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A Versatile Approach to the Synthesis of 4,5-Dioxoaporphine and 3,4-Dioxocularine Alkaloids. One-Pot Sequential C/B Ring Formation from Arylacetamides.

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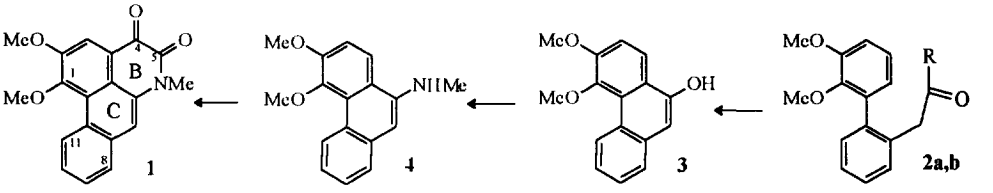
Abstract: Cyclization of biarylacetamides to their phenanthrene derivatives is promoted by oxalyl chloride/stannyl chloride. The reaction proceeds with a second cyclization in which the oxalyl fragment acts as an α-dicarbonyl transfer agent to give 4,5-dioxoaporphine alkaloids in a single step. This double cyclization was also applied to aryloxyphenyl acetamides to give the corresponding 3,4-dioxocularine alkaloids. Decarbonylated aristocularine alkaloids were also formed in this case.

In the course of our ongoing research into the chemical and biological properties of isoquinoline alkaloids, we developed a synthesis for the 4,5-dioxoaporphine cepharadione-B (**1**) and some 2-demethoxy analogs.[1] The synthetic approach is based on the preformed biaryl bond of fluorenones, the starting compounds (Scheme 1). The key steps in the synthesis include cyclization of the acetamide (**2a**, R= 4-morpholine), hydrolysis to the phenanthrol (**3**) and Bucherer reaction to the phenanthrylamine (**4**). The amine is converted to the α-chloroacetamide and photochemical cyclization is followed by air oxidation.



Scheme 1

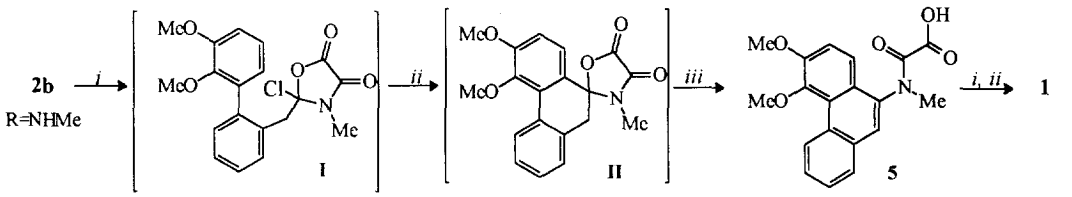
Such a simple approach, however, is subject to serious hindrance: increasing the number of methoxy substituents in the phenanthrol, slows down the the Bucherer reaction, and produces oxidation to the phenanthrone exclusively. One straightforward solution could be direct access to the phenanthrylamine (**4**) by cyclization of the amide **2b** (R=-NHMe), however, no reaction is observed under Bischler-Napieralsky conditions ($POCl_3$).

One alternative approach involves activating *N*-methyl acetamides via acyliminium ions,[2] which combined with modern strategies in biaryl bond formation,[3] might provide a novel, versatile entry to aporphinoids.[4] This paper

demonstrates that 4,5-dioxoaporphine alkaloids can be obtained by sequential formation of rings C and B in a single step from appropriate biarylacetamides by reaction with oxalyl chloride and stannyl chloride. The method has been extended to the cyclization of aryloxyphenyl acetamides to give 3,4-dioxocularine alkaloids.[5] This last reaction also yields competitive aristocularine alkaloids.

Oxalyl chloride is known to react with secondary amides to give 2-chlorooxazolidine-4,5-dione.[6] Addition of a Lewis acid to these heterocycles, derived from phenethylamides, yields acyliminium ions, which make superior acylating agents.[7] After cyclization, oxalyl adducts of isoquinolines are obtained that are readily hydrolysed and decarboxylated. The reaction has been used as a modified Bischler-Napieralsky procedure for the synthesis of 3-aryl[7] and 1-alkyl[8] 3,4-dihydroisoquinolines.

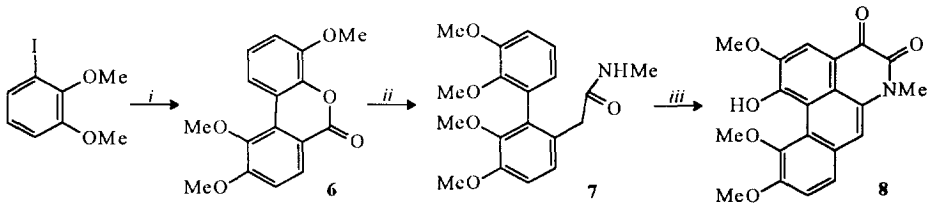
Treating the *N*-methyl acetamide (**2b**) with oxalyl chloride (1 eq) produced oxazolidinedione (**I**) quantitatively; the subsequent addition of stannyl chloride (1 eq) gave rise to cyclization to **II**, as the main process, as checked by ^{1}H-NMR (Scheme 2). Contrary to our expectations, acid hydrolysis of the cyclized spiroxazolidinedione (**II**) afforded no 10-*N*-methyl-3,4-dimethoxy phenanthrene (**4**); rather the oxalylamide (**5**)[9] was isolated in 30% yield. Conversion of **5** to the acid chloride (oxalyl chloride) and Friedel-Craft cyclization ($SnCl_4$) afforded the dioxoaporphine cepharadione B (**1**).



