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# Synthesis of Novel 4,5-Dihydro-1,2,4,5-oxatriazine-6-one from the Reaction of Benzonitrile Oxide with 1-Ethoxycarbonyl-1-methylhydrazine

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Benzonitrile oxide (**2**) reacts with 1-ethoxycarbonyl-1-methylhydrazine **3** to give the acyclic hydrazidoxime (**4**) as a stable product, which cyclizes to the novel 4,5-dihydro-1,2,4,5-oxatriazine-6-one (**5**) upon stirring with NaH in dry THF at room temperature. The fragmentation of (**5**) in the mass spectrometer is discussed.

## INTRODUCTION

The reaction of 1,3-dipoles with nucleophiles incorporating suitably located electrophilic centers represents a good method for the synthesis of five, six or seven membered heterocycles depending on the reacting species.[1-3]

Nitrile oxides are reported to react with α-amino acid esters to form 1,2,4-oxadiazine-6-ones.[4] The reaction of nitrile oxides with 1-ethoxycarbonyl-1-methyl- hydrazine (aza analogue of an α-amino acid ester) remains, however, unexplored in the literature. We now report on the synthesis of novel 4,5-dihydro-1,2,4,5-oxatriazine-6-one (**5**) from the above mentioned reactants.

## EXPERIMENTAL

Melting points were determined on Electrothermal Mel. Temp. apparatus and are uncorrected. IR spectra were obtained by using Perkin-Elmer 237 infrared spectrometer in KBr discs. Mass spectra (electron impact) were performed on a Varian CH-7 spectrometer at 70 eV. $^{1}H$- and $^{13}C$-NMR spectra were recorded on a Bruker-AM 300 MHz instrument for solutions in $CDCl_3$ at 21°C, using TMS as an internal reference. Chemical shifts are expressed in δ(ppm) downfield from TMS and coupling constants are in Hertz (Hz). Benzohydroxamoyl chloride (**1**) was prepared by direct chlorination of benzaldoxime according to reported literature procedure.[5] 1-Ethoxycarbonyl-1-methylhydrazine was prepared from the reaction of methylhydrazine and ethyl chloroformate as reported in the literature.[6]

### Synthesis of 2-benzohydroxamoyl-1-ethoxycarbonyl-1-methylhydrazine (4)

Triethylamine (5.0 g, 0.05 mol) in absolute ethanol (10 mL) was dropwise added to a stirred solution of benzohydroxamoyl chloride (3.12 g, 0.02 mol) and 1-ethoxycarbonyl-1-methylhydrazine (5.9 g, 0.05 mol) in absolute ethanol (60 mL) between –10 and 0°C. The temperature of the reaction mixture was then allowed to rise slowly to room temperature and stirring was continued overnight.

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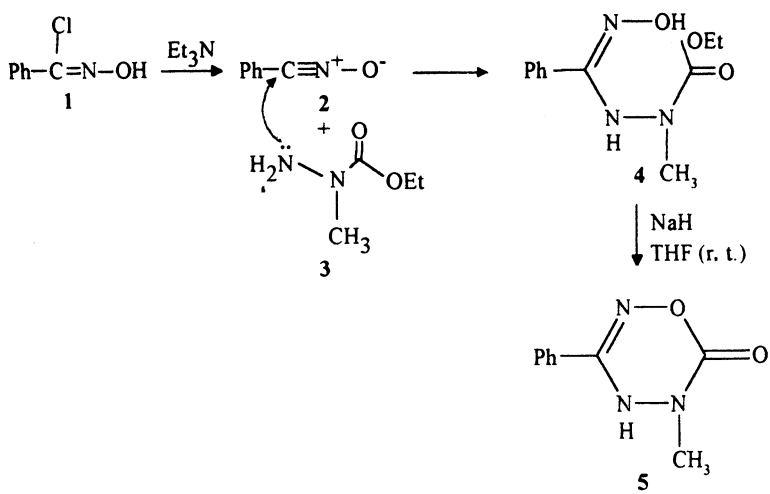
The gelatinous precipitate of the benzonitrile oxide dimer (furoxan) was removed by filtration and the solvent evaporated in *vacuo*. The residual solid was washed with water to get rid of the triethylamine salt, and the residue was crystallized from chloroform/petroleum ether (40–60°C). Yield (1.9 g, 40%). m/z 237 ($M^+$, 30%), 177 (10), 136 (62), 104 (100), 77 (71). $\delta_H$ 1.21 (3 H, t, J 6.5 Hz, —$CH_3$), 3.00 (3H, s, N—$CH_3$), 4.08 (2H, q, J 6.5 Hz, $OCH_2$—); $\delta_C$ 14.55 (—$CH_3$), 38.99 (N—$CH_3$), 62.39 (O—$CH_2$—), 156.12 (C=O), 156.74 (C=N).

