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The first enantioselective synthesis of 4-acetyl-3(*R*)- and 3(*S*)-(hydroxymethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]oxazine

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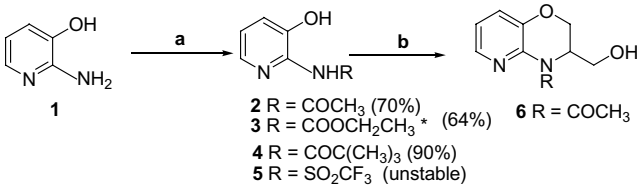
Abstract—A novel short and enantioselective synthetic approach to pyridobenzoxazines is reported in which (*R*)- and (*S*)-3-(hydroxymethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*][1,4]oxazine were first synthesized from readily available chiral glycidyl derivatives.

The 2,3-dihydro-1,4-benzodioxine system has been widely used as a substructure of several biologically interesting agents.[1] Bioisosteric replacement of the one oxygen atom by nitrogen leads to the 1,4-benzoxazines,[2] whereas the replacement of benzene by pyridine produces one of the most characteristic groups required by medicinal chemists today (1,4-dioxinopyridines).[3]

Given that nitrogen heterocycles are frequently found in bioactive structures such as a pharmacophores, we report the preparation and determination of the absolute configuration of pyrido[1,4]oxazines (Scheme 1).

The preparation of pyrido-oxazines was more difficult than expected. In contrast to 2,3-dihydro-1,4-benzodioxines and 2,3-dihydro-1,4-benzoxazines, which can be readily prepared by alkylation of the catechol or the 2-aminophenol with the ethyl 2,3-dibromopropionate or 2-chloroacrylonitrile, no similar procedures gave the desired compounds directly from the commercially available 3-hydroxy-2-aminopyridine. For these reasons we considered modifying our former synthetic approach in order to devise a new and reliable method for the preparation of pyrido-oxazines substituted on the oxazine moiety. After considering several possible synthetic pathways, we prepared a conveniently protected 3-hydroxy-2-aminopyridine as previous attempts without N-protection did not give the expected pyrido-oxazine due to the reactivity of the 3-amino group.[4] Thus the acyl derivatives (**2**–**4**) were obtained under the usual conditions (RCOCl, Et_3N, CH_2Cl_2 at room temperature) from 3-hydroxy-2-aminopyridine **1**, whereas the treatment of **1** with trifluoromethanesulfonic anhydride in basic media led to the expected sulfonamide **5**, which was unstable for the following synthetic process.



Scheme 1. Reagents and conditions: (a) $CH_3COCl/Et_3N/CH_2Cl_2$ or $CH_3CH_2OCOCl/Et_3N/CH_2Cl_2$ or $(CH_3)_3CCOCl$ or $(CF_3SO_2)_2O/Et_3N/CH_2Cl_2$ all at rt; (b) epichlorohydrin, K_2CO_3, DMF, 60 °C or glycidyl tosylate, K_2CO_3, DMF or acetonitrile, 60 °C. *Using CH_3CH_2OCOCl the carbamate **3** was obtained (64% yield) together with the carbonate (16% yield).

The amino group of **1** was expected to be more nucleophilic than the hydroxyl group and this was confirmed by treatment with acetyl chloride (2 equiv) in basic media in dichloromethane at room temperature. After 1 h, the acetamide **2** was obtained as a single isomer. Under these reaction conditions the addition of trimethylacetyl chloride to **1** afforded the amide **4**

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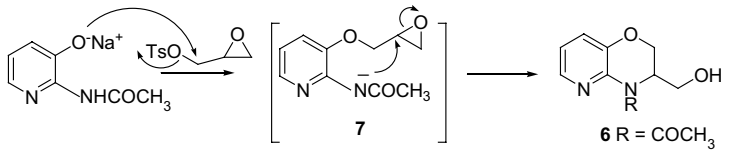
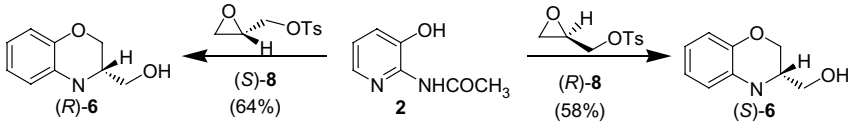


Scheme 2.



