Synthesis of tryptanthrin and deoxyvasicinone by a regioselective lithiation-intramolecular electrophilic reaction approach

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Abstract
An efficient synthesis of the 4(*3H*)-quinazolinone-based alkaloids, tryptanthrin and deoxyvasicinone has been achieved in good overall yields by using the strategy of regioselective lithiation-intramolecular electrophilic reaction as a key–step. Both the molecules have been synthesized in just two-steps from readily available starting materials.

Keywords: 4(3*H*)-Quinazolinone heterocycles, lithiation-intramolecular electrophilic reaction, tryptanthrin, deoxyvasicinone

Introduction

4(3*H*)-Quinazolinone is a building block for approximately 150 naturally occurring alkaloids isolated to date from a number of families of the plant kingdom, from animals, and from micro-organisms. All the 4(3*H*)-quinazolinone- based natural products have interesting biological activities and have therefore been extensively investigated for pharmaceutical activities. The 4(3*H*)-quinazolinone ring is regarded as a 'privileged structure' in combinatorial synthesis.[1] These are structures which represent molecules that are capable of binding at multiple sites with high affinity and facilitate more rapid discovery of useful medicinally active compounds.[1]

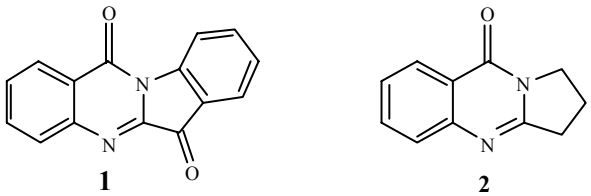


Figure 1

Tryptanthrin (indolo[2,1-*b*]quinazoline-6,12-dione) **1** (Fig. 1) is a weak basic alkaloid found in a number of plant species.[2] Tryptanthrin is the active principal of a traditional Japanese herbal remedy for fungal infections.[3] It possesses anti-bacterial activity against a variety of pathogenic bacteria, particularly the causative agent of tuberculosis,[4] and has displayed remarkable *in vitro* anti-leishmanial activity against *Leishmania donovani*,[5] and against *Trypanosoma brucei*, an extracellular protozoan parasite that is transmitted by tsetse flies.[6] Tryptanthrin can be produced by *Candida lipolytica* when grown in media containing an excess of tryptophan,[7] hence the name tryptanthrin. In recent years, tryptanthrin has attracted much attention as an aryl hydrocarbon receptor agonist,[8] anti-inflammatory agent,[9] inducer of caspase-3/Fas mediated apoptosis,[10] and as an anti-cancer agent.[11]

Deoxyvasicinone (2,3-dihydropyrrolo[2,1-*b*]quinazolin-9(1*H*)-one) **2** is an alkaloid isolated from the aerial parts of *Adhatoda vasica* (from the family Acanthacea, Sankrit-Vasaka), an evergreen sub-herbaceous bush, used extensively in indigenous medicine for cold, cough, bronchitis, and asthma.[12] Deoxyvasicinone possesses antimicrobial, anti-inflammatory and anti-depressant activities.[13] In addition, deoxyvasicinone is very important key intermediate for the synthesis of various natural products such as vasicinone,[14] isaindigotone,[15] and luotonin A.[15]

In view of the importance of tryptanthrin and its attractive *in vitro* properties, synthesis of tryptanthrin has been pursued intensively. It includes annulation of quinazolinone,[16] reductive N-hetero-cyclization,[17] acyl radical cyclization,[18] from isatin,[5] and from 2-indolinone.[19] Similarly, deoxyvasicinone has been synthesized using various methods. It includes intramolecular aza-Wittig reaction,[20] reductive N-heterocyclization,[21] azido-reductive cyclization,[14] solid-phase synthesis,[22] microwave-assisted domino reactions,[23] polymer-supported reagents,[24] radical cyclization,[18] and many other methods.[25] Among these none have employed the strategy of regioselective lithiation at C-2 of quinazolinone followed by reaction with an electrophile in an intramolecular fashion forming C-C bond to generate the cyclized product. As a part of our interest on the synthesis of biologically active N-heterocycles,[26] we became interested in the synthesis of tryptanthrin and deoxyvasicinone using the above- mentioned strategy.

