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Starting from 2,5-hexanedione (**4**), a one-pot preparation of 3-acetyl-5-methylisoxazole (**1**) is described. 3-Acetyl-5-methylisoxazole (**1**) is a useful compound for the preparation of 3-oxobutyronitrile (**10**) and for 3-vinyl-(5-methyl isoxazolyl) ketone (**2**).

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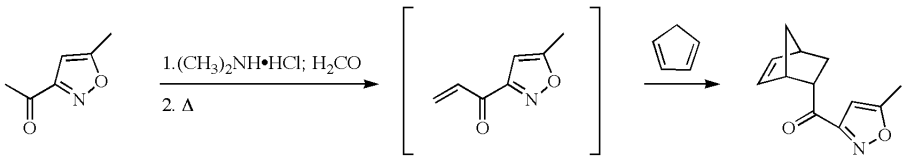
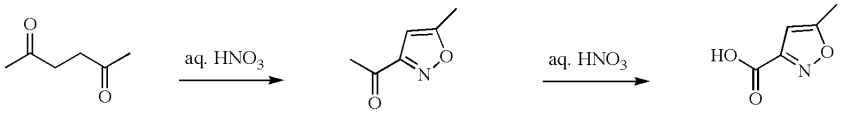
During studies relating to the photochemistry of the norbornenyl isoxazole ketone **3**, a synthesis of 3-acetyl-5-methylisoxazole (**1**) was required.[1]



1 **2** **3**

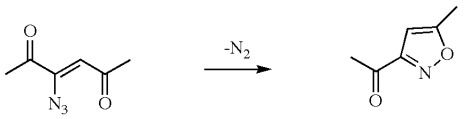
Figure 1

A known preparation of 3-acetyl-5-methylisoxazole (**1**) involves a nitric acid oxidation of an aqueous solution of 2,5-hexanedione (**4**).[2] In our laboratories, this procedure yielded varying amounts of isoxazole ketone **1** and 5-methylisoxazolyl-3-carboxylic acid (**5**). Although these compounds could be readily separated from one another, this oxidation was extremely violent in that the heat of reaction from the oxidation was able to maintain a sustained reflux. This temperature was required in order to ensure a complete consumption of starting material **4**. For use in the synthesis of ketone **3** and also, ultimately for the study of the photochemistry of isoxazole ketone **1**, a safer and more reliable procedure was required [1,3].



4 **1** **5**

Figure 2



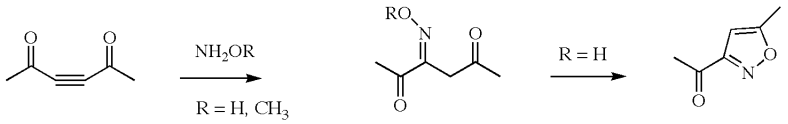
6 **1**

Figure 1

Although the isoxazole ketone **1** could be prepared from *Z*-3-azido-3-hexene-2,5-dione (**6**), a more direct approach would use 2,5-hexanedione (**4**) as the starting material.[3]

We had also considered the addition of hydroxylamine to diacetylacetylene (**7**) since this method was useful for the preparation of hexane-2,3,5-trione-3-(*O*-methyoxime) (**9**) [4]. This potential method was compromised by the fact that diacetylacetylene (**7**) is not a shelf stable compound and the preparation of gram quantities of this compound is hindered by its instability. For our purposes, a reliable multi-gram preparation was necessary.

In the method described by Cusmano, 2,5-hexanedione (**4**) is initially nitrosated to yield *in-situ* hexane-2,3,5-trione-3-oxime (**8**) [2]. Cyclization and dehydration of oxime



7 R = H, **8**
R = CH_3, **9** **1**

Figure 4

8 affords the isoxazole ketone **1**. Due to the harsh reaction conditions, this isoxazole ketone **1** is subsequently nitrosated and undergoes an abnormal Beckman rearrangement to ultimately yield the carboxylic acid **5** [5]. If milder conditions could be developed for the initial nitrosation, then the subsequent nitrosation could be suppressed.

Attempts to use nitrous acid as a reagent were unsuccessful due to the fact that ketone **4** was unreactive under conditions by which this reagent was stable. The use of commercially available isoamyl nitrite was fruitful in converting the ketone to the isoxazole; however the separation of the by-product, isoamyl alcohol, from the ketone by distillation was difficult. For this reason, we investigated the use of ethyl nitrite as a nitrosating agent.

