Pergamon

Tetrahedron Letters, Vol. 35, No. 24, pp. 4099-4102, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)E0775-S

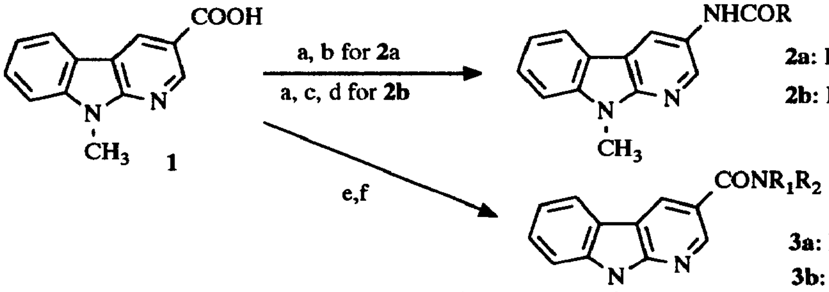
Study of the Lithiation of 3-Substituted α-Carbolines A New Route to 3,4-Disubstituted Derivatives

Cyril Papamicaël, Georges Dupas*, Jean Bourguignon and Guy Quéguiner.

Laboratoire de Chimie Organique Fine et Hétérocyclique de l'IRCOF, associé au CNRS, Institut National
des Sciences Appliquées de Rouen, BP 08, 76131 Mont-Saint-Aignan Cédex, France.

Abstract: The synthesis of new 3-substituted α-carbolines is described and these products were subjected to ortho-lithiation experiments. 3-pivalamido and 3-carboxamido derivatives are cleanly lithiated at 4-position. The results are correlated with MNDO calculations. Various 3,4-disubstituted α-carbolines are obtained in excellent yields.

Our group has been interested for a long time in the metalation of π-deficient heterocycles. Good results were obtained in the pyridine and diazines series.[1] Nowadays, the association between metalation and cross-coupling reactions has become a powerful tool to obtain a large variety of natural products.[2] We found interesting to study the metalation of tricyclic structures like α-carbolines because there is a lack of functionalization methods affording 2,3- or 3,4-disubstituted products in this series. Moreover, these compounds may be versatile intermediates in the synthesis of natural products, like grossularines- 1 or -2,[3] or tetracyclic structures possessing an indole ring. A recent report of Dodd *et al* [4] concerning the metalation of some β-carboline derivatives prompted us to describe our own results in the α-carboline series. We have recently reported the synthesis of 9-methyl[9H]pyrido[2,3-b]indole-3-carboxylic acid **1** starting from the readily available 1-methyl-2-tosylaminoindole, in an easy one pot process followed by alkaline hydrolysis of the intermediate carbonitrile.[5,6]

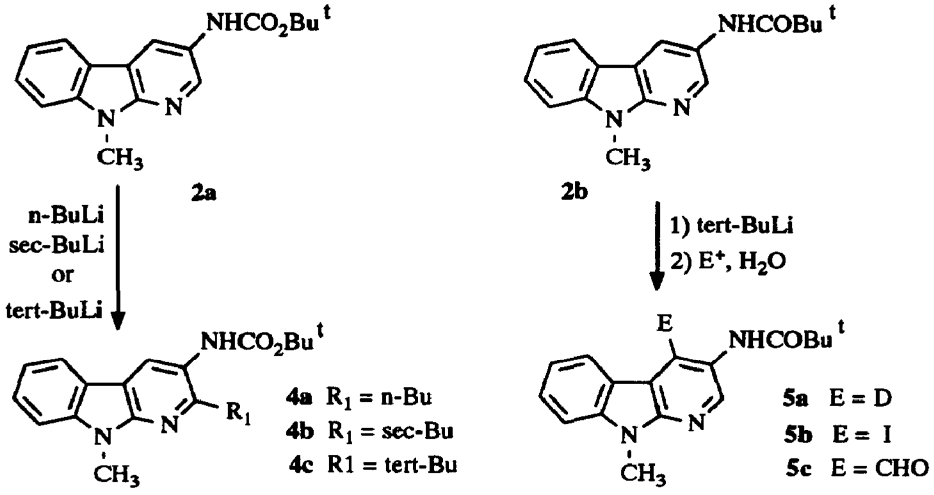


a) $(PhO)_2PON_3/NEt_3$; b)tBuOH, reflux 23 h; c)H_2O/H^+ Δ, pH 2 d)ClCOtBu/THF/NEt_3; e) $SOCl_2$ reflux; f) R_1R_2NH

