Syntheses of Oxazolo[4,5-*c*]pyridine and 6-Azaindole

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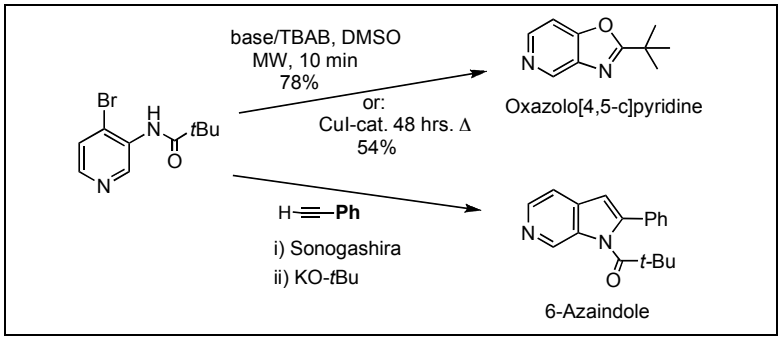

The preparation of oxazolo[4,5-*c*]pyridine and 6-azaindole from 4-bromo-3-pivaloylaminopyridine (**8**) is reported. The oxazolopyridine 2-*tert*-butyl-oxazolo[4,5-*c*]pyridine (**9**) was successfully prepared from **8** in 78% yield by a new base/TBAB promoted non-catalyzed microwave cyclisation strategy (10 min) or, alternatively, in 54% yield by conventional heating (48 hrs) and CuI catalysis. The 6-azaindole 2-phenyl-1-(trimethylacetyl)-6-azaindole (**13**) was prepared from **8** in a two step procedure, including a Sonogashira coupling reaction.

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INTRODUCTION

Pyridine-fused analogues of benzo-fused bis-heterocycles may in general offer some advantages from a medicinal chemistry point of view, since the pyridine fragment may provide better water solubility by offering an additional site for protonation or salt formation or it might enhance intermolecular interactions by formation of an additional hydrogen bond to target proteins. We have studied the transformation of a pyridine substrate into both oxazolopyridine and 6-azaindole, which are N-analogues of benzoxazole and indole, respectively (Figure 1).

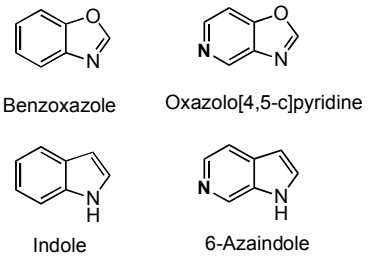


Figure 1. Structures of benzoxazole, indole and corresponding N-analogues.

Benzoxazoles are bis-heterocyclic compounds consisting of a benzene-fused oxazole ring skeleton. The ring system is found in a range of natural and biologically active compounds, see Figure 2.

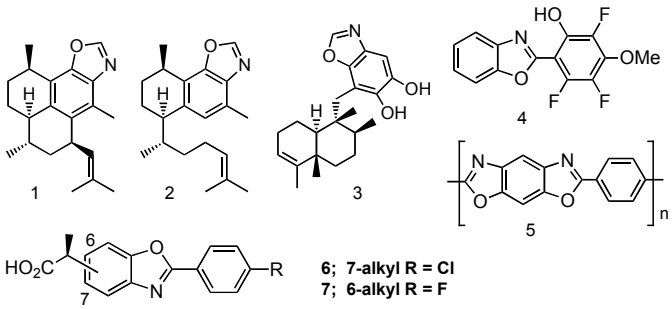


Figure 2. Benzoxazoles: biologically active natural products (**1-3**), material science compounds (**4,5**), benoxaprofen (**6**) and flunoxaprofen (**7**) pharmaceuticals.

