TBAHS-Catalyzed Synthesis of 2-Dihydroquinazolin-2-ylquinoline: An Efficient and Practical Synthesis of Naturally Occurring Alkaloids Luotonin A, B, and E

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Abstract: A synthesis of 2-dihydroquinazolin-2-ylquinoline using a phase-transfer catalyst (TBAHS) in semi-aqueous phase, followed by Mitsunobu cyclization as key steps for an efficient and practical synthesis of naturally occurring alkaloids luotonin A, B, and E starting from *o*-nitrobenzaldehyde is reported. The new approach presents the advantage of a shorter route with high overall yield (57%, 45%, and 37%, respectively) and ease of operation.

Key words: luotonins, 2-dihydroquinazolin-2-ylquinoline, tetrabutylammonium hydrogen sulfate (TBAHS), Mitsunobu

Luotonin A–F, six natural alkaloids possess the pyrroloquinazolinoquinoline ring system, were first isolated by Nomura and co-workers[1] in 1997 from an aerial part of the Chinese medicinal plant, *Peganum nigellastrum* Bunge (*luo-tuo-hao*, Figure 1). Luotonins are used in traditional Chinese medicine and are reported to exhibit diverse activities against a range of ailments including rheumatism, inflammation, influenza, hepatitis, and leukemia. Luotonin A is cytotoxic towards the murine leukemia P-388 cell line (IC_{50}, 1.8 μg/mL).[1] It has received increased attention in the last few decades, due to its structural similarity with the well-known cytotoxic alkaloid camptothecin (CPT).[2] Hecht and co-workers[3a] demonstrated that luotonin A stabilizes the human DNA topoisomerase I–DNA covalent binary complex and mediates topisomerase I dependent cytotoxicity in intact cells, like camptothecin and its analogues.[3] After the first report of its isolation, several synthetic routes of luotonin A have been reported using a variety of elegant synthetic strategies.[1,4] Most of the multistep synthesis of linear pentacyclic alkaloid luotonin A have been completed using two suitable building blocks for the construction of ring B and D. These methods typically suffered from either the low efficiency or the lack of generality and low overall yields. Argade and Mhaske[5] reported the synthesis of luotonins using *ortho* lithiation of quinoline moiety. Recently, Chu and co-workers[6] reported the synthesis of luotonin A and its analogues in a one-pot, self-directed chemical process with the aid of a single metal triflate for the construction of quinazoline and pyrroloquinoline rings (B, C, and D).

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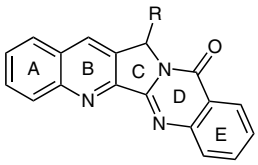
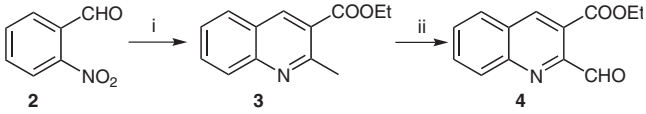
Tetrabutylammonium hydrogen sulfate (TBAHS) was used as a phase-transfer catalyst in our earlier report[7] on the synthesis of 4*H*-pyrimido[2,1-*b*]benzothiazole. The TBAHS catalyst is acidic in nature, water-soluble, thermally stable, mild, and inexpensive.[8] The synthesis of dihydroquinazolinone had been reported[9] and our effort is directed towards a more efficient method. In continuation of our studies[10] on the synthesis of bioactive compounds, herein we report on an improved and reliable approach for the synthesis of a 2-dihydroquinazolin-2-ylquinoline using TBAHS catalyst and then Mitsunobu cyclization to render direct and easy access to naturally occurring alkaloids, luotonins A, B, and E, in overall high yields.



luotonin A (**1a**): R = H
luotonin B (**1b**): R = OH
luotonin E (**1c**): R = OMe

Figure 1 Structure of luotonins **1a–c**

Syntheses of luotonins A, B, and E were achieved from the commercially available *o*-nitrobenzaldehye (**2**). The quinoline **3** was synthesized in one step by condensation of *o*-nitrobenzaldehyde (**2**) with ethyl acetoacetate (EAA) in presence of $SnCl_2$ and $ZnCl_2$ with 96% yield, followed by oxidation with SeO_2 in 1,4-dioxane at a reflux temperature to give aldehyde **4** with 95% yield (Scheme 1).



