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A versatile approach to 3-alkyl and 2,3-dialkylpyrroles

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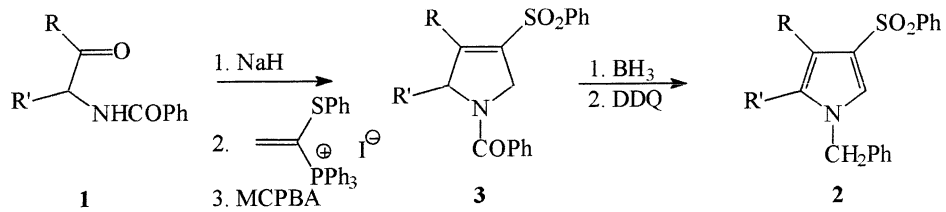
Abstract

A route is described towards *N*-benzoyl-3-alkyl and *N*-benzoyl-2,3-dialkyl pyrroles from α-amido-ketones via an intramolecular Wittig reaction to afford 4-phenylthio-3-pyrrolines which are then oxidised to the corresponding sulphones and aromatised by treatment with potassium *t*-butoxide.

Keywords: pyrrolines; aromatisation; pyrroles; intramolecular Wittig.

The pyrrole unit occurs widely in a range of natural products, drugs, dyes and polymers[1] and its synthesis continues to attract attention.[2–5] A wide variety of chemistry has been used, but most of the available methods lead to a pyrrole which is substituted at various positions with functional groups such as esters, and which requires further synthetic operations such as reduction or hydrolysis/decarboxylation to afford the simple alkyl substituted heterocycle. Routes to 3-alkyl pyrroles are attractive in terms of the specific importance of such compounds in preparing conducting polymers and natural products,[6] and routes to 2,3-dialkylpyrroles are not common.[7,8] We have previously reported[9] a route to the pyrrole ring system which relies on an intramolecular Wittig reaction to build up the heterocyclic ring from the readily available



Scheme 1.

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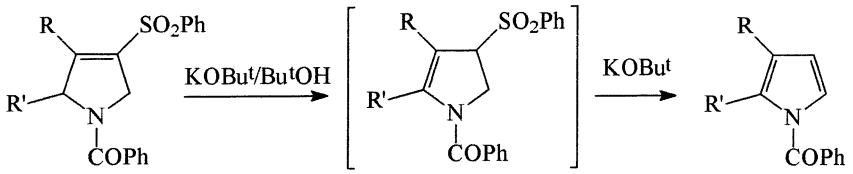
α-amidoketones **1**, followed by functional group manipulation to afford the *N*-benzyl-4-phenylsulphonylpyrroles **2** (Scheme 1).

Although the method is versatile in terms of R and R′, it suffers in that the ring is substituted with the phenylsulphonyl group, which is not always easy to remove from such systems, and the nitrogen is *N*-benzylated rather than being protected with a more easily removable acyl group. We describe here a simple extension of the chemistry in Scheme 1 which circumvents both of these problems. Treatment of the intermediate 4-phenylsulphonyl-3-pyrrolines **3a**–**f**[9] with potassium *tert*-butoxide gave directly, in good yield, the 2,3-dialkyl pyrroles **4a**–**f**. It is presumed that the reaction proceeds by deconjugation of the vinyl sulphone, followed by elimination of benzene sulphinic acid (Scheme 2); the hindered base appears not to react with the N-COPh group during the aromatisation process. *N*-Acyl pyrroles are known to readily hydrolyse with aqueous hydroxide at room temperature,[10] so the procedure described here allows ready access to the corresponding pyrroles.



3 **4**

Scheme 2.

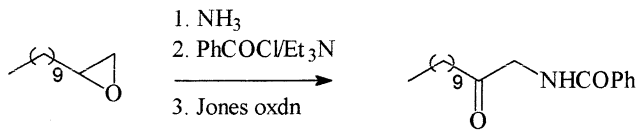
The method was then extended to afford the 3-alkyl pyrroles **4g**–**i** (Table 1). The precursor ketone **1g** was prepared (80%) from the sodium salt of *N*-benzoylglycine (acetic anhydride/pyridine to afford the oxazolone then aqueous reflux);[11] **1h** was prepared (52%) from *N*-benzoylglycine (1 equiv. BuLi then 3 equiv. EtMgBr, THF/ether, −78°C);[12] **1i** was prepared (44% overall), as shown in Scheme 3. These three approaches to the α-amidoketones **1** illustrate how readily a variety of substituents R and R′ can be introduced into the pyrrole ring using this methodology.