The compounds pseudoteroxazole (**1**) and *seco*-pseudoteroxazole (**2**) can be isolated from the coral *Pseudopterogorgia elisabethae* and are active as inhibitors of *M. tuberculosis* growth [1]. Nakijinol (**3**) was isolated from a marine sponge in the Spongiidae family [2]. The benzoxazole **4** has been reported to act as a fluorescent probe for sensing magnesium cation [3], while the polymer marketed as Zylon$^{(R)}$ (**5**), a benzobisoxazole, shows excellent thermo-oxidative stabilities, mechanical tenacity and optoelectronic properties and has been used to make monolayer luminescense devices (Figure 2) [4]. The benzoxazoles benoxaprofen (**6**) and flunoxaprofen (**7**) are non-steroidal anti-inflammatory drugs (NSAIDs) [5]. Benoxaprofen (**6**) has been withdrawn from the U.S. and British markets due to increased fatality in elderly patients

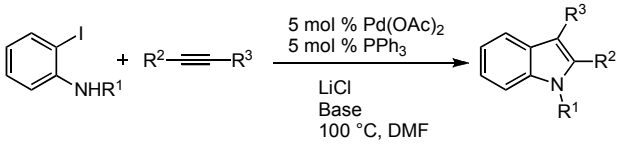
[6]. There has however, not been any reported fatal adverse effects of flunoxaprofen (**7**) [5].

While there are many examples of benzoxazoles in the literature, the occurrence of the N-analogues, the oxazolopyridines (see Figure 1) is far less common, even though they may be important supplements, which can be used for altering the properties of benzoxazoles.

The indoles constitute an important class of heterocycles. Since the indole structure is present in a wide number of naturally occurring and pharmaceutical compounds, the indole chemistry is one of the most active research fields in heterocyclic chemistry. The N-analogues azaindoles, also called pyrrolopyridines, are essential subunits in many pharmaceutically important compounds as well. The synthesis of azaindoles has been a great synthetic challenge for chemists [7]. Many classical methods for indole synthesis can often not effectively be applied to the synthesis of the corresponding azaindoles (Figure 1). In recent years, advances in organometallic chemistry have enabled a number of novel and efficient methodologies for azaindole formation.

The Larock heteroannulation represents a simple approach to indoles, involving the palladium catalysed heteroannulation of alkynes using *o*-iodoaniline derivatives, as shown in Scheme 1 [8]. The reaction is highly regioselective when unsymmetrical alkynes are used. The most sterically bulky group is attached next to the nitrogen atom in the indole product. The reaction is also tolerant with regards to the aniline moiety, which can be both unsubstituted and substituted. The method is, however, reported to be successful only with iodoanilines, while bromoanilines were in general unreactive [8,9]. 3-Amino-4-iodopyridines have also been reported to undergo Larock heteroannulation [10].

Scheme 1



We wanted to explore the versatility of 4-bromo-3-pivaloylaminopyridine (**8**) as a key substrate for the formation of both pyridine-fused heterocycles; the oxazolopyridine 2-*tert*-butyl-oxazolo[4,5-*c*]pyridine (**9**) and 6-azaindoles, the 2-phenyl-1*H*-pyrrolo[2,3-*c*]pyridines (**11** or **13**). Product **9** would be synthesised by an intramolecular displacement of the bromine atom with the amide carbonyl oxygen to give cyclisation, and azaindoles **11**, respectively, by the one-step Larock heteroannulation reaction or, alternatively **13**, by the Sonogashira coupling reaction followed by cyclisation.

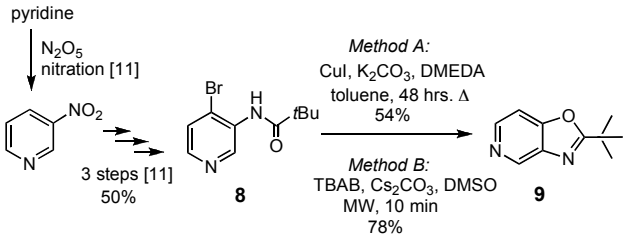
Based on the fact that a number of 3-nitropyridines have been readily available through an improved nitration method [11a,b], an investigation of the chemistry of nitropyridines is now in progress in our laboratories. 4-Bromo-3-pivaloylaminopyridine (**8**) is readily available from 3-nitropyridine in approximately 50% yield in a three step procedure [11c] (Scheme 2).

