Cleavage of CC Double Bonds by a Novel Cycloaddition–Cycloreversion Sequence

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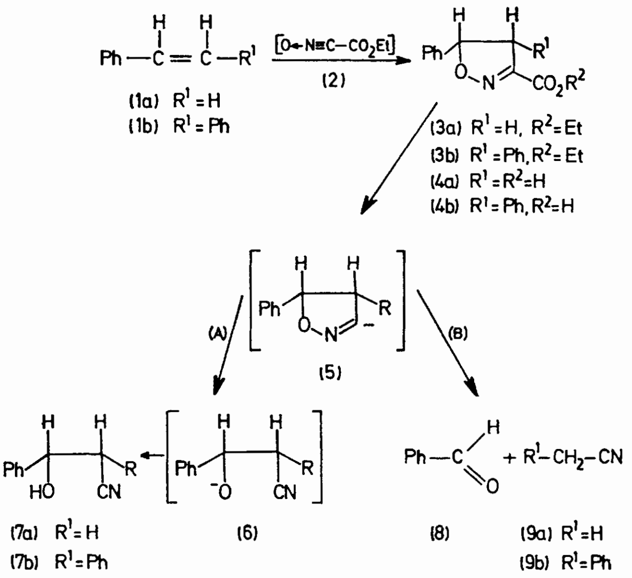
Summary CC-double bonds are cleaved with simultaneous generation of a carbonyl compound and a nitrile by a sequence involving 1,3 dipolar addition of ethoxycarbonylformonitrile oxide to the olefin, hydrolysis of the 3-ethoxycarbonyl-isoxazoline which is formed to the free acid, and thermal decarboxylation.

Oxidative procedures, *e.g.* ozonolysis, or hydroxylation followed by glycol cleavage, are generally used for the rupture of olefinic double bonds. In a search for an alternative, which would allow the cleavage of (exocyclic) double bonds even in compounds which are very sensitive towards oxidation, such as sulphur-containing molecules, we have developed a two-step reaction sequence incorporating a cycloaddition and a cycloreversion.[1] It is known[2] that nitrile oxides add very easily in a 1,3-dipolar manner to olefins giving rise to 3-substituted Δ^2-isoxazolines. This (3+2) cycloaddition generally is highly regioselective,[3] allowing the introduction of an oxygen function at the more substituted end of CC-double bonds.[2]



(1a) $R^1 = H$
(1b) $R^1 = Ph$

(3a) $R^1 = H, R^2 = Et$
(3b) $R^1 = Ph, R^2 = Et$
(4a) $R^1 = R^2 = H$
(4b) $R^1 = Ph, R^2 = H$

(5)

(7a) $R^1 = H$
(7b) $R^1 = Ph$

(6)

(8)

(9a) $R^1 = H$
(9b) $R^1 = Ph$

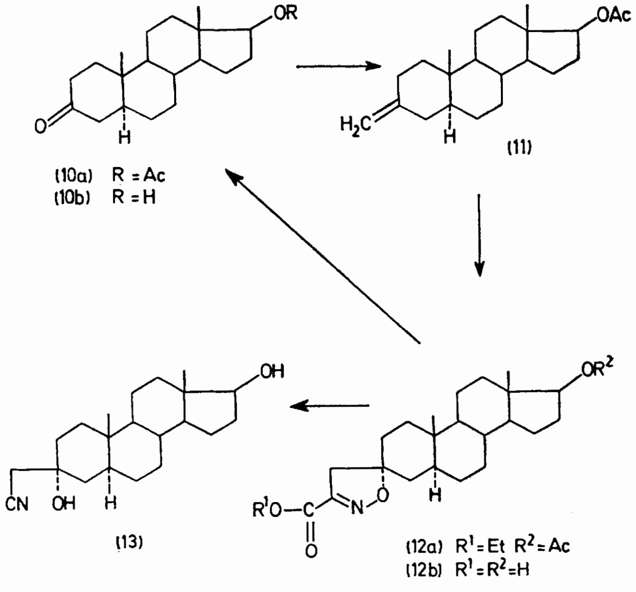
With the nitrile oxide (**2**)[4] as the 1,3-dipole a 3-ethoxycarbonyl-isoxazoline of type (**3**) would be formed. During the decarboxylation of the corresponding free acid (**4**) a carbanion of type (**5**) might be formed. Rupture of the weakest bond would generate the hydroxy-nitrile anion (**6**) (pathway A), or depending on the strength of the 4,5-bond, a synchronous fragmentation might occur yielding directly the desired carbonyl compound (**8**) and the nitrile (**9**) (pathway B).