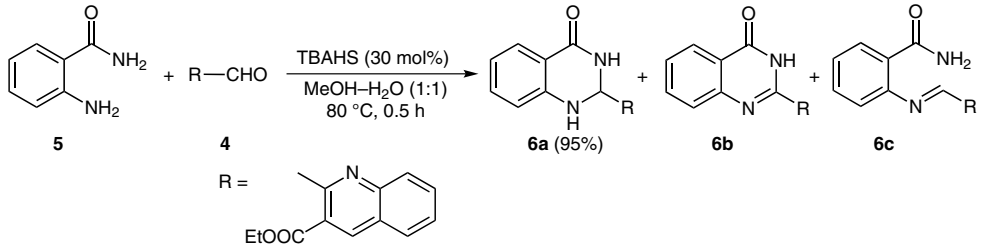
2 **3** **4**

Scheme 1 *Reagents and conditions*: i) EAA, $SnCl_2$, $ZnCl_2$, 4 Å MS, 70 °C, 3 h, 96%; ii) SeO_2, 1,4-dioxane, reflux, 2 h, 95%.

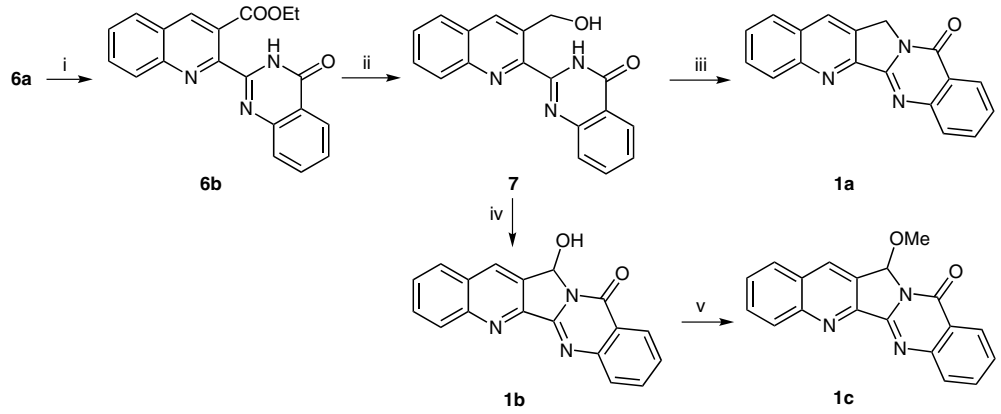
To investigate the use of phase-transfer catalyst for the synthesis of a 2-dihydroquinazolin-2-ylquinoline in a facile and convenient manner, the reaction of the two components *o*-aminobenzamide (**5**) and ethyl 2-formylquinoline-3-carboxylate (**4**) was initially examined (Scheme 2).[11] To optimize the reaction conditions, different solvents and catalysts were screened. The results

showed that 95% of the desired product **6a** was obtained predominantly using TBAHS (30 mol%) in MeOH–H_2O (1:1, semi-aqueous phase) at 80 °C. When the amount of TBAHS was increased to 50 mol%, the yield slightly decreased from 95% to 91% (Table 1, entries 2–5). Several other catalysts were tested (Table 1, entries 8–11) and a mixture of products **6a**, **6b**, and **6c** were observed. Compound **6a** was identified by its ^{1}H NMR spectrum which showed a characteristic methine proton at δ = 6.53, its ^{13}C NMR spectrum which showed a peak at δ = 71.79 ppm, and its HRMS data which gave an *m/z* value of 370.1173 $[M + H]^+$.

Based on our observation for the synthesis of 2-dihydroquinazolin-2-ylquinoline, we used TBAHS as the phase-transfer catalyst for the dehydration and cyclization steps. The desired product **6a** was obtained in almost quantitative yield (95%) with the reaction of aldehyde **4** and *o*-aminobenzamide (**5**) in the presence of TBAHS (30



Scheme 2 Synthesis of 2-dihydroquinazolin-2-ylquinoline **6a**



Scheme 3 *Reagents and conditions*: i) $KMnO_4$, acetone, reflux, 0.5 h, 93%; ii) $NaBH_4$, $CaCl_2$, MeOH, r.t., 12 h, 86%; iii) a) Ph_3P, DEAD, THF, r.t., 1 h, 81%; or b) 60% ethanolic H_2SO_4, reflux, 3 h, 83%; iv) PCC, 4 Å MS, CH_2Cl_2, r.t., 1 h, 65%; v) PTSA, MeOH, reflux, 3 h, 82%.

