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A short synthesis of quinazolinocarboline alkaloids rutaecarpine, hortiacine, euxylophoricine A and euxylophoricine D from methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilates

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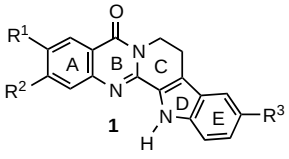
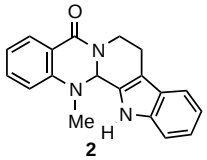
Abstract—Reactions of methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilates with tryptamine at room temperature produced 2-cyano-3-[2-(indol-3-yl)ethyl]-4(3*H*)-quinazolinones, which underwent cyclization on heating with TFAA/HCl(g) to afford quinazolinocarboline alkaloids rutaecarpine (**1a**), hortiacine (**1b**), euxylophoricine A (**1c**) and euxylophoricine D (**1d**) in excellent yields.

The dried fruit of *Evodia rutaecarpa* has been used in traditional Chinese medicine under the name Wu-Chu-Yu[1] and Shih-Hu[2] against e.g. headache, dysentery, cholera, worm infections and postpartum disturbances.[3] Extracts of the drug contain quinazolinocarboline alkaloids rutaecarpine (**1a**) and evodiamine (**2**). Recently, callus tissue cultured from the stem of *Phellodendron amurense* has been shown to produce **1a** along with a variety of other alkaloids.[4] In modern literature **1a** and its derivatives have been reported to display strong cycloxygenase (COX-2) inhibitory activity.[5] It was also found to suppress platelet plug formation in mesenteric venules and increase intracellular Ca^{2+} in endothelial cells.[6] Asahina isolated **1a** first around 1915 and more than a decade later the first total synthesis was reported[7] by Asahina, Manske and Robinson. Since then several routes[8] have been developed for the synthesis of **1a**. Some of the problems involved in these syntheses are the low yield (44%) in the final cyclization step coupled with unavoidable side products[9] and longer reaction time (166 h).[10] All these problems prompted us to develop a new efficient methodology.

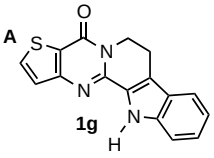
As a part of our ongoing research program, we have already been involved in exploiting the potential synthetic applications of 5-arylimino 4-chloro-5*H*-1,2,3-dithiazoles and recently reported the synthesis of various heterocyclic and spiroheterocyclic compounds.[11] We wished to utilize the easily accessible





1a, R^1= R^2= R^3= H, **Rutaecarpine**
b, R^1= R^2= H, R^3= OMe, **Hortiacine**
c, R^1= R^2= OMe, R^3= H, **Euxylophoricine A**
d, R^1= R^2= R^3= OMe, **Euxylophoricine D**
e, R^1= Br, R^2= R^3= H
f, R^1= H, R^2= Cl, R^3= H

Evodiamine



starting materials methyl *N*-(4-chloro-5*H*-1,2,3-dithiazol-5-ylidene)anthranilates (**4**) in the context of natural product synthesis and in this paper we report the total synthesis of quinazolinocarboline alkaloids **1a**, hortiacine (**1b**),[12a] euxylophoricine A (**1c**),[12b] euxylophoricine D (**1d**)[12c] and their analogues **1e–g**, respectively, from **4a–e**.

Our synthetic strategy for quinazolinocarboline alkaloids **1** is to construct B ring and build the connection between the B and D rings starting from **4** and tryptamine (**5**) (Scheme 1).

Starting materials **4a–d** can be prepared from the respective anthranilates **6a–d** and 4,5-dichloro-1,2,3-dithiazolium chloride (Appel's salt)[13] in good yields (67–78%) according to the literature[14] procedure (Scheme 2). Reaction of **4a** (287 mg, 1 mmol) with tryptamine **5a** (R^3 = H, 160 mg, 1 mmol) in dry CH_2Cl_2 at rt for 29 h afforded 2-cyano-3-[2-(indol-3-yl)ethyl]-

Keywords: alkaloids; dithiazoles; quinazolinones.

