New and Effective Reagents for 1,4 Reduction of α,β-Unsaturated Ketones, $LiAlH_4$–CuI and Its Reactive Species H_2AlI

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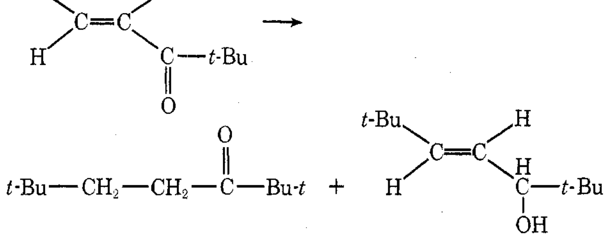
Conjugate reduction of six enones by the new reagent $LiAlH_4$–CuI has been studied. The optimum conditions for conjugate reduction depend on the ratio of $LiAlH_4$:CuI:enone, temperature, solvent, and reaction time involving contact of $LiAlH_4$ and CuI before the enone is added. Enone I can be reduced in quantitative yield and 100% regioselectivity in 1 h or less when the ratio of $LiAlH_4$:CuI:enone is 1:4:1, the solvent is THF, and the temperature is 0 °C. The enones II–VI also can be reduced in high yield and 100% regioselectivity. Reduction of enones I and III with $LiAlH_4$–$TiCl_3$ proceeds with 100% regioselectivity; however, the yields are lower (66 and 34%, respectively) compared to the results obtained with the $LiAlH_4$–CuI reagent. The reagent $LiAlH_4$–$FeCl_3$ was found to be ineffective for conjugate reduction. The new reagents ($LiAlH_4$–CuI and $LiAlH_4$–$TiCl_3$) show different stereoselectivity than $LiAlH_4$ toward 4-*tert*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone. Compared with $LiAlH_4$–CuI, related reagents ($LiAlH_4$–CuCl, $LiAlH_4$–HgI_2, and $LiAlH_4$–$HgCl_2$) show less regioselectivity in enone reduction; however, the reagent AlH_3–CuI is as effective in conjugate reduction as $LiAlH_4$–CuI. H_2AlI has been found to be the reactive species of the reagents $LiAlH_4$–CuI and AlH_3–CuI. The compounds H_2AlX and $HAlX_2$ where X = I, Br, and Cl were synthesized independently and were evaluated as conjugate reducing agents.

Catalytic hydrogenation[1] (H_2–Pd/C) and dissolving metal reduction[2] (Na–aqueous NH_3) are the most common methods for effecting conjugate reduction of enones. The shortcomings of these methods are mainly inconvenience and in many cases low yields. Recently, LiCuRH[3] and KB(*sec*-Bu)$_3$H[4] have been reported as effective reagents for conjugate reduction of enones. However, in the former case the reagent is quite difficult to prepare whereas in the latter case only 1,2 reduction is observed when β substituents are present in the enone. A method of accomplishing conjugate reduction of α,β-unsaturated carbonyl compounds by the use of an easily prepared reagent would indeed be very useful.

It is well known that $LiAlH_4$ favors 1,2 reduction of enones.[5] On the other hand, the reactivity of $LiAlH_4$ can be substantially modified by the addition of metal salts. In this connection $LiAlH_4$–$AlCl_3$[6] has found unusual applicability in epoxide reductions, $LiAl(OCH_3)_3H$–CuI[7] can effect reductive removal of halo and mesyloxy groups, and $LiAlH_4$–$TiCl_3$[8] has been found to be an excellent coupling reagent. Since $LiAlH_4$ is commercially available and convenient to handle as a standardized solution in ether or THF, its ability, in admixture with certain metal halides e.g., CuI, CuBr, CuCl, $TiCl_3$, HgI_2, $HgCl_2$, and $FeCl_3$, to effect conjugate reduction of enones was studied.

Results and Discussion

The enone 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one (enone I) was chosen as a representative enone for this study (eq 1). Reaction products were identified by NMR and compared with authentic samples. Yields were determined by GLC using an internal standard.



