

A novel spiroketalization reaction of 1,7-dihydroxyhepta-2,5-diyn-4-ones

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Treatment of 1,7-dihydroxyhepta-2,5-diyn-4-ones with hydrogen halide in AcOH gave halogenated spiroketals in good yield.

Introduction

Spiroketals are found in a wide variety of biologically active natural products, including insect pheromones, steroidal saponins, marine macrolides, and microbial metabolites.¹ The development of new methods for the synthesis of spiroketals has thus attracted much attention in recent years. During our studies on the synthesis of benzocyclobutene derivatives *via* thermal cyclization of diallenes,² we found unexpectedly that 1,7-dihydroxyhepta-2,5-diyn-4-ones (**3**) can be smoothly converted into halogenated spiroketals (**4**) by simple treatment with aq. hydrogen halides in AcOH. Optically active halogenated spiroketals (**4**) were also obtained by the reaction of optically active 1,7-dihydroxyhepta-2,5-diyn-4-ones (**3**) without any racemization.

Results and discussion

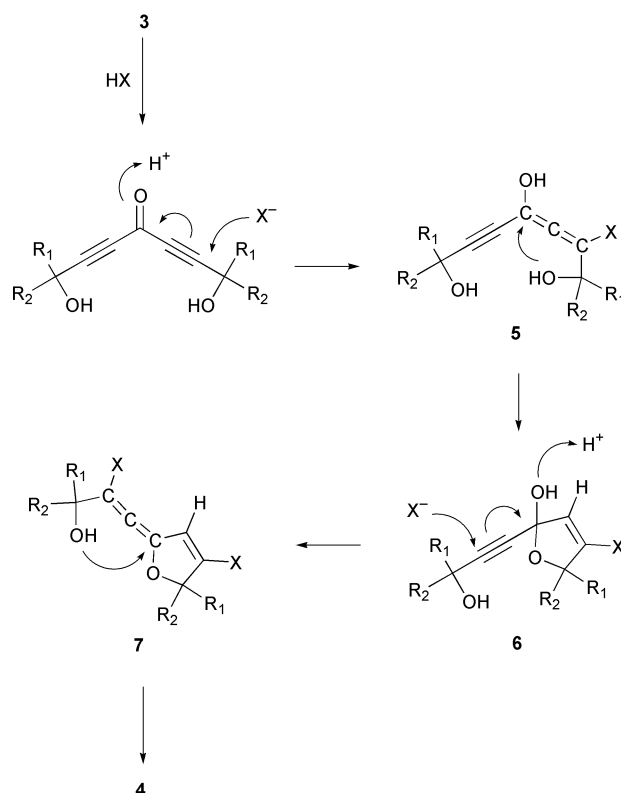
1,7-Dihydroxyhepta-2,5-diyn-4-ones (**3**) were prepared by active MnO₂ oxidation of the corresponding hepta-2,5-diyne-1,4,7-triol (**2**) obtained by Grignard reaction of the dimagnesium salt of propargyl alcohol (prop-2-yn-1-ol, **1**) to ethyl formate in ether–benzene. Treatment of **3a** with conc. HCl in AcOH at 0 °C for 1 h gave the 3,8-dichloro-2,2,7,7-tetraphenyl-1,6-dioxaspiro[4.4]nona-3,8-diene (**4a**, X = Cl) in 85% yield. Similar treatment of **3a** with HBr and HI afforded the corresponding dibromo- (**4a**, X = Br) and diiodospiroketals (**4a**, X = I) in 72 and 68% yields, respectively. Dihydroxydiynones (**3b–3g**) also gave the corresponding spiroketals (**4b–4g**) in yields of 62–97% (Table 1).

A plausible mechanism for this spiroketalization reaction probably involves the allene intermediate (**5**) formed by HX addition to **3** (Scheme 1). Intramolecular cyclization of the OH group of **5** gives **6** which again reacts with another HX to give allene (**7**). Finally, cyclization of the OH of **7** leads to dihalospiroketal (**4**).

