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The Facile 1,5-Hydrogen Shift in 6-Hydroxy-2,4-cycloheptadien-1-ones

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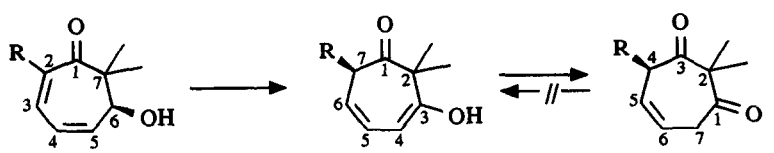
Abstract - Nonenolizable 6-hydroxy-2,4-cycloheptadien-1-ones, including spiro[4.6] and spiro[5.6] annulated derivatives, have been prepared and shown to rearrange intramolecularly into 5-cyclohepten-1,3-diones at room temperature and even at -18 °C. The rearrangement is accelerated in solvent DMSO.

1,5-Hydrogen shift is a pericyclic transformation characteristic of cis-1,3-pentadienes. It has been observed in many ring systems[1-4] and most recently, in a buckminsterfullerene - morpholine adduct $C_{60}H_6[N(CH_2CH_2)_2O]_6$.[5] Typical examples are substituted cyclohepta-1,3-dienes and cycloheptatrienes which rearrange thermally at 60 - 140 °C.[1]

We here show that previously unknown 7,7-dialkylated 6-hydroxy-2,4-cycloheptadien-1-ones[6] rearrange easily and irreversibly into 5-cyclohepten-1,3-diones. For example, when freshly prepared, neat 6-hydroxy-2,7,7-trimethyl-2,4-cycloheptadien-1-one (**1a**) was stored in a freezer (-18 °C) and resubmitted to spectroscopy after a few weeks, a different compound was present, identified and isolated as **3a** in high yield (81%) after chromatography.

Scheme 1.



1a R = Me
1b R = H

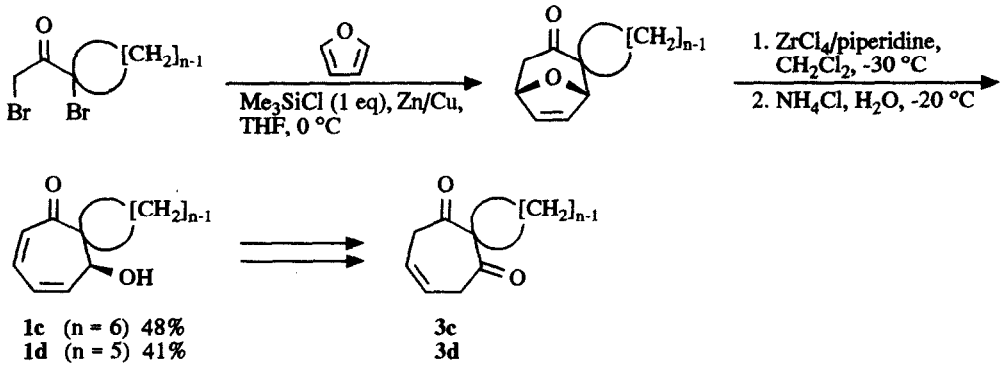
2a
2b

3a
3b

In order to cast further light on the scope and mechanism of this transformation we also prepared spiro systems **1c,d** in two steps, i.e. by spiroannulating metaloxyallyl cation cycloaddition to furan,[7] followed by $ZrCl_4$/piperidine mediated opening of the resulting tricyclic β-keto ether[6].

Geminal dialkylation (Scheme 2) in **1b-d** means that the product molecules **3b-d** contain a mirror plane. Thus, NMR spectral interpretation of the rate of rearrangement is simplified.