RESULTS AND DISCUSSION

Oxazolo[4,5-*c*]pyridine. The oxazolopyridine **9** was initially prepared according to a procedure developed for Cu-catalysed benzoxazole formation between primary amines and *o*-dihalobenzenes [12]. The bromoamide **8** [11] was refluxed in toluene under nitrogen atmosphere with K_2CO_3, catalytic amounts of CuI, and *N,N*-dimethylethylenediamine (DMEDA, Scheme 2, Method A). The Cu-catalysed C-O cross-coupling of the bromoamide **8** had taken place in 48 hours and 2-*tert*-butyl-oxazolo[4,5-*c*]pyridine (**9**) was isolated by chromatography in moderate yield (54%). The bis-heterocycle **9** may thus be prepared from pyridine in five steps.

However, we have experienced that microwave (MW) irradiation has been successful for a number of reactions [13,14]. A non-catalysed MW method, including modified reaction conditions, was therefore tested for the cyclisation of **8** in order to yield the bis-heterocycle **9** (Scheme 2, Method B). After 10 minutes MW irradiation (800 W) of a DMSO solution of bromopyridineamide **8**, Cs_2CO_3 and tetrabutylammonium bromide (TBAB), the desired cyclisation product **9** was isolated in 78% yield. Thus, Cu-catalysis was not required for this 4-bromopyridine substrate (**8**), since a general nucleophilic aromatic substitution had taken place. This base [15] and MW promoted cyclisation would be the method of choice for the preparation of oxazolo[4,5-*c*]pyridines, since high yields are obtained within few minutes. The results demonstrate the general fact that 4-bromopyridines may be displaced by good nucleophiles due to the electron-deficient character of the pyridine moiety and the stabilisation gained from the *para* pyridine N-atom. In addition, the presence of the TBAB ammonium ion would activate the substrate for 4-bromo-substitution. The results are also in accordance with the general experience that microwave-accelerated reactions often offer the great advantage of enhanced reaction rates and yields. The present method represents an alternative to a previously reported general oxazolopyridine preparation method [16], based on a two step synthesis including amide formation (50-80% yield) of 3-amino-4-hydroxypyridine and a carboxylic acid, followed by cyclodehydration (40-90%) by an intramolecular triphenylphosphine condensation. Our method avoids the difficult removal of triphenylphosphonium oxide.

Scheme 2



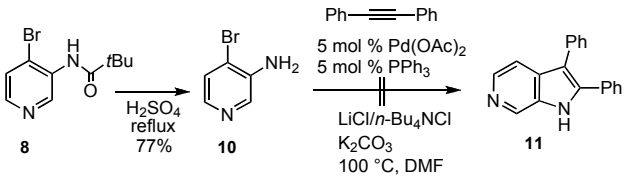
6-Azaindole. Acidic hydrolysis of bromoamide (**8**) [11] afforded 3-amino-4-bromopyridine (**10**) (77%, Scheme 3). Compound **10** may alternatively be prepared (76%) by KOH/MeOH hydrolysis of **8** [17]. Product **10** has previously been prepared by photolysis (15%) of 4-azidopyridine in HBr [18].

The Larock heteroannulation reaction has in general only been successful for iodoaniline [8,9] and 4-iodopyridine [10] substrates. Two different approaches to successfully replace the iodoaryl substrates with the much cheaper but less reactive 2-bromo or 2-chloroaryl compounds would be either to apply a more reactive and electron-rich Pd catalytic system or, alternatively, to use more reactive aryl halide substrates. Some activated catalytic systems have been developed for the Larock cyclisation [19] and represent the first approach; by the proper choice among a series of ligands, base, solvent and concentration, 2-bromo- and 2-chloroanilines were reactive in the Larock heteroannulation reaction to form indoles.

