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SILYL NITRONATES IN ORGANIC SYNTHESIS. SYNTHESIS OF 3(2H)-FURANONES

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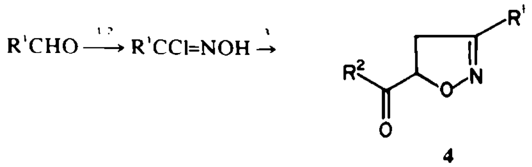
Abstract—A synthesis of 3(2H)-furanones, a structural element of several natural products, has been developed in which silyl nitronates or nitrile oxides are condensed with vinyl ketones to form 5-acyl-2-isoxazolines which are reduced with titanous ions or catalytically to 1,4-diketo-2-ols and cyclized with sodium acetate in acetic acid.

In conjunction with our exploratory work on the chemistry of silyl nitronates, a novel route to 3(2H)-furanones was discovered.[1] In the present paper the synthesis is extended to the preparation of further derivatives including some naturally occurring aroma constituents.

The 3(2H)-furanone nucleus is contained in several naturally occurring compounds, e.g. jatrophone,[2] the eremantholides,[3] geiparvarin,[4] and its dihydroderivate,[5,6] bullatenone,[7] ascofuranone,[8] 2,5-dimethyl-4-hydroxy-3-furanone, an aroma constituent in pineapple,[9] and strawberries,[10] 2,5-dimethyl-4-methoxy-3-furanone, a characteristic aroma constituent of the delicious arctic bramble, *Rubus arcticus*,[11] and a number of other simple alkyl substituted 3-furanones[12] giving flavour to soy sauce,[13] baked bread,[14] onions,[15] coffee,[16] etc.

Synthesis of 3(2*H*)-*furanones*. It was shown in a preceding article[1] that 2-isoxazolines, prepared by dipolar addition of silyl nitronates to vinyl ketones, can be reduced and cyclized to 3-furanones (eqn 1). This reaction has now been applied to other derivatives. The steps 1-3, leading to **1a–e**, can be carried out as a one pot reaction. The Ti^{3+} reduction gives a crude product, **2a–e**, that was cyclized directly to **3a–d** without purification. The 5-acyl-2-isoxazolines can also with advantage be prepared by the nitrile oxide method *via* hydroxamic acid chloride[17] (eqn 2) and then processed further into 3(2H)-furanones according to eqn (1) as shown in the accompanying paper.[18] This reaction was applied for $R^1 = C_6H_5$, $R^2 = CH_3$. In Tables 1–3 the physical data of the compounds prepared are collected.



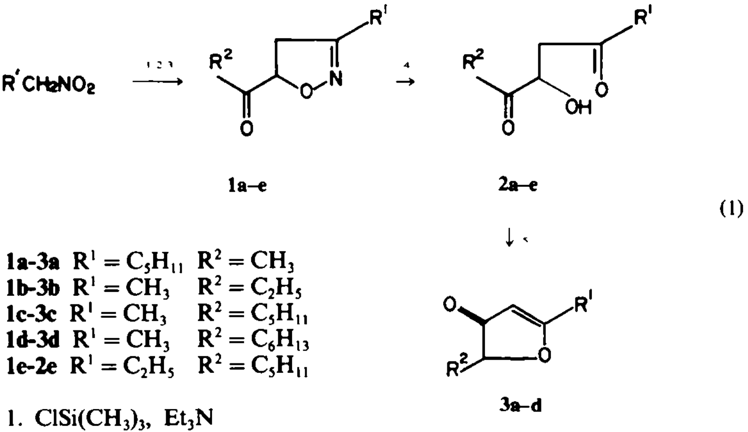
4

(2)

1. H_2NOH 2. Cl_2 3. Et_3N, $R^2COCH=CH_2$

As flavouring matters the 3(2H)-furanones have attracted interest for several synthetic studies.[19-25] We described in our earlier paper[1] the synthesis of 2,5-di-methyl-3(2H)-furanones and a few other 3-furanones. Compound **3d**, described in the present paper, is a constituent of onion oil.

