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A Short Procedure for the Preparation of Highly Functionalized Di- and Tetrahydropyridines

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Abstract: The addition of a series of stabilized carbon nucleophiles to 3-acyl-1-alkylpyridinium salts, followed by acylation of the intermediate dihydropyridines with trichloroacetic anhydride has been studied. The C-4 adducts resulting from the addition of α-(methylsulfanyl)ester enolates have been converted into synthetically useful 1,2,3,4-tetrahydropyridines.

Keywords: Acylation; enolates; pyridinium salts; pyridines.

In previous papers we reported that the addition of 2-acetylindole enolates to 3-acyl-1-alkylpyridinium salts, followed by acylation of the intermediate 1,4-dihydropyridines with trichloroacetic anhydride (TCAA) gives 3,5-diacyl-1,4-dihydropyridines,[1] from which we have accomplished the total synthesis of several ervatamine alkaloids.[2] The use of the higher order heterocuprate $Ph_2Cu(CN)Li_2$ in this one-pot, two-step sequence allows the preparation of valuable 3,5-diacyl-4-phenyl-1,4-dihydropyridines.[3]

In this context, we decided to study an extension of the above addition-acylation sequence to a series of stabilized carbon nucleophiles in order to prepare regioselectively highly functionalized 1,4-dihydropyridines. Chemoselective catalytic hydrogenation of the products would provide access to synthetically useful polysubstituted 1,2,3,4-tetrahydropyridines. The introduction of a functionalized alkyl group at the γ-position of the pyridine ring from *N*-acylpyridinium salts[4] has previously been effected using silyl enol ethers or silyl ketene acetals,[5] titanium enolates,[6] Reformatsky reagents,[7] and copper derivatives.[8,9] However, in most cases, the initially formed *N*-acyl-1,4-dihydropyridines are rapidly oxidized to the corresponding pyridines.

For our study we selected *N*-methylpyridinium salts **1a** and **1b** and *N*-benzylpyridinium salt **1c** (Scheme 1), which differ in the electron-withdrawing group at the β-position of the ring, and allowed them to react with anions derived from the compounds listed in Table 1. It is worth mentioning that initial attempts, using the highly stabilized enolates derived from dimethyl malonate, methyl (phenylsulfonyl)acetate or Meldrum's acid, in the addition-acylation sequence from pyridinium salts **1a** or **1b** did not lead to any acylated dihydropyridines, probably due to the reversibility of the addition step.[10a]

As can be observed in Table 1, sulfur stabilized carbanions (entries 1-4) react preferently at the C-6 position of the ring to give, after the acylation step, the corresponding C-6 adducts in low to moderate yields. The process was very dependent on the nature of the electron-withdrawing group (Y) since complex mixtures were obtained in the reactions of the anions derived from methyl phenyl sulfone and bis(methylsulfanyl)methane with pyridinium salts **1a** and **1b**, respectively.

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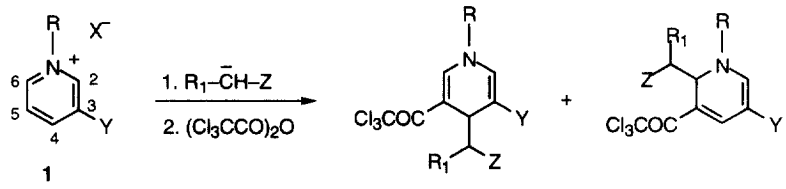

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a. R = Me; Y = CO_2Me; X = I
b. R = Me; Y = $CH{=}CHCO_2Me$; X = I
c. R = Bn; Y = COMe; X = Cl

Scheme 1

Table 1
Reaction of Pyridinium Salts **1** with Stabilized Carbon Nucleophiles with Subsequent TCAA Acylation

Entry	Anion Derived From[a]	Pyridinium Salt	C-4/C-6[b]	Yield (%)
1	$PhSO_2Me$	**1a**	*c*	-
2	$PhSO_2Me$	**1b**	0/100	20
3	$MeSCH_2SMe$	**1a**	0/100	34
4	$MeSCH_2SMe$	**1b**	*c*	-
5	γ-butyrolactone	**1b**	50/50	60
6	CH_3CO_2Me	**1a**	15/85[d]	60
7	CH_3CO_2Me	**1b**	40/60	60
8	CH_3CO_2Me[e]	**1b**	50/50	30
9	CH_3CO_2Me	**1c**	*c*	–
10	$MeSCH_2CO_2Me$	**1a**	50/50	80[f]
11	$MeSCH_2CO_2Me$	**1b**	70/30	65[f]
12	$MeSCH_2CO_2Me$	**1c**	100/0	47[f]
13	$CH_3CH_2(MeS)CHCO_2Me$	**1c**	100/0	57[f]
14	Methyl 2-(methylsulfanyl)-4-(1-methyl-3-indolyl)butyrate	**1c**	100/0	34[f]

