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Rearrangement of imine double bond in activated quinazolinones: Synthesis of phaitanthrin E

Sagar D Vaidya & Narshinha P Argade*

Division of Organic Chemistry, CSIR-National Chemical Laboratory, Pune 411 008, India
E-mail: np.argade@ncl.res.in

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Wolff-Kishner reduction of tryptanthrin to indoloquinazolinone followed by lithium diisorpropylamide induced acylation of the active methylene group with methyl chloroformate directly furnishes the phaitanthrin E in very good yield. Similar acylations of indoloquinazolinone have also been performed with four different acyl chlorides. In all examples, facile rearrangement of imine double bond from quinazolinone to indole moiety to form the corresponding α,β-unsaturated carbonyl system is observed.

Keywords: Tryptanthrin, Wolff-Kishner reduction, indoloquinazolinone, base, acylation, prototropic shift, phaitanthrin E and analogues

Quinazolinones alkaloids encompass several important members and some of them are in clinical use[1-10]. Recently, Wu *et al*. have added five new members phaitanthrins A–E to the class and all of them were isolated from the Taiwanese orchid *Phaius mishmensis* (Figure 1)[11-13]. The imine double bond in quinazolinone motif is a backbone and it is responsible for their stability. A careful study of phaitanthrin E structure indicated an interesting formation of a new α,β-unsaturated carbonyl system at the expense of internal imine double bond. In our continuing studies on synthesis of bioactive natural and unnatural quinazolinones[14-18], in two different instances we noticed the similar formation/migration of double bonds directly delivering the products isoindolodihydroquinazoline and phaitanthrin E during the course of intramolecularcyclization reactions (Scheme I)[17,18]. In this context, we herein report the synthesis of indoloquinazolinone and its base catalyzed acylation studies accomplishing practical synthesis of phaitanthrin E *via* an instant shuffling of the imine double bond position (Table I).

The chemistry of tryptanthrin (**6**) has been recently reviewed by Tucker and Grundt[19]. We synthesized our precursor tryptanthrin in 94% yield by employing the aryne insertion approach[14]. Several syntheses of indoloquinazolinone **7** have been well-known in the literature[20-23]. Generally indoloquinazolinone **7** is prepared from tryptanthrin by using a two-step protocol involving sodium borohydride reduction of both ketone and imine followed by the dehydration sequence[23]. Alternatively the Wolff-Kishner reduction of tryptanthrin would form the desired indoloquinazolinone in one-step. Providentially, treatment of tryptanthrin (**6**) with hydrazine hydrate/potassium hydroxide furnished the indoloquinazolinone **7** in 61% yield. The analytical and spectral data obtained for the desired product **7** was in complete agreement with the reported data[24]. Indoloquinazolinone is highly prone for air oxidation and gets back transformed to the tryptanthrin under normal atmospheric conditions. Thus the obtained product was either preserved under argon atmosphere in a refrigerator or immediately used for the next synthetic steps for stability reasons. The base-catalyzed intermolecular acylation reactions of indoloquinazolinone **7** using different acyl chlorides were planned to study the product specificity and their relative stability (**8a**-**e** and/or **5a**-**e**). Reaction of lithium diisorpropylamide (LDA, 1.20 equiv) with indoloquinazolinone **7** formed the corresponding stable allylic-benzylic carbanionic species which on treatment with methyl chloroformate directly delivered the desired natural product phaitanthrin E (**5a**) in 91% yield (Table I, entry 1). The analytical and spectral data obtained for the synthetic phaitanthrin E was in agreement with the assigned structure[11,18,23]. It is noteworthy that the electron rich carbon atom in the five membered ring in product **5a** appeared only at 86.6 ppm; possibly due to the electron donating effect of the neighboring nitrogen

