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Synthesis of substituted 4-pyridones and 4-aminopyridinium salts via a one-pot pyridine synthesis

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ABSTRACT

Synthesis of substituted 4-benzyloxypyridinium salts by the addition of Grignard reagents to pyridine *N*-oxides provides an efficient route for obtaining substituted 4-pyridones or 4-aminopyridinium salts.

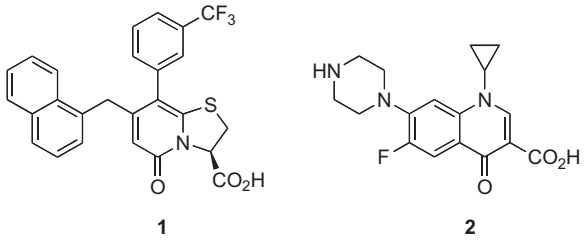
Six-membered nitrogen-containing heterocyclic compounds are known to be prominent in medicinal chemistry (e.g., pyridines,[1–6] piperidines,[7–9] and piperazines[10–13]) and this has encouraged researchers to develop new and efficient synthetic protocols to such moieties. Other privileged heterocyclic structures are 2- and 4-pyridones, which are typically found in different antibacterial agents such as pilicides, curlicides **1**, and ciprofloxacin (**2**)[14–19] (Fig. 1). In addition, the corresponding 4-aminopyridinium salts have been shown to be important in a variety of biological processes.[20–23] Although there are a number of synthetic methods to prepare 4-pyridones, that is, cyclization of triketones with ammonia or an amine,[24,25] or the reaction of amines with diketenes,[26,27] there is still a need for improvements, and in particular, an efficient methodology amenable for parallel synthesis of substituted 4-pyridones is desirable. The synthesis of 4-aminopyridinium salts has only been scarcely reported, and to the best of our knowledge the only reported method involves nucleophilic substitution between amines and 4-halopyridines.[28]

Comins et al. reported the formation of 2,3-dihydro-4-pyridones by the addition of Grignard reagents to acyl-activated pyridinium salts,[29] a procedure that was later used to synthesize 2,3-disubstituted 4-pyridones by Kitagawa et al. in their efforts to find an enoyl-ACP reductase FabI inhibitor.[15,16] Inspired by these reports, the synthesis of 2-substituted 4-pyridones from 4-benzyloxy pyridine *N*-oxide starting with our recently developed methodology for the regioselective synthesis of 2-substituted pyridines seemed possible.[4,5] However, to make the procedure amenable to parallel synthesis the current method requiring a two-step protocol involving a liquid–liquid extractive work-up needs to be improved. Hence, by using a solid-supported ion exchanger for the purification of the intermediate pyridine a more practical one-pot procedure would be possible. Here we report an efficient synthesis of substituted 4-pyridones in which simply adding an amine during the benzyloxy cleavage step made possible the synthesis of substituted 4-aminopyridinium salts.

Recently Dudley and co-worker reported an interesting synthesis of 2-benzyloxy-1-methylpyridinium triflate from the corresponding pyridine using methyl triflate as the *N*-alkylating agent.[30] The triflate salt was then used in combination with an appropriate base as a benzylating reagent for alcohols. Hence, combining this method with our one-pot pyridine synthesis resulted in an attractive alternative for the synthesis of substituted 4-pyridones **6** (Table 1).

In addition, by exchanging the nucleophile from hydroxide to ammonia in the microwave-assisted debenzylation reaction, the corresponding substituted 4-aminopyridinium salts **7** could be obtained.

By varying the Grignard reagent in the first reaction and by using two different debenzylation reactions, a small set of 2-substituted 4-pyridones **6** and 4-aminopyridinium salts **7** was prepared.



1 2

Figure 1. Examples of two biologically active 2- and 4-pyridones, the antibacterial curlicide **1**, and the antibiotic ciprofloxacin (**2**), respectively.

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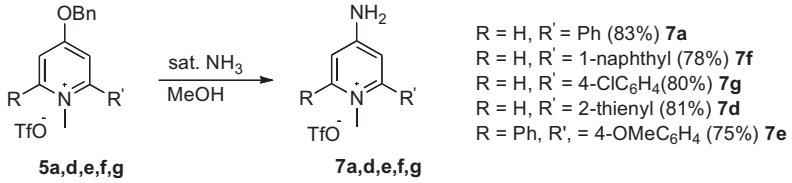
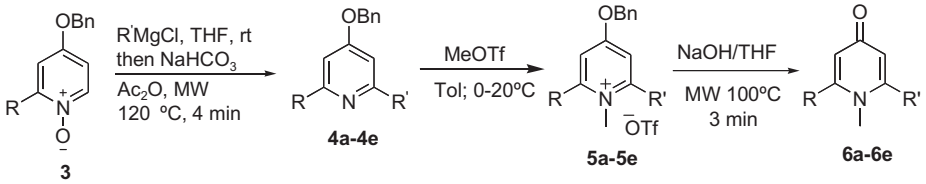


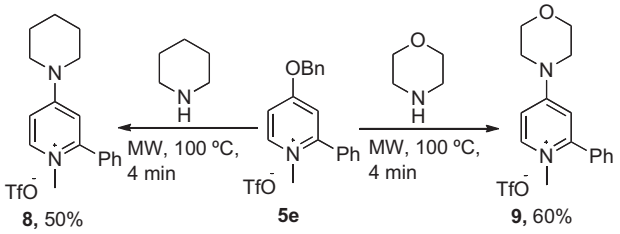
Scheme 1. Synthesis of 4-aminopyridinium salts.[32]

Table 1
Synthesis of 4-pyridones[31]



Entry	R	R′	Yield (%) **4**	Yield[a] (%) **6**
1	H	Ph	69	81
2	H	4-Cl-C_6H_4	73	74
3	H	*N*-Me-indole	72	79
4	H	2-thienyl	69	82
5	Ph	4-OMe-C_6H_4	76	70

Reaction conditions: pyridine *N*-oxide (1 equiv) in THF, Grignard reagent (1.2 equiv) at rt, pH 6–8, Ac_2O (10 equiv), 4 min at 120 °C.
[a] Isolated yield.



