A New, Efficient Approach to α,β-Unsaturated Ketones and β-Hydroxy Ketones From 4,5-Dihydroisoxazoles

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2-(*N*-Nitrosomethylamino-oxy)ethyl ketones (**3**), obtained from solvolysis with sodium nitrite of *N*-methyl-4,5-dihydroisoxazolium methylsulphates (**2**), were converted into α,β-unsaturated ketones (**4**) by treatment with base or into β-hydroxy ketones (**5**) by treatment with carboxylic acids.

4,5-Dihydroisoxazoles are valuable substrates for the preparation of β-hydroxy ketones and α,β-unsaturated ketones, which are useful intermediates in the synthesis of many bioactive compounds.[1] According to the literature[2] these transformations may be brought about chiefly by reductive methods. Thus their H_2–Raney Ni reduction in acidic media[3] yields β-hydroxy ketones, while the action of lithium diisopropylamide followed by treatment with $TiCl_3$ gives α,β-unsaturated ketones.[4]

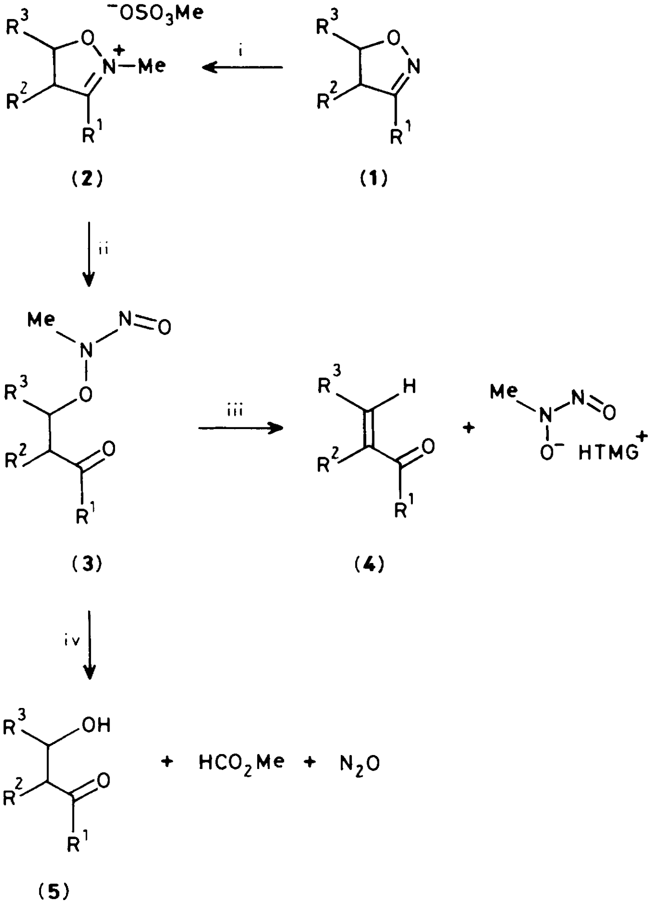
This communication reports new, mild, nonreductive methods for transformations of 4,5-dihydroisoxazoles (**1**), enabling ketone derivatives (**4**) and (**5**) to be synthesised (Scheme 1, Table 1) which contain groups which are not resistant to the conditions in previous methods.

The 4,5-dihydroisoxazolium methylsulphates[5] (**2**) were obtained quantitatively by heating at 50 °C a toluene solution of an equimolar mixture of the 4,5-dihydroisoxazole[6] (**1**) with dimethyl sulphate; they were obtained as viscous oils insoluble in toluene. The crude salts (**2**) were converted in very good yields into the ketones (**3**) by stirring at room temperature their aqueous or CH_2Cl_2 solutions with aqueous $NaNO_2$, and extraction of the product [yellow–orange oils or fine pale

Table 1. Preparation of α,β-unsaturated (4) and β-hydroxy ketones (5).