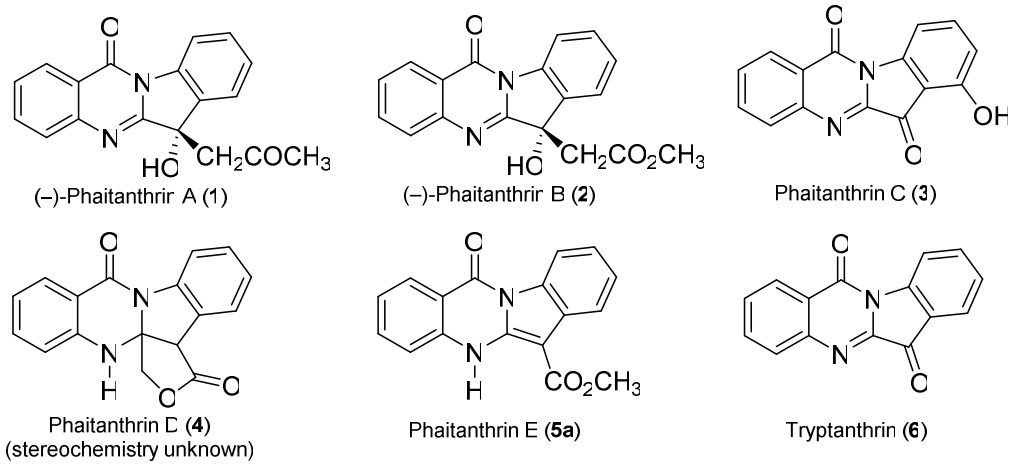
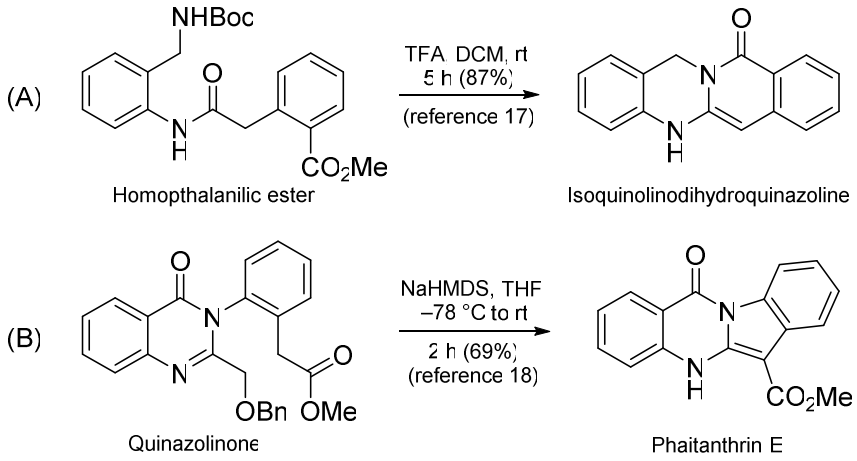
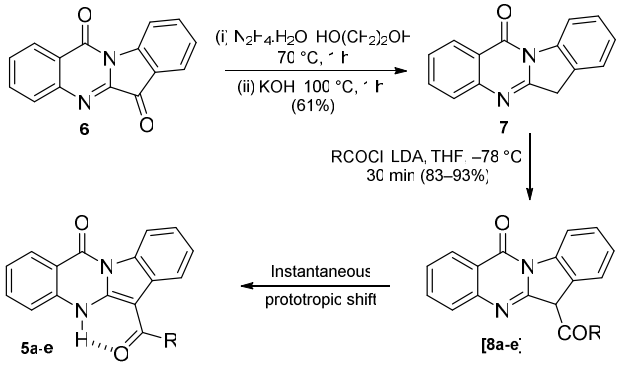


Figure 1 — Recently isolated quinazolinone based alkaloids



Scheme I — Earlier examples on intramolecular cyclizations leading to dihydroquinazolinones

