Antitumour Heterocycles. Part 15.[1] The Synthesis of 2-Substituted Pyrroloindoles by Acid-catalysed Condensations of Pyrroles

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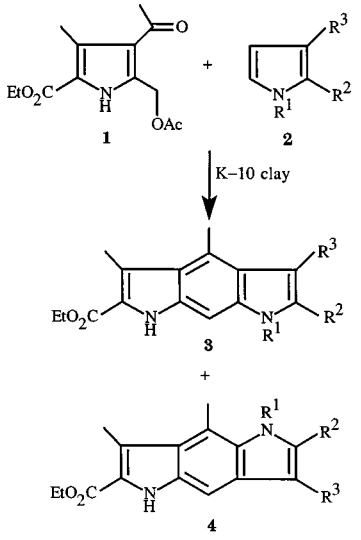
Acid-catalysed condensation of 2-acetoxymethyl-3-acetyl-substituted pyrroles is a viable route to pyrrolo[3,2-*f*]indole derivatives.

In a recent paper,[1] we showed that K-10-catalysed condensation of the pyrrole **1** with pyrroles of structure **2** is a novel route to both pyrrolo-[3,2-*f*]- and -[2,3-*f*]-indoles **3** and **4** respectively (Scheme 1). In this paper we describe the application and development of the reaction as a source of a variety of heterocyclic isosteres of pyrrolo[3,2-*f*]indole 2- and 6-esters.

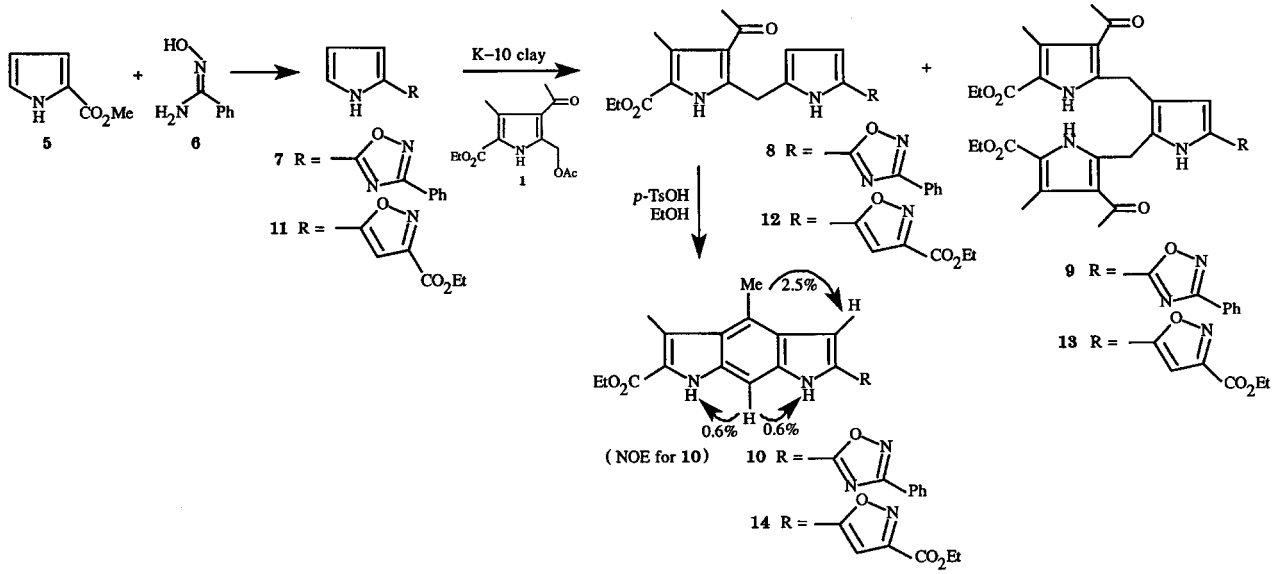


Scheme 1

Treatment of the methyl ester **5** with benzamidoxime **6** and sodium ethoxide in refluxing ethanol gave the 1,2,4-oxadiazole **7**. This with Montmorillonite K-10 clay and the pyrrole **1** gaved a mixture of the 2-monosubstituted and 2,3-disubstituted pyrroles **8** (32%) and **9** (22%) respectively (Scheme 2). Unlike in our earlier work,[1] no pyrroloindoles were formed directly with clay, but the dipyrrolylmethane **8** was cyclised with toluene-*p*-sulfonic acid in refluxing ethanol to the 2-(1,2,4-oxadiazol-5-yl)pyrrolo[3,2-*f*]indole **10** (82%). Similarly, the isoxazole **11**[2] condensed with pyrrole **1** in the presence of clay to give the isoxazoles **12** (34%) and **13** (14%), of which **12** was cyclised with toluene-*p*-sulfonic acid to the pyrroloindole **14** (81%).

