2-Aminopyridine Derivatives as Potential Chiral Auxiliaries

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2-Bromopyridine and 2-bromo-6-methoxymethylpyridine reacted with an excess of 1-phenylethylamine at reflux giving the aminopyridine derivatives **3a** and **3b** respectively.

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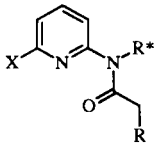
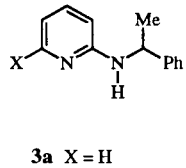
Pyridine derivatives **1** in which the group R* is a chiral substituent could undergo asymmetric alkylation reactions at the amide moiety and the resulting alkylated products could, for example, act as precursors to other chiral molecules such as carboxylic acids. Thus, deprotonation of amides **1** by the action of a strong base such as lithium diisopropylamide would be expected to give enolates **2** in which rotation about the N-C bond would be precluded because of coordination of the lithium atom to the pyridine nitrogen atom. When the group X = methoxymethyl there will be additional coordination of the methoxymethyl oxygen atom to the lithium atom in enolate **2**. These coordination effects might be expected to assist in the asymmetic alkylation of enolates such as **2**. We therefore set out to prepare pyridines **3a** and **3b** as precursors to amides **1** and hence enolates **2**.



1 X = H or CH_2OMe

2



3a X = H
3b X = CH_2OMe

Racemic *N*-(1-phenylethyl)-2-aminopyridine **3a** has been prepared previously from *N*-benzylidene-2-aminopyridine and methylmagnesium iodide in 75% yield [1]. (*R*)-*N*-(1-phenylethyl)-2-aminopyridine **3a** has also been synthesized under forcing conditions from (*R*)-1-phenylethylamine and 2-fluoropyridine in a sealed tube at 140° for 2-4 days [2]. No yield was reported for this reaction. We required a simple procedure for synthesizing **3a** and related compounds and therefore investigated the reaction of 2-bromopyridine with an excess of boiling racemic 1-phenylethylamine. Both (*R*) and (*S*)-1-phenylethylamine are commercially available and therefore both enantiomers of heterocycle **3a** and other related heterocycles would be amenable to synthesis using this methodology. This reaction gave, after removal of the excess amine by vacuum distillation and recrystallization of the residue, a 29% yield of racemic compound **3a**. Similarly, heating a mixture of 1-phenylethylamine and 2-bromo-6-methoxymethylpyridine [3] gave racemic heterocycle **3b** (58% yield) after column chromatography. Heterocycles **3a** and **3b** are therefore available under relatively mild reaction conditions from readily available starting materials.

EXPERIMENTAL

Proton nmr spectra were recorded at 90 MHz in deuteriochloroform solution.

N-(1-Phenylethyl)-2-aminopyridine **3a**.

A mixture of 1-phenylethylamine (30.0 g) and 2-bromopyridine (5.0 g) were heated at reflux for 6 hours under a nitrogen atmosphere. The reaction mixture was allowed to cool to room temperature and poured into saturated potassium hydrogen carbonate solution (50 ml). The mixture was then extracted with dichloromethane (4 x 20 ml) and the combined organic extracts were dried (magnesium sulfate) and evaporated. The unreacted 1-phenylethylamine was removed by distillation under reduced pressure. The residue was recrystallized from aqueous ethanol giving compound **3a**, 1.38 g (29%), mp 93°, lit mp 91-92° [1].

N-(1-Phenylethyl)-2-amino-6-methoxymethylpyridine **3b**.

Compound **3b**, 3.36 g (58%) was obtained as an oil from 1-phenylethylamine (22.5 g) and 2-bromo-6-methoxymethylpyridine (4.80 g) [3] by a similar procedure to that described above. After distillation of the excess 1-phenylethylamine, the residue was purified by column chromatography over silica gel (eluent, petroleum ether:ethyl acetate, 2:1). A small quantity (0.39 g) of an unknown compound was eluted before compound **3b**. Compound **3b** had; ^1H nmr: δ 7.25 (6H, m, ArH), 6.60 (1H, d, J = 9 Hz, ArH), 6.05 (1H, d, J = 9 Hz, ArH), 5.00 (1H, broad s, >NH), 4.60 (1H, q, J = 6.5 Hz, >CH-), 4.36 (2H, s, $-CH_2-$), 3.45 (3H, s, -OMe) and 1.50 (3H, d, J = 6.5 Hz, C-Me) ppm.

Compound **3b** gave a picrate, mp 153-154°.

Anal. Calcd. for $C_{21}H_{21}N_5O_8$: C, 53.5; H, 4.5; N, 14.9. Found: C, 53.55; H, 4.55; N, 14.75.

Acknowledgements.

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