1,4-Diketones via Isoxazole Intermediates

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Reductive ring cleavage reactions of 3,5-disubstituted isoxazoles to α,β-unsaturated 1,4-ketones are reported. The 2,5-undecanedione (**5**) was prepared by two different procedures starting from the masked isoxazoles **2** and **6**. Conversion of **2** and **6** to α,β-unsaturated ketones **3** and **10**, followed by selective reduction with an iron-based complex under mild reaction conditions and removal of the protecting ketal group, gave **5**.

Although a number of methods have been described for the preparation of 1,4-diketones, new routes are still popular synthetic goals.[1]

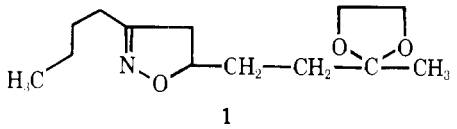
The efficiency of a new route is invariably measured by the ease of synthesis of undecane-2,5-dione (**5**), the precursor of dihydrojasmone. In connection with our interest in the construction of substances by means of 3,5-disubstituted isoxazole intermediates, we wish to report a novel approach to 1,4-dicarbonyl compounds starting from disubstituted isoxazoles **2** and **6**.

The recently disclosed procedures for the ring cleavage of these heterocycles[2-4] to isomeric α,β-unsaturated ketones are of interest in that they provide the possibility for the construction of a wide range of functionalized carbon chains, which can be further elaborated.

Reaction of the nitriloxide generated in situ[5] from 1-nitropentane and 2-methyl-2-(3-butenyl)-1,3-dioxolane[6] afforded isoxazoline **1**, which was quantitatively transformed by means of active γ-MnO_2[7] into the corresponding isoxazole **2**. The latter compound was also prepared directly when 2-methyl-2-(3-butynyl)-1,3-dioxolane[8] was used as the dipolarophile.

Reduction[2] of **2** with sodium in liquid ammonia in the presence of *tert*-butyl alcohol gave enone **3** in excellent yield. The transformation of **3** into saturated ketone **4** proceeded smoothly via hydridoiron complexes.[9]

Deketalization of **4** by mild acid treatment led to known **5**,



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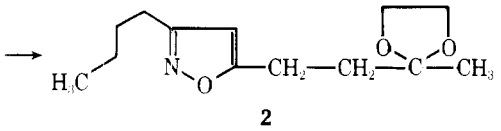

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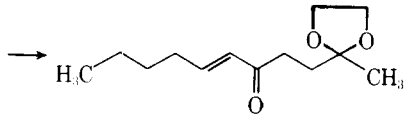

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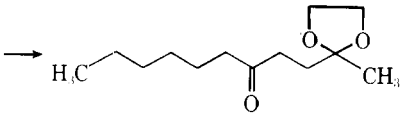

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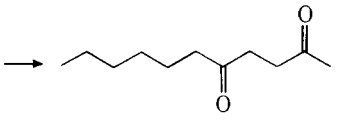

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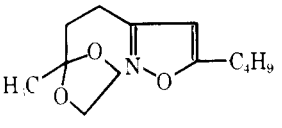
which was further characterized by conversion of **5** into dihydrojasmone[10] in essentially a quantitative yield.

Diketone **5** was also prepared by an alternative reaction sequence utilizing isoxazole **6**, which is readily available from the reaction of the nitriloxide derived from 2-methyl-2-(3-nitropropyl)-1,3-dioxolane[11] and 1-hexyne.

Reductive ring opening of isoxazole **6** and subsequent benzoylation of the resulting vinylogous amide **7** gave **8**. Hydride reduction of **8** afforded **9**, which, without purification, yielded **10** on treatment with dilute sulfuric acid.

Enone **10** was converted to **5** as mentioned[9] above.



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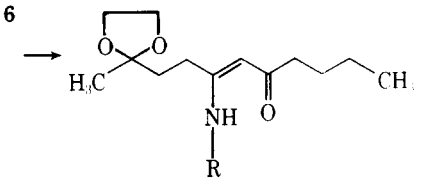
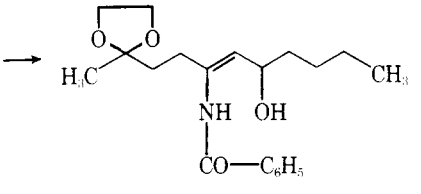


7, R = H
8, R = COC_6H_5



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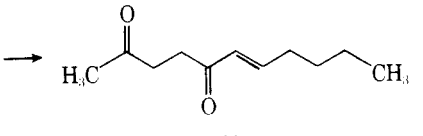

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Since a large variety of 3,5-disubstituted isoxazoles can be readily prepared from two independent units, the utilization of these isoxazoles as synthons in the construction of functionalized 1,4-diketones should prove to be of general synthetic value.