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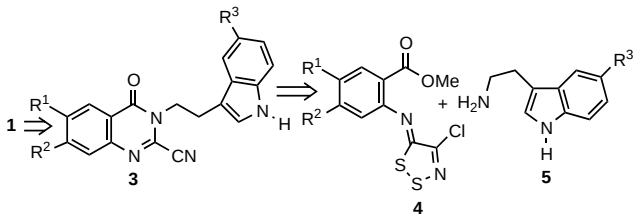
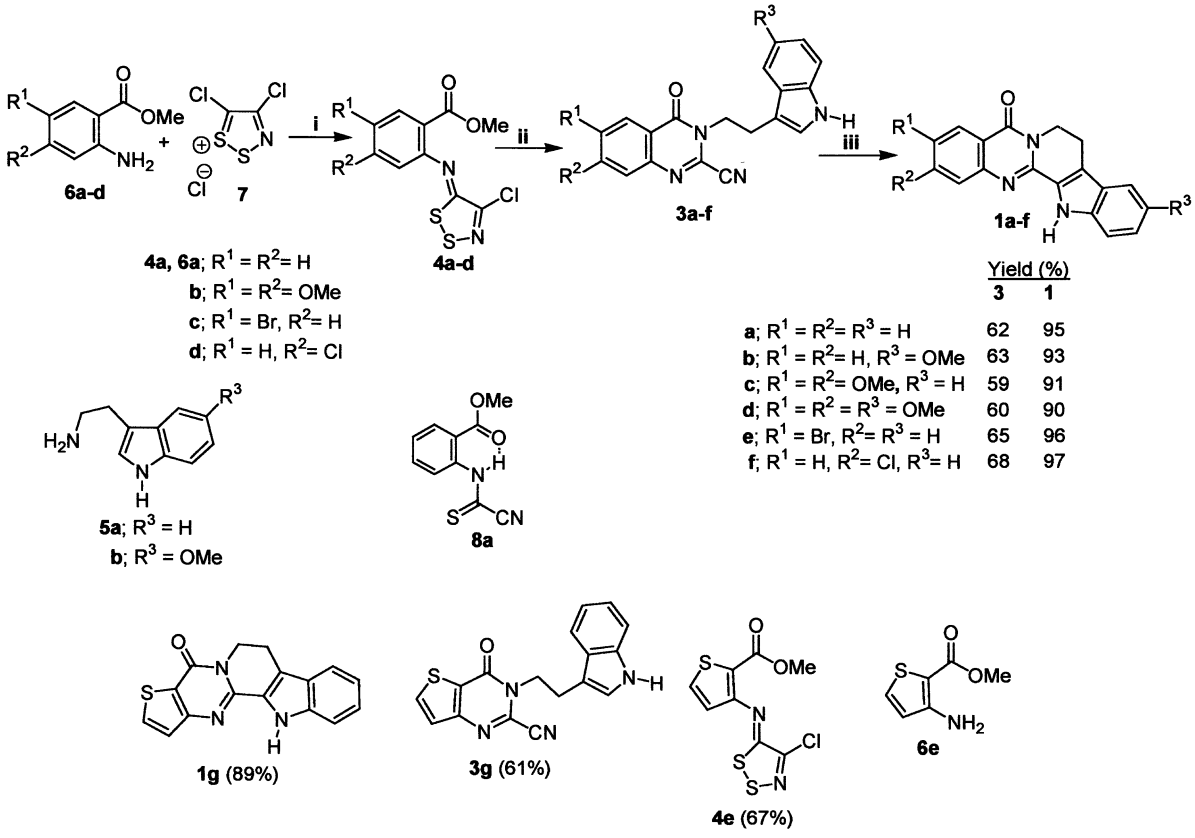


Scheme 1.

