7.39 (m, 5H, Ar-H), 7.52 (s, 1H, Ar-H), 7.83 (dd, 2H, *J* = 1.2, 8.0 Hz, Ar-H), 7.95–7.97 (dd, 2H, *J* = 1.2, 7.6 Hz, Ar-H); MS(EI) for $C_{21}H_{20}N_2O_3S$, calcd. $(M + H)^+$: 381.1, found: 381.0 $(M + H)^+$.

5-(1′-Benzenesulfonylindol-3′-yl)-2-benzyloxazole (2f). m.p. 140°C (Lit. [5] mp 138–142°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 3.28 (s, 2H, CH_2), 7.16 (s, 1H, Ar-H), 7.26–7.59 (m, 10H, Ar-H), 7.58 (s, 1H, Ar-H), 7.83 (dd, 2H, *J* = 1.2, 8.0 Hz, Ar-H), 8.06 (dd, 2H, *J* = 1.2, 7.6 Hz, Ar-H); MS(EI) for $C_{24}H_{18}N_2O_3S$, calcd. $(M + H)^+$: 415.1, found: 415.2 $(M + H)^+$.

5-(1′-Benzenesulfonylindol-3′-yl)-2-butyloxazole (2g). m.p. 148°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 0.96 (t, 3H, *J* = 6.8 Hz, CH_3), 1.43 (m, 2H, CH_2), 1.77 (m, 2H, CH_2), 2.83 (t, 2H, *J* = 6.7 Hz), 7.15 (s, 1H, Ar-H), 7.24–7.29 (m, 5H, Ar-H), 7.55–7.82 (5H, m, Ar-H); HRMS for $C_{21}H_{20}N_2O_3S$, calcd. $(M + H)^+$: 381.1273; found: 381.1285 $(M + H)^+$.

5-(1′-Benzenesulfonylindol-3′-yl)-2-(pyridin-3″-yl)oxazole (2h). m.p. 194°C; ^{1}H NMR (400 MHz, $CDCl_3$): δ_H = 7.24 (s, 1H, Ar-H), 7.32–7.36 (m, 5H, Ar-H), 7.45 (d, 1H, *J* = 7.56 Hz, Ar-H), 7.51 (dd, 2H, *J* = 1.7, 8.0 Hz, Ar-H), 7.55–7.59 (m, 4H, Ar-H), 7.76 (dd, 2H, *J* = 1.8, 7.6 Hz, Ar-H); HRMS for $C_{22}H_{15}N_3O_3S$, calcd. $(M)^+$: 401.0834; found: 401.1001 $(M)^+$.

General procedure for the preparation of 2-substituted-5-(3′-indolyl)oxazoles 3. A stirred solution of oxazole **2** (0.19 mmol) and sodium hydroxide (0.02 g, 0.50 mmol) in aqueous ethanol (6 mL) was refluxed for 2 h. After removal of ethanol under vacuum, the aqueous phase was extracted with dichloromethane (3 × 5 mL). The combined organic phase was dried over anhydrous sodium sulfate and concentrated under vacuum.

2-(3′-Pyridinylmethyl)-5-(3′-indolyl)oxazole (3a). Yield 95%; m.p. 195–198°C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.39 (s, 2H, CH_2), 7.15–7.40 (m, 7H, Ar-H), 7.69 (s, 1H, Ar-H), 8.00 (s, 1H, Ar-H), 8.61 (s, 1H, Ar-H); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 39.68, 110.28, 111.49, 112.51, 119.95, 120.48, 122.40, 123,79, 125.04, 127.08, 128.72, 129.11, 136.49, 137.92, 150.41, 169.82; HRMS for $C_{17}H_{13}N_3O$, calcd. $(M)^+$: 275.1059; found: 275.1123 $(M)^+$.

2-(Phenyl)-5-(3′-indolyl)oxazole (3b). Yield 81%; m.p. 213–216°C (Lit. [5] m.p. 216°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 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, $CDCl_3$): δ = 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) for $C_{17}H_{12}N_2O$, calcd. $(M + H)^+$: 261.1; found: 261.1 $(M + H)^+$.

