A Versatile New Method for the Synthesis of Various Pyrrolidin-1-oxyl Fatty Acids

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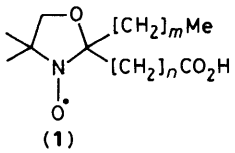
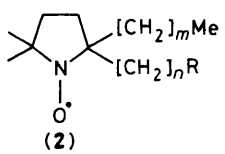
Mono- and di-carboxylic acid derivatives of various structural isomers of the pyrrolidin-1-oxyl ring containing a stable free radical (spin label) can be obtained by Michael addition of a nitroalkane to an α,β-unsaturated ketone to give a γ-nitroketone, followed by ring closure to a pyrrolin-1-yl oxide which reacts with Grignard reagents to give a pyrrolidin-1-oxyl compound, which undergoes phase-transfer oxidation of its terminal unsaturated bond.

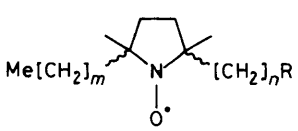
There is considerable interest in the preparation and application of spin-labelled fatty acids as the introduction of a stable free radical (spin label) containing a fatty acid or lipid allows the use of e.s.r. spectroscopy to study microenvironments within a membrane.[1] Minimal steric perturbance is an essential requirement. Three types of nitroxide fatty acids, (**1**),[2] (**2**),[3] and (**3**)[4] are known at present.



(**1**)



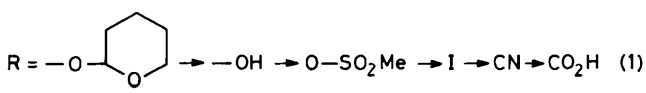
(**2**)



(**3**)

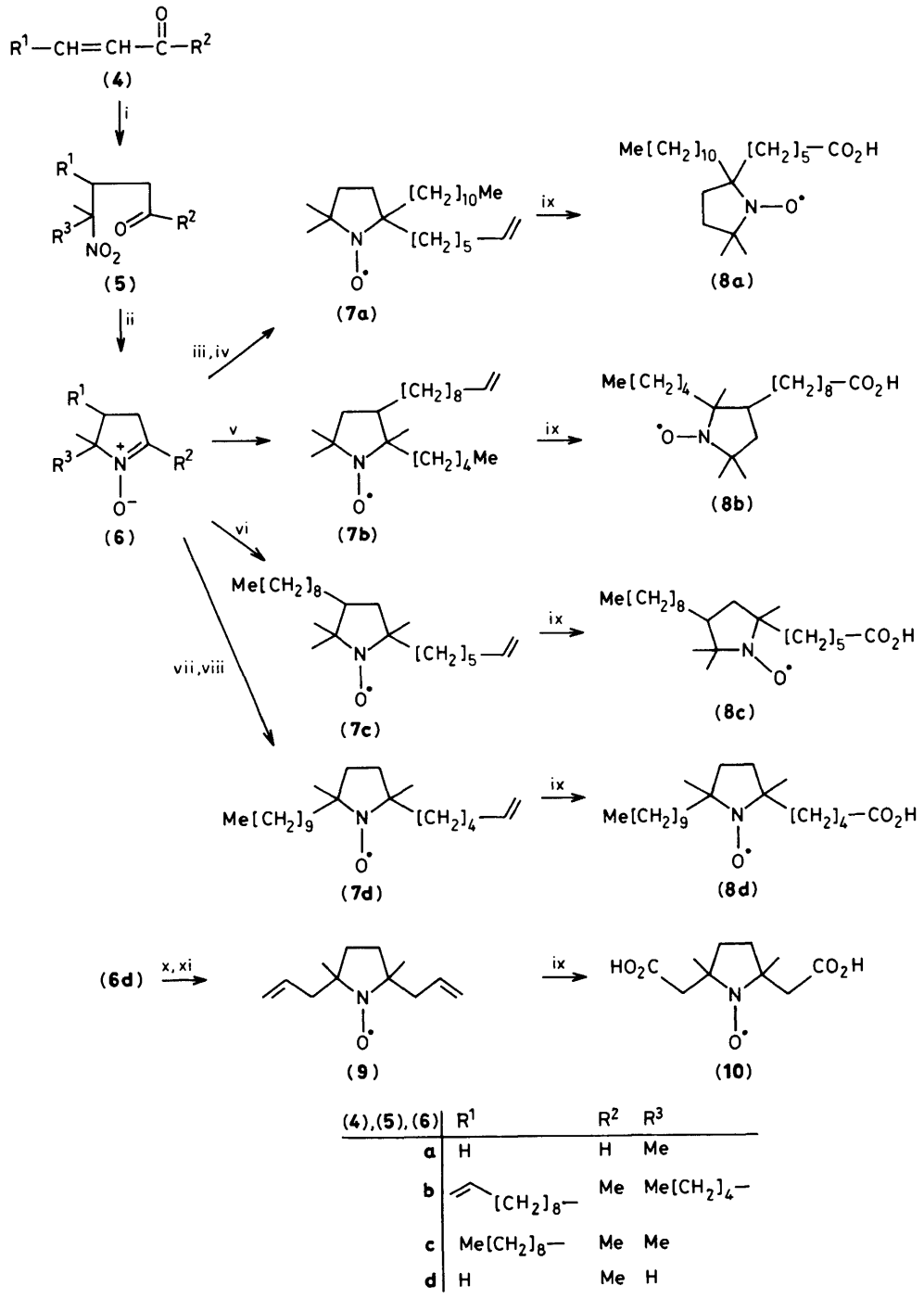
However, the carboxylic acids (**2**) and (**3**) (R = CO_2H) are only available *via* an elaborate multistep synthesis. The most frequent method for the introduction of the carboxylic group is shown in equation (1).[5] It would be useful if other structural isomers (having a different >N–O axis to the fatty acid chain) were available for the study of comparative motional properties in membranes by e.s.r. spectroscopy.

