

Activation of Reducing Agents. Sodium Hydride Containing Complex Reducing Agents. 11.¹ Regioselective Reduction of α,β -Unsaturated Ketones

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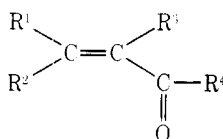
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Complex reducing agents NaH-RONa-MX_n (MCRA) and $\text{NaH-RONa-MX}_n\text{-MgBr}_2$ (MCRA-MgBr₂) are described as very efficient reagents for the 100% regioselective reduction of α,β -unsaturated ketones in THF. Selective 1,4 reductions were observed with $\text{MX}_n = \text{Ni(OAc)}_2$ while selective 1,2 reductions were obtained with $\text{MX}_n = \text{ZnCl}_2$. Finally, control experiments pointed out some unexpected reducing properties of $\text{NaH-ZnCl}_2\text{-MgBr}_2$ systems.

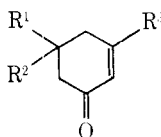
The selective reduction of either the double bond or carbonyl group of α,β -unsaturated ketones has been investigated by other workers²⁻⁴ without complete success. Our work on the reduction of saturated ketones⁵ by complex reducing agents (MCRA), NaH-RONa-MX_n ^{6,7} suggested trial of these cheap, safe, and easily handled reagents for the regioselective reduction of enones.

Results and Discussion

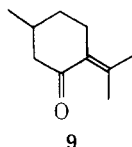
In previous work, we have shown that NiCRA ($\text{NaH-RONa-Ni(OAc)}_2$) was able to reduce carbon-carbon double bonds^{8,9} and that NiCRA- M^1X_n (M^1X_n = alkaline or alkaline earth metal salt) were good reagents for the reduction of saturated ketones.⁵ On the other hand, it was found that ZnCRA (NaH-RONa-ZnCl_2) exhibited very poor reducing properties toward carbon-carbon double bonds⁹ but led to good results for the reduction of carbonyl groups, specially when mixed with alkaline or alkaline earth metal salts.⁵ From these observations, one might conjecture that nickel-based reducing agents could be good candidates for the conjugate reduction of enones and zinc-based ones for the regioselective reduction of the carbonyl group of enones.



- 1, $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{Me}$
 2, $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{Me}$
 3, $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{Me}$; $\text{R}^4 = \text{Me}$
 4, $\text{R}^1 = t\text{-Bu}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = t\text{-Bu}$
 5, $\text{R}^1 = \text{C}_6\text{H}_5$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{Me}$
 6, $\text{R}^1 = \text{C}_6\text{H}_5$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{H}$; $\text{R}^4 = \text{C}_6\text{H}_5$



- 7, $\text{R}^1 = \text{H}$; $\text{R}^2 = \text{H}$; $\text{R}^3 = \text{H}$
 8, $\text{R}^1 = \text{Me}$; $\text{R}^2 = \text{Me}$; $\text{R}^3 = \text{Me}$



9

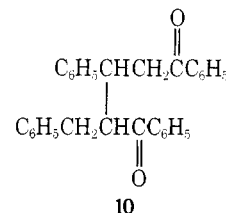
Enones 1-9 were chosen for this study. In our opinion, they are representative of the different situations which may be encountered.

First, a short systematic study was performed on three representative ketones 2, 4, and 8. From the results (summarized in Table I), the following observations were made: (i) as expected from our hypothesis, NiCRA led essentially to conjugate reduction while ZnCRA led to selective reduction of the

carbonyl group; (ii) addition of alkaline or alkaline earth metal salts generally improves the CRA's performances; (iii) 40 °C is an adequate reaction temperature, allowing fast reductions; however, with the most sensitive α,β -unsaturated ketones, reduction must be carried out at 20 °C to avoid too large formation of byproducts. The optimum conditions thus defined were applied to the reduction of enones 1-9 in THF (Table II).

Variation of the nature of the metal induces a dramatic variation of the reducing properties of CRA. Although reduction yields were not quantitative in all cases, it is noteworthy that the regioselectivity was always 100%, with both cyclic and acyclic enones.

