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Research Paper

A Convenient and Facile Synthesis of Naturally Occurring 2,5-Diaryloxazoles

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Abstract: A facile and high yielding synthesis of naturally occurring 2,5-diaryloxazoles including annuloline, balsoxin, texamine and texaline, has been reported. The protocol involves initial reaction of [hydroxy(tosyloxy)iodo]benzene with enolizable ketones to prepare α-tosyloxy ketones, which upon treatment with HMTA and followed by hydrolysis in presence of hydrochloric acid led to α-amino ketones in fairly good yields. Acylation of α-amino ketones produced α-acylamino ketones which upon cyclodehydration in presence of triphenylphosphine and iodine led to 2,5-diaryloxazoles in very good yields .

Introduction

The oxazole heterocycle is found in many naturally occurring and synthetic compounds of immense biological interests [1]. In the recent past, many 2,5-diaryloxazoles have been isolated from marine and plant sources with interesting antitumor, antiviral and antimicrobial activities [2]. The oxazole-containing alkaloids, namely pimprinine, pimprinethine, pimprinaphine were isolated from *Streptoverticillium Olivareticuli* [2e, 3]. Pimprinine is known to inhibit monoamine oxidase and also showed antiepileptic effects [4]. Pimprinine analogues, WS-30581 A and B were isolated from *Streptoverticillium Waksmanii* and subsequently reported to display potent inhibitory effects on platelet aggregation [5]. More recently reported, labradorins 1 and 2 were isolated from *Pseudomonas syringae pv. Coronafaciens* as potent growth inhibitors of various human cancer cells [2e]. Many simple alkaloids containing 2,5-diaryloxazole scaffold such as annuloline, balsoxin, texamine and texaline were also isolated and evaluated for their biological properties. Annuloline was isolated from the roots of ryegrass (*Lolium multiflorum*) and showed an intense blue fluorescence upon exposure to UV irradiation [6]. Texaline and Balsoxin were isolated from the plants of *Amyris* species in the Caribbean [7]. Texamine, a bioisoster of texaline, was isolated from the roots of the plant *Amyris texana* and found to inhibit the growth of *M. tuberculosis*, *M. avium* and *M. kansasii* (MIC 25 μg/ml) [8].

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Most of the reported synthetic protocols for the construction of 2,5-diaryloxazoles mainly utilize key intermediates including α-bromoketones [8a], α-acylaminocarbonyl [9], α-diazo-ketones [10] and α-azidoketones [11] that require harsh reaction conditions, toxic chemicals and afford products in moderate yields. On the other hand, the recent reports for the synthesis of 2,5-diaryloxazoles involve the transition-metal catalyzed direct arylation of oxazole ring using catalysts such as $Pd(OAc)_2$, $PdCl_2(PPh_3)_2$, $Pd(dppf)Cl_2$ and $NiCl_2(PPh_3)_2$ [12]. Despite the improved synthetic utility of existing protocols; these methodologies involve costly reagents, ligands or special experimental conditions. Hence there is further scope to develop protocol that requires easily accessible starting materials and relatively benign reagents. Hypervalent iodine reagents have been utilized as efficient, mild and environmentally benign oxidants to construct diverse heterocycles due to their easy handling, stability at room temperature and relatively low toxicity when compared with transition-metal based reagents [13]. Our previous reports on iodine (III)-mediated construction of bioactive heterocycles successfully led to the identification of indolyl oxazoles, bis(indolyl)-1,2,4-thiadiazoles and indolyl-1,3,4-oxadiazoles as potent anticancer agents [14]. In a way to explore utility of hypervalent iodine reagents to develop benign synthetic protocols for the preparation of naturally occurring bioactive heterocycles, herein we report the synthesis of 2,5-diaryloxazoles including balsoxin, annuloline, texaline and texamine *via* the key intermediates α-tosyloxy ketones, α-amino ketones and α-acylamino ketones.

