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A new protocol for the construction of pyrrolo[4,3,2-*de*]quinolinones†

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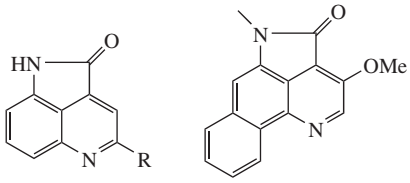
A facile method has been suggested for constructing pyrrolo[4,3,2-*de*]quinolinones by addition of acetophenones to 4-nitroisatin followed by reduction of the nitro group and spontaneous cyclisation.

Pyrrolo[4,3,2-*de*]quinolinones **1** constitute a rare and hardly accessible class of heterocyclic condensed systems. *Eupaluramine* alkaloid **2**[1] incorporating this tricyclic frame has been isolated from *Eupomatia bennettii* brush growing on Australian seacoast.

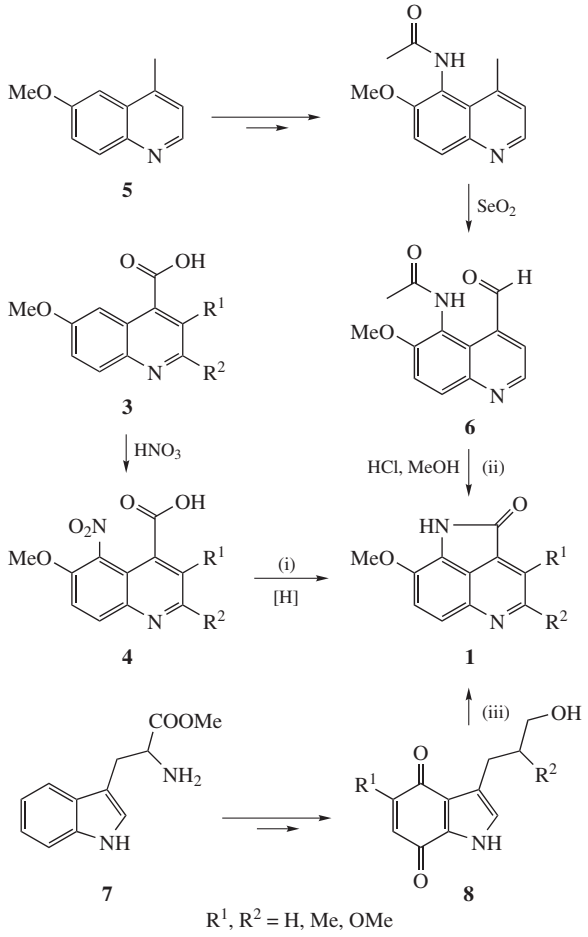


1 **2**

Note that the structure of **1** includes fragments of both quinoline and indole, whose derivatives are widely used as bioactive compounds.[2–5] Obviously, derivatives of compound **1** may be interesting as potential bioactive targets. The derivatives of pyrrolo[4,3,2-*de*]quinolinone possessing an antiallergic activity have been reported.[6]

Scheme 1 demonstrates the known methods for constructing the pyrrolo[4,3,2-*de*]quinoline frame. (i) The first most popular method involves nitration at the 5-position of 4-quinolinecarboxylic acids **3** followed by reduction of compounds **4** with tin(II) chloride in hydrochloric acid accompanied by spontaneous cyclisation. This method was used to obtain both unsubstituted pyrroloquinolinone and its methoxy and alkyl derivatives.[7] (ii) A variation of the first method, where nitration of readily available 4-methylquinoline **5** at the 5-position makes it possible to incorporate a nitro group, which is then reduced. Oxidation with selenium dioxide of 4-alkyl-substituted quinolines incorporating a protected amino group at the 5-position followed by removal of the protective group resulting in cyclisation.[8] (iii) The only method based on an indole-type precursor was used to synthesise Lymphostina, a natural immunodepressant. In this case, the cage of the target structure of **1** was formed by heating compound **8** in DMF; compound **8** was synthesised in several stages from original indole **7**.[10] Note that all these approaches either start from poorly accessible original compounds or involve multiple stages; the overall yields are very low. What is more, these approaches impose considerable restrictions of the type and mutual arrangement of substituents, since nitration is only possible if compounds **3** and **5** contain electron-donating substituents. This is a considerable drawback.

