Reaction of Acetone Oxime with Dialkylmalonyl Chlorides. Synthesis of 2-(2-Propenyl)isoxazolidine-3,5-diones and 2,2-*bis*-(2-(4,4-Dialkylisoxazolidine-3,5-dione))propanes

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Reaction of acetone oxime with dialkylmalonyl chlorides in the presence of triethylamine gave as products 2-(2-propenyl)-4,4-dialkylisoxazolidine-3,5-diones **4** and 2,2-*bis*-(2-(4,4-dialkylisoxazolidine-3,5-dione))propanes **5**. The 4,4-dialkylisoxazolidine-3,5-diones **6** and dimethylketoximyl 4,4-dialkylmalonates **7** were formed as minor products. Compounds **4** are stable in refluxing ethanol and in aqueous solution. Compounds **5** are stable when heated in refluxing toluene in the presence of either pyridine or monochloroacetic acid.

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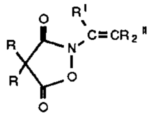
Isoxazolidine-3,5-diones substituted at position-2 are cyclic *N*-substituted analogs of hydroxamic acids. They are generally prepared by the reaction of *N*-substituted hydroxylamines with either malonyl chlorides in the presence of an organic base or malonate esters [1-3]. No examples of either 2-alkenylisoxazolidine-3,5-diones **4** or *N*-alkenylhydroxamic acids appear in the literature. The formation of compounds **4** can be considered to arise by the reaction of the tautomeric forms **1A** of oximes **1** by either of these two literature methods. Because the equilibrium predominately favors **1**, it has not been obvious that either method can be used to prepare **4**.

Reaction of oximes with monocarboxylic acid chlorides to give *O*-acylated oxime esters were reported in the earlier literature [4-6]. However, no examples of the corresponding reaction of oximes with dicarboxylic acid chlorides have been published. As part of our studies involving the synthesis of functionalized five-membered



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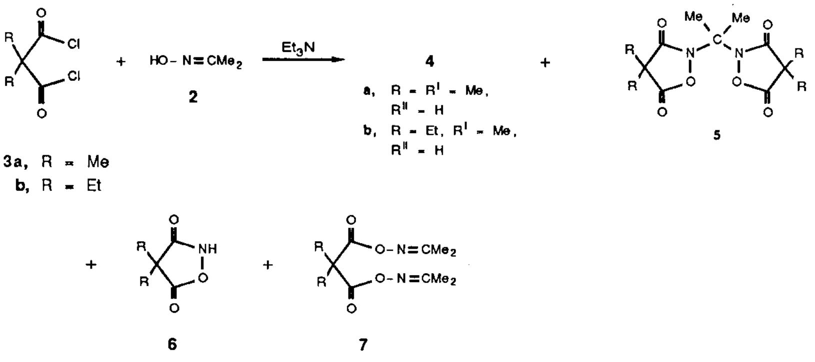

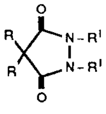

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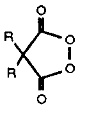

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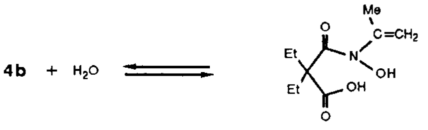

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heterocyclic systems, we investigated the reaction of acetone oxime with malonyl chlorides. Our results are presented in this report.

Acetone oxime (**2**) reacted with dialkylmalonyl chlorides **3** in the presence of triethylamine at 0° to give 2-(2-propenyl)isoxazolidine-3,5-diones **4** and 2,2-*bis*-(2-(isoxalolidine-3,5-dione))-propanes **5** as products. The 4,4-dialkylisoxazolidine-3,5-diones **6** and dimethylketoximyl malonates **7** were formed as minor products. Table I lists the percent yield data for the isolated products. The percent yields of both **4b** and **5b** were significantly increased when the reaction between **2** and **3b** was carried out in the presence of excess triethylamine.

