Tetrahedron Letters 54 (2013) 3144–3146

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

An efficient and concise total synthesis of the antimalarial alkaloid quindoline

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ARTICLE INFO

Article history:
Received 16 March 2013
Revised 2 April 2013
Accepted 3 April 2013
Available online 10 April 2013

Keywords:
Quindoline
Heteroaromatic lithiation
Malaria
Indoloquinolines

ABSTRACT

The preparation of the alkaloid quindoline (**1**) from indol (**3**) through a very direct synthetic approach is described in this work. Several successive heteroaromatic lithiation reaction steps were performed in the same medium producing benzylic alcohol (**7**) in excellent yield. The alcohol was submitted to catalytic reduction, undergoing concomitant cyclization and aromatization, yielding quindoline (**1**) in 55% overall yield.

The [3,2-*b*] indolo-quinoline alkaloids are relatively rare in nature. Quindoline (**1**) possesses the simplest structure of this class of compounds and can be isolated from the species *Cryptolepis sanguinolenta* (Lind.), family Asclepiadaceae, together with its natural derivative cryptolepine (**2**) (Fig. 1).[1]

The aqueous extract of the root and leaves of this species is used traditionally in West and Central Africa for treatment of malaria and other diseases.[2] Several reports are available in the literature describing the pharmacological activity of the [3,2-*b*] indolo-quinoline alkaloids, revealing important biological activities, such as antifungal, hypoglycemic, and antitumoral.[3–5]

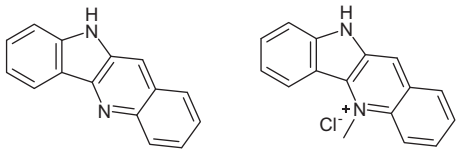
The first synthesis of quindoline (**1**) was achieved by Fichter and Boehringer in 1906.[6] Since this work, several research groups have developed alternative syntheses for the preparation of this natural product and derivatives through approaches involving cross-coupling reactions catalyzed by palladium,[7] reductive cyclization mediated by transition metals,[8] and photochemical reactions,[9] among others.[4,10] These synthetic routes require a large number of steps via complicated synthetic disconnections or expensive reagents and low overall yields in addition to starting reagents that need previous preparation.[7–11]

Here, we report an extraordinarily concise total synthesis of quindoline in two steps from indole and *o*-nitrobenzaldehyde. Our route to the natural product is based on the C-2 lithiation of indole (**3**). Typically, such lithiations are carried out with a protective and directing group linked to the indole nitrogen that must be easily removed subsequently.[12] In the case of aromatic or heteroaromatic lithiation reactions, some of these groups can be very useful in a range of regioselective functionalization types as *ortho*-metallation directing agents.[13]

One of the most elegant methods to promote indole C-2 lithiation was developed by Katritzky, using carbon dioxide as the N-protecting group. In this procedure, the N-protecting group is inserted in situ and removed upon workup at the end of the reaction, eliminating a separate deprotection step. [14]

We treated indole (**3**) dissolved in THF with 1.1 equiv of *n*-butyl lithium at −70 °C, leading to the formation of 1-lithio-indole (**4**) Scheme 1.

A stream of carbon dioxide gas was then passed through the reaction medium to protect the indole nitrogen as the lithium carbamoyl anion and also direct the metallation reaction at position C2. In Katritzky's work, the reagent *tert*-butyl lithium is used for the C-2 metallation. Instead, we employed *sec*-butyl lithium as it is more stable and of lower cost. The reaction between **5** and



quindoline (**1**) cryptolepine (**2**)

Figure 1. [3,2-*b*] indolo-quinoline alkaloids extracted from *Cryptolepis sanguinolenta*.

