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Synthesis of 3,5-diacyl-4-phenyl-1,4-dihydropyridines

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Abstract

3,5-Diacyl-4-phenyl-1,4-dihydropyridines have been synthesized *via* a regio- and chemoselective addition of $Ph_2Cu(CN)Li_2$ to β-substituted *N*-alkylpyridinium salts, followed by acylation of the intermediate 1,4-dihydropyridines with trichloroacetic anhydride and subsequent haloform-type reaction. A similar sequence using an *N*-silylpyridinium salt and PhMgBr allows the preparation of the corresponding *N*-unsubstituted dihydropyridines. © 1998 Elsevier Science Ltd. All rights reserved.

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The nucleophilic addition of indole-containing enolates to pyridinium salts has emerged as a powerful tool for the synthesis of indole alkaloids [1]. In particular, the addition of 2-acetylindole enolates to *N*-alkylpyridinium salts bearing an electron-withdrawing substituent at the β-position, followed by acylation of the intermediate 1,4-dihydropyridines with trichloroacetic anhydride (TCAA) gives 3,5-diacyl substituted 1,4-dihydropyridines [2], from which the total synthesis of several ervatamine alkaloids has been successfully accomplished in our laboratory [3,4]. However, the major drawback of the methodology involving the addition of enolates to pyridinium salts is the moderate regioselectivity of the nucleophilic attack. In order to further expand the scope of the above nucleophilic addition-acylation sequence, we focused our attention on the synthesis of 3,5-diacyl-4-phenyl-1,4-dihydropyridines, which are structurally related to nifedipine-type compounds [5].

For our purpose, the chemo- and regioselective introduction of a phenyl group at the γ-position of an *N*-alkylpyridinium salt by means of a suitable organometallic reagent was required. In this context, good to excellent C-4 regioselectivity upon reaction with *N*-acylpyridinium salts has usually been achieved with organocopper reagents [6–10], although there is scarce information about the same process with *N*-alkylpyridinium salts [10,11]. Moreover, in most cases the initially formed *N*-acyl-1,4-dihydropyridines are rapidly oxidized to the corresponding pyridines and there are only a few examples dealing with the acylation of these dihydropyridines [8,12,13].

For our study we selected a variety of *N*-methyl and *N*-benzylpyridinium salts **1a-g**, which differ in the electron-withdrawing group at the β-position of the ring, and the organocopper reagents **2-4** [14] (Scheme 1). After a comparative study of the addition-TCAA acylation sequence starting from pyridinium salt **1a** (Table 1, entries 1-3), the higher order heterocuprate $Ph_2Cu(CN)Li_2$ (**4**) proved to be the most efficient reagent for the regioselective introduction of a phenyl group.

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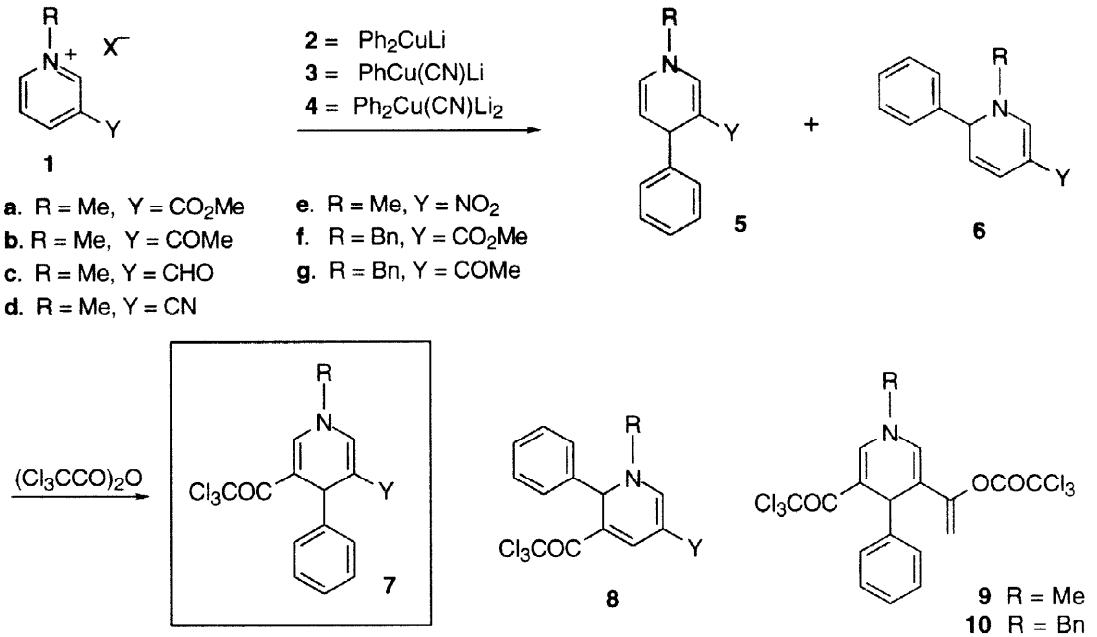