(1)

(1,4 reduction product) (1,2 reduction product)

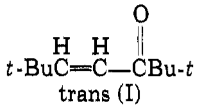
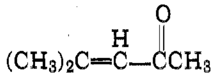
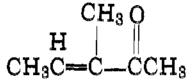
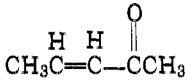
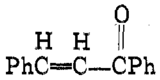
The effect of $LiAlH_4$–CuI on enone I has been studied in detail and the results are shown in Table I. Since $LiAlH_4$ (runs 1 and 2) and $LiAlH_4$–CuI (catalytic amount of CuI, run 3) give mostly 1,2 reduction, the 1,4 reduction product is assumed to arise from a species other than $LiAlH_4$. We have studied a wide variety of stoichiometric ratios of $LiAlH_4$:CuI:enone (runs 4–19) and have found that a ratio of 1:4:1 gives the best results under the conditions that $LiAlH_4$ and CuI are allowed to react before the addition of enone. At this stoichiometric ratio enone I was reduced in quantitative yield and 100% regioselectivity to the conjugate reduction product in THF at 0 °C when the reaction was allowed to proceed for 1 h. Stoichiometry relating the reactive species to ketone is important (runs 14–16) since a significant amount of enone is recovered unreacted when the $LiAlH_4$:CuI:enone ratio is 1:4:4 or 1:4:2. When the $LiAlH_4$–CuI ratio is 1:1 or 1:2 a significant amount of 1,2 product or unreacted ketone or both are observed (runs 4–11).

When $LiAlH_4$ and CuI are mixed at 0 °C in THF a deep black color immediately results with some gas evolution. It was found that ~3 min reaction time is required (runs 17–19) for all of the $LiAlH_4$ to be consumed so that no 1,2 reduction product is observed. Reaction of the active reagent with the enone appears to be over in 30–60 min.

Temperature studies clarify the stability of the $LiAlH_4$–CuI reagent. No reaction between $LiAlH_4$ and CuI occurs at −78 °C (run 26), slow reaction at −20 °C with some 1,2 reduction and recovered enone (run 27), and partial decomposition of the active reagent at room temperature (run 28). When $LiAlH_4$ and CuI were mixed at 0 °C and then cooled to −78 °C, no reaction took place as evidenced by complete recovery of the enone (run 26). On the other hand, generation of the active reagent at 0 °C followed by cooling to −20 °C before enone addition (run 27) resulted in 84% reaction with 100% regioselective formation of the conjugate reduction product. Since 10% ketone was recovered, it is clear that reduction of the substrate at −20 °C has no advantage over reduction at 0 °C. On the other hand, when the reagent was generated at 0 °C and allowed to warm to room temperature, 67% conjugate reduction product was observed with 29% recovery of the ketone. Apparently enough of the reagent decomposes at room temperature that a substantial amount of the starting material is recovered. It appears then, that the optimum temperature for generation of the reagent and addition of the substrate is 0 °C.

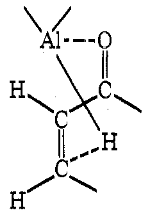
The optimum conditions (1:4:1 stoichiometry, 0 °C, THF) have been applied to other enones (III, IV, V, and VI). The yields are generally high and the regioselectivity is 100%. However, the slower reaction rate for cis enone II and the

