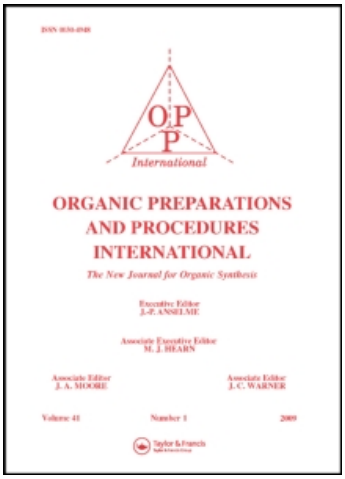

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A CONVENIENT METHOD FOR THE GENERATION OF NITRILE OXIDE AND ITS APPLICATION TO THE SYNTHESIS OF 2-ISOXAZOLINES

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9. Compound **2a:** ^{1}H NMR (250 MHz) ($CDCl_3$): δ 0.85 (d, 3H, CH_3), 0.95 (d, 3H, CH_3), 0.95-1.15 (m, 6H, 6ax.cycl), 1.4 (s, 9H, *t*Bu), 1.65 (m, 7H, 5eq.cycl, CH_2), 2.1 (m, 1H, C*H*Me_2), 3.95 (m, 1H, C*H*CO), 5.1 (m, 2H, CH, NH), 6.8 (m, 1H, NH), 7.18 (m, 2H, pyr), 7.6 (m, 1H, pyr), 8.5 (m, 1H, pyr).
Compound **3a (SS):** ^{1}H NMR ($CDCl_3$): δ 0.85 (d, 3H, CH_3), 0.95 (d, 3H, CH_3), 0.9-1.15 (m, 6H, 6ax.cycl), 1.4 (br, 2H, NH_2), 1.7 (m, 7H, 5eq, CH_2), 2.3 (m, 1H, C*H*Me_2), 3.2 (d, 1H, C*H*CO), 5.15 (dd, 1H, CH), 7.15 (m, 1H, pyr), 7.2 (d, 1H, pyr), 7.60 (m, 1H, pyr), 7.95 (br, 1H, NH), 8.55 (d, 1H, pyr).
Compound **3a (SR):** ^{1}H NMR ($CDCl_3$): δ 0.7 (d, 3H, CH_3), 0.92 (d, 3H, CH_3), 0.9-1.15 (m, 6H, 6ax.cycl), 1.5 (s, 2H, NH_2), 1.65 (m, 7H, 5eq, CH_2), 2.2 (m, 1H, C*H*Me_2), 3.2 (d, 1H, C*H*CO), 5.15 (dd, 1H, CH), 7.1 (m, 1H, pyr), 7.2 (m, 1H, pyr), 7.6 (m, 1H, pyr), 7.8 (br, 1H, NH), 8.55 (m, 1H, pyr).
Compound **1a,(+)-S:** ^{1}H NMR ($CDCl_3$): δ 0.95 (m, 3H, 3ax.cycl), 1.5-1.7 (m, 7H, 5eq.cycl, CH_2), 1.72 (br, 2H, NH_2), 4.05 (m, 1H, CH), 7.15 (m, 1H, pyr), 7.25 (m, 1H, pyr), 7.6 (t, 1H, pyr), 8.55 (m, 1H, pyr).
Compound **1a,(-)-R:** Identical NMR spectrum as **1a (S)**.
Data for the 3-pyridyl derivatives: **2b, 3b (SS), 3b (SR),** and **1b (S), 1b (R)**.

10. **3a (SS)** does not crystallize as a dihydrochloride, and **3a (SR)** does not crystallize as the ditosylate.

11. It was slightly less pure chemically, 97% by HPLC, because of incomplete hydrolysis.

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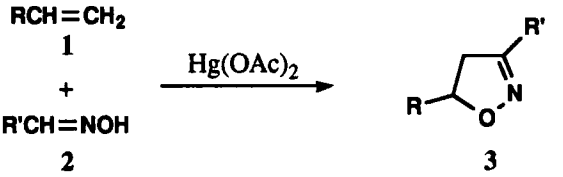
The 1,3-dipolar cycloaddition reaction is one of the most important and versatile methods for the construction of 5-membered heterocycles.[1] Among the various 1,3-dipoles known, nitrile oxides have been used extensively. The usual synthesis of nitrile oxides involves the oxidative dehydrogenation of aldoximes using oxidants such as lead tetraacetate,[2] alkali hypohalites,[3] N-bromosuccinimide in dimethylformamide followed by base treatment,[4] chloramine-T[5] or 1-chlorobenzotriazole[6] as well as the reaction of nitro compounds with an aryl isocyanate.[7] We now report the use of mercuric

acetate as a new efficient reagent for the conversion of aldoximes to nitrile oxides.

