# *O*-Ethoxycarbonyl Hydroximoyl Chloride as Nitrile Oxide Precursor

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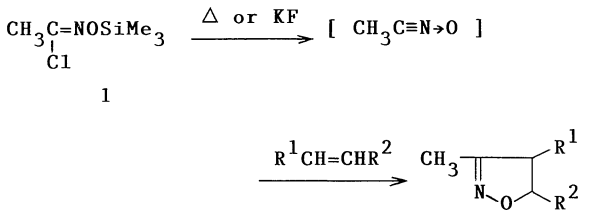
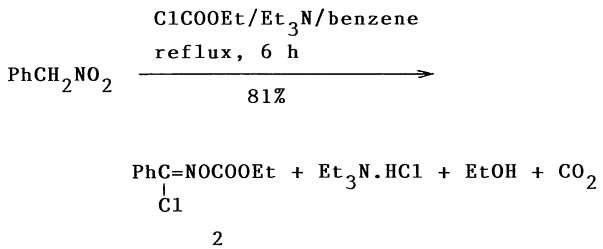
**Synopsis.** *O*-Ethoxycarbonyl hydroximoyl chloride serves as a stable precursor for nitrile oxide and is converted into the 1, 3-dipole when heated under reflux in pyridine.

2-Isoxazoline and isoxazole derivatives show various biological activities,[1] and are often found in natural products.[2] They are synthetically versatile heterocycles since they are readily converted into γ-amino alcohols and β-hydroxy ketones by reductive cleavage of the ring.[3,4] The most general synthetic approach to these heterocycles is the cycloaddition of olefins or acetylenes with nitrile oxides which have been generated by a variety of methods.[5,6] Of these the most widely used method is the dehydrochlorination of hydroximoyl chloride with base. Recently, an *O*-substituted hydroximoyl chloride has been employed as nitrile oxide precursor, i. e., *O*-(trimethylsilyl)acetohydroximoyl chloride (**1**) undergoes the thermolysis in refluxing toluene to generate acetonitrile oxide.[7]



We report here a unique method for the generation of benzonitrile oxide from *O*-ethoxycarbonyl hydroximoyl chloride, *O*-ethoxycarbonylbenzohydroximoyl chloride (**2**), that can be prepared in high yield (81%) by the reaction of (nitromethyl)benzene with ethyl chloroformate in the presence of triethylamine.[8]

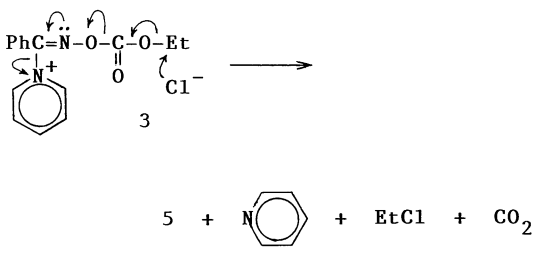


## Results and Discussion

The thermal decomposition of **2** was carried out in pyridine at the refluxing temperature for 3 h in the presence of olefin. 2-Isoxazolines (**6a—i**) were isolated from the reaction mixture in good yields as shown in Table 1. During the reaction, evolution of carbon dioxide and ethyl chloride was observed. From these evidences, a probable mechanism of the formation of the cycloadducts may be as follows (see Scheme 1); i) the formation of pyridinium chloride (**3**), ii) the nucleophilic substitution at the carbon atom of carbonate group by chloride ion giving the betaine (**4**), iii) the generation of benzonitrile oxide (**5**) and pyridine in an equiliblium with **4**, and iv) 1,3-dipolar cycloaddition reaction of the nitrile oxide with olefins would give 2-isoxazolines (**6**). This mechanism is in accoord with that reported on the generation of nitrile oxides by the reaction of *O*-unsubstituted hydroximoyl chloride with tertiary amines.[14] It is known that **4** attains an equiliblium with **5** and pyridine.[15]

It is known that ethyl chloroformate decomposes to carbon dioxide and ethyl chloride on refluxing in pyridine.[16] Trapping of carbon dioxode and ethyl chloride in our reaction suggests the formation of ethyl chloroformate.