Table I. Reduction of Enones with $LiAlH_4$-CuI in THF

		Molar ratio					Products, %^{a}	
Expt	Enone	$LiAlH_4$	CuI	Enone^{b}	Temp, °C	Enone, % recovered	1,4	1,2
1	 $t\text{-BuCH}{=}\text{CHC(=O)Bu-}t$ trans (I)	1.0	0	4.0	0	12	3	83
2	I	1.0	0	1.0	0	0	0	99
3	I	0.42	0.01	1.0	0	0	7	92
4	I	1.0	1.0	2.0^{c}	0	0	40	50
5	I	1.0	1.0	1.0	0	0	64	27
6	I	1.0	1.0	0.5	0	0	49	~44
7	I	1.0	2.0	4.0^{c}	0	54	46	6
8	I	1.0	2.0	2.0^{c}	0	6	81	9
9	I	1.0	2.0	$2.0^{c,d}$	0	0	58	34
10	I	1.0	2.0	2.0^{c}	RT	62	38	<1
11	I	1.0	2.0	1.0	0	0	95	6
12	I	1.0	2.0	0.5	0	0	82	~1
13	I	1.0	3.0	1.0	0	0	87	7
14	I	1.0	4.0	4.0	0	69	26	0
15	I	1.0	4.0	4.0^{e}	0	20	21	59
16	I	1.0	4.0	2.0	0	21	69	0
17	I	1.0	4.0	1.0^{c}	0	0	82	7
18	I	1.0	4.0	1.0^{f}	0	0	69	16
19	I	1.0	4.0	1.0	0	0	99	0
20	I	1.0	4.0	1.0^{d}	0	0	78	20
21	I	1.0	4.0	1.0^{c}	RT	0	63	24
22	I	1.0	4.0	1.0	RT	47	34	<1
23	I	1.0	4.0	4.0	−30	47	38	7
24	I	1.0	4.0	1.0	−20	0	88	11
25	I	1.0	4.0	1.0	−78	0	0	93
26	I	1.0	4.0	1.0	$0 \rightarrow -78^{g}$	101	0	0
27	I	1.0	4.0	1.0	$0 \rightarrow -20^{g}$	10	84	0
28	I	1.0	4.0	1.0	$0 \rightarrow \text{RT}^{h}$	29	67	~1
29	cis (II)	1.0	4.0	1.0	0	33	40	0
30	 $(CH_3)_2C{=}CHC(=O)CH_3$ (III)	1.0	4.0	1.0	0	3	66	~1
31	III	1.0	4.0	0.5	0	8	70	0
32	 $CH_3CH{=}C(CH_3)C(=O)CH_3$ (IV)	1.0	4.0	1.0	0	0	97	0
33	 $CH_3CH{=}CHC(=O)CH_3$ (V)	1.0	4.0	1.0	0	0	78	0
34	 $PhCH{=}CHC(=O)Ph$ (VI)	1.0	4.0	1.0	0	0	101	0

[a] Product is based on ketone used. Reaction time for all reactions is 30–60 min, counted from ketone addition. [b] All reaction mixtures were stirred for 3 min between $LiAlH_4$ addition and ketone addition, except when noted. [c] $LiAlH_4$ was added rapidly, stirred for 1 min, then the ketone added dropwise. [d] Et_2O was used instead of THF. [e] $LiAlH_4$ was added to the ketone-CuI mixture. [f] Same as *c*, but interval was 10 s. [g] $LiAlH_4$ was added at 0 °C, ketone was added at −78 or −20 °C. [h] Stirred at RT for 10 min before ketone addition.

observation of no reaction with cyclohexenone and 3,3,5-trimethylcyclohexenone suggests to us a mechanism involving a six-center transition state (A). It is more difficult for the rigid cyclohexenone systems, cis enones, and trans enones possessing disubstitution at the β carbon of the enone to accommodate such a transition state (A) and hence these kinds of compounds should react more slowly.



A

Reduction of enones I and III (Table II) with $LiAlH_4$-$TiCl_3$ was found not to be as effective as reduction with $LiAlH_4$-CuI. As might have been expected, the most effective ratio of $LiAlH_4$:$TiCl_3$ was different from that found for $LiAlH_4$-CuI. Also one might expect that the optimum reaction temperature would be different since the reactive titanium species would

Table II. Reduction of Enones with $LiAlH_4$–$TiCl_3$ in THF

		Molar ratio						Products, %	
Expt	Enone	$LiAlH_4$	$TiCl_3$	Enone	Temp, °C	Reaction time	Enone recovered	1,4	1,2
35	I	2.0	1.0	1.0	0	1 h	0	12	70
36	I	1.0	1.0	1.0	0	1 h	0	13	53
37	I	1.0	2.0	1.0	0	1 h	0	46	24
38	I	1.0	3.0	1.0	0	1 h	0	29	34
39	I	1.0	1.0	1.0	RT	10 min	0	53	0
40	I	1.0	1.0	1.0	RT	30 min	0	63	0
41	I	1.0	1.0	1.0	RT	1 h	0	58	0
42	I	1.0	1.0	1.0	RT	1.5 h	0	55	0
43	I	1.0	1.0	1.0	RT	12 h	0	53	0
44	I	2.0	2.0	1.0	RT	1 h	0	66	0
45	I	2.0	1.0	1.0	RT	1 h	0	63	0
46	I	2.0	1.0	1.0	Reflux	1 h	0	60	0
47	I	4.0	4.0	1.0	RT	8 h	0	46	0
48	I	1.0	2.0	1.0	RT	1 h	0	29	~1
49	I	1.0	2.0	1.0	RT	8 h	0	35	0
50	I	1.0	2.0	1.0	RT → 0[g]	1 h	0	35	~1
51	I	3.0	4.0	1.0	RT	1 h	0	18	25
52	I	1.0	3.0	1.0	RT	1 h	0	14	0
53	I	3.0	1.0	1.0	RT	1 h	0	28	41
54	I	2.0	2.0	1.0[f]	RT	10 min	0	6	31
55	III	1.0	1.0	1.0	RT → 0[g]	1 h	~1	34	0
56	III	1.0	2.0	1.0	RT → 0[g]	1 h	~2	18	0
57	III	2.0	2.0	1.0[i]	RT	1 h	0	33	0
58	III	2.0	2.0	1.0[f]	RT	1 h	9	0	25