Scheme 1

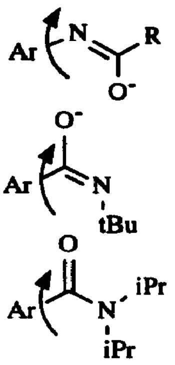
Starting from carboxylic acid **1**, we synthesized compounds **2a-b** and **3a-b** possessing as orthodirecting metalation groups (DMG): N-substituted carboxamides, pivalamido and N-(tert-butyloxycarbonylamino) functions (Scheme 1). To obtain the amino derivatives, we used a variation of the Curtius reaction.[7] After reaction of **1** with diphenylphosphoryl azide, the intermediate carbonyl azide was refluxed with tert-butylalcohol leading to the carbamate **2a** in a 70 % overall yield,[8] or was heated in acidic water, and the amine subsequently treated with pivaloyl-chloride leading to carboxamide **2b** in a 72 % overall yield .[8] Finally, when acid **1** was reacted with thionyl chloride and subsequently treated with tert-butylamine or diisopropylamine the carboxamido derivatives **3a** and **3b** were obtained in 80 % and 90 % yields respectively.[8]

Metalation of amine derivatives 2a-b:



Scheme 2

We first studied the metalation reaction of carbamate **2a** (Scheme 2), with various alkyllithiums under conditions used in the pyridine series.[7] But after quenching with EtOD, we obtained only mixtures of unreacted **2a** and **4a-c** resulting from nucleophilic addition of the alkylithium probably to the 2-position of the α-carboline. The aromatization of the intermediate dihydropyridine derivative occurred during the work-up and compounds **4a-c** were always isolated after flash chromatography. The study of CPK molecular models and modelisation sofwares showed that the 4-position of the pyridine ring is sterically crowded by the bulky carbamate group and the vicinity of the H_5 hydrogen on the benzene ring (the distance between the two hydrogens was about 2,7 Å as shown by modelisation softwares).[9] As a consequence a tert-butyl group could not be introduced in the 4-position and addition occured in 2-position. Some experiments were performed with methyl lithium or lithium 2,2,6,6-tetramethylpiperidide (LTMP, in order to avoid addition) but unreacted **2a** was always obtained. In order to rationalize these surprising results and to try to make previsions concerning the best DMG, we performed some MNDO calculations [9] with α-carboline derivatives **2a-b** and **3a-b**. The LUMO energies were compared to that obtained with the corresponding pyridine analogues. Obviously, in the case of **2a-b** and **3a**, the computed structures respectively **2'a-b** and **3'a** were intermediates resulting from N-H abstraction by the first equivalent of alkylithium (Table 1).



2'a: R = OtBu
2'b: R = tBu

3'a

3b

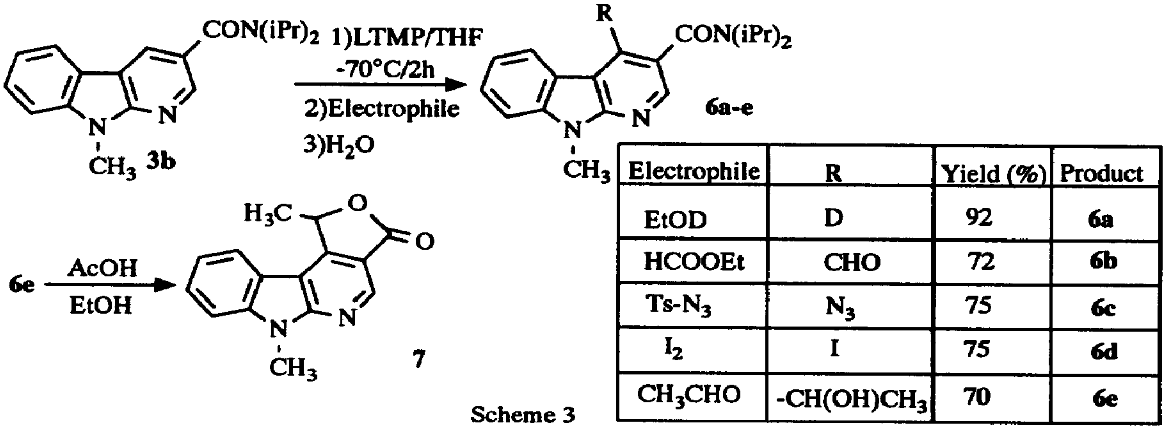
Computed structure *	E_{LUMO} (eV) Ar = 3-carboline	E_{LUMO} (eV) Ar = 3-pyridyl
2'a	1.7	4.3
2'b	2.7	4.4
3'a	2.1	3.3
3b	-0.56	-0.47

* The LUMO energies were computed for various conformations of the 3-substituent (s-cis and s-trans were also considered) and only small changes were observed. As a consequence, averaged values are given in the table.