Scheme 2.

The 2-substituted pyridines **4** were purified simply by a catch and release protocol using a solid-supported ion exchange resin and they were used without further purification in the remaining steps. These included *N*-methylation with methyl triflate to give the activated pyridinium salts **5** followed by a microwave-assisted debenzylation. The target compounds **6** and **7** were obtained in good overall yields (Table 1 and Scheme 1).

Although 4-aminopyridinium salts **7** are easily accessible via this new method, more diverse 4-aminopyridinium salts would be obtained if amines other than ammonia could be used in the debenzylation step. Indeed, by using either piperidine or morpholine, 4-aminopyridiniums **8** and **9** were synthesized in 50% and 60% yields, respectively (Scheme 2).

In summary, we have developed a practical method for the synthesis of a diverse set of substituted 4-pyridones as well as 4-aminopyridinium salts. Deprotection of the methyl pyridinium triflates using NaOH in THF at room temperature generated substituted 4-pyridones. Moreover, by exchanging NaOH for ammonia, or other amines, followed by microwave heating, resulted in substituted 4-aminopyridinium salts. In addition, a new one-pot synthesis of substituted pyridines was developed, which together with the deprotection strategy described above, constitutes a platform for library synthesis of substituted 4-pyridones and 4-aminopyridinium salts.

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31. *General procedure for the synthesis of 4-pyridones* **6a–e**, *exemplified with* **6a**. To pyridine **4a** (0.18 g, 0.69 mmol) cooled in an ice-bath was added MeOTf (0.12 g, 0.76 mmol) dropwise. The resulting solution was allowed to warm to rt and monitored by TLC (heptane/EtOAc 1:1, the reaction was complete in 30 min in all cases) and upon completion the reaction mixture was concentrated. The residue was dissolved in THF (5 mL) and 2 M aqueous NaOH (0.08 g, 2.07 mmol) was added. The mixture was stirred at rt and monitored by TLC (CH_2Cl_2/MeOH 9:1, the reaction was complete in 1.5 h in all cases). The mixture turned red when the reaction was complete. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with 2 M aqueous NaOH and brine (3×5 mL). The aqueous layer was extracted until no longer UV-active and the combined organic layers were dried over Na_2SO_4. The resulting 4-pyridone was purified using column chromatography (EtOAc/EtOH 8:2) which gave **6a** as a clear oil (0.18 g, 81%).
IR (ν_{max}/cm^{-1}) 3062, 1798, 1565, 1515, 1438, 1267, 1154, 1092, 812, 762, 698.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45–7.43 (m, 3H), 7.38 (d, J = 7.6 Hz, 1H), 7.23–7.28 (m, 2H), 6.37 (dd, J = 7.6, 2.8 Hz, 1H), 6.30 (d, J = 2.8 Hz, 1H), 3.40, (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 178.8, 151.9, 141.8, 134.1, 129.5, 128.7, 128.3, 119.7, 117.9, 41.8.
LRMS calcd for $[M+H]^+$ $C_{12}H_{11}NO$ 185.08, obsd 185.08.
32. *General procedure for the synthesis of 4-aminopyridinium salts* **7a**,**d**,**e**,**f**,**g**, *exemplified with* **7a**. To pyridine **4a** (0.17 g, 0.63 mmol) cooled in an ice-bath was added MeOTf (0.11 g, 0.70 mmol) dropwise. The solution was allowed to warm to rt and monitored by TLC (heptane/EtOAc 1:1, the reaction was complete in 30 min in all cases) and upon completion the mixture was concentrated. The residue was dissolved in ammonia-saturated THF solution (5 mL) and heated under microwave irradiation at 100 °C for 3 min. The mixture was concentrated under reduced pressure and the residue was purified using column chromatography (EtOAc/EtOH 8:2) to give **7a** as a white solid (0.18 g, 83%).
IR (ν_{max}/cm^{-1}) 3051, 1672, 1455, 1310, 1299, 1176, 802, 798, 612.
^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.10 (d, J = 7.3 Hz, 1H) 7.61–7.54 (m, 3H) 7.53–7.48 (m, 2H) 6.87 (dd, J = 7.3, 2.8 Hz, 1H) 6.76 (d, J = 2.8 Hz, 1H) 3.68 (s, 3H).
^{13}C NMR (100 MHz, $CDCl_3$) δ: 160.6, 155.7, 146.0, 134.1, 131.7, 130.2, 129.7, 126.5, 123.3, 120.1, 117.0, 112.1, 110.1, 44.1.
LRMS calcd for $[M+H]^+$ $C_{13}H_{13}F_3N_2O_3S$ 334.06, obsd 334.06.