Table I

Products Isolated from the Reaction of Acetone Oxime with Dialkylmalonyl Chlorides

Product	Yield, %
4a	13 [a]
4b	6 [a]
	23 [b]
5a	21 [a]
5b	22 [a]
	51 [b]
6a	2 [a]

[a] The reaction was carried out with a stoichiometric quantity of triethylamine. [b] The reaction was carried out with a 50% excess of triethylamine.

The structures of **4** and **5** were determined from their spectral and elemental analyses data. Products **4** gave abundant ms molecular ion peaks. Products **5** did not show ms molecular ion peaks but showed instead in the high mass region peaks resulting from α-cleavage of an isoxazolidine-3,5-dione radical from the central carbon atom of the molecular ions [7]. The uv spectral data for **4a** and **4b** represent the first reported uv data for isoxazolidine-3,5-diones. The compounds absorbed at λ max (acetonitrile) 222 nm and 223 nm, respectively. These values are intermediate between those of 4,4-dialkylpyrazolidine-3,5-diones **8** and 4,4-dialkyl-1,2-dioxolane-3,5-diones **9**. Compound **8** (R = Et, R′ = H), for example, shows λ max (water) 253 nm (ϵ 3600) [8], and compound **9** (R = *n*-Bu) does not absorb above 210 nm [9,10].

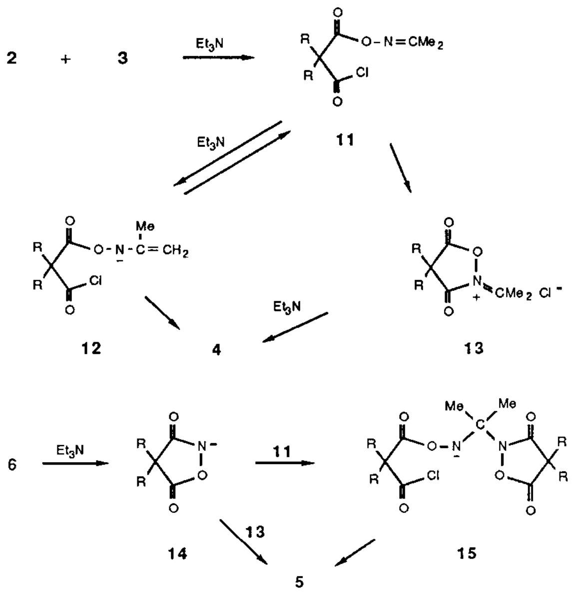
Compound **6a** was isolated as a white crystalline solid. It has been previously reported [1]. Compound **6b** was obtained in low yield as part of a mixture with **5b**. Its presence in the mixture was indicated by mass spectrometry which showed m/z 157.0737 (M^+) and by ^1H nmr spectroscopy which showed the NH bond of **6b** as a broad singlet at δ 9-10. Extraction of a methylene chloride solution of the mixture with aqueous sodium carbonate caused the NH peak of **6b** to be removed from the ^1H nmr spectrum. Similarly, **7a** and **7b** were formed in very low yields and were not isolated pure. Each was observed as a component of a viscous liquid containing **5** and **7**. The ^1H nmr spectrum of each liquid showed the methyl groups of **7** as singlets at δ 1.92 and 2.00. Peak integration indicated that the liquids contained approximately 50% each of **5** and **7**.

It was observed that **4a** slowly decomposed at room temperature over a two-month period as shown by the gradual disappearance of the vinyl proton singlets and the broadening of the upfield methyl group singlet in its ^1H nmr spectrum. Compound **4b** is indefinitely stable at room temperature. In contrast, no products containing an isoxazolidine-3,5-dione moiety could be isolated from the reaction of **2** with **3** (R = H). This latter reaction proceeded very vigorously at 0° to yield a liquid product mixture whose ^1H nmr spectrum indicated that one of the two acyl groups of **3** (R = H) had been lost. It appears then that sufficiently large groups at C-4 of **4** must be present in order to impart stability to the molecule [11].

