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A Convenient Regioselective Synthesis of Pyrano[3,2-*b*]acridones Involving Nucleophilic Addition to Benzyne

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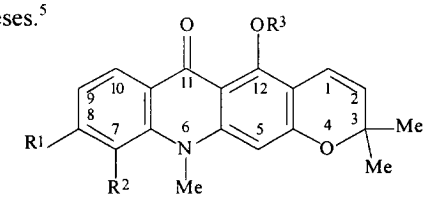
Abstract

Acridone **8** was prepared by the nucleophilic addition of aniline **4** to benzyne **5**. Hydrolysis of the ester group, followed by cyclisation gave the acridone **8**, which was subsequently converted to the pyrano[3,2-b]acridin-4-ones **11** and **17**.

Keywords: acridines, alkaloids, arynes, pyrones

Alkaloids based on the pyrano[3,2-*b*]acridone ring system occur in several *Citrus* species *e.g.* honyumine **1** from *Citrus grandis*[1] and *Citrus funadako*[2] or yukocitrine **2** from *Citrus yuko*.[3] The regioselective synthesis of pyrano[3,2-*b*]acridones has previously been reported only by Reisch *et al.*[4] Most synthetic pyrano[3,2-*b*]acridones have been obtained as by-products during the preparation of pyrano[2,3-*a*]acridones, *e.g.* isoacronycine **3** or its derivatives have been obtained in low yields as by-products in most acronycine syntheses.[5]



1 R^1 = OH, R^2 = OMe, R^3 = H
2 R^1 = R^3 = H, R^2 = OH
3 R^1 = R^2 = H, R^3 = Me

As a part of our ongoing program in the search for inhibitors of growth-factor mediated cell proliferation 2-phenylpyrano[2,3-*a*]acridin-4-one derivatives were tested in biological assays, along with some naturally occurring pyranoacridones.[6] The promising results from these experiments prompted us to elaborate a convenient and regioselective synthetic sequence for the preparation of pyrano[3,2-*b*]acridone derivatives.

To achieve this goal we initially required a range of substituted 2-acetyl-3-hydroxyacridones **8**, the immediate precursors of these ring systems.[7] We have devised the readily available, highly substituted benzene derivatives **4**[8] as starting materials for this synthetic route. After several fruitless attempts at the direct arylation of the amino group, we decided on the use of nucleophilic coupling with arynes. The

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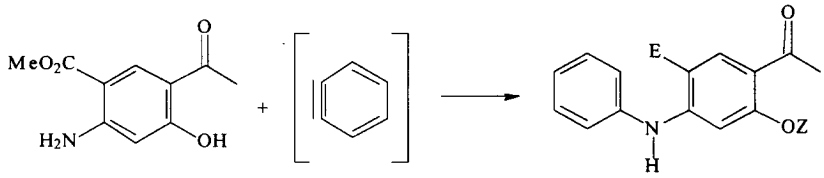
method of benzyne generation was restricted by the nature of the neighbouring substituents on the aniline derivative and for our purposes the preparation and thermolysis of benzenediazonium carboxylates (prepared from the corresponding anthranilic acid derivatives) was suspected to be superior over the other known methods.[9,10] The highly substituted aniline derivative **4** and benzyne **5** reacted smoothly with high chemoselectivity to give the biarylamine **6** (Scheme 1).

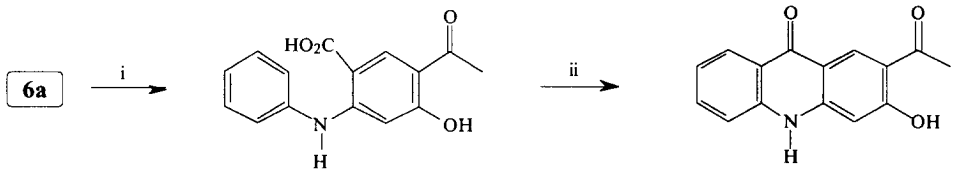


4 **5**

6a E = CO_2Me, Z = H (62%)
6b E = CO_2Me, Z = Ph (5%)

Scheme 1 *Reagents and conditions:* dichloroethane, 80 °C.

