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ENOLATE IONS: SYNTHETIC EQUIVALENTS OF 1,3-DIANIONS**

CONVENIENT SYNTHESIS OF SUBSTITUTED 3,4-DIHYDRO-5-OXO-2H,5H-PYRANO[3,4-b]PYRANS

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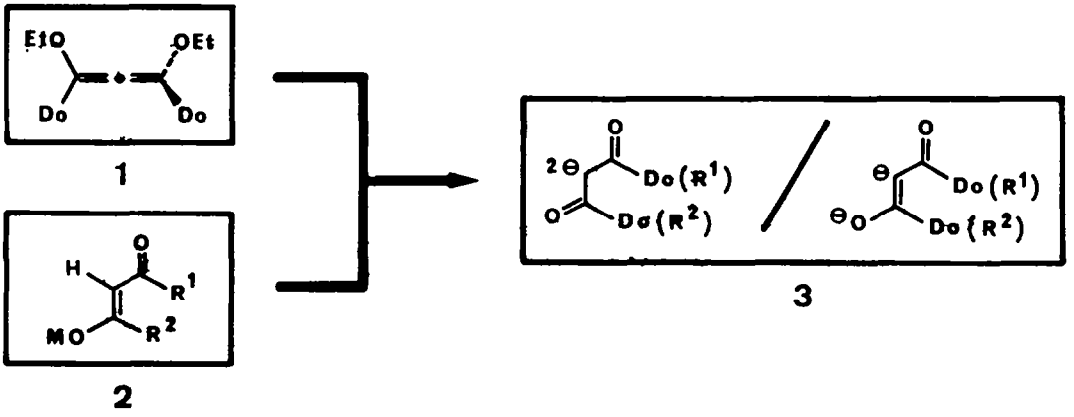
Abstract: Our investigations on tetradonor-substituted allenes prompted us to use enolate ions and trimethylsilyl enol ethers as 1,3-dianion equivalents.- A mixture of chloro(trimethyl)silane and cyclobutane-1,1-dicarboxylic acid dichloride (6) reacts with enolates 2a,b and 4a-c to give 5,9-dioxo-6-oxaspiro[3.5]non-7-enes 8a,b and 11a-c, whereas carboethoxy ketene ethyl trimethylsilyl acetal (2c) and acid chloride 6 yield ethyl 9-hydroxy-5,7-dioxo-6-oxaspiro[3.5]non-8-ene-carboxylate (9). The 9-oxaspiro[3.5]nonenes 8a and 11a-c are isomerized thermally to 3,4-dihydro-5-oxo-2H,5H-pyrano[3,4-b]pyrans 10 and 12a-c respectively.

For some years we have focused our investigations on tetradonor substituted allenes 1 (Do = OEt, NR_2). These react formally with bifunctional electrophiles like 1,1-/1,3-dianions 3 (Do = OEt, NR_2) of malonic ester and malonic amides /1/. In expansion of this concept, primarily developed for the allenes 1, enolate ions and trimethylsilyl enol ethers of 1,3-dicarbonyl compounds 2 (M = Li, $SiMe_3$) are expected also to react as equivalents of 1,3-dianions 3 (substituents R^1/R^2 in 2 and 3 see scheme 1).