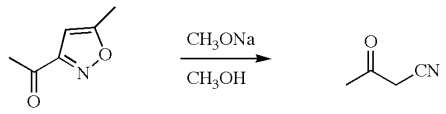
Concentrated hydrochloric acid was added to a neat 40 °C solution of 2,5-hexanedione (**4**). A gaseous stream of ethyl nitrite was slowly added to the solution and the reaction temperature was maintained below 50 °C. The course of the reaction was monitored by ^{1}H nmr. The reaction was selective and there was no evidence for nitrosation at the methyl group of either the starting material **4** or the product **1**. After an extractive workup, the product was distilled to afford a 67% yield of the 3-acetyl-5-methylisoxazole (**1**). The spectral properties of the ketone **1** were in agreement with the product obtained by the nitric acid oxidation of 2,5-hexanedione (**4**).

4 **1**

Figure 5

In addition to its use as a substrate for the preparation of the vinyl isoxazole ketone **2**, this isoxazole ketone **1** proved to be useful for the synthesis of 3-oxobutyronitrile (**10**). In the course of the study on the photochemistry of isoxazole ketone **1**, a product that was observed was cyanoacetone (**10**) [6]. A known method to prepare cyanoacetone (**10**) is by the base-catalyzed cleavage of 5-methylisoxazole in which the driving force in this cleavage reaction is the formation of the carbanion of cyanoacetone [7]. Alternatively, this same anion can be generated by the base-catalyzed cleavage of isoxazole ketone **1**. As expected, treatment of isoxazole ketone **1** with sodium methoxide in methanol afforded cyanoacetone (**10**) in a 75% yield. The spectral properties of this compound were in agreement with the assigned structure.

In summary, a convenient one-pot procedure for the preparation of isoxazole ketone **1** is described. In addition, uses for this ketone **1** such as a substrate in the Mannich



1 **10**

Figure 6

reaction as well as for the preparation of 3-oxobutyronitrile (**10**) are also disclosed. The preparation of cyanoacetone (**10**) and related compounds from the isoxazole ketone **1** and its derivatives may also have potential utility in combinatorial synthesis due to the fact that the isoxazole ketone **1** is a latent protecting group for cyanoacetone (**10**) [8]. Tethering of the acyl group to a polymer chain by polymerization of ketone **2**, followed by base-catalyzed cleavage would allow for release of the cyanoacetone fragment from the polymer [9].

Further, addition of an *O*-resin-bound hydroxylamine reagent to diacetylacetylene (**7**) and related compounds, followed by deprotection, would also allow for a combinatorial synthesis of isoxazoles [10,11]. Although diacetylacetylene (**7**) is not a stable compound, when neat, its good reactivity in the conjugate addition reaction with methoxyamine may be useful in solid state synthesis wherein the reactivity of the polymer-bound nucleophile is reduced [12]. In addition, the likely acidity of carbon 4 in polymer-bound derivatives of oxime **9** may allow for the introduction of additional functionality at the 4 position of 3-acyl substituted isoxazole ketones.

Acknowledgement.

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EXPERIMENTAL

3-Acetyl-5-methylisoxazole (**1**).

2,5-Hexanedione (**4**) (42.8 g, 0.375 mole) was heated to 40 °C at which point, 4.5 mL (0.055 mole) of concentrated hydrochloric acid was added. Ethyl nitrite was generated by the addition of a solution of 54.36 g (0.79 mole) of sodium nitrite in a mixture of 24 mL of 95% ethanol and 215 mL of water to a solution of 22 mL of sulfuric acid in a mixture of 24 mL of 95% ethanol and 215 mL of water [13,14]. Ethyl nitrite was bubbled into the reaction mixture over a 6.5 hour period while maintaining the temperature below 50 °C. Upon completion of the reaction as evident by ^{1}H nmr, the batch was cooled and ether was added. The organic layer was washed with saturated sodium bicarbonate solution and saturated sodium chloride solution. The organic layer was dried over magnesium sulfate and the solvent was evaporated. The product was distilled at 73-77 °C at 13 mm (lit 76-77 °C at 19 mm)[15] to afford 31.30 g (67%) of 3-acetyl-5-methylisoxazole (**1**); ir (film): 1701 (C=O), 1600 (C=N), 1460,

1361 (C-O), 1271, 1181, 1149 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.50 (s, 3H, CH_3), 2.60 (s, 3H, CH_3), 6.30 (s, 1H, CH); uv (acetonitrile): λ = 306 (ε = 77.5), λ = 245 (ε = 1950).

3-Oxobutyronitrile (**10**).

