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An expeditious synthesis of isoxazoline using cetyltrimethylammonium cerium nitrate: A phase transferring oxidative 1,3-dipolar cycloaddition

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Abstract

An expeditious and effective method for synthesis of isoxazoline from aldoximes and activated alkenes using cetyltrimethylammonium cerium nitrate at room temperature is described. Reaction was completed within short time period in high yields at room temperature.

Keywords: Cetyltrimethylammonium cerium nitrate; Isoxazoline; Oxime; Activated alkene; 1,3-Dipolar addition

Isoxazole and its dihydro derivative isoxazoline is essential motif found in several important bioactive molecules and act as a starting material for the synthesis of certain biological active compounds [1]. Muscimol formed from the mushroom *Amanita muscaria* has powerful psychotropic effects. Muscimol shows activity in brain nerve cell, which use γ-aminobutyric acid (GABA) as a neurotransmitter. Some of the compounds [2] containing isoxazole or isoxazoline ring have been known to be antipsychotic, analgesic, antituberculosis, antitumor and semi-synthetic antibiotic drugs such as muscimol, valdecoxib, cycloserine, isoxazoline and oxacilline (Fig. 1).

Cerium (IV) ammonium nitrate (CAN) is one of the most interesting oxidants in organic synthesis since it is stable in different solvents and is commercially available. The use of this reagent for numerous reactions involving C–S, C–N, C–Se and C–Cl bond formation has been evaluated [3–6]. However, application of CAN is limited due to poor solubility in common organic solvents. Therefore, phase transfer oxidant cetyltrimethylammonium cerium nitrate [7,8] is a good alternative of CAN and soluble in water as well as in common organic solvents.

Encouraged by these observations, in this communication synthesis of isoxazoline from aldoximes and activated alkenes using cetyltrimethylammonium cerium nitrate is demonstrated.

The reagent is easily prepared by addition of a weighed amount of cerium ammonium nitrate (0.01 mol) to an aqueous solution of cetyltrimethylammonium bromide (0.025 mol) [8,9]. Aldoximes of benzaldehyde, 2-chlorobenzaldehyde and 3-nitrobenzaldehyde were synthesized and then reacted with activated alkenes (methyl

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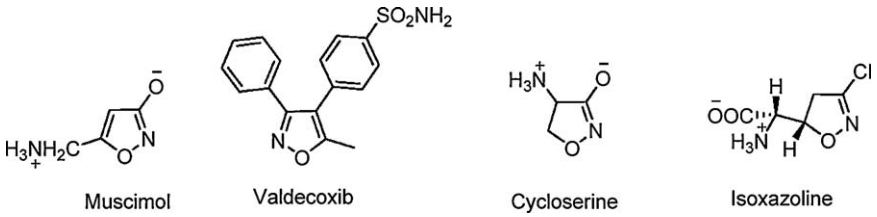
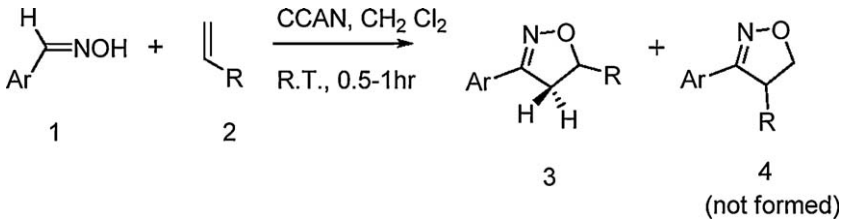


Fig. 1. Known drugs having isoxazole or isoxazoline ring.



Scheme 1.

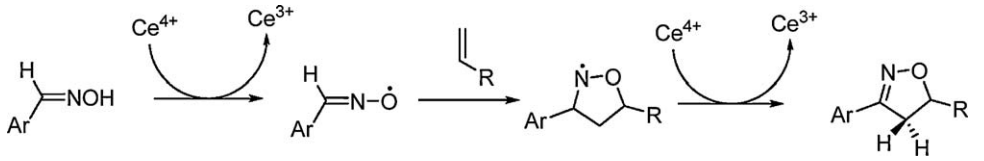
acrylate, acrylonitrile and vinyl acetate) in the presence of cetyltrimethylammonium cerium nitrate to produce isoxazolines in high yields (Scheme 1) (Table 1).