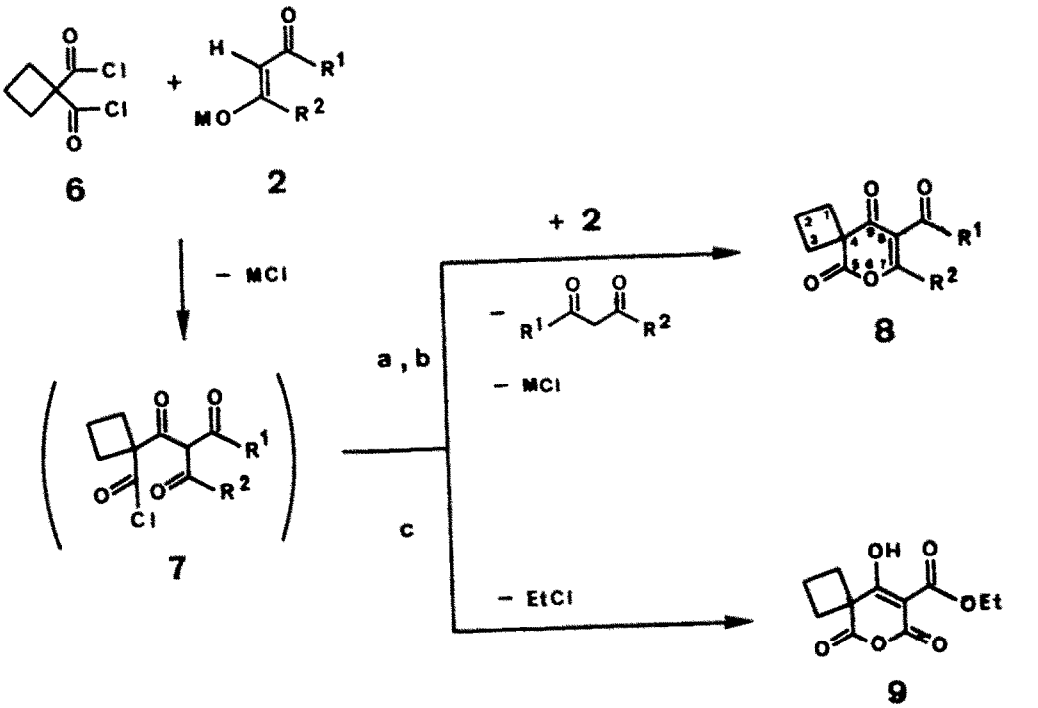


For the reasons described earlier, lithium enolates 4 of methyl ketones can also be considered as 1,3-dianion equivalents 5 (substituents R in 4 and 5 see scheme 2).

4 5

Ethyl acetoacetate /2/, keto enol ethers /3/, trimethylsilyl enol ethers /4/ and the thallium(I) salt of t-butyl acetoacetate /5/ are acylated by malonyl dichlorides and cyclized to afford 2H-pyran-2-ones /6/. Since 2H-pyran-2-ones are widespread in nature and of diverse biological activity /7/, we wish to report our versatile approach to the synthesis of this class of compounds. We obtained 3,4-dihydro-5-oxo-2H,5H-pyrano[3,4-b]pyrans 10 and 12 starting from lithium enolates or trimethylsilyl enol ethers of carbonyl compounds 2 and 4 and cyclobutane-1,1-dicarboxylic acid dichloride (6).

On treatment of a mixture of chloro(trimethyl)silane and cyclobutane-1,1-dicarboxylic acid dichloride (6) (molar ratio 2:1) /8/ with enolate ions 2a,b, the



2, 3, 7, 8	M	R^1	R^2
a	Li	C_6H_5	C_6H_5
b	Li	OEt	C_6H_5
c	Me_3Si	OEt	OEt

Scheme 1

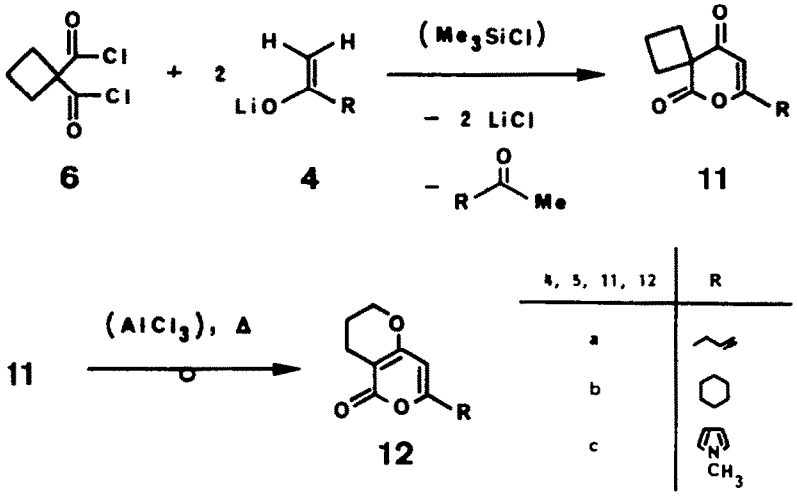
intermediates 7a,b are first generated. Deprotonation of 7a,b by a second mol of 2a,b and cyclization of the primarily formed anions yield 5,9-dioxo-6-oxaspiro[3,5]non-7-enes 8a,b (data see table 1, 2).

Ethoxycarbonyl-ketene-(ethyl-trimethylsilyl)-acetal (2c) /9/ reacts with dicarboxylic acid chloride 6 analogously to 2a,b to give 7c. However, contrary to 7a,b, acid chloride 7c is converted directly to ethyl-9-hydroxy-5,7-dioxo-6-oxaspiro[3,5]non-8-ene-8-carboxylate (9) (data see table 1, 2).

Isomerization of 6-oxaspiro[3,5]nonene 8a in the presence of aluminum chloride yields 8-benzoyl-3,4-dihydro-5-oxo-7-phenyl-2H,5H-pyrano[4,3-b]pyran (10) on heating (data see table 1, 2) /10/.

It is practical to generate the enolates 4 from the corresponding silyl enol ethers with methyl lithium /11/.

