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NOVEL REACTIONS OF CARBON SUBOXIDE. IX. SYNTHESIS OF 2*H*-PYRAN-2-ONE DERIVATIVES

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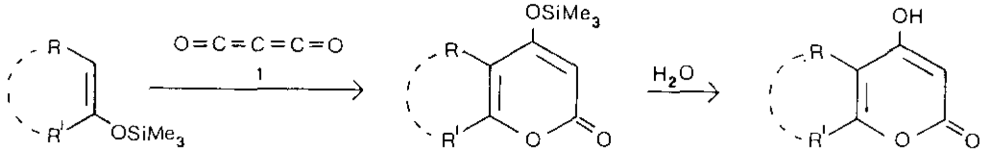
Abstract - Trimethylsilyl enol ethers of aldehydes and acyclic or cyclic ketones react with carbon suboxide to give substituted 4-[(trimethylsilyl)oxy]-2*H*-pyran-2-ones in good yields, which were treated with water to afford the corresponding 4-hydroxy-2*H*-pyran-2-ones.

It is already known that α-pyronic derivatives are an important class of heterocyclic compounds present in a large number of natural substances.[1,2] Recently, α-pyronic derivatives were isolated from South African *Helichrysum* species;[3] some of them are constituents of the toxin of *Alternaria citri*;[4] some are metabolites of *Penicillium citreo-viride*;[5] some others were found in *Penicillium* species.[6]

α-Pyronic derivatives display biological activity as selective inhibitors of human leukocyte elastase,[7] as potential photochemotherapeutic agents for the treatment of psoriasis[8] and are interesting as probes for platelet anti-aggregatory mechanism studies.[9] Some substituted α-pyrones have antihistamine[10], antibiotic[11] and antiulcer[12] activity. One of them is used as a preservative in oral pharmaceutical preparations.[13]

It is already known that α-pyronic derivatives can be used in cycloaddition reactions, in the synthesis of highly substituted benzenes and in the preparation of natural substances as potential 1,3-dienes.[14-17]

In previous works[14, 15] pyronic derivatives were obtained by reacting enol ethers of ketones with malonyl chloride or trimethylsilyl enol ethers of aldehydes and of ketones with the same compound yielding, respectively, a mixture of α-pyrone and fluoroglucinol[14] or various compounds according to the enol ether[15] used.

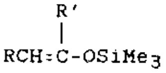
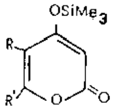
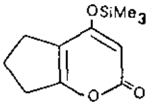


2a-h 3a-h 4a-h

Scheme 1

In this paper, following our previous research[18, 19] and considering the high reactivity and selectivity of carbon suboxide, we investigated a new synthesis of pure α-pyronic derivatives.

Table 1. 4-[(Trimethylsilyl)oxy]-2*H*-pyran-2-ones from trimethylsilyl enol ethers and carbon suboxide

Enol ether			Pyran-2-one			Yield (%)
 $RCH{=}\overset{R'}{\overset{|}{C}}{-}OSiMe_3$	R=R'=H	(**2a**)		R=R'=H	(**3a**)	78
	R=Me, R'=H	(**2b**)		R=Me, R'=H	(**3b**)	87
	R=Et, R'=H	(**2c**)		R=Et, R'=H	(**3c**)	77
	R=H, R'=Me	(**2d**)		R=H, R'=Me	(**3d**)	85
	R=H, R'=Et	(**2e**)		R=H, R'=Et	(**3e**)	75
	R=R'=Me	(**2f**)		R=R'=Me	(**3f**)	81
	R=H, R'=C_6H_4Me-4	(**2g**)		R=H, R'=C_6H_4Me-4	(**3g**)	95
		(**2h**)			(**3h**)	88

The reactions were carried out by reacting equimolar amounts of trimethylsilyl enol ethers (**2a-h**) with carbon suboxide (**1**) in an ether solution.

The temperature was kept at about -20°C. The results were satisfactory in all cases (see Scheme 1 and Table 1). The pyronic compounds were isolated and identified as trimethylsilyl enol ethers (**3a-h**). After treatment with water, the corresponding hydroxy derivatives (**4a-h**) were obtained. In all cases compounds were obtained in high yields (75-95%).

In particular:

i) 5-Substituted 4-[(trimethylsilyl)oxy]-2*H*-pyran-2-ones were obtained starting from trimethylsilyl enol ethers of aldehydes. The formation of either fluoroglucinic derivatives or polymers was not observed.

ii) 6-Substituted pyran-2-ones were obtained with methylenic trimethylsilyl enol ethers of methyl ketones; 5,6-disubstituted pyran-2-ones were obtained with non methylenic trimethylsilyl enol ethers.