Materials and Methods

Commercially available reagents were used as such without any further purification. Melting points were recorded on *EZ*-Melt MPA120 and are uncorrected. Infrared spectra were recorded on Shimadzu IR Prestige-21 FT-IR spectrophotometer. ^{1}H NMR spectra were recorded on Bruker Avance II 400 NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are given in parts per million (δ) and coupling constants (*J*) in Hz. Thin layer chromatography (TLC) was performed on Merck silica gel 60 F254 precoated aluminium sheets.

Chemistry

Synthesis of α-tosyloxy-3,4-dimethoxyacetophenone (2a): [Hydroxy(tosyloxy)iodo] benzene (1 mmol) was added in portions to a stirred solution of 3,4-dimethoxyacetophenone (1 mmol) in acetonitrile (10 mL) and allowed to stir the contents for 7 h at room temperature. After completion of the reaction, acetonitrile was removed at reduced pressure and the residue so obtained was recrystallized from methanol to afford pure **2a** in 82% yield. mp 92-93 °C ; IR (KBr, ν cm^{-1}): 1690, 1590, 1510, 1420, 1350, 1270, 830, 760; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 2.45 (s, 3H, CH_3), 3.91(s, 3H, OCH_3), 3.95 (s, 3H, OCH_3), 5.22 (s, 2H, CH_2), 6.88 (d, 1H, *J* = 8.36 Hz, Ar-H), 7.35 (d, 2H, *J* = 8.00 Hz, Ar-H), 7.45 (d, 1H, *J* = 2.12 Hz, Ar-H), 7.47 (d, 1H, *J* = 1.96 Hz, Ar-H), 7.85 (s, 1H, Ar-H), 7.86 (d, 1H, *J* = 1.6 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 21.75, 56.09, 56.22, 69.82, 110.08, 110.16, 115.4,116.6, 122.78, 126.51, 128.18, 129.94, 132.66, 145.31, 149.37, 154.19, 188.86; EI-MS: *m/z* calcd. for $C_{17}H_{18}O_6S$ 350.0824, obsd 350.0142 $[M]^+$.

α-Tosyloxy-4-methoxyacetophenone (2b). Yield 78%, mp 69-70 °C; IR (KBr, ν, cm^{-1}): 1690, 1617, 1575, 1420, 1370, 1250, 1174, 875, 830; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 2.44 (s, 3H, CH_3), 3.87(s, 3H, OCH_3),

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5.20 (s, 2H, CH_2), 6.94-6.91 (m, 2H, Ar-H), 7.34 (d, 2H, *J* = 8.00 Hz, Ar-H), 7.81-7.86 (m, 4H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 21.76, 55.65, 69.88, 114.17, 126.05, 126.75, 128.98, 129.96, 130.47, 132.63, 145.33, 188.78; EI-MS: *m/z* calcd. for $C_{16}H_{16}O_5S$ 320.0718, obsd. 320.0740 $[M]^+$.

α-Tosyloxy-3,4-(methylenedioxy)acetophenone (2c): [Hydroxy (tosyloxy)iodo] benzene (1 mmol) was added to a stirred solution of 3,4-methylenedioxyacetophenone (1 mmol) in acetonitrile (6 mL) and continued stirring at 15 °C for 2 h then at room temperature for 3 h. After completion of the reaction, solvent was removed at reduced pressure and the residue so obtained was recrystallized from methanol to afford pure **2c** in 72% yield. mp 112-115 °C; IR (KBr, ν cm^{-1}): 1690, 1570, 1520, 1420, 1350, 1270, 1150, 830, 760. ^{1}H NMR (400 MHz, DMSO-d_6, δ): 2.37 (s, 3H, CH_3), 5.09 (s, 2H, CH_2), 5.97 (s, 2H, CH_2), 6.76 (d, 1H, *J* = 8.00 Hz, Ar-H), 7.23 (d, 1H, *J* = 1.64 Hz, Ar-H), 7.27 (d, 2H , *J* = 8.16 Hz, Ar-H), 7.34 (dd, 1H, *J* = 8.16, *J* = 1.76 Hz, Ar-H), 7.77 (d, 2H, *J* = 8.32 Hz, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6, δ): 16.73, 65.15, 97.22, 102.57, 103.25, 119.52, 123.04, 123.33, 125.05, 127.60, 140.42, 143.51, 147.76, 183.33; EI-MS, *m/z* calcd. for $C_{16}H_{14}O_6S$ 334.0511, obsd. 334.05 $[M]^+$.

