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Addition of organocopper reagents to *N*-alkylpyridinium salts. A flexible access to polysubstituted dihydropyridines

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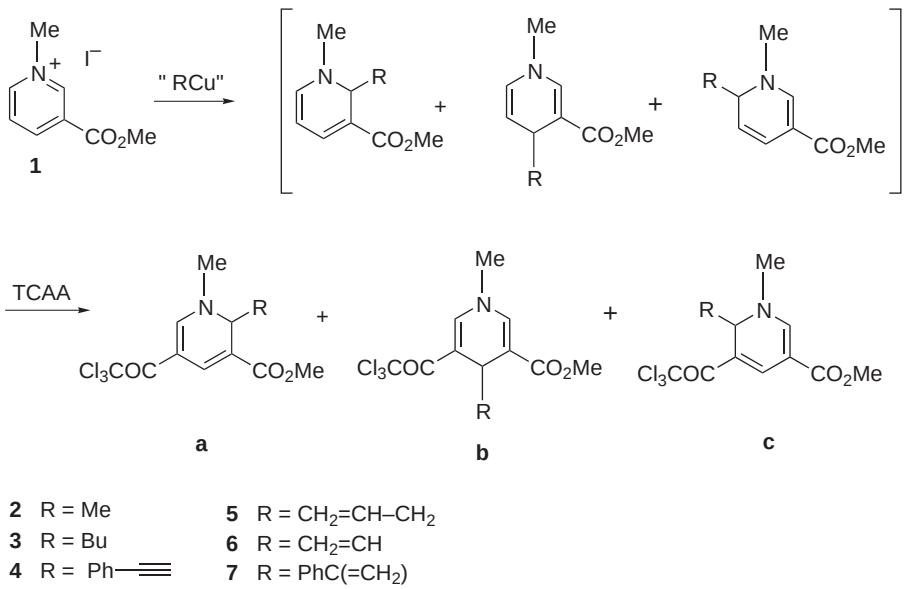
Abstract—The addition of a series of organocopper (alkyl, vinyl, allyl, and ethynyl) reagents to 3-acyl-*N*-alkylpyridinium salts, followed by acylation of the intermediate 1,4- or 1,2-dihydropyridines with trichloroacetic anhydride has been studied.

Good C-4 regioselectivity upon reaction with *N*-acylpyridinium salts has usually been achieved with organocopper reagents.[1] Thus, Gilman homocuprates (R_2CuLi),[1a] copper-catalyzed Grignard reagents,[1b,c] mono-organocopper reagents (RCu),[1d,f] and mixed copper–zinc organometallics[1e] have been shown to afford 4-substituted *N*-acyl-1,4-dihydropyridines. In contrast, there is scarce information about the same process with *N*-alkylpyridinium salts.[1f,2] In this context, we have recently developed a synthetic entry to 3,5-diacyl-4-phenyl-1,4-dihydropyridines by the use of the chemo- and regioselective addition of the higher order (HO) heterocuprate $Ph_2Cu(CN)Li_2$ to the 4-position of several 3-acyl-*N*-alkylpyridinium salts, with subsequent acylation of the resulting 1,4-dihydropyridines with trichloroacetic anhydride (TCAA).[3]



2 R = Me
3 R = Bu
4 R = Ph—≡
5 R = CH_2=CH–CH_2
6 R = CH_2=CH
7 R = PhC(=CH_2)

Scheme 1.

Keywords: acylation; copper and compounds; pyridines; pyridinium salts.

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We present here a complete study of the above addition–acylation sequence using a series of alkyl, vinyl, allyl and ethynyl organocopper reagents ('RCu', Scheme 1) in order to prepare diversely substituted 3,5-diacylated 1,2- and 1,4-dihydropyridines. 1,2-Dihydropyridines are useful building blocks for alkaloid synthesis,[4] whereas 1,4-dihydropyridines can be considered as privileged structures in Medicinal Chemistry since they display binding at a variety of receptor sites.[5]

For our study we initially selected *N*-methylpyridinium salt **1** and allowed it to react with the organocopper reagents[6] listed in Table 1.

In contrast with the results reported in the phenyl series,[3] the use of alkyl (methyl or butyl) HO cyanocuprates $R_2Cu(CN)Li_2$ (entries 1 and 2) gave only low yields of mixtures of C-4 and C-6 adducts (**2b**,**c** and **3b**,**c**) after treatment of the crude reaction mixtures with TCAA. In these series, the corresponding Gilman homocuprates Me_2CuLi and Bu_2CuLi (entries 3 and 4) proved to be the most efficient reagents for the regioselective introduction of an alkyl group at the 4-position of the pyridine ring as occurs in previous examples found in the literature.[1f,2a] With these cuprates, the addition–acylation sequence led to the 3,5-diacylated C-4 adducts **2b** and **3b** as the major products in good yields, especially in the butyl series.