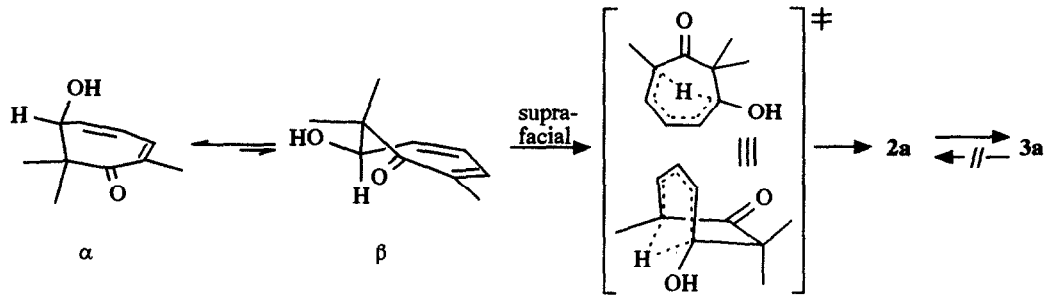
Scheme 2.



1c (n = 6) 48%
1d (n = 5) 41%

3c
3d

We assume a rapid 1,5-hydrogen shift[1-5] and consider two conformers α and β for the rearrangement:

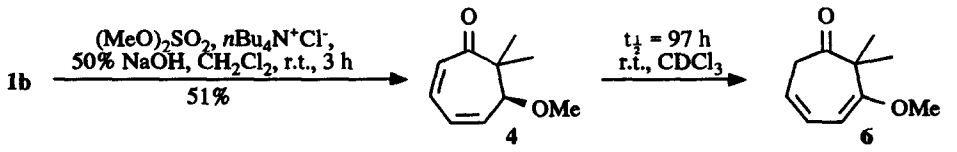


Conformer β (which according to MMX calculations is thermodynamically less stable) allows an estimated approach to within 2.77 Å of hydrogen at migration origin and π orbital at migration terminus. In conformer α a 1,5-shift is sterically impossible. While the nature of the geminal dialkyl groups might influence the population of the β-conformer in the ground state, calculations (MMX) suggest only minor changes in the α ⟵⟶ β equilibrium along the spiro series **1c-f** (n = 6,5,4,3).

In fact, the rearrangement rates of the three hydroxydienones **1b-d** were found to vary within a factor of 2 under standard conditions ($CDCl_3$, r.t.). For **1f** (n = 3), spiroconjugation in the transition state is feasible and its rearrangement was calculated to be very fast. The synthesis of **1f** and **1e** (n = 4) is more difficult and has not yet been attempted.

In solvent DMSO-d_6, the rate of 1,5-hydrogen shift of monocyclic **1b** was ca. 9 times faster than in solvent $CDCl_3$. To our knowledge, a solvent effect of this magnitude on a 1,5 shift[1-5] is without precedent. As expected,[8] dienol **2b** was spectroscopically identifiable[9] in high concentration under these conditions. In the presence of base (2,6-di-*t*-butyl-4-methylpyridine, 1 eq, $CDCl_3$) a slight increase in rearrangement rate of **1b** was observed (Table 1).

In a further study of substituent effect on rearrangement rate we prepared methyl ether **4**[10] and O-acetyl derivative **5**[11] from **1b**. Unlike dienol **2b**, the rearrangement products (**4** → **6**, **5** → **7**) do not ketonize under the reaction conditions. The conversion **1b** → **4** was not trivial. Treatment of **1b** with MeI in the presence of alkali and also NaH following standard procedures was not successful and gave dark solutions, without any of the desired **4**. A two phase procedure afforded methyl ether **4** in 51% yield.



Compared with hydroxy system **1b** (→**2b**→**3b**, $t_{\frac{1}{2}}$ = 78 h, r.t.) the rearrangement of O-methyl derivative **4** (→**6**, $t_{\frac{1}{2}}$ = 97 h) was marginally retarded.

In contrast, 1,5-hydrogen shift in the acetyl derivative **5**[11] was "frozen" (no reaction after 4 weeks).

