

ACTIVATION OF REDUCING AGENTS. SODIUM HYDRIDE CONTAINING COMPLEX REDUCING AGENTS 28.  
STEREOCHEMISTRY OF REDUCTION OF KETONES BY COMPLEX REDUCING AGENTS

A. FEGHOULI, Y. FORT, R. VANDERESSE and P. CAUBERE\*

Laboratoire de Chimie Organique I, associé au CNRS - Université de Nancy I  
B.P. 239, 54506 VANDOEUVRE LES NANCY (FRANCE)

*Abstract* : The stereochemistry of reduction of selected ketones by a variety of Complex Reducing Agents (MCRA) has been investigated. The selectivity depends on the nature of the CRA constituents and principally on that of the metal salt.

In a previous publication,<sup>1</sup> we have shown that Complex Reducing Agents  $\text{NaH-RONa-MX}_n$  (x/y/z)<sup>\*</sup> (MCRA, where M is a metal) easily prepared by simple mixing of a metallic salt, NaH and an alcohol, are versatile and inexpensive reagents. We also found that addition of  $\text{Me}_3\text{SiCl}$  to a MCRA gives a  $\text{MCRASi(NaH-RONa-MX}_n\text{-Me}_3\text{SiCl (x/y/z/t))}^{\dagger}$  and increases the reactivity and the selectivity of these reagents. Thus, very highly regioselective reductions of  $\alpha,\beta$ -unsaturated carbonyl derivatives were performed with  $\text{ZnCRASi}^2$  and  $\text{NiCRASi}^3$ .

A very interesting problem concerns the stereoselective reduction of cyclic ketones, for which a large number of reducing agents have been studied.<sup>4</sup> Generally these reagents are sophisticated and more expensive than our sodium hydride containing reagents. Some of the described reducing systems contain metal salt. However the influence of the nature of the metal compound on the stereochemistry of the reduction has never been studied.

In the present note we report the first results showing that our reagents present rather good stereoselectivities, variable with the nature of the metal salt. We also show that the nature of the activating agent (RONa) may also have an influence.

Most of the results of the Table have been obtained with MCRASi. Unreported experiments showed that the corresponding MCRA was less efficient.

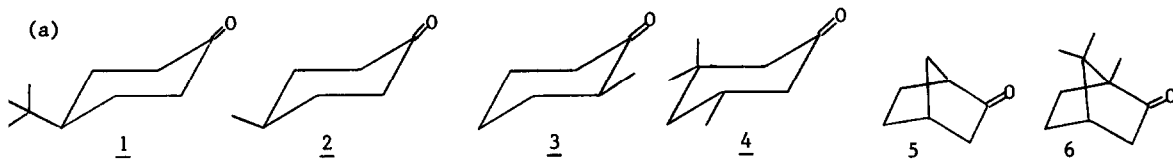
For a given reagent, comparison of the ratios of the two alcohols formed as a function of reaction time shows that Ni, Co and to a certain extent CdCRASi have the strongest propensity to isomerize the reaction products towards the most stable alkoxides.

We have verified that longer reaction times than the ones reported in the Table led to no further change on the products ratio.

\*In this paper we have adopted the convention of ref.<sup>1</sup>. Thus a MCRASi (metal atom M specified) prepared from NaH, RONa (alkoxide), metallic salt, and  $\text{Me}_3\text{SiCl}$  will be abbreviated MCRASi (x/y/z/t) where the molar ratio  $\text{NaH/RONa/MX}_n/\text{Me}_3\text{SiCl}$  (in that order) is equal to x/y/z/t.

