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New synthesis of arcyriaflavin-A via silyl enol ether-mediated and Fischer indolisations

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Abstract—A new synthesis of the natural product arcyriaflavin-A is described. It was brought about through Diels–Alder cycloaddition and two indolisations based on silyl enol ether nucleophilic attack and Fischer processes.

Some time ago, we began a research project aimed at the synthesis of indolocarbazole alkaloid[1] analogues, taking arcyriaflavin-A as the simplest model. We have already described the preparation of a broad variety of this family of compounds, some of them displaying an interesting cytotoxic profile.[2] The synthetic methodology used for this purpose was a combination of a Diels–Alder reaction between aryl-siloxy-butadienes and a maleimide derivative followed by a Fischer indolisation.

During the course of those studies, we performed a new synthesis[3] of arcyriaflavin-A, in which the last indole unit of the indolocarbazole system was assembled by a triethylphosphite-mediated formal nitrene insertion (Cadogan and Sundberg's procedure).[4]

Since one drawback arising from that synthesis was the decrease in yield due to the formation of two regioisomers in the key Fischer indolisation process, we decided to overcome this problem by changing the synthetic approach. For this purpose, we planned to build the indolocarbazole skeleton by reductive cyclisation of the cycloadduct **2** followed by the Fischer reaction of the resulting ketone **3**, as shown in Scheme 1.

In order to obtain pyrrolocarbazoletrione **3**, it was necessary to explore the reductive cyclisation of silyl enol ether **2**, which can readily be prepared[3] from *o*-nitrobenzaldehyde through a Diels–Alder reaction between the nitrophenylsiloxydiene **1** and maleimide (Scheme 2).

To our knowledge, there are no references describing the use of a silyl enol ether as a substrate for the reductive cyclisation of aromatic nitro compounds. While there are examples of nitrene-mediated insertions on silyl enol ethers, all reported cases involve the generation of the nitrene species from azide derivatives.[5–7]

When the cycloadduct **2** was reacted with neat triethylphosphite at 160 °C, compound **3a** was obtained in 75% yield. If nitrene insertion is taken into consideration as the cyclisation process, the expected reaction product, **3b**, would have the 2,3-dihydroindole moiety (Scheme 3a). Accordingly, an alternative cyclisation mechanism, instead of a simple nitrene insertion, must be involved.

The cyclisation process during the treatment of olefins and nitroaromatic derivatives is usually explained in terms of the formation of a nitrene intermediate under $P(OEt)_3$ reducing conditions.[4] This explanation, valid for most cases,[4,8] is not satisfactory for the formation of our synthetic intermediate towards arcyriaflavin-A. As depicted in Scheme 3a, the nucleophilic attack by the silyl enol ether on the electrophilic nitrene would result in a dihydroindole moiety (compound **3b**), which requires a further oxidation process to yield **3a**.

As stated by Sundberg, while this type of reductive cyclisations can formally be considered to be nitrenoid