The stability of products **4b** and **5b** to heat and to nucleophilic solvents was studied. It was found that **4b** was recovered unchanged when heated for 24 hours in refluxing absolute ethanol or when allowed to stand for 24 hours in water:1,2-dimethoxyethane (25:75). In the latter instance the aqueous solution of **4b** was acidic to litmus. This suggests that an equilibrium between **4b** and **10b** was established in the aqueous medium, analogous to the hydrolytic equilibria that are commonly observed in lactones [12a]. This suggests also that the *N*-alkenylhydroxamic acid group in **10b** is stable to aqueous acid. Compound **5b** was recovered unchanged when heated for 24 hours in refluxing toluene in the presence of either pyridine or monochloroacetic acid. The stability exhibited by **4b** and **5b** under these conditions indicates that they are not convertible under the reaction conditions or workup conditions used to isolate them, and, therefore, they must have formed from **2** and **3** by separate reaction pathways.

Products **4** likely arise from the initial formation of oxime ester **11** (Scheme I). Intermediate **11** can lose a methyl hydrogen to triethylamine to give **4** *via* anion **12**. The pK_A of triethylamine hydrochloride is 10.75 [12b], and it is not likely that **11** can be deprotonated by triethylamine to a large extent. However, the concentration of **12** might be sufficiently high to effect an appreciable rate of conversion of **11** to **4** because its negative charge is stabilized by conjugation to the carbon to carbon double bond and by the electron-withdrawing effect of the adjacent oxygen atom. Alternately the weakly basic nitrogen atom of **11** might displace chloride ion to produce the ion-pair intermediate **13** which can then react with triethylamine to yield **4**. If the rate of formation of **13** from **11** is much lower than the rate of deprotonation of **13** to **4**, the presence of excess triethylamine would be expected to enhance the rate of the reaction through **12** but not the rate of the reaction through **13**. The increased yield of **4b** that was observed under this condition is in agreement with the expected enhancement of the former process. However, in the absence of further data neither of the two pathways can be ruled out.

Scheme I



The formation of products **5** is presently not as easily rationalized. A possible explanation involves the intermediacy of **14** derived from **6**. Compounds **6** are likely to be acidic enough to be significantly deprotonated by triethylamine [13]. Addition of **14** to either the carbon to nitrogen double bond of **13** or the carbon to nitrogen double bond of **11** followed by displacement of chloride ion would give **5**.

EXPERIMENTAL

Melting points and boiling points are uncorrected. Infrared spectra were recorded on a Beckman Acculab 10 spectrophotometer. Ultraviolet spectra were obtained on a Beckman DBG spectrophotometer. ^{1}H nmr spectra were recorded on a Varian EM-360A spectrometer. Mass spectra were determined on an AEI-902 mass spectrometer at the Research Triangle Institute of Mass Spectrometry, Research Triangle Park, NC. Elemental analyses were performed by Integral Microanalytical Laboratories, Raleigh, NC. Acetone oxime, diethylmalonyl chloride, and malonyl chloride were purchased commercially. Dimethylmalonyl chloride was prepared by the published procedure [14]. Ethyl ether was dried by distillation over lithium aluminum hydride.

General Procedure for the Reaction of Acetone Oxime (2) with Malonyl Chlorides (13).

A solution containing 3.65 g (5.00 mmoles) of acetone oxime (**2**) and 5.00 mmoles of triethylamine in 150 ml of dry ethyl ether was cooled to 0-5° with stirring. A solution of 5.00 mmoles of the malonyl chloride **3** in 150 ml of dry ethyl ether was added dropwise over 1 hour. Stirring was continued for 1 hour at 0-5°. The precipitate of triethylamine hydrochloride was removed by filtration, and the filtrate was concentrated *in vacuo*, to yield the product residue. When the reaction was carried out with a 50% excess of triethylamine, the ether filtrate was washed with 10% hydrochloric acid to remove the excess triethylamine and dried (magnesium sulfate) prior to concentration.