Experimental Section

Melting and boiling points are uncorrected. NMR spectra were recorded on a Hitachi Perkin-Elmer R24A instrument using Me_4Si as an internal standard; IR spectra were run on a IR Perkin-Elmer Model 257. Column chromatography was carried out using silica gel with Et_2O–petroleum ether (1:1) as the eluting solvent. Anhydrous sodium sulfate was used for all drying operations.

3-Butyl-5-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]-Δ^2-isoxazoline (1). Phenyl isocyanate (12.5 mL, 0.11 mol) in 20 mL of ben-

0022-3263/79/1944-0105$01.00/0

zene was added dropwise to a solution of 1-nitropentane (5.7 g, 0.049 mol) and 2-methyl-2-(3-butenyl)-1,3-dioxolane[6] (9 g, 0.063 mol) in 40 mL of benzene containing several drops of triethylamine. The mixture was stirred overnight and then refluxed for 2 h. The precipitated diphenylurea was removed by filtration and the filtrate concentrated in vacuo. The residue was chromatographed on silica gel to afford 8.0 g (68%) of **1** as an oil: bp 102–103 °C (0.01 mm); NMR (CCl_4) δ 0.9 (t, 3 H, J = 6 Hz), 1.27 (s, 3 H), 2.44 (dd, 1 H, J = 17 and 8 Hz), 2.93 (dd, 1 H, J = 17 and 10 Hz), 3.82 (s, 4 H), 4.1–4.5 (m br, 1 H). Anal. Calcd for $C_{13}H_{23}NO_3$: C, 64.70; H, 9.61; N, 5.80. Found: C, 64.61; H, 9.53; N, 5.71.

3-Butyl-5-[2-(2-methyl-1,3-dioxolan-2-yl)-ethyl]isoxazole (2). Isoxazoline **1** (4 g, 0.016 mol) in 60 mL of benzene was refluxed for 10 h in the presence of active γ-MnO_2 (20 g) as previously described.[7] Filtration of the reaction mixture through Celite and evaporation of the solvent afforded 3.64 g (92%) of **2**: bp 98–100 °C (0.01 mm); NMR ($CDCl_3$) δ 0.93 (t, 3 H, J = 6 Hz), 1.48 (s, 3 H), 3.9 (s, 4 H), 5.85 (s, 1 H); IR (film) 1600 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.20; H, 8.79; N, 5.72.

Compound **2** was also prepared directly from the reaction of 2-methyl-2-(3-butynyl)-1,3-dioxolane[8] and 1-nitropentane in 70% yield utilizing the procedure outlined above for the synthesis of **1**. The NMR spectrum was identical to that derived from the MnO_2 oxidation reaction.

1-(2-Methyl-1,3-dioxolan-2-yl)-4-nonen-3-one (3). Sodium was added to a stirred mixture of isoxazole **2** (2.39 g, 0.01 mol), *tert*-butyl alcohol (2.23 g, 0.03 mol), and THF (30 mL) in 200 mL of liquid ammonia until the solution remained dark blue. The reaction mixture was stirred for an additional 20 min and NH_4Cl was then added to obtain decolorization. The ammonia was evaporated and the residue extracted with Et_2O. The residue, after evaporation of the solvent, was dissolved in toluene (20 mL) containing a trace of *p*-toluenesulfonic acid. The resulting reaction mixture was refluxed for 24 h, concentrated in vacuo, and chromatographed to give 1.98 g (88%) of **3**: NMR (CCl_4) δ 0.89 (t, 3 H, J = 5 Hz), 3.8 (s, 4 H), 5.9 (dt, 1 H, J = 2 and 16 Hz), 6.7 (dt, 1 H, J = 7 and 16 Hz); IR (film) 1665 and 1630 cm^{-1}. Anal. Calcd for $C_{13}H_{22}O_3$: C, 68.99; H, 9.80. Found: C, 68.82; H, 9.69.

1-(2-Methyl-1,3-dioxolan-2-yl)-3-nonanone (4). Reaction of **3** (1.98 g, 0.0088 mol) with the reducing agent prepared in situ[9] from $Fe(CO)_5$ and NaOH in 95% MeOH and subsequent chromatography afforded 1.84 g (92%) of **4**: NMR (CCl_4) δ 0.86 (t, 3 H, J = 5 Hz), 1.2 (s, 3 H), 3.8 (s, 4 H); IR (film) 1710 cm^{-1}. Anal. Calcd for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.23; H, 10.63.

