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Tetrahedron Letters 44 (2003) 1883–1886

TETRAHEDRON LETTERS

A facile synthesis of simple alkaloids—synthesis of 2,3-polymethylene-4(3*H*)-quinazolinones and related alkaloids

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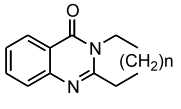
Received 6 December 2002; revised 8 January 2003; accepted 8 January 2003

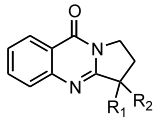
Abstract—An efficient procedure for preparation of the simple alkaloids, 2,3-polymethylene-4(3*H*)-quinazolinones, luotonin A, tryptanthrin, and rutaecarpine has been established by the reaction of lactam-HCl salts with $POCl_3$ followed by cyclization with methyl anthranilate. © 2003 Published by Elsevier Science Ltd.

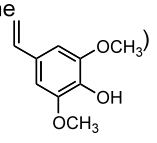
The 2,3-polymethylene-4(3*H*)-quinazolinones (**1a**,**b**) are not the only alkaloids isolated from plants,[1] but are the part of a family of intriguing alkaloids including the bronchodilator vasicinone (**2a**),[2] antiendotoxic isaindigotone (**2b**),[3] cytotoxic luotonins (**3**),[4] antibiotic tryptanthrin (**4**),[5] and antiinflammatory rutacearpine (**3**)[6] and related alkaloids.[6f]

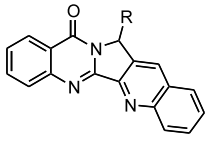
Since Niementowski's preparation of 4(3*H*)-quinazolinone by fusing anthranilic acid with formamide,[7] several methods aimed toward the synthesis of modified quinazolinones have been pursued.[8] Although most of these are applicable to acyclic amides, methods for cyclic amides, especially without aryl group as a part, are somewhat limited.[8] These limitations have led to the continuous development of new procedures for cyclic amides, such as cyclocondensation of isatoic anhydride and lactams,[1c] metal catalyzed reductive *N*-heterocyclization of *N*-(2-nitrobenzoyl)lactams in the presence of CO,[1d,g] intramolecular aza-Wittig reaction of *N*-(2-azidobenzoyl)lactams,[1f,h] condensation of anthranilic acid with *O*-alkyllactims,[1i,k] and reaction of anthranilic



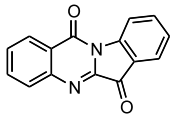
1a Deoxyvasicinone (n = 1)
b n = 2



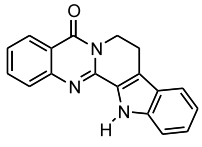
2a Vasicinone (R_1 = H, R_2 = OH)
b Isaindigotone
(R_1, R_2 = )



3a Luotonin A (R = H)
b Luotonin B (R = OH)



4 Tryptanthrin



5 Rutaecarpine

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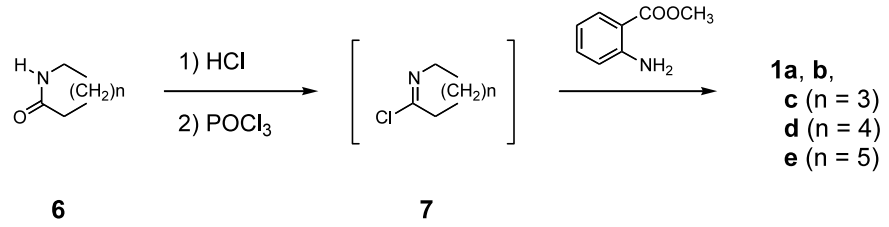
PII: S0040-4039(03)00080-7



acid with $SOCl_2$ followed by cyclization with lactams.[1j] Nevertheless, up to this point the development of simple procedures for modified quinazolinone synthesis relied on the use of rather toxic or expensive reagents.

As a part of our research on biologically important natural products, we herein describe a modified procedure for the efficient preparation of **1** as well as alkaloids **3a**, **4** and **5**.

The synthetic strategy stems from the reactivity of *N*-arylbenziminochlorides[9] which are known to condense with anthranilic acid and its derivatives to yield corresponding quinazolinones. We have exploited this reactivity by employing cyclic iminochlorides (**7**) as active intermediates in the synthesis of a series of modified quinazolinones.

