SILVER(I) SALT PROMOTED GENERATION OF NITRILE OXIDES FROM HYDROXIMOYL CHLORIDES

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Abstract——*Treatment of hydroximoyl chlorides with silver(I) salt in the presence of* olefins as dipolarophiles caused the formation of nitrile oxides and the subsequent intermolecular 1,3-dipolar cycloaddition forming corresponding isoxazoline derivatives in high yields.

1,3-Dipolar cycloaddition of nitrile oxides with olefinic compounds is a synthetically important tool since the product isoxazolines are useful intermediates for the preparation of bifunctional compounds.[1] We have achieved stereoselective syntheses of steroids and sesquiterpenoids using this reaction as a key step.[2] Nitrile oxides can be generated by many methods which include dehydration of primary nitro compounds,[3] oxidation of oximes,[4] ring-fragmentation of furazans,[5] and dehydrohalogenation of hydroximoyl chlorides.[6] Several conditions for the dehydrohalogenation have been reported; e.g. treatments with base,[6a] molecular sieves,[6b] and alkali metal fluoride.[6c]

We now wish to report a simple and efficient method for the generation of nitrile oxides from hydroximoyl chlorides in the presence of silver(I) acetate. Outcomes of the 1,3-dipolar cycloaddition of the resulting nitrile oxides are summarized in Table. When **1a** was treated with silver(I) acetate in the presence of styrene (**2a**), **4a** was obtained in 96% yield as a single isomer (entry 1). In the same manner, hydroximoyl chlorides (**1a-d**)[7] were converted into the corresponding isoxazolines (**4b-g**, **5b-g**) in good yields, respectively. Regioselectivities were similar to those obtained by other methods.[4, b, c, 6a, b, c, 8] It is probable that generation of nitrile oxides (**3**) from hydroximoyl chlorides (**1**) readily occurs because of high affinity of silver(I) ion with chloride ion. The cycloaddition of hydroximoyl chloride (**1a**) with styrene using other silver(I) salts such as silver(I) cyanide and silver(I) carbonate also gave isoxazoline (**4a**) in good yields.

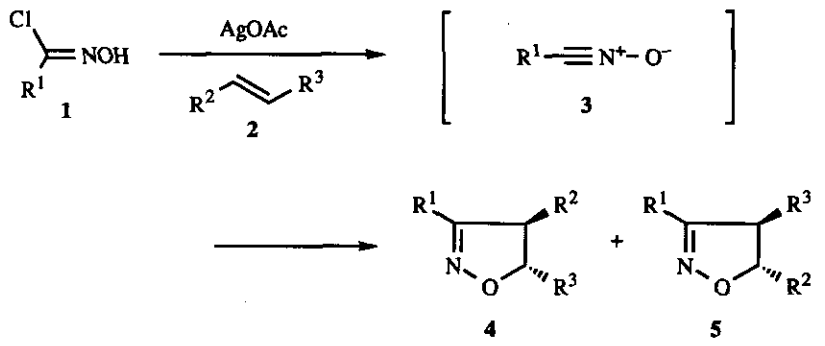

Table Synthesis of Isoxazolines

Entry	Hydroximoyl Chloride (1)	Olefin (2)	Isoxazolines	Yield (%)	Ratio (4 : 5)[a]
1	**1a** : R^1 = Ph	**2a** : R^2 = H, R^3 = Ph	**4a** and **5a**	96	> 99 : 1
2	**1a** : R^1 = Ph	**2b** : R^2 = H, R^3 = CO_2Me	**4b** and **5b**	98	55 : 1
3	**1a** : R^1 = Ph	**2c** : R^2 = CH_2OH, R^3 = Me	**4c** and **5c**	94	1:4 : 1
4	**1b** : R^1 = 2-$MeOC_6H_4$	**2a** : R^2 = H, R^3 = Ph	**4d** and **5d**	89	>99 : 1
5	**1c** : R^1 = 2, 6-Cl_2 C_6H_3	**2a** : R^2 = H, R^3 = Ph	**4e** and **5e**	81	66 : 1
6	**1c** : R^1 = 2, 6-Cl_2 C_6H_3	**2a** : R^2 = H, R^3 = CO_2Me	**4f** and **5f**	89	11 : 1
7	**1d** : R^1 = PhCO	**2b** : R^2 = H, R^3 = CO_2Me	**4g** and **5g**	76	>99 : 1

[a] The ratios were determined by ^{1}H-nmr.

In conclusion, we have developed a facile and effective procedure to convert hydroximoyl chlorides into the corresponding nitrile oxides which give isoxazolines *via* 1,3-dipolar cycloaddition. Since these conditions are compatible with the presence of sensitive functionalities to base, this methodology is applicable to a variety types of substrates.

EXPERIMENTAL

Mp are uncorrected. Ir spectra were taken by JASCO-IR Report-100 spectrophotometer. ^{1}H-Nmr spectra were measured on Hitachi R-3000 and Varian Gemini 3000 spectrometers. Chemical shifts were reported as δ H values relative to internal TMS. Ms spectra were recorded on JEOL-JMS-DX-303 and JEOL-JMS-AX-500 spectrometers.