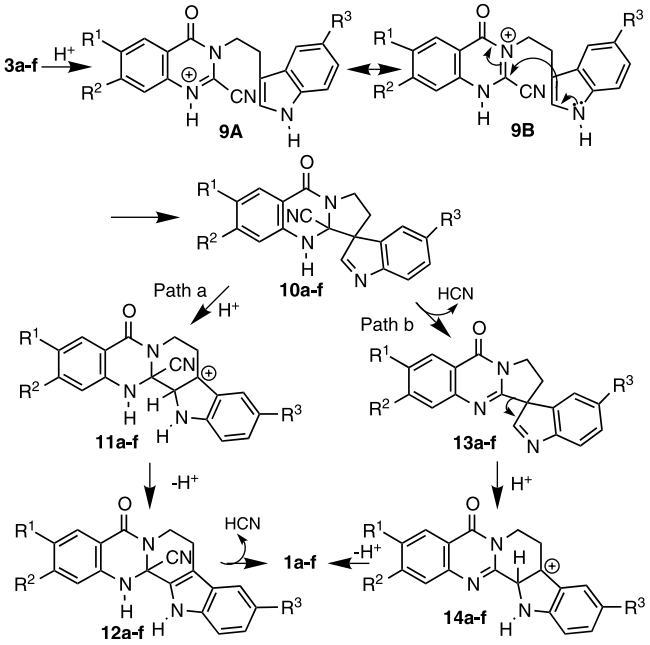
4(3*H*)-quinazolin-4-one (**3a**) in (195 mg) 62% yield with sulfur and unreacted starting materials **4a** (60 mg, 21%) and **5a** (Scheme 2). To improve yield of **3a**, the reaction mixture was stirred at rt for longer time (72 h) to give a mixture of cyanothioformamide **8a**[14] (19%) and **3a** (62%) along with starting materials **4a** and **5a**. Similarly **4b–d** reacted with **5a** at rt for 24–31 h to afford **3c**, **3e** and **3f** in 59–68% yields. Compounds **3b** and **3d** were also obtained in 63% and 60% yields, respectively, when 5-methoxytryptamine (**5b**) was reacted with **4a** and **4b** under the similar conditions. Similarly, thienopyrimidone **3g** was obtained from the reaction of **4e**, prepared from methyl 3-amino-2-thiophenecarboxylate (**6e**) and **7** under the same conditions as for **4**, with **5a** in 61% yield. Compounds **3a–g** were characterized from their spectroscopic (^{1}H, ^{13}C NMR, IR, and MS) and analytical data.[15]

2-Cyano-3-[2-(indol-3-yl)ethyl]-4(3*H*)-quinazolinone **3a** served as an excellent intermediate for the synthesis of **1a**. In a typical experiment, **3a** (150 mg, 0.47 mmol) was heated (120–130°C) with TFAA (3.4 mL, 23.8 mmol)/HCl(g) for 3.5 h. The solid separated out on pouring the reaction mixture onto ice-cold water was filtered and on recrystallization from ethanol afforded **1a** in pure form (130 mg, 95%, mp 257°C, lit.[8a] 258°C) (Scheme 2). Hortiacine (**1b**), isolated from the plant *Hortia arborea*[12a] was obtained in 93% yield from **3b** under the same conditions. Similarly the other quinazolinocarboline alkaloids euxylophoricine A (**1c**)[12b] and euxylophoricine D (**1d**)[12c] extracted from the bark of the *Euxylophora paraensis* Hub were also synthesized from **3c** and **3d** in 91% and 90% yields, respectively, under similar conditions. A comparison of spectroscopic data (NMR, MS) of **1a–d** showed good agreement with the reported data. Bromo-**3e** and chloro-**3f** derivatives of quinazolin-4-ones on heating with TFAA/HCl(g) gave bromo-**1e** and chlororutaecarpine **1f** [15] in 96% and 97% yields, respectively. When 2-cyanothieno[3,2-*d*]-pyrimidone **3g** was treated with TFFA/HCl(g) at 120°C, **1g**[15] was obtained in 89% yield.

The plausible mechanism for the formation of **1** can be rationalized as the protonation of 2-cyano-3-tryptophylquinazolin-4-one **3** to form an aza-stabilized[9] carbocation, which suffers nucleophilic attack by the enaminocarbon of the pyrrole moiety of **9B** leading to a spiro intermediate **10** (Scheme 3). The intermediate **10** undergoes rearrangement to more stable pentacyclic structure **12** (Path a) via **11**. Extrusion of HCN from **12**



Scheme 2. *Reagents and conditions*: (i) CH_2Cl_2/pyridine/rt/2–3 h; (ii) 5/CH_2Cl_2/rt/24–31 h; (iii) TFAA/HCl(g)/ 120–130°C/3–4 h.