In conjunction with the synthesis of prostaglandins **8** and **9** were prepared.[31] When they were subjected to refluxing acetic acid in the presence of sodium acetate, the 3-furanones **10** and **11** were formed. In

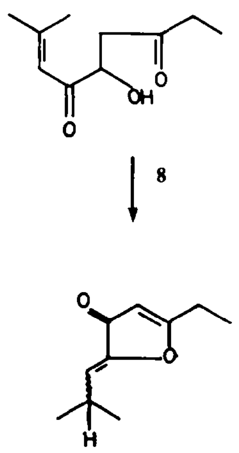


1a–e **2a–e** (1)

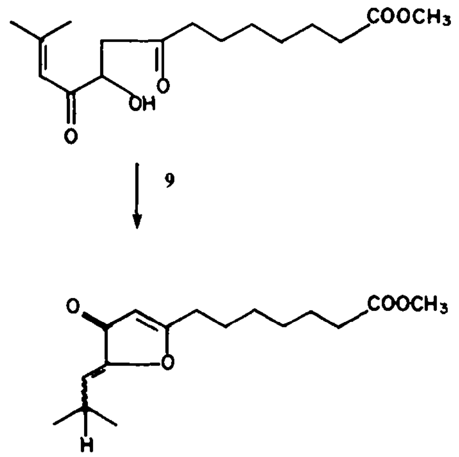
3a–d

1a-3a $R^1 = C_5H_{11}$ $R^2 = CH_3$
1b-3b $R^1 = CH_3$ $R^2 = C_2H_5$
1c-3c $R^1 = CH_3$ $R^2 = C_5H_{11}$
1d-3d $R^1 = CH_3$ $R^2 = C_6H_{13}$
1e-2e $R^1 = C_2H_5$ $R^2 = C_5H_{11}$

1. $ClSi(CH_3)_3$, Et_3N
2. $R^2COCH = CH_2$
3. $H^{\oplus}$
4. $Ti^{3\oplus}$ or RaNi, H_2
5. NaOAc, HOAc, 100°, 2-3 hr


8

10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11

Table 1. Properties of 2-isoxazolines

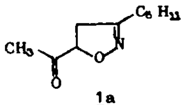
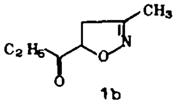
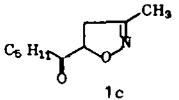
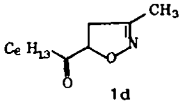
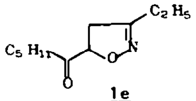
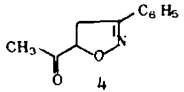
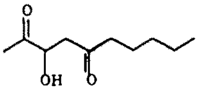
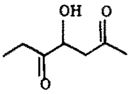
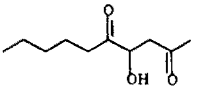
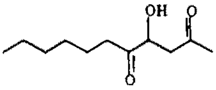
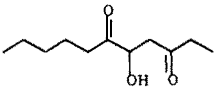
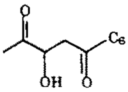
2-Isoxazoline	b.p. ℃/mmHg	Yield %	^{1}H NMR values (CDCl$_3$) δ ppm multiplicity, J_{HH} Hz
 1a	92-94/0.05	36	0.90 (3H,t,J6), 1.05-1.8 (6H, m), 2.27 (3H,s), 2.36 (2H,t, J6.6), 3.12 (1H,d,J9.6), 3.14 (1H,d,J7.2), 4.81 (1H,dd,J7.2, 9.6)
 1b	83/0.15	40	1.06 (3H,t,J7.2), 2.00 (3H,t, J1.0), 2.70 (2H,q,J7.2), 3.05, 3.25 (2H,m), 4.91 (1H,dd,J 7.7,10.2)
 1c	111-114/0.15	38	0.88 (3H,t,J6), 1.15-1.75 (6H, m), 1.99 (3H,t,J1.0), 2.65 (2H, t,J7.0), 3.14 (2H,br.d,J10.2, 7.8), 4.86 (1H,dd,J10.2,7.8)
 1d	126-129/0.17	28	0.87 (3H,t,J6), 1.25-1.75 (8H, m), 1.99 (3H,T,J1.0), 2.65 (2 H,t,J7.0), 3.14 (1H,d,J10.3), 3.15 (1H,d,J7.7), 4.85 (1H,dd, J7.7,10.3)
 1e	102/0.10	31	0.89 (3H,t,J6), 1.16 (3H,t,J 7.5), 1.1-1.8 (6H,m), 2.39 (2H,q,J7.5), 2.66 (2H,t,J6.6), 3.13 (1H,d,J10.2), 3.15 (1H,d, J7.8), 4.84 (1H,dd,J7.8,10.2)
 4	65 ℃ (m.p.)	60	2.28 (3H,s), 3.47 (1H,d,J10.5) 3.50 (1H,d,J7.5), 4.95 (1H,dd, J7.5,10.5), 7.2-7.7 (5H,m)