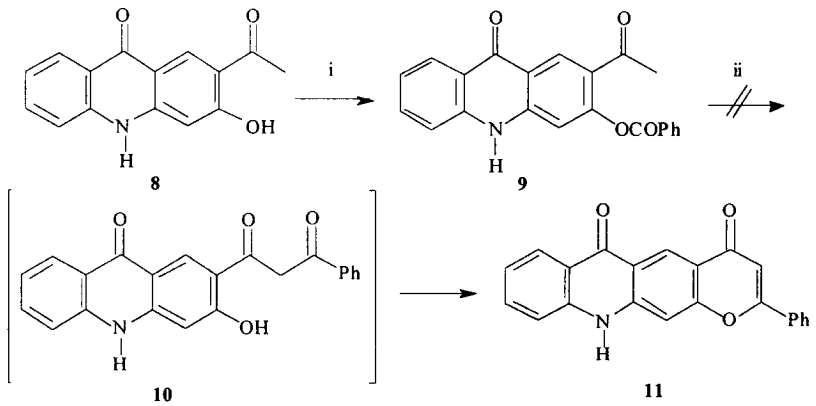
The bisarylated derivative **6b** (Z = Ph) was formed as a minor product in low yield. Alkaline hydrolysis of the ester **6a**, was followed by the polyphosphate ester (PPE) mediated ring-closure of the acid **7** to give the previously unknown acridone derivative **8** in high yield (Scheme 2).



7 **8**

Scheme 2 *Reagents and conditions:* i, NaOH, EtOH, 80 °C (100 %); ii, PPE, $CHCl_3$, 60 °C, (95 %).

Our first attempts at the apparently straightforward preparation of the title heterocycle proved fruitless as the benzoyl derivative **9** did not rearrange under the usual range of Baker-Venkataraman conditions (Scheme 3).[11]

