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

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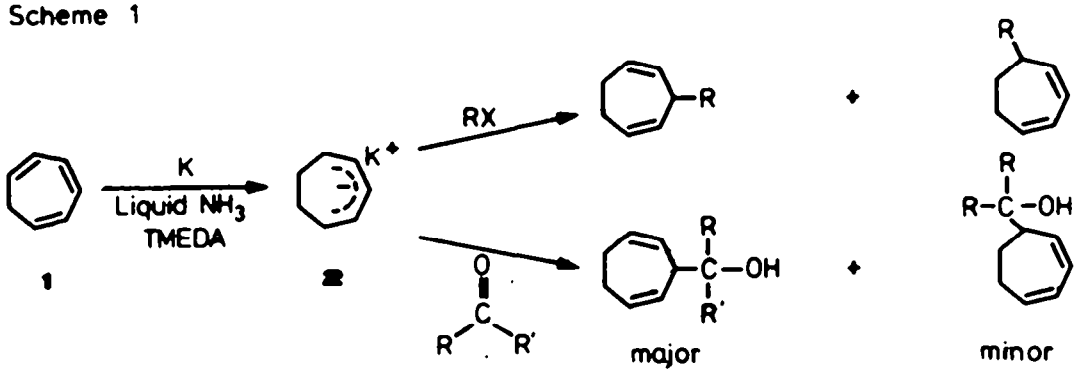
Abstract: The Lewis acid catalysed reaction of 5-chloro-1,3-cycloheptadiene **4** with silyl enol ethers yields α-cycloheptadienyl substituted carbonyl compounds in high yield. Since **4** is easily prepared from cycloheptatriene, and the cycloheptadienyl cation **3** is preferably attacked at 3-position,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

Whereas five and six membered ring compounds can usually be prepared via cyclisation 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].

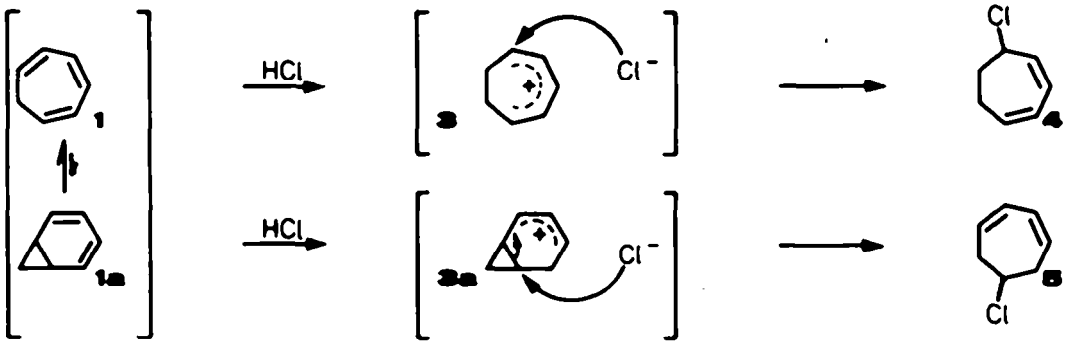
Scheme 1



The cationic counterpart of **2**, the cycloheptadienyl cation **3**, has previously not been used as a synthon in CC-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°C yielded the carbonyl compounds **11-15** in 56 - 98% yield (Tables 1 and 2). Attempts to employ (trimethylsiloxy)ethene or 1-(trimethylsiloxy)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].