[i] Same as *f* in Table I but 60 min.

Table III. Reduction of Enone I with $LiAlH_4$–HgI_2, $LiAlH_4$–$HgCl_2$, or $LiAlH_4$–CuCl in THF

	Molar ratio				Enone	Products	
Expt	$LiAlH_4$	HgI_2	Enone	Temp, °C	recovered, %	1,4	1,2
59	1.0	1.0	1.0	0	0	65	22
60	1.0	1.5	1.0	0	0	86	8
61	1.0	2.0	1.0	0	0	93	5
62	1.0	4.0	1.0	0	75	8	0
		$HgCl_2$					
63	1.0	1.0	1.0	0	0	46	56
64	1.0	1.5	1.0	0	42	32	17
		CuCl					
65	1	4	1	0	55	32	4

be expected to have different stability and different reactivity characteristics compared to the copper reagent. It appears that optimum results are obtained using a $LiAlH_4$:$TiCl_3$:enone ratio of 1:1:1 at room temperature for 30 min (yield 63%). Lower reaction temperatures (0 °C) for enone I produced a substantial amount of 1,2 reduction product and a wide variation in reactant stoichiometry and reaction time seemed to have either little or adverse effect on the desired results.

Reduction of enone III with $LiAlH_4$–$TiCl_3$ was correspondingly slower than that observed for $LiAlH_4$–CuI. The best conditions of stoichiometry, temperature, and reaction time were similar to that observed for enone I except that the yields were lower (~33%).

$LiAlH_4$ was allowed to react with $FeCl_3$ at −78 °C, 0 °C, and room temperature followed by addition of enone I. In no case did the enone react.

Two other metal salts, HgI_2 and $HgCl_2$, were also admixed with $LiAlH_4$ (Table III). The regioselectivity was dependent on the ratio of $LiAlH_4$:HgX_2 and also on the halide. When the metal halide was changed from HgI_2 to $HgCl_2$ the unusual regioselective is lost corresponding to the same trend observed when the salt is changed from CuI to CuCl.

Since $LiAlH_4$–CuI and $LiAlH_4$–$TiCl_3$ produced a species in solution different than either of the reactants, and gave 100% regioselectivity, it was decided to evaluate these reagents as stereoselective reducing agents. Both $LiAlH_4$–CuI and $LiAlH_4$–$TiCl_3$ were allowed to react with 4-*tert*-butylcyclohexanone (VII) and 3,3,5-trimethylcyclohexanone (VIII) in THF. The results of Table IV show that both reagents give considerably more equatorial attack compared to $LiAlH_4$ and that the $LiAlH_4$–$TiCl_3$ reagent gives considerably more equatorial attack compared to the $LiAlH_4$–CuI reagent on both ketones.

The unusual effectiveness of the reagent $LiAlH_4$–CuI for conjugate reduction of the enones encouraged us to study the nature of this reagent in solution. We found that the reactive intermediate is H_2AlI and not CuH or $CuAlH_4$.[9] Equation 2 explains the observation of a black precipitate and gas evolution when this reaction is carried out. The compound H_2AlI was synthesized independently and was found to produce the same results as observed with $LiAlH_4$–CuI (1:4) (run 75). Actually, after most of these studies were complete, we found that the 1:4 ratio of $LiAlH_4$–CuI is not necessary. When the mixing period for $LiAlH_4$ and CuI was changed from 3 to 20 min (runs 11 and 73) we found that the enone was reduced in 98 and 100% regioselectivity.