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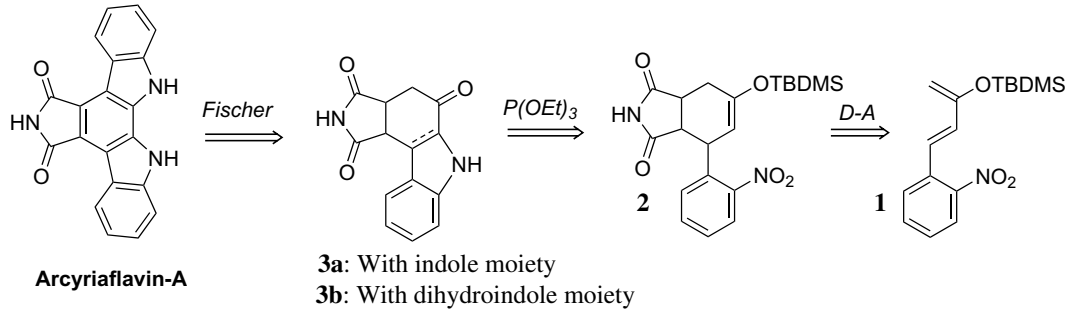
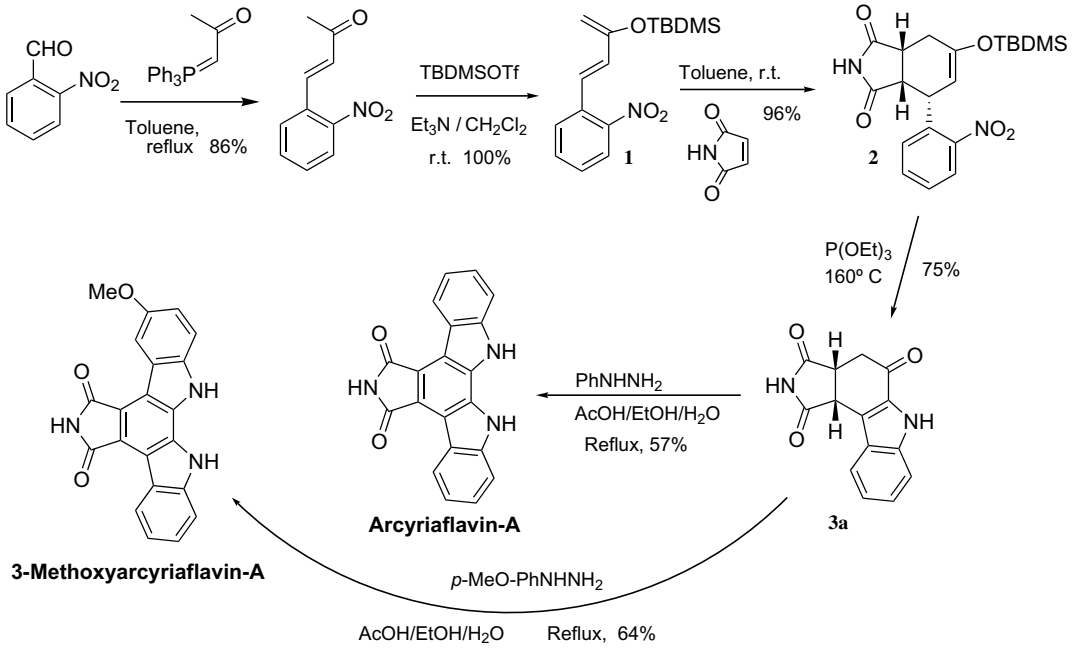


Scheme 1.



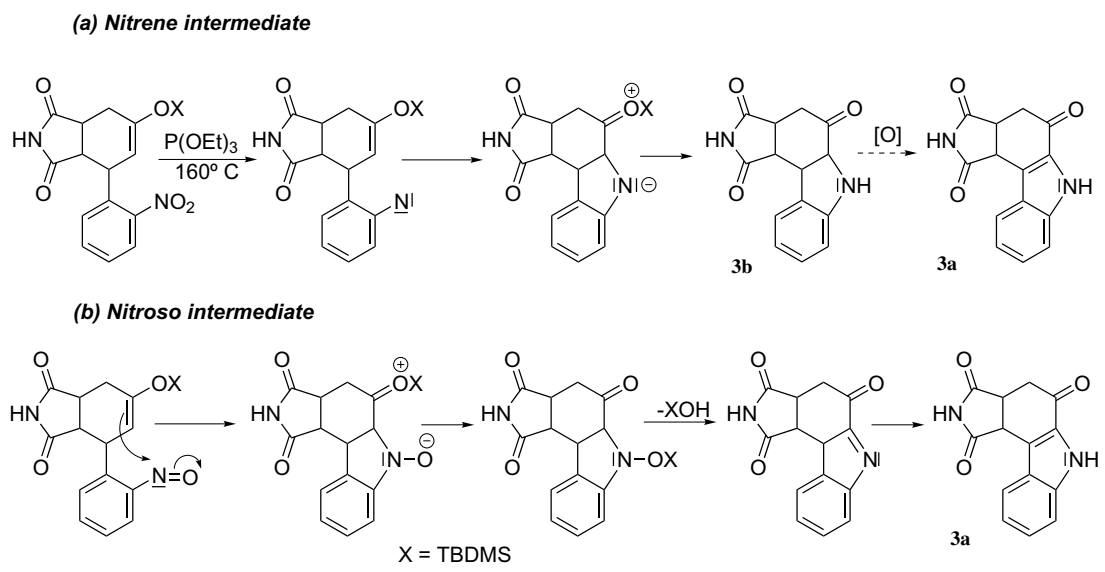
Scheme 2.

in character, several observations suggest this to be an oversimplification.[9] It seems more likely that each of the reductants would generate a specific electrophilic nitrogen intermediate that would attack the adjacent double bond, such that the structure of the reactive intermediate could vary with the reducing agent.