All reactions were carried out at room temperature and completed with in a short time period (0.5–1 h). Reactions proceed smoothly and the effect of an electron donating or an electron-withdrawing group on the aromatic ring of the aldoximes was not observed. However, when aldoxime of *m*-hydroxybenzaldehyde was used, a dark brown coloured solution was obtained and no isoxazoline ring was formed. This might be due to oxidation of phenolic group. The influence of various solvents was also investigated using H_2O, CH_2Cl_2, $CHCl_3$, CH_3CN and THF. All organic solvent gave comparable result and best reaction temperature was room temperature. However, in water deoximination product was obtained as major product. The probable mechanism of the reaction is shown in Scheme 2. The mechanism involves 1,3-dipolar addition of nitrile oxides, formed from the aldoximes, to the activated alkenes. Using optimized reaction conditions [10], various isoxazolines were synthesized in high yield. The appearance of doublet of doublet in the region δ 5.3–6.8 (1H, dd) in ^{1}H NMR spectra of compound **3** clearly indicates that other regioisomers **4** (2H, $-OCH_2-$) were not at all formed. The literature survey shows that cerium ammonium nitrate has been already used in the synthesis of isoxazolines [11]. Due to insolubility or partially solubility of cerium ammonium nitrate in organic solvent, reaction time period was long and more deoximination occurred, led to low yield.

In conclusion, cetyltrimethylammonium cerium nitrate has been employed for the first time as a mild and efficient reagent for 1,3-dipolar intermolecular cycloaddition reaction. The procedure proved to be simple either in conducting the reaction or in isolation of the products.

Table 1
Cetyltrimethylammonium cerium nitrate mediated synthesis of isoxazolines **3**.

Serial no.	Product	Ar	R	Time (min)	Yield	Mp (°C)	Lit. mp (°C) [11,12]
1	**3a**	*m*-NO_2–C_6H_4–	CN	30	93	107–108	106–107
2	**3b**	*o*-Cl–C_6H_4–	CN	30	92	Viscous oil	Semisolid
3	**3c**	C_6H_5–	CN	30	93	Viscous oil	–
4	**3d**	*m*-NO_2–C_6H_4–	$COOCH_3$	30	92	100–101	99–100
5	**3e**	*o*-Cl–C_6H_4–	$COOCH_3$	30	94	Viscous oil	Semisolid
6	**3f**	C_6H_5–	$COOCH_3$	30	93	Viscous oil	–
7	**3g**	*m*-NO_2–C_6H_4–	$OCOCH_3$	45	92	103–104	104–105
8	**3h**	*o*-Cl–C_6H_4–	$OCOCH_3$	45	90	Viscous oil	Semisolid
9	**3i**	C_6H_5–	$OCOCH_3$	45	92	Viscous oil	–



Scheme 2.

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[9] Synthesis of cetyltrimethylammonium cerium (IV) nitrate: Cerium (IV) ammonium nitrate (0.01 mol) in 10 mL water was added slowly to an aqueous solution of cetyltrimethylammonium bromide (0.025 mol) with continuous stirring on a magnetic stirrer. A yellow coloured compound appeared slowly. Stirring was continued for 30 min. The resulting yellow coloured compound was filtered with water for several times till no trace of bromide ion was detected in the filtrate. It was vacuum dried and kept in a dark bottle inside desiccator, yield 93%. Anal. Calcd. for $C_{38}H_{84}N_8O_{15}Ce$: C, 42.22; H, 7.77; N, 13.37. Found: C, 42.50; H, 7.96; N, 13.32%.

