Doubly Catalyzed Cyclization of ε-Acetylenic Carbonyl Compounds

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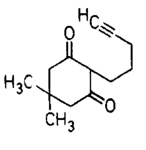
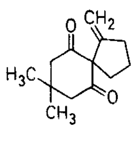
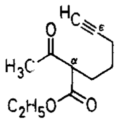
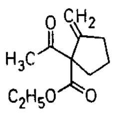
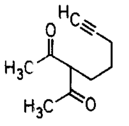
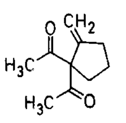
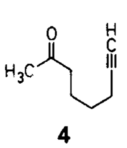
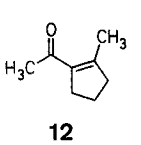
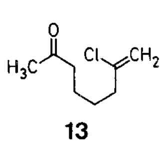
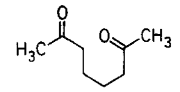
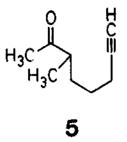
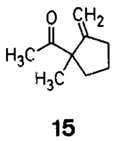
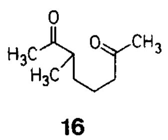
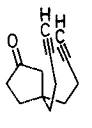
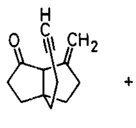
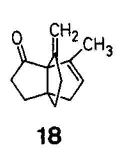
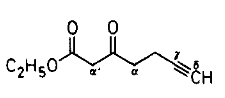
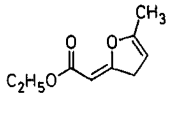
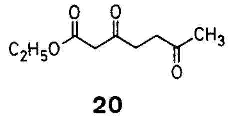
Double catalysis by $H^{\oplus}/Hg^{\oplus\oplus}$ of the intramolecular ene reactions of 5-alkynyl ketones (**4, 5, 6**), 2-(4′-alkynyl)-1,3-diketones (**1, 3**), and acetylenic ketoesters (**2, 7**) allows their cyclization at lower temperature than by the vapor- or liquid-phase thermal process. Comparison of the $H^{\oplus}/Hg^{\oplus\oplus}$ system with tin(IV) chloride or ethylaluminum dichloride shows the greater efficiency of the $H^{\oplus}/Hg^{\oplus\oplus}$ system.

The thermal cyclization of unsaturated carbonyl compounds has been extensively studied (for a review, see Ref.[1]) and applied to the synthesis of natural products[2], or structurally

Table 1. Catalyzed Cyclization of ε-Acetylenic Carbonyl Compounds

Educt	Products[a]	Experiment No.	Solvent[b]	Temperature [°C], time [h]	Catalyst[c]	Yield [%][d] or products	Molecular formula[e] or Lit. reference
 **1**	 **9**	1	TCE	70°, 8	A+C	**9**: 88	[8]
		2	TCE	70°, 8	A	**9**: 88	
		3	TCE	70°, 8	—	**9**: 88	
 **2**	 **10**	4	TCE	70°, 4	A+C	**10**: 83	$C_{11}H_{16}O_3$ (196.25)
		5	CH_2Cl_2	35°, 8	A+C	**10**: 83	
		6	TCE	70°, 4	A	**10**: 0	
		7	TCE	70°, 4	C	**10**: 0	
		8	CH_2Cl_2	35°, 8	E	**10**: 15	
		9	CH_2Cl_2	30°, 3	F	**10**: 80	
 **3**	 **11**	10	TCE	70°, 1.5	A+C	**11**: 93	$C_{10}H_{14}O_2$ (166.2)
		11	TCE	35°, 5	A+C	**11**: 93	
		12	CH_2Cl_2	40°, 8	A	**11**: 0	
		13	CH_2Cl_2	40°, 8	C	**11**: 0	
		14	CH_2Cl_2	40°, 8	E	**11**: <15	
		15	CH_2Cl_2	30°, 3	F	**11**: 90	
 **4**	 **12** +  **13** +  **14**	16	TCE	70°, 24	A+C	**12**: 38; **13**: 17; **14**: 25	**12**[10]
		17	TCE	70°, 24	B+D	**12**: 78	
		18	TCE	70°, 24	E	**12**: 70	
		19	CH_2Cl_2	30°, 30	F	**12**: 5	
 **5**	 **15** +  **16**	20	TCE	90°, 50	A+C	**15**: 45; **16**: 18	$C_9H_{14}O$ (138.2)
		21	TCE	90°, 24	B+D	**15**: 39	
		22	TCE	90°, 24	E	**15**: <5	
		23	CH_2Cl_2	30°, 50	F	**15**: 0	
 **6**	 **17** +  **18**	24	TCE	70°, 4	A+C	**17**: 70	**17**[3], **18**[3]
		25	TCE	110°, 8	A+C	**17**: 23; **18**: 43	
		26	TCE	90°, 24	E	**17**: <5	
		27	CH_2Cl_2	30°, 36	F	**17**: <5	
 **7**	 **19** +  **20**	28	CH_2Cl_2	35°, 4	A+C	**19**: 16; **20**: 80	**19**: $C_9H_{12}O_3$ (168.2)
		29	CH_2Cl_2	35°, 12	B+D	**19**: 75	
		30	CH_2Cl_2	30°, 12	F	**19**: <5	