Scheme 1

Table 1
Reaction of Pyridinium Salts **1** with "PhCu"

Entry	"PhCu"	Pyridinium Salt[a]	Addition Products[b] [ratio, yield (%)]	Addition + TCAA Acylation[c] Products [ratio, overall yield(%)]
1	**2**	**1a**	--	**7a + 8a** (3:1, 35)
2	**3**	**1a**	--	**7a + 8a** (2:1, 35)
3	**4**	**1a**	**5a + 6a** (10:1, 75)	**7a + 8a** (6:1, 63)
4	**4**	**1b**	**5b** (70)	**7b** (55)[d]
5	**4**	**1c**	**5c + 6c** (5:3, 40)	---
6	**4**	**1d**	**5d + 6d** (5:1, 60)	**7d** (90)[e]
7	**4**	**1e**	**5e** (42)	---
8	**4**	**1f**	—	**7f + 8f** (3:1, 45)
9	**4**	**1g**	—	**7g + 10** (40)[f]

[a] Series **a-e**: X = I; series **f** and **g**: X = Cl.

[b] In a typical run, pyridinium salt **1** (2 mmol) was added in portions to a cooled (-40 °C) solution of **4** (6 mmol) in THF (30 ml), and the resulting mixture was stirred at -40 °C for 1.5 h. After extractive workup and flash chromatography (SiO_2, hexanes-ethyl acetate) of the residue (A), dihydropyridine **5** was obtained.

[c] In a typical run, a solution of the above crude residue (A) in THF (30 ml) at 0 °C was treated with TCAA (4 mmol) for 2 h. Workup and flash chromatography as above gave dihydropyridine **7**.

[d] In some runs dihydropyridine **9** was also detected.

[e] Acylation effected from the previously isolated 1,4-dihydropyridine **5d**.

[f] Variable ratio.

The results of the addition reaction or (in most cases) the addition-acylation sequence with this reagent are listed in Table 1, entries 3-9. Several points deserve comment:

(i) The addition of **4** to pyridinium salts **1a**, **1b**, and **1d** occurs regio- and chemoselectively to give 1,4-dihydropyridines **5a**,[1] **5b**, and **5d** (entries 3, 4, and 6) as the major or exclusive (**5b**) products in good yields. Subsequent acylation of the crude reaction mixtures