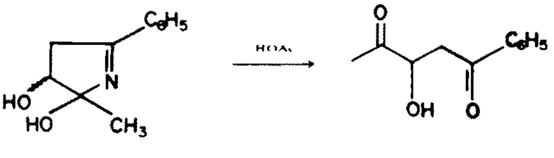
Table 2. Reduction of 2-isoxazolines to 2-hydroxy-1,4-diketones with titanous ions

Compound		Yield %	^1H NMR values ($CDCl_3$) δ ppm multiplicity, J_{HH} Hz
	2a	76[a,b]	0.89 (3H,t,J5), 1.1-1.8 (6H,m), 2.22 (3H,s), 2.47 (2H,t,J7.2), 2.87 (2H,d,J6.6), 2.89 (1H,d,J 4.5), 4.01 (1H,br.s), 4.33 (1H, dd,J4.5,6.6)
	2b	86[a]	1.06 (3H,t,J7.5), 2.17 (3H,s), 2.57 (2H,q,J7.5), 2.86 (1H,d, J7.0), 2.88 (1H,d,J4.0), 3.80 (1H,br.s), 4.34 (1H,dd,J4.0,7.0)
	2c	95[c]	0.87 (3H,t,J5), 1.1-1.7 (6H,m), 2.18 (3H,s), 2.54 (2H,t,J6.5), 2.85 (1H,d,J6.0), 2.86 (1H,d,J 4.5), 4.05 (1H,br.s), 4.33 (1H, dd,J4.5,6.0)
	2d	94[c]	0.88 (3H,t,J5), 1.05-1.9 (8H,m), 2.20 (3H,s), 2.56 (2H,t,J6.6), 2.85 (1H,d,J6.6), 2.87 (1H,d,J4.8), 4.10 (1H,br.s), 4.34 (1H,dd,J4.8, 6.6)
	2e	88[c]	0.87 (3H,t,J5), 1.03 (3H,t,J 7.0), 1.1-1.8 (6H,m), 2.49 (2H, q,J7.0), 2.54 (2H,t,J7.0), 2.83 (1H,d,J6.0), 2.84 (1H,d,J5.0), 3.89 (1H,br.s), 4.34 (1H,dd,J 5.0,6.0)
	5	15[a,d]	2.27 (3H,s), 3.40 (1H,d,J5.4), 3.43 (1H,d,J4.0), 3.77 (1H,br.s), 4.48 (1H,dd,J4.0,5.4), 7.2-8.0 (5H,m)

[a] Purified by prep.TLC [b] 3a, 20 % was isolated [c] crude yield, contains traces of the corresponding 3 (2H)-furanone [d] see Experimental

the process the double bond was shifted into conjugation with the carbonyl group.

The reduction of the phenyl derivatives **4** with Ti^{3+} is a sluggish reaction[26] and proceeds in a poor yield (*ca* 15%). Catalytic reduction with Raney nickel and H_2 in ethanol at atmospheric pressure showed a rapid uptake of 1 mole of hydrogen within 3-4 h. Evaporation gave a crystalline product, the spectroscopic data of which are in agreement with **12**. Hydrolysis of **12** with acetic acid at room temperature gives **5** which was cyclized to **7**.



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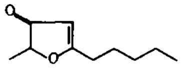
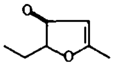
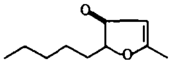
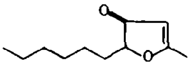
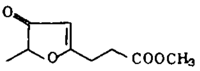
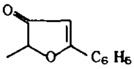
EXPERIMENTAL

Vinyl ketones. The methyl and ethyl vinyl ketones were commercially available. The pentyl and hexyl vinyl ketones were prepared by reacting trimethylvinylsilane (1 mole) with pentanoyl or hexanoyl chloride (1 mole), respectively, in methylene chloride at room temperature for 15 min with aluminium chloride (1 mole) as catalyst.[27,28] The product is worked up by hydrolysis with ice-water containing ammonium chloride. The organic phase was washed with water and aqueous solium bicarbonate, dried over sodium sulfate and evaporated. The crude product was sufficiently pure for immediate further use. The yields were *ca* 70%.

Synthesis of 2-*isoxazolines* **1a-e**. A one pot procedure is described in our earlier paper.[1] Alternatively, the trimethylsilyl nitronate is prepared separately from nitroethane or nitropropane[29,30] and left to react at room temperature over night with the vinyl ketone. Treatment of the product with *p*-TsOH and usual work-up gives the 2-isoxazolines **1a-e**. The yields are *ca* 40% (Table 1).

