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NOVEL PATHWAYS FOR THE FORMATION OF PHENYLPYRROLES

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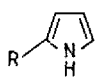
Summary: *Treatment of 3-phenyl-5,6-dihydro-(4H)-1,2-oxazine (5) with KOH/DMSO at 100 °C gave 2-phenylpyrrole (2a); similar treatment of the nitrone (6) gave 2-methyl-5-phenylpyrrole* **(12)**.

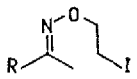
Recently Reese *et al.* reported[1] a method for the conversion of methyl ketones **(1)** to pyrroles **(2)** by treatment of *O*-(2-iodoethyl) oximes **(3)** with potassium *t*-butoxide in *t*-butanol. Under milder conditions, the *O*-vinyl oxime **(4)** can be isolated and subsequently converted into 2-phenylpyrrole **(2a)**. We now report our investigations into the possibility that 3-phenyl-5,6-dihydro-(4H)-1,2-oxazine **(5)** is an intermediate in the overall conversion of **(3a)** to **(2a)**.

(1)



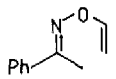
(2)

(2a, R=Ph)

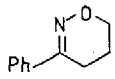


(3)

(3a, R=Ph)



(4)



(5)

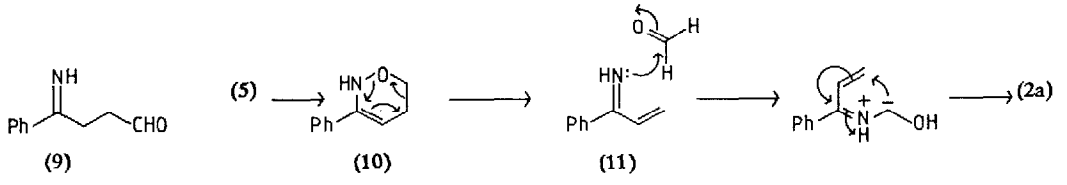
Three methods for the synthesis of the oxazine **(5)** have been reported, two of which involve multistep sequences.[2,3] We were unable to repeat the third method,[4] obtaining a low yield of a mixture of compounds, and the limited physical data reported suggests that the product originally isolated was in fact the isomeric nitrone **(6)**. Treatment of γ-chlorobutyrophenone **(7)** with hydroxylamine hydrochloride and potassium carbonate in ethanol at *room temperature* gave the corresponding oxime **(8)** as a mixture of stereoisomers.[5] This mixture, without purification, was then treated on a 10 mmol scale with potassium *t*-butoxide in *t*-butanol at 20 °C giving the oxazine **(5)** (91 % from **(7)**). On scaling the cyclisation reaction up (50 mmol), the nitrone **(6**, 16%) was formed, together with the oxazine **(5**, 71%) (Scheme 1).

(7) **(8)** **(5)** **(6)**

Scheme 1

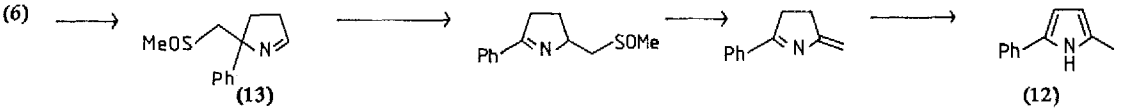
Treatment of the oxazine **(5)** under the Reese conditions[1] did give 2-phenylpyrrole **(2a**, 4%), with significant recovery of starting oxazine **(5)**, but the extremely low yield rules out the oxazine **(5)** as an intermediate in the conversion of **(3a)** to **(2a)**. However, treatment of the oxazine **(5)** with potassium

hydroxide (10 equiv.) in dimethylsulphoxide at 100 °C for 1 h gave 2-phenylpyrrole (**2a**, 44 %). Since we have been unable to isolate any intermediates, the mechanism of this unusual conversion is unclear. The following three possibilities exist. Fragmentation of the oxazine *via* N–O bond cleavage,[6] induced by base, could lead to the imine (**9**), which is an obvious precursor to 2-phenylpyrrole. An alternative fragmentation can lead to the *O*-vinyl oxime (**4**) , which is converted to (**2a**) on treatment with potassium hydroxide in dimethylsulphoxide at 100 °C.[7] A final possibility involves base-promoted isomerisation of the oxazine (**5**) to the isomeric oxazine (**10**), followed by fragmentation[8,9] to the unsaturated imine (**11**) and methanal. Recombination[10] followed by ring-closure can then lead to (**2a**) (Scheme 2). Other transformations of oxazines to pyrroles have been reported,[3,11,12,13] although none under strongly basic conditions.



Scheme 2

For comparison purposes the nitrone (**6**) was treated with KOH/DMSO for 3 h at 100 °C and 2-methyl-5-phenylpyrrole (**12**, 35 %), identified by comparison with reported spectral data[14] and m.p.,[15] was isolated. A reasonable mechanism for this conversion involves nucleophilic addition of dimsyl potassium to (**6**),[16] and dehydration to give the cyclic imine (**13**). Addition of dimsyl potassium to (**13**), followed by elimination of dimethylsulphoxide and MeSOH, and aromatisation, can then give (**12**) (Scheme 3).



Scheme 3

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