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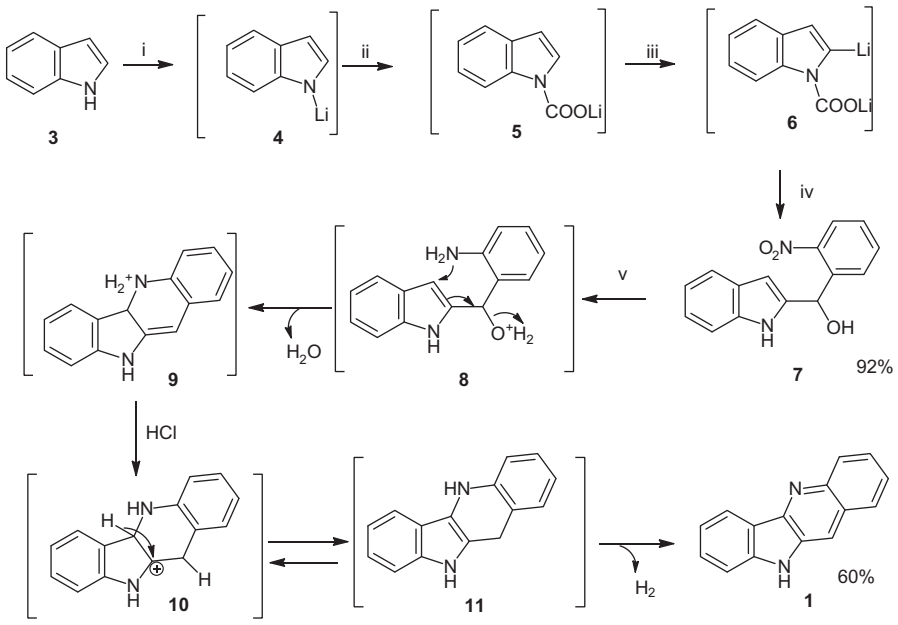
http://dx.doi.org/10.1016/j.tetlet.2013.04.010



Scheme 1. Synthesis of quindoline (**1**). Reagents and conditions: (i) *n*-butyl lithium, THF −70 °C, 30 min; (ii) CO_2, THF, 10 min; (iii) *sec*-butyl lithium, THF, −70 °C, 1 h; (iv) *o*-nitrobenzaldehyde, THF, −70 °C, 1 h; H_2O; (v) H_2 35 psi, Pd–C, CH_3OH, $CHCl_3$ (drops), 12 h.

1.1 equiv of *sec*-butyl lithium at −70 °C, in THF led to the dianion **6**, which upon treatment with 1.0 equiv of the electrophile *o*-nitrobenzaldehyde and workup, produced the desired alcohol **7** in 92% yield.

To our delight, catalytic hydrogenation of the nitro group in **7** directly yielded the natural product quindoline (**1**) in 60% yield. The reduction was performed in methanol containing a few drops of chloroform, with the purpose of generating catalytic amounts of hydrochloric acid in the reaction medium.[15] Under these reaction conditions, we believe intermediate (**8**) undergoes intramolecular cyclization to (**9**) through nucleophilic attack[16] by the aniline with parallel elimination of a molecule of water. Subsequently, isomerization of the exo double bound leads via the cationic intermediate (**10**) to dihydroquinoline (**11**) with the restoration of aromaticity.[17]

The unusual dehydrogenation reaction of the dihydroquinoline (**11**), presumably was mediated by Pd–C. A similar dehydrogenation/aromatization reaction in hydrogen atmosphere using Pd–C as catalyst was also described by Moggridge & Plant in the conversion of tetrahydrocarbazoles to carbazoles.[18]

Overall, our short sequence leads to quindoline (**1**) in only two steps and 55% yield from indole (**3**).[19,20] The efficiency of our route enabled the preparation of **1** on a millimolar scale, and holds promise for the preparation of additional indolo[3,2-*b*]quinoline derivatives for the purpose of evaluation in multiple biological assays.

Acknowledgements

This work is dedicated to Professors Clayton H. Heathcock, UC Berkeley, USA, and Victor A. Snieckus, Queen's University, Canada, for their many contributions to our academic careers.

We thank CAPES and CNPq for scholarships to D.S.B., A.C.S. and FAPERJ for financial support.

Supplementary data

Supplementary data (analytical data and copies of IR, ^1H and ^{13}C NMR spectra of compounds **7** and **1**) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.04.010.