**Synthesis of 4,5-dihydro-1,2,4,5-oxatriazine-6-one (5)**

To a stirred solution of **4** (1.2 g, 0.005 mol) in dry THF (30 mL) was carefully added sodium hydride (oil suspension, 0.01 mol) at room temperature. The reaction mixtrue was stirred for 2 h under dry conditions. Sodium hydride was then destroyed using drops of glacial acetic acid until no more bubbles were observed. The solvent was then evaporated in *vacuo* and the product extracted with chloroform (3 times with 20 mL). The combined organic extracts were dried over anhydrous magnesium sulfate and the solvent removed under reduced pressure. The solid product was finally crystallized from chloroform/petroleum ether (40–60°C). Yield (0.84 g, 88%). m/z 191 ($M^+$, 100%), 174 (82), 159 (25), 146 (15), 131 (18), 103 (48), 77 (40), 51 (25), 43 (73). $\delta_H$ 3.51 (3H, s, N—$CH_3$), 12.2 (1H, br. s., NH); $\delta_C$ 33.38 (N—$CH_3$), 142.97 (C=O), 152.27 (C=N).

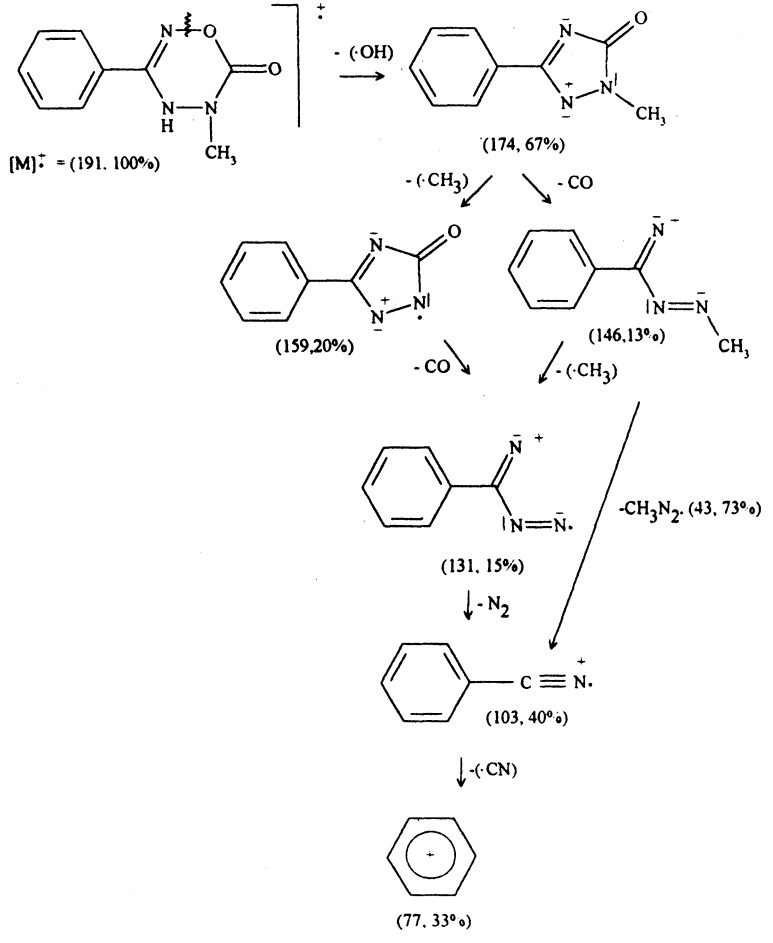
## RESULTS AND DISCUSION

In the present work, we found that 1-ethoxycarbonyl-1-methylhydrazine (**3**) reacts readily with the nitrile oxide (**2**), generated *in situ* from the action of triethylamine onto benzohydroxamoyl chloride (**1**), yielding the acyclic 2-benzohydroxamoyl-1-ethoxycarbonyl-1-methylhydrazine (**4**) in moderate yield. The latter cyclizes almost quantitatively to the corresponding 4,5-dihydro-1,2,4,5-oxatriazine-6-one (**5**) by stirring it with excess sodium hydride in dry tetrahydrofuran for 30 min at room temperature (Scheme I).




Scheme I

Six-membered heterocycles containing oxygen and nitrogen are uncommon. Examples of 1,2,4-oxadiazine-6-ones[4] and 4,5-dihydro-oxatriazines[7] are described by El-Abadelah *et al.* in the last years. To our best of knowledge, 4,5-dihydro-1,2,4,5-oxatriazine-6-one (**5**) is hitherto undescribed in the literature. Comparison of this reaction with that of nitrile oxides with α-amino acid esters shows that the latter reaction gives directly the cyclized product without the possibility of the isolation of the intermediate acyclic adduct. However, this reaction gives the acyclic adduct (**4**) as a stable product that needs a strong base to promote cyclization. This may be attributed to the weak electrophilicity of the C=O of (**3**) due to the electronic effect of the lone pair of electrons present on N—Me group.




Scheme II

Structural assignment of compounds (**4**) and (**5**) is based on elemental analysis and spectral data (Table-1).