In the present case, an intermediate product in the $P(OEt)_3$ treatment of the nitro group, which could maintain the electrophilic character together with a not fully reduced state, would explain the formation of **3a**. The generally accepted formation of a nitroso derivative during this kind of reduction[10] could account for this, as depicted in Scheme 3b. The appearance of an oxy-amino intermediate as a consequence of cyclisation mediated by the nitroso group, would only require an elimination step in order to produce the observed product, being compatible with the reaction conditions.

With compound **3a** in hand, two synthetic steps remained in order to complete the synthesis of arcyriaflavin-A. When **3a** was subjected to Fischer indolisation, arcyriaflavin-A was isolated directly by crystallisation (57% yield), thus implying that an aromatisation process to generate an indole ring occurs readily under the reaction conditions. An unsymmetrical analogue of arcyriaflavin-A (3-methoxy-derivative) was obtained following a similar procedure, but in this case using *p*-methoxyphenylhydrazine for the indolisation reaction (see Scheme 2, for the complete synthesis).[11]

In conclusion, the sequence described here (aryl-siloxydiene Diels–Alder reaction, and nitro-reductive silyl enol ether-mediated and Fischer indolisations) provides a new high-yielding synthesis of the alkaloid arcyriaflavin-A and its 3-substituted unsymmetrical analogue (35% and 40% overall yields from *o*-nitrobenzaldehyde, respectively), thus representing a noticeable improvement to our previous procedure (12% overall yield). The pyrrolocarbazoletrione **3a** has a very interesting structure as a possible synthetic intermediate for the preparation of other natural or unnatural fused polyheterocyclic products.



Scheme 3.

Acknowledgements

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References and notes

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11. All the analytical data for the compounds synthesised are consistent with their structure, as for instance: **3a**: Yellow solid, mp 294 °C ($CHCl_3$). ^1H NMR (400 MHz, DMSO) (δ ppm) 11.95 (1H, s, N–H), 11.31 (1H, s, N–H), 8.01 (1H, d, J = 8.0 Hz, H-10), 7.41 (1H, d, J = 8.0 Hz, H-7), 7.34 (1H, t, J = 8.0 Hz, H-8), 7.14 (1H, t, J = 8.0 Hz, H-9), 4.54 (1H, d, J = 7.4 Hz, H-10c), 3.90 (1H, m, H-3a), 2.90 (2H, m, H-4). ^{13}C NMR (δ ppm) 186.5, 178.1, 175.7, 138.5, 130.3, 126.7, 125.2, 123.2, 120.5, 119.7, 112.9, 40.3, 39.9, 34.1. MS found for $C_{14}H_{10}N_2O_3$ *m/z*: 254. 3-Methoxyarcyriaflavin-A: Brown solid, mp 320 °C ($CHCl_3$). ^1H NMR (400 MHz, DMSO) (δ ppm) 11.76 (1H, s, N–H), 11.59 (1H, s, N–H), 10.95 (1H, s, N–H), 8.96 (1H, d, J = 7.4 Hz, H-8), 8.55 (1H, s, H-4), 7.76 (1H, d, J = 7.4 Hz, H-11), 7.68 (1H, d, J = 8.6 Hz, H-1), 7.52 (1H, t, J = 7.4 Hz, H-10), 7.32 (1H, t, J = 7.4 Hz, H-9), 7.17 (1H, d, J = 8.6 Hz, H-2), 3.41 (3H, s, OMe). ^{13}C NMR (δ ppm) 171.4 (×2), 153.8, 140.2, 135.2, 129.6, 129.1, 126.6, 124.3, 122.1, 121.7, 120.2, 120.0, 119.5, 116.0, 115.6, 115.3, 112.7, 112.0, 106.6, 55.5. HRMS (FAB) *m/z* calcd for $C_{21}H_{13}N_3O_3$ 355.0957, found 355.1001. Arcyriaflavin-A: the analytical data agree with those reported in Gribble, G. W.; Berthel, S. J. *Tetrahedron* **1992**, *48*, 8869–8880.