We wanted to study the second approach; whether the electron deficient character of the pyridine ring would make the bromoamine **10** reactive enough to prepare 2,3-diphenyl-6-azaindole (**11**) by the general Larock palladium catalyzed heteroannulation. This is based on our experience with 4-bromopyridines, which are sufficiently activated for other palladium catalyzed cross-coupling reactions and give high yields (85-90%) of a number of new coupling products [11].

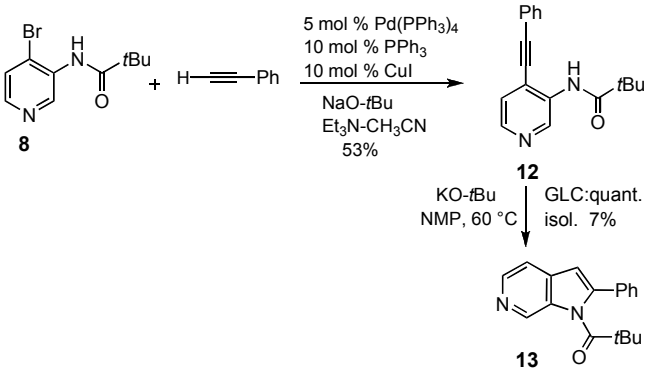
The bromoamine **10** was therefore reacted with diphenylacetylene with LiCl, K_2CO_3 and catalytic amounts of $Pd(OAc)_2/PPh_3$ in DMF at 100 °C (Scheme 3). No reaction had taken place after 20 hours. The 6-azaindole **11** was not observed and substrate **10** was recovered. Replacing LiCl with *n*-Bu_4NCl was not successful either. The general Larock heteroannulation reaction conditions were thus not successful for the electron-deficient bromopyridine **10**.

Scheme 3



Using an alternative step-wise strategy for the 6-azaindole preparation, the bromoamide **8** was reacted with phenylacetylene in a Sonogashira reaction (Scheme 4). Using $Pd(PPh_3)_4$, PPh_3 and CuI as catalysts and NaO*t*Bu as base, *N*-(4-(phenylethynyl)pyridin-3-yl)-2-dimethyl-propanamide (**12**) was isolated after chromatography in 53% yield. The new 6-azaindole, 2-phenyl-1-(trimethyl-acetyl)-6-azaindole (**13**), was prepared in 7% yield by heating compound **12** with KO*t*Bu in 1-methyl-2-pyrrol-idinone (NMP) at 60 °C for 24 hours [20].

Scheme 4



The low yield of compound **13** may be due to instability of the product. Full conversion and no traces of the substrate or by-products were observed after 24 hours of reaction time, as indicated both by TLC and GLC. However, the product seemed to decompose during work-up and chromatography. Special precautions and more gentle treatment of the 6-azaindole **13** would potentially afford higher yields.

In conclusion, two different cyclisation strategies have been used for the preparation of, respectively, the oxazolo[4,5-*c*]pyridine **9** and the 6-azaindole **13** from 4-bromo-3-pivaloylaminopyridine (**8**). The oxazolopyridine 2-*tert*-butyl-oxazolo[4,5-*c*]pyridine (**9**) was successfully prepared from **8** in 78% yield by a new base/TBAB promoted microwave cyclisation strategy or, alternatively, in 54% yield by conventional heating and CuI catalysis. The preparation of the 6-azaindole 2-phenyl-1-(trimethyl-acetyl)-6-azaindole (**13**) was not successful by the Larock heteroannulation method, but the 6-azaindole **13** was prepared from **8** by a two step procedure, including a Sonogashira coupling reaction. The bis-heterocycles **9** and **13** may thus be prepared from pyridine in five and six steps, respectively.

