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A New Synthesis of Imidazoles

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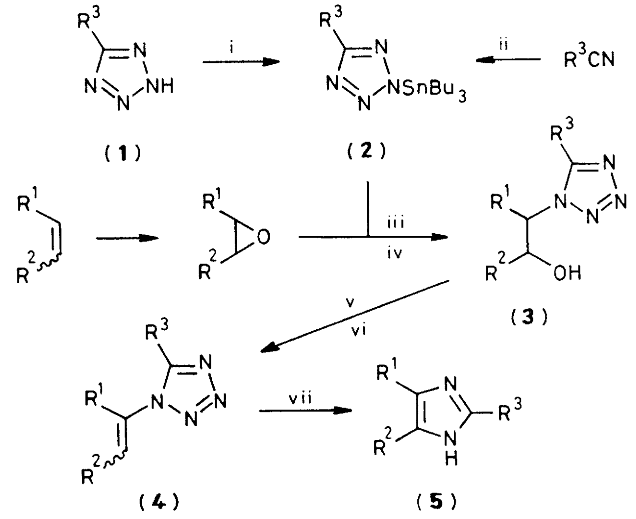
Alkenes are converted into imidazoles through their epoxides by treatment with 2-tri-n-butylstannyltetrazoles (**2**), followed by dehydration with methyltriphenoxyphosphonium iodide in an improved procedure, and photolysis of the resulting vinyltetrazoles (**4**).

The importance of the imidazole nucleus in biological processes and the application of imidazoles as pharmaceutical products has stimulated considerable interest in its chemistry in recent years.[1] However, there is no single, widely applicable method available for the synthesis of the imidazole ring. We now report a new synthesis of imidazoles which starts from alkenes, and appears to have considerable generality.

We have previously described a synthesis of benzimidazoles which involves cyclisation of *N*-arylimidoyl nitrenes generated by photolysis of sulphimides[2] or 1-aryltetrazoles.[3] Cyclisation of *N*-vinylimidoyl nitrenes would therefore be expected to give imidazoles, and there is one report in the literature of a copper-catalysed pyrolysis of 1-acryloyltetrazoles to give imidazoles.[4] We now find that *N*-vinylimidoyl nitrenes, generated by the photolysis of 1-vinyltetrazoles (**4**), do indeed cyclise to give imidazoles (**5**) (Scheme 1).



Scheme 1. Reagents: i, $(Bu^n_3Sn)_2O$; ii, $Bu^n_3SnN_3$; iii, ether, room temp.; iv, HCl gas; v, $(PhO)_3\overset{+}{P}Me\ \overset{-}{I}$, HMPA or DMF, room temp.; vi, 10% aqueous NaOH; vii, *h*ν, 254 nm, solvent (see text and Table 1).

A few routes to 1-vinyltetrazoles have been reported,[5] but all are of limited scope. A new general route has now been developed based on the ring opening of epoxides. Tetrazole anions are poor nucleophiles and are usually alkylated on N-2 predominantly. However, these problems have been overcome by use of 2-tri-n-butylstannyltetrazoles (**2**),[6] readily prepared from the 5-substituted tetrazoles (**1**) or from nitriles, as shown in Scheme 1. Thus, epoxides are ring opened under mild conditions by treatment with (**2**) in ether at room temperature. The alkylation is mainly on N-1 of the tetrazole, as expected, and the ease of reaction may be due in part to the formation of a strong tin–oxygen bond. Cleavage of the intermediate stannyl ethers with gaseous hydrogen chloride gave the required alcohols (**3**) in reasonable yields (Table 1). Yields from the 5-unsubstituted tetrazole (**2**, R^3 = H) were generally less good, although these were slightly improved by making the reaction catalytic in the stannyltetrazole (**2**), either by using the tetrazole (**1**) with a catalytic amount of (**2**) or, more conveniently, with a catalytic amount of tri-n-butyltin oxide.

The alcohols (**3**), after chromatography, were readily dehydrated to the vinyltetrazoles (**4**) by treatment with methyl-

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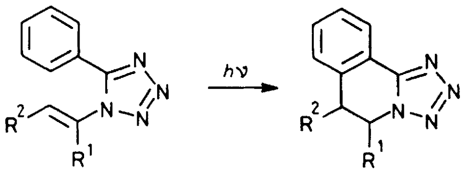
Table 1

			(3)		(4)			
R^1	R^2	R^3	Yield (%)	M.p. (t/°C)	Yield (%)	M.p. (t/°C)	Yield (**5**) (%)	Photolysis solvent
H	H	H	44[a], 43[b]	Oil	69	Oil	32	EtOH
H	H	Ph	80	79—80	93	104—106	61	EtOH[d]
H	Me	H	33, 42[a]	Oil	67	59—61	62	EtOH
H	Me	Me	70	Oil	73	41.5—43.5	73	H_2O
H	Me	Ph	78[a]	90—92	86	60—63	66	Petrol[e]
$-[CH_2]_4-$		Ph	57	156—158	79	102.5—104.5	64	,,
H	Ph	Ph	45[c]	112—115	85	147—149	66	,,
Ph	H	Ph	34[c]	130—132	89	89.5—90.5	38	EtOH

[a] Yield from catalytic procedure: (**1**) + 10 mol% (**2**). [b] Yield from alternative catalytic procedure: (**1**) + 10 mol % $(Bu^n{}_3Sn)_2O$. [c] Epoxide ring opening carried out in refluxing benzene. [d] With 2 equiv. of trifluoroacetic acid. [e] B.p. 60—80 °C.



(**6**)

triphenoxyphosphonium iodide (MTPI) in hexamethylphosphoramide (HMPA) or dimethylformamide (DMF) at room temperature, followed by stirring with 10% aqueous sodium hydroxide for a few hours. This modified procedure represents a considerable improvement over the use of MTPI alone.[7] The use of sodium hydroxide as base means that only one equivalent of MTPI is required and that milder conditions can be used. The reaction, previously applicable only to secondary alcohols, can now be extended to primary alcohols since the intermediate primary alkyl iodides are readily dehydrohalogenated under the modified conditions. The work-up is also greatly facilitated since the by-product, diphenyl methylphosphonate, is hydrolysed and therefore remains in the aqueous layer. The required vinyltetrazoles are obtained in high purity and high yield (Table 1).

Irradiation of the vinyltetrazoles (**4**) at 254 nm in a variety of solvents gave the expected imidazoles (**5**) as the major products. In the case of the 5-phenyltetrazoles (**4**, R^3 = Ph), a competing photo-cyclisation occurred to give (**6**). The yields of imidazoles were found to be very solvent dependent. In acetone, photocyclisation was favoured, and the product (**6**, $R^1R^2 = -[CH_2]_4-$) predominated. However, good yields of imidazoles were obtained in all cases (Table 1) when the photolysis was carried out in light petroleum (b.p. 60—80 °C) or in ethanol. Addition of trifluoroacetic acid (2 equiv.) to the ethanol solution of the tetrazole also increased the yield of the imidazole.

Most routes to imidazoles are based on α-substituted ketones which can be difficult to obtain, and harsh conditions are often necessary. The present method is based on alkenes and epoxides, uses readily available reagents under mild conditions, and gives acceptable overall yields.

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