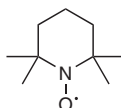


2,2,6,6-Tetramethylpiperidin-1-oxyl (TEMPO) and Related Reagents



Alternative names: 2,2,6,6-Tetramethylpiperidin-1-yloxy free radical; TEMPO; (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl; 2,2,6,6-tetramethylpiperidinoxy radical

CAS number: 2564-83-2
FW: 156.2453
MF: C₉H₁₈NO

Key Science of Synthesis Articles

Studer, A.; Vogler, T., *SOS*, (2009) **40b**, 846 (Section 40.2.1.1) (synthesis of nitroxides)
 Podlech, J., *SOS*, (2007) **25**, 41 (Section 25.1.2.2.4) (applications)
 Ditrich, K., *SOS*, (2007) **25**, 547 (Section 25.6.2.2.9) (applications)

Usage

Versatile oxidizing agent used primarily in the synthesis of aldehydes and ketones from primary and secondary alcohols, respectively.^[1] 2,2,6,6-Tetramethylpiperidin-1-oxyl has been used as a catalyst in many oxidations.^[1-3] The most important is commercial bleach solution (**NaOCl**) in the presence of potassium bromide as co-catalyst (the Anelli oxidation).^[4,5] It has also been used in the synthesis of carboxylic acids and their esters.^[1,6] It can also be used for the oxidation of 2-hydroxycarboxylic acid esters to give 2-oxocarboxylic acid esters, and amines to give nitriles.^[7]

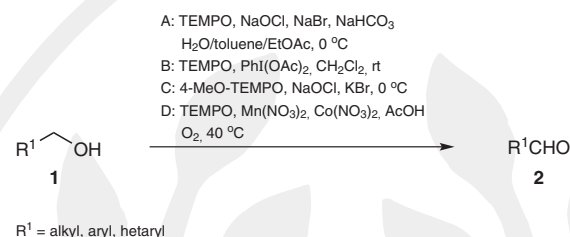
Availability

2,2,6,6-Tetramethylpiperidin-1-oxyl is relatively expensive, commercially available, and easy to handle. It is also available as polymer-bound TEMPO and on silica gel. 2,2,6,6-Tetramethylpiperidin-1-oxyl and its derivatives can either be used in stoichiometric amounts^[8,9] or, preferably, as catalysts in combination with another, stoichiometrically employed oxidant. TEMPO can be prepared by oxidation of the corresponding tetramethylpiperidine or tetramethylpiperidine hydroxide.^[10]

Related 4-substituted TEMPO reagents have also been covered here; examples are 4-methoxy-2,2,6,6-tetramethylpiperidin-1-oxyl (*4-MeO-TEMPO*), 4-(benzyloxy)-2,2,6,6-tetramethylpiperidin-1-oxyl (*4-BzO-TEMPO*), 4-(acetylamino)-2,2,6,6-tetramethylpiperidin-1-oxyl (*4-AcNH-TEMPO*). 2,2,6,6-Tetramethylpiperidin-1-oxyl and its 4-substituted derivatives are precursors of the corresponding oxoammonium salts, which also function as oxidizing agents; these include: 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate, 2,2,6,6-tetramethyl-1-oxopiperidinium chloride, and 2,2,6,6-tetramethyl-1-oxopiperidinium perchlorate.

for references see p 5

Sample Transformations

Scheme 1 Oxidation of Primary Alcohols with 2,2,6,6-Tetramethylpiperidin-1-oxyl^[4,11-13]**(S)-2-(Benzyloxycarbonylamino)-3-(tert-butyltrimethylsilyloxy)propanal**[2, R¹ = CH(NHCbz)CH₂OTBDMS]; **Typical Procedure:**^[11]

Method A: Aq NaOCl (1.1 mmol) and NaHCO₃ (2.9 mmol) were added dropwise over a period of 1–2 h to a cold (0 °C), rapidly stirred (>1000 rpm) biphasic mixture of the (S)-isomer of the alcohol 1 [R¹ = CH(NHCbz)CH₂OTBDMS; 1 mmol], TEMPO (0.02 mmol), NaBr (1 mmol), toluene (3 mL), EtOAc (3 mL), and H₂O (0.5 mL). After the reaction, the aqueous layer was separated and washed with Et₂O (5 mL). The combined extracts were washed in turn with KI (8 mg) in 10% aq KHSO₄ (2 mL), 10% aq Na₂S₂O₃ (1 mL), and brine (2 mL), and then dried (MgSO₄). Filtration and concentration under reduced pressure afforded the desired aldehyde, which was used immediately in further reactions; yield: 94%.