Table I — Synthesis and base induced acylations of indoloquinazolinone



Entry	Acyl Chloride	Product	Yield (%)
1	$ClCO_2Me$	**5a** (R = OMe)	91
2	$ClCO_2Bn$	**5b** (R = OBn)	89
3	MeCOCl	**5c** (R = Me)	87
4	$ClCOCO_2Et$	**5d** (R = CO_2Et)	83
5	$ClCOCH_2Cl$	**5e** (R = CH_2Cl)	93
6	$BrCOCH_2Br$	decomposition	0

atom. Similarly, the LDA-stimulated reactions of indoloquinazolinone **7** with benzyl chloroformate, acetyl chloride, ethyl chlorooxaloacetate and chloroacetyl chloride were also selective and exclusively provided the corresponding double bond rearranged products **5b-e** in 83-93% yields (Table I, entries 2–5). Unfortunately, the same reaction with bromoacetyl bromide resulted in decomposition, plausibly due to its higher reactivity (Table I, entry 6).

Mechanistically, LDA abstracts an acidic proton from the activated methylene carbon in indoloquinazolinone **7** and the formed carbanion reacts with acyl chlorides to form the corresponding unisolable intermediates **8a**–**e**. The methine proton in intermediates **8a**–**e** is highly acidic due to its allylic and benzylic character coupled with the α-position to carbonyl groups. Thus the stability driven instantaneous carbon to nitrogen prototropic shifts[25,26] take place to form the products **5a**–**e** in excellent

yields. Accordingly the formed products are thermodynamically more stable due to (i) formation of new α,β-unsaturated carbonyl systems with extended conjugation with the lone of nitrogen atoms at γ/γ'-positions, (ii) the formation of intramolecular six-membered hydrogen bonding and moreover (iii) gain of quasi-aromatic characters with the involvement of lone pairs on both the nitrogen atoms in a π-cloud system. In the transformation of indoloquinazolinone **7** to provide **5a**–**e**, we did not notice the formation of any gem-diacylated products due to the above described concomitant structural rearrangement.

In summary, starting from tryptanthrin we have described a two steps synthesis of phaitanthrin E *via* an acylation of indoloquinazolinone. The witnessed spontaneous rearrangement of *β*-imino esters/ketones to the corresponding *γ*-amino *α*,*β*-unsaturated carbonyl systems is noteworthy from basic chemistry point of view and it takes place because of overall negative Gibbs free energy. The present protocol is general in nature and will be useful for the synthesis of analogues and congeners of phaitanthrins. We also feel that these compounds will serve as potential building blocks for the synthesis of novel heterocyclic architectures.

Experimental Section

Melting points are uncorrected. The ^{1}H NMR spectra were recorded on 200 MHz NMR, 400 MHz NMR and 500 MHz NMR spectrometers using TMS as an internal standard. The ^{13}C NMR spectra were recorded on 400 NMR spectrometer (100 MHz) and 500 NMR spectrometer (125 MHz). Mass spectra were taken on MS-TOF mass spectrometer. HRMS (ESI) were taken on Orbitrap (quadrupole plus ion trap) and TOF mass analyzer. The IR spectra were recorded on an FT-IR spectrometer. Column chromatographic separations were carried out on silica gel (60-120 mesh). Commercially available hydrazine hydrate, methyl chloroformate, benzyl chloroformate, acetyl chloride, ethyl chlorooxaloacetate, chloroacetyl chloride and bromoacetyl bromide were used.

