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A synthetic entry to 3,5-disubstituted pyridines

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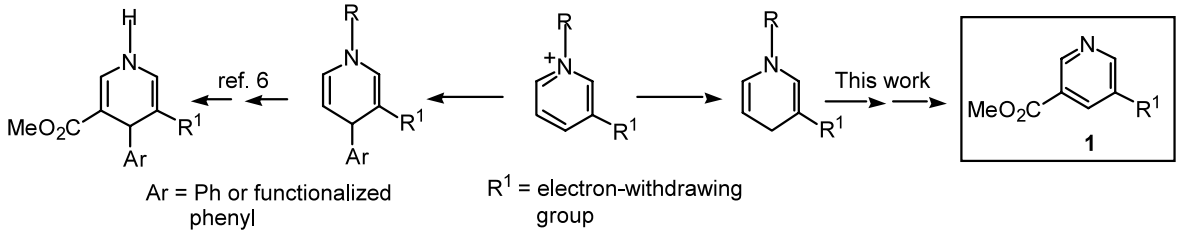
Abstract—A straightforward entry to 3,5-disubstituted pyridines from 3-substituted pyridines, based on the acylation of *N*-alkyl-1,4-dihydropyridine derivatives followed by a tandem *N*-dealkylation–oxidation sequence is reported.

Pyridines are useful intermediates in natural product synthesis as well as common building blocks found in many biologically active molecules.[1] Recently, we required an efficient synthesis of 3,5-disubstituted pyridines of general formula **1** (Scheme 1), as potential intermediates in the synthesis of some dihydropyridine alkaloids (lyaline, lyadine).[2] An inspection of the literature data revealed that, apart from condensation reactions leading to the dihydropyridine ring,[1,3,4] the reported strategies rely on the suitable manipulation of pre-existing annular substituents, in particular through transition metal catalyzed cross-coupling reactions.[5]

With the final aim of developing a common synthetic entry to 3,5-disubstituted pyridines from readily available β-monosubstituted pyridine starting materials, we decided to take advantage of the nucleophilic character of the unsubstituted enaminic side of 1,4-dihydro derivatives of *N*-alkyl-3-acylpyridinium salts to introduce an additional acyl substituent at the 5-position. This would represent an extension of our previous work,[6] in which the intermediate 1,4-dihydropyridine adducts were generated by the chemo- and regioselective addition of arylcopper reagents, giving access to valuable 3,5-diacyl-4-aryl-1,4-dihydropyridines. The acylation conditions would now have to be adapted to 4-unsubstituted 1,4-dihydropyridines,[7] which would be generated by the classical sodium dithionite reduction[8] of the starting pyridinium substrates. Moreover, we would have to be able to efficiently promote the final *N*-dealkylation with subsequent oxidation.

To test the feasibility of this proposal, we first decided to study the introduction of a methoxycarbonyl substituent at the 5-position of commercially available 3-substituted pyridines: methyl nicotinate, 3-acetylpyridine and 3-bromopyridine (Scheme 2, Table 1). The benzhydryl group was selected as the nitrogen substituent for the required pyridinium salts **2** since it is easily installed in a 3-acylpyridine and can be removed from the dihydropyridine nitrogen in relatively mild conditions.[6b,9] As expected, sodium dithionite reduction of **2a** gave the corresponding 1,4-dihydropyridine (**3**, $R^1 = CO_2Me$), which was directly treated with trichloroacetic anhydride in the presence of triethylamine. The resulting (trichloroacetyl)dihydropyridine **4a** smoothly underwent a haloform reaction with sodium methoxide to give diester **5a** in 50% overall



Scheme 1.

Keywords: dihydropyridines; pyridines; acylation; oxidation.