The purpose of this study was to develop an efficient and convenient approach for the construction of the pyrrolo[4,3,2-*de*]-quinoline tricyclic system from readily available reagents.



R^1, R^2 = H, Me, OMe

Scheme 1

We planned to synthesise the target compounds from commercially available 3-nitroaniline **9** (Scheme 2). Nitroaniline **9** can be converted to corresponding 4-nitroisatin **10**.‡ Subsequent addition of ketones **11** to **10** under conditions of alkaline catalysis should result in hydroxyindolinones **13**, which generally undergo instant Pfitzinger rearrangement[11] in the presence of bases to give derivatives of 4-quinolinecarboxylic acids **12** (Scheme 2). It was expected that the subsequent reduction of

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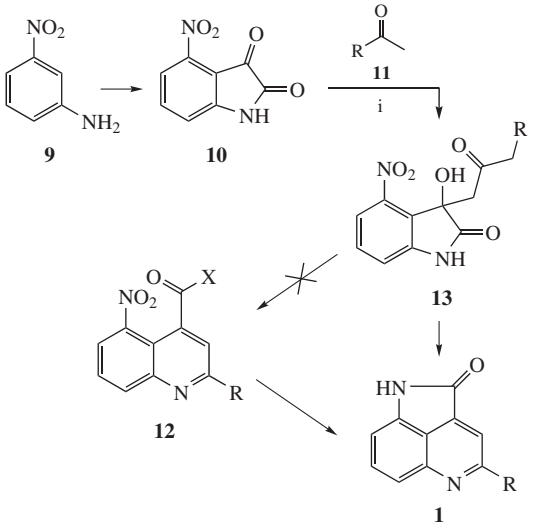
‡ ^{1}H NMR spectra were recorded on a Bruker AM spectrometer (250 and 300 MHz); chemical shifts were measured relative to tetramethylsilane. Mass spectra were recorded with a FINNIGAN MAT.INCOS 50 instrument.

For **10**: mp 231–234 °C (lit.,[12] mp 248–250 °C). ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.23 (d, 1H, C^{7}H, ^3J 8.9 Hz), 7.55 (d, 1H, C^{5}H, ^3J 9.0 Hz), 7.79 (t, 1H, C^{6}H, ^3J 18.0 Hz), 11.43 (s, 1H, NH).



a R = Ph
b R = 2,4-$Cl_2C_6H_3$
c R = 4-ClC_6H_4
d R = 4-MeC_6H_4
e R = 4-BrC_6H_4
f R = 3,4-$Cl_2C_6H_3$
g R = 4-$MeOC_6H_4$
h R = 3,4-$(MeO)_2C_6H_3$
i R = 4-EtC_6H_4
j R = 3,4-ethylenedioxyphenyl
k R = 1-naphthyl

Scheme 2 *Reagents and conditions*: i, pyrrolidine, EtOH, reflux, 3 h.

the nitro group followed by intramolecular cyclisation would yield target compounds **1**.

4-Nitroisatin was synthesised from 3-nitroaniline in 21% yield using the so-called Gassman method.[12] However, our attempts to obtain 4-quinolinecarboxylic acids **12** (X = OH) by condensation of ketones with isatin **10** in the presence of sodium hydroxide by the classical Pfitzinger reaction failed.

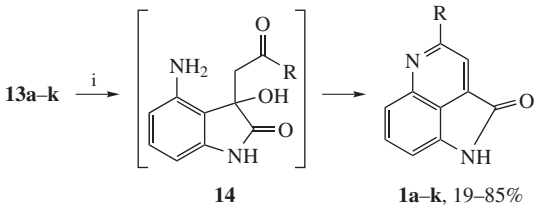
Aqueous ammonia is used as a base in the modified Pfitzinger method, which usually allows isatins to be converted to 4-quinolinecarboxamides **12** (X = NH_2) in high yields.[11] However, we have found that the reaction of isatin **10** with acetophenones **11** stops at the addition stage to give compounds **13**; subsequent rearrangement to quinoline derivative **12** (Scheme 2) does not occur.

Note that if ammonia, which serves as the catalyst of addition, is replaced with secondary amines, the yields of compounds **13a–k** increase several times (from 14 to 41% for **13d**); the highest yields were obtained with pyrrolidine.§

It could be expected that upon reduction of the nitro group in compounds **13a–k** to an amino group, intermediate **14** would undergo spontaneous intramolecular cyclisation (Scheme 3); this involves addition of the amino group at carbonyl followed by aromatization of the pyridine ring due to water elimination.