EXPERIMENTAL

Chemicals CuI, $Pd(PPh_3)_4$, KO-*t*Bu (Fluka), Cs_2CO_3, K_2CO_3, PPh_3, 25 %H_2SO_4 (Merck), *N*,*N*-dimethylethylenediamine (DMEDA), diphenylacetylene, *n*-Bu_4NBr (TBAB) (Aldrich),

LiCl (Kebo lab), $Pd(OAc)_2$ (Strem Chemicals); Solvents: *pro analysi* quality. ^1H/ ^{13}C nmr: Bruker Avance DPX 300 and 400 spectrometers, chemical shifts are reported in ppm downfield from TMS. *J* values are given in Hz. ms: Finnigan MAT 95 XL (EI/ 70 eV. ir: Nicolet 20SXC FT-IR spectrophotometer. Microwave irradiation was performed in a household microwave oven (Elram M8017NP-CF), modified with a reflux condenser, at 800 W output. Flash chromatography: Silica (sds, 60 Å, 40-63 μm). 4-Bromo-3-pivaloylaminopyridine (**8**) was prepared according to the literature [11]. All reactions were conducted under nitrogen atmosphere unless otherwise noted.

2-*tert*-Butyloxazolo[4,5-c]pyridine (9) [16]. The title product was preferentially prepared by Method B below:

Method A. CuI (8 mg, 0.04 mmol) and K_2CO_3 (110 mg, 0,78 mmol) was dissolved in toluene (13 ml) and heated to reflux (110 °C). Toluene (10 ml) was removed by distillation before a toluene (3 mL) solution of bromoamide (**8**) (100 mg, 0.39 mmol) and DMEDA (5 mg, 0.039 mmol) was added. The reaction was refluxed for 48 hours before the reaction was cooled to room temperature and the pH was adjusted to 11 with aqueous NH_3 (25%). After extraction, drying and concentration *in vacuo*, the crystalline product was obtained (37 mg, 54%) by flash chromatography (ethyl acetate/n-pentane 1:5), pure by ^1H nmr.

Method B. Bromopyridineamide (**8**, 50 mg, 0.195 mmol), TBAB (63 mg, 0.195 mmol, 1 equiv.), Cs_2CO_3 (254 mg, 0.78 mmol, 4 equiv.) were dissolved in DMSO (18 ml) and irradiated by MW (800 W) in 10 minutes. After addition of water (20 mL), extraction by CH_2Cl_2 (2x20 mL), drying and concentration *in vacuo*, the crystalline product was obtained (27 mg, 78%), pure by ^1H nmr; ^1H nmr (300 MHz, d_6-aceton): δ 1.51 (s, 9H, $C(CH_3)_3$, 7.47 (d, 1H, *J* 5.0, H-4), 8.54 (d, 1H, *J* 5.0, H-5), 9.02 (s, 1H, H-7); ^{13}C nmr (100 MHz, $CHCl_3$): δ 28.6 ($C(CH_3)_3$), 34.6 ($C(CH_3)_3$, 106.5 (pyr-C5), 139.3 (pyr-C3), 142.4 (pyr-C2), 145.2 (pyr-C6), 156.2 (pyr-C4), 174.6 (O-*C*(tBu)=N); HRMS: calcd for $C_{10}H_{12}N_2O$; 176.0950, observed 176,9042.

3-Amino-4-bromopyridine (10) [17,18]. The bromoamide (**8**) (1.5 g, 5.9 mmol) was dissolved in H_2SO_4 (25% aq, 100 ml) and heated to reflux (120 °C) for 3 hours before cooling to room temperature. The pH was adjusted to 11-12 with aqueous NH_3 (25%), extracted with diethyl ether and concentrated *in vacuo*. The crude product was purified by flash chromatography (4% NEt_3 in ethyl acetate/*n*-pentane 2:1,) yielding 800 mg (4.5 mmol, 77%) product, pure by ^1H and ^{13}C nmr; ^1H nmr (300 MHz, $CDCl_3$): δ 4.12 (br s, 2H, NH_2), 7.34 (d, 1H, *J* 5.1, H-5), 7.81 (d, 1H, *J* 5.1, H-6), 8.11 (s, 1H, H-2); ^{13}C nmr (100 MHz, $CHCl_3$): δ 117.9 (C-4), 127.4 (C-5), 137.4 (C-2), 139.6 (C-6), 141.5 (C-3); HRMS: calcd for $C_5H_5BrN_2$; 171.9636, observed 171.9639.