$$LiAlH_4 + 2CuI \rightarrow H_2AlI + LiI + Cu^\circ + H_2 \quad (2)$$

Since H_2AlI was found to react just as the reagent $LiAlH_4$–CuI, it was decided to evaluate other halogenoaluminum hydrides. We prepared[10] the series H_2AlI, $HAlI_2$, H_2AlBr, $HAlBr_2$, H_2AlCl, and $HAlCl_2$ expecting that for steric reasons the $HAlX_2$ compounds would be more regioselective than the H_2AlX compounds and that the regioselectivity of the reduction would decrease as the steric requirement of the hydrogen decreases (I > Br > Cl). It is clear from Table V that indeed the iodo compounds are more selective than the bromo or chloro compounds and that $HAlX_2$ compounds are also highly regioselective. However, owing to the steric requirement of $HAlI_2$ the reaction with enone I is much slower com-

Table IV. Stereoselective Reduction of 4-*tert*-Butylcyclohexanone (VII) or 3,3,5-trimethylcyclohexanone (VIII) with $LiAlH_4$–CuI and $LiAlH_4$–$TiCl_3$ in THF

		Molar ratio				Ketone recovered,	Rel yield, %		
Expt	Ketone	$LiAlH_4$	CuI (or $TiCl_3$)	Ketone	Conditions	%	ax OH	eq OH	Mass balance
67	VII	1.5	0	1.0	0 °C, 2 h	0	8	92	~100
68	VII	1.0	4.0 (CuI)	1.0	0 °C, 1 h	0	29	71	~100
69	VII	1.0	1.0 ($TiCl_3$)	1.0	RT, 1 h	0	70	30	81
70	VIII	1.5	0	1.0	0 °C, 2 h	0	80	20	~100
71	VIII	1.0	4.0 (CuI)	1.0	0 °C, 1 h	0	85	15	~100
72	VIII	1.0	1.0 ($TiCl_3$)	1.0	RT, 1 h	0	97	3	74

Table V. Reduction of Enone I with the Reagents $LiAlH_4$–CuI, AlH_3–CuI, H_2AlI, $HAlI_2$, H_2AlBr, $HAlBr_2$, H_2AlCl, and $HAlCl_2$ in THF

					Enone,	Products, %	
Expt	Molar ratio			Conditions	% recovered	1,4	1,2
	$LiAlH_4$	CuI	Enone[j]				
73	1	2	I	0 °C, 15 min	0	98	0
	AlH_3	CuI	Enone[j]				
74	1	3	I	0 °C, 15 min	0	99	<1
	H_2AlI	CuI	Enone[j]				
75	1	0	1	0 °C, 1 h	0	98	<0.5
76	1	0	1[d]	0 °C, 1 h	0	70	12
77	1	~10	1	0 °C, 1 h	77	11	0
	$HAlI_2$	CuI	Enone				
78	1		1	0 °C, 1 h	84	0.5	0
79	2		1	RT, 4 h	33	59	5
80	4		1	RT, 1 h	16	80	2
	H_2AlBr	CuI	Enone				
81	1		1	0 °C, THF, 1 h	0	86	12
	$HAlBr_2$	CuI	Enone				
82	1		1	0 °C, THF, 1 h	0	92	6
	H_2AlCl	CuI	Enone				
83	1		1	0 °C, 10 min	0	86	15
	$HAlCl_2$	CuI	Enone				
84	2		1	0 °C, 1 h	8	86	7

[d] Et_2O solvent. [j] The mixing period of $LiAlH_4$–CuI or AlH_3–CuI was 20 min before enone addition.

pared to H_2AlI and hence $HAlI_2$ is not as attractive a reagent. Because $HAlI_2$ reacts so slowly the regioselectivity suffers slightly probably owing to the small equilibrium amount of AlH_3 expected in THF solutions of $HAlI_2$.