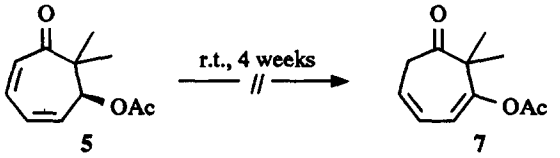


Table 1. First Half-life $t_{\frac{1}{2}}$ of 6-Hydroxy-2,4-cycloheptadien-1-ones in Solution at 23±2 °C

Compound	Solvent	$t_{\frac{1}{2}}$ [h]	Compound	Solvent	$t_{\frac{1}{2}}$ [h]
1b	$CDCl_3$	78	**1c**	$CDCl_3$	248 [days[b]]
1b	$CDCl_3$[a]	50	**1d**	$CDCl_3$	73
1b	DMSO-d_6	9	**4**	$CDCl_3$	97
1c	$CDCl_3$	37			

[a] 2,6-Di-*t*-butyl-4-methylpyridine (1 eq) added. [b] At -18 °C. It is noticeable that the rearrangement of **1c** in solvent $CDCl_3$ takes much longer than the rearrangement of *neat* **1a** and **1b** ($t_{\frac{1}{2}}$ < 5 weeks).

Clearly, acceptor substituents at C-6 retard rearrangement (**5** —//→ **7**) and thus help to stabilize the array of functionality present in **1**. Apparently, a special retarding substituent is the zirconoxy group, which freezes 1,5-hydrogen shift during preparation of the title compounds **1** (Scheme 2).[6] Only after aqueous work-up and liberation of free **1** does rearrangement set in readily.

From a theoretical viewpoint the nature and interpretation of substituent effects on 1,5-hydrogen shift is not yet completely clear. Houk and Hehre[12] have postulated a changing polarization of the carbon skeleton on going from cyclopentadiene ("anionic skeleton") to cycloheptatriene ("cationic skeleton") and acyclic systems (slightly "cationic").[13] In our case, the carbon skeleton contains a quaternary centre which blocks a tropylium cation type interaction. However, the combination of donor substitution at the migration origin and acceptor substitution at the migration terminus facilitates rearrangement decisively. The donor properties of the hydroxy group in **1** is enhanced further in solvent DMSO, which accelerates the 1,5-shift by about one order of magnitude (Table 1). Conversely, solvent $CDCl_3$ probably "deuterates" the hydroxy oxygen atom and thus shows down rearrangement relative to the *neat* system (Table 1, footnote b).[14]

From a preparative viewpoint the efficient, two step construction of spirocyclic systems **1c,d**, in which the 7-membered ring is functionalized, is of interest. A literature survey (CAS online) shows that these systems have hardly been studied.[15]