2-Amino-1-(3,4-dimethoxy phenyl)ethanone hydrochloride (3a). To a stirred solution of hexamethylenetetramine (1.2 mmol) in dry chloroform (15 mL) was added α-tosyloxy-3,4-dimethoxyacetophenone (1 mmol) over a period of 1 h and continued the stirring for another 10 h at room temperature. The precipitated white coloured salt was filtered, dried and added to a warm solution of water/ethanol/2N hydrochloric acid (1:4:1, v/v) and stirred for 4 h. The pure amine hydrochloride salt was precipitated out, filtered and recrystallized from methanol-chloroform mixture to obtain pure **3a** in 84% yield. mp 205 °C (dec.); IR (KBr, ν cm^{-1}): 3190, 2950, 1460, 1354, 1228, 762, 715; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.58 (s, 6H, OCH_3), 5.22 (s, 2H, CH_2), 7.34-7.32 (m, 3H, Ar-H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 38.87, 39.08, 39.29, 39.7, 39.91, 40.12, 149.37, 154.19, 188.86; EI-MS: *m/z* calcd. for $C_{10}H_{13}NO_3$.HCl 195.0895, obsd. 195.1149 $[M]^+$.

2-Amino-1-(4-methoxyphenyl)ethanone hydrochloride (3b). Yield 65%, mp 185 °C (dec.); IR (KBr, ν cm^{-1}): 3240, 3045, 1690, 1620, 1530, 1250, 1165, 1020, 830; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 3.87(s, 3H, OCH_3), 4.44 (s, 2H, CH_2), 7.70 (d, 2H , *J* = 8.00 Hz, Ar-H), 7.89 (d, 2H, *J* = 8.00 Hz, Ar-H), 8.49 (s, 2H, -NH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 44.27, 55.65, 113.17, 125.95, 128.12, 130.03, 188.78; EI-MS *m/z* calcd. for $C_9H_{11}NO_2$.HCl 165.0790, obsd. 165.0272 $[M]^+$.

2-Amino-1-(3,4-methylenedioxy phenyl)ethanone hydrochloride (3c). Yield 75%, mp 217 °C (dec.); IR (KBr, ν cm^{-1}): 3230, 2990, 1710, 1620, 1530, 1250, 1165, 1080, 830,750; ^{1}H NMR (400 MHz, DMSO-d_6, δ ppm): 4.34 (s, 2H, CH_2), 6.03 (s, 2H, CH_2), 6.81 (d, 1H, *J* = 8.20 Hz, Ar-H), 7.30 (s, 1H, Ar-H), 7.45 (dd, 1H, *J* = 8.12, *J* = 1.02 Hz, Ar-H), 8.39 (s, 2H, NH_2); ^{13}C NMR (100 MHz, DMSO-d_6, δ ppm): 49.64, 107.06, 112.22, 113.08, 129.71, 144.01, 148.23, 153.28, 194.58; EI-MS, *m/z* calcd. for $C_9H_9NO_3$.HCl 179.058, obsd. 179.056 $[M]^+$.

