

Alkylation of 3,4-Dihydro- β -carboline

Masako Nakagawa,* Tomohiko Kawate, Hitoshi Yamazaki, and Tohru Hino*

Faculty of Pharmaceutical Sciences, Chiba University, 1-33 Yayoi-cho, Chiba-shi, 260, Japan

Alkylation of 3,4-dihydro- β -carboline has been accomplished with organo-copper and -lithium reagents by activation of $\text{BF}_3\cdot\text{OEt}_2$ 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 B¹ and C² and eudistomins³ 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

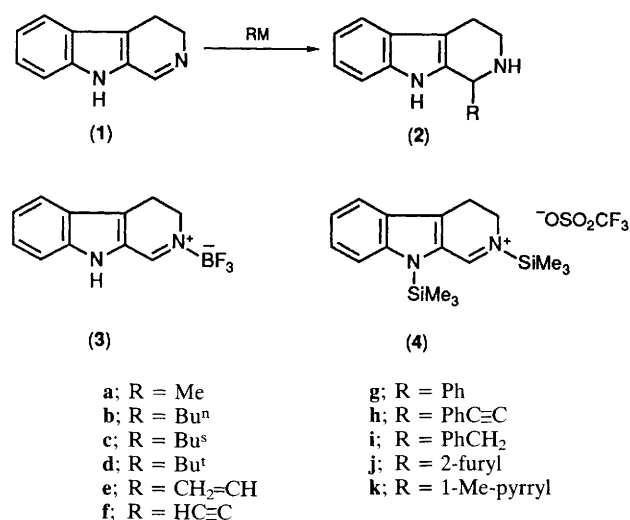
Run	Nucleophile (mol equiv.)	<i>T</i> /°C	<i>t</i> /h	Product ^{b,c} /%
1	Me_2CuLi (5)	-23	0.5	(2a) 74 ^d
2	Bu^n_2CuLi (5)	-78	2.0	(2b) 61 ^d
3	Bu^s_2CuLi (5)	-45	1.5	(2c) 56 ^e
4	Bu^t_2CuLi (3)	-50	1.5	(2d) 48
5	$(\text{CH}_2=\text{CH})_2\text{CuMgBr}$ (3)	-42	1.5	(2e) 29
6	$(\text{HC}\equiv\text{C})_2\text{CuLi}$ (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 $\text{BF}_3\cdot\text{OEt}_2$ (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.)	<i>T</i> /°C	<i>t</i> /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	$\text{HC}\equiv\text{CLi}$ (3)	— ^e	— ^e	(2f) 47
7	$\text{PhC}\equiv\text{CLi}$ (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-pyrrol-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.



Scheme 1

We first carried out the alkylation of the C=N double bond of (1) with MeLi, MeMgBr, and Me₂CuLi 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 BF₃-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-

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.

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, R₂Cu(CN)Li₂, was less effective.

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.

Financial support from the Ministry of Education, Science, and Culture, in the form of a Grant-in-Aid for Scientific Research, and from the Fujisawa Foundation is acknowledged. We thank Mrs. H. Seki, Miss R. Hara, and Mr. T. Kuramochi at the Analytical Centre of Chiba University for measurement of spectral data (NMR and mass).

Received, 10th April 1990; Com. 0/01618G

References

- 1 M. Nakagawa, S. Kodato, M. Hongu, T. Kawate, and T. Hino, *Tetrahedron Lett.*, 1986, **27**, 6217; *Tetrahedron*, 1988, **44**, 359.
- 2 T. Hino, T. Kawate, and M. Nakagawa, *Tetrahedron*, 1989, **45**, 1941.
- 3 M. Nakagawa, J.-J. Liu, and T. Hino, *J. Am. Chem. Soc.*, 1989, **111**, 2721; J.-J. Liu, M. Nakagawa, N. Harada, A. Tsuruoka, A. Hasegawa, J. Ma, and T. Hino, *Heterocycles*, 1990, **31**, 229.
- 4 A. I. Meyers, D. B. Miller, and F. H. White, *J. Am. Chem. Soc.*, 1988, **110**, 4778, and references cited therein.
- 5 K. Yamada, M. Takeda, and T. Iwakuma, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2665.
- 6 Jahangir, D. B. MacLean, M. A. Brook, and H. L. Holland, *J. Chem. Soc., Chem. Commun.*, 1986, 1608; D. B. Repke, Jahangir, R. D. Clark, and D. B. MacLean, *ibid.*, 1988, 439; D. B. Repke, Jahangir, R. D. Clark, and J. T. Nelson, *Heterocycles*, 1988, **27**, 2289; P. A. Grieco and A. Bahsas, *J. Org. Chem.*, 1987, **52**, 1378; S. F. Martin, B. Benage, and J. E. Hunter, *J. Am. Chem. Soc.*, 1988, **110**, 5925.

[†] Typical experimental procedure (run 8): BF₃·OEt₂ (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 Et₂O, 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 Et₂O-THF. The reaction was quenched by the addition of 20% aqueous K₂CO₃ (5 ml). Extractive work-up and column chromatography (SiO₂, AcOEt:MeOH 1:0–4:1) gave (2a) (147 mg, 79%).