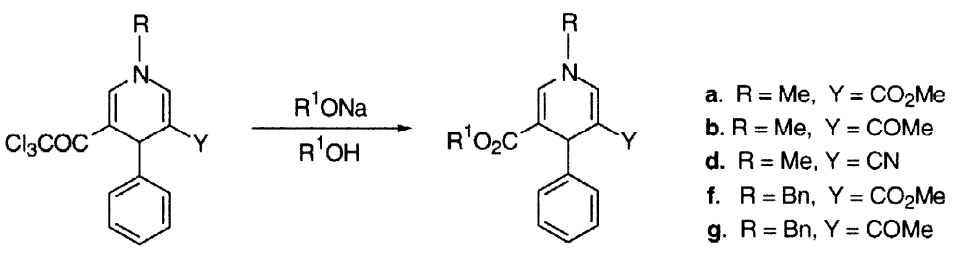
[1] Compound **5a**: ^{1}H-NMR (300 MHz, $CDCl_3$) 3.07 (s, 3H, NMe), 3.57 (s, 3H, OMe), 4.49 (d, J = 4.9 Hz, 1H, 4-H), 4.90 (dd, J = 7.7, 4.9 Hz, 1H, 5-H), 5.84 (ddd, J = 7.7, 1.6, 0.8 Hz, 1H, 6-H), 7.23 (d, J = 1.6 Hz, 1H, 2-H), 7.15-7.40 (m, 5H, Ar). ^{13}C-NMR ($CDCl_3$, 75 MHz) 37.8 (C-4), 40.8 (NMe), 50.5 (OMe), 108.3 (C-5), 110.8 (C-3), 125.9 (C-6), 126.0, 127.4, 128.0 (Ph), 140.8 (C-2), 147.9 (Ph), 168.1 (CO).

gave the corresponding (trichloroacetyl)-1,4-dihydropyridines **7a**,[2] **7b**, and **7d** in acceptable overall yields.

(ii) The yield of the addition step is slightly lower from pyridinium salts **1c** and **1e** (entries 5 and 7), which are substituted with stronger electron-withdrawing groups. From **1c** the regioselectivity is low. In these cases, the resulting dihydropyridines **5c** or **5e** did not undergo acylation under the usual conditions.

(iii) The yields of the addition-acylation sequence from benzylpyridinium salts **1f** and **1g** are similar to those obtained in the methyl series. However, from **1f** the regioselectivity is lower than from **1a**. It is worth mentioning that, again, no 1,2-dihydropyridine could be detected from acetylpyridinium salt **1g**.

As could be expected from our previous work [2-4], (trichloroacetyl)dihydropyridines **7a**, **7b**, **7d**, **7f**, and **7g** underwent a haloform-type reaction with sodium methoxide[3] to give the corresponding methyl esters **11a** (80%),[4] **11b** (93%), **11d** (85%), **11f** (90%), and **11g** (86%). The use of alkoxides different than methoxide allows the preparation of 1,4-dihydropyridines bearing two different ester groups at the β-positions (Scheme 2). Thus, treatment of **7a** with sodium isopropoxide in isopropanol led to dihydropyridine **12a** in 75% yield.



7

11 R^1 = Me

12 R^1 = *i*-Pr

Scheme 2

For the preparation of *N*-unsubstituted 3,5-diacyl-4-phenyl-1,4-dihydropyridines we took advantage of the regioselective addition of organomagnesium compounds to *N*-(*tert*-butyldimethylsilyl)pyridinium salts [8]. Thus, reaction of methyl nicotinate with *tert*-butyldimethylsilyl triflate gave the corresponding pyridinium salt, which was treated with phenylmagnesium chloride (THF, -40 °C) and then with TBAF (-40 °C to 0 °C). Acylation of the resulting crude 1,4-dihydropyridine **13** with TCAA, as above, gave (trichloroacetyl)-1,4-dihydropyridine **14** in 40% overall yield from methyl nicotinate (Scheme 3). Subsequent haloform reaction with sodium methoxide or sodium isopropoxide gave esters **15** or **16** in 80 and 75% yield, respectively.