Table 1

The calculation results on carboline and pyridine derivatives depend at a small extent on the actual conformation of the 3-substituent. As shown in Table 1, the LUMO energies of carboline derivatives are always lower than those of their homologs in the pyridine series. This fact could explain the observed addition reactions .[4] However, the difference is smaller in the case of pivalamide **2b** (intermediate **2'b**) and we decided to carry out the metalation experiments with this compound. With n-BuLi (-70°C or -20°C) or sec-BuLi (-40°C), only mixtures of the starting material and the aromatized addition products were observed. However, with tert-BuLi in THF at -70°C, with a reaction time of 6 hours and quenching with EtOD (Scheme 2) we observed the formation of a deuterated compound **5a** in good yield (80 %, with five equivalents of tert-BuLi). Carefull analysis of the NMR spectra of **5a** compared to that of **2b** showed unambigously that deuterium incorporation had occured in the 4-position of the pyridine ring of the α-carboline system. Comparatively, in the pyridine series metalation also occurred at C-4 with n-BuLi, but at higher temperature.[10] In order to confirm the synthetic interest of this new metalation reaction, we quenched the reaction medium with iodine or ethyl formate and obtained an iodo derivative **5b** and a formyl derivative **5c**.[11]

Metalation of carboxamide derivatives 3a-b:



Electrophile	R	Yield (%)	Product
EtOD	D	92	6a
HCOOEt	CHO	72	6b
Ts-N_3	N_3	75	6c
I_2	I	75	6d
CH_3CHO	$-CH(OH)CH_3$	70	6e

Scheme 3

While metalation experiments on compound **3a** always afforded mixtures of addition product and unreacted **3a**, **3b** was cleanly lithiated at carbon C-4 under the conditions used in the pyridine series (LTMP, -70 °C).[12]

These experimental results can again be rationalized with MNDO calculations.[9] As can be seen in Table 1, the LUMO energies of the carboline carboxamides are again lower than those of the pyridine series. However the difference is very small in the case of diisopropylcarboxamides **3b** and rather important in the case of mono-tert-butylcarboxamides. After metalation of **3b**, the reaction mixture was quenched with various electrophiles (Scheme 3) and 3,4-disubstituted α-carbolines **6a-e** were obtained with good yields. The regioselectivity of the metalation reaction was confirmed by the important deshielding of proton H-5 in the NMR spectra of compounds **6b-e** [13] and nuclear Overhauser experiments. Acid hydrolysis of the carboxamide **6e** gave the lactone **7** with a non-optimized yield of 50 %.[14]