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[a] All products are liquids. Their purity was checked by G.L.C. analysis: >99%.

[b] TCE = 1,1,2,2-tetrachloroethane.

[c] A: 0.1 mol $H^{\oplus}$/mol of educt as a 20% (w/vol) solution of hydrogen chloride in water.

B: 0.1 mol $H^{\oplus}$/mol of educt as a 1% (w/vol) solution of *p*-toluenesulfonic acid in ether.

C: 0.1 mol $Hg^{\oplus\oplus}$/mol of educt as a 10% (w/vol) solution of $HgCl_2$ in ethanol.

D: 0.1 mol $Hg^{\oplus\oplus}$/mol of educt as a 1% (w/vol) solution of $HgCl_2$ in ether.

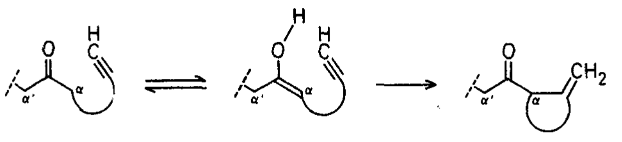
E: 0.2 mol distilled $SnCl_4$/mol of educt.

F: 1 mol of $C_2H_5AlCl_2$/mol of educt.

[d] Yields of products isolated by column chromatography.

[e] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.38; H, ±0.31.

complicated molecules[3,4]. The reaction which successively implies (a) enolisation, a catalytic process, and (b) an internal hydrogen shift (Scheme), a thermal process involving an intramolecular ene reaction, requires rather high temperatures (210-370°C for enones, 180-320°C for ynones) which impairs the convenience of the method; moreover, the olefinic products obtained from acetylenic starting materials in this manner have frequently undergone isomerization.



1-7 **8** **9-20**

In a few cases, catalysts have been used, more or less successfully, e.g., water[5] to accelerate the enolization of the unsaturated carbonyl compounds at high temperatures, zinc iodide[6], zinc stearate[7], and tin(IV) chloride[6]. We have now investigated the reaction in order to find conditions under which the reaction temperature can be lowered and migration of the unsaturated center be avoided. We report here the results obtained with the system $H^{\oplus}$ (to accelerate enolization)/$Hg^{\oplus\oplus}$ (to activate the triple bond toward nucleophilic addition of the enol). The reactions were performed either in 1,1,2,2-tetrachloroethane (for reactions above 40°C) or in dichloromethane (for reactions below 40°C). The catalysts used were: (1) 20% (w/vol) solutions of hydrogen chloride in water or (when side reactions such as hydration or hydrochlorination of the triple bond occurred) *p*-toluenesulfonic acid in ether; (2) 10% (w/vol) solutions of mercury(II) chloride in ethanol. The ratio $H^{\oplus}/Hg^{\oplus\oplus}$ used was 1/1 and the ratio catalyst/ynone 1/10.

Compounds **1-6** and **17** have previously been cyclized thermally in sealed tubes under the following conditions: **1** (235°C)[8], **2** (~250°C)[9], **3** (~250°C)[9], **4** (300°C)[10], **5** (~290°C)[9], **6** (240°C in decalin)[11], **17** (290°C in decalin)[3].