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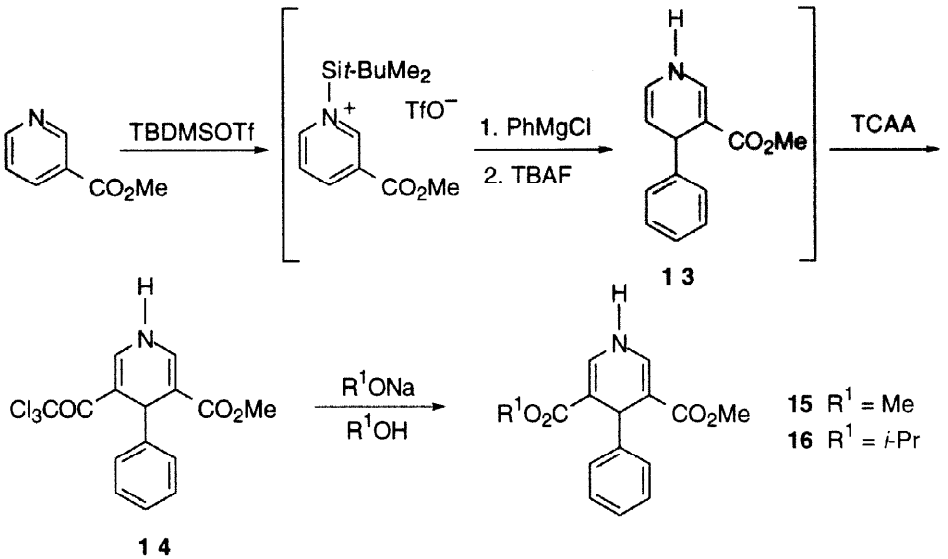
[2] Compound **7a**: ^{1}H-NMR (300 MHz, $CDCl_3$) 3.36 (s, 3H, NMe), 3.66 (s, 3H, OMe), 5.03 (s, 1H, 4-H), 7.10-7.35 (m, 6H, Ph, 2-H), 7.83 (s, 1H, 6-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) 37.0 (C-4), 42.4 (NMe), 51.6 (OMe), 96.5 (CCl_3), 106.7 (C-3), 111.5 (C-5), 126.7, 128.0, 128.2 (Ph), 136.3 (C-2), 143.7 (C-6), 145.0 (Ph), 166.5, 178.7 (CO). HRMS calcd for $C_{16}H_{14}NO_3Cl_3$: 373.0039, found 373.0047.

[3] Standard procedure: Dihydropyridine **7** (0.5 mmol) in MeOH-THF (1:1, 20 ml) was added to a solution of MeONa (1.5 mmol) in MeOH (20 ml), and the resulting solution was stirred at rt for 1 min. The solvent was evaporated, and the residue was partitioned between H_2O and ether, and extracted with ether. Evaporation of the solvent followed by flash chromatography (hexanes-ethyl acetate) gave dihydropyridine **11**.

[4] Compound **11a**: mp 192 °C (acetone). ^{1}H-NMR ($CDCl_3$, 300 MHz) 3.25 (s, 3H, NMe), 3.62 (s, 6H, OMe), 4.87 (s, 1H, 4-H), 7.10-7.40 (m, 7H, Ph, 2-H, 6-H). ^{13}C-NMR ($CDCl_3$, 75 MHz) 36.8 (C-4), 41.4 (NMe), 51.1 (OMe), 108.1 (C-3, C-5), 126.3, 127.9 (Ph), 138.3 (C-2, C-6), 146.4 (Ph), 167.1 (CO). Anal. Calcd. for $C_{16}H_{17}NO_4$: C, 66.89; H, 5.96; N, 4.87. Found: C, 66.75; H, 6.08; N, 4.89.



Scheme 3

1,4-Dihydropyridines **7**, **11**, **12**, and **14-16**, with two electron-withdrawing substituents at the β-positions, are crystalline solids, stable enough to be characterized by elemental analysis and/or HRMS. In contrast, dihydropyridines **5** are prone to undergo oxidation and could be identified only by NMR data.

The above results not only establish a convenient synthetic method for the preparation of valuable 3,5-diacyl-4-aryl-1,4-dihydropyridines but also demonstrate that the addition of the higher order heterocuprate $Ph_2Cu(CN)Li_2$ to *N*-alkylpyridinium salts takes place with higher regioselectivity and better yield than the addition of enolates.

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