Unprecedented Rearrangement of 5-Benzoyl Substituted Bicyclic Isoxazolidines to Dehydro Pyrrolizidin-2-ones and Indolizidin-2-ones

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5-Benzoyl substituted isoxazolidines **3**, obtained by 1,3-dipolar cycloadditions of pyrroline *N*-oxide and tetrahydropyridine *N*-oxide to phenyl vinyl ketone, undergo a rearrangement to dehydro 3-phenyl-pyrrolizidin-2-one and 3-phenylindolizidin-2-one catalysed by Al_2O_3; the rearrangement products undergo a Michael addition to a second molecule of phenyl vinyl ketone.

In connection with our ongoing programme to develop new methods for the synthesis of substituted *N*-bridgehead azaheterocycles[1] we envisioned a new method for the synthesis of 3-phenyl substituted pyrrolizidin-2-one (n = 1) **1** and indolizidin-2-one (n = 2) **2** according to the following retrosynthetic scheme (Scheme 1).[2]

In contrast to the vast collection of the literature dealing with the 1,3-dipolar cycloadditions of nitrones with alkenes,[3] there are no reports on the cycloadditions to phenyl vinyl ketone.

The cycloaddition of nitrones **4a** and **4b** to phenyl vinyl ketone **5**, easily available from the corresponding Mannich base,[4] gave the isoxazolidines **3a** and **3b**, respectively, in complex mixtures together with 4-regioisomers **6a** and **6b** in ratio 6:1 and 5:1, respectively, (Scheme 2).

Each regioisomer was present as a pair of diastereoisomers, deriving from an *exo* or *endo* approach of the reactants, detectable only for the 5-regioisomeric compounds. The *exo*:*endo* ratio was found to be 1.4:1 for **3a** and 2.5:1 for **3b** and only tentatively assigned on the basis of the observation of the coupling pattern of the H-5 (isoxazolidine numberings) resonance in the ^{1}H NMR spectrum.[5] The formation of 4-regioisomers is expected by FMO consideration, because of the strong electron-withdrawing character of the benzoyl group.[6] However, Tufariello in the cycloaddition of the nitrone **4b** with methyl vinyl ketone obtained regioselectively a 5-acetyl isoxazolidine.[7]

The separation and purification of the complex cycloaddition mixtures proved to be impracticable owing to the very low stability of the adducts, particularly of those from the five-membered nitrone **4a**. Only small amounts of enriched mixtures of the stereoisomers were obtained after quick column chromatography.

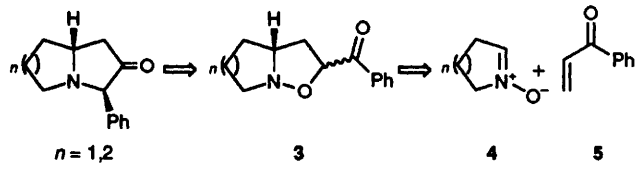
The observation of the low stability, particularly on treatment on silica gel, of the benzoyl isoxazolidines, attracted our interest and prompted us to study various conditions to steer efficaciously the reactivity of the compounds. It was found that treatment of the isoxazolidines with an excess of phenyl vinyl ketone in the presence of neutral alumina (Type I) gave the dehydro-pyrrolizidinone **7** and indolizidinone **8** (Scheme 3). For synthetic purposes, it was found practical to run the cycloaddition of the nitrone with excess of the phenyl vinyl ketone (4–5 equiv.) to obtain overall yields of 60% for **7** and 50% for **8**.

The structural assignment was based on the analysis of ^{1}H and ^{13}C NMR spectra. The enaminone moiety is evidenced by the presence of a singlet for the proton (at δ 5.10 for **7** and 5.02 for **8**) and appropriate resonances for C-1 and C-2 carbon atoms (δ 90.8 and 198.8 for **7** and 95.7 and 199.1 for **8**, respectively). The phenyl group resonances result was also highly diagnostic for the assignment of the structure, showing two different phenyl groups, only one vicinal to a carbonyl.