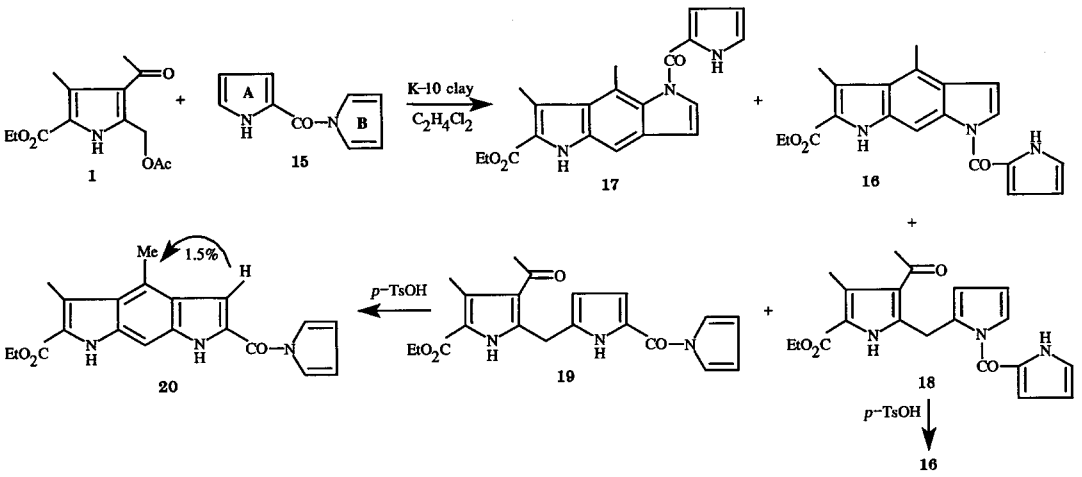
For the amide **15**[3] attack by the pyrrolylmethyl cation from **1** took place on both rings (see Scheme 3) to give four products, **16**, **17**, **18** and **19**. The pyrroloindoles **16** (8%) and **17** (1%) from reaction at the more reactive ring B of **15** were formed directly with clay but were accompanied by the monosubstituted product **18** (11.5%) which could be cyclised with toluene-*p*-sulfonic acid to the [3,2-*f*]isomer **16** in 50% yield. Likewise, the 2-monosubstituted product from ring A in **15**, the dipyrrolylmethane **19** (7%), was cyclised to the pyrrolo[3,2-*f*]indole **20** shown to have its structural orientation by the NOE effect indicated.

The 2-(1,3,4-oxadiazolyl)pyrrole **21** was prepared from methyl pyrrole-2-carboxylate and hydrazine hydrate followed by cyclisation of the hydrazide with triethyl orthopropionate. A major by-product was the novel pyrrolo[1,2-*d*][1,2,4]triazine **22** whose methyl analogue has been described previously.[4]

