Tetrahedron Letters,Vol.24,No.48,pp 5385-5386,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain ©1983 Pergamon Press Ltd.

STEREOSELECTIVE REDUCTION OF 3-OXO AMIDES WITH ZINC BOROHYDRIDE

Yoshio Ito and Masaru Yamaguchi*
Department of Chemistry, Kyushu University 33, Higashi-ku, Fukuoka 812, Japan

Summary: 2-Alkyl-3-oxo amides were reduced to the corresponding *syn*-2-alkyl-3-hydroxy amides with high stereoselectivity by zinc borohydride.

In the search for new stereoselective reducing agents, T. Nakata and T. Oishi[1] found that the reduction of 4-unsaturated (phenyl or carbon-carbon double bond) 2-alkyl-3-oxo esters with $Zn(BH_4)_2$ in ether gave *syn*-2-alkyl-3-hydroxy esters almost exclusively.[2] They suggested that the high stereoselectivity of the reaction may be due to the conformational fixation by six-membered chelate ring formation which was promoted by the enhanced donating ability of a conjugated 3-oxo group.[3] In fact, the reduction of the saturated analogues did not give good selectivity.[1]

Since 2-alkyl-3-oxo acid derivatives are readily available and the *syn*-2-alkyl-3-hydroxy acid structure is often encountered in a variety of natural products, it seemed very attractive to extend the availability of this method to saturated analogues, as an alternative of recently developed stereoselective aldol condensation.

After the unsuccessful attempt to stabilize the presumed zinc chelate intermediate by an additional donation of another O-function embedded in the alcoholic moiety of the oxo esters [for example, esters of diethylene glycol, 1,2,6-hexanetriol, 2-methoxyethanol, 2-(2-ethoxyethoxy)-ethanol, 2-(2-tetrahydropyranyloxyethoxy)ethanol, etc. with *syn/anti* ratios of 3/1~3/2], we examined the reduction of 2-alkyl-3-oxo amides since the amide carbonyl was considered to be a better donor than the ester carbonyl.

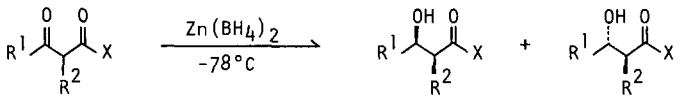
As the result, it has been revealed that 2-alkyl-3-oxo amides are reduced by $Zn(BH_4)_2$ in ether at -78°C to the corresponding *syn*-2-alkyl-3-hydroxy amides with high stereoselectivity in good yield. Amides of aromatic and primary and secondary aliphatic amines or even nonsubstituted amides could be reduced invariably with high selectivity. Some examples are shown in the Table. Similar results were also obtained in the reduction with $NaBH_4$ at -78°C when $Zn(ClO_4)_2 \cdot 6H_2O$ was added before the addition of the reducing agent. Additives such as $Mg(ClO_4)_2$, Cp_2ZrCl_2, and $Ti(O^iPr)_4$ were not effective. Elevated temperature usually resulted in the decrease in selectivity. For example, 2-methyl-3-oxo-butyranilide was reduced at 0°C giving a *syn/anti* ratio of 75/25. However, in this particular case, reduction with $NaBH_4$ at 0°C after the addition of $Zn(ClO_4)_2 \cdot 6H_2O$ to a THF solution of the substrate gave a *syn/anti* ratio of 92/8. While a slightly low ratio (*syn/anti* = 9/1) was observed in the reduction of the amide of 2-aminoethanol which was chosen in order to facilitate the subsequent hydrolysis of the reduced amide to the corresponding hydroxy acid through N→O acyl transfer,[4] the satisfactory selectivity (*syn/anti* = 98/2) was attained when the free hydroxyl group of the substrate was protected by acid-labile *t*-butyldimethylsilyl group.

A typical procedure of the reduction was exemplified below.

A solution of $Zn(BH_4)_2$[5] in ether (4 ml, ca 0.75 mmol) was added to a solution of N-(2-*t*-

butyldimethylsiloxyethyl)-2-methylacetoacetamide (54.0 mg, 0.20 mmol) in anhydrous ether (6 ml) under nitrogen at -78°C. After stirring for 15 min at -78°C, 3% aqueous phosphoric acid (0.6 ml) was added and stirring was continued for 30 min. The organic layer was washed with saturated aqueous sodium chloride. The solution was dried over sodium sulfate and evaporated to give N-(2-*t*-butyldimethylsiloxyethyl)-3-hydroxy-2-methylbutyramide (54.0 mg, 99%).

Table. Reduction of 2-Alkyl-3-oxo Amides with $Zn(BH_4)_2$ at -78°C



Entry	Amide			Solvent	Product Ratio	Yield(%)[a,b]
	R^1	R^2	X		*syn* : *anti*	
1	CH_3	CH_3	NH_2	THF	98 : 2[c]	83[g]
2	CH_3	CH_3	NHPh	ether	98 : 2[c]	99
3	CH_3	CH_3	NH^nBu	ether	98 : 2[d]	91
4	CH_3	CH_3	$NHCH_2Ph$	ether	97 : 3[d]	87
5	CH_3	CH_3	$N(c\text{-}C_6H_{11})_2$	ether	98 : 2[c]	99
6	CH_3	CH_3	NH OTBDMS	ether	98 : 2[e]	99(97)
7	CH_3	C_2H_5	NH OTBDMS	ether	99 : 1[f]	99(92)
8	$(CH_3)_2CH$	CH_3	NCH_3 OTBDMS	ether	98 : 2[e]	98(94)
9	$(CH_3)_3C$	CH_3	$N(CH_2Ph)_2$	THF	99 : 1[f]	99

a) All the products gave satisfactory NMR and elementary analyses. b) Isolated yield of the corresponding acid after hydrolysis is given in parentheses. Hydrolysis: 1) 1.5N-HCl, 100°C, 2h. 2) pH 7(sat. $NaHCO_3$), rt, 5 min. c) The ratio was determined by ^{1}H-NMR after acetylation. d) The ratio was determined by HPLC of O-acetate or O-benzoate. e) The ratio was determined by GLPC of the corresponding methyl ester, after hydrolysis and subsequent esterification(CH_2N_2). f) The ratio was determined by ^{1}H-NMR. g) Isolated yield after O-acetylation.

Support from the Foundation for the Promotion of Research on Medicinal Resources is gratefully acknowledged.

References

1) T. Nakata and T. Oishi, Tetrahedron Lett., 21, 1641 (1980).
2) A system of stereochemical designation proposed by Masamune et al. is tentatively adopted in this communication. S. Masamune, S. A. Ali, S. L. Snitman, and D. S. Garvey, Angew. Chem. Int. Ed. Engl., 19, 557 (1980).
3) T. Oishi and T. Nakata, J. Synth. Org. Chem. Jpn., 39, 633 (1981).
4) D. A. Evans and L. R. McGee, J. Am. Chem. Soc., 103, 2876 (1981).
5) W. J. Gensler, F. A. Johnson, and A. D. B. Sloan, J. Am. Chem. Soc., 82, 6074 (1960).

(Received in Japan 1 September 1983)