Results of Table II deserve some further comments. First, in a few cases, reductions were accompanied by formation of intractable byproducts. Second, in most cases, reduction by



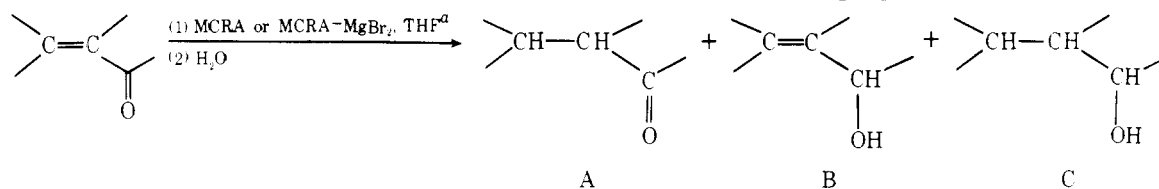
10

nickel-based reagents gave small amounts of saturated alcohols if the reaction times were increased. Finally, the reduction of 6 was accompanied by the formation of diketone 10 (50% yield) arising from Michael addition of the saturated ketone enolate to 6.

Comparison of these results with those described for usual reagents showed that CRA are very efficient reagents for the regioselective reduction of α,β -unsaturated ketones, leading either to saturated ketones (with nickel-based reagents) or to allylic alcohols (with zinc-based reagents).

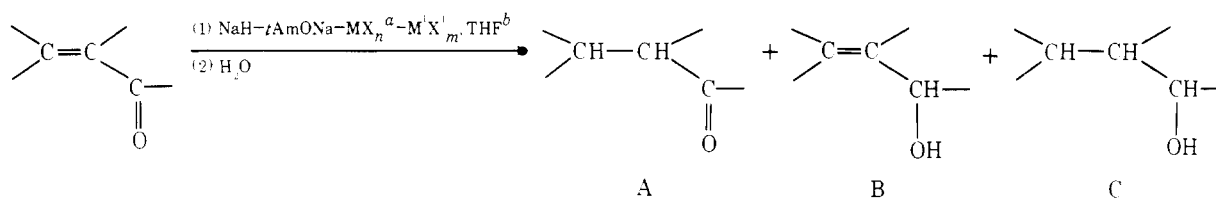
Control experiments on the reducing ability of CRA's components were performed with ketones 2, 4, and 8 which were easily reduced by either NiCRA or ZnCRA. It was found that NaH , $\text{NaH-}t\text{-AmONa}$, NaH-Ni(OAc)_2 , NaH-MgBr_2 , and $\text{NaH-}t\text{-AmONa-MgBr}_2$ systems exhibited very poor reducing ability toward enones 2, 4, and 8. Except for 2 (which was destroyed when treated by NaH , $\text{NaH-}t\text{-AmONa}$, NaH-Ni(OAc)_2 , or $\text{NaH-}t\text{-AmONa-MgBr}_2$), the ketones were quantitatively recovered in all other cases. It was also found that $\text{NaH-Ni(OAc)}_2\text{-MgBr}_2$ effected the conjugate reduction of 8 in 20 h (instead of 30 mn with NiCRA-MgBr_2) while 2 and 4 were quantitatively recovered after 20 h at 20 °C.

Although very poor reducing properties were found for NaH-ZnCl_2 (see Table III) and NaH-MgBr_2 (vide supra), their mixture ($\text{NaH/ZnCl}_2\text{/MgBr}_2$ 40/10/10 mM) was able to reduce enones to α,β -unsaturated alcohols in very good yields. However, it must be noted that reaction times were twice those