Interestingly, spiroketalization of optically active 1,7-dihydroxy-1,7-bis(*o*-chlorophenyl)-1,7-diphenylhepta-2,5-diyn-4-one (**3h**) with aq. HX in AcOH was found to produce optically active spiroketals (**4h**) without any racemization. In a typical experiment a mixture of (*S,S*)-(-)-**3h** (0.1 g, 0.20 mmol) prepared from optically pure propargyl alcohol (**1h**),³ and 47% aq. HBr (0.2 ml) in AcOH (10 ml) was stirred at 0 °C for 1 h. A crystalline powder formed which was filtered, washed with water and dried to give (*R,R*)-(+)-**4h** (X = Br) (0.09 g, 70% yield) as colorless prisms (mp 285–288 °C, [α]_D +386° (c 1.2, CHCl₃). The optical purity was determined by chiral HPLC (Chiralcel OD, Daicel). Similarly (*S,S*)-(-)-**4h** (X = Br) of 100% ee was obtained by the reaction of (*R,R*)-(+)-**3h** with aq. HBr in AcOH (Table 2). Similar treatment of (-)-**3h** with HCl and HI in AcOH gave the corresponding optically pure dichloro- and diiodospiroketals (+)-**4h** (X = Cl) and (+)-**4h**

Table 1 Yields and melting points of halogenated spiroketals (**4**)

Spiroketal	Yield (%)	Mp/°C
4a (X = Cl)	85	168–171
4a (X = Br)	72	152–155
4a (X = I)	68	198–202
4b (X = Cl)	73	219–225
4b (X = Br)	63	226–230
4b (X = I)	77	280–283
4c (X = Cl)	62	268–274
4c (X = Br)	63	293–297
4c (X = I)	62	267–273
4d (X = Cl)	72	115–116
4d (X = Br)	97	135–138
4d (X = I)	64	109–112
4e (X = Cl)	78	84–87
4e (X = Br)	63	99–103
4e (X = I)	64	128–131
4f (X = Cl)	75	Oil
4f (X = Br)	85	Oil
4f (X = I)	82	Oil
4g (X = Cl)	81	Oil
4g (X = Br)	84	Oil
4g (X = I)	77	Oil

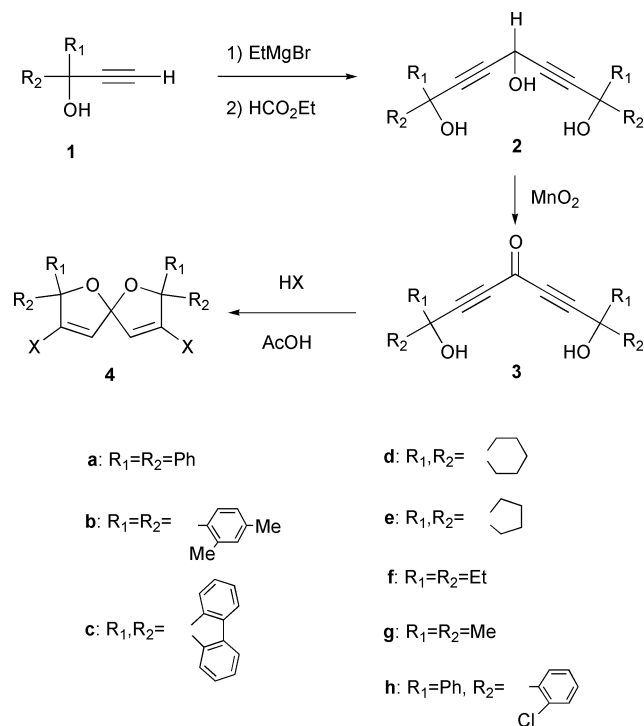


Scheme 1

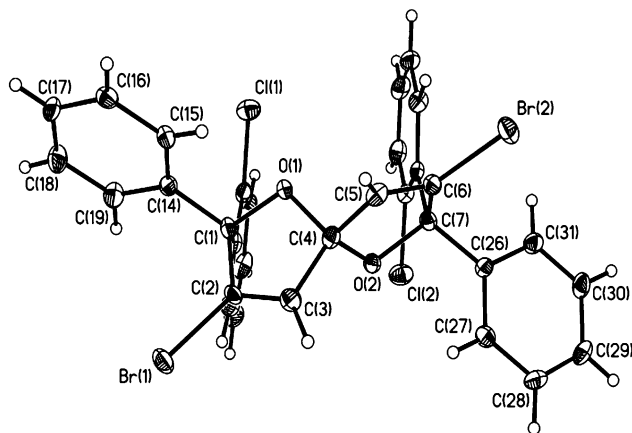
Table 2 Optically active halogenated spiroketals (**4h**)

Spiroketal	Yield (%)	Mp/ ^o C	[α] _D ²⁰ ^a	Ee (%) ^b
(+)- 4h (X = Cl)	68	284–286	+392	100
(+)- 4h (X = Br)	70	285–288	+386	100
(+)- 4h (X = I)	68	277–284	+368	100
(-)- 4h (X = Cl)	77	284–286	+394	100
(-)- 4h (X = Br)	62	285–288	+387	100
(-)- 4h (X = I)	69	284–286	+362	100

^a Measured in CHCl₃. ^b Optical purity was determined by HPLC (Chiralcel OD, Daicel).