Aldehydes 2; General Procedure Using (Diacetoxyiodo)benzene as Co-oxidant:^[12]

Method B: PhI(OAc)₂ (354 mg, 1.1 mmol) was added to a soln of an alcohol (1 mmol) and TEMPO (15 mg, 0.1 mmol) in CH₂Cl₂ (1 mL). The mixture was stirred until the alcohol was no longer detectable (TLC), and then it was diluted with CH₂Cl₂ (5 mL). The mixture was washed with sat. aq Na₂S₂O₃ (5 mL) and extracted with CH₂Cl₂ (4 × 5 mL). The combined organic extracts were washed with aq NaHCO₃ (5 mL) and brine (5 mL), dried (Na₂SO₄), and concentrated under reduced pressure. Flash chromatography or crystallization afforded pure products.

Benzaldehyde (2, Ar¹ = Ph); Typical Procedure:^[4]

Method C: BnOH (1, Ar¹ = Ph; 0.43 g, 4 mmol) and 4-methoxy-2,2,6,6-tetramethylpiperidin-1-oxyl (4-MeO-TEMPO; 0.074 g, 0.04 mmol) were dissolved in CH₂Cl₂ (10 mL) and cooled to 0 °C. While keeping the temperature at 0 °C, 0.5 M aq KBr (0.8 mL, 0.4 mmol) was introduced followed by the addition of 0.35 M aq NaOCl (14.3 mL, 5 mmol) until the pH was adjusted to ca. 8.6. The biphasic mixture was vigorously stirred (1300 min⁻¹) for 3 min, then the orange organic phase was separated, and the aqueous phase was extracted with CH₂Cl₂ (5 mL). The combined organic extracts were dried (MgSO₄) and the solvent was evaporated under reduced pressure. The remainder was purified by chromatography (silica gel); yield: 0.38 g (90%).

2-Nitrobenzaldehyde (2, Ar¹ = 2-O₂NC₆H₄); Typical Procedure:^[13]

Method D: (2-Nitrophenyl)methanol (1, Ar¹ = 2-O₂NC₆H₄; 7.5 g, 49 mmol), TEMPO (156 mg, 1 mmol), Mn(NO₃)₂ (179 mg, 1 mmol), and Co(NO₃)₂ (183 mg, 1 mmol) were dissolved in AcOH (39 mL). The mixture was heated to 40 °C and stirred for 6 h under O₂ at atmospheric pressure. After this time, GLC indicated complete consumption of the starting material. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (silica gel, CH₂Cl₂); yield: 6.9 g (93%); mp 44 °C.

Applications Found in Science of Synthesis**Heteroarenes by Dehydrogenation**

Pyridinium salts by oxidation of 1-substituted 1,4-dihydropyridines

- Section 15.1.3.3.1 [Vol. **15** (2005), p 238] (2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate)

Nitriles by Oxidation of Primary Amines ($\text{CH}_2\text{NH}_2 \rightarrow \text{CN}$)

Nitriles by oxidation of primary amines

- ▲ – Section 19.5.8.1.1 [Vol. **19** (2004), p 217] (with trichloroisocyanuric acid)

Carboxylic Acids by Oxidation of Primary Alcohols ($\text{CH}_2\text{OH} \rightarrow \text{CO}_2\text{H}$)

Spiropentaneacetic acid by oxidation of 2-(spiro[2.2]pent-1-yl)ethanols

- Section 7.1.9.6.3 [Vol. **7** (2004), p 292]

Pyridinedicarboxylic acids by oxidation of (hydroxymethyl)pyridines

- Section 15.1.1.4.4.5.1 [Vol. **15** (2005), p 197] (with NaOCl and NaClO₂)

Carboxylic acids by oxidation of primary alcohols

- ▲ – Section 20.2.1.5.2.1.1 [Vol. **20a** (2006), p 193] (with NaOCl)
- ▲ – Section 20.2.1.5.2.1.3 [Vol. **20a** (2006), p 196] (with trichloroisocyanuric acid)

Morpholine-2-carboxylic acids by oxidation of (hydroxymethyl)morpholines

- ▲ – Section 20.2.1.5.2.1.2 [Vol. **20a** (2006), p 195] [with PhI(OAc)₂]

Propargylic carboxylic acids by oxidation of propargylic alcohols

- Section 20.2.9.1.1.1 [Vol. **20a** (2006), p 507] [with PhI(OAc)₂]

Aldehydes by Oxidation of Primary Alcohols ($\text{CH}_2\text{OH} \rightarrow \text{CHO}$)

Aldehydes by oxidation of primary alcohols with metal salts in high oxidation states

- Section 25.1.2.2.1 [Vol. **25** (2007), p 28] (with PhIO)

Aldehydes by oxidation of primary alcohols

- ▲ – Section 25.1.2.2.4 [Vol. **25** (2007), p 41] (with a co-oxidant)
- ▲ – Section 25.1.2.2.5 [Vol. **25** (2007), p 43] (with O₂)

2-Oxyaldehydes by oxidation/aminooxylation of primary alcohols

- ▲ – Section 25.4.2.1.4 [Vol. **25** (2007), p 480] (4-BzO-TEMPO)

Aldehydes by oxidation of arylmethanols with *N*-oxoammonium salts

- ▲ – Section 25.6.2.2.9 [Vol. **25** (2007), p 547]