3-[2-(2-Methyl-1,3-dioxolan-2-yl)-ethyl]-5-butylisoxazole (6). Cycloaddition of 2-methyl-2-(3-nitropropyl)-1,3-dioxolane[11] (3.5 g, 0.02 mol) and 1-hexyne (4 g, 0.0476 mol) following the procedure described above for the preparation of **1** afforded 3.82 g (80%) of **6**: NMR (CCl_4) δ 0.9 (t, 3 H, J = 6 Hz), 1.2 (s, 3 H), 3.8 (s, 4 H), 5.8 (s, 1 H); IR (film) 1600 cm^{-1}. Anal. Calcd for $C_{13}H_{21}NO_3$: C, 65.24; H, 8.85; N, 5.85. Found: C, 65.30; H, 8.75; N, 5.69.

1-(2-Methyl-1,3-dioxolan-2-yl)-3-amino-3-nonen-5-one (7). Reduction of **6** (2.39 g, 0.01 mol) with H_2 in MeOH in the presence of PtO_2 and subsequent removal of the catalyst and solvent afforded a quantitative yield of **7**: NMR ($CDCl_3$) δ 0.9 (t, 3 H, J = 6 Hz), 1.3 (s, 3 H), 3.9 (s, 4 H), 5.0 (s, 1 H), 9.7 (s br, 2 H); IR (film) 3350, 1620, and 1525 cm^{-1}.

Compound **7** was benzoylated without further purification.

1-(2-Methyl-1,3-dioxolan-2-yl)-3-benzamido-3-nonen-5-one (8). Reaction of **7** (2.41 g, 0.01 mol) and benzoyl chloride (1.4 g, 0.01 mol) in 10 mL of anhydrous pyridine gave 2.97 g (86%) of **8**: mp 73 °C (Et_2O–petroleum ether 1:1); NMR ($CDCl_3$) δ 0.9 (t, 3 H, J = 6 Hz), 1.4 (s, 3 H), 3.9 (s, 4 H), 5.5 (s, 1 H), 7.4–8.3 (m, 5 H), 13.3 (s br, 1 H); IR ($CHCl_3$) 3200, 1690, 1630 and 1600 cm^{-1}. Anal. Calcd for $C_{20}H_{27}NO_4$: C, 69.54; H, 7.88; N, 4.06. Found: C, 69.45; H, 7.93; N, 3.98.

6-Undecene-2,5-dione (10). A solution of **8** (2.96 g, 0.008 mol) in 40 mL of MeOH was treated with $NaBH_4$ (0.5 g, 0.0132 mol) at room temperature and the resulting reaction mixture was stirred for 4 h. H_2O (40 mL) was added and the reaction mixture was extracted with two 15-mL portions of CH_2Cl_2. To the combined organic extracts was added dilute H_2SO_4 (16 mL) and the reaction mixture was stirred for 12 h at room temperature. After usual workup the residue was purified by chromatography to afford 1.19 g (76%) of **10**: NMR (CCl_4) δ 0.86 (t, 3 H, J = 6 Hz), 2.7 (s, 3 H), 6.0 (dt, 1 H, J = 16 and 2 Hz), 6.73 (dt, 1 H, J = 16 and 7 Hz); IR (film) 1720, 1680, and 1625 cm^{-1}; 2,4-dinitrophenylhydrazone mp 166–167 °C (ethyl acetate). Anal. Calcd for $C_{23}H_{26}N_8O_8$: C, 50.92; H, 4.83; N, 20.65. Found: C, 50.99; H, 4.77; N, 20.59.

2,5-Undecanedione (5). Known[10] **5** was obtained in 75% yield from the hydrolysis of **4** with dilute HCl for 5 h at room temperature or in 72% yield by reducing **10** as previously described[9] above for the reduction of **4**.

Transformation of **5** into dihydrojasmone was achieved according to known procedures.[10]

Registry No.—**1**, 68036-48-6; **2**, 68036-49-7; **3**, 68036-50-0; **4**, 55834-23-6; **5**, 7018-92-0; **6**, 68036-51-1; **7**, 68036-52-2; **8**, 68036-53-3; **9**, 68036-54-4; **10**, 68036-55-5; **10** 2,4-DNP, 68036-56-6; 1-nitropentane, 628-05-7; 2-methyl-2-(3-butenyl)-1,3-dioxolane, 20449-21-2; 2-methyl-2-(3-nitropropyl)-1,3-dioxolane, 19639-74-8; 1-hexyne, 693-02-7.

References and Notes

(1) For recent synthesis of 1,4-dicarbonyl compounds, see M. Miyashita, T. Yanomi, and A. Yoshikoshi, *J. Am. Chem. Soc.*, **98**, 4679 (1976), and references cited therein.
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