Table 1 Reaction of **5** and **4** under Different Reaction Conditions and Catalysts

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield of **6a** (%)[a]	Yield of **6b** (%)[a]	Yield of **6c** (%)[a]
1	–	MeOH	12	–	–	76
2	TBAHS (10)	MeOH–H_2O (1:1)	0.5	75	10	–
3	TBAHS (20)	MeOH–H_2O (1:1)	0.5	87	4	–
4	TBAHS (30)	MeOH–H_2O (1:1)	0.5	95	1	–
5	TBAHS (50)	MeOH–H_2O (1:1)	0.5	91	2	–
6	TBAHS (30)	MeOH	12	68	–	23
7	TBAHS (30)	H_2O	12	50	–	–
8	PTSA (30)	MeOH	12	38	10	17
9	TBAB (10)	MeOH	12	43	19	–
10	$Yb(OTf)_3$ (30)	MeOH	12	18	32	–
11	$FeCl_3$ (50)	H_2O	12	55	5	–

[a] Isolated yields obtained after column chromatography.

mol%) in a semi-aqueous phase (MeOH–H_2O) at 80 °C (Scheme 2). The oxidation of **6a** with $KMnO_4$ in acetone gave quinolinequinazolinone **6b** in quantitative yield. The regioselective reduction of ester **6b** using $NaBH_4$ and $CaCl_2$ in ethanol gave alcohol **7** with 86% yield, followed by Mitsunobu cyclization at 80 °C furnished the bioactive natural product luotonin A in 81% yield. Under acidic conditions the alcohol **7** also furnished luotonin A in 83% yield. The PCC oxidation of alcohol **7** in CH_2Cl_2 furnished luotonin B in 65% yield. Luotonin B (**1b**) on treatment with PTSA in methanol provided luotonin E in 82% yield (Scheme 3). Thus using the TBAHS-catalyzed reaction, we accomplished a straightforward synthesis of luotonin A (57%), B (45%), and E (37%), with overall high yields starting from a commercially available *o*-nitrobenzaldehyde. The analytical and spectral data obtained for all luotonins were in complete agreement with the reported data.[1,4,5]

In conclusion, we have demonstrated a new approach for the synthesis of 2-dihydroquinazolin-2-ylquinoline using TBAHS catalyst, followed by Mitsnuobu cyclization for the highly efficient, short, and practical synthesis of naturally occurring promising anticancer agents. Luotonin A, B, and E were accomplished in direct fashion with high overall yields (57%, 45%, and 37%, respectively). Further application of this approach for the construction of aryl- and heteroaryl-substituted quinazolinone system will be highly useful for the synthesis of a large number of desired complex quinazolinone alkaloids and its analogues for SAR studies.

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(11) **General Procedure for the Synthesis of 2-Dihydroquinazolin-2-ylquinoline (6a)**

Aldehyde **4** (4 g, 17.46 mmol), *o*-aminobenzamide (2.38 g, 17.46 mmol), and TBAHS (1.8 g, 5.42 mmol) were added to MeOH–H_2O (5 mL, 1:1) at r.t. The resulting mixture was heated at 80 °C for 0.5 h, and completion of the reaction was monitored by TLC (EtOAc–hexane = 7:3). After completion of the reaction, reaction mixture was allowed to cool, diluted with H_2O, and extracted with EtOAc. The organic layer were combined and washed thoroughly with sat. aq NaCl, dried over Na_2SO_4. The organic layer was evaporated under vacuum, the residue obtained was subjected to chromatography on silica gel. The desired 2-dihydroquinazolin-2-ylquinoline (**6a**) was obtained in 95% yield; mp 194–196 °C. IR (KBr): ν_{max} = 3327, 3247, 2924, 1710, 1653, 1611, 1511, 1137, 1018, 776, 747 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ = 1.48 (t, *J* = 7.17 Hz, 3 H, CH_3), 4.48 (q, *J* = 7.17 Hz, 2 H, CH_2), 6.47 (br s, 1 H, NH), 6.53 (s, 1 H, CH), 6.66 (t, *J* = 8.28 Hz, 2 H, ArH), 7.11 (t, *J* = 7.65 Hz, 1 H, ArH), 7.60 (t, *J* = 7.36 Hz, 1 H, ArH), 7.65–7.83 (m, 3 H, ArH), 7.90–8.03 (m, 2 H, ArH), 8.89 (s, 1 H, NH). ^{13}C NMR (75 MHz, DMSO-d_6): δ = 14.19, 61.38, 71.79, 120.76, 124.81, 126.52, 126.98, 127.18, 127.69, 127.87, 129.07, 130.16 (2 C), 130.67, 134.18 (2 C), 138.03, 146.84, 158.80, 165.37. HRMS (ESI^+): *m/z* calcd for $C_{20}H_{17}N_3O_3$ $[M + Na]^+$: 370.1167; found: 370.1173.