***N*-[2-(3, 4-Dimethoxyphenyl)-2-oxoethyl] benzamide (4a).** To a solution of 2-amino-1-(3,4-dimethoxyphenyl)ethanone

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hydrochloride **3a** (1 mmol) in dichloromethane (10 mL) was added dropwise benzoyl chloride (1 mmol) at 5 °C . To this reaction mixture triethylamine (1.8 mmol) was added and stirred for 30 min. The mixture was brought to room temperature, taken into water (20 mL) and extracted with dichloromethane (2 × 30 mL). The combined organic layers were washed with brine solution, dried over anhydrous sodium sulphate and the solvent was removed under vacuum to afford pure **4a** in 72 % yield. mp 112-115 °C ; IR (KBr, ν cm^{-1}): 3300, 2920, 1680, 1620, 1530, 1460, 1280, 810, 715 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.96 (s, 3H, OCH_3), 3.97 (s, 3H, OCH_3), 4.92 (s, 2H, CH_2), 6.94 (d, 1H, *J* = 8.44 Hz, Ar-H), 7.37 (s, 1H, Ar-H), 7.37-7.55 (m, 4H, Ar-H), 7.67(d, 1H, *J* = 8 Hz, Ar-H), 7.87 (d, 1H, *J* = 1.4 Hz, Ar-H), 7.89 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 46.5, 56.14, 56.24, 109.89, 110.41, 122.83, 127.17,127.41, 127.49, 128.69, 131.81, 132.06, 133.99, 149.33, 154.22, 167.45, 192.75; EI-MS, *m/z* calcd. for $C_{17}H_{17}NO_4$ 299.115, obsd. 299.200 $[M]^+$.

3-(3,4-Dimethoxyphenyl)-N-[2-(4-methoxyphenyl)-2-oxoethyl]acrylamide (4b). Yield 70%, mp 160-165 °C; IR (KBr, ν cm^{-1}): 3280, 1675, 1633, 1590, 1520, 1260, 1160, 1130, 1020, 762, 720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.89 (s, 3H, OCH_3), 3.91(s, 3H, OCH_3), 3.92(s, 3H, OCH_3), 4.86 (s, 2H, CH_2), 6.46 (d, 1H, *J* = 15.6 Hz, -C=C-H), 6.86 (d, 2H, *J* = 8.32 Hz, Ar-H), 6.97(d, 2H, *J* = 8.6 Hz, Ar-H), 7.06 (s, 1H, Ar-H), 7.11 (d, 2H, *J* = 8.16 Hz, Ar-H), 7.61 (d, 1H, *J* = 15.5 Hz, -C=C-H), 7.99 (d, 2H, *J* = 8.6 Hz, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 46.34, 55.63, 55.89, 55.98, 109.56, 111.03, 114.17, 118.11, 122.17, 127.38, 127.72, 130.38, 141.30, 149.12, 150.64, 164.36, 166.18, 192.71; EI-MS, *m/z* calcd. for $C_{20}H_{21}NO_5$ 355.1450, obsd. 355.2392 $[M]^+$.

***N*-[2-(3,4-Methylenedioxyphenyl)-2-oxoethyl]benzamide (4c)**. Yield 78%, mp 143-146 °C (dec.); IR (KBr, ν cm^{-1}): 3240, 1680, 1640, 1550, 1510, 1260, 1160, 1100, 1020, 765, 730; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.89 (s, 2H, -CH_2), 6.07 (s, 2H, -CH_2), 6.90 (d, 1H, *J* = 8.20 Hz, Ar-H), 7.48-54 (m, 4H, Ar-H), 7.55-58 (m, 1H, Ar-H), 7.64 (d, 1H, *J* = 8.12 Hz, Ar-H), 7.88 (d, 1H, *J* = 8.00 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 46.63, 102.13, 107.67, 108.32, 124.56, 127.40, 128.63, 129.66, 131.79, 133.88, 148.52, 152.77, 167.46, 192.28; EI- MS, *m/z* calcd. for $C_{16}H_{13}NO_4$ 283.084, obsd. 283.083 $[M]^+$,.

***N*-(2-(Benzo[*d*][1,3]dioxol-6-yl)-2-oxoethyl)nicotinamide (4d).** Yield 45%, mp 123-125 °C; IR (KBr, ν, cm^{-1}): 3300, 3215, 1788, 1690, 1580, 1440, 1220, 810. ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 4.88 (s, 2H, -CH_2), 6.08 (s, 2H, -CH_2), 6.90 (d, 1H, *J* = 8.20 Hz, Ar-H), 7.20 (d, 1H, *J* = 8.12 Hz, Ar-H), 7.34 (s, 1H, Ar-H), 7.41 (m, 1H), 8.32 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.68 (m, 1H, Ar-H), 9.30 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 46.3, 102.13, 107.67, 108.32, 124.56, 127.40, 127.63, 130.66, 131.79, 133.88, 146.8 148.52, 152.77, 166.46, 193.0; EI- MS, *m/z* calcd. for $C_{15}H_{12}N_2O_4$ 284.079, obsd. 285.103 $[M+H]^+$.