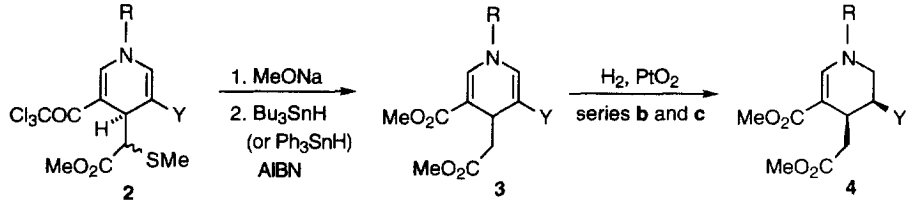
[a] Anions were generated following standard protocols: LDA (or *n*-BuLi, entries 1-4), THF, -70 °C, 30 min.
[b] In a typical run, pyridinium salt **1** (1.5 mmol) was added in portions to a cooled (-70 °C) solution of the anion (1.7 mmol) in THF (35 ml), and the resulting mixture was allowed to rise to -40 °C and stirred at -40 °C for 1.5 h. TCAA (7.5 mmol) was added, and the mixture was stirred at 0 °C for 2 h. Acylated dihydropyridines were isolated after extractive workup and flash chromatography (SiO_2, hexane-ethyl acetate).
[c] Complex mixtures.
[d] In this case C-6 refers to an equimolecular mixture of C-2 and C-6 regioisomers.
[e] Titanium enolate generated by treatment of the lithium enolate with $Ti(i\text{-}PrO)_4$ at -78°C for 30 min.
[f] Mixture of stereoisomers.

More satisfactorily, simple ester enolates (entries 5-9) gave acceptable overall yields of the addition-acylation products, although the regioselectivity of the process was low, since mixtures of 1,2- and 1,4-dihydropyridines were obtained. With the lithium enolate of methyl acetate, the α-attack was preponderant, in particular when the substituent Y is methoxycarbonyl (salt **1a**). In contrast to the reported results with *N*-acylpyridinium salts,[6] the use of the corresponding titanium enolate (entry 8) in the reaction with pyridinium salt **1b** did not substantially improve the C-4 regioselectivity of the addition step, and the overall yield was lower. Complex mixtures were obtained from acetylpyridinium salt **1c**.

The use of the lithium enolate of methyl α-(methylsulfanyl)acetate[10b,c] (entries 10-12) increased the extent of γ-addition to the pyridine ring as compared with the results obtained from simple ester enolates. The most interesting results from the synthetic standpoint were obtained when the addition-acylation sequence was carried out starting from pyridinium salt **1b** (entry 11) and, particularly, with 3-acetylpyridinium salt **1c** (entry

12). The latter reaction was extended to more complex α-(methylsulfanyl)esters (entries 13 and 14). In these reactions involving salt **1c** no C-6 adduct was detected from the reaction mixtures.

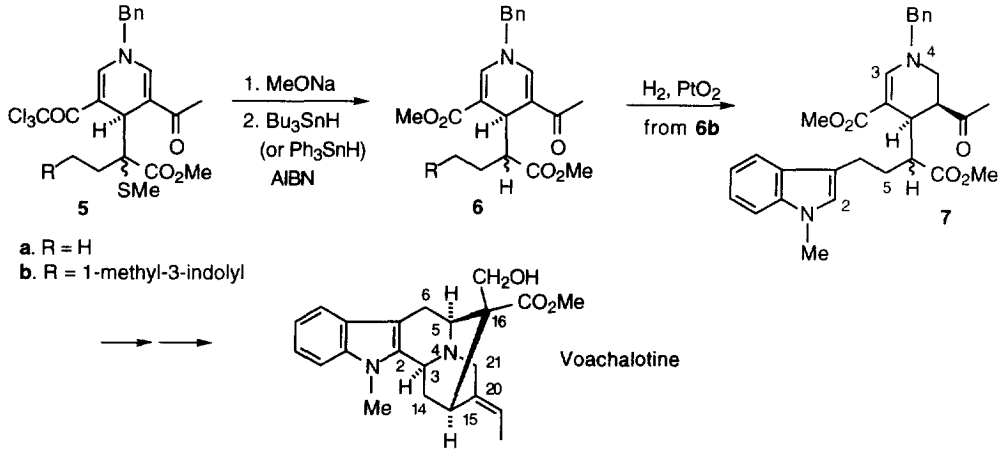
α-(Methylsulfanyl)-1,4-dihydropyridine-4-acetates **2** (*i.e.*, the C-4 adducts from entries 10-12, Table 1) were converted into the highly functionalized tetrahydropyridines **4**, as outlined in Scheme 2. Conversion of the trichloroacetyl group into a methoxycarbonyl group by a haloform-type reaction with sodium methoxide in methanol,[1-3] followed by a radical desulfurization with Bu_3SnH (or Ph_3SnH)-AIBN in refluxing benzene gave dihydropyridines **3** [overall yield 65% (**3a**), 62% (**3b**) and 70% (**3c**)]. Subsequent chemo- and stereoselective catalytic hydrogenation (PtO_2)[11] of **3b** (methanol-THF) and **3c** (ethyl acetate) gave the corresponding *cis*-tetrahydropyridine-4-acetates **4b** (40%) and **4c** (70%).[12]