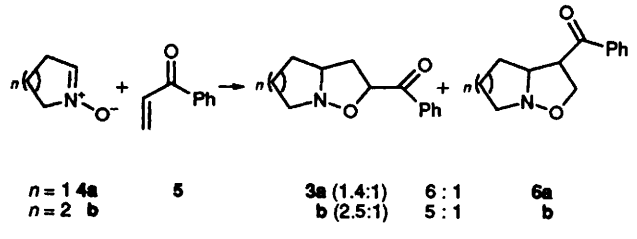
A tentative explanation for the rearrangement took origin from the observed influence of silica gel or alumina in affecting the stability of the isoxazolidine. In these conditions, the benzoylisoxazolidines **3** must give the enolised isomer **9** which undergoes an isoxazolidine-pyrrolidine rearrangement to give the ketone **10** (Scheme 4). Elimination of H_2O from this intermediate gives the pyrrole derivative **11**, which is in equilibrium with the enaminone **11'**. Finally, **11** gives a Michael addition to a second molecule of phenyl vinyl ketone.

As a confirmation of the mechanism, the intermediate **11'** can also be isolated from the isoxazolidine **3a**, even if it showed likewise very low stability on purification on silica gel. Moreover, an analogous methyl substituted isoxazolidine **12** under the same conditions (alumina, excess phenyl vinyl ketone, methylene chloride) underwent complete decomposition. This compound cannot, in fact, give the intermediate **11** (or **11'**) by elimination of H_2O.

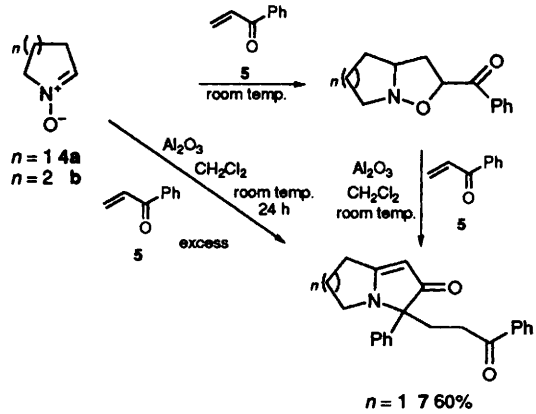
This rearrangement of 5-benzoylisoxazolidines has only one close precedent in the thermal rearrangement of *exo*-methylene isoxazolidines to pyrrolidinones discovered by Uccella and coworkers[8] and later reinvestigated by other researchers.[9] In the present case, however, the dehydropyrrolidinones **11'** (or 3-hydroxy pyrroles **11**) are formed at room temperature by



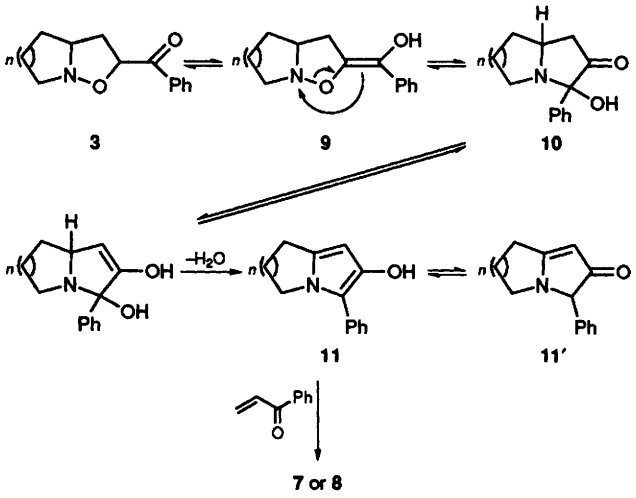
Scheme 1



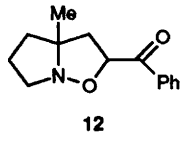
Scheme 2



Scheme 3



Scheme 4



simple catalysis of alumina. On the other hand, a similar reactivity of 3-hydroxy pyrroles **11** has been recently documented by Wasserman and coworkers.[10]

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