TABLE

Keto- nes (a)	CRA (b)	ZnCRASi (c) (4/1/1/3)	CdCRASi (d) (4/1/1/3)	NiCRASi (c) (5/1/1/1)	CoCRASi (d) (5/1/1/1)	MnCRASi (d) (5/1/1/3)	NiCRA (d,e) (4/1/1)
<u>1</u>	t (h)	0 0.25	0 3	0 2	0 18	2 24	0 3
	Alcohol (%)	90 99	5 90	20 96	14 94	12 22	39 97
	ax/eq	24/76 20/80	70/30 63/37	45/55 38/62	61/39 61/39	80/20 80/20	25/75 6/94
<u>2</u>	t (h)	0 0.25	0.25 3	0 1	0 3	2 18	0 18
	Alcohol (%)	98 99	12 91	35 95	22 90	6 72	26 94
	cis/trans	29/71 30/70	47/53 58/42	56/44 41/59	56/44 54/46	67/33 66/33	16/84 5/95
<u>3</u>	t (h)	0 0.25	0 3	0 2	0 1	2 18	0 18
	Alcohol (%)	76 99	10 91	39 90	3 72	9 70	47 96
	cis/trans	40/60 39/61	54/46 67/33	36/64 37/63	39/61 53/47	54/46 56/44	35/65 7/93
<u>4</u>	t (h)	0 1	1 24	0 1	0 24	3 18	0 18
	Alcohol (%)	52 98	21 91	28 92	16 93	24 74	13 92
	ax/eq	83/17 83/17	86/14 89/11	60/40 63/37	51/49 25/75	83/17 90/10	35/65 1/99
<u>5</u>	t (h)	0 0.25	0 18	0 1	0 2	4 18	0 18
	Alcohol (%)	70 99	1 50	50 97	21 95	8 63	42 90
	endo/exo	85/15 87/13	99/1 98/2	36/64 33/67	66/34 49/51	95/5 97/3	41/59 10/90
<u>6</u>	t (h)	0 1	0 4	0 0.25	0.25 1	4 18	0 18
	Alcohol (%)	42 96	5 90	57 95	53 63	11 25	28 98
	endo/exo	92/8 95/5	84/16 92/8	92/8 89/11	77/23 65/35	75/25 62/38	88/12 25/75



(b) ZnCRASi, CdCRASi, CoCRASi, MnCRASi were prepared from  $MCl_2$ ; NiCRASi were prepared from  $Ni(OAc)_2$

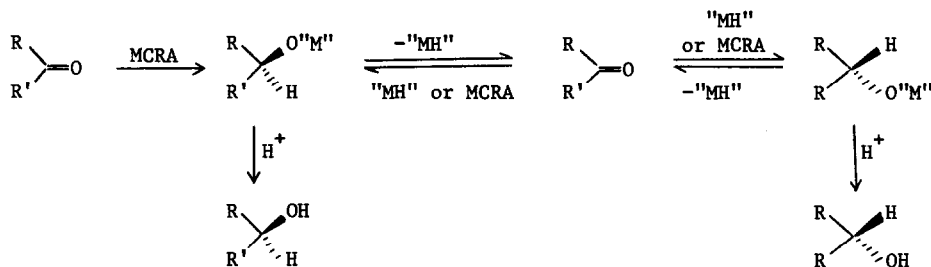
(c) Reaction performed at 45°C in THF

(d) Reaction performed at 63°C in THF

(e) NiCRA prepared from the sodium alkoxide of 2,5-dimethylhexanediol.

Without  $\text{Me}_3\text{SiCl}$ , replacement of  $\text{AmONa}$  by the sodium alkoxide of 2,5-dimethyl hexane-2,5-diol led to the most isomerizing reagent, allowing the formation of the most stable alkoxide in good to very good yields.

Taking into account the behaviour of transition metal alkoxides,<sup>5</sup> the observed isomerizations can be interpreted as equilibrations due to  $\beta$ -eliminations, leading to the formation of the starting ketone followed by reduction (Scheme).



Scheme

In control experiments, we verified the formation of the corresponding ketones when alcohols are added to NiCRA, NiCRASi and CoCRASi.

Obviously the  $\beta$ -elimination of the metal hydride cannot be put forward for isomerizations observed with CdCRASi. An equilibration by a Meerwein-Ponndorf type reaction between the unreacted ketone and the formed alkoxides seems much more probable.

Examination of the results obtained with 3,3,5-trimethyl cyclohexanone, norbornanone and camphor shows that, like the usual reducing agents, CRAs are sensitive to steric hindrance.

