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Regio and Enantioselective Synthesis of 4-Carbomethoxymethyl-1,4 Dihydropyridines

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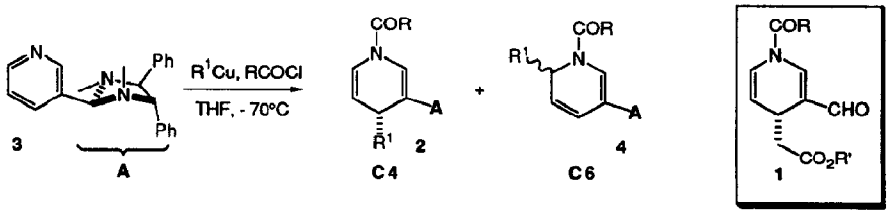
Abstract : Regio and enantioselective 1,4 addition of ethoxyvinyl copper reagent on a pyridine bearing in position 3 a chiral aminal is described. This reaction allows the synthesis of various chiral N-acyl-4-methoxymethyl-1,4-dihydropyridines.

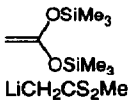
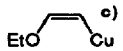
Regio and enantioselective introduction of carbalkoxymethyl group onto a functionalized pyridine is an important challenge for a synthetic point of view. A recent paper dealing with such subject in achiral version[1] prompted us to present our results on this field. From our part, we were interested by synthesis of chiral 4-carbalkoxymethyl-1,4-dihydropyridines **1**. Recently, we have proposed a synthesis of chiral 4-substituted-1,4-dihydropyridines **2** (C4 adduct) from chiral aminal **3** by a regio and diastereoselective 1,4-addition of organocopper reagents in the presence of an acylating reagent [2] (Scheme 1 and entry 1 in the Table). Among the several functionalized organocopper used, it was found that the reagent $CuCH_2CO_2Et$ afforded exclusively the C6 adduct **4** (Scheme 1) whatever the acylating reagent (methyl chloroformate or pivaloyl chloride, entry 2).



Scheme 1

Some 1,4 selectivity has been reported by addition of the Reformastky reagent derived from ethyl bromoacetate, on N-acyl pyridinium salts.[3] In our case, in the presence of methyl chloroformate, this reagent was found to be unreactive (entry 3).

Table

Entry	R^1 [a]	R	C4 / C6	Yield (%)[b]
1	R^1 Cu (R^1= primary or secondary alkyl, vinyl, aryl (ref 2)	CH_3O, CH_3	100 / 0	77-95
2	$CuCH_2CO_2Et$ (ref 2)	CH_3O, tBu	0 /100	20-25
3	$BrZnCH_2CO_2Et$	CH_3O	-	-
4		CH_3O	0 /100	80
5	$LiCH_2CS_2Me$	CH_3O	-	-
6	$LiCu(CH_2CS_2Me)_2$	CH_3O	0 /100	30
7	$CuCH(SiMe_3)CO_2Et$[c]	CH_3	23 / 77	50[d]
8	"	Ph	10 / 90	70[d]
9	"	tBu	-	-
10		CH_3O	15 / 85	80
11	"	Ph	90 / 10	75

a) All the reactions were performed in THF from - 70°C to 0°C except for entry 4. In this case, the reaction was performed in CH_2Cl_2 at R.T. b) For all the C6 adducts, de = 0. c) Prepared with an excess of soluble copper salt (2 CuBr,Me_2S, 4 LiBr). d) The de of the C4 adduct was not determined.

