

## A CARBOCATIONIC ROUTE TO 3-SUBSTITUTED 1,4-CYCLOHEPTADIENES

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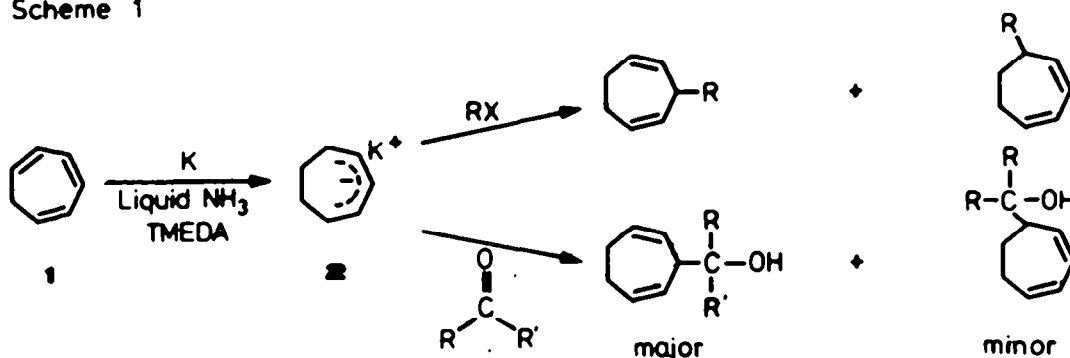
(Received in Germany 30 September 1986)

**Abstract:** The Lewis acid catalysed reaction of 5-chloro-1,3-cycloheptadiene **4** with silyl enol ethers yields  $\alpha$ -cycloheptadienyl substituted carbonyl compounds in high yield. Since **4** is easily prepared from cycloheptatriene, and the cycloheptadienyl cation **3** is preferably attacked at 3-position, this reaction opens an efficient access to 3-substituted 1,4-cycloheptadienes.

Whereas five and six membered ring compounds can usually be prepared via cyclization or cycloaddition reactions [1], these methods are often not applicable for the synthesis of seven membered carbocycles [2]. Therefore, there is interest in procedures that use readily available seven membered ring compounds as building blocks.

Cycloheptatriene **1**, which is the least expensive seven membered carbocycle [3], can be employed to synthesize substituted cycloheptadienes as illustrated in Scheme 1 [4].

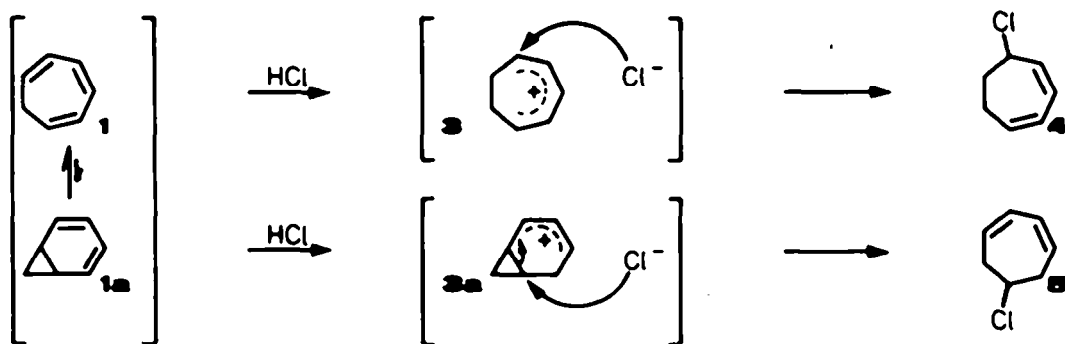
Scheme 1



The cationic counterpart of **2**, the cycloheptadienyl cation **3**, has previously not been used as a synthon in C-C bond forming reactions [5]. Replacement of **2** by **3**, which corresponds to an Umpolung of reactivity [6], should open the way to cycloheptadiene derivatives of different functionality. In this work, we studied the reactions of **3** with silyl enol ethers, employing the methodology developed by Reetz and coworkers [7].