In the case of starting materials which can be easily cyclized thermally (**2, 3, 6**), catalytic amounts of $H^{\oplus}$ and $HgCl_2$ exert a strong effect so that cyclization proceeds already at temperatures below 70°C (experiments 4, 5, 10, 11, 24); $H^{\oplus}$ or $HgCl_2$ alone has no effect (experiments 6, 7, 12, 13). Diketone **1** displays a special behavior since it cyclizes on simple heating in 1,1,2,2-tetrachloroethane or deuterochloroform. All these readily proceeding reactions lead to the formation of exomethylene compounds (**9, 10, 11, 17**). The cyclization of compound **4** is accompanied by hydrochlorination and hydration (experiment 16) and that of compound **5** by hydration (experiment 20). The particular behaviour of ethyl 3-oxo-6-heptynoate (**7**) on treatment with the $H^{\oplus}/Hg^{\oplus\oplus}$ system is worthy of note: in anhydrous medium, the furan derivative **19** (i.e., the product of an intramolecular *O*-alkenylation) is obtained in 75% yield; a similar reaction has been observed in the attempted tin(IV) chloride-mediated cyclization of the analogous ethyl 3-oxo-6-heptenoate[12]; in this latter case, Baldwin's empirical rules for ring closure[13] are followed whereas these rules do not apply to ester **7**. Our results are consistent with the hitherto existing knowledge about this type of cyclization reaction: the cyclization **2**→**10** forming an α,ε bond is of the α type which is known to proceed readily[1]; whereas the analogous cyclization of **7** forming an α',γ bond would be of the α' type which is known to be a very difficult reaction[1].

Comparative experiments with other reagents were performed to assess the efficiency of the system $H^{\oplus}/Hg^{\oplus\oplus}$ in these cyclizations. It was found that tin(IV) chloride (distilled before use) is in general of only little efficiency in the reaction (cf. experiments 8, 14, 18, 22, 26) and that ethylaluminum dichloride (stoichiometric amounts)[14] works only with dicarbonyl compounds (experiments 9, 15, 19, 23, 27, 30).

Table 2. Spectral Data of the Cyclization Products obtained

Compound	I.R. (CCl_4) ν [cm^{-1}]	^{1}H-N.M.R. (CCl_4/TMS_{int}) δ [ppm]
9		in agreement with Ref.[8]
10	3100 (w), 1740 (s) 1715 (s), 1650 (m)	1.25 (t, J=7 Hz, 3H); 1.5-2.5 (m, 6H); 2.10 (s, 3H); 4.10 (q, J=5 Hz, 2H); 5.10 (t, J=2 Hz, 2H)
11	3090 (w), 1715 (s) 1700 (s), 1650 (m)[a]	1.5-2.6 (m, 6H); 2.10 (s, 6H); 5.10 (t, J=2 Hz, 1H); 5.22 (t, J=2 Hz, 1H)
12		in agreement with Ref.[10]
15	3090 (w), 1710 (s) 1650 (m)[b]	1.2 (s, 3H); 1.3-2.2 (m, 6H); 2.0 (s, 3H); 4.75 (t, 1H); 4.92 (t, 1H)
17		in agreement with Ref.[3]
18		in agreement with Ref.[3]
19	3150 (w), 1735 (s) 1650 (w)	1.22 (t, J=7 Hz, 3H); 2.21 (s, 3H); 3.45 (s, 2H); 4.05 (q, J=7 Hz, 2H); 5.75 (s, 1H); 5.90 (s, 1H)

[a] As film.
[b] In $CDCl_3$.

Ethyl 1-Acetyl-2-methylenecyclopentanecarboxylate (10); Typical Cyclization Procedure:

In a two-necked flask fitted with reflux condenser, nitrogen inlet, and stirrer are placed ethyl 2-acetyl-6-heptynoate (**2**; 1.00 g, 5.2 mmol) and purified (column with basic alumina, 100 g/1000 ml) 1,1,2,2-tetrachloroethane (12 ml). To this is added with stirring, at room temperature, a 10% (w/vol) solution of mercury(II) chloride in ethanol (1.4 ml, 0.1 mol/mol of **2**) and a 20% (w/vol) solution of hydrogen chloride in water (~100 μl, 0.1 mol/mol of **2**). The mixture is then stirred at 70°C for 4 h. The solvent is removed under vacuum (oil pump) at 40-45°C and the residue is dissolved in ether (15 ml). This solution is washed with 1 normal hydrochloric acid (3 ml) and saturated aqueous ammonium chloride (2×3 ml) and is dried with sodium sulfate. The ether is removed under reduced pressure and the residual product column-chromatographed on silica gel (25 g) using hexane/ether (90/10) as eluent to give the pure product **10**; yield: 0.83 g (83%); oil.

$C_{11}H_{16}O_3$	calc.	C 67.32	H 8.22
(196.25)	found	67.26	8.24

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