Typically the cycloaddition is carried out by heating an equimolar mixture of the alkene (**1**), the aldoxime (**2**), and mercuric acetate in ethanol under reflux for 3 hrs.



a) R = 3,4-$(OCH_2O)CH_6CH_2$, R' = 3,4,5-$(MeO)_3C_6H_2$
b) R = 3,4-$(OCH_2O)C_6H_3CH_2$, R' = 4-$MeOC_6H_4$
c) R = CO_2Et, R' = 3,4,5-$(MeO)_3C_6H_2$
d) R = 3,4-$(OCH_2O)C_6H_3CH_2$, R' = 3,4$(OCH_2O)C_6H_3$,
e) R = CO_2Et, R' = 3,4-$(MeO)_2C_6H_2$ f) R = CO_2Et, R' = C_3H_7

The reaction with mercuric acetate proceeds with aromatic as well as aliphatic aldehydes (**1a-e**)(see Table. 1). The three known compounds exhibit identical NMR spectra (60 MHz), mixed mps and TLC behavior with those of authentic samples.

TABLE 1. Yield and Physical data of 2-Isoxazoline (**3**)

Product	Yield (%)	mp. (°C)	lit.[1] mp (°C)	Elemental Analysis (Found) C	H	N
3a	80	122-126	124-125[5]	-	-	-
3b	75	80-82	82-84[5]	-	-	-
3c[a]	82	58-61	-	58.27 (58.10)	6.15 (6.00)	4.54 (4.48)
3d[b]	70	61-63	-	66.46 (66.30)	4.62 (4.50)	4.38 (4.32)
3e[c]	80	45-50	-	60.20 (60.02)	6.09 (6.00)	5.01 (4.90)
3f[d]	40	oil[5]	-	58.38 (58.02)	8.11 (7.95)	7.57 (7.65)

(a) ^{1}H NMR: δ 1.30 (t, 3H), 2.70 (bd, 2H), 3.85 (s, 9H), 4.20(q, 2H), 4.95 (m, 1H), 6.70 (s, 2H); (b) ^{1}H NMR: δ 2.80 (d, 2H, J = 6 Hz), 3.50(d, 2H, J = 9 Hz), 5.00 (bm, 1H), 6.00 (s, 4H), 6.75 (bd, 4H) 6.90 (bd, 2H); (c) ^{1}H NMR: δ 1.30 (t, 3H), 2.80 (bd, 2H), 3.80 (s, 6H), 4.10 (q, 2H), 4.80 (m, 1H) 6.80 (b, 3H); (d) ^{1}H NMR: δ 1.00 (t, 3H), 1.32 (t, 3H), 1.62 (bq, 2H), 2.34 (bt, 2H), 3.12 (bd, 2H), 4.15 (bq, 2H), 4.90 (m, 1H).

EXPERIMENTAL SECTION

Mps were determined in open capillary tubes using a Thomas Hoover capillary melting point apparatus and are uncorrected. The ^{1}H NMR spectra were obtained in $CDCl_3$ on a Varian 60MHz, spectrometer using TMS as internal standard. Chemical shifts are expressed in ppm(δ). The purity of the compounds were monitored by TLC performed on silica gel plates (Merck) using chloroform-

acetone (7:1) as the eluent.

Preparation of Isoxazolines (3). Typical Procedure.- A mixture of aldoxime **2c** (1.65 g, 10 mmol), safrole **1a** (1.62 g, 10 mmol) and mercuric acetate (3.18 g, 10 mmol) in absolute ethanol was refluxed for 3 hrs. After the reaction was complete, the solvent was removed by evaporation under reduced pressure. The residual solid was dissolved in ether and was thoroughly washed with water (3 x 25 ml) and finally with brine solution (25 mL). After drying over anhydrous Na_2SO_4, it was evaporated to give a gummy material, which was dissolved in small amount of chloroform and precipitated with pet ether. Crystallization of the solid from alcohol gave 2.31 g (70%) of isoxazoline **3d**.

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