Synthesis of Balsoxin (**5a**). To a solution of *N*-[2-(3,4-dimethoxyphenyl)-2-oxoethyl]benzamide (1 mmol) in dry dichloromethane (10 mL) were sequentially added triphenylphosphine (2 mmol), iodine (2 mmol) and triethylamine (4 mmol) at 0 °C. The cooling bath was removed after 30 min and stirred the reaction mixture at room temperature for 2 h. The reaction contents were diluted with water (10 mL), stirred for another 1h and then extracted with dichloromethane (2 × 20 mL). The organic phase was washed with brine solution and

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dried over anhydrous $MgSO_4$. The excess of dichloromethane was removed under vacuum and the residue so obtained was purified by silica gel column chromatography using ethylacetate-hexane as eluent to afford pure oxazole **5a** in 78% yield. Analytical data were in agreement with the literature report [7a]. IR (KBr, ν cm^{-1}): 1420, 1190, 1120, 720, 690; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.93 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.93 (d, 1H, *J* = 8.32 Hz, Ar-H), 7.19 (s, 1H, Ar-H), 7.37-7.55 (m, 4H , Ar-H), 7.67 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.87 (d, 1H, *J* = 1.4 Hz, Ar-H), 7.89 (s, 1H, Ar-H); ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 56.14, 56.24, 109.89, 110.41, 122.83, 127.17,127.41, 127.49, 128.69, 131.81, 132.06, 133.99, 149.33, 154.22, 167.45; EI-MS, *m/z* calcd. for $C_{17}H_{15}NO_3$ 281.1052, obsd. 280.1129 $[M-1]^+$.

Annuloline (5b). Yield 75%, mp 104-106 °C. (lit [2g] mp 105-106 °C); IR (KBr, ν cm^{-1}): 2350, 1510, 1430, 1130, 720, 690; ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 3.86 (s, 3H, OCH_3), 3.92(s, 3H, OCH_3), 3.92(s, 3H, OCH_3), 6.83 (d, 1H, *J* = 16.4 Hz, C=C-H), 6.87 (d, 1H, *J* = 7.9 Hz, Ar-H), 6.97 (d, 2H, *J* = 8.9 Hz, Ar-H), 7.12 (m, 2H, Ar-H), 7.29 (s, 1H, Ar-H), 7.49 (d, 1H, *J* = 16.4 Hz, C=CH), 7.63 (d, 2H, *J* = 8.9 Hz, Ar-H), ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 55.33, 55.83, 55.92, 108.8, 111.1, 111.9, 114.23, 120.81, 121.17, 122.3, 125.62, 128.57, 135.1, 149.12, 150.14, 150.72, 159.7, 160.7; EI-MS, *m/z* calcd. for $C_{20}H_{19}NO_4$ 337.1314, obsd. 338.2772 $[M+H]^+$.

Texamine (5c). Yield 80%, mp 134-136 °C (lit [8a]. mp 134-137 °C); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 6.02 (s, 2H, $-CH_2$), 6.89 (d, 1H, *J* = 8.0 Hz, Ar-H), 7.18-7.26 (m, 2H, Ar-H), 7.31 (s, 1H, Ar-H) 7.44-7.52 (m, 3H, Ar-H), 8.06 (d, 2H, *J* = 8.00 Hz); ^{13}C NMR (100 MHz, $CDCl_3$, □ ppm): □□□.13, 104.67, 108.8, 118.3, 122.2, 122.3, 126.1, 127.40, 128.8, 130.2, 147.5, 148.2, 151.1, 160.6; EI- MS, *m/z* calcd. for $C_{16}H_{11}NO_3$ 265.0739, obsd. 266.0614 $[M+1]^+$.