Indolo[2,1-b]quinazolin-12(6*H*)-one, 7

To a stirred solution of tryptanthrin (**6**, 1.20 g, 4.83 mmol) in ethylene glycol (10 mL) was added hydrazine hydrate (1.20 mL, 4.83 mmol) and the reaction mixture was heated at 70°C for 1 h. To the reaction mixture was added KOH (539 mg, 9.62 mmol) and then it was heated at 100°C for 1 h. The reaction mixture was allowed to cool to RT and diluted with water (20 mL). The total reaction mixture was extracted with ethyl acetate (3 × 20 mL) and the organic layer was washed with water (25 mL), brine (25 mL) and dried over Na_2SO_4. Concentration of the dried organic layer *in vacuo* followed by rapid silica gel (60–120 mesh) column chromatographic purification of the obtained residue using ethyl acetate:petroleum ether (7:3) as an eluent gave product **7**. White solid;[20] 690 mg (61%); Mp 214–216°C; IR ($CHCl_3$): 1728, 1686 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 4.25 (s, 2H), 7.27–7.60 (m, 4H), 7.65–7.85 (m, 2H), 8.43 (d, J = 8 Hz, 1H), 8.61 (d, J = 8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 35.9, 117.4, 121.1, 124.5, 126.4 (2 C), 126.8, 126.88, 126.94, 128.5, 134.4, 141.0, 147.2, 157.4, 160.1; MS (ESI): *m*/z = 257 $[M+Na]^+$.

General procedure for acylation of indoloquinazolinone, 7

To a stirred solution of indoloquinazolinone **7** (0.50 mmol) in THF (2 mL) was added freshly prepared solution of LDA in THF (1 M, 0.60 mL, 0.60 mmol) at −78°C under argon atmosphere. The reaction mixture was further stirred for 30 min at same temperature and acyl chloride (0.60 mmol) was added in a drop wise fashion. The reaction was quenched after 30 min with saturated aq NH_4Cl solution (1 mL). The reaction mixture was concentrated *in vacuo* and the obtained residue was directly purified by silica gel (60–120 mesh) column chromatography using ethyl acetate:petroleum ether (6:4) as an eluent to obtain the desired product **5**.

Methyl 12-oxo-5,12-dihydroindolo[2,1-*b*] quinazoline -6-carboxylate (Phaitanthrin E), 5a: Amorphous white solid;[11] 132 mg (91%); Mp 251–253°C; IR ($CHCl_3$): 3057, 1730, 1653 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.00 (s, 3H), 7.25–7.35 (m, 3H), 7.41 (t, J = 8 Hz, 1H), 7.70 (t, J = 8 Hz, 1H), 7.92 (d, J = 8 Hz, 1H), 8.37 (d, J = 8 Hz, 1H), 8.68 (d, J = 8 Hz, 1H), 10.25 (br s, 1H); ^{13}C NMR ($CDCl_3$,100 MHz): δ 51.3, 86.6, 114.2, 115.6, 116.1, 119.3, 122.3, 123.0, 125.6, 126.2, 128.6, 130.2, 135.2, 138.1, 143.9, 158.4, 167.2; MS (ESI): *m*/z = 331 $[M+K]^+$.

Benzyl 12-oxo-5,12-dihydroindolo[2,1-*b*]quinazoline -6-carboxylate, 5b: Gummy white solid; 163 mg (89%). IR ($CHCl_3$): 3021, 1740, 1684, 1627 cm^{-1}; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.49 (s, 2H), 7.22–7.46 (m, 7H), 7.53 (d, J = 10 Hz, 2H), 7.71 (t, J = 10 Hz, 1H), 7.98 (d, J = 10 Hz, 1H), 8.40 (d, J = 10 Hz, 1H), 8.72 (d, J = 10 Hz, 1H), 10.34 (br s, 1H); ^{13}C NMR ($CDCl_3$,125 MHz) δ 65.9, 86.6, 114.3, 115.6, 116.2, 119.5, 122.4, 123.1, 125.7, 126.3, 127.9, 128.2, 128.6,

128.7, 130.3, 135.2, 136.5, 138.1, 144.3, 158.4, 166.6; HRMS (ESI): calcd for $C_{23}H_{17}N_2O_3$ 369.1234; found: 369.1227.