Under a nitrogen atmosphere, 0.30 g (0.013 mole) of sodium was added to 25 mL of methanol. After the reaction had subsided, 1.25 g (0.01 mole) of 3-acetyl-5-methylisoxazole (**1**) was added. The solution was heated to reflux for 5 hours. The solvent was removed under vacuum and ether and water were added. The layers were separated and the aqueous layer was washed with additional ether. The aqueous layer was acidified with concentrated hydrochloric acid and saturated with solid sodium chloride. Drying over magnesium sulfate was followed by evaporation of the solvent. There was obtained 0.62 g (75%) of impure 3-oxobutyrontrile (**10**). A molecular distillation at 50 °C and 0.6 mm (lit bp 92-94 °C at 10 mm)[16] purified the product; ir (methylene chloride): 3497-3401, 2252 (C≡N), 1730 (C=O), 1600 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.37 (s, 3H, CH_3), 3.46 (s, 2H, CH_2).

Hexane-2,3,5-Trione-3-(*O*-methyloxime) (**9**).

To a magnetically stirred solution of 0.33 g (5.00 mmole) of potassium hydroxide in 2 mL of water, 10 mL of chloroform was added. Methoxyamine hydrochloride (0.42 g, 5 mmole) was added and the mixture was held for 5 minutes. Hex-3-yne-2,5-dione (**7**) (0.55 g, 5 mmole) was added. After the addition, the reaction was complete as shown by ^1H nmr. Drying of the chloroform layer over magnesium sulfate was followed by evaporation of the solvent. There was obtained 0.70 g (89%) of hexane-2,3,5-trione-3-(*O*-methyloxime) (**9**). An analytical sample was prepared by flash chromatography using a mixture of 65% hexane and 35% ethyl acetate as the eluent; ir (film): 1721 (C=O), 1689 (C=O), 1600 (C=N), 1361 cm^{-1}. ^1H nmr (deuteriochloroform): δ 2.17 (s, 3H, CH_3), 2.40 (s,3H, CH_3), 3.62 (s, 2H, CH_2), 4.05 (s, 3H, OCH_3).

Anal. Calcd. For $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.30; H, 7.44; N, 8.89.

Hex-3-yne-2,5-dione (**7**).

To a mechanically stirred, -10 °C, solution of 34.24 g (0.3 mole) of hex-3-yne-2,5-diol in 300 mL of spectrograde acetone, a solution of 3.2 *M* CrO_3 in 4 *M* aqueous H_2SO_4 (127 mL, 0.41 mole) was added slowly over a 2 hour period. Saturated sodium chloride solution (300 mL) was added and the supernatant was decanted. The reduced salts were washed with 600 mL of ether. The organic layer was separated and the aqueous layer was extracted with an additional 300 mL of ether. The organic extracts were combined and washed with aqueous sodium bicarbonate solution (250 mL) and saturated sodium chloride solution (100 mL). The organic layer was dried over magnesium sulfate and the dessicant was removed by filtration. After the solvent was evaporated, the product was fractionally distilled at 58-60 °C and 0.25 mm (lit bp 57-63 °C at 0.10 mm) [17b] to afford 18.53 g (55% yield) of 5-hydroxy-hex-3-yne-2-one (**11**) [17,18]; ^1H nmr (deuteriochloroform): δ 1.56 (d, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.40 (b, 1H, OH), 4.66 (q, 1H, CH).

To a –10 °C solution of 5.6 g (0.05 mole) of 5-hydroxy-hex-3-yne-2-one (**11**) in 50 mL of spectrograde acetone, a 3.2 *M* CrO_3 solution in 4 *M* sulfuric acid (11 mL, 3.3 mmole) was added over a 0.5 hour period. The suspension was stirred for an additional 0.5 h. Saturated sodium chloride solution (50 mL) was added; the inorganic salts were filtered and the cake was washed with 100 mL of ether. The layers were separated and the aqueous layer was extracted with an additional 50 mL of ether. The combined organic layers were washed with saturated sodium bicarbonate solution (50 mL), saturated sodium chloride solution (50 mL) and dried over magnesium sulfate. The solvent was evaporated at room temperature at reduced pressure. The product was distilled at 20-25 °C and 0.2 mm. (lit bp 26-38 °C at 0.1 mm) [17b] and condensed in a Dry Ice-acetone bath to yield 2.21 g (40% yield) of hex-3-yne-2,5-dione (**7**) as a yellow oil [18]; ir (film): 1715 (C=O), 1361, 1220 cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.36 (s, 6H, CH_3).

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