The preparation of dihydropyridine **3b** is representative. In a typical run, pyridinium salt **1** (0.5 g, 1.79 mmol) was added in portions to a cooled (−40°C) solution of Bu_2CuLi (4.5 mmol) in anhydrous THF (35 ml), and the mixture was stirred at this temperature for 1.5 h. After extractive workup and concentration, the resulting residue was dissolved in anhydrous THF (35 ml) and treated with TCAA (0.6 ml, 3.6 mmol) at 0°C for 3 h. Workup followed by flash chromatography (SiO_2, 8:2 hexanes–AcOEt) gave pure **3b** (0.44 g, 70%).

Table 1. Reactions of pyridinium salt **1** with organocopper reagents with subsequent TCAA acylation

Entry	RCu[a]	Product[b]	**a**/**b**/**c** ratio	Yield (%)[c]
1	$Me_2Cu(CN)Li_2$	**2**	0/10/90	20
2	$Bu_2Cu(CN)Li_2$	**3**	0/55/45	20
3	Me_2CuLi	**2**	0/70/30	40
4	Bu_2CuLi	**3**	0/90/10	77
5	$(PhC{\equiv}C)_2Cu(CN)Li_2$	**4**	50/0/50	68
6	$(PhC{\equiv}C)Cu(CN)Li$	**4**	40/0/60	30
7	$(PhC{\equiv}C)_2Cu(CN)(ZnCl)_2$[d]	**4**	20/0/80	18
8	$(PhC{\equiv}C)Cu(CN)(ZnCl)$	**4**	0/0/100	<10
9	$(PhC{\equiv}C)MgBr/CuI_{cat}$	**4**	100/0/0	65
10	$(CH_2{=}CH\text{-}CH_2)_2CuLi$	**5**	40/20/40	86
11	$(CH_2{=}CH\text{-}CH_2)_2Cu(CN)Li_2$	**5**	50/0/50	75
12	$(CH_2{=}CH)_2CuLi$	**6**	50/0/50	30
13	$(CH_2{=}CH)_2Cu(CN)Li_2$	**6**	40/20/40	55
14	$(CH_2{=}CH)MeCu(CN)Li_2$	**6**	30/40/30	60
15	$[PhC(=CH_2)]MeCu(CN)Li_2$[e]	**7**	0/20/80	90
16	$[PhC(=CH_2)]MgBr/CuI_{cat}$	**7**	0/15/85	65

[a] Prepared following general procedures reported in reference 6.
[b] All products were fully characterized by spectroscopic analysis (NMR) and gave satisfactory HRMS and/or combustion data.
[c] Isolated yields of chromatographically pure material.
[d] Prepared according to reference 7.
[e] Prepared from α-(trimethylstannyl)styrene according to reference 9b.

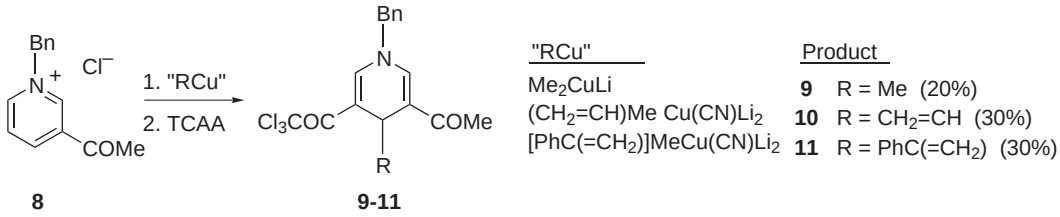
In contrast, (phenylethynyl)copper reagents (entries 5–8) react preferentially at the α-position of the pyridine ring to give mixtures of C-2 and C-6 adducts (**4a** and **4c**). As can be observed in Table 1, the lower the reactivity of the organometallic reagent [(HO cyanocuprate>lower order (LO) cyanocuprate>HO zinc cyanocuprate[7]>LO zinc cyanocuprate], the higher the C-6 regioselectivity, although the yield progressively decreases. Interestingly, the corresponding copper-catalyzed Grignard reagent (entry 9) afforded exclusively the C-2 adduct **4a**. This result probably reflects a coordination between magnesium and the carbonyl oxygen atom of **1**.