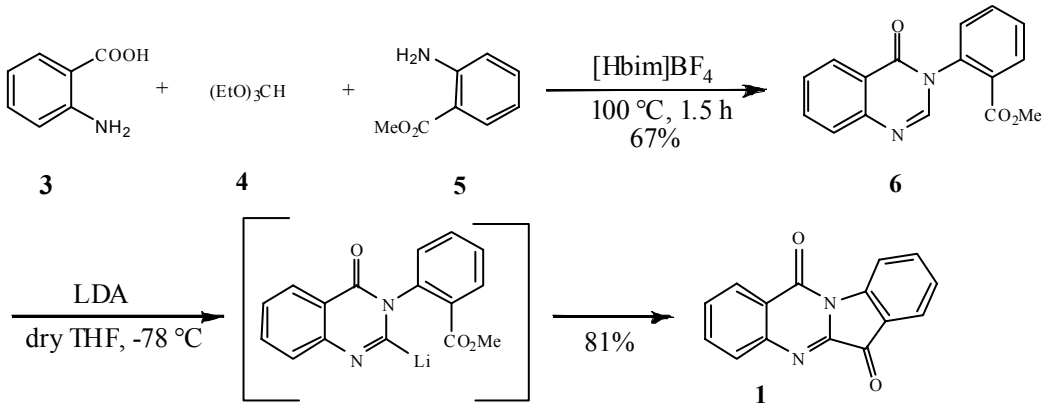
Results and Discussion

Dai and Virgil reported the synthesis of 2-substituted-4(3*H*)-quinazolinone by direct lithiation of 2-unsubstituted quinazolinone followed by reaction of intermediate with electrophile.[27] We expected that the lithiation of 2-unsubstituted quinazolinone at 2-position would be facilitated by the acidity of the proton at this position. If the regioselective lithiation could be realized, its subsequent reaction in an intramolecular fashion with electrophile situated in the appropriate position should afford the cyclized product in a straightforward fashion. To the best of our knowledge, there is no report on regioselective lithiation of 2-unsubstituted quinazolinone at C-2 together with the subsequent reaction with an electrophile in an intramolecular fashion to afford

cyclized products. So we sought to use this strategy for the synthesis of tryptanthrin and deoxyvasicinone.

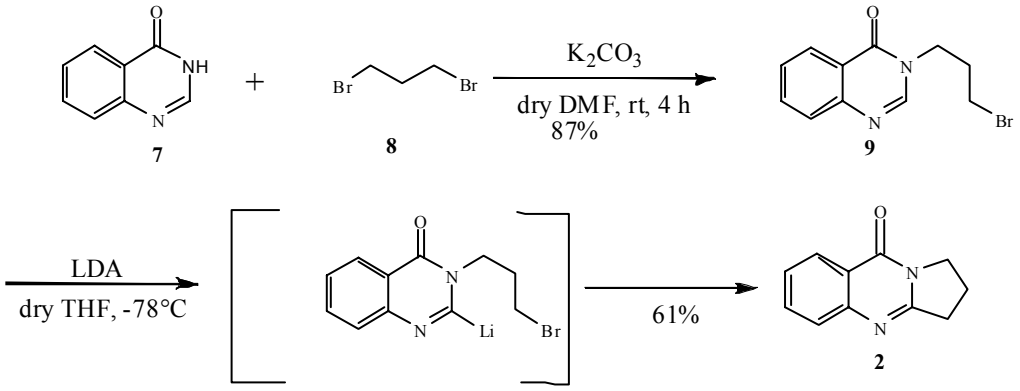
The synthesis of tryptanthrin **1** was initiated with the formation of methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate, **6.** The synthesis of methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate **6** was obtained by condensing anthranilic acid **3** with methyl anthranilate **5** and triethyl orthoformate **4** in the ionic liquid (IL), 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) in 67% yield. This condensation reaction is promoted by the Brønsted acidity of the IL and in this case, the IL plays a dual role as reaction medium as well as a promoter. The structure of **6** was confirmed by mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The ^{1}H NMR spectrum of **6** shows singlet at δ 3.69 ppm corresponding to methyl carboxylate group. Furthermore, compound **6** shows singlet of single hydrogen at δ 8.00 ppm corresponding to hydrogen at C-2 of quinazolinone, which is characteristic peak for quinazolinone, confirming its structure. Furthermore, ^{13}C NMR spectrum also supported the structure of **6**. Then, regioselective lithiation of **6** at C-2 was achieved by using lithium diisopropylamide (LDA) which proceeded readily at -78 °C in dry THF under inert atmosphere to give a reddish solution indicating the formation of lithiated anion which subsequently reacted with the electrophile viz. methyl carboxylate in an intramolecular fashion by forming C-C bond to afford the cyclized product tryptanthrin **1** (Scheme 1). The structure of tryptanthrin **1** was confirmed by mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The ^{1}H NMR spectra of **1** shows the absence of peak as singlet at δ 3.69 ppm and δ 8.00 ppm support its formation. Furthermore, the ^{13}C NMR spectra of **1** shows peak at δ 182.5 ppm corresponding to carbonyl carbon of the ketone. Furthermore, the disappearance of peak at δ 52.4 ppm corresponding to methyl of carboxylic acid ester supports this structure. Thus, by this way we have successfully achieved the synthesis of tryptanthrin in only two steps.

