2,2,6,6-Tetramethylpiperidine 1-oxyl, free radical

Product Code: FT09614
CAS Number: 2564-83-2
Chemical Formula: C₉H₁₈NO
Molecular Weight: 156.25

Synonym: TEMPO

2,2,6,6-Tetramethylpiperidine 1-oxyl is a remarkably stable nitroxyl radical, commonly also known as TEMPO. This red-orange solid was first reported in 1960 by Lebedev and Kazarnovskii,¹ and is typically synthesized by the oxidation of 2,2,6,6-tetramethylpiperidine. The stability of the radical has been proposed to be due to the steric influence of the methyl groups which flank the nitroxyl group.²

TEMPO finds frequent use in organic synthesis as a catalytic oxidant, with the N-oxoammonium salt, derived from TEMPO under the reaction conditions, being the actual oxidant. This is illustrated in Scheme 1, where sodium hypochlorite (NaOCl) in stoichiometric quantities forms the N-oxoammonium salt via generation of hypochlorous acid (HOCI).

\[
\text{HOCl} + \text{TEMPO} \rightarrow \text{N-oxoammonium salt}
\]

Scheme 1

These reaction conditions forms the basis of a fast, cheap and highly selective catalytic process for the synthesis of aldehydes from primary alcohols.³ Further oxidation of aldehydes to carboxylic acids is slow, though the rate can be increased by the addition of a catalytic quantity of a phase transfer catalyst. The reaction takes place in a two-phase system of dichloromethane-water, with the aqueous sodium hypochlorite solution pH adjusted to ensure the formation of HOCI. Under these conditions, a variety of saturated primary alkyl and aryl alkyl (benzyl) alcohols are efficiently converted to the corresponding aldehydes, as illustrated in Scheme 2 for (S)-2-methyl-1-butanol, which is the subject of a robust Organic Synthesis preparation.⁴ Under these conditions, secondary alcohols can also be oxidised to ketones. Substrates containing double bonds, whether isolated or conjugated, are reported to be prone to side reactions, lowering selectivities and yields.⁵ The use of TEMPO and related stable nitroxyl radicals in alcohol oxidations has been reviewed.⁶
A related procedure uses catalytic quantities of TEMPO and sodium hypochlorite in combination with stoichiometric sodium chlorite ($\text{NaClO}_2$) to oxidise primary alcohols to carboxylic acids, as shown in Scheme 3 for the preparation of 4-methoxyphenylacetic acid.\(^6\) Substrates with sensitive chiral centres are well tolerated under the conditions, although in common with the oxidation of alcohols to aldehydes or ketones, alkenic alcohols and those containing significantly electron-rich aromatic rings are not tolerated. The procedure is an adaptation of the biphasic (dichloromethane–water) process using sodium hypochlorite alone as the stoichiometric oxidant,\(^5\) and has the advantage of improved yields and purities, as well as the environmental benefit of dispensing with the requirement for a chlorinated solvent.

TEMPO also participates in numerous synthetically and analytically useful radical reactions. For example TEMPO can act as a radical scavenger to facilitate the identification of peptide- and protein-based radicals by mass spectrometry,\(^9\) and as a carbon-radical trapping reagent in cascade and cyclisation reactions.\(^7\)

An example of the latter case is shown in Scheme 4, where pyrrolidinones 1 and 2 are formed in good yields from the acyclic trichloroethanamide or iodide precursors respectively under dimanganese decacarbonyl promoted conditions.\(^10\) Trapping sequences of this sort are useful as they introduce oxygen functionality at the product radical centre as a hydroxylamine group. The hydroxylamine can subsequently be cleaved to a hydroxyl group under reductive conditions using zinc and acetic acid, or oxidised to aldehydes.\(^10,11\)

\[\text{Scheme 2}\]

\[\text{Scheme 3}\]

\[\text{Scheme 4}\]

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Ollivier has reported the TEMPO-induced generation of alkyl radicals from alkylcatecholboranes, which in the presence of excess TEMPO can be trapped to yield alkoxyamine derivatives, Scheme 5.12

Scheme 5

‘Living’ free radical polymerisation techniques are of considerable interest to material scientists as a way of controlling macromolecular structure and yielding narrow polydispersity polymers with controlled molecular weights and chain architectures. TEMPO mediated polymerisation procedures have attracted considerable attention,13 and the initial limiting requirements of high temperatures and extended reaction times for these TEMPO mediated ‘living’ polymerisations have been addressed by the identification of rate enhancing TEMPO additives.

References: