Synthesis and Properties of 4*H*-Imidazoles

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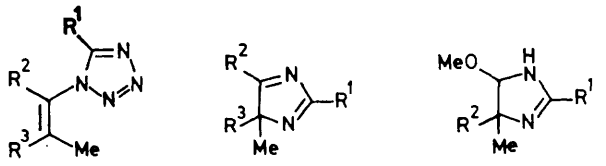
Photolysis of alkenyltetrazoles (**1**) provides the first rational route to simple 4*H*-imidazoles (**2**); when unsubstituted at C-5 these are highly reactive towards nucleophiles and rearrange rapidly to the aromatic 1*H*-imidazoles on heating.

In contrast to the extensive studies on the biologically and pharmacologically important 1*H*-imidazoles,[1] very little attention has been paid to their non-aromatic 4*H*-isomers.[2] However, these are of interest because of their unusual and



(1) (2) (3)

a; R^1 = Ph, R^2 = H, R^3 = Me
b; R^1 = R^3 = Me, R^2 = H
c; R^1 = R^2 = H, R^3 = Me
d; R^1 = Ph, R^2R^3 = -$[CH_2]_4$-

(3) a; R^1 = Ph, R^2 = Me
b; R^1 = R^2 = Me
c; R^1 = R^2 = H

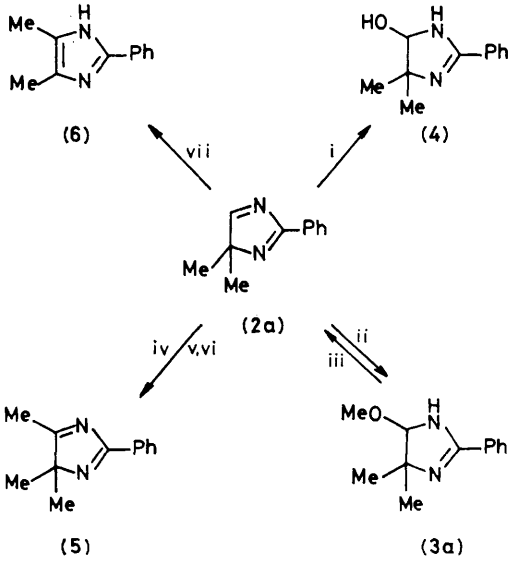
potentially reactive diazadiene structure, and because they afford an opportunity to study the isomerisation processes which give rise to the aromatic 1*H*-isomers. We have recently described a new synthesis of 1*H*-imidazoles by photolysis of 1-alkenyltetrazoles,[3] and we now report the extension of this method to the preparation of the simplest 4*H*-imidazoles yet described. Preliminary results show that these simple systems are indeed highly reactive.

The required alkenyltetrazoles (**1a**), m.p. 66—67 °C, (**1b**), m.p. 41—43 °C, and (**1c**), b.p. 90 °C at 0.4 mmHg, were prepared from isobutyraldehyde by conversion into the corresponding enamide, Me_2C=CHNHCOR[1], by reaction with the appropriate primary amide in refluxing benzene containing a catalytic amount of toluene-*p*-sulphonic acid, followed by conversion into the imidoyl chloride (or the vinyl isonitrile in the case where R^1 = H) and reaction with azide anion. This method, although a simple extension of the well-known conversion of secondary amides into 1,5-disubstituted tetrazoles,[4] has apparently not been applied to enamides before, and appears to have considerable generality. The tetrazole (**1d**), m.p. 81—82.5 °C, was prepared from 1-(2-hydroxycyclohexyl)-5-phenyltetrazole[3] by oxidation to the corresponding ketone, addition of methylmagnesium iodide, and dehydration of the resulting alcohol with phosphorus oxychloride in pyridine. Although the required vinyl tetrazole (**1d**) was only a minor product in the dehydration step, the unwanted allyl tetrazole isomers could be isomerised to (**1d**) by treatment with potassamide on alumina.

Photolysis of the tetrazoles (**1a,d**) in petrol (b.p. 60—80 °C) gave the corresponding 4*H*-imidazoles, (**2a**), m.p. 40—44 °C, and (**2d**), m.p. 100—113 °C, both in 55% yield. When the tetrazoles (**1b,c**) were photolysed under similar conditions complex mixtures containing only traces of the required 4*H*-imidazoles were formed. However, when the photolyses were carried out in methanol, n.m.r. spectroscopy indicated that the corresponding methanol adducts (**3b,c**) were formed, presumably by way of the 4*H*-imidazoles. The 4*H*-imidazole (**2b**) was finally isolated as a volatile liquid by carrying out the reaction in dilute petrol (b.p. 30—40 °C) solution at 0 °C, though when the tetrazole (**1c**) was photolysed under similar conditions only traces of (**2c**) were detected after evaporation of the photolysate.

It is clear that the preparation of simple, lightly substituted 4*H*-imidazoles presents considerable problems because of their reactivity and volatility. The mildness of the photochemical method is crucial in overcoming these problems, and thus provides a route to the 4*H*-imidazole ring system.

Since 5-unsubstituted 4*H*-imidazoles have not previously been reported, a preliminary study of the chemistry of (**2a**) was undertaken (Scheme 1). The 4*H*-imidazole (**2a**) was rapidly hydrated on attempted chromatography on alumina to give



Scheme 1. *Reagents:* i, chromatography on alumina; ii, MeOH; iii, heat in benzene, with azeotropic removal of MeOH; iv, MeMgI; v, Bu^tOCl; vi, DBU; vii, 120 °C in [$^2H_6$]DMSO.

the hydrate (**4**). Similarly, addition of methanol gave the adduct (**3a**) from which the imidazole (**2a**) could be regenerated by heating in benzene with azeotropic removal of methanol. Addition of methylmagnesium iodide to (**2a**) was very rapid and gave the expected 5-methylimidazoline (90%). Dehydrogenation of this imidazoline by *N*-chlorination followed by treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) gave the 5-methyl-4*H*-imidazole (**5**), m.p. 57—60 °C, albeit in low yield. As expected this 5-substituted 4*H*-imidazole is much less susceptible to nucleophiles and can be readily purified by chromatography on alumina. Thus these simple 5-unsubstituted 4*H*-imidazoles are a highly electrophilic species, and react readily with nucleophiles at the 5-position.

On heating to 120 °C in [$^2H_6$]dimethyl sulphoxide ([$^2H_6$]-DMSO), the 4*H*-imidazole (**2a**) rearranged to the aromatic 4,5-dimethyl-2-phenylimidazole (**6**) in quantitative yield. The reaction had first-order kinetics with a half-life of 0.5 h, and no intermediates were detected by n.m.r. spectroscopy. This is consistent with a rate-determining [1,5]methyl migration to C-5, followed by a rapid aromatising hydrogen shift. These results accord with the relatively facile alkyl shifts to carbon in other non-aromatic 5-membered heterocyclic compounds, such as the 3*H*-pyrazoles.[5]

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References

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