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Synthesis of dipyrrolo[2,3-*a*:1′,2′,3′-*fg*]acridin-12(1*H*)-ones

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ABSTRACT

Acylation reactions of 4,6-dimethoxyindoles with glyoxyloyl chlorides were achieved by the use of graphite powder in 1,2-dichloroethane at reflux. The products were monoketones as a result of decarbonylation, rather than the expected 1,2-diketones. Treatment of these monoketones with base led to their cyclisation and elimination of methanol to afford the novel dipyrrolo[2.3-*a*:1′,2′,3′-*fg*]acridin-12(1*H*)-ones.

Introduction

One of the features of the chemistry of 4,6-dimethoxyindoles is their ability to undergo electrophilic substitution at C7 [1–4]. However, there are several aspects of this reactivity that are important, two of which are relevant to the current discussion. One is that electrophilic substitutions at C7 quite often require vigorous conditions. The other is that the introduction of a substituent at C7 enables the possibility of cyclisation from C7 back on to the indole ring. There are numerous examples where cyclisation between C7 and N1 leads to a new ring fused to the indole [1,5–11]. However, in this paper, an example of cyclisation from C7 to C6 is described. This process is made possible as a result of an unexpected outcome of a vigorous acylation reaction at C7. This latter aspect is dealt with first.

Results and discussion

Although the Friedel-Crafts acylation reaction of 4,6-dimethoxy-2,3-diphenylindole **1** with phenylglyoxyl chloride can be carried out, it requires the use of graphite powder in 1,2-dichloroethane at reflux. Graphite powder has been found to promote Friedel-Crafts acylation of aromatic compounds with acyl halides to give the corresponding acylated products in high yields [12]. However, the product of the above reaction was found not to be the diketone **2**, but rather the monoketone, the 7-benzoylindole **3**, presumably resulting from decarbonylation at the reaction temperature of 83 °C (Scheme 1). The new compound **3** was fully characterised by its analytical and spectroscopic data. On the other hand, the indole **1** can be easily reacted with oxalyl chloride in dry tetrahydrofuran to give the 7-indolylglyoxylic acid chloride **4** [13,14], but other acylation reactions of the indole **1** similarly required the above vigorous conditions using graphite powder in 1,2-dichloroethane at reflux. Consequently, the acylation of the indole **1** with the related glyoxylic acid chloride **4** resulted in formation of the symmetrical 7,7′-diindolylketone **5** in 52% yield, rather than the related diketone (Scheme 1).

Decarbonylation once again occurred. The structure of the product **5** was clarified by analytical and spectroscopic data, and in particular by X-ray crystal structure determination. The ORTEP diagram of the monoketone **5** is shown in Fig. 1.

Given the formation of the 7,7′-diindolylketone **5**, the possibility of a cyclisation reaction onto C6 was investigated. When the diindolylketone **5** was heated at reflux in acetone with benzyltrimethylammonium hydroxide [18], the new dipyrrolo-acridone **6** was formed in 75% yield (Scheme 1). The structure was indicated by the presence of three methoxy groups and only one indole NH in the ^{1}H NMR spectrum. An X-ray crystal structure of the acridinone **6** confirmed the structure, and the ORTEP diagram is shown in Fig. 2.

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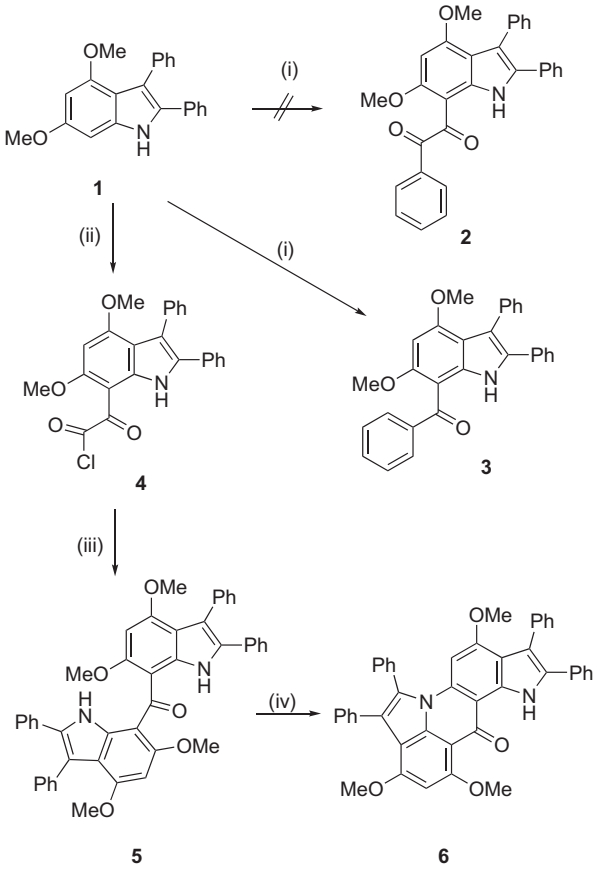


Scheme 1. Reagents and conditions: (i) PhCOCOCl, graphite powder, 1,2-dichloroethane, reflux, 48 h, 12%; (ii) ClCOCOCl, benzene [2]; (iii) **1**, graphite powder, 1,2-dichloroethane, reflux, 20 h, 52%; (iv) benzyltrimethylammonium hydroxide, acetone, reflux, 75%.