Starting from non symmetric ketones, two different trimethylsilyl enol ethers were obtained. The reaction with carbon suboxide was carried out in two different ways: a) by separate reactions of the trimethylsilyl enol ethers which had been separated by common physical techniques, or b) by reacting their mixture. In the latter case it was necessary to separate the pyronic derivatives. To confirm whether this separation is possible, we also carried out the reaction with butanone, which gave trimethylsilyl enol ethers (**2e-g**).

Also in these cases fluoroglucinic compounds or polymers were not observed.

EXPERIMENTAL

Melting points were obtained on a Kofler hot stage microscope and are uncorrected. Ir spectra were run using NaCl plates on a Perkin-Elmer 157G grating spectrophotometer. ^{1}H-Nmr spectra were recorded on a Varian FT80A spectrometer using Me_4Si as the internal standard. Mass spectra were obtained with an "Hitachi" Perkin-Elmer RMU-6D spectrometer at 70 eV, using a direct-inlet system.

Literature procedures were followed in the preparation of **1**[21] and trimethylsilyl enol ethers (**2a-h**).[15,20] The analytical and spectral data of unknown **2g** are reported:

1-[(Trimethylsilyl)oxy]-1-(4-methylphenyl)ethene(2g). Yield 82%; bp 130-131°C (20 mm); ^{1}H-nmr ($CDCl_3$): δ 7.35 (m, 4H, Ar-*H*), 4.56 (d, J 3.5 Hz, 1H, CH_2) 4.13 (d, J 3.5 Hz, 1H, CH_2), 2.03 (s, 3H, Ar-CH_3), 0.65 (s, 9H, $Si(CH_3)_3$); Anal. Calcd for $C_{12}H_{18}OSi$: C, 69.85; H, 8.79. Found: C, 69.90; H, 8.81.

4-[(Trimethylsylil)oxy]-2*H*-pyran-2-one (3a). To a vigorously stirred solution of **2a** (35 mmol) in anhydrous ether (400 ml) **(1)** (35 mmol) was added at -20 °C. At completion, the mixture was stirred at -20°C for 3 h and then kept at room temperature for 24 h under stirring. The reaction mixture was evaporated to leave a residual liquid, which was fraction-distilled through a short Vigreux column. Yield 78%; bp 120-121 °C (0.8 mm). The structure was confirmed by comparison with published data.[15]

A solution of **3a** (20 mmol) and ether (50 ml) was treated with water (5 ml). The resulting mixture was stirred at 30 °C for 1 h. The organic layer was separated, dried over anhydrous sodium sulfate and concentrated. The product was identified as **4-hydroxy-2*H*-pyran-2-one** (**4a**). Yield 97%, mp 183-184 °C (from methanol) (lit.,[15] mp 180-183 °C).

Analogously, starting from **1** and **2b**, **2c**, **2d**, **2e**, **2f**, **2g** and **2h**, the following compounds were obtained:

5-Methyl-4-[(trimethylsilyl)oxy]-2*H*-pyran-2-one (3b). Yield 87%; bp 100-101 °C (0.05 mm). The structure was confirmed by comparison with published data.[15]

After treatment with water, **3b** yielded **4-hydroxy-5-methyl-2*H*-pyran-2-one (4b)**. Yield 95%, mp 196-197 °C (from methanol) (lit.,[15] mp 196 °C).

5-Ethyl-4-[(trimethylsilyl)oxy]-2*H*-pyran-2-one (3c). Yield 77%; bp 170 °C (20 mm); ir (liquid film): 1730 cm^{-1} (C=O); ^{1}H-nmr (CDCl$_3$): δ 6.45 (s, 1H, *H*-6), 5.50 (s, 1H, *H*-3), 2.35 (q, J 7.6 Hz, 2H, CH_2-CH$_3$), 1.10 (t, J 7.6 Hz, 3H, CH$_2$-CH_3), 0.35 (s, 9H, Si(CH_3)$_3$); ms, *m/z* 212. Anal. Calcd for $C_{10}H_{16}O_3Si$: C, 56.57; H, 7.60. Found: C: 56.40; H, 7.49.

After treatment with water, **3c** yielded **5-ethyl-4-hydroxy-2*H*-pyran-2-one (4c)**. Yield 95%, mp 202 °C (from methanol); ir (nujol): 3400 (OH), 1740, 1730 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d$_6$): δ 9.45 (s, 1H, OH, D$_2$O exchanged), 6.50 (s, 1H, *H*-6), 5.60 (s, 1H, *H*-3), 2.20 (q, J 7.6 Hz, 2H, CH_2-CH$_3$), 1.20 (t, J 7.6 Hz, 3H, CH$_2$-CH_3); ms, *m/z* 140. Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 60.01; H, 5.80.

6-Methyl-4-[(trimethylsilyl)oxy]-2*H*-pyran-2-one (3d). Yield 85%; bp 103-104 °C (0.1 mm). The structure was confirmed by comparison with published data[15].

