Tetrahedron Letters,Vol.29,No.5,pp 525-528,1988
Printed in Great Britain

0040-4039/88 $3.00 + .00
Pergamon Journals Ltd.

SELECTIVE CYCLOALKANONE REDUCTIONS USING ALUMINUM AMALGAM

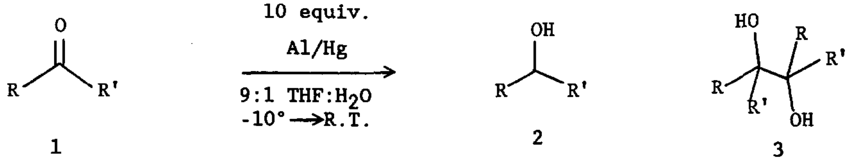
Martin Hulce* and Timothy LaVaute

Department of Chemistry
University of Maryland Baltimore County
Baltimore, MD 21228

Abstract. Aluminum amalgam in aqueous tetrahydrofuran reduces cycloalkanones to their respective alcohols. The reaction exhibits sensitivity to the ring size and steric environment of the ketone.

Aluminum amalgam (Al/Hg) is a convenient, neutral reducing reagent that has found wide use in organic synthesis: it reduces various nitrogen-containing functional groups,[1] causes organosulfur moieties to undergo reductive cleavage[2] and is employed in other reductive transformations.[3] Although a dissolving metal Bouveault-Blanc type[4] reduction of ketones using an excess of Al/Hg in a protic solvent could result in the formation alcohols, such a reaction result rarely is observed;[5] pinacolic dimerization of the ketyl species formed typically produces 1,2-diols as the sole products.[6]

We have found that in aqueous tetrahydrofuran (THF) at low (-12 to 25°C) temperatures, Al/Hg does indeed reduce ketones to their respective alcohols (Eq. 1 and TABLE). Moreover, this alcohol synthesis has proven to be surprisingly chemoselective: while nearly inert to aliphatic ketones, the reaction conditions reduce four, five and six-membered ring ketones in moderate to excellent yields. This observation prompted investigation of the various factors influencing the tendency of the substrate ketone to be reduced, leading to the following observations: First, within a homologous series of cycloalkanones, clear ring-size bias is demonstrated. Cyclohexanone is reduced in excellent yield, whereas both smaller and larger cycloalkanones are reduced in far more modest yields, if at all. Even a one-carbon change in ring size from the optimum cyclohexane structure causes the production of alcohol to fall by some 80%. The only anomaly in this trend is with cyclobutanone, which appears to be somewhat easier to reduce than cyclopentanone. Secondly, steric hindrance of the carbonyl moiety in the cycloalkanone severely inhibits reduction. While 3- or 4-methylcyclohexanone are reduced nearly effectively as cyclohexanone itself, 2-methylcyclohexanone is less prone to reduction; carbonyl groups with greater steric congestion such as norcamphor, camphor and menthone are reduced in trace amounts or not at all. Last, in a series of aliphatic carbonyl-con-



(1)

TABLE

Al/Hg Reductions of Ketones

Ketone 1	Ratio 1:2:3	Yield 2,%^{a,b}	Yield 3,%^{c}
cyclobutanone	67:33:0	33	--
cyclopentanone	79:21:0	12-18	--
cyclohexanone	5:95:0	94	--
2-methylcyclohexanone	49:51:0	42	--
3-methylcyclohexanone	12:88:0	71	--
4-methylcyclohexanone	10:90:0	70	--
cycloheptanone	85:15:0	14	--
cyclooctanone	>98:trace:0	trace	--
cyclononanone	>98:trace:0	trace	--
cyclododecanone	98:trace:0	trace	--
norcamphor	96:4:0	2	--
camphor	100:0:0	--	--
menthone	100:0:0	--	--
heptanal	54:46:0	20	--
2-heptanone	98:2:0	2	--
3-heptanone	99:1:0	1	--
4-heptanone	>99:1:0	<1	--
2-cyclohexenone	d	--	--
benzaldehyde	0:0:>98	--	95
acetophenone	0:0:>98	--	94
benzophenone	0:0:>98	--	90

a. Yields based on GC by internal standardization. Not optimized. b. GC performed on 6' x 1/8" 10% SE-30 or 5% FFAP columns. c. Isolated yield. d. Reductive dimerization of allylic ketyl produced various diols.

taining heptanes, the reaction conditions are equally inert to the various positional isomers. Only heptanal is reduced to an appreciable extent; even so, this aldehyde is reduced in yields inferior to those of cyclohexanones.

In a separate series of experiments, when more easily reduced cyclohexenone or aromatic aldehydes and ketones are submitted to Al/Hg reduction in aqueous THF, the anticipated pinacolic dimerization results and only traces of alcohols are observed in the crude products. In the cases of benzaldehyde and acetophenone where diastereomeric pinacol products can be produced, stereochemical results similar to those reported[6b] for the reduction of acetophenone are observed; the *R**,*R**-isomers are formed[7,8] with little or none of the *meso* diastereomeres being produced. The reaction, therefore, appears to produce results that overall are intermediate to those observed when a more activated Al(0) species such as Rieke aluminum is used[9] to generate pinacols, and milder reductants such as Ti(II) complexes[10] and Zn(0)/KOH[11] are employed, which can generate pinacols or alcohols and alcohols, respectively.