Experimental Section

Materials and Techniques. Manipulations of air-sensitive compounds were performed under nitrogen in a glove box equipped with a recirculating system described elsewhere.[11] THF and Et_2O were distilled from $NaAlH_4$ and $LiAlH_4$, respectively, prior to use. $LiAlH_4$ solutions were prepared by refluxing $LiAlH_4$ (Alfa Inorganics) in THF for at least 24 h followed by filtration through a fritted glass funnel in a box. The clear solution was standardized for aluminum content by EDTA. CuI (Fisher) was purified by dissolving it in saturated potassium iodide solution followed by treatment with decolorizing charcoal, filtration, and precipitation by dilution with water. The purified CuI was collected and washed with absolute EtOH and dry Et_2O in the drybox. Anhydrous ferric chloride (Fisher sublimed) titanium trichloride (Alfa), mesityl oxide (Eastman), 4-*tert*-butylcyclohexanone (Friton), 3,3,5-trimethylcyclohexanone (Chemical Samples Co.), and enones IV, V, and VI (Aldrich) were used without further purification. 2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one [sublimed, 45 °C (5–10 mmHg)] was prepared as previously described.[12] Mercuric iodide and chloride were dried by heating at 90–100 °C under vacuum for 4 h and standard THF solutions of these salts were prepared in the drybox. The reagent H_2AlI was obtained by adding I_2–THF solution to AlH_3–THF at <0 °C. The resulting solid was then filtered and washed carefully with THF.[10] The $HAlI_2$, H_2AlCl, and $HAlCl_2$ reagents were prepared by following literature methods.[10] The ratio of H:Al was satisfied for each haloalane within experimental error.

Reduction Procedure. A 10-ml Erlenmeyer flask with a Teflon coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen flush. CuI, CuCl, $TiCl_3$, or $FeCl_3$ (ca. 2 mmol) was transferred to the flask in the drybox; it was sealed with a rubber septum, removed from the box, and connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil filled bubbler. THF or Et_2O solvent (4 ml) was introduced into the reaction vessel and temperatures regulated by ice–water (0 °C), dry ice–acetone (−78 °C), or dry ice–carbon tetrachloride (−20 °C). A known concentration of $LiAlH_4$ solution was then added to the slurry. On addition a deep black color is immediately produced with gas evolution except in the case of CuI at −78 °C. After an indicated period, enone with internal standard, n-$C_{12}H_{26}$, was added dropwise. After the designated reaction time the reaction mixture was quenched with a minimum of distilled water and the resulting solution dried over $MgSO_4$. Analysis of the product and yield data was obtained by GLC, using a 15-ft 10% Carbowax 20M on Chromosorb W. Authentic samples were used to identify the retention times of the 1,4 and 1,2 reduction products.

Reduction of 4-*tert*-butylcyclohexanone and 3,3,5-trimethylcyclohexanone was carried out by a similar procedure as described for the enone. Product yields were also determined by GLC.

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Registry No.—I, 20859-13-6; II, 29569-89-9; III, 141-79-7; IV, 565-62-8; V, 625-33-2; VI, 94-41-7; VII, 98-53-3; VIII, 873-94-9; $LiAlH_4$, 16853-85-3; AlH_3, 7784-21-6; H_2AlI, 58602-50-9; $HAlI_2$, 58602-51-0; H_2AlCl, 14644-71-4; $HAlCl_2$, 13497-97-7; CuI, 7681-65-4; $TiCl_3$, 7705-07-9; HgI_2, 7774-29-0; $HgCl_2$, 7487-94-7; CuCl, 7758-89-6.

References and Notes

(1) R. L. Augustine et al., *J. Org. Chem.*, **34**, 1074 (1969).
(2) H. O. House, "Modern Synthetic Reactions", W. A. Benjamin, Menlo Park, Calif., 1972, p 173.
(3) (a) R. K. Boeckman, Jr., and R. Michalak, *J. Am. Chem. Soc.*, **96**, 1623 (1974); (b) S. Masamune, G. S. Bates, and P. E. Georghiou, *ibid.*, **96**, 3686 (1974).
(4) B. Ganem, *J. Org. Chem.*, **40**, 146 (1975).
(5) H. C. Brown and H. M. Hess, *J. Org. Chem.*, **34**, 2206 (1969).
(6) E. C. Ashby and B. Cooke, *J. Am. Chem. Soc.*, **90**, 1625 (1968), and references cited therein.
(7) S. Masamune, P. A. Rossy, and G. S. Bates, *J. Am. Chem. Soc.*, **95**, 6452 (1973).
(8) J. E. McMurry and M. P. Fleming, *J. Am. Chem. Soc.*, **96**, 4708 (1974).
(9) To be reported in more detail shortly.
(10) D. L. Schmidt and E. E. Flagg, *Inorg. Chem.*, **6**, 1262 (1967).
(11) E. C. Ashby and R. D. Schwartz, *J. Chem. Educ.*, **51**, 65 (1974).
(12) H. O. House and P. D. Weeks, *J. Am. Chem. Soc.*, **97**, 2770 (1975).