We report here a new synthetic route which is generally applicable to the preparation of the pyrrolidin-1-oxyl fatty acid isomers (**8a—d**). The method can also be applied to the synthesis of spin-labelled pyrrolidin-1-oxyl dicarboxylic acids (**10**) (Scheme 1).†



(1)

† All new compounds were fully characterized by spectroscopic and microanalytical data.



(4),(5),(6)	R^1	R^2	R^3
a	H	H	Me
b	$CH_2=CH[CH_2]_8$—	Me	$Me[CH_2]_4$—
c	$Me[CH_2]_8$—	Me	Me
d	H	Me	H

Scheme 1. *Reagents:* i, $R^3CH(Me)NO_2$, Triton B; ii, Zn, NH_4Cl; iii, $Me[CH_2]_{10}MgBr$, Cu^{2+}, O_2; iv, $CH_2=CH[CH_2]_5MgBr$, Cu^{2+}, O_2; v, MeMgBr, Cu^{2+}, O_2; vi, $CH_2=CH[CH_2]_5MgBr$, Cu^{2+}, O_2; vii, $Me[CH_2]_9MgBr$, Cu^{2+}, O_2; viii, $CH_2=CH[CH_2]_4MgBr$, Cu^{2+}, O_2; ix, $KMnO_4$, 18-crown-6; x, $CH_2=CHCH_2MgBr$, Cu^{2+}, O_2; xi, $CH_2=CHCH_2MgBr$, Cu^{2+}, O_2.

The starting compounds are the α,β-unsaturated ketones (**4a—d**), two of which were prepared by Wittig reaction of the corresponding aldehydes and the phosphorane obtained from chloroacetone and triphenylphosphine [(**4b**) 78% and (**4c**) 85%].

The Michael addition of 2-nitroalkanes to (**4a—d**) was carried out in the presence of a basic catalyst [*e.g.*, benzyltrimethylammonium hydroxide (Triton B)], using a method described earlier, to give the γ-nitroketones (**5a—d**)[6] [(**5b**) 76% and (**5c**) 62%].

The conversion of (**5a—d**) into the corresponding nitrones (**6a—d**) was performed by a known route using zinc powder and ammonium chloride.[7] The unpurified but dried nitrones (**6a—d**) were treated with Grignard reagents to give *N*-hydroxy derivatives which were oxidized to *N*-oxyl compounds {(**7a**) 13%, M^+ 364; (**7b**) 19% [based on (**5b**)], M^+

336; (**7c**) 11% [based on (**5c**)], M^+ 350; (**7d**) 12%, M^+ 336} using the Cu^{2+}-ion as catalyst.

The terminal unsaturated bond of (**7a—d**) was oxidized to give the stearic acid nitroxide analogue [(**8a**) 14%, M^+ 382; (**8b**) 15%, M^+ 354; (**8c**) 11%, M^+ 368; (**8d**) 19%, M^+ 354] by a phase-transfer reaction in benzene with potassium permanganate[8] in the presence of 18-crown-6.

The 2,5-diallyl nitroxide compound (**9**) was synthesized (36%, M^+ 194) using the above reaction sequences and was then oxidized to the dicarboxylic acid (**10**) (13%, M^+ 230).

We thank the Hungarian Academy of Sciences for a supporting grant.

Received, 22nd June 1984; Com. 881

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