(X = I), respectively. Optically pure spiroketals (–)-**4h** (X = Cl) and (–)-**4h** (X = I) were also prepared by the reaction of (+)-**3h** with HCl and HI in AcOH, respectively. The absolute configuration of the optically active spiroketal (*S,S*)-(–)-**4h** (X = Br) was determined by X-ray crystal structure analysis⁴ (Fig. 1).

**Fig. 1** X-Ray crystal structure of (*S,S*)-(–)-**4h** (X = Br).

Conclusion

In conclusion, we have developed a simple and efficient synthesis of symmetrical halogenated spiroketals in good yields

by the reaction of 1,7-dihydroxyhepta-2,5-diyne-4-ones (**3**) with HX in AcOH. Further studies directed at broadening the scope of this spiroketalization are now under way.

Experimental

Typical procedure for the spiroketalization of **3a** to **4a**

When a mixture of **3a** (0.20 g, 0.45 mmol) and conc. HCl (0.4 ml) in AcOH (20 ml) was stirred at 0 °C for 1 h, a crystalline powder was formed. The crude product was filtered, washed with water and dried to give **4a** (0.19 g, 85% yield). Recrystallization of the crude product from AcOEt gave pure **4a** as colorless prisms (mp 168–171 °C). IR (ν /cm⁻¹) 1627 (C=C); $\lambda_{\text{max}}/\text{nm}$ (CHCl₃) 241 ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$, 700), 253 (ϵ 670), 259 (ϵ 840), 265 (ϵ 700); ¹H-NMR (300 MHz, CDCl₃) δ 7.50–7.21 (m, 20 H), 5.96 (s, 2 H); ¹³C-NMR (75 MHz, CDCl₃) δ 94.0, 117.3, 124.8, 127.7, 127.8, 128.0, 128.2, 140.8, 140.9, 141.1. Anal. Calcd for C₃₁H₂₂O₂Cl₂: C, 74.85; H, 4.46. Found: C, 74.88; H, 4.54%.

Typical procedure for the spiroketalization of (*S,S*)-(–)-**3h** to (*R,R*)-(+)-**4h** (X = Br)

When a mixture of (*S,S*)-(–)-**3h** (0.10 g, 0.20 mmol) and conc. HBr (0.2 ml) in AcOH (10 ml) was stirred at 0 °C for 1 h, a crystalline powder was formed. The crude product was filtered, washed with water and dried to give (*R,R*)-(+)-**4h** (X = Br) (0.09 g, 70% yield). Recrystallization of the crude product from AcOEt gave pure (*R,R*)-(+)-**4h** (X = Br) as colorless prisms (mp 285–288 °C). IR (ν /cm⁻¹) 1610 (C=C); $\lambda_{\text{max}}/\text{nm}$ (CHCl₃) 243 ($\epsilon/\text{dm}^3 \text{ mol}^{-1} \text{ cm}^{-1}$, 16900), 255 (ϵ 7370), 261 (ϵ 9290), 267 (ϵ 9050), 276 (ϵ 4740); ¹H-NMR (300 MHz, CDCl₃) δ 7.73–7.07 (m, 18 H), 6.44 (s, 2 H); ¹³C-NMR (75 MHz, CDCl₃) δ 93.7, 118.3, 126.1, 127.8, 129.2, 129.4, 130.0, 131.2, 133.0, 134.2, 138.3, 140.1. Anal. Calcd for C₃₁H₂₀O₂Br₂Cl₂: C, 56.83; H, 3.08. Found: C, 56.85; H, 3.16%.

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- Crystal data for (*S,S*)-(–)-**4h** (X = Br): C₃₁H₂₀Br₂Cl₂O₂, *M* = 655.19, orthorhombic, *a* = 12.0964(14), *b* = 13.5239(15), *c* = 16.1906(19) Å, $\alpha = 90^\circ$, $\beta = 90^\circ$, $\gamma = 90^\circ$, *V* = 2648.6(5) Å³, *T* = 100 K, space group *P*2₁2₁2₁, *Z* = 4, μ (Mo-K α) = 3.291 mm⁻¹, 22651 reflections measured, 8166 unique (*R*_{int} = 0.0223) which were used in all calculations. Final *R* indices [*I* > 2 σ (*I*): *R*₁ = 0.0215, *wR*₂ = 0.0327. CCDC reference number 177772. See <http://www.rsc.org/suppdata/p1/b2/b200215a> for crystallographic files in .cif or other electronic format.