Scheme 3.

regioselectively in 90% yield, whereas the addition of ethyl chloroformate gave the carbamate as the main product, and traces of the carbonate (due to reaction with the hydroxyl group on C-3) were also obtained.

Its stability and easy preparation turned our attention to the use of acetyl as a protecting group. In our first route to the pyrido-oxazine bicyclic system, epichlorohydrin was used in basic media in acetonitrile or DMF affording the alcohol **6** albeit in very low yield (18%), accompanied by degradation products. Replacement of epichlorohydrin by glycidyl tosylate proved to be effective, and the racemic alcohol **6** was obtained in good yield (75%) in a one-pot procedure. Treatment of **2** with glycidyl tosylate in DMF or acetonitrile resulted in selective displacement of the tosylate moiety[5,6] by the corresponding sodium aryloxide formed in situ giving the intermediate **7** (Scheme 2).

Next, epoxide opening was effected by the acetamide nitrogen at the more hindered position giving the pyrido-oxazine by ring closure. This reaction was extremely rapid and, so it was difficult to study the postulate intermediate **7**. Under these conditions only the isomer substituted at the C-3 was obtained. The structure of the alcohol **6** was confirmed by ^{13}C NMR data, which showed the presence of two CH_2–O– signals at 65.0 and 63.7 ppm, and a CH–N signal at 48.7 ppm (assigned to C-3) confirming the formation of only one regioisomer. This result shows the effect of the N-protector group; thus upon basic treatment **1** gave the sodium aryloxide, which reacted with the glycidyl tosylate before the acetamido group.

The stereochemical outcome can be rationalized by considering the preferential mechanism described for a similar condensation[7] (catechol, K_2CO_3, DMF, 60 °C), and the analytical results.

Similarly, for the enantioselective synthesis of pyrido-oxazines, commercially available chiral glycidyl tosylates (*R*)- and (*S*)- were used as starting materials. Condensation of (*S*)-glycidyl tosylate [α_D^{25} +17 (*c* 0.1, $CHCl_3$)] and 3-hydroxy-2-aminopyridine afforded the 4-acetyl-3(*R*)-(hydroxymethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]oxazine. Column chromatography of the crude reaction mixture (silica gel, ethyl acetate, hexane) afforded (*R*)-**6** in high optical purity [α_D^{25} +38 (*c* 8, $CHCl_3$)]. 4-Acetyl-3(*S*)-(hydroxymethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]oxazine ((*S*)-**6**) [α_D^{25} −36 (*c* 3, $CHCl_3$)] was easily accessible by condensation of the (*R*)-tosylate [α_D^{25} −17 (*c* 0.7, $CHCl_3$)] with 3-hydroxy-2-aminopyridine (Scheme 3).

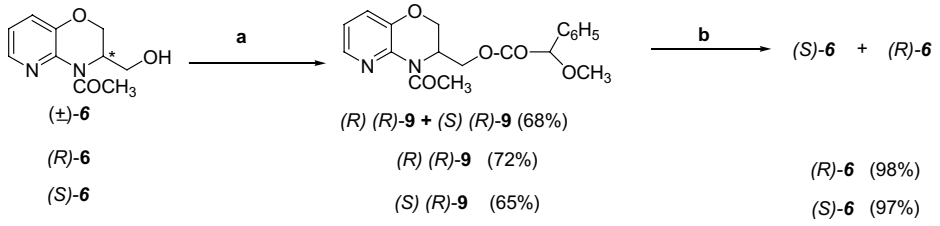
Detailed investigations of the selectivity of the glycidyl tosylate reaction with other sodium aryloxides have been reported previously.[5–10]

Developments in methods for the determination of enantiomeric excess have been reviewed by Mislow and Raban.[11] The use of MPA [(*S*)-2-methoxyphenylacetic acid] as a resolving agent, for the determination of enantiomeric composition, and as a reagent for establishing absolute configuration of stereogenic centres has been explored.[12,13] This reagent can react *via* its acid chloride[14] with chiral alcohols to give mixtures of diastereomeric esters whose NMR spectra can be used for quantitative analysis of the enantiomeric composition of the chiral alcohol from which it was made. In this case, we had two diastereomers with a fixed (*S*)-configuration at the acid moiety but with unknown (*R*)- or (*S*)-configurations at the stereogenic centre of the pyrido-oxazine framework.