[10] General experimental procedure for synthesis of **3**: An aldoxime **1** (1.0 mmol) and methyl acrylate/acrylonitrile/vinyl acetate (1.2 mmol) were taken in anhydrous CH_2Cl_2 (25 mL). Cetyltrimethylammonium cerium nitrate (2.36 g, 2.2 mmol) was added and the reaction mixture was stirred at room temperature for the time as indicated in Table 1. The reaction was monitored by TLC. After completion, water (20 mL) was added and shaken well. Separated the organic layer and again washed with water (10 mL), dried over $MgSO_4$ and concentrated. The residue was subjected to column chromatography over silica gel using hexane–ethylacetate (5:2) as eluent to obtain pure isoxazoline **3**. Spectral data of synthesized oxazoline are given below: **3a** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.46 (d, 1H, J = 2.1 Hz), 8.35 (dd, 1H, J = 8.0, 2.1 Hz), 8.09 (dd, 1H, J = 8.0, 2.0 Hz), 7.69 (m, 1H), 5.48 (dd, 1H, J = 8.0, 5.8 Hz), 3.83 (dd, 1H, J = 11.5, 8.0 Hz), 3.71 (dd, 1H, J = 11.5, 5.8 Hz); MS (EI): m/z 217.05 ($M^{\bullet+}$) (Found: C, 55.39; H, 3.33; N, 19.27. $C_{10}H_7N_3O_3$ requires: C, 55.30; H, 3.25; N, 19.35%). **3b** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.74 (dd, 1H, J = 7.9, 2.2 Hz), 7.50–7.28 (m, 3H), 5.38 (dd, 1H, J = 8.0, 4.3 Hz), 3.94 (dd, 1H, J = 11.6, 8.0 Hz), 3.79 (dd, 1H, J = 11.6, 4.3 Hz); MS (EI): m/z 206.02, 208.02 ($M^{\bullet+}$) (Found: C, 58.23; H, 3.37; N, 13.44. $C_{10}H_7ClN_2O$. requires: C, 58.13; H, 3.41; N, 13.56; %). **3c** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (m, 2H), 7.45 (m, 3H), 5.35 (dd, 1H, J = 8.0, 5.7 Hz), 3.83 (dd, 1H, J = 11.5, 8.0 Hz), 3.71 (dd, 1H, J = 11.5, 5.7 Hz); MS (EI): m/z 172.06 ($M^{\bullet+}$) (Found: C, 69.64; H, 4.78; N, 16.32. $C_{10}H_8N_2O$ requires: C, 69.76; H, 4.68; N, 16.27%). **3d** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.44 (d, 1H, J = 2.2 Hz), 8.30 (dd, 1H, J = 8.0, 2.2 Hz), 8.10 (dd, 1H, J = 8.0, 2.0 Hz), 7.68 (m, 1H), 5.28 (dd, 1H, J = 8.2, 3.8 Hz), 3.83 (s, 3H), 3.78 (dd, 1H, J = 11.5, 8.2 Hz), 3.62 (dd, 1H, J = 11.5, 3.8 Hz); MS (EI): m/z 250.06 ($M^{\bullet+}$) (Found: C, 52.92; H, 4.12; N, 11.24. $C_{11}H_{10}N_2O_5$ requires: C, 52.80; H, 4.03; N, 11.20%). **3e** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.73 (dd, 1H, J = 7.9, 2.2 Hz), 7.42–7.25 (m, 3H), 5.16 (dd, 1H, J = 7.9, 3.9 Hz), 3.79 (dd, 1H, J = 11.6, 7.9 Hz), 3.62 (dd, 1H, J = 11.6, 3.9 Hz), 3.85 (s, 3H); MS (EI): m/z 239.03, 241.03 ($M^{\bullet+}$) (Found: C, 55.22; H, 4.27; N, 5.74. $C_{11}H_{10}ClNO_3$ requires: C, 55.13; H, 4.21; N, 5.84%). **3f** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, 2H, J = 7.5 Hz), 7.45 (m, 3H), 5.17 (dd, 1H, J = 8.1, 4.2 Hz), 3.79 (dd, 1H, J = 11.6, 8.1 Hz), 3.62 (dd, 1H, J = 11.6, 4.2 Hz), 3.85 (s, 3H); MS (EI): m/z 205.07 ($M^{\bullet+}$) (Found: C, 64.45; H, 5.51; N, 7.02. $C_{11}H_{11}NO_3$ requires: C, 64.38; H, 5.40; N, 6.83%). **3g** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.45 (d, 1H, J = 2.2 Hz), 8.30 (dd, 1H, J = 8.0, 2.2 Hz), 8.09 (dd, 1H, J = 8.0, 2.0 Hz), 7.67 (m, 1H), 6.83 (dd, 1H, J = 8.2, 3.8 Hz), 3.68 (dd, 1H, J = 11.5, 8.2 Hz), 3.40 (dd, 1H, J = 11.5, 3.8 Hz), 2.12, (s, 3H); MS (EI): m/z 250.06 ($M^{\bullet+}$) (Found: C, 52.94; H, 3.97; N,

11.14. $C_{11}H_{10}N_2O_5$ requires: C, 52.80; H, 4.03; N, 11.20%). **3h** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.79 (dd, 1H, J = 8.1, 1.9 Hz), 7.48–7.23 (m, 3H), 6.80 (dd, 1H, J = 8.8, 3.9 Hz), 3.82 (dd, 1H, J = 11.6, 8.8 Hz), 3.42 (dd, 1H, J = 11.6, 3.9 Hz), 2.16 (s, 3H); MS (EI): *m/z* 239.03, 241.03 ($M^{\bullet+}$) (Found: C, 55.24; H, 4.19; N, 5.92. $C_{11}H_{10}ClNO_3$ requires: C, 55.13; H, 4.21; N, 5.84%). **3i** ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.76 (m, 2H), 7.45 (m, 3H), 6.73 (dd, 1H, J = 8.6, 3.6 Hz), 3.78 (dd, 1H, J = 11.6, 8.6 Hz), 3.50 (dd, 1H, J = 11.6, 3.6 Hz), 2.16 (s, 3H); MS (EI): *m/z* 205.07 ($M^{\bullet+}$) (Found: C, 64.22; H, 5.33; N, 6.98. $C_{11}H_{11}NO_3$ requires: C, 64.38; H, 5.40; N, 6.83%).

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