The reduction of the 2-*isoxazolines* **1a-e** *to* **2a-e** was carried out in aqueous methanol or acetic acid with 2,5 eq Ti^{3+} under nitrogen for *ca* 3 days at 25°. The crude product is sufficiently pure for the further cyclization to the 3(2H)-furanone. The yields were 80-90% (Table 2). The reduction can with advantage be carried out catalytically with Raney nickel (commercial catalyst, suspended in H_2O) in ethanol and at atmospheric pressure. One mole of H_2 is absorbed after 3-4 h.

Table 3. ^1H NMR data of 3(2H)-furanones

3(2H)-Furanone		Yield %	^1H NMR values ($CDCl_3$) δ ppm multiplicity, J_{hh} Hz
	3a	77^a	0.94 (3H,t,J5), 1.1-1.75 (6H, m), 1.42 (3H,d,J7.2), 2.51 (2H, t,J7.0), 4.47 (1H,q,J7.2), 5.40 (1H,s)
	3b	48^a	0.97 (3H,t,J7.5), 1.3-2.1 (2H, m), 2.22 (3H,s), 4.36 (1H,t, J7.5), 5.38 (1H,s)
	3c	60^a	0.89 (3H,t,J5), 1.1-1.9 (8H, m), 2.23 (3H,s), 4.43 (1H,br.t), 5.41 (1H,s)
	3d	63^a	0.90 (3H,t,J5), 1.1-1.9 (10H, m), 2.24 (3H,s), 4.45 (1H,br. t), 5.40 (1H,s)
 	6	87^b	1.42 (3H,d,J7.0), 2.55-2.85 (4H,m), 3.68 (3H,s), 4.48 (1H, q,J7.0), 5.41 (1H,s)
 	7	55^{a,c}	1.53 (3H,d,J6.6), 4.66 (1H,q, J6.6), 5.95 (1H,s), 7.3-8.0 (5H,m)

a) Purified by TLC   b) b.p. 138-144 °C/10 mmHg   c) See Experimental

Cyclization of **2a-d**, **5**, **8**,[31] **9**,[31] *and methyl 6-hydroxy-4,7-dioxo-octanoate*[1] *to the corresponding 3-furanones* **3a-d**, **7**, **10**, **11** *and* **6** was carried out in refluxing acetic acid in the presence of sodium acetate.[1] The products were purified by distillation *in vacuo* or by chromatography on silica gel ($CHCl_3$, 2% MeOH). The yields are *ca* 80% (Table 3). **10** and **11** are purified by TLC ($CHCl_3$, 3% EtOAc), 70% and 54% yield (impure). ^1H NMR ($CDCl_3$) **10**: δ 1.12 (6H, d, J 6.5 Hz), 1.0-3.0 (6H, m), 5.4-5.9 (2H, m). **11**: δ 0.9-2.9 (13H, m), 1.10 (6H, d, J 6.7 Hz), 3.63 (3H, s), 5.35-5.9 (2H, m). MS **10**: (M^+) 166; **11** (M^+) 280.

4[32] was prepared from methyl vinyl ketone and benzenehydroxamic acid chloride.[18]

2-Phenyl-4,5-dihydroxy-5-methyl-1-pyrroline, **12**. **4** was catalytically reduced in ethanol over Raney nickel (active in H_2O, commercial) at atmospheric pressure and 25°. One mole of H_2 was absorbed within *ca* 4 h. The catalyst was filtered off and the solvent evaporated *in vacuo*. A light yellow oil **12** was obtained which rapidly solidified and was recrystallized from acetonitrile (part decomposition), m.p. 128-130°. IR (KBr): 2600-3500 (br.s), 1628 (s), 1590 (m). MS: 191 (M^+) 173, 148, 120, 104. ^1H NMR ($CDCl_3$): δ 1.40 (3H, s), 3.02 (2H, d, J 3.4 Hz), 4.13 (1H, t, J 3.4 Hz), 7.2-7.5 (3H, m), 7.6-8.0 (2H, m).

5 was obtained by hydrolysis of **12** in acetic acid for 24 h at 25°. Evaporation of the solvent and purification by TLC (silica, $CHCl_3$) gave **5** in *ca* 40% yield.

5 was also obtained in 10-20% yield by reduction of **4** with titanous ions in aqueous acetic acid for 12 days according to the usual procedure. Most of the starting material **4** could be recovered.

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