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A CONVENIENT SYNTHESIS OF SUBSTITUTED OXAZOLO-[5,4-b]PYRIDINES USING LEAD TETRAACETATE AS OXIDATIVE CYCLIZING AGENT

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Abstract: Various substituted oxazolo[5,4-b]pyridines **5a-d** have been synthesized by condensation of appropriate hydroxyaminopyridines and aldehydes followed by oxidative cyclization of the resulting Schiff's bases with lead tetra-acetate. This method has been extended to the synthesis of the DNA minor groove binding ligands **5e** and **5f** related to Hoechst 33258 **1**.

Synthesis of oxazolo[5,4-b]pyridines is of interest because of their established biological activity.[1] This group of compounds exhibits antiinflammatory, anti-pyretic and analgesic properties. These compounds are also used as optical whitening agents[2] and dye intermediates.[3]

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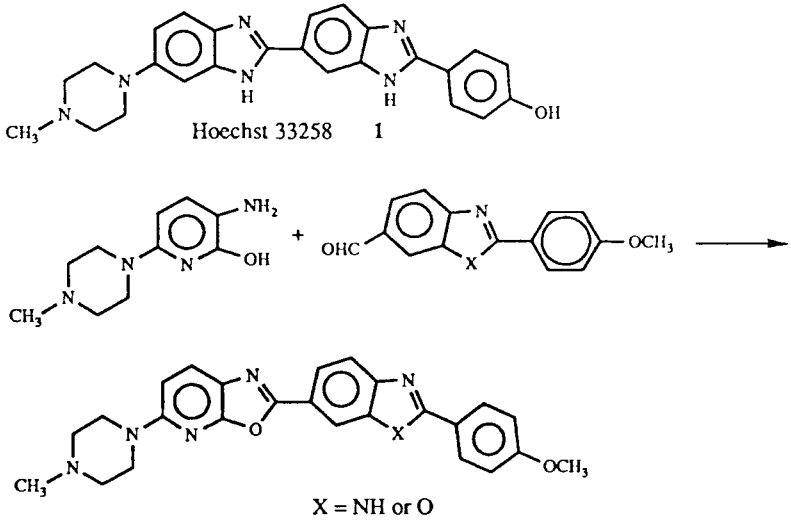
In our continuing study into the structural components that control the molecular recognition between DNA and ligands,[4] we planned to synthesize and examine oxazolo[5,4-b]pyridine containing ligands related to Hoechst 33258 **1**. This synthesis requires a procedure for the construction of 2-aryl-6-substituted oxazolo[5,4-b]pyridine ring system under mild reaction conditions (Scheme I).

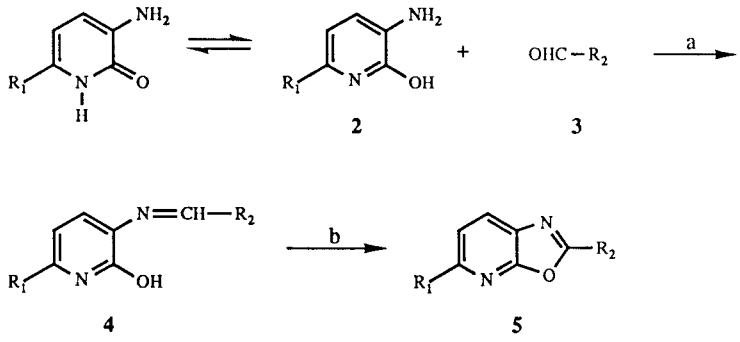
Scheme I



The synthesis of 2-aryl oxazolo[5,4-b]pyridines is known from 3-aminopyridin-2-(1H)-one (or from 3-amino-2-chloropyridine) *via* N-acylation followed by cyclization using dehydrating reagents like phosphorous pentoxide,[5] phosphorous oxychloride,[1a], polyphosphoric acid,[3,6] trimethylsilyl polyphosphate ester[7] at higher temperature (180-200°C). Such strong acidic and high temperature reaction conditions cannot be tolerated by functional groups like piperazine. Therefore we have explored preparation of oxazolopyridines *via* an alternative aldehyde method. It is known in the literature that the Schiff's bases of *o*-hydroxyanilines can be

cyclized to benzoxazoles with a variety of oxidizing agents.[8,10] To our knowledge this kind of cyclization has not been reported for the synthesis of oxazolopyridines. Oxazolo[5,4-b]pyridines are also obtained from isoxazolo[5,4-b]pyridines *via* photochemical rearrangement.[9] Here we report the synthesis of oxazolo[5,4-b]-pyridines from pyridine-2(1H)-one and aldehydes *via* oxidative cyclization of intermediate imine **4** (Scheme II).