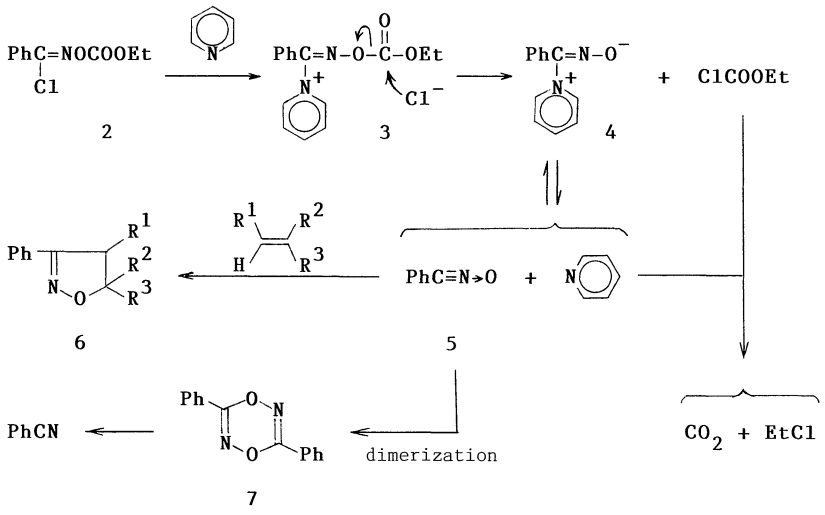
Another mechanism involving direct formation of **5** from **3** by E2 type elimination shown below would also be supposed.



We also investigated the reaction of **2** with pyridine in the absence of dipolarophile and obtained ethyl *N*-phenylcarbamate and benzonitrile in 17% and 20% yields, respectively. These yields were not so varied when the reaction was carried out in the presence of a small amont of water or ethanol. The formation of benzonitrile may be ascribed to the thermal fragmentation[17] of 3,6-diphenyl-1,4,2,5-dioxadiazine (**7**) from (**3**+**3**) head-to-tail dimerization[18] in the presence of pyridine. Although we have no definite evidences for a plausible mechanism of the formation of the carbamate, Beckmann rearrangement of **2** may be involved in the formation during which benzonitrile may be formed as a side product.

Using phenylacetylene as a dipolarophile, 3,5-diphenylisoxazole was obtained in 62% yield.

3-Methoxycarbonylisoxazolines (**9**) were obtained in poor yields (5—30%) from the similar reaction using methyl 2-chloro-2-(ethoxycarbonyloxyimino)acetate (**8**) instead of **2**. On the other hand, no cycloadducts were



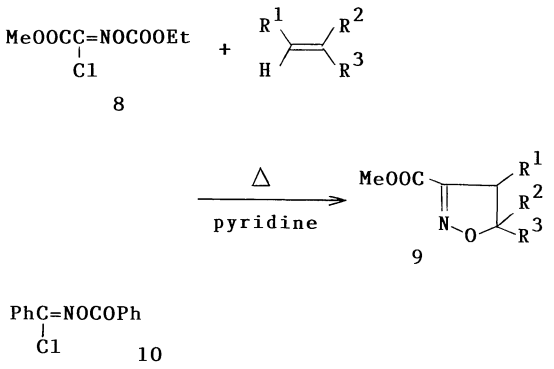
Scheme 1.

Table 1. Yields and Melting (or Boiling) Points of 2-Isoxazolines (**6**)