It is to be noted that we wish to highlight the synthesis of the alkaloids, tryptanthrin and deoxyvasicinone rather than highlight the methodology. In the case of tryptanthrin, the overall yield of the process is better than those reported in the literature. Furthermore, both the processes are characterized by easy availability of raw materials, and simple and less hazardous reaction procedures than the reported methods.



Scheme 1

In a similar manner, deoxyvasicinone was synthesized employing the strategy of regioselective lithiation-intramolecular electrophilic reaction. The synthesis of deoxyvasicinone **2** was initiated with the formation of 3-(3-bromopropyl)quinazolin-4(3*H*)-one **9**, obtained by alkylation of 4(3*H*)-quinazolinone **7** with 1,3-dibromopropane **8**, and potassium carbonate in dry DMF at room temperature. The unknown compound **9** is fully characterized. The absence of band in IR spectra in the region 3300-3400 cm^{-1} corresponding to -NH and presence of band in the region 2800-3000 cm^{-1} corresponding to methyl group suggest the formation of N-alkyl derivative. The ^{1}H NMR of **9** shows peaks at δ ppm 2.33-2.45 (m, 2H), 3.42-3.48 (t, 2H), 4.16-4.22 (t, 2H) corresponding to the group (-$CH_2CH_2CH_2$-) suggests the presence of a propyl group. Furthermore, the ^{13}C NMR spectrum of **9** showing peaks at δ 29.7, 31.0, 45.4 ppm respectively for the carbon of propyl group confirmed the structure. Very similar to tryptanthrin, the regioselective lithiation of **9** at C-2 was achieved by using LDA which proceeded readily at -78 °C in dry THF under inert atmosphere to form lithiated anion which subsequently reacted with the electrophile viz. methylene bromide in an intramolecular fashion by forming C-C bond to afford the cyclized product, deoxyvasicinone **2** (Scheme 2). Thus, by this way we have successfully achieved the synthesis of deoxyvasicinone also in only two-steps. The structure of deoxyvasicinone **2** was confirmed by mp, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The ^{1}H NMR spectrum of **2** with the absence of peak as singlet at δ 8.12 ppm corresponding to hydrogen at C-2 of quinazolinone supports its formation. Furthermore, ^{13}C NMR spectra of **2** shows a peak at δ 159.0 ppm indicating that C-alkylation has taken place at the 2-position of 4(3*H*)-quinazolinone. For known compounds, the values were in good agreement with those reported in literature.



Scheme 2

Conclusions

In conclusion, we have achieved the synthesis of tryptanthrin and deoxyvasicinone in only two-steps in good overall yields of 54 and 53% respectively. The key-step for the reaction is the regioselective lithiation at 2-position of 4(3*H*)-quinazolinone followed by subsequent reaction of the lithiated intermediate with the respective electrophiles in an intramolecular fashion to afford the corresponding cyclized product. The advantage of this method is the access to both bio-active molecules, tryptanthrin and deoxyvasicinone from readily available starting materials in only two-steps using a common protocol. The methodology can be extended to the synthesis of other natural products and their mimics to prove its generality.