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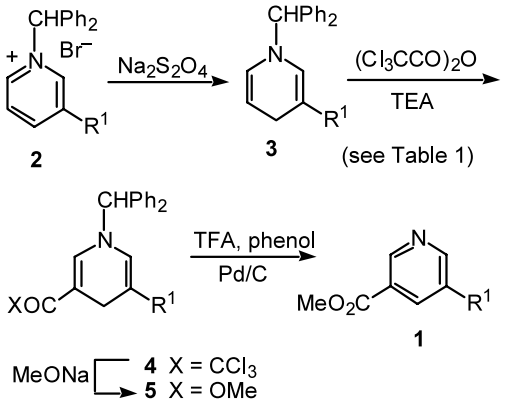


Scheme 2.

yield from **2a**. Satisfactorily, when the above sodium dithionite reduction–acylation–haloform reaction sequence was applied to *N*-(benzhydryl)pyridinium salts **2b** and **2c**, asymmetrically substituted dihydropyridines **5b** and **5c** (through **4b** and **4c**) were obtained in similar yields. Acetyl derivative **5b** could also be obtained by radical reduction of the trichloroacetyl group of **4a** with tributylstannane–AIBN, although the yield was less satisfactory (50% for the single step). It is worth noting that the best yields in the above transformations were observed when chromatographic purifications were avoided and, instead, the crude reaction products were digested with ether. In fact, unlike 4-aryl derivatives,[6] dihydropyridines **4** and **5** were somewhat unstable and acid sensitive and were only identified by their NMR data.

With dihydropyridines **5** in hand, attention was turned to the oxidative step. The oxidation of 1,4-dihydropyridines to pyridines or pyridiniums has been extensively studied, in large part due to the occurrence of the 1,4-dihydropyridine ring system in the reduced forms of NADH and NADPH, which are responsible for a number of biological oxidations and reductions. From a synthetic standpoint, most of the information of the literature deals with *N*-unsubstituted dihydropyridines having electron withdrawing substituents at the β-positions (Hantzsch dihydropyridines).[10,11] For our purposes, by analogy with our previous experience,[6b] *N*-(benzhydryl)dihydropyridine **5a** was treated with TFA–phenol at 50°C in order to first promote *N*-dealkylation. However, under these acidic conditions pyridine **1a** was isolated in 40% yield along with highly polar substances. Oxidation of the formed *N*-unsubstituted dihydropyridine, either by air (it was not rigourously excluded from the reaction vessel) or by disproportionation, can account for this result. Satisfactorily, the yield of pyridine **1a** increased (75%) when, inspired by the recent report of Hayashi,[12] the dealkylation with TFA–phenol was effected in the presence of a Pd/C catalyst. This tandem *N*-dealkylation–oxidation sequence was successfully applied to dihydropyridines **5b** and **5c** to give pyridines **1b** and **1c**.

Representative experimental procedure: synthesis of pyridine 1b. $Na_2S_2O_4$ (17.4 g, 0.1 mol) was added under Ar to a mixture of pyridinium bromide **2b** (3.31 g, 9 mmol) in CH_2Cl_2 (220 mL) and 1 M aqueous $NaHCO_3$ (200 mL). After stirring at rt in the dark for 5 h, the mixture was extracted with CH_2Cl_2 (3×200 mL) and the organic extracts were dried and concentrated. The crude residue was dissolved in anhydrous THF (90 mL), treated with Et_3N (3.75 mL, 27 mmol) and TCAA (4.93 mL, 27 mmol) at 0°C, and stirred at 0°C overnight. The reaction mixture was poured into saturated aqueous Na_2CO_3 (90 mL) and extracted with AcOEt (3×90 mL). The organic extracts were dried and concentrated. The resulting residue was digested with Et_2O (3×100 mL) and the ethereal extracts were concentrated to afford **4b**. A solution of **4b** in MeOH–THF (1:1, 50 mL) was added dropwise to a solution of MeONa (27 mmol) in MeOH (90 mL), and the mixture was stirred at rt for 3 min. The solvent was removed, and the resulting residue was partitioned between CH_2Cl_2 (100 mL) and H_2O (100 mL), and extracted with CH_2Cl_2 (2×100 mL). After removal of the solvent, the resulting residue was digested with Et_2O (3×100 mL) and the ethereal extracts were concentrated to give dihydropyridine **5b** (1.9 g, 60%).