Table I. Reduction of Enones with MCRA and MCRA-MgBr₂ in THF

ketone	reducing system	T, °C	reaction time	% A ^b	% B ^b	% C ^b
2	NiCRA ^c	20	2 h	98		
	NiCRA-MgBr ₂ ^d	20	15 min	95		
	ZnCRA ^e	20	2 h		10-15 ^f	
	ZnCRA-MgBr ₂ ^d	20	2 h		98	
4	NiCRA	20	2 h	95		
	NiCRA-MgBr ₂	20	2.5 h	95		
	ZnCRA	40	2 h		95	
	ZnCRA-MgBr ₂	40	3 h		95	
8	NiCRA	40	4.5 h	91		5
	NiCRA-MgBr ₂	40	30 min	93		5
	ZnCRA	40	1 h ^h		68 ^k	
	ZnCRA-MgBr ₂	40	3.5 h	traces	90	

^a 40-45 ml. ^b Absolute yields determined by GLC analysis with internal standards. ^c NaH/*t*-AmONa/Ni(OAc)₂/ketone = 40/10/10/10 mM. ^d MgBr₂, 2 THF (10 mM) (see ref 5) was used. ^e NaH/*t*-AmONa/ZnCl₂/ketone = 40/10/10/10/ mM. ^f No recovered starting enone. ^g 30% unreacted enone was still present. ^h No further evolution (20 h).

Table II. Reduction of α,β -Unsaturated Ketones by NaH-*t*-AmONa-MX_n-M¹X¹_m in THF

ketone	MX _n	M ¹ X ¹ _m	T, °C	reaction time	% A ^c	% B ^c	% C ^c
1	Ni(OAc) ₂	MgBr ₂ ^d	20	30 min	30		
	ZnCl ₂	MgBr ₂ ^d	20	30 min		55-60	traces
2	Ni(OAc) ₂	MgBr ₂ ^d	20	15 min	98		traces
	ZnCl ₂	MgBr ₂ ^d	20	2 h		98	traces
3	Ni(OAc) ₂	MgBr ₂ ^d	20	45 min	99 (65)		
	ZnCl ₂	MgBr ₂ ^d	40	2 h		93 (75)	
4	Ni(OAc) ₂	MgBr ₂ ^d	20	2.5 h	93 (91)		
	ZnCl ₂	MgBr ₂ ^d	40	3 h		93 (90)	
5	Ni(OAc) ₂	LiI ^e	20	15 min	85 (83)		
	ZnCl ₂	MgBr ₂ ^d	20	20 h		45-50 (35)	
6	Ni(OAc) ₂	MgBr ₂ ^d	20	3.5 h	50 (50) ^f		
	ZnCl ₂	MgBr ₂ ^d	20	4 h		98 (95)	
7	Ni(OAc) ₂	LiI ^e	20	30 min	98		
	ZnCl ₂	MgBr ₂ ^d	20	6 h		50	25
8	Ni(OAc) ₂	MgBr ₂ ^d	40	30 min	93		5
	ZnCl ₂	MgBr ₂ ^d	40	3.5 h		90	traces
9	Ni(OAc) ₂	MgBr ₂ ^d	20	1.5 h	95 (90) ^g		
	ZnCl ₂	MgBr ₂ ^d	40	3 h		93 (78) ^h	

^a NaH/*t*-AmONa/MX_n/ketone = 40/10/10/10/ mM. ^b 40-45 mL. ^c Absolute yields determined by GLC with internal standards. Isolated yields in parentheses. ^d MgBr₂, 2THF (10 mM) was used, see ref 5. ^e LiI, 2H₂O (20 mM) was used. ^f Ketone 10 was isolated in 50% yield. ^g A mixture of isomers. ^h The stereochemistry of the allylic alcohol was not determined.

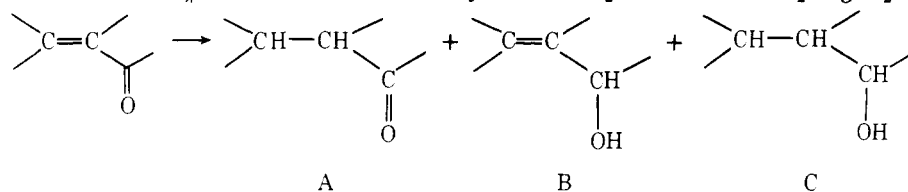
obtained for ZnCRA-MgBr₂. Moreover, lower reduction yields were obtained for the most sensitive ketones 1, 5, and 7.