Nonheteroatom-substituted α,β -unsaturated aldehydes by oxidation of allylic alcohols

- ▲ – Section 25.8.1.1.2 [Vol. **25** (2007), p 734] [with PhI(OAc)₂]

Aldehydes by oxidation of aziridinyl alcohols, then intramolecular ring opening of aziridines by a nitronate

- Section 40.1.5.2.1.2.4 [Vol. **40a** (2009), p 721]

Application of nitroxyl radicals (nitroxides) to alcohol oxidation

- Section 40.2.2.1 [Vol. **40b** (2009), p 849]

Aldehydes by Oxidation of RCH_2X Compounds ($\text{X} = \text{OR}, \text{N}, \text{S}, \text{Hal}, \text{B}, \text{etc.}$) ($\text{CH}_2\text{X} \rightarrow \text{CHO}$)

Substituted benzaldehydes by oxidation of amines

- Section 25.1.2.5 [Vol. **25** (2007), p 49]

for references see p 5

Aldehydes or Ketones by Oxidation of Methylene Groups in RCH₂R compounds**(R = carbon group) [CH₂R → C(O)R]**

1,2,3,9-Tetrahydro-4*H*-carbazol-4(1*H*)-one by oxidation of 1,2,3,4-tetrahydro-9*H*-carbazole

- ▲ – Section 10.13.1.5.2.4 [Vol. **10** (2000), p 582] (2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate)

Ketones by Oxidation of Secondary Alcohols (R₂CHOH → R₂C=O)

2-Oxoalkanoic acid esters by oxidation of α-hydroxy esters

- Section 20.5.8.1.4.1 [Vol. **20b** (2007), p 1098]

Ketones by oxidation of secondary alcohols

- ▲ – Section 26.1.1.2.5.2 [Vol. **26** (2005), p 61] (4-MeO-TEMPO with NaOCl)
- Section 26.1.1.2.5.4 [Vol. **26** (2005), p 65] (with bromo compounds)
- Section 26.1.1.2.5.5 [Vol. **26** (2005), p 68] (with periodate)
- ▲ – Section 26.1.1.2.5.7 [Vol. **26** (2005), p 71] [with organic iodine(III) compounds]
- Section 26.1.1.2.6.1 [Vol. **26** (2005), p 75] (with O₂ and Ru)
- Section 26.1.1.2.6.4 [Vol. **26** (2005), p 78] (with O₂ and Cu)
- Section 26.1.1.2.6.6 [Vol. **26** (2005), p 82] (with O₂ and nitrates)
- Section 26.1.1.2.8.2 [Vol. **26** (2005), p 87] (with MCPBA)
- ▲ – Section 26.1.1.2.11.9 [Vol. **26** (2005), p 95] (with Oxone)
- ▲ – Section 26.1.1.2.12.1 [Vol. **26** (2005), p 96] (4-AcNH-TEMPO)
- ▲ – Section 26.1.1.2.15 [Vol. **26** (2005), p 105] (4-BzO-TEMPO)

1,2-Diketones by oxidation of 1,2-diols

- Section 26.4.1.1.3.4 [Vol. **26** (2005), p 678] (4-AcNH-TEMPO)

α-Alkoxy-α-amino and α-amino-α-hydroxy ketones by oxidation of α-hydroxy *N,O*-acetals

- Section 26.5.10.1.2 [Vol. **26** (2005), p 818]

O,N,N-Trisubstituted hydroxylamines from 1,3-dicarbonyl compound enolates

- Section 40.5.2.1.3.5 [Vol. **40b** (2009), p 1058] (2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate)

Quinones by Oxidation of Arenes or Partially Unsaturated Cyclic Hydrocarbon Skeletons

Naphtho-1,4-quinones by oxidation of naphthols

- Section 28.3.1.2.2 [Vol. **28** (2006), p 260] (2,2,6,6-tetramethyl-1-oxopiperidinium chloride)

Naphtho-1,2-quinones by oxidation of 2-naphthols

- Section 28.4.1.1.7.1 [Vol. **28** (2006), p 336] (2,2,6,6-tetramethyl-1-oxopiperidinium chloride)

Sulfoxides by Oxidation of Sulfides (or Se, Te analogues) [RSR → RS(O)R]

Acyclic dialkyl sulfoxides by oxidation of dialkyl sulfides

- Section 31.6.1.1.2 [Vol. **39** (2008), p 266] (with H₂O₂)

Other Oxidations

Applications of alkylmercury(II) compounds with 2,2,6,6-tetramethylpiperidin-1-oxyl

- Section 3.3.6, Applications [Vol. **3** (2004), p 274]

2-Benzopyrylium salts by oxidative fragmentation of 1*H*-2-benzopyrans (isochromans)

- Section 14.2.2.2.2 [Vol. **14** (2003), p 250] (2,2,6,6-tetramethyl-1-oxopiperidinium perchlorate)

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