COMMUNICATION

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

Koichi Tanaka * and Naoyuki Harada

Department of Applied Chemistry, Faculty of Engineering, Ehime University, Matsuyama, Ehime 790-8577, Japan. E-mail: tanaka@en3.ehime-u.ac.jp

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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.

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

85

72

68

73

63

77

62

63

62

72

Spiroketal

4a (X = Cl)

4a(X = Br)

4a(X = I)

4b(X = Cl)

 $4\mathbf{b}(\mathbf{X} = \mathbf{Br})$

 $4\mathbf{b} (\mathbf{X} = \mathbf{I})$

4c (X = Cl)

4c(X = Br)

4d(X = Cl)

4f(X = Br)

4g(X = Cl)

 $4\mathbf{g}(\mathbf{X} = \mathbf{Br})$

4g(X = I)

4f(X = I)

4c(X = I)

Yield (%)

Mp/°C

168-171

152-155

198-202

219-225

226-230

280-283

268-274

293-297

267-273

115-116

Oil

Oil

Oil

Oil

Oil

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 <i>via</i> thermal cyclization of diallenes, ² we found unexpectedly that 1,7-dihydroxyhepta-2,5-diyn-4-ones (3) can be smoothly con- verted into halogenated spiroketals (4) by simple treatment with aq. hydrogen halides in AcOH. Optically active halogen- ated spiroketals (4) were also obtained by the reaction of ontically 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-4one (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, [a]_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 4d(X = Br)97 135-138 64 109-112 4d(X = I)4e(X = Cl)78 84-87 63 99-103 4e(X = Br)4e (X = I)64 128-131 4f(X = Cl)75 Oil

85

82

81

84

77



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Table 2 Optically active halogenated spiroketals (4h)

Spiroketal	Yield (%)	Mp/°C	$[a]_{\mathbf{D}}/^{\circ a}$	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-diyn-4-ones (3) with HX in AcOH. Further studies directed at broadening the scope of this spiroketalization protocol 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); λ_{max} /nm (CHCl₃) 241 (ϵ /dm³ mol⁻¹ 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); $\lambda_{max/nm}$ (CHCl₃) 243 (ϵ /dm³ mol⁻¹ 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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- 4 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, $a = 90^{\circ}$, $\beta = 90^{\circ}$, $\gamma = 90^{\circ}$, V = 2648.6(5) Å³, T = 100 K, space group $P2_{12}, 2_{1}, Z = 4$, μ (Mo-Ka) = 3.291 mm⁻¹, 22651 reflections measured, 8166 unique ($R_{int} = 0.0223$) which were used in all calculations. Final R indices [$I > 2\sigma(I)$]: R1 = 0.0215, wR2 = 0.0327. CCDC reference number 177772. See http://www.rsc.org/suppdata/p1/b2/b200215a for crystallographic files in .cif or other electronic format.