Scheme II

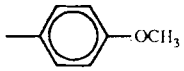
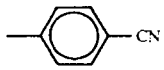
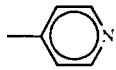
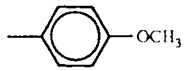
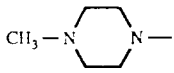
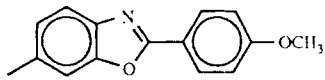
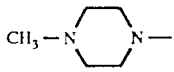
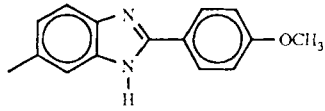


a) AcOH/Benzene; b) $Pb(OAC)_4$/Benzene

Condensation of aminopyridine **2** with an aldehyde **3** in the presence of acetic acid afforded the Schiff's base **4**, which on treatment with lead tetraacetate at room temperature underwent oxidative cyclization to give oxazolo[5,4-b]pyridines **5**. Except in the case of example **d** (Table), the overall yield of the reaction is moderate to high (60-75%). The intermediate imines are very sensitive to moisture and readily undergo hydrolysis. Hence it is necessary to conduct the reaction under very dry conditions.

The condensation of bromopyridine **2d** and anisaldehyde followed by cyclization resulted in a modest yield (40%) of **5d** and a small amount (10%) of

Table

	R_1	R_2	isolated % Yield
5a	H		75
5b	H		70
5c	H		60
5d	Br		40
5e			65
5f			68

unexpected compound. High resolution mass spectrum of this compound showed M^+ 284.0797 for $C_{15}H_{12}N_2O_4$. The IR spectrum showed absorption for ester carbonyl group (1760 cm^{-1}) and the ^1H NMR spectrum, in addition to the methoxyl and aromatic protons, showed additional absorption at 2.36 for acetoxyl group. Based on the spectral data the structure of this new compound was assigned as 6-acetoxy-2-(4-methoxyphenyl)oxazolo[5,4-b]pyridine **5** (R_1 = OAc; R_2 = C_6H_4-4-OMe). In this reaction lead tetraacetate not only cyclizes the intermediate imine but also displaces bromine. This side reaction shows susceptability of 2-halopyridines to nucleophilic attack.

In summary we have demonstrated a convenient one pot synthesis for 2-aryl-oxazolo[5,4-b]pyridines which has wider scope for the introduction of a variety of functional groups either on pyridine ring or phenyl ring.

Experimental

Melting points were determined on an Electrothermal melting point apparatus and are uncorrected. The IR spectra were recorded on a Nicolet 7199 FT spectrophotometer, and only the principal bands are reported. The ^{1}H-NMR spectra were recorded on Bruker WH-200 and WH-400 spectrometers. Mass spectra were determined on Associate Electrical Industries (AEI) MS-9 and MS-50 focusing high resolution mass spectrometers. Kieselgel 60 (230-400 mesh) of E. Merck and florisil (60-100 mesh) was used for chromatography, and precoated silica gel 60F-254 sheets were used for TLC. TLC plates were visualized using UV light or 2.5% phosphomolybdic acid in methanol with heating.

All compounds obtained commercially were used without further purification unless otherwise stated. Lead tetraacetate was purchased from Aldrich, benzene was dried over sodium wire, tetrahydrofuran was distilled from sodium/benzophenone under an atmosphere of dry argon; ether was from phosphorous pentoxide and stored over molecular sieves 3Å.

General Procedure for Preparation of Oxazolo[5,4-b]pyridines

A mixture of 2-amino-3-hydroxypyridine **2** (1 mmol), aldehyde **3** (1 mmol) and acetic acid (0.5 mL) in benzene (30 mL) was heated under reflux for 24 h with azeotropic water removal. Then the solvent was removed under reduced pressure and the resulting residue was co-evaporated with hexane (3 × 20 mL) and triturated with hexane to give the Schiff's base **4**. The latter compound was treated with lead tetraacetate (1 mmol) in benzene (25 mL) at room temperature. After stirring the reaction mixture for 4 h, water was added. The organic layer was removed, and the aqueous layer was extracted with ethyl acetate (2 × 20 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), evaporated and the resulting

solid was purified on a column of silica gel (or florisil) (hexane:ethyl acetate) to give the title compound **5**.