Experimental Section

General Procedures. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV-200 spectrometer in $CDCl_3$ using TMS as internal standard. Infrared spectra were recorded with ATI MATT-SON RS-1 FTIR spectrometer using KBr pellets. Elemental analyses were obtained using a flash EA 1112 thermoFinnigan instrument and were carried out at the National Chemical Laboratory, Pune. Melting points were recorded in open capillary on Büchi melting Point B-540 apparatus. All solvents and chemicals were of research grade and were used as obtained from Merck and Lancaster. The progress of the reaction was monitored by TLC. Column chromatography was performed using silica gel (60–120 mesh size). Petroleum has boiling point 60-80 °C. RT denotes room temperature.

Methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate (6). A mixture of anthranilic acid **3** (0.27 g, 2 mmol), methyl anthranilate **5** (0.33 g, 2.2 mmol) and triethyl orthoformate **4** (0.32 g, 2.2 mmol) in the ionic liquid, 1-*n*-butylimidazolium tetrafluoroborate ([Hbim]BF_4) (4 mL) was heated with

stirring at 100 °C for 1.5 h. The progress of the reaction was monitored by TLC. After completion of reaction, the reaction mixture was poured into water (10 mL) and product was extracted using ethyl acetate (3x10 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in *vacuo* to give crude product which was purified by column chromatography with petroleum: ethyl acetate (6.5:3.5) to afford 0.38 g of pure methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate **6** (67%) as white needles. mp 181-182; IR (KBr, cm^{-1}) 3019, 2954, 1725, 1683, 1612, 1473, 1274, 1215, 917, 756; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.69 (s, 3H, OCH_3), 7.38 (dd, *J* = 7.73, 1.38 Hz, 1H, ArH), 7.47-7.5 (m, 1H, ArH), 7.61 (dd, *J* = 7.70, 1.44 Hz, 1H, ArH), 7.69 (dd, *J* = 7.70, 1.75 Hz, 1H, ArH), 7.74-7.79 (m, 2H, ArH), 8.00 (s, 1H, $C_2\underline{H}$ quinazolinone), 8.17 (dd, *J* = 7.70, 1.70 Hz, 1H, ArH), 8.29-8.34 (m, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 52.4, 122.1, 127.0, 127.4, 127.5, 128.1, 129.3, 129.7, 131.8, 133.6, 134.5, 137.3, 145.8, 147.9, 161.0, 164.8; Anal Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99%. Found: C, 68.39; H, 4.48; N, 10.13%.

Indolo[2,1-*b*]quinazoline-6,12-dione (tryptanthrin) (1). To a freshly prepared solution of LDA (0.16 g, 1.5 mmol) in anhydrous THF (8 mL) at -78 °C under nitrogen atmosphere, a solution of methyl 2-(4-oxoquinazolin-3(4*H*)-yl)benzoate **6** (0.28 g, 1 mmol) dissolved in dry THF (5 mL) was added dropwise. The reaction mixture was stirred at -78 °C for an additional 2 h followed by stirring at RT for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3x15 mL). The combined organic layer was washed with brine solution and dried over anhydrous sodium sulfate. The solvent was evaporated in *vacuo* to give crude product which was purified by column chromatography with petroleum:ethyl acetate (8.5:1.5) to afford 0.20 g of the pure tryptanthrin **1** (81%) as yellow needles. mp 266-267 (lit.[19] 267-268); IR (KBr, cm^{-1}) 1725, 1680, 1645, 1555, 1428; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.37-7.45 (ddd, *J* = 7.59, 0.84 Hz, 1H, ArH), 7.62-7.92 (m, 4H, ArH), 8.02 (dd, *J* = 8.07, 0.91 Hz, 1H, ArH), 8.42 (dd, *J* = 7.89, 1.56 Hz, 1H, ArH), 8.61 (d, *J* = 8.12 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 117.9, 121.9, 123.7, 125.3, 127.1, 127.5, 130.2, 130.6, 135.1, 138.2, 144.3, 146.3, 146.6, 158.0, 182.5; Anal Calcd for $C_{15}H_8N_2O_2$: C, 72.58; H, 3.25; N, 11.28%. Found: C, 72.71; H, 3.12; N, 11.17%.