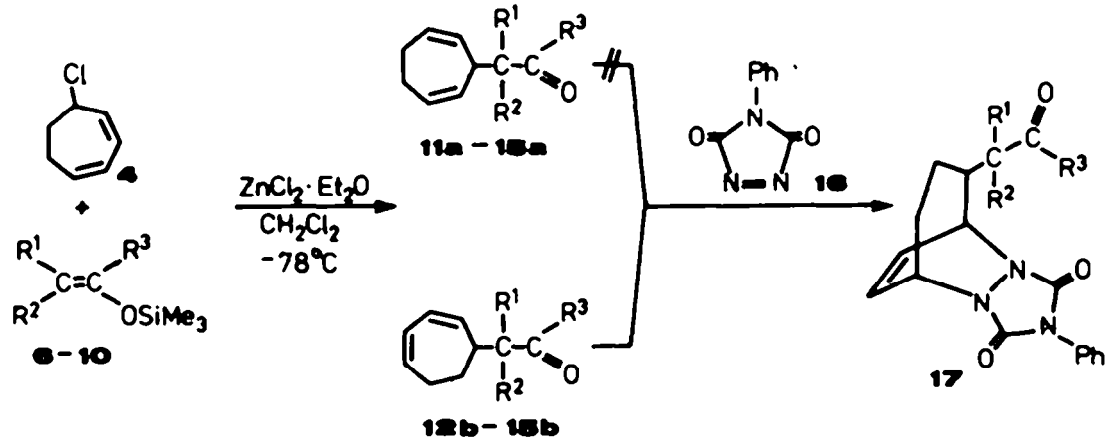
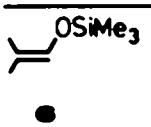
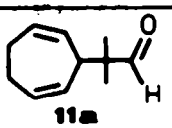
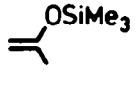
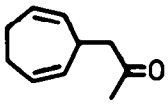
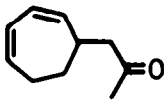
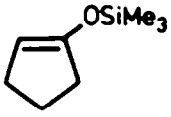
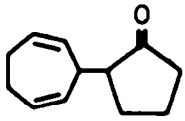
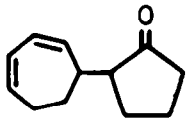
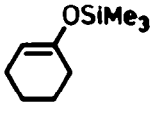
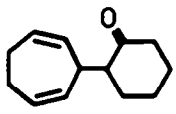
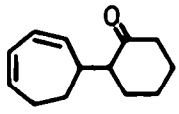
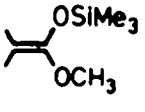
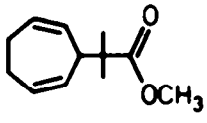
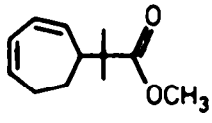


Table 1. Zinc Chloride Catalysed Reactions of 5-Chloro-1,3-cycloheptadiene 4 with the Silyl Enol Ethers 6-10 in Dichloromethane at -78°C

Silyl enol ether	Products		% Yield (Isomer ratio)[a]	Isolated Yield % of 12a - 15a[b]
 6	 11a		56 (100 : 0)	56
 7	 12a	 12b	80 (62 : 38)	45
 8	 13a	 13b	83 (50 : 50)	27
 9	 14a	 14b	79 (66 : 34)	40
 10	 15a	 15b	98 (44 : 56)	39

a) Estimated from the intensities of corresponding ^{13}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

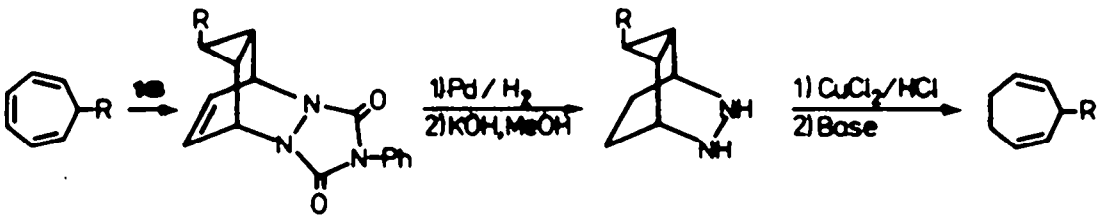
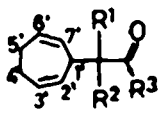
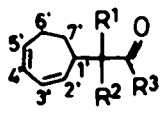


Table 2. ^{13}C NMR Chemical Shifts of the Substituted Cycloheptadienes 11 - 15.