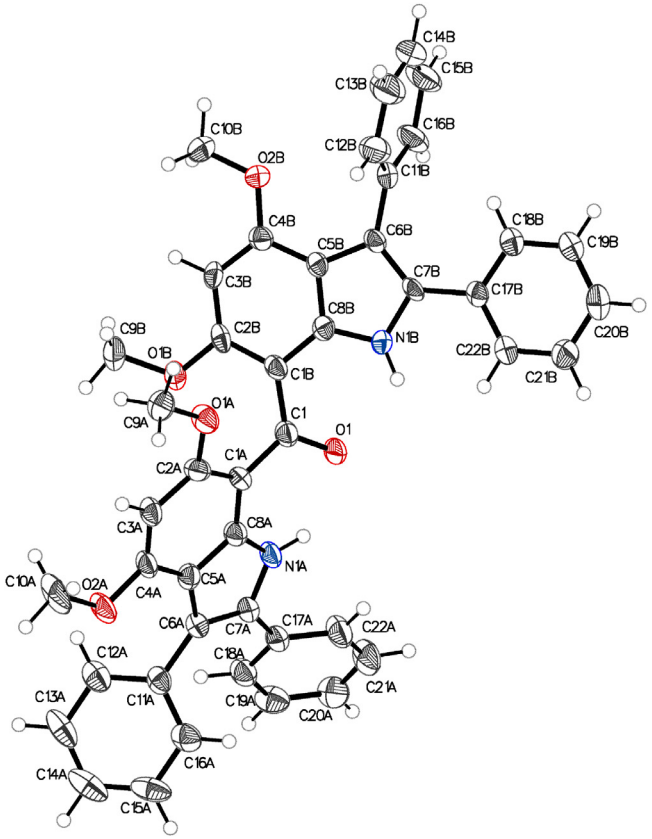


Fig. 1. ORTEP diagram of ketone **5**.

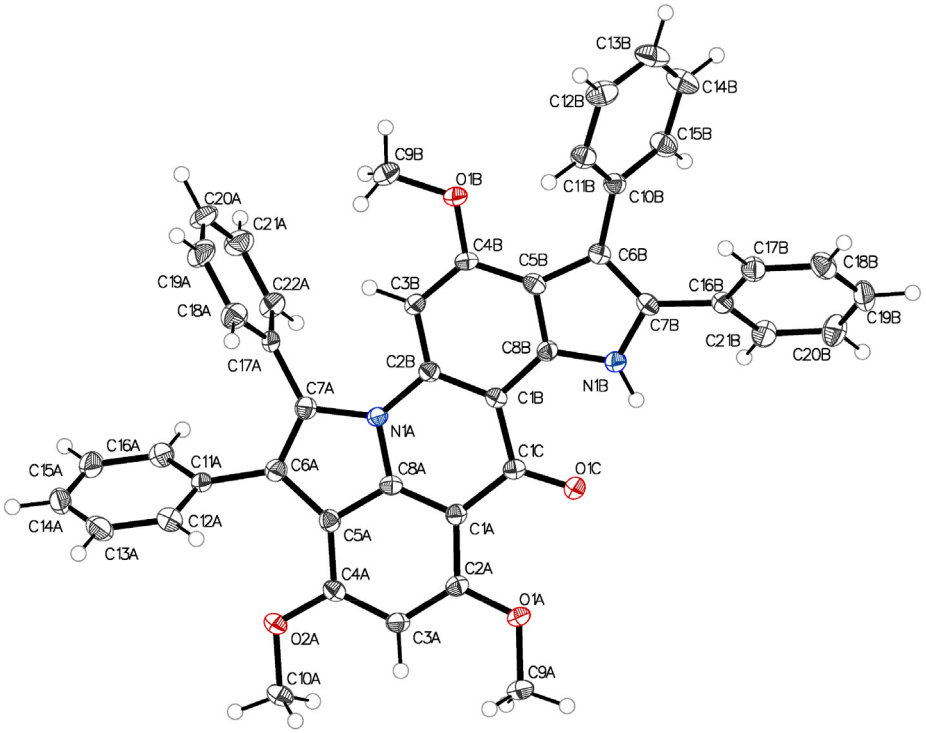
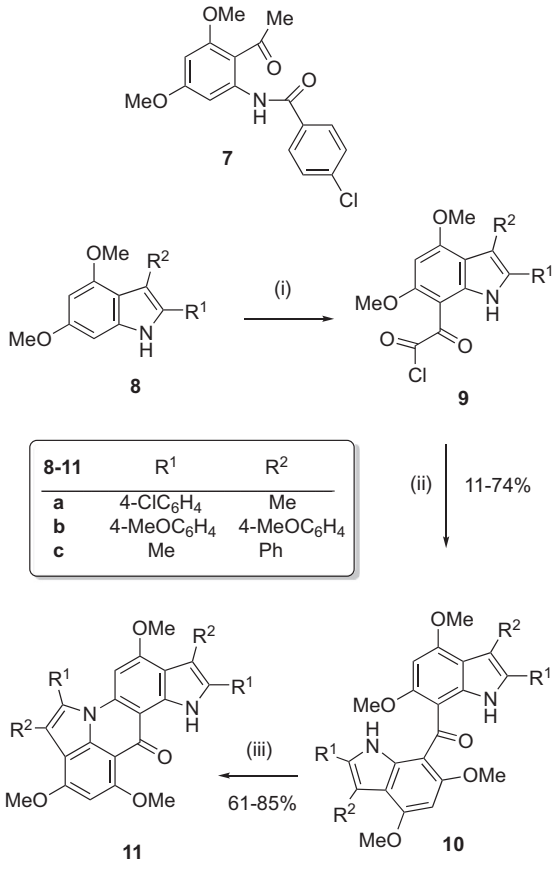
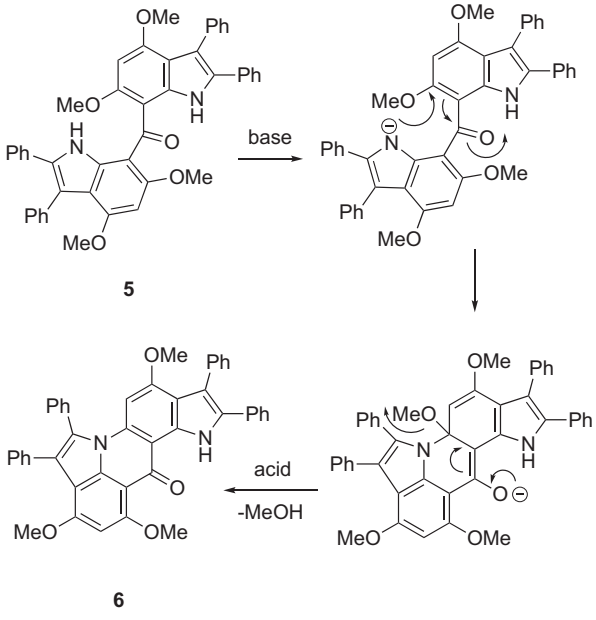


