Pericyclic reactions in the synthesis of natural products

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Abstract: 3,3-Sigmatropic reactions involving the cleavage of N-O or N-N bonds will be described and the methodology applied in the synthesis of biologically active nitrogen containing molecules.

Pericyclic reactions, in contrast to polar or radical chemical transformations, are one-step processes proceeding through a cyclic transition state (ref. 1). They are thus classified as concerted reactions. Among these 3,3-sigmatropic reactions represent a specially useful category (ref. 2).

We present in this lecture synthetic applications of this type of reactions, where at least two heteroatoms are involved in the basic rearrangement framework.

**Pericyclic reactions involving cleavage of the N-O bond**

Let us consider Scheme 1, where X and Y represent carbon or other heteroatoms. At the heart of the 3,3-sigmatropic rearrangement, which converts 1 to 2, a sigma N-O bond is broken and a new sigma C-Y bond is formed. The required starting material 1 derives from an enehydroxylamine, which is tautomeric with the corresponding nitrone. The enehydroxylamine framework is encountered intact in aromatic hydroxylamines (ref. 3), and indeed appropriate derivatives, such as 3, have been found to

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![Scheme 2](image-url)

Let us consider Scheme 2, where X and Y represent carbon or other heteroatoms. At the heart of the 3,3-sigmatropic rearrangement, which converts 3 to 4, a sigma N-O bond is broken and a new sigma C-Y bond is formed. The required starting material 3 derives from an enehydroxylamine, which is tautomeric with the corresponding nitrone. The enehydroxylamine framework is encountered intact in aromatic hydroxylamines (ref. 3), and indeed appropriate derivatives, such as 5, have been found to
rearrange easily in the presence of say bromocyanogen (ref. 4) (Scheme 2). The intermediate 4 suffers a spontaneous 3,3-sigmatropic rearrangement leading to 5, that upon rearomatisation and intramolecular cyclisation affords the benzimidazolone 6. Of course the necessary framework for the 3,3-rearrangement can also be generated in situ from stable and suitable N,O-diacylhydroxylamines. For example β-phenylthio derivatives 7 (Scheme 3), on exposure to LDA and TMSCI yielded the phenylacetic acids 8 in good yields. Cyclisation of these acids with either DCC or NaOAc-Ac₂O provided synthetically useful N-protected 3,3-disubstituted oxindoles derivatives 2 (ref. 5). Indole derivatives are accessible with the use of propiolic esters and this method is exemplified in the obtention of the Amaryllidaceae alkaloid pratosine (ref. 6) (Scheme 4). The boron complex 10 of the starting hydroxamic acid 11 freezes the
productive conformation for photocyclisation (ref. 7), leading to the phenanthridine 12. Removal of the boron bridge yields the required 13, which on reaction with the propiolate ester affords the Michael adduct 14. Heating 14 in DMSO, in the presence of water, initiates a cascade of reactions, namely, a 3,3-sigmatropic reaction, hydrolysis of the ester, decarboxylation and cyclisation, to afford pratosine 15 in one step, albeit in modest yield. In order to improve the yield of the alkaloid, from the final sequence of reactions, alternative methods were sought to obtain 16 (Scheme 5) directly. A possibility would be to make use of the Michael adduct 17 (conceivably obtained from 18 and phenylvinylsulphoxide). However, in model experiments performed with 19, no Michael adduct could be isolated. Instead the aziridine 20 and benzoic acid were some of the products formed (Scheme 6). The formation of 20 is believed to occur via the isomeric N-phenyl O-acyl-hydroxylamine 21 produced by a fast base catalysed N to O transacylation, followed by Michael addition and ring closure with elimination of benzoic acid. This reaction was subsequently developed into a new mild aziridination method (ref. 8). Use of quaternary salts of Cinchona alkaloids as a chiral phase transfer reagent in toluene and aq. NaOH provided an economical route to chiral aziridines (ee. 16-53 %) (ref. 9).

We then turned our attention to enehydroxylamines in a carbocyclic framework (ref. 10). Derivatives 22 and 23 were easily obtained from the corresponding 1,3-diones and found spectroscopically ($^1$H NMR) to exist in solution mainly as the enehydroxylamine tautomers (Scheme 7). Reaction with several
electrophiles yielded a variety of derivatives, resulting from facile 3,3-sigmatropic reactions (ref. 10). This reaction was extended to the biologically important barbiturate (ref. 11) derived system 24 (Scheme 8) and a similar reactivity pattern was also observed (ref. 12).

**Scheme 8**

Pericyclic reactions involving cleavage of the N-N bond

Enehydrazines 25 (Scheme 9) were studied next. We selected for biological studies as our synthetic target the mutagenic and carcinogenic amine 26 (Scheme 10), produced while cooking proteins at high temperature (ref. 13).
Reaction of the arylhydrazine 27 with bromocyanogen yielded 28, which when boiled in diphenyl ether, provided a short synthesis of the aminoimidazole 29 (ref. 14), the immediate precursor of 26 (ref. 15). The method was extended with slight modifications to the preparation of benzimidazole derivatives 30 utilising a variety of 1-acyl-1-cyano-2-aryl hydrazines 31 (Scheme 11).

The system of hexahydroindole is present in many alkaloids with interesting pharmacological properties (ref. 16). We tested the feasibility of using a pericyclic rearrangement as a key reaction in the synthesis of desoxyeseroline (32) (Scheme 12). Accordingly the known N-methylamine skatole (ref. 17) was converted into the bis-enamine 33 by reaction with methyl propiolate. The Michael adduct 33 on thermolysis generated the product 34 which was converted to desoxyeseroline (32) by standard chemical transformations (ref. 18).

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