Table 1

Entry	R	R′	Yield (%) for **1**→**3**[a]	Yield (%) for **3**→**4**[a]
a	CH_3	CH_3	85	93
b	CH_3CH_2	CH_3	78	72
c	CH_3	$PhCH_2$	56	79
d	CH_3CH_2	$PhCH_2$	51	78
e	CH_3	$(CH_3)_2CH$	52	70
f	CH_3	$CH_3S(CH_2)_2$	62[b]	61[b]
g	CH_3	H	69	83
h	CH_3CH_2	H	65	78
i	$CH_3(CH_2)_9$	H	59	65

[a] For **3a**–**3e** see Ref. 9; for **4a** see Ref. 13; all other compounds were characterised by the usual analytical and spectroscopic methods.

[b] R′ is $CH_3S(CH_2)_2$ in **1** but $CH_3SO_2(CH_2)_2$ in **3** and **4**.

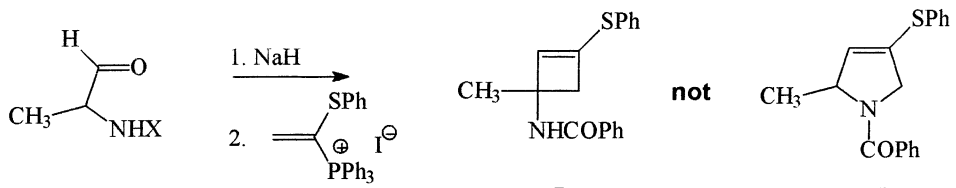


1i

Scheme 3.

Typical procedure for **3** to **4**: The sulphone **3a** (0.52 g, 1.5 mmol) was dissolved in dry THF (20 cm^3), and 1 M potassium *tert*-butoxide in *tert*-butanol (1.5 cm^3, 1.5 mmol) was added. The solution was refluxed for 2 hours, the THF was removed under reduced pressure and the residue was partitioned between water and ethyl acetate. Flash chromatography (ethyl acetate–petroleum spirit, 1:4) gave **4a**[13] as an oil (0.28 g, 93%); (found M^+ 199.0985. $C_{13}H_{13}NO$ requires 199.0997); δ_H (250 MHz; $CDCl_3$) 2.06 (3H, s, CH_3), 2.48 (3H, s, CH_3), 6.02 (1H, d, *J* 3.3, pyrrole H-4), 6.72 (1H, d, *J* 3.3, pyrrole H-5), 7.44–7.61 (3H, m, ArH), 7.72 (2H, m, ArH); δ_C (62.5 MHz; $CDCl_3$) 11.2, 12.6, 113.6, 121.2, 122.1, 128.6, 129.9, 132.3, 135.1, 169.5.

It was expected that application of the method to α-amidoaldehydes would afford 2-alkylpyrroles **5**, but the intramolecular Wittig reaction took a different course. Thus the aldehyde **6**, obtained by oxidation of *N*-benzoylalaninol with DMSO/$(COCl)_2$/Et_3N, on treatment with NaH followed by the 1-phenylthiovinyl triphenylphosphonium iodide gave, in 35% yield, the cyclobutene **7**, mp 119–121°C, δ_H (250 MHz; $CDCl_3$) 1.65 (3H, s, CH_3), 2.70 (1H, d, *J* 12.5, CH), 2.90 (1H, d, *J* 12.5, CH), 6.05 (1H, s, C=CH), 6.75 (1H, br s, NH), 7.2–7.5 (8H, m, ArH), 7.6–7.85 (2H, m, ArH). Apparently in changing from the ketone **1a** to the aldehyde **6** as substrate, there is a change in the relative acidities of the NH proton and the α-H such that, for **6**, it is the α-H which is removed. It is worth noting that use of the *N*-Cbz protected aldehyde **8** gave a complex mixture under the conditions of the intramolecular Wittig reaction and no cyclised product was isolated (Scheme 4).



6, X = COPh
8, X = CO_2CH_2Ph

7

5

Scheme 4.

Acknowledgements

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