The preferential attack at the α-positions of the pyridine ring was also observed with allylcopper reagents (entries 10 and 11), formation of the C-4 adduct **5b** only being detected from the Gilman homocuprate $(allyl)_2CuLi$. No reaction took place with allyltributyltin.[8]

The α-regioselectivity obtained with the above (phenylethynyl)- and allylcopper reagents was not surprising since it is known that these reagents are prone to undergoing 1,2-addition to enones.[6] Similarly, complete C-6 regioselectivity has been observed in the reaction of a 3-substituted *N*-acylpyridinium salt with $(Me_3SiC{\equiv}C)_2CuLi$ or $(allyl)Cu$.[1f]

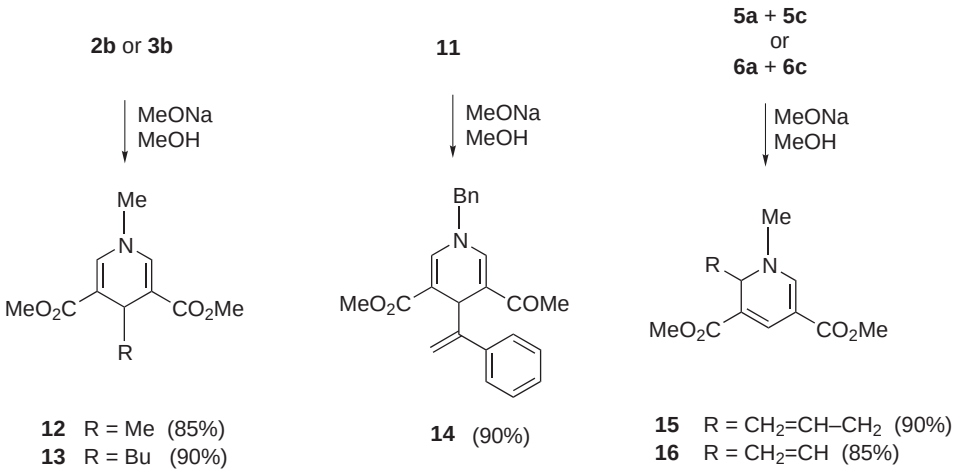
With respect to the introduction of a vinyl residue upon the pyridine ring we first investigated the behavior of a 'simple' vinyl group: the Gilman homocuprate (entry 12) only provided α-adducts, whereas the HO cyanocuprate (entry 13) led to mixtures of α- and γ-adducts; the best ratio of the C-4 vinyl adduct **6b** was obtained using the mixed alkyl vinyl HO cyanocuprate[9] (entry 14). In contrast, a complex mixture was obtained when pyridinium salt **1** was allowed to react with vinylmagnesium chloride in the presence of $CeCl_3$,[10] and no reaction was observed with $(vinyl)_2Cu(CN)(MgCl)_2$. On the other hand, the mixed methyl α-styryl HO cyanocuprate (entry 15) reacts preferentially at the C-6 position of the pyridine ring to give dihydropyridine **7c** as the major product in high yield. A similar result was obtained from the corresponding copper-catalyzed vinyl Grignard reagent (entry 16).

It is worth mentioning that the extension of the addition-TCAA acylation sequence from 3-acetylpyridinium salt **8** and the organocopper reagents depicted in Scheme 2 (in each case we selected the reagent that had provided the best γ-regioselectivity from salt **1**) afforded only the corresponding C-4 adducts **9**–**11**, although the overall yields were considerably lower than in the above methoxycarbonyl series. This result might reflect the instability of the initially formed α-adducts under the acylation conditions.



8 9-11

Scheme 2.



Scheme 3.

Finally, (trichloroacetyl)-1,4-dihydropyridines **2b**, **3b** and **11** were subjected to a haloform-type reaction with sodium methoxide in methanol[11] to give the corresponding diesters **12**–**14** in excellent yields (Scheme 3). Interestingly, this transformation allows the conversion of the mixtures of trichloroacetylated C-2 and C-6 adducts **5a**,**c** and **6a**,**c** into single 1,2-dihydropyridine-3,5-dicarboxylic esters **15** and **16**, respectively.

In conclusion, the above results provide a flexible route to diversely substituted 1,2- and 1,4-dihydropyridines bearing electron-withdrawing groups at the 3- and 5-positions. Starting from easily accessible 3-acyl-*N*-alkylpyridinium salts, our approach involves the sequential introduction of substituents at the α- (or γ) and the free β-position of the pyridine ring by nucleophilic addition of a suitable organocopper reagent followed by acylation of the resultant 1,2- (or 1,4-) dihydropyridine.

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