Remarks

Previous studies^{7,9} have shown that 1,2-dimethoxyethane (DME) is often a convenient solvent for reductions by CRA. Examination of enone reduction by nickel- or zinc-based systems in DME led us to the following observations: (i) Quantitative 1,4 reductions of the less sensitive ketones such

as 2, 4, 8 could be easily achieved by NiCRA in DME. Thus, this solvent may eliminate the use of MgBr₂ in such cases. (ii) However, more sensitive ketones such as 1, 5, and 7 were largely destroyed by NiCRA or NiCRA-MgBr₂ in DME. (iii) ZnCRA and ZnCRA-MgBr₂ exhibited lower reducing abilities in DME than in THF.

Thus, it can be concluded that, except for some isolated cases, DME is a much less convenient solvent than THF for the reduction of α,β -unsaturated ketones by CRA.

Table III. Reduction of α,β -Unsaturated Ketones by NaH-ZnCl₂^a and NaH-ZnCl₂-MgBr₂^b in THF^c

reducing system	ketone	T, °C	reaction time, h	% A ^d	% B ^d	% C ^d	% enone ^d recovered
NaH-ZnCl ₂	2	20	16		10-15		
	4	40	7		78	14	
	8	40	20		45		48
NaH-ZnCl ₂ -MgBr ₂	1	20	1		40		
	2	20	6		95		
	4	40	7		99		
	5	20	5		10		
	7	20	20	5	10	5	
	8	40	6		95		

^a NaH/ZnCl₂/ketone = 40/10/10/mM. ^b NaH/ZnCl₂/MgBr₂/ketone = 40/10/10/10 mM; MgBr₂, 2THF (see ref 5) was used. ^c 40-45 mL. ^d Absolute yields determined by GLC analysis with internal standards.

Conclusion

This work confirms the remarkable versatility of complex reducing agents in the field of reduction.

NiCRA exhibit a 100% regioselectivity for the conjugate reduction of α,β -unsaturated ketones, while under the same conditions ZnCRA are effective reagents for the regioselective 1,2 reduction of enones. Addition of magnesium bromide enhances the activity of CRA.

Investigations to extend the usefulness of complex reducing agents in the field of selective reductions are currently under study in our laboratory.

Experimental Section

Materials. Fluka sodium hydride (55-60% in oil) was used and washed several times with THF. Badische Anilin reagent grade THF was distilled from benzophenone-sodium couple and stored on sodium wires. α,β -Unsaturated ketones (Fluka or Aldrich) were purified by distillation; *tert*-amyl alcohol was distilled from sodium before use. Metallic salts (Prolabo) were dried under vacuum for 12-15 h at 80-120 °C, as were alkaline and alkaline earth metal salts. Magnesium bromide was prepared by reaction of 1,2-dibromoethane with magnesium in THF as previously described.⁵ All metallic salts were stored under argon. All reactions were performed under nitrogen.

General. GLC analyses were performed on a Girdel 3000 apparatus using Carbowax 20 M and Squalene capillary columns. Infrared spectra were recorded with a Perkin-Elmer 457 spectrometer and NMR spectra with a Perkin-Elmer R 12 instrument. Satisfactory elemental analyses were obtained for all isolated compounds.

General Reduction Procedure. The preparation of NiCRA, ZnCRA, and their use in mixture with alkaline or alkaline earth metal salts has been described in detail.⁵ Reduction of enones 1-9 was carried out using the general procedure reported for the reduction of saturated ketones.⁵ Molar ratios of reactants are given in the footnotes of Tables I, II, and III. The 1,4 and 1,2 reduction products of enones 1, 2, 7, and 8 were identified by comparison of GLC retention times (Carbowax and Squalene) with those of authentic samples. Reduction products of enones 3, 4, 5, 6, and 9 were isolated and identified by comparison (IR, NMR) with authentic samples. Ketone 10 was identified on the basis of its spectroscopic properties (IR, ¹H NMR, and ¹³C NMR).