TABLE-1
PREPARATION OF AND PHYSICAL DATA FOR COMPOUNDS (**4**) AND (**5**)

| Compd. no. | Yield (%) | m.p. (°C) | Mol. formula (m.w.) | $\nu_{max}/cm^{-1}$ (KBr) | Analysis, Found (Calcd.) % | | |
|---|---|---|---|---|---|---|---|
| | | | | | C | H | N |
| **4** | 40 | 110 | $C_{11}H_{15}N_3O_3$ (237.11) | 3396 ν(OH) 3310 ν(NH) 1668 ν(C=O) | 55.69 (55.86) | 6.37 (6.17) | 17.71 (17.48) |
| **5** | 88 | 197 | $C_9H_9N_3O_2$ (191.07) | 3227 ν(NH) 1677 ν(C=O) | 56.54 (56.66) | 4.74 (4.86) | 21.98 (21.88) |

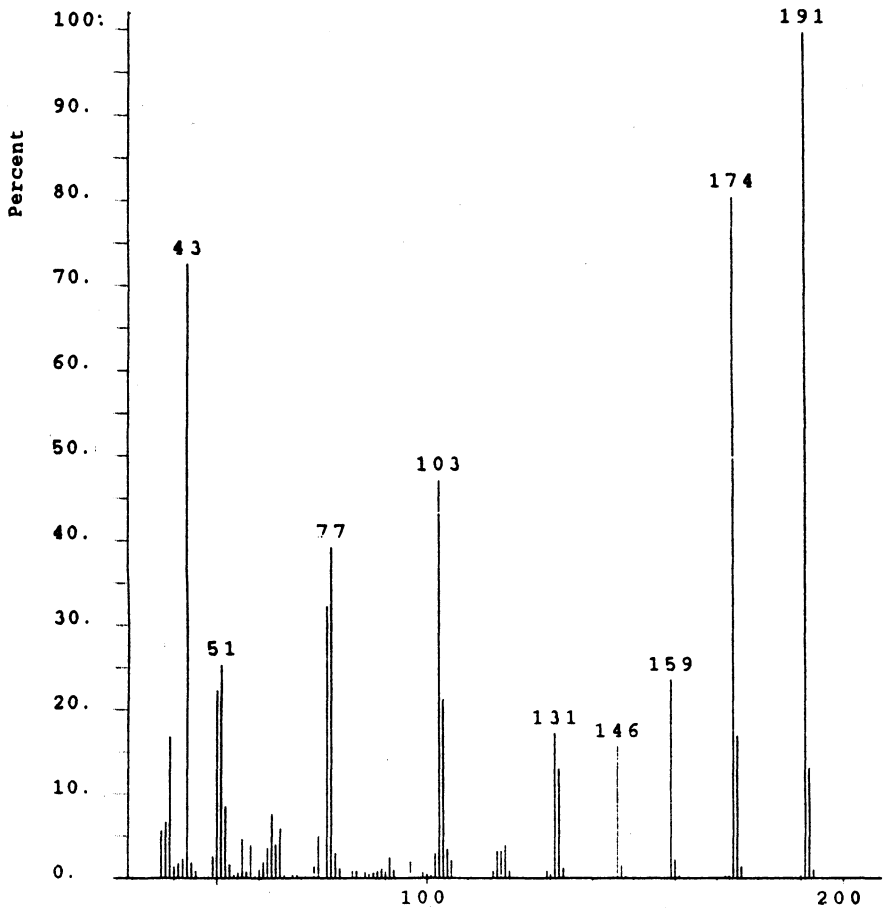



Fig. 1 Mass spectrum of compound 5.

The mass spectra of (**5**) (Figure 1) displays the correct molecular ion as base peak. It shows a fragmentation pathway involving the rupture of the weak N—O bond. Displacement of the H-atom followed by loss of OH radical gives rise to the ion m/e = 174, which suffers further fragmentation as shown in Scheme-II. This ring fragmentation of compound (**5**) could be viewed as unique evidence in support of its structure. The IR spectrum of (**4**) showed characteristic absorption bands at 3396 $cm^{-1}$ ν(OH), 3311 $cm^{-1}$ ν(NH) and 1668 $cm^{-1}$ ν(C=O for the ester carbonyl group).

The signals of the ethyl group in both $^{1}H$- and $^{13}C$-NMR spectra are of particular importance in support of the suggested acyclic structure (**4**). These signals disappear when this compound cyclizes to **5**, and only the NH (12.3 ppm) and N—$CH_3$ (3.5 ppm) appear in addition to the signals of the phenyl ring. The two carbons of this novel heterocyclic system appear at 142.97 ppm (C=O) and 152.27 ppm (C=N). It is noteworthy to mention that the C=O chemical shift changes from 156 ppm in the acyclic adduct (**4**) to 142.97 in (**5**) where it is incorporated within a six-membered hetero ring system and flanked by two electronegative atoms (oxygen and nitrogen).

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