5-Chloro-1,3-cycloheptadiene **4**, the precursor of **3**, was obtained by addition of hydrogen chloride to **1** in glacial acetic acid solution, analogous to the procedure described for the preparation of the corresponding bromide by Willstätter [8]. Whereas 3-chloro-1,4-cycloheptadiene was not observed as a side product of this reaction, compound **4** was accompanied by 20% of the anti-Markovnikov adduct **5**. Since the **4**/**5** ratio was not altered when the reaction was carried out in the presence of hydroquinone, a radical chain mechanism cannot account for the formation of **5**.

### Scheme 2



The protonation of norcaradiene **1a**, which may be considered as a cyclopropyl substituted cyclohexadiene, can be expected to be much faster than the protonation of cycloheptatriene **1** [9]. Therefore, the small concentration of **1a** [10], which rapidly equilibrates [11] with **1**, may be responsible for the formation of **5**. The last step of the sequence formulated in Scheme 2 is analogous to the mechanism of the acid catalyzed rearrangement of 2-methoxy-bicyclo[4.1.0]hept-3-ene to 6-methoxy-1,3-cycloheptadiene [12]. Since **5** proved to be inert under the conditions of the Lewis acid catalyzed addition reactions, attempts to separate **4** and **5** have not been undertaken.

The zinc chloride/ether catalyzed reaction of **5** with the silyl enol ethers **6-10** at  $-78^{\circ}\text{C}$  yielded the carbonyl compounds **11-15** in 56 - 98% yield (Tables 1 and 2). Attempts to employ (trimethylsilyloxy)ethene or 1-(trimethylsilyloxy)propene for this reaction have not been successful.

With the exception of **6**, all reactions gave mixtures of 1,4-cycloheptadienes and 1,3-cycloheptadienes. As the aldehyde derivative **6** selectively attacks C-3 of the cycloheptadienyl cation [13], while the ketone derivatives **7-9** show a slight preference for C-3 attack and the ketene acetal **10** yields more **15b** than **15a**, one might conclude that increasing nucleophilicity raises the percentage of C-1 attack. This interpretation cannot hold generally, however, since isobutene, which is considerably less nucleophilic than **6** was found to react at both positions [5].