Fig. 2. ORTEP diagram of acridinone **6**.



Scheme 2. Reagents and conditions: (i) ClCOCOCl, THF, reflux, 1.5 h, 69%; (ii) **8**, graphite powder, 1,2-dichloroethane, reflux, 1 week, 11–74%; (iii) benzyltrimethylammonium hydroxide, THF, reflux, 1.5 h, 61–85%.



Scheme 3. Plausible mechanism for cyclisation of ketone **5** to acridone **6**.

The new 7-glyoxyloyl chloride **9a** was also prepared in 69% yield by reaction of oxalyl chloride with the new 4,6-dimethoxyindole **8a**, which in turn was synthesised in 81% yield by the McMurry coupling of the acetyl-anilide **7**. Indole **8b** was synthesised from 3,5-dimethoxy anilinium hydrochloride and anisoin in 99% yield, and indole **8c** has previously been reported [19]. Combination of the glyoxyloyl chlorides **9** with the respective indoles **8**, under the influence of graphite in 1,2-dichloroethane at reflux, gave the monoketones **10**. Treatment of these monoketones with benzyltrimethylammonium hydroxide in tetrahydrofuran afforded the acridinones **11** in 61–85% yield (Scheme 2).

The cyclisation reaction of the diindolylketones to form the acridinones presumably proceeds by formation of an indolyl anion, followed by its Michael-type addition to what is effectively an unsaturated ketone to generate a cyclic intermediate which loses methanol so as to restore the aromaticity of the structure (Scheme 3). This reaction is unprecedented and there appear to be no prior examples of the displacement of a 6-methoxy group from a 7-acylindole by addition–elimination of a *N*-nucleophile as proposed.

Conclusion

Polycyclic systems containing acridine, acridone and pyrrole rings are of particular interest since they possess a variety of biological activities. To date, there are no reports of the dipyrroloacridinones described here.

However, there are several examples of the simpler pyrrolo [*3,2,1-de*]acridin-6(1*H*)-ones. This structure has been achieved by cyclisation of an *N*-(2-carboxyphenyl)indoline followed by dehydrogenation [15], or alternatively by cyclisation of an *N*-allylcarbazole [16] or an *N*-(2-carboxyphenyl)indole [17].

In summary, new dipyrrolo-acridinones can be synthesised by treatment of 7,7′-diindolylketones with base. The reaction appears to be general and an investigation of the broader scope of this chemistry is under way.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2018.11.011.

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