Reaction of 2 with Dimethylmalonyl Chloride (3a).

The product residue was heated in 65 ml of hot cyclohexane. The hot solution was decanted from an isoluble oil and cooled. The white precipitate was removed by filtration and heated in 15 ml of petroleum ether. The insoluble solid was filtered to give 2% of 4,4-dimethylisoxazolidine-3,5-dione (**6a**) as a white solid, mp 106-109° (lit [8] mp 116-118°); ^{1}H nmr (deuterioacetone): δ 9.45 (br s, 1 H), 1.44 (s, 6 H); ms: m/z, Calcd. for $C_5H_7NO_3$: 129.0425. Found: 129.0428. The petroleum ether filtrate was cooled and filtered to remove pure 2,2-*bis*-(2-(4,4-dimethylisoxazolidine-3,5-dione))propane (**5a**) as white crystals, mp 114-116°; ir (Nujol): 1830, 1760 (s), 1710 (s) cm^{-1}; uv (acetonitrile): λ max 222 nm (ϵ 5200); ^{1}H nmr (deuteriochloroform): δ 2.33 (s, 6 H), 1.73 (s, 12 H); ms: m/z, Calcd. for $C_8H_{12}NO_3$ (M − $C_5H_6NO_3$): 170.0816. Found: 170.0816.

Anal. Calcd. for $C_{13}H_{18}N_2O_6$: C, 52.35; H, 6.08; N, 9.39. Found: C, 52.13; H, 6.05; N, 9.37.

The petroleum ether filtrate was evaporated *in vacuo* to give a small quantity of a viscous liquid containing **5a** and dimethylketoximyl dimethylmalonate (**7a**); ^{1}H nmr (deuteriochloroform): δ 2.33 (s), 2.00 (s), 1.92 (s), 1.73 (s). Treatment with a few ml of petroleum ether dissolved most of the viscous liquid. The mixture was filtered to remove a small quantity of **5a** and concentrated *in vacuo*. The process was repeated. Integration of the ^{1}H nmr spectrum of the resulting viscous liquid indicated the presence of approximately 50% each of **5a** and **7a**. The cyclohexane filtrate was concentrated *in vacuo* to a yellow viscous liquid. Distillation of the liquid gave 13% of 2-(2-propenyl)-4,4-dimethylisoxazolidine-3,5-dione (**4a**) as a colorless liquid, bp 51-72° (0.40 torr). Redistillation gave analytically pure **4a**, bp 55-57° (0.35 torr); ir (neat): 1830 (s), 1735 (s) cm^{-1}; uv (acetonitrile): λ max 258 nm (ϵ 7320), 226 (ϵ 7200); ^{1}H nmr (deuteriochloroform): δ 4.9 (s, 1 H), 4.1 (s, 1 H), 2.15 (s, 3 H), 1.4 (s, 6 H); ms: m/z (relative intensity): 169 (89) M$^+$, 70 (97) $Me_2C=C=O^+$, 55 (100).

Anal. Calcd. for $C_8H_{11}NO_3$: C, 56.79; H, 6.56; N, 8.28. Found: C, 56.55; H, 6.72; N, 8.11.

Reaction of 2 with Diethylmalonyl Chloride (3b). A. In the Presence of a Stoichiometric Quantity of Triethylamine.

The viscous product residue was distilled under reduced pressure to give a fraction, bp 64-79° (0.30 torr), and a fraction, bp 75-106° (0.30 torr). The higher boiling fraction solidified on standing. It was recrystallized from petroleum ether to give 2,2-*bis*-(2-(4,4-diethylisoxazolidine-3,5-dione))propane (**5b**) as a white solid, mp 78-80°; ir (Nujol): 1845 (s), 1740 (s) cm^{-1}; uv (acetonitrile): λ max 223 nm (ϵ 8540); ^{1}H nmr (deuteriochloroform): 2.1 (s, 6 H), 1.9 (q, 8 H), 0.9 (t, 12 H); ms: m/z, Calcd. for $C_{10}H_{16}NO_3$ (M - $C_7H_{10}NO_3$): 198.1129. Found: 198.1133.

