Alkylation of 3,4-Dihydro-β-carboline

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Alkylation of 3,4-dihydro-β-carboline has been accomplished with organo-copper and -lithium reagents by activation of BF_3·OEt_2 or trimethylsilyl trifluoromethanesulphonate.

There are a number of indole alkaloids which contain the 1-substituted tetrahydro-β-carboline ring system, *e.g.*, the simple alkaloid tetrahydroharman. Recently, we have reported the total syntheses of fumitremorgin B[1] and C[2] and eudistomins[3] which have the tetrahydro-β-carboline ring system. Meyers *et al.* have reported a general method to obtain the optically active 1-substituted tetrahydro-β-carbolines.[4] The asymmetric reduction of 1-substituted dihydro-β-carboline with chiral sodium acyloxyborohydrides has also been reported.[5] More recently several groups have reported the reaction of 3,4-dihydro-β-carboline (**1**) with nucleophiles to give 1-substituted tetrahydro-β-carbolines.[6]

We herein report a new approach to obtain 1-substituted tetrahydro-β-carbolines by a simple alkylation of 3,4-dihydro-β-carboline (**1**), which is readily accessible by the conventional Bischler-Napieralski reaction of N^b-formyltryptamine, with highly reactive organometallic compounds (Scheme 1).

Table 1. The alkylation of the BF_3–iminium salt (**3**) of 3,4-dihydro-β-carboline.[a]

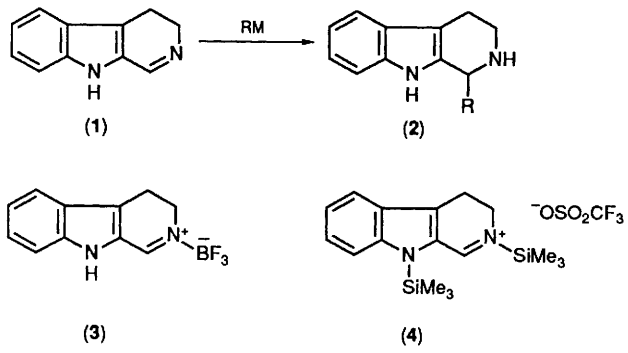
Run	Nucleophile (mol equiv.)	*T*/°C	*t*/h	Product[b,c] /%
1	Me_2CuLi (5)	−23	0.5	(**2a**) 74[d]
2	Bu^n_2CuLi (5)	−78	2.0	(**2b**) 61[d]
3	Bu^s_2CuLi (5)	−45	1.5	(**2c**) 56[e]
4	Bu^t_2CuLi (3)	−50	1.5	(**2d**) 48
5	$(CH_2{=}CH)_2CuMgBr$ (3)	−42	1.5	(**2e**) 29
6	$(HC{\equiv}C)_2CuLi$ (3)	−78	1.0	(**2f**) 29
7	Ph_2CuLi (3)	−23	1.0	(**2g**) 0
8	MeLi (3)	−23	2.5	(**2a**) 79
9	Bu^nLi (5)	−23	6.0	(**2b**) 64
10	Bu^sLi (3)	−23	2.0	(**2c**) 48[e]
11	Bu^tLi (3)	−23	5.0	(**2d**) 89
12	PhLi (3)	−23	3.0	(**2g**) 75

[a] BF_3·OEt_2 (1.1 mol equiv.) was used as an activator. [b] All compounds were confirmed by NMR, mass, IR, and UV spectra. Compounds (**2a**, **b**, and **g**) and (**2a**, **b**, **d**, and **g**) were confirmed by comparison with authentic samples prepared by the Bischler–Napieralski and Pictet–Spengler reactions, respectively. [c] Yields are based on isolated material. [d] Isolated as the N^b-methoxycarbonyl derivative. [e] Mixture of diastereoisomers, which were not separated.

Table 2. The alkylation of the TMS–iminium salt (**4**) of 3,4-dihydro-β-carboline with alkyl-lithiums.