Analogously to the enolates 2a,b, reaction of a mixture of chloro(trimethyl)silane and cyclobutane-1,1-dicarboxylic acid dichloride (6) (molar ratio 2:1) with two moles of the lithium enolates 4a-c leads to 7-alkyl(aryl)-5,9-dioxo-6-oxaspiro[3,5]non-7-enes 11a-c. In the presence of aluminum chloride, 11a-c can be isomerized to 7-alkyl(aryl)-3,4-dihydro-5-oxo-2H,5H-pyrano[4,3-b]pyrans 12 (data see table 1, 2).



Scheme 2

Experimental Section

The enolates 2a,b are generated from the corresponding 1,3-dicarbonyl compounds at -78°C in dry THF with methyl lithium.

The enolates 4 are generated from the corresponding trimethylsilyl enol ethers at 25°C in dry THF with methyl lithium.

General Procedure for the Synthesis of 8, 9 and 11: To a solution of 15 mmol of the enolates 2a,b and 4 respectively [7.5 mmol trimethylsilyl enol ether 2c] in 50 mL dry THF at -78°C under stirring was added dropwise a solution of 15 mmol chloro(trimethyl)silane [in the case of 2c the addition of chloro(trimethyl)silane is not required] and 1.2 g (6.8 mmol) cyclobutane-1,1-dicarboxylic acid dichloride (6) in 10 mL dry THF. The reaction mixture was allowed to warm to room temperature

during 16 h and stirring was continued for another 1.5 h at 65°C. After cooling to 20°C, the solvent was evaporated in vacuo. The oily residue was extracted with a mixture of 100 mL chloroform/diethyl ether(1:3). Hereafter, the resulting solution was filtered and the solvent removed in vacuo. In the case of 8 and 9 the residue crystallized on addition of 15 mL of a mixture of n-hexane/diethyl ether (1:3). Recrystallization afforded pure 8 and 9. The spirans 11 were purified by bulb-to-bulb distillation (110 - 125°C/0.06 Torr) followed by recrystallisation.

General Procedure for the Synthesis of 10 and 12: 0.2 mmol of the spirans 8 and 11 were mixed with 0.25 g aluminum chloride, heated for 1 h to 130 - 150°C and purified by bulb-to-bulb distillation (140 - 150°C/0.06 Torr) followed by recrystallization.

Table 1: Compounds prepared 8, 9, 10, 11, 12

Product	Yield [%]	b.p.[°C]/Torr m.p.[°C] (Solvent)[a]	MS m/z (M^+)	IR (KBr*/100%) [cm^{-1}]	^{1}H-NMR ($CDCl_3$*/CCl_4/TMS) [ppm]	^{13}C-NMR ($CDCl_3$/TMS) [ppm]
8a	70	158 (I)	332	1780,1685, 1660 (CO).*	2.15, 2.32, 2.87 (mc, 6H, CH_2); 7.26-7.86 (mc, 10H, CH).*	15.30, 29.10 (CH_2); 54.30 (Cq); 116.40 (=C); 128.50 128.71, 128.79, 129.00, 129.10, 130.10, 132.30, 133.90, 136.70 (arom. C); 163.10, 169.50, 190.90, 192.30 (=C, CO).
8b	40	96-100	300	1780, 1720, 1670 (CO).*	1.09 (t, 3H, CH_3); 2.24 (mc, 2H, CH_2); 2.72 (t, 4H, CH_2); 4.16 (q, 2H, CH_2); 7.52 (mc, 5H, CH).*	13.59 (CH_2); 15.13, 29.09 (CH_2); 54.02 (Cq); 61.94 (CH_2); 112.20 (=C); 127.95, 128.53, 130.16, 132.35 (arom. C); 164.14, 169.05, 189.22 (=C, CO).
9	15	87 (II)	240	1780, 1750, 1655 (CO).*	1.42 (t, 3H, CH_3); 2.32 (mc, 2H, CH_2); 2.68 (t, 4H, CH_2); 4.46 (q, 2H, CH_2); 15.41 (s, 1H, OH).*	14.05 (CH_3); 15.71, 30.41 (CH_2); 47.23 (Cq); 63.21 (OCH_2); 91.95 (=C); 155.35, 168.32, 170.97, 187.47 (=C, CO).
10	75	185 (I)	332	1730, 1680 (CO).*	2.01 (q, 2H, CH_2); 2.58 (t, 2H, CH_2); 4.14 (t, 2H, CH_2); 7.18, 7.46, 7.87 (mc, 10H, CH).*	18.65, 20.62 (CH_2); 67.76 (OCH_2); 100.04, 112.78 (=C); 127.98, 128.37, 128.62, 129.22, 130.62, 131.04, 133.86, 136.59 (arom. C); 156.77, 162.55, 162.92, 191.74 (=C, CO).
11a	46	105/0.02	206	1780, 1675 (CO).	2.42 (mc, 10H, CH_2); 4.91 (mc, 1H, CH); 5.10 (mc, 1H, CH); 5.42 (s, 1H, CH); 5.66 (mc, 1H, CH).	15.37, 28.96, 29.66, 33.03 (CH_2); 54.17 (Cq); 104.26, 116.39, 135.41 (=C); 169.63, 170.99, 192.65 (=C, CO).