| Compd | $R^1$ | $R^2$ | $R^3$ | Yield[a] % | Mp($\theta_m$/°C) [Bp($\theta_m$/°C)/mmHg] | Lit, Mp($\theta_m$/°C) [Bp($\theta_m$/°C)/mmHg][b] |
|---|---|---|---|---|---|---|
| **6a** | H | $C_{12}H_{25}$-*n* | H | 75 | 72—73 | 72—73[9] |
| **6b** | H | $CH_2Ph$ | H | 37 | 63—64 | 64—65[9] |
| **6c** | H | $CH_2OC_6H_4NO_2$-*p* | H | 77 | 151—153 | 152—153[9] |
| **6d** | H | $C_6H_5$ | H | 60 | 72—74 | 75—76[10] |
| **6e** | H | CN | H | 51 | 64—66 | 66—67[11] |
| **6f** | H | $OCOCH_3$ | H | 42 | 97—98 | 90—91[12] |
| **6g** | H | $OC_4H_9$-*n* | H | 68 | [155/1.5] | [141/1.0][8] |
| **6h** | -CON(Ph)CO- | | H | 95 | 168—171 | 170—172[9] |
| **6i** | H | $COOCH_3$ | $CH_3$ | 63 | [145/1.3] | 60[13] |

a) Yields of the isolated products based on **2**. b) 1 mmHg=133.322 Pa.

obtained by the reaction using *O*-benzoyl derivative (**10**) of benzohydroximoyl chloride as the nitrile oxide precursor.



Compared with conventional nitrile oxide precursors, hydroximoyl chlorides [RC(Cl)=NOH] and their *O*-trimethylsilyl derivatives (**1**), our new precursor (**2**) gave more satisfactory results from the standpoints of simple preparative method and the stability of the precursor [in fact, this reagent is so stable to be distilled in vacuo (115°C/0.3 mmHg, 1 mmHg=133.322 Pa) and is stable during the storage for a long time at ambient temperature even in the presence of moisture].

## Experimental

**Measurements and Materials.** All melting and boiling points are uncorrected. *O*-Ethoxycarbonylbenzohydroximoyl chloride (**2**) was prepared similarly according to the method in literature[8] except for the usage of the substrates, (nitromethyl)benzene, ethyl chloroformate, and triethylamine, in 1:3:3 molar ratio [the yield of **2** was improved to 81% yield based on (nitromethyl)benzene by this modification]. Methyl 2-chloro-2-(ethoxycarbonyloxyimino)acetate (**8**) was prepared according to the method in literature.[8] The other reagents were of commercial origin and were used without further purification.

**Preparation of 3-Phenyl-2-isoxazolines (6) and 3, 5-Diphenylisoxazole: General Procedure:** An equimolar mixture of **2** (1.14 g, 5 mmol) and olefin (5 mmol) in pyridine (30 ml) was heated to reflux for 3 h. Gradual evolution of carbon dioxide (trapped as $CaCO_3$) and ethyl chloride (captured by a chilled trap and identified by $^1H$ NMR spectral analysis) was observed in the course of the reaction. After evaporation of pyridine, the residue was treated with water and extracted with chloroform. The chloroform layer was dried over anhydrous sodium sulfate and the solvent was evaporated to give crude products. Crystalline crude products were recrystallized from appropriate solvent to give pure cycloadducts (**6a—f** and **6h**) in yields shown in Table 1. 3,5-Diphenylisoxazole was ob-

tained in crystalline state from the reaction of **2** with phenylacetylene; yield; 600 mg (62%); mp 139—141 °C (methanol) (lit,[19] mp 141—142 °C). Oily products obtained from the reaction using butyl vinyl ether or methyl methacrylate as dipolarophile were distilled in vacuo to give pure isoxazolines (**6g** and **6i**) in yields shown in Table 1. All the melting and boiling points of the cycloadducts are well agreed with those appeared in literatures.[8-13,19] $^1$H NMR spectra of **6a—c**,[9] **6d—f**,[20] **6g**,[8] **6h**,[9] and **6i**[20] appeared in literatures are fully agreed with those of specimens prepared here.

**Thermal Treatment of 2 in Pyridine.** A solution of **2** (1.14 g, 5 mmol) in pyridine was heated to reflux for 3 h. The reaction mixture was treated according to the procedure described above. Oily residue, thus obtained, was distilled in vacuo to give two fractions, bp 75 °C/15 mmHg and 110 °C/2 mmHg. The former fraction was found to be benzonitrile (0.20 g, 20% yield) and the latter one found to be ethyl phenylcarbamate (0.28 g, 17% yield) by comparison with authentic specimens.

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