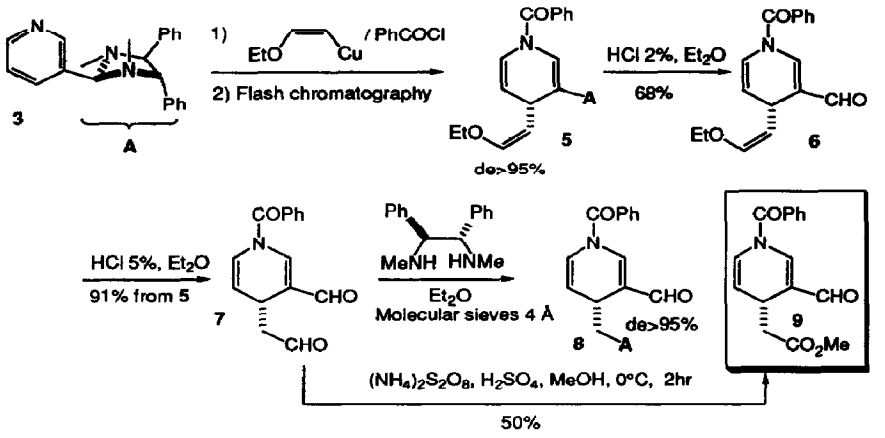
By analogy to the observed regioselective 1,4 addition of silyl enol ethers onto N-acyl pyridinium salts[4], a silyl ketene acetal[5] was opposed to the aminal **3** in the presence of methyl chloroformate in CH_2Cl_2 to give exclusively the C6 adduct[6] (entry 4).

The soft reagent $Cu(CH_2CS_2Me)_2$[7], obtained from the corresponding lithio derivative[8] (which gave the starting marerial, entry 5), yielded also, in the presence of methyl chloroformate, exclusively to the C6 adduct (entry 6).

1,4-additions of lithium salt of silyl acetates on enones[9] and N-alkylpyridinium salts,[10] has been reported. Therefore a conjugate addition was attempted with a silyl copper enolate (entry 7) on **3** in the presence of acetyl chloride. A mixture of C4 and C6 adducts was obtained in a 23/77 ratio (entry 7). Attempts to increase the C4 selectivity by changing the acyl chloride [11] were unsuccessfull (entries 8 and 9).

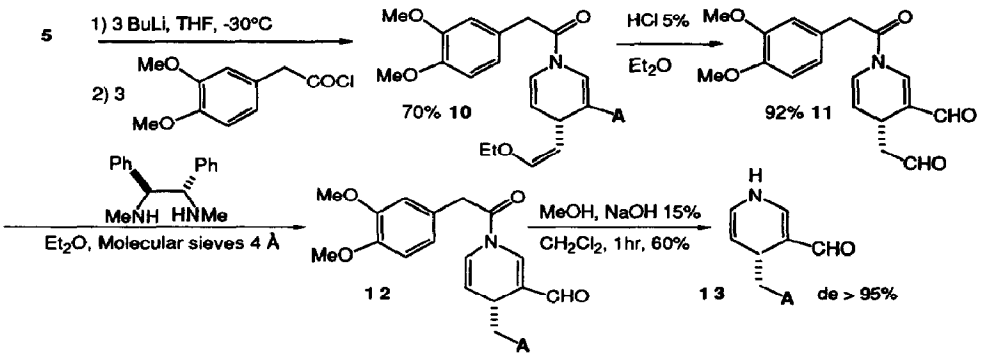
We decided then to use the ethoxyvinyl copper [12] which is an equivalent of $^-CH_2$-CHO. With this reagent, in the presence of methyl chloroformate (entry 10), a mixture of C4 and C6 adducts was obtained in a 15/85 ratio. On the other hand with benzyl chloride the C4 adduct was obtained with a very good selectivity (90/10, entry 11). No explanations were found for this unexpected regioselectivity.

The diastereomeric purity of the so obtained 1,4-dihydropyridine was measured by ^1H NMR and found to be good (de = 80%). Furthermore, the two diastereomers are easily separable by flash chromatography (SiO_2, C_6H_{12}/Et_2O,80/20) to give the pure major diasteromer **5** in 67% yield (Scheme 2). A mild acidic hydrolysis (HCl 2%) afforded the monoaldehyde **6** and, by more forcing the conditions (HCl 5%), the dialdehyde **7**[13] was obtained in good yield (Scheme 2). The optical purity of **7** was measured by ^1H NMR of the corresponding monoaminal **8** and found to be excellent (ee > 95%). Finally, the dialdehyde **7** was oxidized [14] to give the desired ester **9**[15] (Scheme 2).