Scheme 3.

finally gives **1**. Alternatively, one may envisage that elimination of HCN from **10** (Path b) to give **13**, followed by 1,2-migration leading to **14** and subsequent deprotonation would give **1**. To our knowledge the nitrile elimination from 2-position of quinazolin-4-one is not known in the literature. However, α-aminotriles are reported[16] to liberate cyanide ion under acidic conditions and this strategy has been utilized for the synthesis of various indole alkaloids.

In conclusion, we have achieved total synthesis of quinazolinocarboline alkaloids **1a**–**d** and their analogues **1e**–**g** in good yields requiring only two steps from dithiazoles **4a**–**e**.

Acknowledgements

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15. **3e**: Crystals ($CHCl_3$-*n*-hexane), mp 232–233°C; IR (KBr) 3408, 1664, 1568, 1452 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.18 (t, $J=7.41$ Hz, 2H), 4.36 (t, $J=7.43$ Hz, 2H), 6.91 (t, $J=7.47$ Hz, 1H), 7.06 (t, $J=7.53$ Hz, 1H), 7.19 (d, $J=2.10$ Hz, 1H), 7.36 (d, $J=8.09$ Hz, 1H), 7.51 (d, $J=7.85$ Hz, 1H), 7.74 (d, $J=8.68$ Hz, 1H), 8.10 (dd, $J=2.90$, 8.67 Hz, 1H), 8.34 (d, $J=2.24$ Hz, 1H), 10.96 (brs, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.55, 48.84, 110.35, 112.43, 112.49, 118.61, 119.40, 122.03, 123.58, 124.65, 124.81, 127.88, 129.47, 131.01, 133.49, 137.11, 138.99, 145.82, 159.29; MS *m*/*z* (%) 394 (M^++1); 393 (M^+); 392 (M^+−1), 144, 143 (100%). Anal. calcd for $C_{19}H_{13}BrN_4O$: C, 58.03; H, 3.33; N, 14.25. Found: C, 58.17; H, 3.41; N, 13.92.
3f: Crystals ($CHCl_3$-*n*-hexane), mp 210–211°C; IR (KBr) 3403, 1670, 1574, 1449 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.19 (t, $J=7.38$ Hz, 2H), 4.37 (t, $J=7.34$ Hz, 2H), 6.91 (t, $J=7.44$ Hz, 1H), 7.06 (t, $J=7.51$ Hz, 1H), 7.18 (d, $J=2.10$ Hz, 1H), 7.35 (d, $J=6.48$ Hz, 1H), 7.49 (d, $J=7.87$ Hz, 1H), 7.77 (dd, $J=1.96$, 8.57 Hz, 1H), 7.90 (d, $J=1.87$ Hz, 1H), 8.28 (d, $J=8.56$ Hz, 1H), 10.95 (brs, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.03, 46.06, 107.57, 109.49, 109.68, 115.87, 116.69, 119.28, 119.38, 121.74, 125.17, 125.22, 126.61, 128.12, 131.45, 134.43, 138.19, 145.14, 157.05; MS *m*/*z* (%) 348 (M^+), 143 (100%). Anal. calcd for $C_{19}H_{13}ClN_4O$: C, 65.43; H, 3.76; N, 16.06. Found C, 65.18; H, 3.81; N, 15.90.
3g: Colorless solid ($CHCl_3$-*n*-hexane), mp 219–220°C; IR (KBr) 3344, 1661, 1580, 1453 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.19 (t, $J=7.47$ Hz, 2H), 4.41 (t, $J=7.50$ Hz, 2H), 6.91 (t, $J=7.41$ Hz, 1H), 7.06 (t, $J=7.50$ Hz, 1H), 7.19 (d, $J=2.27$ Hz, 1H), 7.35 (d, $J=8.12$ Hz, 1H), 7.49 (d, $J=7.87$ Hz, 1H), 7.53 (d, $J=5.28$ Hz, 1H), 8.35 (d, $J=5.27$ Hz, 1H), 10.97 (brs, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 24.79, 48.58, 110.30, 112.41, 112.77, 118.58, 119.35, 122.02, 124.62, 126.07, 126.67, 127.90,

134.04, 137.09, 138.04, 155.63, 156.58; MS m/z (%) 320 (M^+), 164, 143 (100%). Anal. calcd for $C_{17}H_{12}N_4OS$: C, 63.73; H, 3.78; N, 17.49; S, 10.01. Found: C, 63.44; H, 3.70; N, 17.18; S, 10.08.