Table 1: Continued

Product	Yield [%]	b.p. [°C]/Torr m.p. [°C] (Solvent) [a]	MS m/z (M^+)	IR (KBr*/100%) [cm^{-1}]	^{1}H-NMR ($CDCl_3$*/CCl_4/TMS) [ppm]	^{13}C-NMR ($CDCl_3$/TMS) [ppm]
11b	56	49-50 (II)	234	1785, 1675 (CO).	1.39, 1.93, 2.28 (mc, 13H, CH, CH_2); 2.49 (t, 4H, CH_2); 5.44 (s, 1H, CH).	15.19, 25.48, 29.12, 29.48 (CH_2); 42.10 (CH); 54.20 (Cq); 101.89 (=C); 171.39, 174.33, 193.17 (=C, CO).
11c	30	122-123 (II)	231	1780, 1650 (CO).	2.28 (mc, 2H, CH_2); 2.66 (t, 4H, CH_2); 3.86 (s, 3H, CH_3); 5.91 (s, 1H, CH); 6.21 (t, 1H, CH); 6.84 (d, 2H, CH).*	15.31, 29.36 (CH_2); 37.67 (NCH_3); 53.90 (Cq); 98.40, 109.60, 117.15, 123.00, 131.22 (=C); 158.23, 170.78, 191.92 (=C, CO).
12a	67	115/0.02	206	1710 (CO); 1650 C=C).	2.04 (q, 2H, CH_2); 2.32 (t, 2H, CH_2); 2.44 (mc, 4H, CH_2); 4.14 (t, 2H, OCH_2); 4.90 (mc, 1H, CH); 5.12 (mc, 1H, CH); 5.62 (s, 1H, CH); 5.76 (mc, 1H, CH).	18.27, 20.95, 30.53, 32.73 (CH_2); 67.19 (OCH_2); 98.53 99.84, 115.96, 136.07 (=C); 162.29, 164.75, 164.88 (=C, CO).
12b	80	60-61 (II)	234	1710 (CO); 1650 (C=C).	1.36, 1.96, 2.29 (mc, 15H, CH, CH_2); 4.16 (t, 2H, OCH_2); 5.56 (s, 1H, CH).	18.29, 21.02, 25.63, 30.21 (CH_2); 41.74 (CH); 67.13 (OCH_2); 97.40, 98.34 (=C); 164.84, 167.26 (=C, CO).
12c	70	99-101 (II)	231	1705 (CO), 1635 (C=C).	2.02 (q, 2H, CH_2); 2.48 (t, 2H, CH_2); 3.85 (s, 3H, CH_3); 4.18 (t, 2H, OCH_2); 6.06 (s, 1H, CH); 6.12 (d, 1H, CH); 6.64 (mc, 2H, CH).*	18.59, 21.20 (CH_2); 36.97 (NCH_3); 67.37 (OCH_2); 96.91, 97.88, 108.44, 112.84, 124.98, 127.80 (=C); 153.40, 163.98, 165.98 (=C, CO).

[a] Solvent: (I): $CHCl_3$/Et_2O 1:3, (II): Et_2O/n-hexane 3:1.

Table 2: Analytical data of compounds 8, 9, 10, 11, 12

Compound	Formula	Found [%]	Calc. [%]
8a	$C_{21}H_{16}O_4$ (332.17)	C 75.66 H 4.90	C 75.92 H 4.81
8b	$C_{17}H_{16}O_5$ (300.12)	C 67.64 H 5.38	C 68.02 H 5.33
9	$C_{11}H_{12}O_6$ (240.05)	C 54.64 H 5.24	C 55.03 H 4.99
10	$C_{21}H_{16}O_4$ (332.17)	C 75.60 H 4.90	C 75.92 H 4.81

Table 2: Continued

Compound	Formula	Found [%]			Calc. [%]		
11a	$C_{12}H_{14}O_3$ (206.09)	C 69.28	H 7.15		C 69.93	H 6.79	
11b	$C_{14}H_{18}O_3$ (234.11)	C 71.45	H 7.78		C 71.82	H 7.68	
11c	$C_{13}H_{13}NO_3$ (231.10)	C 67.20	H 5.81	N 6.10	C 67.56	H 5.62	N 6.06
12a	$C_{12}H_{14}O_3$ (206.09)	C 69.75	H 7.04		C 69.93	H 6.79	
12b	$C_{14}H_{18}O_3$ (234.11)	C 71.37	H 7.85		C 71.82	H 7.68	
12c	$C_{13}H_{13}NO_3$ (231.10)	C 67.30	H 5.90	N 6.10	C 67.56	H 5.62	N 6.06

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