A Study of the Stork Reductive Cyclization of Steroidal Acetylenic Ketones in Aprotic Media with the Naphthalene Anion Radicals

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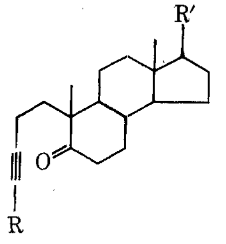
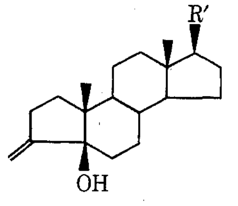
Reductive cyclization of steroidal acetylenic ketones was achieved in THF or DME with $C_{10}H_8\cdot^-M^+$. From 4,5-secocholest-3-yn-5-one (**1a**) the allylic alcohol 3-methylene-*A*-norcholestan-5β-ol (**2a**) is the sole product. With this reagent no overreduction occurs. Recovery of starting material was proved to be due to competitive enolate ion formation. Ratio of reductive cyclization to recovery varied with solvent and counterion as well as with substrate. In a series of 4,5-secocholestan-5-ones the substituent at 10α was varied from $-(CH_2)_2C{\equiv}CH$ (**1a**) and $-(CH_2)_2CH_2C{\equiv}CH$ (**25**) to $-(CH_2)_2C{\equiv}C{-}CH_3$ (**1c**). The observed ratios were 2.3, 8.2, and 0.7, respectively. In each case, the cyclization was regiospecific leading exclusively to an exo double bond. Kinetic control was established when **25** showed the same stereoselectivity as the others and gave an A:B cis product. The formation of different products from **25** and **1c** eliminated allene intermediates. With **1c** the stereochemistry of addition across the acetylene was syn:anti equal to 52:48. This shifted to >80% syn for **5e**. Based on available data, a mechanism is proposed. Electron is transferred preferentially, though reversibly, by $C_{10}H_8Na$ to the ketone group to give a ketyl radical ion. In the next slow step, this attacks the acetylene intramolecularly, as a radical and not as a nucleophile. Equilibration of the resulting vinyl radical with its isomer precedes reduction and protonation to the allyloxy anion precursor of the cyclized product. The initial addition across acetylene is syn. This follows from the change in syn:anti ratio to 70:30 when **1c** is added to excess reducing agent.

The reductive cyclization of γ-ethynyl ketones to allylic alcohols with alkali metals in liquid ammonia was first reported by Stork.[1] In a slightly modified form, this reaction was used for making interesting *A*-nor sterols.[2] The reaction was found to be stereoselective. Thus, the only products obtained from 4,5-secocholest-3-yn-5-one (**1a**) were 3-methylene-*A*-norcholestan-5β-ol (**2a**) and 3-methyl-*A*-norcholest-3-ene (**3a**). The latter was a product of overreduction. With NH_4Cl as a proton source, **3a** was the only product. With *t*-BuOH under carefully controlled conditions, mixtures of **2a** and **3a** resulted. Even under these conditions, **1b** gave only **3b.**

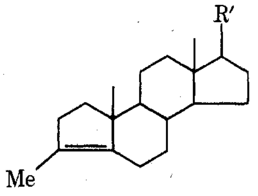
It was expected that overreduction could be avoided with a milder reducing agent used in combination with an aprotic medium. When preliminary work[3] indicated that naphthalene sodium in THF could serve the purpose, a deeper study into several aspects of this reaction was undertaken and is the subject of the present report.[4]



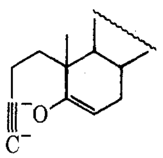
1a, R = H; R′ = C_8H_{17}
b, R = H; R′ = OH
c, R = Me; R′ = C_8H_{17}



2a, R′ = C_8H_{17}
b, R′ = OH
c, R′ = OMe



3a, R′ = C_8H_{17}
b, R′ = OH



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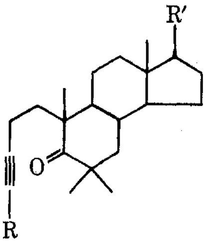

5a, R = H; R′ = C_8H_{17}
b, R = H; R′ = OH
c, R = H; R′ = OMe
d, R = Me; R′ = C_8H_{17}
e, R = D; R′ = C_8H_{17}

A solution of the acetylene ketone **1a** in THF or DME was