Synthesis of (*E*)-4-Oxonon-2-enoic Acid, a Natural Antibiotic Produced by *Streptomyces olivaceus*

Roberto Ballini* and Giovanna Bosica

Dipartimento di Scienze Chimiche dell'Università, via S. Agostino no. 1, 62032 Camerino, Italy

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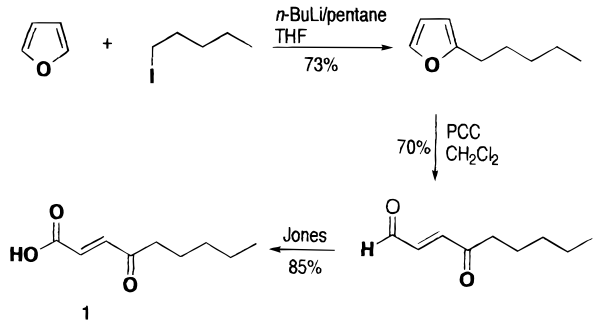
(*E*)-4-Oxonon-2-enoic acid (**1**), a natural antibiotic produced by *Streptomyces olivaceus,* has been conveniently prepared in three steps starting from furan.

(*E*)-4-Oxonon-2-enoic acid (**1**) has been recently isolated by Pfefferle et al.[1] from the mycelium of *Streptomyces olivaceus* Tu 4018. This compound had not been described previously as a natural product but has been made synthetically in the course of a new method for the preparation of (*E*)-3-acylprop-2-enoic acids.[2] Compound **1** is important for its antibacterial activity against various Gram-positive and Gram-negative strains, especially *Staphylococcus aureus* ATCC 11632. Apart from the synthesis previously reported,[2] which starts from the very expensive 3,3-diethoxyprop-1-yne, there are no other literature reports for the preparation of **1**.

Based on our experience during the synthesis of pyrenophorin,[3] we wish now to report a new, convenient synthesis of (*E*)-4-oxonon-2-enoic acid, starting from furan. As outlined in Scheme 1, the monoalkylation of furan was performed using one equivalent of butyllithium and one equivalent of 1-iodopentane. The furan derivative obtained (73%) was then cleaved by an excess (5 times) of (PCC)[4] in CH_2Cl_2 to yield (*E*)-4-oxo-2-nonenal (70%). Finally, further oxidation of 4-oxo-2-nonenal with Jones' reagent afforded the (*E*)-4-oxonon-2-enoic acid in 85% yield (43% overall). Physical properties of the synthetic sample agree well with those reported by the original authors.[1]

Scheme 1



Experimental Section

General Experimental Procedures. IR spectra were recorded with a Perkin−Elmer 1310 spectrophotometer. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 200 MHz on a Varian Gemini 200 spectrometer. Chemical shifts were recorded relative to internal TMS. MS were determined on a Hewlett−Packard GC/MS 5970 (EI, 70 eV). Reactions were monitored with a Carlo Erba Fractovap 4160 gas chromatograph using a capillary column of Duran glass (0.32 mm × 25m), stationary phase OV1 (film thickness 0.4−0.45 nm) or by TLC. Flash chromatography was performed[5] on Merck SiO_2 gel (0.040−0.063 mm) with hexanes−EtOAc as eluent. Microanalyses were performed using a Fisons model EA 1108.

1-(2-Furyl)pentane. Furan (2 g, 29 mmol) in dry THF (120 mL) was metalated, under nitrogen, by using *n*-butyllithium (18.36 mL of 1.6 M solution in hexane, 29 mmol) at −20 °C. After the solution was stirred for 2 h, 1-iodopentane (5.8 g, 29 mmol) in THF (16 mL) was added. The solution was stirred at −20 °C for 1 h and then at room temperature for another hour. The reaction mixture was quenched with H_2O (16 mL) and the aqueous layer extracted (1:1 Et_2O−pentane). The combined organic layer was washed with 5% sodium bisulfite aqueous solution, H_2O, and brine. The crude organic layer was dried ($MgSO_4$), and the solvents were removed under vacuum. The crude product was purified by column chromatography (95:5, cyclohexane−EtOAc) affording 2.9 g (73%) of pure 1-(2-furyl)pentane, as an oil: ^1H NMR δ 0.9 (t, 3H, J = 7.3 Hz), 1.23−1.40 (m, 4H), 1.58−1.70 (m, 2H), 2.61 (t, 2H, J = 7.7 Hz), 5.93−5.98 (m, 1H), 6.25−6.30 (m, 1H), 7.27−7.30 (m, 1H); EIMS (70 eV) *m/z* 138 [M^+, (3%)], 109 (16), 95 (47), 81 (100), 71 (40), 69 (19), 57 (49), 53 (63), 43 (28), 39 (48); *anal*. C 78.06%, H 10.33%, calcd for $C_9H_{14}O$, C 78.21%, H 10.21%.