To test this hypothesis, styrene (**1a**) was treated with (**2**).[4] The ethoxycarbonyl-isoxazoline (**3a**) formed was subsequently saponified to the known free acid (**4a**).[5] On heating compound (**4a**) alone slightly above its m.p. (120 °C), or as a 5% solution in dimethylformamide to *ca.* 130 °C, only minor amounts (5%) of benzaldehyde (**8**) were detected by g.l.c., and the main product isolated (yields $\leqslant$ 90%) was the amorphous hydroxy-nitrile (**7a**).† Decarboxylation of the sodium salt of (**4a**) in DMF at 130 °C also gave compound (**7a**) (*ca.* 63%).

In the reaction of *trans*-stilbene (**1b**) with (**2**), the isoxazoline (**3b**),‡ m.p. 63—65 °C, and, after hydrolysis, the acid (**4b**) m.p. 97—99 °C, were formed. In contrast to the behaviour of (**4a**), a 1 : 1 mixture of benzaldehyde (**8**) and benzyl cyanide (**9b**) was obtained in essentially quantitative yield by decarboxylation of (**4b**) under the conditions cited above (preferably in DMF at 130 °C).

We then examined the application of this sequence to a non-aromatic compound. The 3-methylene compound (**11**), m.p. 104—106 °C,[6] accessible from 5α-dihydro-testosterone acetate (**10a**) by a Wittig reaction was treated with the nitrile oxide (**2**). Besides starting material, the isoxazoline (**12a**), m.p. 205 °C (decomp.), was obtained as the sole product (39%). Hydrolysis of (**12a**) with KOH–MeOH–H_2O at 20 °C gave the free acid (**12b**), m.p. 203—205 °C (decomp.).

The subsequent decarboxylation could be achieved under various conditions. In DMF (60 min; 130 °C) the hydroxy-nitrile (**13**), m.p. 230—232 °C, was formed exclusively (yield 90—92%). Mixtures of (**10b**) and (**13**) were obtained by heating (220 °C) compound (**12b**) alone [60% (**10b**) and



(10a) R = Ac
(10b) R = H

(11)

(13)

(12a) $R^1 = Et$ $R^2 = Ac$
(12b) $R^1 = R^2 = H$

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† All new compounds had spectroscopic (i.r. n.m.r., mass, and u.v.) and analytical data in agreement with the given structures.

‡ The corresponding methyl ester has m.p. 86—88 °C; the *cis*-methyl ester has m.p. 124—126 °C.

30% (**13**)] or as a solution in diethylene glycol [60 min; 150 °C, 10% (**10b**) and 80% (**13**)]. Yields of *ca.* 80% of the ketone (**10b**) were obtained in sulpholan (30 min., 190 °C) or tetralin (30 min; 170 °C), together with up to 10% of the hydroxy-nitrile (**13**).

Other steroidal compounds containing exocyclic as well as endocyclic double bonds have been successfully subjected to the above reaction sequence. A limitation to the generality of this reaction is the necessity for relatively high temperatures (100—200 °C) for the decarboxylation step.

An allowed $[_{\sigma}2_a + {}_{\sigma}2_a + {}_{\omega}2_s]$-cycloreversion of the carbanionic species of type (**5**) seems a plausible explanation for the reaction mechanism. Since compound (**13**) is thermally stable up to 220 °C, a two-step mechanism involving a cyanohydrin of type (**7**) and its transformation into (**8**) and (**9**) is rather unlikely. However, fragmentation of the alkoxide (**6**) formed in the primary step, as well as a synchronous process§ starting directly from (**4**), including the formation of CO_2, may be alternatives.

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§ For an allowed cycloreversion of this type the participation of two additional electrons, *e.g.* from the oxygen atom of the isoxazoline, would have to be postulated.

[1] For other approaches, *cf.* P. Gygax, T. K. Das Gupta, and A. Eschenmoser, *Helv. Chim. Acta*, 1972, **55**, 2205; Y. L. Chow, *J. Amer. Chem. Soc.*, 1965, **87**, 4642.

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[4] G. S. Skinner, *J. Amer. Chem. Soc.*, 1924, **46**, 731.

[5] W. R. Vaugham and J. L. Spencer, *J. Org. Chem.*, 1960, **25**, 1160.

[6] The free alcohol (**11b**), m.p.: 149—150 °C, was described by F. Sondheimer and R. Mechoulam (*J. Amer. Chem. Soc.*, 1957, **79** 5029).