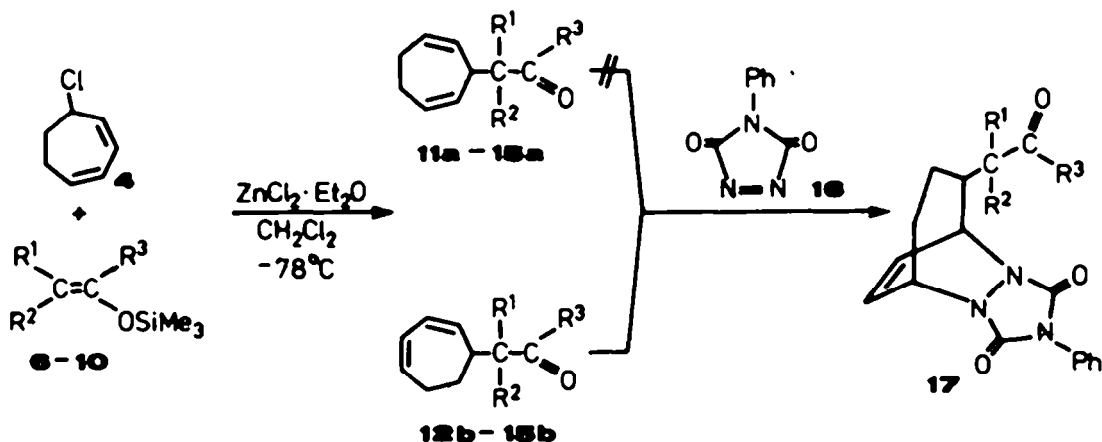

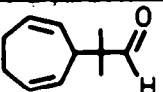
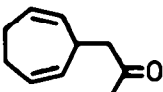
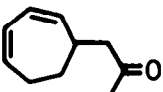
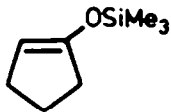
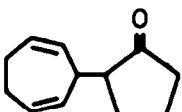
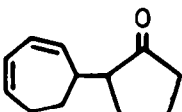
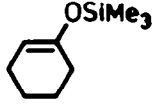
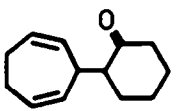
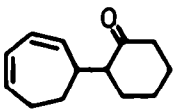
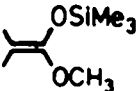
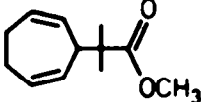
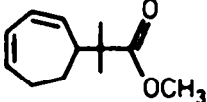


Table 1. Zinc Chloride Catalyzed Reactions of 5-Chloro-1,3-cycloheptadiene **4** with the Silyl Enol Ethers **6-10** in Dichloromethane at  $-78^{\circ}\text{C}$ 

Silyl enol ether	Products	% Yield (Isomer ratio) <sup>a</sup>	Isolated Yield % of <b>12a-15a</b> <sup>b</sup>
		56 (100:0)	56
<b>7</b>	 	80 (62:38)	45
	 	83 (50:50)	27
	 	79 (66:34)	40
	 	98 (44:56)	39

a) Estimated from the intensities of corresponding  $^{13}\text{C}$  NMR signals.

b) After removing **12b-15b** by Diels Alder reaction with **16**.

The 1,3-cycloheptadiene derivatives **12b-15b** react rapidly with 4-phenyl-1,2,4-triazoline-3,5-dione **16**, a highly active dienophile [14]. Therefore, the pure 1,4-cycloheptadiene derivatives **12a-15a** could be isolated by treating the isomer mixtures with **16** and successive distillation or adsorption of the Diels-Alder adducts on silica gel [15].

Compared with the previously reported method for the selective preparation of 3-substituted 1,4-cycloheptadienes (Scheme 3) [16], the routes *via* the cycloheptadienyl synthons **2** and **3** and subsequent destruction of the 1,3-cycloheptadienes appear to be more efficient.

### Scheme 3

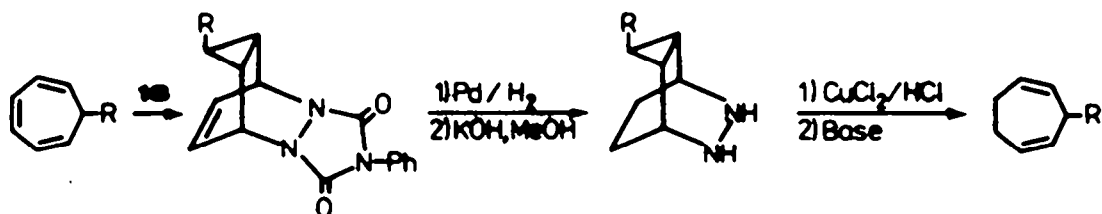


Table 2.  $^{13}\text{C}$  NMR Chemical Shifts of the Substituted Cycloheptadienes 11 - 15.