Texaline (5d). Yield 72%, mp 170-172 °C (lit [8a] mp 171-174 °C); ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm): 6.03 (s, 2H, $-CH_2$), 6.89 (d, 1H, *J* = 8.1 Hz, Ar-H), 7.16 (d, 1H, *J* = 1.6 Hz, Ar-H), 7.24 (dd, 1H, *J* = 8.1 Hz, *J* = 1.6 Hz), 7.34 (s, 1H, Ar-H), 7.41 (m, 1H, Ar-H), 8.32 (d, 1H, *J* = 8.0 Hz, Ar-H), 8.68 (d, 1H, *J* = 3.9 Hz, Ar-H), 9.31 (s, 1H, Ar-H). ^{13}C NMR (100 MHz, $CDCl_3$, δ ppm): 101.4, 104.8, 108.9, 118.5, 121.7, 122.5, 123.5, 123.7, 133.2, 147.4, 148.2, 148.2, 150.7, 151.8, 158.1; EI- MS, *m/z* calcd. for $C_{15}H_{10}N_2O_3$ 266.0691, obsd. 267.0714 $[M+H]^+$.

Results and Discussion

The synthesis of 2,5-diaryloxazoles was initiated with the preparation of α-tosyloxy ketones **2** from appropriate acetophenones **1** (Scheme 1). The α-tosyloxylation of acetophenones **1** bearing electron-donating groups was a difficult task to achieve. The general approach for the preparation of α-tosyloxy ketones **2** involves the reaction of respective enolizable ketone with [hydroxy(tosyloxy)iodo]benzene (HTIB) in acetonitrile [15]. Our attempts to use this literature protocol afforded products with infinitesimal yields. Relentless efforts were applied to develop an optimized method for the preparation of α-tosyloxy ketones **2**. A complete study was carried out by varying reaction solvent and temperature. The reaction solvents were screened including chloroform, dichloromethane, acetonitrile and tetrahydrofuran at different temperatures ranging from subzero to reflux. It was observed that prolonged refluxing afforded a brown colored undesired product. Attempts

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were also made to prepare α-tosyloxy ketones **2** under solvent-free conditions by simple grinding and unconventional energy sources like microwave irradiation. In spite of all our efforts, the α-tosyloxy ketones **2** could not be afforded beyond 40% yield. Moreover, substantial amount of undesired products were formed upon prolonging the reaction under refluxing conditions. During our study, it was ascertained that the addition of HTIB in small portions at room temperature and acetonitrile as the reaction solvent, are essential to afford α-tosyloxy ketones **2** in good yields. Using these optimized reaction conditions, various α-tosyloxy ketones **2a-b** were synthesized with ease. However, the preparation of the α-tosyloxy ketone **2c** was still critical as it required slight modification in the reaction conditions. For **2c**, the HTIB was carefully added while maintaining the temperature at 15-20 °C and allowed to stir the reaction mixture for 2 h. The temperature was then slowly raised to ambient conditions and continued to stir for another 3 h to obtain the desired product **2c** in good yield.

The α-amino ketones **3** were achieved in very good yields by reacting the α-tosyloxy ketones **2** with hexamethylenetetramine at room temperature. The general route for the synthesis of α-amino ketones **3** involves a two step procedure: initial preparation of α-azidoacetophenones from α-tosyloxy ketones and followed by catalytic reduction to α-amino ketones [8a]. Our high yielding synthesis of the desired α-amino ketones **3** is a minor modification of the protocol reported by Loughlin et al. requiring low cost reagents and simple experimentation [16].

The preparation of α-acylamino ketones **4** was carried out by coupling an appropriate acid chloride with α-aminoketones **3** under Schotten-Baumann conditions. Finally, the desired 2,5-diaryloxazoles **5** were obtained by cyclodehydration of α-acylamino ketones **4** in good yields. The α-acylamino ketones generally undergo cyclodehydration under harsh reaction conditions involving dehydrating agents such as sulfuric acid, phosphorus pentachloride, phosphorus oxychloride, polyphosphoric acid, phosgene and anhydrous HF [17]. Our attempts to synthesize the 2,5-diaryloxazoles from α-acylamino ketones **4** using these literature protocols afforded products in low yields. Employment of a mild procedure developed by Brain and Paul [18] using Burgess reagent was also resulted products in less yields. In our travails for the synthesis of 2,5-diaryloxazoles, we identified that the combination of triphenyl phosphine and iodine is appropriate to achieve cyclodehydration of the α-acylamino ketones **4** in good yields [19]. Of the several reaction solvents (chloroform, acetonitrile, dichloromethane, 1,2-dichloroethane and carbon tetrachloride) screened for this transformation, we found dichloromethane is suitable to afford the 2,5-diaryloxazoles in good yields (Table 1).