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9. Spectroscopic data of **2b**: 200 MHz ^{1}H NMR (DMSO-d_6, δ) (inter al. with **1b** and **3b**) 9.42 (s, 1 H, OH), 5.94 (ddt, $^3J_{5,6}$ = 10 Hz, $^3J_{4,5}$ = 6 Hz, $^4J_{5,7}$ = 1 Hz, 1 H, H-5), 5.39 (dt, $^3J_{5,6}$ = 10 Hz, $^3J_{6,7}$ = 6.5 Hz, 1 H, H-6), 5.25 (d, $^3J_{4,5}$ = 6 Hz, 1 H, H-4), 3.13 (br. d, $^3J_{6,7}$ = 6.5 Hz, 2 H, H-7), 1.21 (s, 6 H, CH_3).
10. Preparation of **4**. To a suspension of NaOH (0.43 mL, 5.4 mmol, 50% solution in H_2O), nBu$_4$N$^+$Cl$^-$ (catal.) and $(MeO)_2SO_2$ (0.34 mL, 454 mg, 3.6 mmol) in CH_2Cl_2 (2.5 mL) was added **1b** (270 mg, 1.8 mmol) in CH_2Cl_2 (1 mL). After 3 h at room temperature H_2O and CH_2Cl_2 were added. The aqueous layer was extracted with CH_2Cl_2, the combined organic phases were dried ($MgSO_4$) and evaporated. Chromatography [silica gel, PE/E (4 : 1)] afforded **4**, 150 mg (51%), yellow oil. IR ($CHCl_3$, ν) 2980, 2932, 2872, 2824, 1652, 1588, 1464, 1380, 1356, 1196, 1100 cm^{-1}; 200 MHz ^{1}H NMR ($CDCl_3$, δ) 6.84 (ddd, $^3J_{2,3}$ = 12.5 Hz, $^3J_{3,4}$ = 6.5 Hz, $^4J_{3,5}$ = 1 Hz, 1 H, H-3), 6.36 (dddd, $^3J_{4,5}$ = 11 Hz, $^3J_{5,6}$ = 5 Hz, $^4J_{3,5}$ = 1 Hz, $^wJ_{2,5}$ = 0.5 Hz, 1 H, H-5), 6.13 (dddd, $^3J_{4,5}$ = 11 Hz, $^3J_{3,4}$ = 6.5 Hz, $^4J_{2,4}$ = $^4J_{4,6}$ = 1 Hz, 1 H, H-4), 6.08 (d, $^3J_{2,3}$ = 12.5 Hz, 1 H, H-2), 3.84 (br. d, $^3J_{5,6}$ = 5 Hz, 1 H, H-6), 3.38 (s, 3 H, OCH_3), 1.18, 1.11 (s, 6 H, CH_3); 50 MHz ^{13}C NMR ($CDCl_3$, δ) 204.22 (C=O), 140.70, 134.81, 131.71, 125.93 (4 C, olef. C), 82.14 (*C*OMe), 58.17 (OCH_3), 54.02 ($C(CH_3)_2$), 23.08 (CH_3), 19.21 (CH_3); MS (r.t.), *m/z* (%) 167 (7), 166 (M$^+$, 51), 151 (37), 138 (44), 135 (7), 123 (100), 107 (25), 91 (48), 85 (23), 65 (14), 54 (3), 53 (23). Exact mass calcd for $C_{10}H_{14}O_2$ 166.0994, found 166.0994.
11. Preparation of **5**. To a solution of **1b** (304 mg, 2 mmol) and pyridine (0.32 mL, 316 mg, 4 mmol) in CH_2Cl_2 (4 mL) was added AcCl (0.21 mL, 235 mg, 3 mmol) at -30 °C. After 2 h at -30 °C the reaction mixture was quenched with H_2O at 0 °C. The aqueous phase was extracted with Et_2O and the combined organic layers were dried ($MgSO_4$). Removal of the solvent and chromatography [silica gel, PE/E (3 : 1)] afforded **5**, 270 mg (70%), yellow oil. IR ($CHCl_3$, ν) 2980, 2936, 2876, 1736, 1652, 1596, 1464, 1372, 1240, 1120, 1036, 1017, 984, 971 cm^{-1}; 200 MHz ^{1}H NMR ($CDCl_3$, δ) 6.52 (ddd, $^3J_{2,3}$ = 12.5 Hz, $^3J_{3,4}$ = 6 Hz, $^4J_{3,5}$ = 1 Hz, 1 H, H-3), 6.23 (br. dd, $^3J_{4,5}$ = 11 Hz, $^3J_{5,6}$ = 5.5 Hz, 1 H, H-5), 6.13 (d, $^3J_{2,3}$ = 12.5 Hz, 1 H, H-2), 6.11 (dd, $^3J_{4,5}$ = 11 Hz, $^3J_{3,4}$ = 6 Hz, 1 H, H-4), 5.38 (d, $^3J_{5,6}$ = 5.5 Hz, 1 H, H-6), 2.08 (s, 3 H, CO_2CH_3), 1.17, 1.15 (s, 6 H, CH_3); 50 MHz ^{13}C NMR ($CDCl_3$, δ) 202.55 (C=O), 170.26 (*C*O_2CH_3), 137.16, 134.82, 131.55. 125.87 (4 C, olef. C), 74.52 (COAc), 51.91 ($C(CH_3)_2$), 22.54 (CH_3), 20.76 (CH_3), 20.00 (CH_3); MS (r.t.) *m/z* (%) 195 (3), 194 (M$^+$, 14), 179 (2), 166 (18), 152 (100), 137 (99), 135 (29), 134 (59), 124 (71), 123 (96), 109 (99), 107 (57), 95 (38), 92 (89), 82 (43), 70 (19), 59 (9), 54 (6), 53 (34). Exact mass calcd for $C_{11}H_{14}O_3$ 194.0943, found 194.0943.
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