Since many reducing agents can reduce not only the nitro group but also the keto group, we used tin(II) chloride as the selective reagent that does not affect carbonyl.

In fact, treatment of compounds **13** with tin(II) chloride results in target structures **1a–k**.¶



Scheme 3 *Reagents and conditions*: i: $SnCl_2$, EtOH, 70 °C, 30 min.

Thus, we have developed a facile and efficient general method for synthesising derivatives of pyrrolo[4,3,2-*de*]quinolinone **1** based on the use of commercially available 3-nitroanilines and acetophenones as the key precursors. The method involves just a few stages that are easy to perform; considering the attractive overall yields of the target products, this gives us reasons to believe that fast progress in the chemistry of pyrrolo[4,3,2-*de*]-quinolines will continue.

Online Supplementary Materials

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.mencom.2009.05.016.

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§ *General procedure for the addition of acetophenones* **11a–k** *to 4-nitroisatin* **10**. 4-Nitroisatin **10** (2.1 mmol) was dissolved in ethanol (20 ml); 2.31 mmol of compound **11a–k** and three drops of pyrrolidine as the catalyst were added. The reaction mixture was refluxed for 3 h, cooled and evaporated to dryness. $CHCl_3$ (10 ml) was added to the residue and the mixture was stirred for 1 h. The precipitate formed was filtered off and washed with hexane (2×15 ml). The product was dried in air.

For **13a**: yield 18%, mp 214–215 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 4.00 (d, 1H, CH_2, ^3J 15.6 Hz), 4.4 (d, 1H, CH_2, ^3J 18.7 Hz), 6.41 (s, 1H, OH), 7.25 (d, 1H, C^7H, ^3J 8.7 Hz), 7.52 (m, 3H, C^3HPh, C^4HPh, C^5HPh), 7.65 (m, 2H, C^5H, C^6H), 7.88 (d, 1H, C^2HPh, C^6HPh, ^3J 9.9 Hz), 10.86 (s, 1H, NH).

For characteristics of compounds **13c–f**,**k**, see Online Supplementary Materials.

¶ *General procedure for reduction of* **13a–k**. Compound **13** (0.46 mmol) and tin(II) chloride dihydrate (2.3 mmol) were dissolved with stirring under nitrogen in anhydrous ethanol (4 ml). The reaction mixture was kept for 30 min at 70 °C and poured onto ice. The product was extracted with chloroform (2×70 ml). The extract was dried with anhydrous sodium sulfate and evaporated to dryness. The target structures **1a–k** were isolated by column chromatography using $CHCl_3$–MeOH (10:1) as an eluent.

For **1a**: yield 64%; mp 223–225 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.02 (m, 1H, C^4HPh), 7.57 (d, 2H, C^3HPh, C^5HPh, ^3J 10.0 Hz, J_{AB} 14.6 Hz), 7.72 (t, 2H, C^6H, C^8H, ^3J 3.7 Hz), 8.33 (d, 2H, C^2HPh, C^6HPh, ^3J 9.4 Hz, J_{AB} 14.6 Hz), 8.47 (s, 1H, C^3H), 10.97 (s, 1H, NH). MS, *m*/*z*: 246 [M^+]. Found (%): C, 78.38; H, 4.12; N, 11.05. Calc. for $C_{16}H_{10}N_2O$ (%): C, 78.04; H, 4.09; N, 11.38.

For **1b**: yield 42%, mp 269–271 °C. ^{1}H NMR ([$^2H_6$]DMSO) δ: 7.02 (d, 1H, C^7H, ^3J 6.7 Hz), 7.69 (d, 2H, C^6H, C^8H, ^3J 4.8 Hz), 7.80 (d, 1H, C^6HPh, ^3J 8.9 Hz), 8.30 (d, 1H, C^5HPh, ^3J 9.4 Hz), 8.57 (d, 2H, C^3H, C^2HPh, ^3J 11.9 Hz), 11.60 (s, 1H, NH). MS, *m*/*z*: 314 [M^+]. Found (%): C, 60.71; H, 3.32; N, 8.74. Calc. for $C_{16}H_{10}Cl_2N_2O$ (%): C, 60.59; H, 3.18; N 8.83.

For characteristics of compounds **1c–k**, see Online Supplementary Materials.