5a: m.p. 143-145°C (lit.[1a] m.p. 146-148°C); IR (KBr) ν_{max}: 1620, 1610, 1500, 1400, 1250, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.94 (*s*, 3H, $-OCH_3$), 7.06 (*d*, 2H, Ar-H), 7.32 (*dd*, 1H, Py-H), 8.02 (*dd*, 1H, Py-H), 8.24 (*d*, 2H, Ar-H), 8.32 (*dd*, 1H, Py-H); MS m/z (relative intensity): Calcd. for $C_{13}H_{10}N_2O_2$, 226.0742. Found: 226.0740 (M^+, 100), 211(13), 198(18), 183(13).

5b: m.p. 218-220°C (lit.[1a] m.p. 220-221°C); IR (KBr) ν_{max}: 2230, 1618, 1605, 1494, 1400 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 7.58 (*dd*, 1H, Py-H), 8.12 (*d*, 2H, Ar-H), 8.4 (*dd* and *d* merged, 1 Py-H, 2 Ar-H), 8.46 (*dd*, 1H, Py-H).

5c: m.p. 153-155°C; IR (KBr) ν_{max}: 1595, 1540, 1415, 1400, 1230 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 7.45 (*dd*, 1H, Ar-H), 8.15 (*dd*, *d* merged, 3H, Ar-H), 8.45 (*dd*, 1H, Ar-H), 8.86 (*d*, 2H, Ar-H); MS m/z (relative intensity): Calcd. for $C_{11}H_7N_3O$, 197.0589. Found: 197.0592 (M^+, 100), 168(51).

5d: m.p. 183-185°C; IR (KBr) ν_{max} 1620, 1500, 1460, 1440, 1420 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 3.9 (*s*, 3H, $-OCH_3$), 7.04 (*d*, 2H, Ar-H), 7.48 (*d*, 1H, Py-H), 7.84 (*d*, 1H, Py-H), 8.18 (*d*, 2H, Ar-H); MS m/z (relative intensity): Calcd. for $C_{13}H_9N_2O_2Br$, 303.9847. Found: 303.9817 (M^+, 100), 290(13), 288(12), 225 (6).

5: (R_1 = OAc, R_2 = 4MeO); m.p. 188-190°C; IR (KBr) ν_{max} 1760, 1620, 1500, 1250 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ: 2.36 (*s*, 3H, $COCH_3$), 3.9 (*s*, 3H, $-OCH_3$), 7.02 (*d*, 2H, Ar-H), 7.08 (*d*, 1H, Py-H), 8.06 (*d*, 1H, Py-H), 8.18 (*d*, 2H, Ar-H); MS m/z (relative intensity): Calcd. for $C_{15}H_{12}N_2O_4$, 284.0797. Found: 284.0796 (M^+, 7), 242(100), 135(63).

5e: m.p. 246-248°C; IR (KBr) ν_{max}: 1620, 1600, 1500, 1420, 1260 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 2.23 (*s*, 3H, N-CH_3), 2.44 (*t*, 4H, -CH_2-), 3.6 (*t*, 4H, -CH_2-), 3.9 (*s*, 3H, Ar-OCH_3), 6.94 (*d*, 1H, Ar-H), 7.18 (*d*, 2H, Ar-H), 7.92 (*d*, 1H, Ar-H), 7.98 (*d*, 1H, Ar-H), 8.1-8.25 (*d* and *dd* merged, 3H, Ar-H), 8.38 (*s*, 1H, Ar-H); MS m/z (relative intensity): Calcd. for $C_{25}H_{23}N_5O_3$, 441.1801. Found: 441.1797 (M^+, 48), 426(31), 372(24), 371(100), 71(45), 70(55).

5f: no distinct m.p.; IR (KBr) ν_{max}: 3420, 2920, 2840, 1620, 1580, 1450, 1410 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ: 2.22 (*s*, 3H, N-CH_3), 2.42 (*t*, 4H, -CH_2-), 3.54 (*t*, 4H, -CH_2-), 3.84 (*s*, 3H, Ar-OCH_3), 6.88 (*d*, 1H, Ar-H), 7.08 (*d*, 2H, Ar-H), 7.64 (*d*, 1H, Ar-H), 7.86 (*d*, 1H, Ar-H), 7.93 (*d*, 1H, Ar-H), 8.2 (2*d* merged, 3H, Ar-H); MS m/z (relative intensity): Calcd. for $C_{25}H_{24}N_6O_2$, 440.1964. Found: 440.1958 (M^+, 45), 425(27), 370(100), 71(22), 70(29).

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