Attempts to directly condense the simple lactams (**6**) or their HCl salts with methyl anthranilate or chlorination of **6** with $POCl_3$ followed by reaction with methyl anthranilate yielded unsatisfactory results.[10] Pretreatment of **6** with either 37.5% HCl or dry HCl, however, dramatically improved formation of the desired products (Table 1).

Following our reaction scheme with known lactams, 3-oxo-1*H*-pyrrolo[3,4-*b*]quinoline[11] (entry 6) and 1-oxo-1,2,3,4-tetrahydropyrido[3,4-*b*]indole[12] (entry 7) smoothly led to the production of the corresponding alkaloids, luotonin A (**3a**) and rutaecarpine (**5**) in the yield of 88% and 92%, respectively. It is worthwhile to note that the early synthesis of **5** utilizing lactam **8** and methyl anthranilate in the presence of $POCl_3$ gave 66% yield[6d] while the present procedure afforded 1.4 times higher yield.

The generality of the scheme was examined with 2-indolinone (**9**) to provide the corresponding quinazolinone derivative **10** in 82% yield. Two-step conversion of **10** gives the known alkaloid **4** in 76% yield.[13]

In conclusion, a simple procedure for the preparation of 2,3-polymethylene-4(3*H*)-quinazolinones has been established by reacting lactam-HCl salts with $POCl_3$ followed by cyclization with methyl anthranilate. The described procedure was applied to the preparation of two simple alkaloids, luotonin A and rutaecarpine, as well as indolo[2,1-*b*]quinoazolin-12(6*H*)-one, a key intermediate for the preparation of tryptanthrin.

General Procedure: Into a solution of 2-azacyclononanone (14.1 g, 0.1 mole) in $CHCl_3$ (100 mL) was passed dry HCl gas. The lactam-HCl salt precipitated was collected and suspended in $POCl_3$ (30 mL). The suspension was warmed to 40°C and stirred for 2 h to give a clear solution. Removal of excess $POCl_3$ in vacuo afforded an oil, which was neither isolated nor characterized, but instead was dissolved in dry THF (100 mL). Into this solution was added methyl anthranilate (22.7 g, 0.15 mole). The mixture was stirred for 12 h at room temperature and diluted with water (80 mL). The reaction mixture was made basic with NH_4OH (100 mL) and extracted with CH_2Cl_2 (100 mL×3). The organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent gave a solid which was crystallized from EtOH to yield 20.56 g (85%) of **7,8,9,10,11,12-**

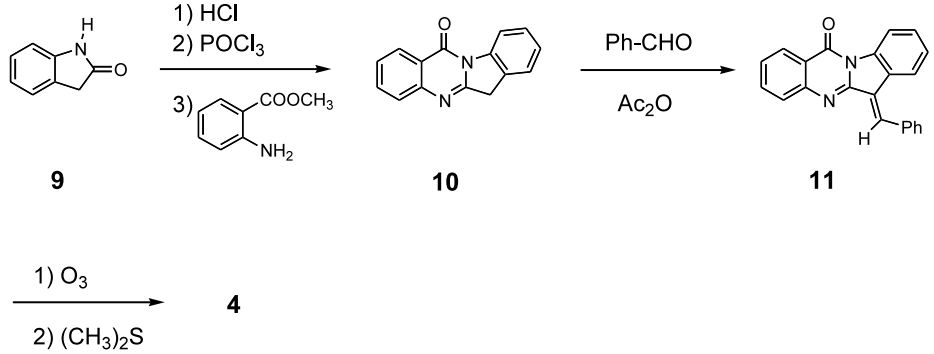
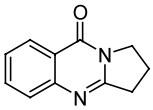
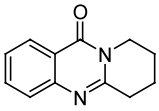
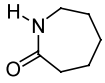
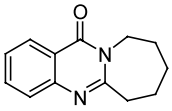
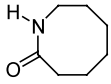
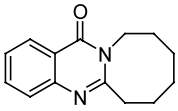
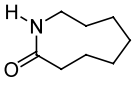
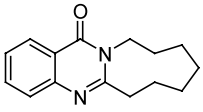
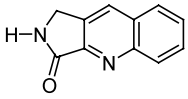
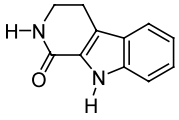


Table 1. Synthesis of 2,3-polymethylene-4(3*H*)-quinazolinones and related alkaloids