	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	C-1	C-2	C-1'	C-2' C-7'	C-3' C-6'	C-4' C-5'	R <sup>1</sup> - R <sup>2</sup>
11a	CH <sub>3</sub>	CH <sub>3</sub>	H	206.05	49.61	43.26	131.93	129.01	26.27	19.03
12a	H	H	CH <sub>3</sub>	207.58	50.15	34.08	132.72	130.65	26.36	30.38
13a	H	-(CH <sub>3</sub> ) <sub>2</sub> -		220.04	54.39	39.60	132.02 <sup>*</sup> 132.12 <sup>*</sup>	130.94 <sup>*</sup> 129.43 <sup>*</sup>	26.76 <sup>*</sup> 27.07 <sup>*</sup>	20.59, 25.65, 39.16
14a	H	-(CH <sub>3</sub> ) <sub>2</sub> -		211.63	55.70	38.06	132.42 <sup>**</sup> ***	130.85 <sup>**</sup> 130.69 <sup>**</sup>	26.68 <sup>**</sup> 26.75 <sup>**</sup>	25.04, 27.47, 29.34, 42.25
15a	CH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>	178.13	46.01	45.40	131.22	129.87	26.26	22.17, 51.87
12b	H	H	CH <sub>3</sub>	207.72	49.35	36.72	136.55 30.66 <sup>*</sup>	124.57 <sup>*</sup> 29.05 <sup>*</sup>	124.70 <sup>*</sup> 134.22	30.48
13b <sup>**</sup>	H	-(CH <sub>3</sub> ) <sub>2</sub> -		220.23	54.49	40.94	136.51 30.37 <sup>*</sup>	124.65 <sup>*</sup> 28.40 <sup>*</sup>	125.87 <sup>*</sup> 134.01	20.63, 25.39, 38.99
				220.53	54.14	41.41	134.29 31.02 <sup>*</sup>	124.79 <sup>*</sup> 30.11 <sup>*</sup>	124.92 <sup>*</sup> ***	20.71, 26.01, 38.92
14b <sup>**</sup>	H	-(CH <sub>3</sub> ) <sub>2</sub> -		212.05	55.04	39.58	135.31 30.05 <sup>*</sup>	124.52 <sup>*</sup> 25.93 <sup>*</sup>	124.80 <sup>*</sup> 133.83	24.70, 27.80, 29.04, 42.33
				212.44	***	39.75	137.05 30.33 <sup>*</sup>	124.72 <sup>*</sup> 28.32 <sup>*</sup>	124.83 <sup>*</sup> 134.36	25.55, 27.99, 29.94, 43.91
15b	CH <sub>3</sub>	CH <sub>3</sub>	OCH <sub>3</sub>	178.38	45.88	48.10	134.27 31.66 <sup>*</sup>	124.82 <sup>*</sup> 29.23 <sup>*</sup>	125.25 <sup>*</sup> 133.76	21.59 <sup>*</sup> , 22.80 <sup>*</sup> , 51.76

\* Assignment uncertain; \*\* Approximately 1:1 mixtures of diastereomers, signals assigned to the corresponding isomers may be interchanged; \*\*\* Signal covered.

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for support of this work.

## EXPERIMENTAL

NMR: XL 200 (Varian);  $^{13}\text{C}$  NMR data are given in Table 2. - Mass spectra: 70-250 (VG) - IR: IR-435 (Shimadzu). The commercially available compounds 8-10 have been purified by distillation, the silyl enol ethers 6 and 7 have been synthesized according to House's procedure [17].

**5-Chloro-1,3-cycloheptadiene 4.** A stream of HCl was passed into a solution of 1 (130 g, 1.41 mol) in 400 mL of glacial acetic acid. The solution was slowly cooled to 0°C avoiding freezing. After absorption of 0.96 equivalents of HCl (49.4 g) the cooling bath was removed and the solution was stirred at ambient temperature for 24 h. Ice cubes (= 400 g) were added, the organic layer was separated, and the aqueous layer was extracted twice with 150 mL of ether. The combined organic layers were washed with cold 10% aqueous NaHCO<sub>3</sub> solution until the aqueous layer showed a neutral reaction. The ethereal solution was then washed twice with 50 mL of cold water, dried with CaCl<sub>2</sub>, and distilled. After evaporation of the ether, 47.0 g of unreacted 1 was isolated in the forerun and used for further reactions. The main fraction (47.0 g, 41% with respect to reacted 1) with bp 66 - 71°C/19 mbar contained 4 and 5 in a 4:1 ratio. The residue (58.4 g) was a mixture of higher chlorinated compounds. 4:  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta$  1.98 - 2.15 (m, 1 H, 6-H), 2.22 - 2.46 (m, 2 H, 6,7-H), 2.54 - 2.76 (m, 1 H, 7-H), 4.85 (mc, 1 H, 5-H), 5.76 - 6.13 (m, 4 H, 1,2,3,4-H). -  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>): see preceding publication [5].