Scheme 2

For synthetic purposes, it was interesting to test the possibility to exchange the N-acyl group on aminal **5** where the aldehyde function is still protected. Addition of 3 equivalents of BuLi on **5**, in THF at -30°C, gave the corresponding amide which was directly acylated by a new acyl chloride to give, in a good yield, the dihydropyridine **10**. This compound was hydrolyzed into the dialdehyde **11**[16] and then, transformed into the corresponding aminal **12** in order to measure the optical purity. Unfortunately, this was not possible by ^1H NMR (presence of conformers), and **12** was converted into **13** by alcaline hydrolysis. An accurate measure was then possible and the de was found to be exactly the same than the starting aminal **5** (de > 95%). Therefore no epimerisation occurs during all the procedure.



Scheme 3

In conclusion it is possible to introduce selectively in 4 position an equivalent of $^-CH_2CHO$ which is a precursor of the corresponding ester. Furthermore the possibility of changing the N-acyl group allows usefull synthetic applications.

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6 The resulted C6 adduct was directly transformed into the ethyl ester (EtOH, DCC, DMAP, 12 hr.)

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13 $[\alpha]_D^{25}$ = -151 (*c*= 1.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 9.6 (t, J = 1.5 Hz, 1H), 9.2 (s, 1H), 7.6 (s, 1H), 7.5-7.2 (m, 5H), 6.8 (d, J = 8 Hz, 1H), 5.2 (dd, J = 8 Hz, J = 5Hz, 1H), 3.7 (m, 1H), 2.8 and 2.5 (2 ddd, J = 17.3, J = 8 Hz, J = 4.2 Hz, J = 1.5 Hz, 2H); ^{13}C NMR (100 MHz) 200.3, 190.7, 167.6, 142.9, 132.3, 131.9, 128.8, 123.6, 121.8, 112.4, 49.5, 26.5.

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15 $[\alpha]_D^{25}$ = -97 (*c*= 6.5, $CHCl_3$); ^1H NMR ($CDCl_3$, 200 MHz) δ 9.3 (s, 1H), 7.7 (s, 1H), 7.7-7.3 (m, 5H), 6.9 (d, J = 8.2 Hz, 1H), 5.3 (dd, J = 8.2 Hz, J = 4.8 Hz, 1H), 3.6 (m, 1H), 3.3 (s, 3H), 1.98 and 1.75 (2 ddd, J = 13.8 Hz, J = 8.4 Hz, J = 6.2 Hz, J = 5.4 Hz, J = 4.2 Hz, 2H); ^{13}C NMR (100 MHz) 190.7, 167.6, 141.9, 132.1, 128.9, 128.7, 123.9, 123, 113.6, 102, 53.3, 38.8, 27.7

16 $[\alpha]_D^{25}$ = -485 (*c*= 1.1, $CHCl_3$, ee = 80%); ^1H NMR ($CDCl_3$, 200 MHz) δ 9.7 (t, J = 1.5 Hz, 1H), 9.4 (m, 1H), 7.9 (m, 1H), 6.8 (m, 4H), 5.3 (m, 1H), 3.8 (m, 9H), 2.8 and 2.5 (2 ddd, J = 17.3 Hz, J = 9.8 Hz, J = 5.3 Hz, J = 1.3 Hz, J = 0.5 Hz, 2H); ^{13}C NMR (100 MHz) 200.9, 167.5, 157.5, 149.4, 148.5, 142, 124.5, 123, 120.9, 112.9, 111.6, 111.4, 55.9, 49.5, 40.2, 29.6, 26.1

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