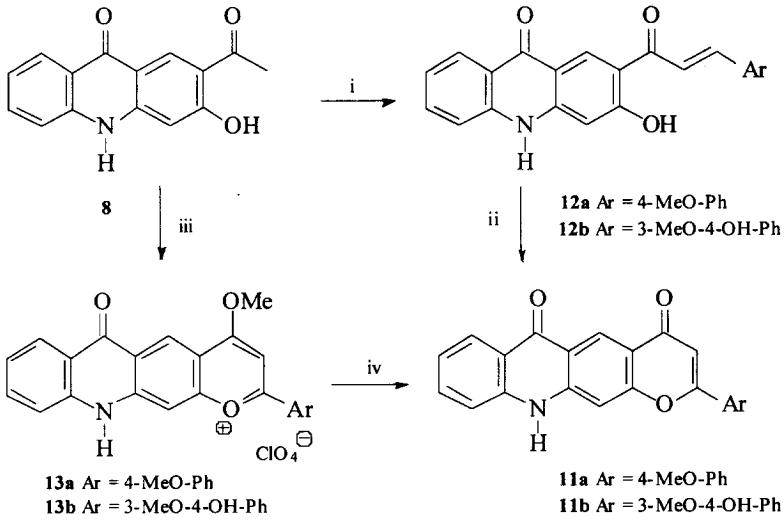


8 **9**

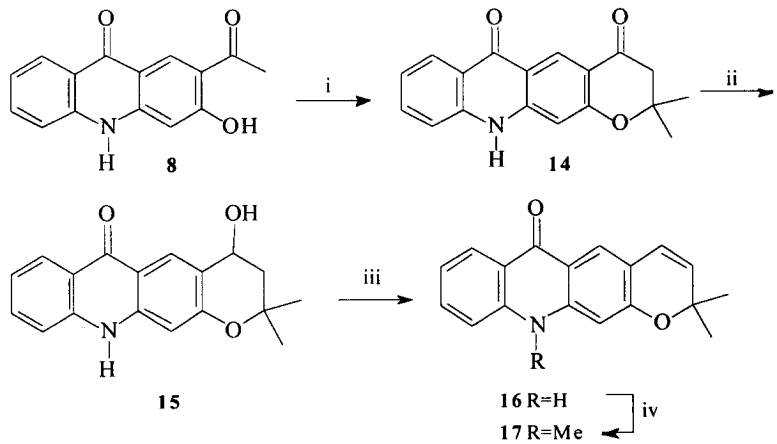
10 **11**

Scheme 3 *Reagents and conditions:* i, PhCOCl, pyridine, r.t. (100 %); ii, KOH, pyridine or NaH, DMF or DBU, pyridine.

The application of another standard method for flavonoid synthesis[12] did, however, lead to the desired pyrano[3,2-*b*]acridone derivatives. The reaction of acridone **8** with aromatic aldehydes, in aqueous - ethanolic potassium hydroxide, gave the chalcones **12**, which were converted to the 2-aryl-pyrano[3,2-*b*]acridin-4-ones **11**[13] upon oxidative cyclisation with DMSO/iodine.[14] We could improve the yield and purity of **11** in an alternative procedure[15] using perchloric acid and trimethyl orthoformate for the construction of pyranone ring (Scheme 4).



Scheme 4 *Reagents and conditions:* i, 40 % aqueous NaOH, EtOH, r.t., ArCHO (45-50 %); ii, DMSO, I_2, 200 °C (80-87%); iii. ArCHO, $HC(OMe)_3$, 70 % $HClO_4$; iv. DMF, reflux (65-70 %).



Scheme 5 *Reagents and conditions:* i, excess CH_3COCH_3, piperidine, DMF, 80 °C (83 %); ii, $NaBH_4$, MeOH, reflux (100 %); iii, PTSA; toluene, THF, reflux (96 %); iv, MeI, K_2CO_3, Bu_4NBr (70 %).

Alternatively, the reaction of the key intermediate acridone **8** with acetone, in the presence of piperidine as a base, gave **14** which was converted to demethoxynorisoacronycine **16**[16] in two simple steps. Methylation then gave the demethoxyisoacronycine **17** in 70 % yield.

In conclusion, the protocol described here is simple and efficient for the preparation of a range of pyrano[3,2-*b*]acridine derivatives, giving access to a wide range of potentially biologically active compounds.

Acknowledgements

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References and Notes

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13. All compounds gave satisfactory elemental and spectroscopic analyses. **11b** δ_H (500 MHz, DMSO-[D]$_6$) 11.96 (1H, s, NH), 9.96 (1H, s, OH), 8.89 (1H, s, H-12), 8.22 (1H, d, *J* 7.5 Hz, H-10), 7.77 (1H, t, *J* 8.3 Hz, H-8), 7.64 (1H, dd, *J* 8.3 Hz, *J* 2.2 Hz, Ar-6'), 7.61 (1H, d, *J* 2.2 Hz, Ar-2'), 7.59 (1H, s, H-5), 7.53 (1H, d, *J* 8.3 Hz, H-7), 7.30 (1H, t, *J* 7.5 Hz, H-9), 6.98 (1H, d, *J* 8.3 Hz, Ar-5'), 6.93 (1H, s, H-2), 3.93 (3H, s, OMe).
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16. *Compound* **17** $_{H}$ (270 MHz, DMSO-[D]$_6$) 8.28 (1H, d, *J* 7.5 Hz, H-10), 8.02 (1H, s, H-12), 7.76 (2H, m, H-7 and H-8), 7.29 (1H, t, *J* 7.5 Hz, H-9), 7.08 (1H, s, H-5), 6.62 (1H, d, *J* 10 Hz, H-1), 5.86 (1H, d, *J* 10 Hz, H-2), 3.81 (3H, s, NMe), 1.45 (6H, s, 2 × Me)