REFERENCES AND NOTES

1. a) G. Quéguiner, F. Marsais, V. Snieckus and J. Epsztajn, *Advances in Heterocyclic Chemistry*, 1991, **52**, 186-304. b) A. Turck, N. Plé and G. Quéguiner, *Heterocycles*, in press.
2. a) See (1). b) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879-933.
3. S. Achab, M. Guyot and P. Potier, *Tetrahedron Lett.*, 1993, 34, 2127-2130 and references cited therein.
4. A. Mehta and R. H. Dodd, *J. Org. Chem.*, 1993, **58**, 7587-7590.
5. V. Levacher, N. Boussad, G. Dupas, J. Bourguignon and G. Quéguiner, *Tetrahedron*, 1992, **48**, 831-840.
6. An other route leading to α-carbolines was recently published. I. T. Forbes, C. N. Johnson and M. Thompson, *Syn. Commun.*, 1993, **23**, 715-723.
7. M. C. Venuti, R. A. Stephenson, R. Alvarez, J. J. Bruno and A. M. Strosberg, *J. Med. Chem*, 1988, **31**, 2136-2145.
8. **2a**: mp = 179 °C. ^{1}H NMR (DMSO d-6, 200 MHz): δ 1.49(s, 9H); 3.86(s, 3H); 7.19-7.26(m, 1H, H_6); 7.46-7.60(m, 2H, $H_{7\text{-}8}$); 8.13(m, 1H, H_5); 8.42(d, J = 2.3 Hz, 1H, H_2); 8.62(m, 1H, H_4); 9.44(m, 1H, NH). **2b**: mp = 194 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40(s, 9H); 3.88(s, 3H); 7.22-7.57(m, 3H, $H_{6\text{-}7\text{-}8}$); 7.59(m, 1H, NH); 8.01(m, 1H, H_5); 8.32(d, J = 2.4 Hz, 1H, H_2); 8.77(d, J = 2.4 Hz, 1H, H_4). It must be pointed out that, in the case of compounds **2a-b**, the proton H_4 is more deshielded than the proton H_2. This inversion of chemical shifts was confirmed by nuclear Overhauser experiments (N.O.E.) on H_5 and H_4 which are separated by only 2.7 Å. **3a**: mp = 178 °C. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 1.5(s, 9H); 3.9(s, 3H); 6.1(m, 1H, NH); 7.15-7.6(m, 3H, $H_{6\text{-}7\text{-}8}$); 7.9-8.1(m, 1H, H_5); 8.6(d, J = 2 Hz, 1H, H_4); 8.8(d; J = 2 Hz, 1H, H_2). **3b**: mp = 139 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.43(m, 12H); 3.7-3.99(m, 5H); 7.28-7.36(m, 1H, H_6); 7.46-7.62(m, 2H, $H_{7\text{-}8}$); 8.08(m, 1H, H_5); 8.36(d, 1H, H_4); 8.51(d, 1H, H_2). For compounds **3a-b**, no inversions of chemical shifts between H_4 and H_2 were observed, as confirmed by N.O.E. experiments.
9. The geometries were first determined after minimization with PCMODEL and MNDO calculations were then performed with MOPAC 6.00 on a PC 486 DX computer.
10. L. Estel, F. Linard, F. Marsais, A. Godard and G. Quéguiner, *J. Heterocyclic Chem.*, 1989, **26**, 105-112.
11. **5b**: ^{1}H NMR (DMSO d-6, 200 MHz): δ 1.31(s, 9H); 3.92(s, 3H); 7.39(m, 1H, H_6); 7.67(m, 2H, $H_{7\text{-}8}$); 8.16(s, 1H, H_2); 8.83(m, 1H, H_5); 9.35(broad, 1H, NH). **5c**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.44(s, 9H); 3.94(s, 3H); 7.27 (m, 1H, H_6); 7.46(m, 1H, H_7); 7.58(m, 1H, H_8); 8.07(m, 1H, H_5); 9.91(s, 1H, H_2); 10.97(broad, 1H, NH); 11.16(s, 1H, CHO). ^{1}H NMR (DMSO d-6, 200 MHz): δ 1.30(s, 9H); 3.93(s, 3H); 7.29(m, 1H, H_6); 7.64(m, 2H, $H_{7\text{-}8}$); 8.67(s, 1H, H_2); 8.74(m, 1H, H_5); 10.08(broad, 1H, NH); 10.33(s, 1H, CHO).
12. a) J. Epsztajn, Z. Berski, J. Z. Brzezinski and A. Jozwiak, *Tetrahedron Lett.*, 1980, **21**, 4739-4742. b) J. Epsztajn, J. Z. Brzezinski and A. Jozwiak, *J. Chem. Res. Synop.*, 1986, 18-19.
13. **6b**: mp (dec)= 211 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.0-1.8(m, 12H); 3.70(m, 2H); 4.02(s, 3H); 7.37(m, 1H, H_6); 7.52(m, 1H, H_7); 7.66(m, 1H, H8); 8.51(s, 1H, H_2); 8.89(m, 1H, H_5); 10.69(s, 1H, CHO). **6c**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.2-1.8(m, 12H); 3.62(m, 2H); 3.95(m, 3H); 7.33(m, 1H, H_6); 7.49(m, 2H, $H_{7\text{-}8}$); 8.35(m, 1H, H_5). **6d**: mp = 244 °C. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 1.2 and 1.65(m, 12H); 3.65(q, J= 7 Hz, 2H); 3.95(s, 3H); 7.2-7.75(m, 3H, $H_{6\text{-}7\text{-}8}$); 8.1(s, 1H, H_2); 8.9(m, 1H, H_5). **6e**: ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.1-2.0(m, 15H); 3.57(m, 2H); 3.97(s, 3H); 5.72(q, J= 7 Hz, 1H); 7.2-7.6(m, 3H, $H_{6\text{-}7\text{-}8}$); 8.23(m, 1H, H_5); 8.27(s, 1H, H_2).
14. **7**: mp = 190 °C. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.88(d, J= 6.7 Hz, 3H); 4.05(s, 3H); 5.94(q, J= 6.7 Hz, 1H); 7.43(m, 1H, H_6); 7.60(m, 2H, $H_{7\text{-}8}$); 7.96(m, 1H, H_5); 9.02(s, 1H, H_2).

(*Received in France* 24 *March* 1994; *accepted* 19 *April* 1994)