**6-Chloro-1,3-cycloheptadiene 5,** the minor component in this mixture, did not react with 6-10 under the conditions used in this work and was obtained in pure form in the forerun of the following addition reactions. -  $^1\text{H}$  NMR (CDCl<sub>3</sub>):  $\delta$  2.64 - 2.94 (m, 4 H, 5,7-H), 4.36 (mc, 1 H, 6-H), 5.63 - 5.77 (m, 2 H, 1,4-H), 5.80 - 5.93 (m, 2 H, 2,3-H). -  $^{13}\text{C}$  NMR (CDCl<sub>3</sub>):  $\delta$  41.10 (t), 58.76 (d), 126.59 (d), 128.22 (d).

**5-Chloro-1,3-cycloheptadiene 4 and 2-Methyl-1-(trimethylsilyloxy)propene 6 (Typical Procedure).** A solution of 6 (2.59 g, 18.0 mmol) in 20 mL of CH<sub>2</sub>Cl<sub>2</sub> was added dropwise with stirring to a cooled (-78°C) solution of 4 (10.0 mmol = 1.60 g of a 4:1 mixture of 4 and 5), ZnCl<sub>2</sub> (2.07 g) and ether (2.48 mL) in 26 mL of CH<sub>2</sub>Cl<sub>2</sub>. After 3 h stirring at -78°C, the reaction mixture was washed with

an aqueous solution of  $\text{NH}_4\text{Cl}$  and water. The organic layer was separated, dried with  $\text{CaCl}_2$ , and distilled to give a fore-run of 5 (180 mg) and 920 mg (56%) of 2-(2,6-cycloheptadienyl)-2-methyl-propanal 11a with bp 40 - 45°C (bath)/0.1 mbar. -  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.07 (s, 6 H, 2  $\text{CH}_3$ ), 2.00 - 2.39 (m, 4 H,  $\text{CH}_2\text{-CH}_2$ ), 3.50 (mc, 1 H, 1'-H), 5.48 (dd,  $J = 11.6$  Hz,  $J = 4.3$  Hz, 2 H, 2',7'-H), 5.70 - 5.87 (m, 2 H, 3',6'-H), 9.52 (s, 1 H, 1-H). - IR (neat): 1722, 1653  $\text{cm}^{-1}$ . - Mass spectrum (70 eV):  $m/z = 164$  (6%,  $\text{M}^+$ ), 149 (4), 131 (7), 121 (5), 94 (9), 93 (100), 87 (13), 86 (13), 79 (16), 77 (39), 72 (6), 71 (6), 65 (9), 55 (13). - The 2,4-dinitrophenylhydrazone of 11a gave orange needles with mp 138 - 138.5°C (Ethanol). Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_4$ : C, 59.29; H, 5.85. Found: C, 58.94; H, 5.93.

**Isolation of the Pure 1,4-Cycloheptadiene Compounds 12a-15a.** The mixtures of 1,3- and 1,4-cycloheptadienes, which were obtained by the procedure described above, were dissolved in acetone (1:1, v/v). A 30% solution of 16 in acetone was added dropwise until the red colour of 16 stopped to fade immediately. The solvent was removed in vacuo and the residue was put on silica gel. Elution with hexane/ether (10/1, v/v) yielded the pure 1,4-cycloheptadienes 12a-15a.

**1-(2,6-Cycloheptadienyl)propan-2-one 12a.** Compound 7 (2.34 g, 18.0 mmol) reacted with 4 (10.0 mmol) in 1 h under the conditions described above to give 1.20 g (80%) of a 62:38 mixture of 12a and 12b with bp 35 - 40°C (bath)/0.1 mbar. - Mass spectrum (70 eV):  $m/z = 150$  (16%,  $\text{M}^+$ ), 43 (100). - Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{O}$  (150.2): C, 79.96; H, 9.39. Found: C, 79.75; H, 9.20. - When 12b was removed with 16, 0.678 g (45% total yield) of 12a was obtained. -  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  2.00 - 2.44 (m, 4 H, 4',5'-H), 2.13 (s, 3 H, 3-H), 2.59 (d,  $J = 7.4$  Hz, 2 H, 1-H), 3.58 - 3.74 (m, 1 H, 1'-H), 5.40 (br.dd,  $J = 11.1$  Hz,  $J = 4.2$  Hz, 2 H, 2',7'-H), 5.71 (ddd,  $J = 11.1$  Hz,  $J = 5.9$  Hz,  $J = 2.1$  Hz, further splitting due to homoallylic coupling, 2 H, 3',6'-H). - IR (neat): 1709 (C=O), 1653, 1643 (C=C).