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Registry—1, 625-33-2; 2, 141-79-7; 3, 684-94-6; 4, 1653-94-7; 5, 122-57-6; 6, 94-41-7; 7, 930-68-7; 8, 78-59-1; 9, 15932-80-6; 10, 38335-02-3; 4-methyl-2-pentanone, 108-10-1; 3,4-dimethyl-2-pentanone, 565-78-6; 2,2,6,6-tetramethyl-3-heptanone, 40239-53-0; 4-phenyl-2-butanone, 2550-26-7; 2-pentanone, 107-87-9; cyclohexanone, 108-94-1; 3,3,5-trimethylcyclohexanone, 873-94-9; *cis*-5-methyl-2-(1-methyl ethyl)cyclohexanone, 491-07-6; 3-penten-2-ol, 1569-50-2; 4-methyl-3-penten-2-ol, 4325-82-0; 3,4-dimethyl-3-penten-2-ol, 2747-54-8; 2,2,6,6-tetramethyl-4-hepten-3-ol, 69897-40-1; 4-phenyl-3-buten-2-ol, 17488-65-2; 1,3-diphenyl-2-propen-1-ol, 4663-33-6; 2-cyclohexen-1-ol, 822-67-3; 3,5,5-trimethyl-2-cyclohexen-1-ol, 470-99-5; 5-methyl-2-(1-methylethylidene)cyclohexanol, 529-02-2; 2-pentanol, 6032-29-7; 4-methyl-2-pentanol, 108-11-2; 2,2,6,6-tetramethyl-3-heptanol, 69897-43-4; cyclohexanol, 108-93-0; 3,3,5-trimethylcyclohexanol, 116-02-9; *trans*-5-methyl-2-(1-methylethyl)cyclohexanone, 89-80-5; 1,3-diphenyl-1-propanone, 1083-30-3; NaH, 7646-69-7; AmONa, 1941-84-0; Ni(OAc)₂, 373-02-4; dibromobis(tetrahydrofuran); magnesium, 63994-15-0; ZnCl₂, 7646-85-7; LiI, 10377-51-2.

References and Notes

- (1) Part 10: J. J. Brunet, C. Sidot, B. Loubinoux, and P. Caubère, preceding paper in this issue.
- (2) H. O. House, "Modern Synthetic Reactions", 2nd ed., W. A. Benjamin, Menlo Park, Calif., 1972, and references cited therein.
- (3) See, for example: D. N. Kursanov, N. M. Loim, V. A. Baranova, L. V. Moiseeva, L. P. Zalukaev, and Z. N. Parnes, *Synthesis*, 420 (1973); S. Masamune, G. Bates, and P. Georghiou, *J. Am. Chem. Soc.*, **96**, 3686 (1974); R. K. Boeckmann and R. Michalak, *ibid.*, **96**, 1623 (1974); E. C. Ashby and J. J. Lin, *Tetrahedron Lett.*, 4453 (1975); R. O. Hutchins and D. Kandasamy, *J. Org. Chem.*, **40**, 2530 (1975); S. Krishnamurthy and H. C. Brown, *ibid.*, **40**, 1864 (1975); M. F. Semmelhack and R. D. Stauffer, *ibid.*, **40**, 3619 (1975); H. J. Williams, *Tetrahedron Lett.*, 1271 (1975); E. C. Ashby and J. J. Lin, *ibid.*, 3865 (1976); J. M. Fortunato and B. Ganem, *J. Org. Chem.*, **41**, 2194 (1976); M. F. Semmelhack, R. D. Stauffer, and A. Yamashita, *ibid.*, **42**, 3180 (1977); J. P. Collman, R. G. Finke, P. L. Matlock, R. Wahren, R. G. Komoto, and J. I. Brauman, *J. Am. Chem. Soc.*, **100**, 1119 (1978); J. L. Luche, L. R. Hahn, and P. Crabbe, *J. Chem. Soc., Chem. Commun.*, 601 (1978).
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