11a - 15a



12b - 15b

	R^1	R^2	R^3	C-1	C-2	C-1'	C-2' C-7'	C-3' C-6'	C-4' C-5'	R^1 - R^3
11a	CH_3	CH_3	H	206.05	49.61	43.26	131.93	129.01	26.27	19.03
12a	H	H	CH_3	207.58	50.15	34.08	132.72	130.65	26.36	30.38
13a	H	-$(CH_2)_3$-		220.04	54.39	39.60	132.02* 132.12*	130.94* 129.43*	26.76* 27.07*	20.59, 25.65, 39.16
14a	H	-$(CH_2)_4$-		211.63	55.70	38.06	132.42* ***	130.85* 130.69*	26.68* 26.75*	25.04, 27.47, 29.34, 42.25
15a	CH_3	CH_3	OCH_3	178.13	46.01	45.40	131.22	129.87	26.26	22.17, 51.87
12b	H	H	CH_3	207.72	49.35	36.72	136.55 30.66*	124.57* 29.05*	124.70* 134.22	30.48
13b**	H	-$(CH_2)_3$-		220.23	54.49	40.94	136.51 30.37*	124.65* 28.40*	125.87* 134.01	20.63, 25.39, 38.99
				220.53	54.14	41.41	134.29 31.02*	124.79* 30.11*	124.92* ***	20.71, 26.01, 38.92
14b**	H	-$(CH_2)_4$-		212.05	55.04	39.58	135.31 30.05*	124.52* 25.93*	124.80* 133.83	24.70, 27.80, 29.04, 42.33
				212.44	***	39.75	137.05 30.33*	124.72* 28.32*	124.83* 134.36	25.55, 27.99, 29.94, 43.91
15b	CH_3	CH_3	OCH_3	178.38	45.88	48.10	134.27 31.66*	124.82* 29.23*	125.25* 133.76	21.59*, 22.80*, 51.76

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

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EXPERIMENTAL

NMR: XL 200 (Varian); ^{13}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 absorbtion 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 $NaHCO_3$ solution until the aqueous layer showed a neutral reaction. The ethereal solution was then washed twice with 50 mL of cold water, dried with $CaCl_2$, 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: ^1H NMR ($CDCl_3$): δ 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}C NMR ($CDCl_3$): 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. - ^1H NMR ($CDCl_3$): δ 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}C NMR ($CDCl_3$): δ 41.10 (t), 58.76 (d), 126.59 (d), 128.22 (d).

5-Chloro-1,3-cycloheptadiene 4 and 2-Methyl-1-(trimethylsiloxy)propene 6 (Typical Procedure). A solution of 6 (2.59 g, 18.0 mmol) in 20 mL of CH_2Cl_2 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), $ZnCl_2$ (2.07 g) and ether (2.48 mL) in 26 mL of CH_2Cl_2. After 3 h stirring at -78°C, the reaction mixture was washed with

an aqueous solution of NH_4Cl and water. The organic layer was separated, dried with $CaCl_2$, and distilled to give a forerun 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. - ^1H NMR ($CDCl_3$): δ 1.07 (s, 6 H, 2 CH_3), 2.00 - 2.39 (m, 4 H, CH_2-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 cm^{-1}. - Mass spectrum (70 eV): m/z = 164 (6%, 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 $C_{17}H_{20}N_4O_4$: 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 immediatly. 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%, M^+), 43 (100). - **Anal.** Calcd for $C_{10}H_{14}O$ (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. - ^1H NMR ($CDCl_3$): δ 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%, M^+), 92 (100). - **Anal.** Calcd for $C_{12}H_{16}O$ (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**. - ^1H NMR ($CDCl_3$): δ 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%, M^+), 92 (100). - **Anal.** Calcd for $C_{13}H_{18}O$ (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. - ^1H NMR ($CDCl_3$): δ 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%, M^+), 93 (100). - **Anal.** Calcd for $C_{12}H_{18}O_2$ (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**: ^1H NMR ($CDCl_3$): δ 1.19 (s, 6 H, 2 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, 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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