Entry	Substrate	Product[a)]	Yield (%)[b)]
1			88
2			92
3			95
4			90
5			85
6		**3a**	88
7		**5**	92
	8		

a. Spectral data of the products match previously reported data.

b. Isolated but unoptimized yield.

hexahydroazonino[2,1-*b*]quinazolin-14(6*H*)-one (**1e**) as white needles: mp 101–102°C. IR (thin film) *v* 1675, 1610, 1580, 1565, 1410, 1350, 1310 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.27 (dd, $J=8.2$, 1.8 Hz, 1H), 7.73 (ddd, $J=8.2$, 7.2, 1.2 Hz, 1H), 7.66 (dd, $J=8.2$, 1.5 Hz, 1H), 7.44 (ddd, $J=8.2$, 7.2, 1.5 Hz, 1H), 4.34 (br s, 2H), 3.09–3.02 (m, 2H), 2.10–1.67 (m, 4H), 1.62–1.34 (m, 6H). Anal. calcd for C15H18N2O: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.63; H, 7.58; N, 11.43.

Acknowledgements

Financial support by Korea Research Foundation Grant (KRF-2002-005-E00019) is gratefully acknowledged.

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10. Our attempts led to either a mixture of inseparable products or resulted in low yield (<5%) even at elevated temperature (180–200°C). Efforts to isolate any of **7** have not yet been successful.
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13. **Indolo[2,1-*b*]quinazolin-12(6*H*)-one** (**10**): mp 215–216°C (lit.[14] mp 215–216°C). IR (KBr) ν 1680, 1640, 1605, 1560, 1465, 1360, 1330, 1310 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.53 (dd, $J=8.4$, 1.8 Hz, 1H), 8.46 (dd, $J=8.4$, 1.2 Hz, 1H), 8.02 (ddd, $J=8.2$, 1.5, 0.5 Hz, 1H), 7.68 (td, $J=8.2$, 1.5 Hz, 1H), 7.54–7.44 (m, 2H), 7.08 (t, $J=8.2$ Hz, 1H), 6.98 (t, $J=8.4$ Hz, 1H), 4.22 (s, 2H). **6-Benzylidenindolo[2,1-*b*]quinoazolin-12(6*H*)-one** (**11**): A mixture of 11.7 g (0.05 mol) of **10** and 31.8 g (0.30 mol) of benzaldehyde in 80 mL of Ac_2O was refluxed for 48 h. Excess benzaldehyde and Ac_2O were removed under reduced pressure. The resulting mixture was carefully poured into 100 mL of 50% NaOH and extracted with CH_2Cl_2 (50 mL×3). Organic layers were combined and dried over $MgSO_4$. Evaporation of the solvent gave a yellow solid (14.4 g, 89%) whose ^1H NMR spectrum showed presence of two regioisomers (*E*- and *Z*- through the benzylidene double bond). Thus, compound **11** was not fully characterized, but instead carried to the next step. **Trypthanthrin** (**4**): A solution of 3.22 g (0.01 mol) of **11** in 200 mL of CH_2Cl_2 was cooled in an acetone–dry ice bath and O_3 was bubbled through the solution. Excess O_3 was purged and 20 mL of $(CH_3)_2S$ was added to the mixture. Evaporation of the solvent afforded 2.48 g of semi-solid, which was chromatographed on silica gel, eluting with CH_2Cl_2:EtOAc (1:1). The latter fractions gave 2.06 g (83%) of yellow needles after recrystallization from the eluent: mp 265–266°C (lit.[5b] mp 267–268°C, lit.[5g] mp 261°C). IR (KBr) ν 1725, 1675 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$) d 8.68 (dm, $J=8.0$ Hz, H10), 8.48 (ddd, $J=8.2$, 1.5, 0.8 Hz, H1), 8.10 (ddd, $J=8.0$, 1.2, 0.6 Hz, H4), 7.96 (ddd, $J=7.8$, 1.4, 0.6 Hz, H7), 7.91 (ddd, $J=8.2$, 7.5, 1.5 Hz, H3), 7.85 (ddd, $J=8.0$, 7.8, 1.3 Hz, H9), 7.72 (ddd, $J=8.2$, 7.8, 1.5 Hz, H2), 7.45 (ddd, $J=8.0$, 7.5, 1.2 Hz, H8).
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