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19. *(1H-Indol-2-yl)(2-nitrophenyl)methanol* (**7**): *N*-butyl lithium (4.4 mL, 2.28 M hexane solution) was added dropwise to a solution of indole (1.17 g, 10.0 mmol) in dry THF (20 mL) at −70 °C. The resulting suspension was kept at −70 °C for 30 min, CO_2(g) was then bubbled through the mixture for 10 min,

and the clear solution was allowed to stand for 10 min. The solvent was evaporated (0 °C, 1 mmHg), the crystalline residue was dissolved in 20 mL dry THF and cooled to −70 °C, and *sec*-butyl lithium (7.5 mL, 1.35 M pentane solution) was added dropwise. After having held the resulting yellow solution at −70 °C for 1 h, o-nitrobenzaldehyde (1.51 g, 10.0 mmol) was added. The reaction mixture was kept at −70 °C for 1 h, water (1 mL) was then added, and the solution was allowed to reach room temperature. It was then poured into NH_4Cl (saturated aqueous, 50 mL) under stirring and diluted with dichloromethane (50 mL). The organic phase was separated, washed with brine, dried ($MgSO_4$), and evaporated. The solid residue was purified by flash chromatography (hexane/ethyl acetate, 7.5%), yielding 2.47 g (92%) of (1*H*-indol-2-yl)(2-nitrophenyl)methanol, mp 45–48 °C (dec). ^{1}H NMR (Acetone-d_6) δ = 10.3 (s, 1 H, NH), 8.09 (dd, *J* = 8.4 Hz, 2 H), 7.7 (dd, *J* = 7.3 Hz, 1H), 7.5 (dd, *J* = 7.6 Hz, 1 H), 7.5 (d, *J* = 7.6 Hz, 1H), 7,4 (d, *J* = 7.8 Hz, 2 H), 6.9 (m, 2H), 6.5 (s, 1H), 6.0 (s, 1H), 5.3 (s, 1H).^{13}C NMR (Acetone-d_6) δ = 65.3, 99.8, 111.2, 119.2, 120.2, 121.4, 124.2, 128.2, 128.6, 129.0, 133.2, 136.8, 138.2, 140.4, 148.4. IR (cm^{-1}) 3401, 3082, 2927, 1525, 1456, 1342, 1291, 1024, 789, 751, 723. HRMS (*m*/*z*): [M−H] calcd for $C_{15}H_{12}N_2O_3$, 267.0775, found 267.0778.

20. *Quindoline (10H-indolo[3,2-b]quinolone,* **1**): To a hydrogenation flask was added **4** (100 mg, 0.37 mmol) in methanol (10.0 mL), drops of chloroform and catalyst 10% Pd/C (10 mg). The resulting suspension was held under atmosphere of H_2 at 35 psi with vigorous stirring for 12 h. The reaction mixture was neutralized by $NaHCO_3$ (200 mg) and filtered through Whatman 41® filter paper. The solvent was evaporated and the solid residue was purified by flash chromatography (hexane/ethyl acetate, 10%), yielding 48.4 mg (60%) of quindoline mp: 249–251 °C (lit.[4] mp 251–252 °C).^{1}H NMR (200 MHz, DMSO-d_6) δ = 11.43 (s, 1H, NH), 8.38 (d, *J* = 8.4 Hz, 1H), 8.29 (s, 1H), 8.18 (d, *J* = 8.4 Hz, 1H), 8.08 (d, *J* = 8.2 Hz, 1H), 7.69–7.48 (m, 4H), 7.29 (dd, *J* = 7.2 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 145.7, 144.0, 143.3, 132.4, 129.7, 128.6, 127.5, 126.7, 126.0, 124.8, 121.4, 121.0, 119.3, 113.0, 111.5. IR (cm^{-1}) 3452, 1615, 1491, 1461, 1399, 1337, 1223, 1126, 879, 849, 818, 757, 738, 716, 609. HRMS (*m*/*z*): [M−H] calcd for $C_{15}H_{10}N_2$, 217.0771, found 217.0769.