a. R = Me; Y = CO_2Me
b. R = Me; Y = $CH{=}CHCO_2Me$ ($CH_2CH_2CO_2Me$ for **4**)
c. R = Bn; Y = COMe

Scheme 2

The same haloform reaction-radical desulfurization sequence from α-substituted-α-(methylsulfanyl)-1,4-dihydropyridine-4-acetates **5** (*i.e.*, the C-4 adducts from entries 13 and 14) allowed the preparation of dihydropyridines **6** [mixture of stereoisomers, overall yield 70% (**6a**) and 77% (**6b**)]. Catalytic hydrogenation of **6b** (PtO_2, methanol) gave (40%) the *cis*-tetrahydropyridine **7**[13] (Scheme 3).



Scheme 3

The above results establish a short procedure for the preparation of otherwise inaccessible 1,4-dihydro- and 1,2,3,4-tetrahydropyridines bearing functionalized substituents at the 3, 4 and 5 positions. The acetate chain at C-4, *cis* with respect to the substituent at C-3, and the vinylogous urethane moiety make

tetrahydropyridines **4** and **7** potentially useful synthons for alkaloid synthesis. Further elaboration of tetrahydropyridine **7** into indole alkaloids of the akuammidine group (*i.e.* voachalotine),[14] by formation of C_2-C_3 and N_4-C_5 bonds, is currently under study.

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12. Tetrahydropyridine **4c**: ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.15 (dd, J = 15.7, 7.4 Hz, 1H, CH_2CO), 2.26 (dd, J = 15.7, 5.3 Hz, 1H, CH_2CO), 2.28 (s, 3H, MeCO), 2.85 (dt, J = 13, 4.2 Hz, 1H, 3-Hax), 2.92 (ddd, J = 13, 4.2, 1.8 Hz, 1H, 2-Heq), 3.22 (t, J = 13 Hz, 1H, 2-Hax), 3.61 and 3.69 (2s, 6H, OMe), 3.69 (masked, 1H, 4-H), 4.30 and 4.36 (2d, J = 14.9 Hz, 2H, CH_2Ph), 7.19-7.36 (m, 5H, Ph), 7.57 (s, 1H, 6-H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 29.4 (C-4), 30.0 (MeCO), 37.4 (CH_2CO), 41.8 (C-2), 50.7, 51.6 (CO_2Me), 59.8 (CH_2Ph), 97.7 (C-5), 127.4, 128.1, 128.8 136.0 (Ph), 145.7 (C-6), 167.8, 172.2 (CO_2Me), 208.9 (COMe).
13. Tetrahydropyridine **7** (1:1 mixture of stereoisomers): ^{13}C-NMR ($CDCl_3$, 75 MHz): 23.3, 23.8 (CH_2 α-indole), 27.1 (MeCO), 30.4 (CH_2 β-indole), 32.4 (NMe), 34.5, 35.6 (C-4), 42.3, 42.6 (C-2), 46.9 (C-3), 49.3, 49.5 ($CHCO_2Me$), 50.7, 50.8, 51.1, 51.4 (OMe), 59.6, 59.9 (CH_2Ph), 95.3, 95.6 (C-5), 108.9 (indole C-7), 113.9, 114.1 (indole C-3), 118.4 (indole C-4), 118.9 (indole C-5), 121.4 (indole C-6), 126.2 (indole C-2), 127.3, 127.5, 127.7, 127.9, 128.7, 135.9, 136.9 (Ph, indole C-3a, indole C-7a), 145.7, 146.4 (C-6), 168.0, 168.2, 173.7, 175.2, 207.2, 207.8 (CO).
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