2-(Methyl)-5-(3′-indolyl)oxazole (3c). Yield 83%; m.p. 201°C (Lit. [8] mp 204–205°C); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (s, 3H, CH_3), 7.10 (s, 1H, Ar-H), 7.17–7.25 (m, 2H, Ar-H), 7.44 (d, 1H, *J* = 7.60 Hz, Ar-H), 7.50 (d, 1H, *J* = 2.56 Hz, Ar-H), 7.80 (d, 1H, *J* = 7.64 Hz, Ar-H), 10.12 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.39, 104.53, 111.27, 118.89, 119.07, 119.76, 121.50, 121.86, 123.47, 135.95, 147.18, 158.34; MS(EI) for $C_{12}H_{10}N_2O$, calcd. $(M + H)^+$: 199.1; found: 199.1 $(M + H)^+$.

2-(Propyl)-5-(3′-indolyl)oxazole (3d). Yield 81%; m.p. 124°C (Lit. [1b] m.p. 128–130°C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.05 (t, 3H, *J* = 6.9 Hz, CH_3), 1.88 (m, 2H, CH_2), 2.82 (t, 2H, *J* = 7.1 Hz, CH_2), 7.12–7.53 (5H, m, Ar-H), 7.83 (m, 1H, Ar-H), 9.58 (s, 1H, NH); HRMS for $C_{20}H_{18}N_2O_3S$, calcd. $(M + H)^+$: 367.1116; found: 367.1162 $(M + H)^+$.

2-(Isobutyl)-5-(3′-indolyl)oxazole(3e). Yield 74%; m.p. 143°C (Lit. [1c] m.p. 147–148°C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.06 (d, 6H, *J* = 6.6 Hz, $2CH_3$), 2.27 (m, 1H, CH), 2.76 (d, 2H, *J* = 7.8 Hz, CH_2), 7.20 (s, 1H, Ar-H), 7.26–7.29 (m, 2H, Ar-H), 7.44 (d, 1H, *J* = 7.8 Hz), 7.53 (d, 1H, *J* = 2.93 Hz, Ar-H), 7.87 (d, 1H, *J* = 7.8 Hz, Ar-H), 9.30 (s, 1H, NH); MS(EI) for $C_{15}H_{16}N_2O$, calcd. $(M + H)^+$: 241.1, found: 241.3 $(M + H)^+$.

2-(Benzyl)-5-(3′-indolyl)oxazole (3f). Yield 79%; m.p. 174°C (Lit. [5] m.p. 172°C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 3.24 (s, 2H, CH_2), 7.19 (s, 1H, Ar-H), 7.22–7.25 (m, 5H, Ar-H), 7.56 (d, 1H, *J* = 2.53 Hz, Ar-H), 7.79 (dd, 2H, *J* = 1.2, 8.0 Hz, Ar-H), 7.93 (dd, 2H, *J* = 1.2, 7.6 Hz, Ar-H), 9.82 (s, 1H, NH); MS(EI) for $C_{18}H_{14}N_2O$, calcd. $(M + H)^+$: 275.1, found: 275.0 $(M + H)^+$.

2-(Butyl)-5-(3′-indolyl)oxazole (3g). Yield 84%; m.p. 119°C (Lit. [1b] m.p. 123–125°C); ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 1.01 (t, 3H, *J* = 7.0 Hz, CH_3); 1.45 (m, 2H, CH_2), 1.80 (m, 2H, CH_2), 2.84 (t, 2H, *J* = 6.8 Hz), 7.15 (s, 1H, Ar-H), 7.53 (d, 1H, *J* = 2.52 Hz, Ar-H), 7.62–7.92 (4H, m, Ar-H), 9.10 (s, 1H, NH); HRMS for $C_{21}H_{20}N_2O_3S$, calcd. $(M + H)^+$: 381.1273; found: 381.1285 $(M + H)^+$.

2-(Pyridin-3″-yl)-5-(3′-indolyl)oxazole (3h). Yield 79%, m.p. 142–144°C; ^{1}H NMR (400 MHz, DMSO-d_6): δ_H = 7.22 (s, 1H, Ar-H), 7.47 (d, 1H, *J* = 7.60 Hz, Ar-H), 7.53 (dd, 2H, *J* = 1.7, 8.0 Hz, Ar-H), 7.57–7.62 (m, 4H, Ar-H), 7.78 (dd, 2H, *J* = 1.8, 7.8 Hz, Ar-H), 9.58 (s, 1H, NH); HRMS for $C_{16}H_{11}N_3O$, calcd. $(M)^+$: 261.0902; found: 261.1102 $(M)^+$.

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