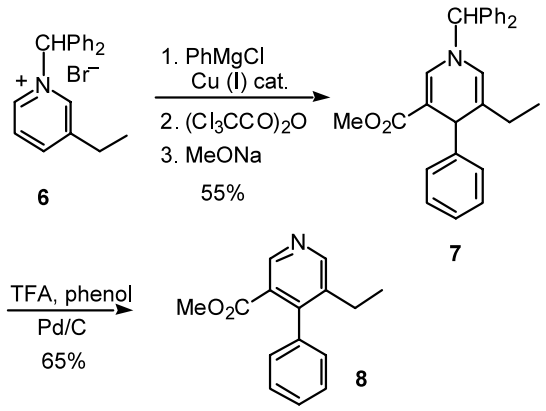
A suspension of 1,4-dihydropyridine **5b** (1.9 g, 5.5 mmol), phenol (1.03 g, 11 mmol) and 10% Pd/C (0.38 g) in TFA (9 mL) was stirred at 50°C for 3 h. The reaction mixture was filtered through Celite and the cake was washed with CH_2Cl_2 (30 mL). The resulting organic solution was poured into a saturated aqueous solution of Na_2CO_3 (50 mL) and extracted with CH_2Cl_2 (3×50 mL). The solvent was removed and the residue was chromatographed (SiO_2, 7:3 hexane–AcOEt) to give **1b** (0.78 g, 80% yield). The spectroscopic data of **1b** were identical with those reported in the literature.[13]

To ascertain the scope of the oxidative aromatization step we focused our attention on 4-phenyl substituted dihydropyridine **7**,[14] which was easily prepared in 55% overall yield as outlined in Scheme 3, by copper-catalyzed addition of phenylmagnesium chloride to 3-ethylpyridinium salt **6**, followed by acylation with trichloroacetic anhydride and the subsequent haloform

Table 1. Synthesis of 3,5-disubstituted pyridines

Pyridinium salt	R^1	Dihydropyridines (overall yield, %)[a]	Pyridine (yield, %)[a]
2a	CO_2Me	**4a**, **5a** (50)	**1a** (75)
2b	COMe	**4b**, **5b** (60)	**1b** (80)
2c	Br	**4c**, **5c** (50)	**1c** (80)

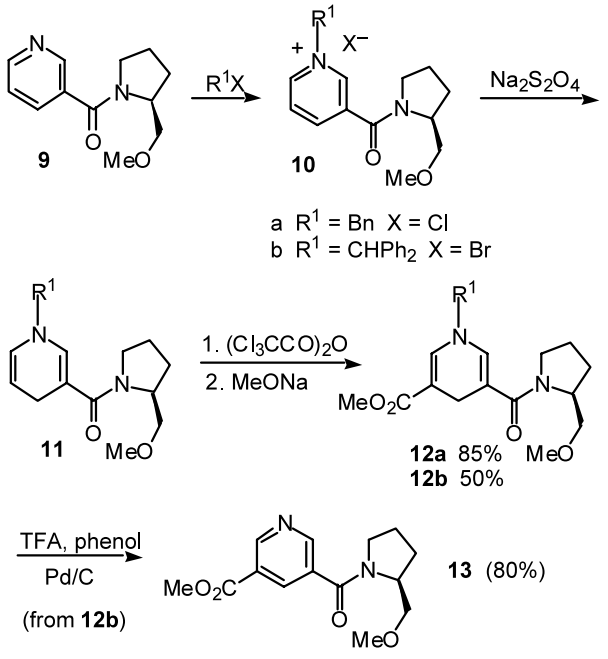
[a] Isolated yields of pure material.



Scheme 3.

reaction. Satisfactorily, the TFA–phenol–Pd/C system also exhibited a high performance since pyridine **8**[15] was obtained in 65% yield from **7**.