More interesting are the results obtained with other ketones and with CRASi differing only by the nature of the metallic salt, which can lead to dramatic changes.

Thus, the following trend of stereochemistry emerges :

- CRAs prepared from  $\text{ZnCl}_2$  and  $\text{Ni}(\text{OAc})_2$  favour the formation of the most stable alkoxides
- CRAs prepared from Cd, Co and above all, Mn chlorides, favour the formation of the less stable alkoxides. Unfortunately, yields with MnCRASi are sometimes rather low. Clearly, steric interactions must not be the only parameter intervening during these reductions. For the present time the results obtained cannot be explained.

Once again, these results show that CRAs are unusual reagents with interesting properties opening new fields of investigation.

#### General procedure

As previously described,<sup>2,3</sup> CRASi were prepared under nitrogen by dropwise addition of the alcohol in THF (10 ml) in a stirred mixture of NaH and an anhydrous metal salt ( $\text{ZnCl}_2$ ,  $\text{CdCl}_2$ ,  $\text{Ni}(\text{OAc})_2$ ,  $\text{CoCl}_2$  and  $\text{MnCl}_2$ ) in THF (20 ml).

After stirring 2 hours at 65°C, the temperature was adjusted if necessary and  $\text{Me}_3\text{SiCl}$  in THF (10 ml) was then added. After 15 min stirring, the substrate (10 mmol) in THF (10 ml) and the adequate internal standard ( $\text{C}_{12}\text{-C}_{16}$ ) was added over a period of 2-3 min. The reaction

was monitored by GC analysis of small aliquots by comparison with authentic alcohols using a Girdel 300 chromatograph (flame ionization) equipped with 50 m Carbowax 20 M capillary column. After completion of the reaction, the excess of NaH was carefully destroyed by dropwise addition of a cold 20 % solution of HCl (50 ml). The organic phase was filtered, and dried over magnesium sulfate. After removing of the solvent, the product was isolated by flash chromatography on a silica column and characterized by direct comparison (GC,  $^1\text{H}$  NMR, IR) with authentic samples.

#### Acknowledgements :

A.F. wishes to acknowledge support from the Algerian Petroleum Institute (Boumerdes, Algeria).

#### References

1. P. CAUBERE, *Angew. Chem. Int. Ed. Engl.*, 22, 599 (1983) ; *Pure Appl. Chem.*, 57, 1875 (1985).
2. J.J. BRUNET, D. BESOZZI and P. CAUBERE, *Synthesis*, 1982, 721.
3. Y. FORT, R. VANDERESSE and P. CAUBERE, *Tetrahedron Lett.*, 27, 5487 (1986).
4. (a) E.C. ASHBY, J.J. LIN and A.B. GOEL, *J. Org. Chem.*, 43, 1557, 1560, 1564 (1978) ;  
(b) J.R. BOONE and E.C. ASHBY, *Top. Stereochem.*, 11, 53 (1979) ; (c) H.C. BROWN and S. KRISHNAMURTHY, *Tetrahedron*, 35, 567 (1979) ; (d) D.C. WIGFIELD, *Tetrahedron*, 35, 449 (1979) ;  
(e) E.C. ASHBY, S.A. NODING and A.N. GOEL, *J. Org. Chem.*, 45, 1028 (1980) ; (f) B. CARO, B. BOYER, G. LAMATY and G. JAUEN, *Bull. Soc. Chim. Fr.*, 1983, II, 281 ; (g) N.M. YOON, K.E. KIM and J. KANG, *J. Org. Chem.*, 51, 226 (1986) ; (h) H.C. BROWN, W.S. PARK, J.S. CHA and B.T. CHO, *J. Org. Chem.*, 51, 337 (1986).
5. (a) E.L. ELIEL and S.H. SCHROETER, *J. Amer. Chem. Soc.*, 87, 5031 (1965).  
(b) G.N. SCHRAUZER "Transition metal in homogeneous catalysis", Marcel Dekker Inc., New York, 1971.

(Received in France 6 November 1987)