Anal. Calcd. for $C_{17}H_{26}N_2O_6$: C, 57.61; H, 7.39; N, 7.90. Found: 57.31; H, 7.46; N, 7.71.

The lower boiling fraction was redistilled to give analytically pure 2-(2-propenyl)-4,4-diethylisoxazolidine-3,5-dione (**4b**), bp 64-66° (0.30 torr); ir (neat): 1830 (s), 1740 (s), 1655 (m) cm^{-1}; uv (acetonitrile): λ max 226 nm (ϵ 6840), 250 (ϵ 5120); ^{1}H nmr (deuteriochloroform): δ 5.0 (s, 1 H), 4.6 (s, 1 H), 2.22 (s, 3 H), 1.9 (q, 4 H), 0.80 (t, 6 H); ms: m/z (relative intensity) 197 (82) M$^+$, 98 (39) ($Et_2C=C=O^+$), 55 (100).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.66; N, 7.10. Found: C, 60.86; H, 7.88; N, 7.32.

B. In the Presence of Excess Triethylamine.

The viscous product residue was distilled under reduced pressure to yield **4b**, bp 65-68° (0.32 torr), and a fraction, bp 71-118° (0.32 torr) which solidified on standing. The solidified fraction was heated in petroleum ether. A small quantity of an insoluble solid containing 4,4-diethylisoxazolidine-3,5-dione (**6b**) was removed by filtration; ^{1}H nmr (deuterioacetone): δ 9-10 (br s); ms: m/z, Calcd. for $C_7H_{11}NO_3$: 157.0738. Found: 157.0737. The petroleum ether filtrate was cooled and filtered to yield pure **5b**, mp 78-80°. The petroleum ether filtrate was concentrated *in vacuo* to give a small quantity of a viscous liquid containing **5b** and dimethylketoximyl diethylmalonate (**7b**); ^{1}H nmr (deuteriochloroform): δ 2.10 (s), 2.00 (s), 1.92 (s), 1.9 (m), 0.9 (m). The viscous liquid was treated two times with petroleum ether as described for **7a**. Integration of the resulting ^{1}H nmr spectrum indicated the presence of approximately 50% each of **5b** and **7b**.

Stability of 2-(2-(Propenyl)-4,4-diethylisoxazolidine-3,5-dione (**4b**).

Solutions containing 1.00 g (5.08 mmoles) each of **4b** were prepared in 15 ml of absolute ethanol, 15 ml of absolute ethanol at reflux, and 15 ml of water:1,2-dimethoxyethane (25:75) at room temperature, respectively. After 24 hours the solvent was removed from each solution *in vacuo*, and the residues were analyzed by ^{1}H nmr spectroscopy. Only unchanged **4b** was isolated in each case.

Stability of 2,2-*bis*-(2-(4,4-Diethylisoxazolidine-3,5-dione))propane (**5b**).

Solutions containing 0.70 g (2.2 mmoles) each of **5b** were prepared in 40 ml of toluene, 40 ml of toluene and 1.0 ml of pyridine, and 40 ml of toluene and 0.10 g of monochloroacetic acid, respectively. The solutions were heated at reflux for 24 hours, concentrated *in vacuo*, and analyzed by ^{1}H nmr spectroscopy. Only unchanged **5b** was isolated in each case.

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[10] Compound **9** shows uv $n \rightarrow \pi^*$ transitions at λ max 250 nm (ϵ 100) and 350 nm (ϵ 8.4). See ref [9].

[11] It is possible that the reaction between **2** and **3** (R = H) followed a different route than those involving **3a,b** because of the presence of the acidic hydrogens in **3** (R = H). Acyl halides are known to undergo dehydrohalogenation with tertiary amines. See W. E. Hanford and J. C. Sauer, *Org. React.*, **3**, 108 (1946).

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