Conclusions

In summary, we have reported a novel approach to prepare naturally occurring 2,5-diaryloxazoles including annuloline, balsoxin, texamine and texaline in good yields. This synthetic protocol offers several advantages such as utility of easily available starting materials, operational simplicity, relatively benign reagents and high product yields. This facile method provides a complementary approach to prepare 2,5-diaryloxazoles and can be extended to prepare a series of analogues with myriad functional group substitutions.

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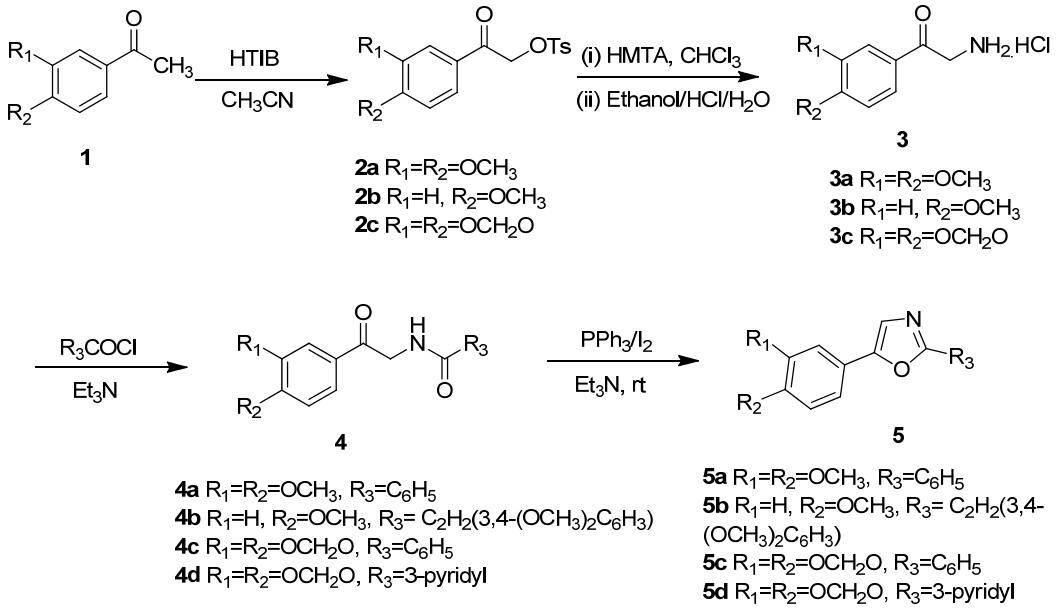
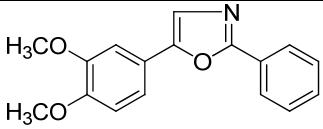
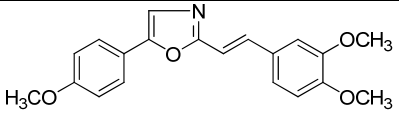
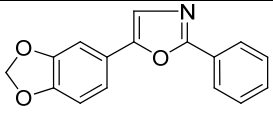
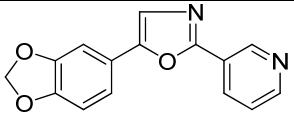


Scheme 1 Synthesis of 2,5-diaryloxazoles **5a-d**

Table 1 Synthesis of 2,5-disubstituted oxazoles (**5a-d**)

2,5-Diaryloxazoles (**5a-d**)	Overall Yield (%)[a]
 Balsoxin (**5a**)	39
 Annuloline (**5b**)	34
 Texamine (**5c**)	34
 Texaline (**5d**)	18

[a]Yields of isolated pure compounds over all three steps

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