The optical purities of pyrido-oxazines were confirmed by ^1H and ^{13}C NMR spectroscopy of the diastereomeric MPA esters (Scheme 4). An enantiomeric excess (ee) of the least 99% was found for both enantiomers (*S*)-**6** and (*R*)-**6**, thus no peaks in the spectra assignable to the opposite enantiomer were observed, whereas the NMR spectrum of a mixture of diastereomers showed doubling of the signals (^1H and ^{13}C). The chemical shifts of the differences between diastereotopic protons were between 0.12 and 0.40 ppm. The purity of each enantiomer was confirmed by HPLC analysis and was determined to be around 99.5%.

Finally, these esters were hydrolyzed in quantitative yields to the corresponding (*S*)-**6** and (*R*)-**6** alcohols by treatment with 1 N NaOH (stirring at rt).

In conclusion, the first enantioselective synthesis approach to two chiral pyrido[1,4]oxazines was accomplished starting from the (*R*)- and (*S*)-glycidyl tosylate



Scheme 4. Reagents and conditions: (a) (*S*)-(+)-2-methoxyphenylacetic chloride; (b) 1 N NaOH rt. For the diastereomeric mixture: (1) separation of diastereomers by column chromatography; (2) 1 N NaOH rt.

and 3-hydroxy-2-acetamidopyridine in one step. Racemization of the products was not observed under any of the reaction conditions. The compounds were obtained with high enantiomeric purities (99% ee). These intermediates, (*R*)- and (*S*)-**6**, may find application in the preparation of serotonin analogues and related compounds.

*Synthesis of 4-acetyl-3-(hydroxymethyl)-3,4-dihydro-2H-pyrido[3,2-*b*]oxazine*. To a suspension of K_2CO_3 (363 mg, 2.63 mmol) in acetonitrile (20 mL) was added 3-acetamido-2-hydroxypyridine (100 mg, 0.66 mmol) and glycidyl tosylate (149 mg, 0.72 mmol). The resulting mixture was stirred at reflux for 24 h. The solvent was evaporated, the residue was suspended in cold water (20 mL) and the aqueous solution was extracted with CH_2Cl_2 (3×15 mL). The combined organic phases were washed with 0.5% $NaHCO_3$, dried (Na_2SO_4) and concentrated to provide crude alcohol. The residue was purified by column chromatography on silica gel eluting with mixtures of ethyl acetate/hexane.

The yields reported correspond to analytically pure isolated compounds. All compounds were characterized by ^1H, ^{13}C NMR and elemental analyses.[15]

Acknowledgements

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15. Analytical data of more representative compounds: 2-acetamido-3-hydroxypyridine (**2**). Mp 98–100 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 3214, 3014, 1661, 1454, 1228, 1114; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.30 (s, 3H, CH_3), 7.15 (dd, $J=3$, $J=5$ Hz, 1H, H-5), 7.40 (dd, $J=1$, $J=5$ Hz, 1H, H-4), 7.87 (dd, $J=1$, $J=3$ Hz, 1H, H-6), 10.98 (s, 2H, OH, NH); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 23.3 (CH_3), 122.7 (CH, C-5), 128.5 (CH, C-4), 138.0 (CH, C-6), 140.6 (C, C-3), 145.3 (C, C-2), 172.0 (C, CO). Anal. Calcd for $C_7H_8N_2O_2$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.58; H, 5.74; N, 18.12.
4-Acetyl-3-(α-methoxyphenylacetoxy)-3,4-dihydro-2*H*-pyrido[3,2-*b*]oxazine (diastereomeric mixture, the esters correspond to the *SS* and *RS* isomers) (**9**). Colourless oil. IR (NaCl) ν (cm^{-1}): 1676, 1452, 1267, 1210; ^1H NMR ($CDCl_3$, 200 MHz) δ (ppm): 1.92 [s, 3H, CH_3 (*SS*)], 2.04 [s, 3H, CH_3 (*RS*)], 3.26 [s, 3H, CH_3 (*SS*)], 3.51 [s, 3H, CH_3 (*RS*)], 3.55 [d, $J=2.8$ Hz, 1H, H-3 (*RS*)], 3.60 [d, $J=2.8$ Hz, 1H, H-3 (*SS*)], 4.12 (m, 2H, CH_2–), 4.27 [dd,

