A General Synthesis of 2-Alkyl(aryl)-4-morpholinopyridines

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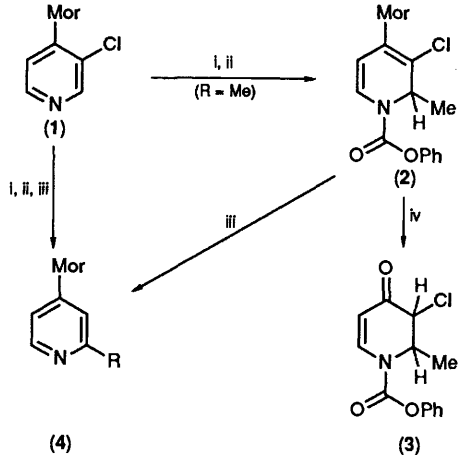
The addition of Grignard reagents to an *N*-acylated 3-chloro-4-morpholinopyridine followed by treatment with potassium t-butoxide provides a general route to 2-alkyl(aryl)-4-morpholinopyridines

During an investigation into alternative synthetic routes of commercial potential for the H^+/K^+ ATP'ase inhibitor 2-(3-chloro-4-morpholino-2-pyridylmethylsulphinyl)-5-methoxy-1*H*-benzimidazole (SK&F 95601),[1] we examined the addition of Grignard reagents to 3-chloro-4-morpholinopyridine in the presence of acylating agents. Whilst such additions have been reported for a number of different classes of pyridines in recent years,[2] there is no report of the addition of a Grignard reagent to an *N*-acylated-4-dialkylaminopyridine. Indeed, attempts to carry out such chemistry on 4-dimethylaminopyridine were unsuccessful.[3] Comins *et al.* have reported the addition of a Grignard reagent to 3-chloropyridine in the presence of phenyl chloroformate and cuprous iodide. Substitution occurred at the 4-position.[4]

We now report that reaction of 3-chloro-4-morpholinopyridine (**1**) with a Grignard reagent and phenyl chloroformate, followed by treatment of the product with potassium t-butoxide in t-butyl alcohol, provides the corresponding 2-alkyl(aryl)-substituted 4-morpholinopyridine (**4**) in good yield.

Our initial studies used methylmagnesium chloride, which we found added regioselectively to the pyridine (**1**) at the 2-position. Although purification of the intermediate enamine (**2**) was not possible because of its instability to chromatography on silica or alumina, acid hydrolysis of the intermediate gave the corresponding 3-chloro-2-methyl-1,2-dihydro-4(3*H*)-pyridone (**3**) in 70% yield as a 5:1 mixture of diastereoisomers, clearly demonstrating the regioselectivity of the addition. None of the regioisomer arising from attack at the 6-position could be isolated, nor could any evidence for its presence be found in the crude reaction mixture before or after hydrolysis.

If, instead of hydrolysing the intermediate enamine (**2**), the crude product is treated with potassium t-butoxide in t-butyl alcohol, a deacylation/dechlorination pathway is followed, which results in formation of 2-methyl-4-morpholinopyridine (**4**; R = Me) in 65% yield. We have now repeated this reaction sequence using a number of Grignard reagents, and the yields of the corresponding 4-morpholinopyridines are shown in the Table.



Scheme. *Reagents and conditions:* i, PhOCOCl/THF, −78 °C; ii, RMgX, −78 °C to r.t.; iii, Bu^{t}OK/Bu^{t}OH, reflux; iv, H^+/H_2O.

Table.

RMgX, R =	% Yield of 4-morpholinopyridine (**4**)
Me	55
Bu	86
Bu^t	26
Ph	61
Cyclohexyl	70

These results represent the first examples of the addition of Grignard reagents to *N*-acylated dialkylaminopyridines. Furthermore, we believe that this reaction sequence offers a simple route to the previously unreported 2-alkyl(aryl)-4-morpholinopyridines, and anticipate that this chemistry will

apply equally well to other dialkylaminopyridines. Work to examine this, and other aspects of this chemistry, is in progress and will be reported in due course.

Experimental

Representative Procedure: for 2-Methyl-4-morpholinopyridine.—To a stirred solution of 3-chloro-4-morpholinopyridine (500 mg, 2.52 mmol) in dry tetrahydrofuran (20 ml) at −78 °C under nitrogen was added phenyl chloroformate (0.32 ml, 2.60 mmol), and the resultant suspension was stirred at −78 °C for 30 min. Methylmagnesium chloride (3.0M) in tetrahydrofuran (0.93 ml, 2.78 mmol) was added over a period of 5 min during which time the suspension dissolved. After being stirred at −78 °C for 10 min, the mixture was allowed to warm to room temperature and then stirred for a further 10 min. Aqueous ammonium chloride was added, and the mixture was extracted with diethyl ether, washed with water, dried, and filtered. The solvent was removed by evaporation under reduced pressure to give the crude dihydropyridine (810 mg). The dihydropyridine was dissolved in t-butyl alcohol (25 ml) and potassium t-butoxide (820 mg, 7.25 mmol) was added. The stirred mixture was heated to reflux for 3 h, and the solvent was removed under reduced pressure. The residue was partitioned between 1M hydrochloric acid and dichloromethane. The organic layer was extracted with 1M hydrochloric acid, the combined aqueous layers were basified to pH 11.0 and extracted with dichloromethane. The combined organic extracts were dried, filtered, and the solvent was removed by evaporation under reduced pressure. The residue was purified by flash chromatography on silica using dichloromethane–methanol, 9:1 (v/v) as eluant to give 2-methyl-4-morpholinopyridine as a pale yellow oil (295 mg, 65%); δ_H(270 MHz; $CDCl_3$; standard Me_4Si) 2.48 (3 H, s, Me), 3.29 [4 H, m, $O(CH_2CH_2)_2N$], 3.84 [4 H, m, $O(CH_2CH_2)_2N$], 6.55 (1 H, d, *J* 6.5 Hz, 5-H), 6.57 (1 H, s, 3-H), 8.18 (1 H, d, *J* 6.5 Hz, 6-H); *m/z* 178 (M^+, 85%) and 120 (100%) *m/z* (HRMS) 178.1109 (Calc. for $C_{10}H_{14}N_2O$: 178.1106).

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