After treatment with water, **3d** yielded **4-hydroxy-6-methyl-2*H*-pyran-2-one (4d)**. Yield 97%, mp 187 °C (from methanol) (lit.,[14] mp 186-187 °C).

6-Ethyl-4-[(trimethylsilyl)oxy]-2*H*-pyran-2-one (3e). Yield 75%; bp 144-145°C (20 mm); ir (liquid film): 1750 cm^{-1} (C=O); ^{1}H-nmr (CDCl$_3$): δ 5.38 (s, 1H, *H*-5), 5.06 (s, 1H, *H*-3), 3.73 (q, J 7.2 Hz, 2H, C*H*$_2$-CH$_3$), 1.30 (t, J 7.2 Hz, 3H, CH$_2$-C*H*$_3$), 0.45 (s, 9H, Si(C*H*$_3$)$_3$); ms, *m/z* 212. Anal. Calcd for $C_{10}H_{16}O_3Si$: C, 56.57; H, 7.60. Found: C, 56.63; H, 7.69.

After treatment with water, **3e** yielded **6-ethyl-4-hydroxy-2*H*-pyran-2-one** (**4e**). Yield 94%, mp 159-160°C (from methanol); ir (nujol): 3400 (OH), 1750, 1740 cm^{-1} (C=O); ^{1}H-nmr (DMSO-d$_6$): 9.55 (s, 1H, OH, D$_2$O exchanged), 5.62 (s, 1H, *H*-5), 5.40 (s, 1H, *H*-3), 2.18 (q, J 7 Hz, 2H, C*H*$_2$-CH$_3$), 1.21 (t, J 7 Hz, 3H, CH$_2$-C*H*$_3$); ms, *m/z* 140. Anal. Calcd for $C_7H_8O_3$: C, 59.99; H, 5.75. Found: C, 59.88; H, 5.64.

5,6-Dimethyl-4-[(trimethylsilyl)oxy]-2*H*-pyran-2-one (3f). Yield 81%; bp 110-111°C (20 mm); ir (liquid film): 1750 cm^{-1} (C=O); ^{1}H-nmr (CDCl$_3$): δ 5.03 (s, 1H, *H*-3), 2.16 (s, 3H, C*H*$_3$-6), 2.05 (s, 3H, C*H*$_3$-5), 0 73 (s, 9H, Si(C*H*$_3$)$_3$); ms, *m/z* 212. Anal. Calcd for $C_{10}H_{16}O_3Si$: C, 56.57; H, 7.60. Found: C, 56.63; H, 7.69.

After treatment with water, **3f** yielded **4-hydroxy-5,6-dimethyl-2*H*-pyran-2-one** (**4f**). Yield 91%, mp 202-203°C (from methanol) (lit.,[22] mp 201-204°C).

A mixture of **3e** and **3f** is obtained if the reaction is carried out starting from **2e** and **2f**, obtained as a mixture from butanone and chlorotrimethylsilane.[20] The final distillation separates **3e** and **3f**.

6-(4-Methylphenyl)-4-[(trimethylsilyl)oxy]-2*H*-pyran-2-one (3g). Yield 95%; bp 145-147°C (10 mm); ir (liquid film): 1730 cm^{-1} (C=O); ^{1}H-nmr (CDCl$_3$): δ 7.45 (m, 4H, arom-*H*), 6.00 (s, 1H, *H*-5), 5.45 (s, 1H, *H*-3), 2.25 (s, 3H, Ar-C*H*$_3$), 0.41 (s, 9H, Si(C*H*$_3$)$_3$); ms, *m/z* 274. Anal. Calcd for $C_{15}H_{18}O_3Si$: C, 65.66; H, 6.61. Found: C, 65.72; H, 6.73.

After treatment with water, **3g** yielded **4-hydroxy-6-(4-methylphenyl)-2*H*-pyran-2-one** (**4g**). Yield 92%, mp 212-213°C (from methanol) (lit.,[23] mp 210-215°C).

6,7-Dihydro-4-[(trimethylsilyl)oxy]cyclopenta[*b*]pyran-2(5*H*)-one (3h). Yield 88%; bp 170-171°C (10 mm); ir (liquid film): 1730 cm^{-1} (C=O); ^{1}H-nmr (CDCl$_3$): δ 5.20 (s, 1H, *H*-3), 2.70 (m, 4H, C*H*$_2$-CH$_2$-C*H*$_2$), 2.00 (m, 2H, CH$_2$-C*H*$_2$-CH$_2$); ms, *m/z* 224. Anal. Calcd for $C_{11}H_{16}O_3Si$: C, 58.90; H, 7.19. Found: C, 58.91; H, 7.25.

After treatment with water, **3h** yielded **6,7-dihydro-4-hydroxycyclopenta[*b*]pyran-2(5*H*)-one** (**4h**) in almost quantitative yield; mp 188-189°C (from methanol) (lit.,[15] mp 187-189°C).

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