Having established a functional protocol for the synthesis of 3,5-diacylpyridines, the above transformations were applied to the synthesis of chiral derivatives. In a preliminary series of experiments, access to dihydropyridine NAD(P)H models[16] was considered. Thus, *N*-benzylpyridinium salt **10a**, derived from (*S*)-*O*-methylprolinol nicotinamide **9**,[17] was reduced with sodium dithionite to **11a**, which was immediately subjected to the acylation–haloform reaction sequence to give chiral 3,5-diacyldihydropyridine **12a**[18] in 85% overall yield from **10a** (Scheme 4). On the other hand, *N*-(benzhydryl)dihydropyridine **12b** was prepared as above in 50% overall yield from pyridinium salt **10b**. As expected, chiral 3,5-disubstituted pyridine **13**[19] was obtained in 80% yield when the tandem *N*-dealkylation–oxidation sequence was effected from **12b**.



Scheme 4.

In summary, we have reported a general method for the synthesis of valuable 3,5-disubstituted pyridines. The method is attractive due to the simplicity of the operational procedure, the mildness of the conditions, and the applicability to a great variety of starting 3-substituted pyridine substrates.

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14. Dihydropyridine **7**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.87 (t, $J=7.5$ Hz, 3H), 1.81 (q, $J=7.5$ Hz, 2H), 3.49 (s, 3H), 4.46 (s, 1H), 5.79 (s, 1H), 5.82 (s, 1H), 7.2–7.4 (m, 16H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 11.5 (CH_3), 25.4 (CH_2), 42.3 (CH), 50.6 (CH_3), 70.2 (CH), 101.5 (C), 121.5 (CH), 122.3 (C), 126.0 (CH), 127.6–128.8 (CH), 138.6 (CH), 138.9 (C), 139.0 (C), 146.4 (C), 168.2 (C).
15. Pyridine **8**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.05 (t, $J=7.4$ Hz, 3H), 2.05 (q, $J=7.8$ Hz, 2H), 3.60 (s, 3H), 7.17 (m, 2H), 7.41 (m, 3H), 8.65 (s, 1H), 8.91 (s, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 15.6 (CH_3), 23.6 (CH_2), 51.9 (CH_3), 126.4 (C), 127.6 (CH), 127.7 (CH), 127.9 (CH), 136.9 (C), 137.7 (C), 148.0 (CH), 149.0 (C), 152.5 (CH), 166.7 (C). Anal. calcd for $C_{15}H_{15}NO_2$: C, 74.67; H, 6.27; N, 5.81. Found: C, 74.84; H, 6.31; N, 5.69.
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18. Dihydropyridine **12a**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.80 (m, 4H), 3.20 (d, $J=15$ Hz, 1H), 3.30 (s, 3H), 3.40 (m, 5H), 3.69 (s, 3H), 4.30 (m, 1H), 4.37 (s, 2H), 6.30 (s, 1H), 7.12 (s, 1H), 7.20–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 23.1 (CH_2), 24.7 (CH_2), 27.7 (CH_2), 49.1 (CH_2), 51.2 (CH_3), 56.8 (CH), 57.6 (CH_2), 59.0 (CH_3), 72.9 (CH_2), 101.3 (C), 110.9 (C), 127.0 (CH), 128.0 (CH), 128.9 (CH), 132.9 (CH), 16.5 (C), 140.0 (CH), 167.8 (C), 169.1 (C). $[\alpha]_D^{22}=-132$ (*c* 1, MeOH).
19. Pyridine **13**: ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.02 (m, 4H), 3.18 (m, 1H), 3.40 (s, 3H), 3.45 (m, 1H), 3.65 (m, 2H), 3.98 (s, 3H), 4.42 (br s, 1H), 8.44 (s, 1H), 8.93 (s, 1H), 9.25 (s, 1H). ^{13}C NMR ($CDCl_3$, 300 MHz): δ 25.1 (CH_2), 27.5 (CH_2), 50.5 (CH_2), 52.6 (CH_3), 57.2 (CH), 59.2 (CH_3), 72.3 (CH_2), 125.5 (C), 132.7 (C), 135.8 (CH), 151.5 (CH), 151.8 (CH), 165.0 (C), 166.2 (C). $[\alpha]_D^{22}=-96$ (*c* 1, MeOH). HRMS calcd for $C_{14}H_{18}N_2O_4$: 278.1260; found: 278.1263.