Scheme 2 . *Reagents: i*) $(COCl)_2$; *ii*) $SnCl_4$; *iii*) H_2O

From these results we assumed that opening of the spiroxazolidinedione intermediate (**II**) and phenanthrene aromatization was catalysed by the hydrogen chloride formed in the reaction. If so, the transformation of the amide **2b** should proceed all the way to the dioxoaporphine in a single step provided two equivalents of oxalyl chloride and stannyl chloride were used. In fact, adding excess oxalyl chloride to a CH_2Cl_2 solution of the amide **2b**, followed by stannyl chloride (2.5 eq) produced a deep reddish color. After 72 h at RT the work up of the reaction afforded cepharadione B (**1**) in 65 % yield.[10]

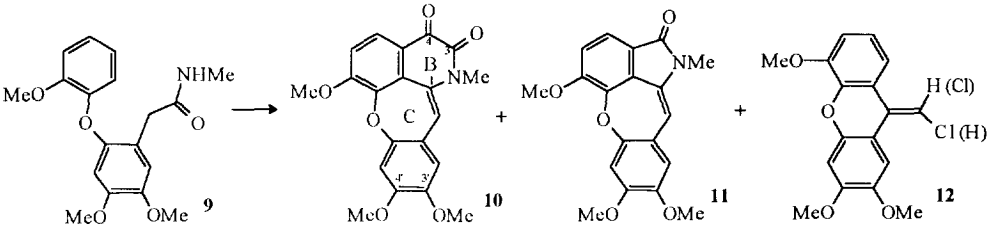
The cytotoxic activity exhibited by this type of alkaloids,[1,11] prompted us to use this method to synthesize dioxoaporphine oxygenated at positions 1,2,10,11 (a substitution pattern that is difficult to obtain by using more conventional designs).[12] The Pd acetate coupling reaction of 1-iodo-2,3-dimethoxybenzene provided 4,9,10-trimethoxy-6*H*-dibenzo[*b*,*d*]pyran,[13] which was readily oxidized to the corresponding pyranone (**6**)(Scheme 3). Opening of the lactone (with KOH) and trapping of the phenoxide (MeI), was followed by a conventional homologation sequence to a biarylacetamide (**7**) bearing the oxygenation pattern sought. The double cyclization took place in good yield (70%) and afforded the trimethoxy-dioxoaporphine (**8**). The loss of the methyl group at position 1 was inferred from the C-1/H-3 correlation observed in the HMBC spectrum.



Scheme 3. *Reaction conditions* : *i*) 1: $Pd(OAc)_2$; 2: PCC ; *ii*) 1: MeI, KOH; 2: $LiAlH_4$, $SOCl_2$, NaCN; 3: HCl/H_2O ; 4: $SOCl_2$, $MeNH_2$; *iii*) $(COCl)_2$, $SnCl_4$, CH_2Cl_2.

This strategy was also applied to the synthesis of cularine alkaloids in a non-biogenetic approach to the benzoxepine[2,3,4-*i,j*]isoquinoline heterocycle.[5] The synthetic approach to cularines based on the multistep C/B ring formation with a dibenzoxepinone (Manske's ketone) as the key intermediate is well documented.[14] The availability of the required arylacetamide (**9**) through the Ullmann reaction makes our strategy attractive for the preparation of not only the 3,4-dioxocularine but also the reduced forms of this type of alkaloid.

The reaction of **9** with $(COCl)_2/SnCl_4$ in refluxing dichloromethane was completed within 5 h. After column



Scheme 4. *Reaction conditions* : CH_2Cl_2, $(COCl)_2$, $SnCl_4$, 60°, N_2, 5h.

chromatography dioxocularine (**10**, 20%), aristocularine (**11**, 40%) and the xanthene derivative **12** (35%, mixture of the E/Z isomers) were separated.

Aristocularines[15] and their aporphine analogs[16] are known to be formed from dioxo compounds by a benzyl-benzylic acid type of rearrangement. However, when **10** was treated under the above-described reaction conditions, no transformation was observed. We assumed that decarbonylation took place before ring B cyclization, a process which is observed when oxalyl chloride reacts in the presence of a Lewis acid.[17] On the other hand, the ring contraction of dibenzoxepines to xanthene derivatives has been documented by Kametani[18] and was recently applied to the synthesis of clavicepine.[19]

In conclusion, a new, straightforward route to dioxoaporphine, dioxocularine and aristocularine[20] alkaloids is proposed. It is worth noting the three fold role played by oxalyl chloride in the synthesis. Thus, i) it forms oxazolidinediones with secondary amides as a masked acyliminium ion that allows ring C formation; ii) it acts as an α-dicarbonyl transfer agent; and iii) it forms the acid chloride required for the Friedel-Crafts acylation reaction.

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9. All new compounds have IR, NMR, MS and combustion analysis data consistent with the structures shown.
10. Experimental procedure: to a degassed (N_2) solution of **2b** (1.14 g, 4 mmol) in CH_2Cl_2 (8 ml) oxalyl chloride (1.0 ml, 12 mmol) was added. The solution was stirred at room temperature for 15 min, cooled at 5 °C, and stannyl chloride (1.2 ml, 10 mmol) added. The mixture was stirred at RT for 72 h and poured into 2 M hydrochloric acid (100 ml) and extracted with CH_2Cl_2. The organic layer was washed (H_2O), dried ($MgSO_4$) and the solvent removed. The crude product was purified by column chromatography (SiO_2, CH_2Cl_2), elution of the orange band (10:1 CH_2Cl_2:CH_3OH) yielded pure cepharadione B (**1**) that was recrystallized from ethanol (835 mg, 65%) (mp: 257-260 °C).[1]
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