6-Acetylindolo[2,1-*b*]quinazolin-12(5*H*)-one, 5c: Gummy white solid; 120 mg (87%). IR ($CHCl_3$): 3022, 1687, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.74 (s, 3H), 7.36 (t, *J* = 8 Hz, 1H), 7.37 (d, *J* = 8 Hz, 1H), 7.39 (t, *J* = 8 Hz, 1H), 7.48 (t, *J* = 8 Hz, 1H), 7.76 (t, *J* = 8 Hz, 1H), 7.80 (d, *J* = 8 Hz, 1H), 8.43 (d, *J* = 8 Hz, 1H), 8.80 (d, *J* = 8 Hz, 1H), 11.80 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 30.0, 97.5, 115.2, 116.3, 116.8, 118.4, 122.5, 123.6, 125.8, 126.4, 128.6, 130.9, 135.3, 138.0, 144.6, 158.4, 194.2; HRMS (ESI): calcd for $C_{17}H_{13}N_2O_2$ 277.0972; found: 277.0968.

Ethyl 2-oxo-2-(12-oxo-5,12-dihydroindolo[2,1-*b*]quinazolin-6-yl)acetate, 5d: Yellow solid; 138 mg (83%); Mp 198°C; IR ($CHCl_3$): 3021, 1734, 1698, 1631 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48 (t, *J* = 8 Hz, 3H), 4.53 (q, *J* = 8 Hz, 2H), 7.30–7.50 (m, 4H), 7.70–7.90 (m, 2H), 8.44 (d, *J* = 8 Hz, 1H), 8.74 (d, *J* = 8 Hz, 1H), 11.86 (br s, 1H); ^{13}C NMR ($CDCl_3$,100 MHz) δ 14.1, 62.3, 95.4, 115.9, 116.5, 116.7, 119.1, 123.7, 124.7 (2C), 126.2, 128.6, 131.4, 135.6, 137.4, 147.7, 157.8, 164.6, 179.2; HRMS (ESI): calcd for $C_{19}H_{15}N_2O_4$ 335.1026; found: 335.1018.

6-(2-Chloroacetyl)indolo[2,1-*b*]quinazolin-12(5*H*)-one, 5e: Brown solid; 144 mg (93%); Mp 245°C; IR ($CHCl_3$): 3021, 1695, 1632 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 4.74 (s, 2H), 7.30–7.47 (m, 3H), 7.49 (t, *J* = 8 Hz, 1H), 7.65 (d, *J* = 8 Hz, 1H), 7.78 (t, *J* = 8 Hz, 1H), 8.42 (d, *J* = 8 Hz, 1H), 8.78 (d, *J* = 8 Hz, 1H), 11.72 (br s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 47.7, 95.5, 115.5, 116.4, 116.9, 118.6, 123.1, 124.2, 124.9, 126.2, 128.6, 131.1, 135.6, 137.7, 146.0, 158.1, 186.6; HRMS (ESI): calcd for $C_{17}H_{12}ClN_2O_2$ 311.0582; found: 311.0576.

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24 We have completed the total synthesis of phaitanthrins A-E (refs. 14 and 18). The obtained 1H and 13C NMR spectral data for polar phenolic natural product phaitanthrin C was in complete agreement with reported data. The reported NMR spectral data of phaitanthrins A, B, D and E was matching with the assigned structures; however there was noticeable difference in the delta values of natural and synthetic samples. We wrote two e-mail request messages to the senior author Professor Pei-Lin Wu (ref. 11) asking for copies of 1H and 13C NMR spectra of natural products phaitanthrins A–E and also for the synthetic phaitanthrin A. Unfortunately, we have not received any response for the same. Wu et al. in their publication have mentioned that "owing to the low solubility of tryptanthrin in organic solvents, it appeared in each fraction, and the combined amount was 0.35 g. Based on our past thirty years' experience in quinazolinone chemistry and the reported spectral data, we conclude that the structural assignments done by Wu et al. have been correct; however the scanned samples were impure or scanned by adding a small amount of an appropriate co-solvent for solubility issues. Hence there were inadvertent inaccuracies in reporting the delta values for several signals.
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