3-(3-Bromopropyl) quinazolin-4(3*H*)-one (9). To a well stirred solution of 4(3*H*)-quinazolinone **7** (0.29 g, 2 mmol) and potassium carbonate (0.30 g, 2.2 mmol) in dry DMF (10 mL) at RT was added 1,3-dibromopropane **8** (0.44 g, 2.2 mmol) dropwise over 15 min and reaction mixture was stirred at RT for 4 h. The progress of the reaction was monitored by TLC. After completion of reaction, the solvent was evaporated under vacuum to obtain solid to which water (20 mL) was added and product was extracted using ethyl acetate (3x15 mL). The combined organic layer was dried over anhydrous sodium sulfate and evaporated in *vacuo* to give crude product which was purified by column chromatography with petroleum:ethyl acetate (6:4) as the eluent to afford 0.46 g of the pure 3-(3-bromopropyl)quinazolin-(3H)-one **9** (87%) as white solid. mp 178-180 °C; IR (KBr, cm^{-1}) 2931, 2854, 1681, 1561, 1450; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.33-2.45 (m, *J* = 6.66, 6.15 Hz, 2H, $NCH_2\underline{CH_2}CH_2$), 3.45 (t, *J* = 6.15 Hz, 2H, $NCH_2CH_2\underline{CH_2}Br$), 4.19 (t, *J* = 6.66 Hz, 2H, $N\underline{CH_2}CH_2CH_2$), 7.48-7.56 (m, 1H, ArH), 7.70-7.82

(m, 2H, ArH), 8.12 (s, 1H, $C_2\underline{H}$ quinazolinone), 8.31 (dd, *J* = 7.96, 1.02 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 29.7, 31.0, 45.4, 121.8, 126.5, 127.3, 134.3, 146.5, 147.8, 160.9; Anal Calcd for $C_{11}H_{11}BrN_2O$: C, 49.46; H, 4.15; N, 10.49%. Found: C, 49.53; H, 4.09; N, 10.57%.

2,3-Dihydropyrrolo-[2,1-*b*]-quinazolin-9(1*H*)-one (deoxyvasicinone) (2). To a freshly prepared solution of LDA (0.16 g, 1.5 mmol) in anhydrous THF (8 mL) at -78 °C under nitrogen atmosphere was added dropwise a solution of 3-(3-bromopropyl)quinazolin-4(3*H*)-one **8** (0.28 g, 1 mmol) dissolved in dry THF (5 mL). The reaction mixture was stirred at -78 °C for additional 2 h followed by stirring at RT for 2 h. The reaction mixture was quenched with saturated ammonium chloride solution and extracted with ethyl acetate (3x15 mL). The combined organic layer was washed with brine solution. The solvent was dried over anhydrous sodium sulfate and evaporated in *vacuo* to give crude product which was purified by column chromatography with petroleum:ethyl acetate (2:8) to afford 0.12 g of the pure deoxyvasicinone 2 (61%) as solid. mp 196-197 (lit.[25a] 196-198); IR (KBr, cm^{-1}) 2931, 2855, 1679, 1600, 1556, 1455; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.21-2.36 (m, *J* = 7.94, 7.21 Hz, 2H, $NCH_2\underline{CH_2}CH_2$), 3.18 (t, *J* = 7.94 Hz, 2H, $NCH_2CH_2\underline{CH_2}$), 4.21 (t, *J* = 7.21 Hz, 2H, $N\underline{CH_2}CH_2CH_2$), 7.40-7.48 (m, 1H, ArH), 7.62-7.77 (m, 2H, ArH), 8.26 (dd, *J* = 8.00, 1.14 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.4, 32.4, 46.4, 120.4, 126.2, 126.3, 126.7, 134.1, 149.0, 159.4, 160.9; Anal Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04%. Found: C, 71.02; H, 5.38; N, 15.17%.

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Supplementary material

The NMR spectra of all the compounds associated with this article can be found as supplementary material.

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