(*E*)-4-Oxo-2-nonenal. To a three-necked flask, equipped with mechanical stirrer and reflux condenser, 1-(2-furyl)pentane was added (1 g, 7.2 mmol) in CH_2Cl_2 (100 mL). The solution was then stirred, and PCC (8.28 g, 38 mmol) was added. The stirring was continued at room temperature over 12 h; the mixture was then refluxed for 36 h (GLC). After cooling, the mixture was diluted with ether (150 mL) and filtered through a bed of Florisil. Removal of the solvent under reduced pressure afforded a crude product, which, after flash chromatography (cyclohexane−EtOAc, 80:20), gave 0.78 g (70%) of pure 4-oxo-2-nonenal as an oil: IR ν 2950, 2920, 2850, 1710, 1670, 1620, 1460, 1375, 1125, 1095 cm^{-1}; ^1H NMR δ 0.92 (t, 3H, J = 7.0 Hz), 1.22−1.39 (m, 4H), 1.58−1.72 (m, 2H), 2.7 (t, 2H, J = 7.3 Hz), 6.78 (dd, 1H, J = 16.2, 6.7 Hz), 6.88 (d, 1H, J = 16.2 Hz), 9.78 (d, 1H, J = 6.7 Hz); ^{13}C NMR δ 13.5 (C9), 22.0 (C8), 22.9 (C7), 30.8 (C6), 40.8 (C5), 136.9 (C3), 144.6

* To whom correspondence should be addressed. Tel.: 073740347. Fax: 07376345. E-mail: ballini@camvax.unicam.it.

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(C2), 193.1 (C1), 199.8 (C4); EIMS (70 eV) *m*/*z* 154 [M^+, (3%)], 125 (9), 111 (15), 98 (100), 97 (32), 83 (56), 57 (60), 55 (68), 43 (40), 41 (28); *anal* C 70.21%, H 9.03, calcd for $C_9H_{14}O_2$, C 70.10%, H 19.15%.

(*E*)-4-Oxonon-2-enoic Acid (1). (*E*)-4-Oxo-2-nonenal (0.33 g, 2.14 mmol) was dissolved in Me_2CO (20 mL). The solution was cooled to 0 °C, and 0.86 mL of Jones' reagent (26.72 g of CrO_3 in 23 mL of concentrated H_2SO_4, then H_2O until volume of 100 mL) were added. The mixture was stirred at 0 °C during 2 h, the Me_2CO was then removed at reduced pressure, and H_2O (20 mL) was added. The mixture was extracted with ether (3 × 15 mL), and the ethereal solution was washed with 10% aqueous Na_2CO_3. The basic solution was acidified with 2N HCl, then extracted with ether, and the ethereal solution was dried ($MgSO_4$). Removing the solvent under reduced pressure and purification of the product by flash chromatography (cyclohexane−EtOAc−EtOH, 6:3.5:0.5) afforded 0.31 g (85%) the title compound **1**: IR ν 3070, 2925, 1680, 1660 and 1625 cm^{-1}; ^1H NMR δ 0.9 (t, 3H, J = 6.9 Hz, CH_3), 1.22−1.4 (m, 4H, CH_2CH_2), 1.58−1.72 (m, 2H, CH_2), 2.62 (t, 2H, J = 7.5 Hz, CH_2CO), 6.68 (d, 1H, J = 16.2 Hz, CH═C), 7.15 (d, 1H, J = 16.2 Hz, C═CH); ^{13}C NMR δ 13.8 (C9), 22.4 (C8), 23.3 (C7), 31.2 (C6), 41.7 (C5), 129.5 (C3), 141.2 (C2), 170.9 (C1), 199.7 (C4); EIMS (70 eV) *m*/*z* 171 [M^+ + 1, (3%)], 152 [M^+ − 18, (13)], 125 (50), 123 (16), 114 (100), 99 (95), 96 (63), 81 (63), 71 (43), 69 (98), 57 (48), 55 (65); *anal*. C 63.67%, H 8.18%, calcd for $C_9H_{14}O_3$, C 63.51%, H 8.29%.

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References and Notes

(1) Pfefferle, C.; Kempter, C.; Metzger, J. W.; Fiedler, H.-P. *J. Antibiotics* **1996**, *49*, 826−828.
(2) Obrect, D.; Weiss, B. *Helv. Chim. Acta* **1989**, *72*, 117−122.
(3) Petrini, M.; Ballini, R.; Rosini, G.; Marotta, E. *Tetrahedron* **1986**, *42*, 151−154.
(4) Piancatelli, G.; Scettri, A.; D'Auria, M. *Tetrahedron* **1980**, *36*, 661−663.
(5) Still, W. C.; Kahan, M.; Mitra, A. *J. Org. Chem*. **1978**, *43*, 2923−2926.

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