Inasmuch as the reduction potentials of the cycloalkanones and aliphatic ketones studied are very similar[12] and given that the reduction proceeds via electron transfer,[4] we rationalize our observations of chemoselectivity in terms of steric inhibition, torsional strain and angle strain: the reduction, occurring at the Al/Hg surface, displays a normal sensitivity to steric congestion that is common for heterogeneous reactions.[13] Conformationally labile aliphatic ketones and the largely conformationally unrestricted cyclodocecanone, possessing effectively greater steric congestion about their carbonyl moieties than relatively conformationally restricted small and medium ring cycloalkanones, therefore are poorer substrates. The reaction, involving a formal hybridization change from sp^2 to sp^3 at the carbonyl carbon[14] during electron transfer to the carbonyl to form a ketyl, therefore is highly subject to any torsional effects which may come into play during reduction. Such a change generates less torsional strain in cyclohexane than cyclopentane systems;[15] larger ring sizes, experiencing transannular strain[16] during rehybridization, consequently also would be less prone to reduction. Finally, in the small ring substrate cyclobutanone, rehybridization from sp^2 to sp^3 of the ring carbonyl carbon during the reduction relieves some angle strain[17] in the molecule, lowering the overall energy barrier for electron transfer compared to its homolog cyclopentanone and making it a slightly superior substrate.

We are actively investigating the intermolecular and intramolecular chemoselectivity of the reagent,[18] stereochemistry of the reduction and are optimizing the conditions of the reaction, all of which will be reported in due course.

Acknowledgement. Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

References and Notes

1. a. Wislicenus, H. *Chem. Ber*. 1896, *29*, 494; b. Wislicenus, H. *J. Prakt. Chem*. 1896, [2], *54*, 18, 54, 65; c. Fischer, E.; Groh, R. *Liebigs Ann. Chem*. 1911, *383*, 633; d. Putochin, N.J.; *Chem. Ber*. 1923, *56*, 2211; e. Drinkwater, D.J.; Smith, P.W.G. *J. Chem. Soc. C* 1971, 1305; f. Calder, A.; Hepburn, S.P. *Org. Syn*. 1972, *52*, 77; g. Ferris, J.P.; Sanchez, R.A.; Mancuso, R.W. *Org. Syn. Coll. Vol*. 1973, *5*, 32; h. Shin, C.; Yonezawa, Y.; Yoshimura, J. *Chem. Lett*. 1976, 1095.

2. a. Johnson, J.R.; Buchanon, J.B. *J. Am. Chem. Soc*. 1953, *75*, 2103; b. Corey, E.J.;

Chaykovsky, M. J. Am. Chem. Soc. 1964, 86, 1639; c. Posner, G.H.; Mallamo, J.P.; Hulce, M.; Frye, L.L. J. Am. Chem. Soc. 1982, 104, 4180.

3. a. Wislicenus, H.; Kaufmann, L. Chem. Ber. 1895, 28, 1323; b. Kuhn, R.; Winterstein, A. Helv. Chim. Acta 1928, 11, 123; c. Kuhn, R.; Fischer, H. Chem. Ber. 1961, 94, 3060; d. Inoi, T.; Gericke, P.; Horton, W.J. J. Org. Chem. 1962, 27, 4597; e. Lautenschlarger, F.; Schwartz, N.Y. J. Org. Chem. 1969, 34, 3991; f. Cooke, M.P., Jr. J. Org. Chem. 1982, 47, 4963; g. cf. Hudlicy, M. "Reductions in Organic Chemistry;" John Wiley and Sons: New York, NY, 1984.

4. House, H.O. "Modern Synthetic Reactions," 2nd ed.; W.A. Benjamin: Menlo Park, CA, 1972, pp. 150-172.

5. For two such examples, a. Harrison, I.T.; Harrison, S. "Compendium of Organic Synthetic Methods," vol. I; John Wiley and Sons: New York, NY, 1971, p. 112; b. Pike, J.E.; Schneider, W.P. U.S. Patent 3931283, 1976; Chem. Abstr. 1976, 85, 46061; see also ref.6b.

6. a. Newman, M.S. J. Org. Chem. 1961, 26, 582; b. Schreibman, A.A.P. Tetrahedron Lett. 1970, 4271.

7. Stocker, J.H.; Jenevein, R.M. J. Org. Chem. 1968, 33, 294.

8. Winstein, S.; Seymour, D. J. Am. Chem. Soc. 1946, 68, 119.

9. Rieke, R.D. Acc. Chem. Res. 1977, 10, 301.

10. Pons, J.-M.; Santelli, M. Tetrahedron Lett. 1986, 4153.

11. Handoo, K.L.; Gadru, K. Tetrahedron Lett. 1986, 1371.

12. Kabasakalian, P.; McGlutten, J. Anal. Chem. 1959, 31, 1091.

13. e.g. Gallois, P.; Brunet, J.-J.; Caubert, P. J. Org. Chem. 1980, 45, 1946.

14. cf. Carey, F.A.; Sundberg, R.J. "Advanced Organic Chemistry," 2nd ed., pt. A; Plenum: New York, NY, 1984, pp. 150.

15. Brown, H.C.; Ichikawa, K. Tetrahedron 1957, 1, 221.

16. Raphail, R.A. Proc. Chem. Soc. 1962, 97.

17. Wilson, A.; Goldhamer, D. J. Chem. Educ. 1963, 40, 504.

18. Exceptionally stereo- and chemoselective reducing agents continue to be coveted goals in chemistry: cf. Yoon, N.M.; Kim, K.E.; Kang, J. J. Org. Chem. 1986, 51, 226.

(Received in USA 12 November 1987)