				% Yield	
	R^1	R^2	R^3	**(4)**[a]	**(5)**[a]
a	Me	H	$CH_2=CH[CH_2]_5-$	77	74[f]
b	Me	H	$Br[CH_2]_4-$	61	73
c	Me	$-CH_2OCH_2OCH_2-$		86	—
d	Me	$-CH(OAc)CH_2CH(OAc)-$		54[b]	59[g]
e	$MeO_2C[CH_2]_5-$	$-CH_2CH_2CH_2-$		81[c]	
f	$OCH_2CH_2OC(Me)CH_2-$	$-CH_2CH_2CH_2-$		41	—
g	EtO_2C	$-CH_2CH_2CH_2-$		88	—
h	H	$-CHCH_2CHCH_2CH_2$		72	58
i	H	H	EtO_2C	75[d]	—
j	Ph	$-CH_2SO_2CH_2-$		94[e]	66
k	Ph	$-CH_2CH_2CH_2-$		92	67
l	Me	H	$PhOCH_2$	—	56[h]
m	Me	$-CHCH_2CHN(CO_2Et)N(CO$		67	—

[a] Products were oils separated by silica gel chromatography unless noted otherwise. [b] *cis*-Isomer, m.p. 83.5—84.5 °C. [c] B.p. 124—125 °C at 0.2 mmHg. [d] In the form of the adduct with cyclopentadiene. [e] M.p. 113—114 °C. [f] B.p. 58—60 °C at 0.5 mmHg. [g] In AcOH, 70 °C, 6 h. [h] M.p. 48.5—50 °C.



Scheme 1. *Reagents and conditions*: i, Me_2SO_4, PhMe, 50 °C, 2—8 h; ii, $NaNO_2$, H_2O, room temp., 1—8 h; iii, TMG, PhMe, room temp., 1—3 h; iv, HCO_2H, CH_2Cl_2, 40 °C, 2—6 h.

yellow crystals: (**3k**), m.p. 67.5—68.5 °C; (**3m**), m.p.114—115.5 °C] with CH_2Cl_2 or benzene. The *N*-nitroso derivatives (**3**) are stable if stored below 0 °C; at room temperature they decompose slowly, mainly to α,β-unsaturated ketones.[1] The action of NEt_3 or tetramethylguanidine (TMG) on toluene solutions of (**3**) led to rapid formation of the α,β-unsaturated ketones,[7] along with the ammonium salts of *N*-nitroso-*N*-methylhydroxylamine which separate from the solution in the form of an oil (NEt_3) or fine crystals, m.p. 123.5—124.5 °C, (TMG). The rate of *N*-nitroso-*N*-methylhydroxylamine anion elimination is much higher for the reactions carried out with TMG (room temp.; *ca.* 1 h), but in the case of products (**4b,d,f,j**)† better yields were obtained using NEt_3 (60 °C; *ca.* 4 h).

The *N*-nitroso-derivatives (**3**) are not stable in the presence of acids. They react with organic acids yielding β-hydroxy ketones (**5**), the methyl ester of the acid used, and N_2O.[8] The rate of reaction depends on the acidity of the acid used; *e.g.* with trifluoroacetic acid the reaction is rapid and exothermic while with acetic acid it is completed in 4 h at 50 °C. The use of formic acid in CH_2Cl_2 is optimal because of the mild conditions (40 °C; 1—3 h) and high yields of β-hydroxyketones (**5**).†

The transformations described could thus be applied for obtaining ketone derivatives as well as α,β-unsaturated aldehydes (**4h,i**) and the α-carbonylcarboxylic ester derivative (**4g**), showing that this method is of more general applicability than those in the literature. The newly synthesised ketones (**3**) are of interest for both synthetic and theoretical reasons. The mechanisms of their transformations with various reactants *e.g.* organic acids and bases, fluoride anion, complexing agents, acyl chlorides, oxidants, and many others is under investigation. The use of the nitroso derivatives (**3**), *e.g.* as

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† All compounds synthesised have spectral data consistent with their structure. The hitherto unknown (**4b,c,d,f,g,h,j,n**) and (**5a,b,d,h,j,l,m**) gave satisfactory elemental analyses.

potential 'Mannich bases' in Michael-type additions of different C–H acids, has been studied intensively and results will be published soon.

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