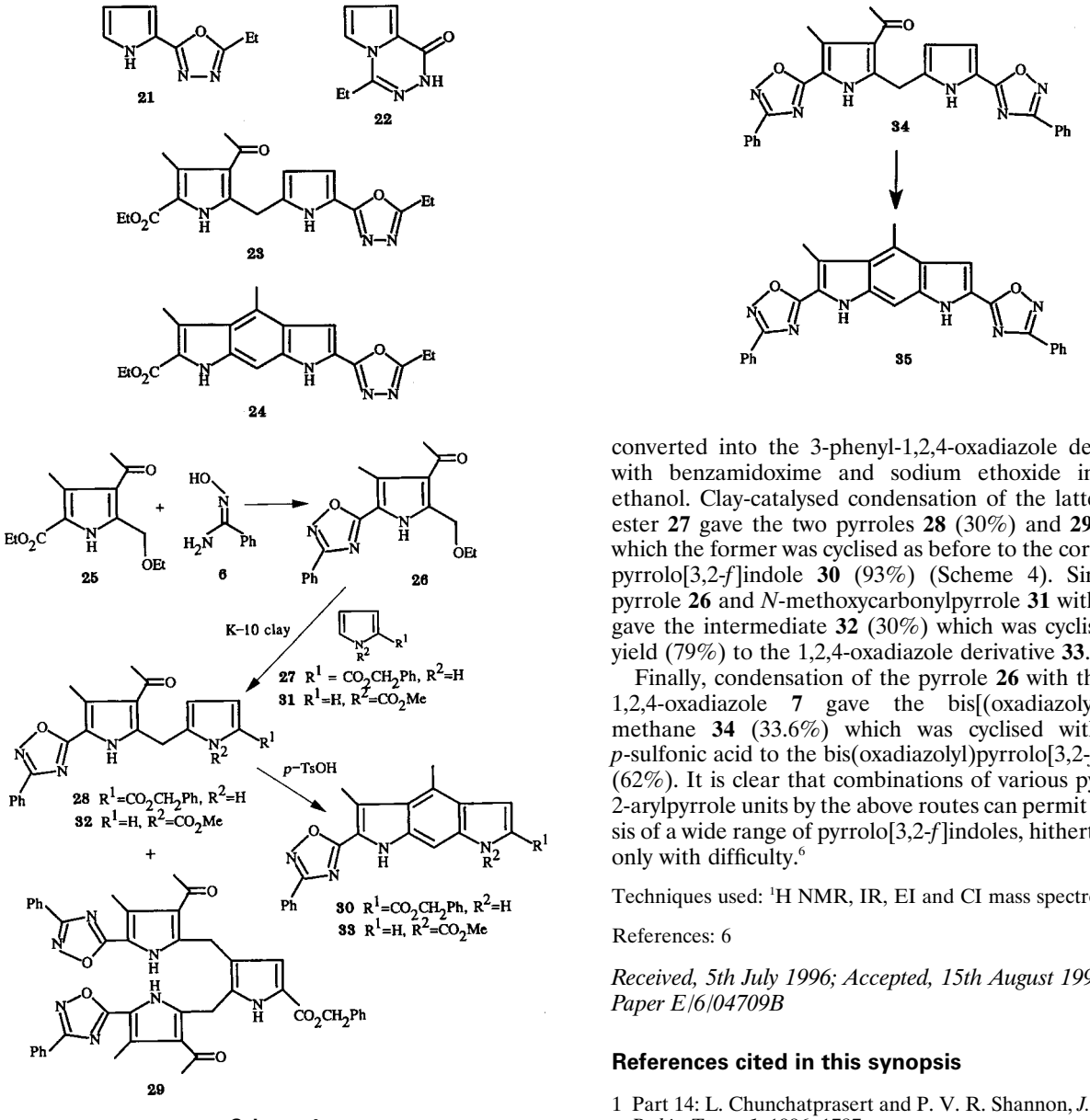


Scheme 2

*To receive any correspondence.



Scheme 3



Scheme 4

The 1,3,4-oxadiazole **21** was predictably less reactive towards the pyrrole **1** under clay-catalysed conditions; nonetheless, the product **23** was isolated and separately cyclised to the [3,2-*f*]isomer **24** (62.5%).

An alternative approach to the pyrroloindoles was made *via* the ethoxymethyl analogue **25**[5] of the pyrrole **1** which was converted into the 3-phenyl-1,2,4-oxadiazole derivative **26** with benzamidoxime and sodium ethoxide in refluxing ethanol. Clay-catalysed condensation of the latter with the ester **27** gave the two pyrroles **28** (30%) and **29** (30%), of which the former was cyclised as before to the corresponding pyrrolo[3,2-*f*]indole **30** (93%) (Scheme 4). Similarly the pyrrole **26** and *N*-methoxycarbonylpyrrole **31** with K-10 clay gave the intermediate **32** (30%) which was cyclised in high yield (79%) to the 1,2,4-oxadiazole derivative **33**.

Finally, condensation of the pyrrole **26** with the pyrrolyl-1,2,4-oxadiazole **7** gave the bis[(oxadiazolyl)pyrrolyl]-methane **34** (33.6%) which was cyclised with toluene-*p*-sulfonic acid to the bis(oxadiazolyl)pyrrolo[3,2-*f*]indole **35** (62%). It is clear that combinations of various pyrroles and 2-arylpyrrole units by the above routes can permit the synthesis of a wide range of pyrrolo[3,2-*f*]indoles, hitherto obtained only with difficulty.[6]

Techniques used: ^{1}H NMR, IR, EI and CI mass spectrometry

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5 This compound was a gift from the late Dr S. F. McDonald.
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