1e: Crystals (EtOH), mp 276–278°C; IR (KBr) 3368, 1670, 1568, 1436 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.20 (t, $J=6.87$ Hz, 2H), 4.44 (t, $J=6.85$ Hz, 2H), 7.10 (t, $J=7.5$ Hz, 1H), 7.28 (t, $J=7.62$ Hz, 1H), 7.49 (d, $J=8.25$ Hz, 1H), 7.62 (d, $J=9.62$ Hz, 1H), 7.65 (d, $J=8.58$ Hz, 1H), 7.95 (dd, $J=2.13$, 8.70 Hz, 1H), 8.22 (d, $J=1.88$ Hz, 1H), 11.89 (s, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.71, 41.92, 113.46, 119.01, 119.24, 120.73, 120.94, 123.09, 125.70, 125.87, 127.69, 129.47, 129.73, 138.13, 139.62, 146.59, 147.30, 160.48; MS m/z (%) 367 (M^++2), 365 (M^+, 100%), 338, 285. Anal. Calcd for $C_{18}H_{12}BrN_3O$: C, 59.03; H, 3.30; N, 11.47; Found: C, 59.39; H, 3.47; N, 11.65.

1f: Crystals (EtOH), mp 290–293°C; IR (KBr) 3344, 1648, 1587, 1444 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.20 (t, $J=6.8$ Hz, 2H), 4.46 (t, $J=6.77$ Hz, 2H), 7.12 (t, $J=7.40$ Hz, 1H), 7.31 (t, $J=7.6$ Hz, 1H), 7.52 (brd, $J=8.25$ Hz, 2H), 7.65 (s, 1H), 7.69 (d, $J=9.76$ Hz, 1H), 8.16 (d, $J=8.51$ Hz, 1H), 11.90 (s, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.72, 41.77, 113.50, 119.49, 120.36, 120.73, 120.97, 125.67, 125.92, 126.20, 126.97, 127.61, 129.57, 139.67, 139.79, 147.41, 149.41, 160.96; MS m/z (%) 322 (M^++2), 321 (M^++1), 320 (M^+, 100%), 292, 257. Anal. calcd for $C_{18}H_{12}ClN_3O$: C, 67.19; H, 3.76; N, 13.06. Found: C, 66.84; H, 3.79; N, 12.88.

1g: Colorless solid (EtOH), mp 279–280°C, IR (KBr) 3424, 1648, 1584, 1488 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 3.17 (t, $J=6.96$ Hz, 2H), 4.46 (t, $J=6.95$ Hz, 2H), 7.09 (t, $J=7.43$ Hz, 1H), 7.26 (t, $J=7.53$ Hz, 1H), 7.40 (d, $J=2.24$ Hz, 1H), 7.46 (d, $J=8.25$ Hz, 1H), 7.64 (d, $J=7.95$ Hz, 1H), 8.19 (d, $J=5.24$ Hz, 1H), 11.92 (s, 1H, N*H*); ^{13}C NMR (75 MHz, DMSO-d_6) δ 19.83, 41.48, 113.38, 118.45, 120.64, 120.81, 121.35, 125.50, 125.57, 125.72, 127.96, 136.37, 139.45, 147.91, 156.76, 157.93; MS m/z (%) 294 (M^++1), 293 (M^+), 292 (M^+−1, 100%), 265. Anal. calcd for $C_{16}H_{11}N_3OS$: C, 65.51; H, 3.78; N, 14.32; S, 10.93. Found: C, 65.29; H, 3.49; N, 14.21; S, 10.62.

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