**2-(2,6-Cycloheptadienyl)cyclopentan-1-one 13a.** Compound 8 (2.81 g, 18.0 mmol) and 4 (10.0 mmol) gave 1.46 g (83%) of a 1:1 mixture of 13a and 13b (reaction time 1 h) with bp 60 - 65°C (bath)/0.2 mbar. - Mass spectrum (70 eV):  $m/z = 176$  (19%,  $\text{M}^+$ ), 92 (100). - Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{O}$  (176.3): C, 81.77; H, 9.15. Found: C, 81.48; H, 9.10. - Treatment of this mixture with 16 gave 0.480 g (27%) of 13a. -  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.60 - 2.45 (m, 11 H, 2,3,4,5-H, 4',5'-H), 3.76 (mc, 1 H, 1'-H), 5.20 (br.dd,  $J = 11.4$  Hz,  $J = 4.2$  Hz, 1 H, 2'-H or 7'-H), 5.46 (br.dd,  $J = 11.3$  Hz,  $J = 4.2$  Hz, 1 H, 2'-H or 7'-H), 5.73 - 5.88 (m, 2 H, 3',6'-H). - IR (neat): 1731 (C=O), 1672, 1657 (C=C).

**2-(2,6-Cycloheptadienyl)cyclohexan-1-one 14a.** Compounds 9 (3.07 g, 18.0 mmol) and 4 (10.0 mmol) reacted within 1 h to yield a 66:34 mixture of 14a and 14b (1.50 g, 79%), with bp 60 - 65°C (bath)/0.1 mbar. - Mass spectrum (70 eV):  $m/z = 190$  (46%,  $\text{M}^+$ ), 92 (100). - Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{O}$  (190.3): C, 82.06; H, 9.53. Found: C, 81.47; H, 9.33. - After removing 14b as the Diels-Alder adduct, 14a (0.764 g, 40%), was obtained as a pure material. -  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.52 - 2.51 (m, 13 H, 2,3,4,5,6-H, 4',5'-H), 3.76 (mc, 1 H, 1'-H), 5.36 - 5.51 (m, 2 H, 2',7'-H), 5.71 - 5.85 (m, 2 H, 3',6'-H). - IR (neat): 1703 (C=O), 1674, 1654 (C=C).

**Methyl-2-(2,6-cycloheptadienyl)-2-methyl-propanoate 15a.** Compounds 10 (3.13 g, 18.0 mmol) and 4 (10.0 mmol) gave 1.90 g (98%) of a 44:56 mixture of 15a and 15b with bp 32 - 36°C (bath)/0.1 mbar. - Mass spectrum (70 eV):  $m/z = 194$  (2%,  $\text{M}^+$ ), 93 (100). - Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{O}_2$  (194.3): C, 74.19; H, 9.34. Found: C, 74.08; H, 9.40. - The 1,4-isomer 15a was isolated in 39% total yield when 15b was reacted with 16. 15a:  $^1\text{H NMR}$  ( $\text{CDCl}_3$ ):  $\delta$  1.19 (s, 6 H, 2  $\text{CH}_3$ ), 1.98 - 2.43 (m, 4 H, 4',5'-H), 3.54 - 3.64 (m, 1 H, 1'-H), 3.68 (s, 3 H,  $\text{OCH}_3$ ), 5.43 (br.dd,  $J = 11.3$  Hz,  $J = 4.2$  Hz, 2 H, 2',7'-H), 5.68 - 5.80 (m, 2 H, 3',6'-H). - IR (neat): 1727 (C=O), 1654, 1645 (C=C).

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