$J = 1.4$, $J = 11.6$ Hz, 1H, H-2, (*RS*)], 4.30 [dd, $J = 1.4$, $J = 11.6$ Hz, 1H, CH_2 (*SS*)], 5.18 [t, $J = 5.8$ Hz, 1H, H-2 (*RS*)], 5.40 [t, $J = 5.8$ Hz, 1H, H-2 (*SS*)], 6.23 [s, 1H, CH (*SS*)], 6.63 [s, 1H, CH (*RS*)], 7.15 (m, 5H, Ar), 7.34 (m, 1H, H-7), 7.65 (dd, $J = 1.4$, $J = 8.2$ Hz, 1H, H-8), 7.98 [dd, $J = 1.4$, $J = 4.4$ Hz, 1H, H-6 (*SS*)], 8.04 [dd, $J = 1.4$, $J = 4.4$ Hz, 1H, H-6 (*RS*)]; ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 20.6 [CH_3 (*SS*)], 20.7 [CH_3 (*RS*)], 46.7 [CH, C-3 (*SS*)], 47.1 [CH, C-3 (*RS*)], 57.0 [CH_3 (*SS*)], 57.4 [CH_3 (*RS*)], 60.6 [CH_2, C-2 (*SS*)], 60.7 [CH_2, C-2 (*RS*)], 64.9 [CH_2 (*RS*)], 65.3 [CH_2 (*SS*)], 82.37 [CH, CH–O (*RS*)], 82.41 [CH, CH–O (*SS*)], 121.0 [CH, C-7 (*SS*)], 121.4 [CH, C-7 (*RS*)], 124.7 (CH, C-8), 127.6 [CH, C-2′ and C-6′ (*SS*)], 128.0 [CH, C-2′ and C-6′ (*RS*)], 128.2 [CH, C-4′ (*SS*)], 128.4 [CH, C-4′ (*RS*)], 128.7 [CH, C-3′ and C-5′ (*SS*)], 136.3 [C, C-1′ (*RS*)], 136.9 [CH, C-1′ (*SS*)], 139.3 [C, C-4a (*SS*)], 139.5 [C, C-4a (*RS*)], 140.3 [C, C-8a (*SS*)], 140.5 [C, C-8a (*RS*)], 170.37 [C, CO (*SS*)], 170.41 [C, CO (*RS*)], 170.5 [C, CO (*RS*)], 171.2 [C, CO (*SS*)]. After comparison of the NMR spectra of the enantiomeric esters with the NMR of diastereomeric mixture the enantiomeric purity of the (*RS*) and (*SS*) isomers was established as >99%. Anal. Calcd for $C_{19}H_{20}N_2O_5$ (diastereomeric mixture): C, 64.04; H, 5.66; N, 7.86. Found: C, 64.45; H, 5.45; N, 7.63.

4-Acetyl-3-(hydroxymethyl)-3,4-dihydro-2*H*-pyrido[3,2-*b*]oxazine (**6**). Mp 81–83 °C (hexane/ethyl acetate). IR (KBr) ν (cm^{-1}): 3211, 1734, 1252; ^{1}H NMR ($CDCl_3$, 200 MHz) δ (ppm): 2.09 (s, 3H, CH_3), 3.91 (m, 1H, H-3), 4.16 (m, 4H, CH_2–O), 5.61 (br s, 1H, OH), 6.58 (ddd, $J = 1$, $J = 5$, $J = 7.6$ Hz, 1H, H-7), 7.00 (dd, $J = 1$, $J = 7.6$ Hz, 1H, H-8), 7.65 (dd, $J = 1$, $J = 5$ Hz, 1H, H-6); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ (ppm): 20.8 (CH_3), 48.7 (CH, C-3), 63.7 (CH_2, CH_2–O), 65.0 (CH_2, CH_2–O), 114.1 (CH, C-7), 122.2 (CH, C-8), 138.8 (C, C-4a), 140.3 (CH, C-6), 146.3 (C, C-8a), 170.6 (C, C=O).

The NMR spectrum of the pure (*S*)-**6** enantiomer was identical with the NMR spectrum of the (*R*)-**6** enantiomer. Anal. calcd for $C_{10}H_{12}N_2O_3$ (*R*)-**6** enantiomer: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.98; H, 5.56; N, 13.09. Anal. calcd for $C_{10}H_{12}N_2O_3$ (*S*)-**6** enantiomer: C, 57.68; H, 5.81; N, 13.45. Found: C, 57.34; H, 5.66; N, 13.32.