Run	Nucleophile (mol equiv.)	*T*/°C	*t*/h	Product[a,b] /%
1	MeLi (3)	−78	1	(**2a**) 70[c]
2	Bu^nLi (3)	−78	1	(**2b**) 80[c]
3	Bu^sLi (3)	−78	1	(**2c**) 37[c,d]
4	Bu^tLi (3)	−78	1	(**2d**) 34[c]
5	PhLi (3)	−78	1	(**2e**) 72
6	$HC{\equiv}CLi$ (3)	—[e]	—[e]	(**2f**) 47
7	$PhC{\equiv}CLi$ (3)	−23	1	(**2h**) 59
8	$PhCH_2Li$ (3)	−78	2	(**2i**) 46
9	Furyl-Li (5)	−23	1	(**2j**) 16[c]
10	1-Me-pyrryl-Li (5)	−23	1	(**2k**) 29[c]

[a–d] See Table 1, footnotes b—e. [e] At −23 °C for 1 h, then at room temp. for 0.3 h.



a; R = Me
b; R = Bu^n
c; R = Bu^s
d; R = Bu^t
e; R = CH_2=CH
f; R = HC≡C
g; R = Ph
h; R = PhC≡C
i; R = $PhCH_2$
j; R = 2-furyl
k; R = 1-Me-pyrryl

Scheme 1

We first carried out the alkylation of the C=N double bond of (**1**) with MeLi, MeMgBr, and Me_2CuLi under various conditions. In contrast to carbonyl compounds, the imine (**1**) did not react with these alkylating agents, suggesting that electrophilic activation of the imine is necessary. The idea of an amphiphilic reaction system was first examined by the addition of an organometallic compound to the BF_3–iminium salt (**3**) in tetrahydrofuran (THF). The results of the alkylation are summarized in Table 1.†

Methyl or primary cuprate gave a 61—74% yield of the corresponding 1-substituted β-carboline (**2**), isolated as the carbamate ester. Secondary and t-butyl derivatives were also obtained in fair yields but the yields of vinyl and acetylene derivatives, (**2d**) and (**2f**), have not been optimized yet.

When the trimethylsilyl (TMS)-activated iminium salt (**4**) was treated with a variety of alkyl-lithium compounds, a facile nucleophilic addition was observed (Table 2), giving a fairly good yield of the corresponding β-carboline (**2**) including furan and pyrrole derivatives. The usefulness of the TMS–iminium salt (**4**) was further demonstrated in the reaction with Grignard reagents (3 mol equiv.), giving a 70—80% yield of (**2**) (Table 3). However, the use of higher order cuprates, $R_2Cu(CN)Li_2$, was less effective.

Table 3. The alkylation of the TMS–iminium salt (**4**) of 3,4-dihydro-β-carboline with Grignard reagents.

Run	Nucleophile (mol equiv.)	*T*/°C	*t*/h	Product[a,b] /%
1	MeMgBr (3)	−42	1	(**2a**) 71[c]
2	PhMgBr (3)	−42	1	(**2g**) 71
3	Bu^{n}MgCl (3)	−42	1	(**2b**) 80[c]
4	Bu^{t}MgCl (3)	−78	1	(**2d**) 10[c]
5	CH_2=CHMgBr (3)	−23	1.5	(**2e**) 27[c]
6	HC≡CMgBr (3)	—[d]	—[d]	(**2f**) 12

[a—c] See Table 1, footnotes b—d. [d] At −23 °C for 1 h, then at room temp. for 1 h.

From these results, it is clear that a variety of organometallic reagents add to the iminium salt of (**1**) to give the corresponding 1-substituted tetrahydro-β-carbolines. The application of these reactions to obtain (**2**) in optically active form is being investigated.

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† Typical experimental procedure (run 8): BF_3·OEt_2 (0.14 ml, 1.1 mmol) was added to a solution of (**1**) (170 mg, 1.0 mmol) in THF (10 ml) at room temperature, and the mixture was cooled to −23 °C. MeLi (1.08 M in Et_2O, 3.0 ml, 3.2 mmol) was added to the mixture and the whole was stirred for 2.5 h at −23 °C. In case of copper reagents, the solution of iminium salt (**3**) in THF was added to the solution of organocopper reagent in Et_2O–THF. The reaction was quenched by the addition of 20% aqueous K_2CO_3 (5 ml). Extractive work-up and column chromatography (SiO_2, AcOEt : MeOH 1 : 0—4 : 1) gave (**2a**) (147 mg, 79%).

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