3,5-Diphenyl-4,5-dihydroisoxazole (4a)

To a solution of hydroximoyl chloride (**1a**)[4c, 6a, c, 8] (132 mg, 0.85 mmol) in styrene (1.5 ml, 13.1 mmol) was added silver(I) acetate (218 mg, 1.27 mmol) at room temperature. After being stirred for 20 min at the same temperature, ether was added to the reaction mixture. The mixture was filtered through Celite. The filtrate was concentrated under reduced pressure. Purification of the residue by column chromatography on silica gel with hexane-ethyl acetate (10 : 1, v/v) as the eluent gave isoxazoline (**4a**)[4b, c, 6a] (181 mg, 96%) as colorless crystals, mp 75-75.5 °C (lit.,[4b] 73-74 °C, [4c] 73-75 °C), whose spectral date were consistent with reported ones.[4c, 6a]

Methyl 3-Phenyl-4,5-dihydroisoxazole-5-carboxylate (4b)

Silver(I) acetate (195 mg, 1.17 mmol) was added to a solution of hydroximoyl chloride (**1a**) (122 mg, 0.78 mmol) and methyl acrylate (673 mg, 7.81 mmol) in methylene chloride (2 ml) at room temperature. After 1 h of stirring at the same temperature, followed by dilution with ether, the reaction mixture was filtered through Celite. The residue upon evaporation of filtrate was chromarographed on silica gel with hexane-ethyl acetate (2 : 1, v/v) as eluent to give a 55 : 1 mixture of isoxazolines (**4b** and **5b**)[4c, 6a, c] (157 mg, 98%). The mixture was recrystallized from hexane-ethyl acetate to give **4b** as colorless crystals, mp 68-69 °C (lit.,[4c] 71-72.5 °C), whose spectral date were consistent with reported ones.[4c, 6a, c]

4-Hydroxymethy-5-methyl-3-phenyl-4,5-dihydroisoxazole (4c) and 5-Hydroxymethy-4-methyl-3-phenyl-4,5-dihydroisoxazole (5c)

By the same procedure as the preparation of **4a**, treatment of hydroximoyl chloride (**1a**) (110 mg, 0.71 mmol) with *trans*-2-butene-1-ol (1 ml, 11.7 mmol) and silver(I) acetate (176 mg, 1.06 mmol) gave a residue, which was chromatographed (hexane-ethyl acetate 3 : 2, v/v) to give a 1.4 : 1 mixture of isoxazolines (**4c** and **5c**)[8] (117 mg, 94%), whose spectral data were consistent with reported ones.[8]

3-(2-Methoxyphenyl)-5-phenyl-4,5-dihydroisoxazole (4d)

By the same procedure as the preparation of **4a**, hydroximoyl chloride (**1b**)[7] (37 mg, 0.20 mmol), styrene (1.1 ml, 10.6 mmol) and silver(I) acetate (50 mg, 0.30 mmol) gave a residue, which was chromatographed (hexane-ethyl acetate 9 : 1, v/v) to give isoxazoline (**4d**) (45 mg, 89%); ir vmax (neat): 1605 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 3.46 (1H, dd, *J* = 17.2 and 10.6 Hz), 3.82 (3H, s), 3.87 (1H, dd, *J* = 17.2 and 8.6 Hz), 5.67 (1H, dd, *J* = 10.6 and 8.6 Hz), 6.89 - 7.02 (2H, m), 7.27 - 7.44 (6H, m), 7.78 (1H, dd, *J* = 7.7 and 1.5 Hz); ms (m/z): 253(M^+); HRms Calcd for $C_{16}H_{15}NO_2$: 253.1103. Found: 253.1097.

3-(2,6-Dichlorophenyl)-5-phenyl-4,5-dihydroisoxazole (4e)

The same procedure using hydroximoyl chloride (**1c**)[6b, c] (188 mg, 0.84 mmol), styrene (1.9 ml, 16.6 mmol) and silver(I) acetate (208 mg, 1.25 mmol) afforded a residue, which was chromatographed (hexane-ethyl acetate 10 : 1, v/v) to give a 66 : 1 mixture of isoxazolines (**4e** and **5e**) (197 mg, 81%). The mixture was recrystallized from hexane-ethyl acetate to give **4e** as colorless crystals, mp 64-65 °C; ir vmax ($CHCl_3$): 1580, 1555 cm^{-1}; ^1H nmr (300 MHz, $CDCl_3$): δ 3.26 (1H, dd, *J* = 17.3 and 8.7 Hz), 3.71 (1H, dd, *J* = 17.3 and 11.1 Hz), 5.80 (1H, dd, *J* = 11.1 and 8.7 Hz), 7.22 - 7.52 (8H, m); ms (m/z): 291(M^+); Anal. Calcd for $C_{15}H_{11}NOCl_2$: C, 61.67; H, 3.79; N, 4.79; Cl, 24.27. Found: C, 61.49; H, 3.91; N, 4.59; Cl, 24.37.

Methyl 3-(2,6-Dichlorophenyl)-4,5-dihydroisoxazole-5-carboxylate (4f)

By the same procedure as the preparation of **4b**, treatment of hydroximoyl chloride (**1c**) (155 mg, 0.69 mmol) with methyl acrylate (593 mg, 6.89 mmol) and silver(I) acetate (172 mg, 1.03 mmol) gave a residue, which was chromatographed (hexane-ethyl acetate 4 : 1, v/v) to give a 11 : 1 mixture of isoxazolines (**4f** and **5f**)[6b,c] (184 mg, 98%). The mixture was recrystallized from hexane-ethyl acetate to give **4f** as colorless crystals, mp 73-74 °C, whose spectral date were consistent with reported ones.[6b]

Methyl 3-Benzoyl-4,5-dihydroisoxazole-5-carboxylate (4g)

The same procedure using hydroximoyl chloride (**1d**)[6b] (85 mg, 0.46 mmol) and methyl acrylate (398 mg, 4.62 mmol) and silver(I) acetate (115 mg, 0.69 mmol) afforded a residue, which was chromatographed (hexane-ethyl acetate 5 : 1, v/v) to give isoxazoline (**4g**)[6b] (82 mg, 76%), whose spectral data were consistent with reported ones.[6b]

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