***N*-(4-(Phenylethynyl)pyridin-3-yl)-2,2-dimethylpropanamide (12).** Bromoamide (**8**) (1 g, 3.9 mmol), $Pd(PPh_3)_4$ (450 mg, 0.4 mmol), *n*-Bu_4NI (2.15 g, 5.8 mmol), CuI (200 mg, 1.2 mmol) and phenylacetylene (400 mg, 4.3 mmol) was dissolved in NEt_3-CH_3CN (25 mL, 1:5) and stirred at room temperature for 24 hours before filtering through celite and concentrating *in vacuo*. The crude product was isolated by flash chromatography (ethyl acetate/n-pentane 1:4) yielding 580 mg (2.07 mmol, 53%) product, pure by ^1H and ^{13}C nmr; ir: (KBr) 3403, 3048, 2953, 2868, 2359, 2215, 1689, 1550, 1512, 1492, 1422, 1302, 1153, 1025, 837, 756, 688 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 1.38 (s, 9H, $C(CH_3)$), 7.46 (m, 4H, H-5,3',4',5'), 7.55 (m, 2H, H-2',6'), 8.22 (d, *J* 5.2, 1H, H-6), 8.35 (s, 1H, H-2), 9.73 (br s, 1H, NH); ^{13}C nmr (100 MHz, $CHCl_3$): δ 27.7 ($C(CH_3)$), 40.1 ($C(CH_3)$), 82.1 (py-*C*≡C), 100.4 (py-C≡*C*), 119.6 (C-4), 121.2 (C-1'), 124.9 (C-5), 128.9 (C-3',5'), 129.9 (C-4'), 131.7 (C-2',6'), 133.1 (C-3), 141.6 (C-2), 144.1 (C-6), 176.5 (*C*=O). Partial ^{13}C nmr assignments are based on HSQC; ms: m/z 278 (M^+, 12%), 258 (11), 256 (11), 194 (11), 174 (24), 172 (25), 85 (34), 57 (100), 41 (44); HRMS: calcd for $C_{18}H_{18}N_2O$; 278.1419, observed 278.1416.

1-(2,2-Dimethyl-1-oxopropyl)-2-phenyl-6-azaindole (13). The amide (**12**) (160 mg, 0.58 mmol) and KO-*t*Bu (80 mg, 0.7 mmol) were stirred in NMP (1-methyl-2-pyrrolidinone, 8 ml) for 24 hours at 60 °C. The reaction mixture was added an aqueous NH_4Cl solution (sat.), extracted with diethyl ether, dried and concentrated *in vacuo*. The product was obtained by flash chromatography (ethyl acetate/*n*-pentane 1:10) in 7% yield (11 mg, 0.036 mmol). The product was pure by ^1H nmr; ir (KBr) 2967, 2925, 2854, 2360, 2342, 1649, 1629, 1416, 1217, 1123, 691 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 1.33 (s, 9H, $C(CH_3)$), 6.58 (s, 1H, H-3), 6.85 (d, *J* 5.2, 1H, H-4), 7.38 (m, 5H, Ph), 8.10 (d, *J* 5.1, 1H, H-5), 8.39 (s, 1H, H-7); ms: m/z 278 (M^+, 6%), 263 (34), 235 (14), 223 (13), 222 (40), 221 (59), 195 (23), 194 (100), 193 (86), 192 (10), 167 (17), 166 (12), 139 (10); HRMS: calcd for $C_{18}H_{18}N_2O$; 278.1419, observed 278.1415.

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