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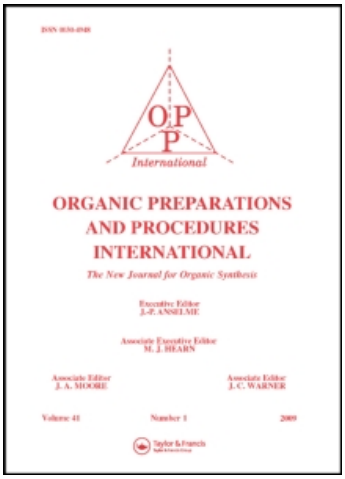

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$NaBH_4$-$MnCl_2$, FOR IMPROVED REDUCTION OF β-KETO ESTERS ATTACHED TO A CHIRAL AUXILIARY. COMPARISON WITH $Zn(BH_4)_2$

P. R. R. Costa[a]; C. V. F. Lima[b]; P. R. Paiva[b]; S. Pinheiro[b]
[a] Laboratório de Química Bioorgnica Nücleo de Pesquisas de Produtos Naturais, CCS Universidade do Brasil Cidade Universitária, Rio de Janeiro, RJ, Brazil [b] Departamento de Química Orgnica Instituto de Química, Universidade Federal Fluminense Outeiro de S. João Batista s/n Centro, Niterói, RJ, Brazil

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$NaBH_4$-$MnCl_2$ FOR IMPROVED REDUCTION OF β-KETO ESTERS ATTACHED TO A CHIRAL AUXILIARY. COMPARISON WITH $Zn(BH_4)_2$

Submitted by (10/10/01)

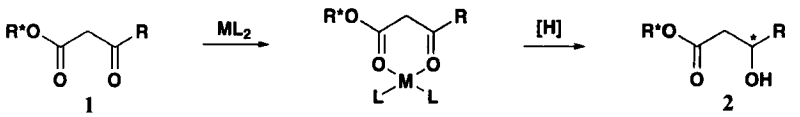
P. R. R. Costa,*[†] C. V. F. Lima,[††] P. R. Paiva[††] and S. Pinheiro*[††]

[†] *Laboratório de Química Bioorgânica*
Núcleo de Pesquisas de Produtos Naturais, CCS Universidade do Brasil
Cidade Universitária, 21941-590, Rio de Janeiro, RJ, BRAZIL.

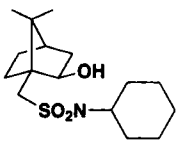
[††]*Departamento de Química Orgânica*
Instituto de Química, Universidade Federal Fluminense
Outeiro de S. João Batista s/n, Centro, 24210-150, Niterói, RJ, BRAZIL

The chemo- and stereoselective reduction of β-keto esters is an efficient and useful strategy for the synthesis of biologically active compounds such as natural products,[1] β-lactam antibiotics,[2] fluoxetine[3] and the HR 780,[4] an HMG-CoA reductase inhibitor. In spite of the extensively investigated enantioselective approaches,[5] the use of chiral auxiliaries remains a common and reliable method for the stereoselective reduction of β-keto acids derivatives with hydrides in moderate to high levels of asymmetric induction.[6] Usually these reactions are carried out with $Zn(BH_4)_2$ in the presence of $ZnCl_2$ as the complexing additive of both carbonyls of the β-keto ester **1** in order to prevent carbon-

carbon bond rotation.[6b,c] The π-facial stereoselection in the reduction of the coordinated species leading to chiral β-hydroxyester **2** is due to the preferential blockade of one face of the ketone carbonyl by the chiral auxiliary (R*).



Some time ago, $NaBH_4$-$MnCl_2$ was successfully employed to control the relative configuration in the reduction of both cyclic and acyclic α-substituted keto esters and derivatives.[7,8] This system was proved to be simpler and more efficient than $NaBH_4$-$ZnCl_2$.[8] This paper reports the first comparison between $Zn(BH_4)_2$-$ZnCl_2$ and $NaBH_4$-$MnCl_2$ systems in the reduction of β-keto esters. To the best of our knowledge, this work also represents the first application of the commercially available Oppolzer's auxiliary (-)-10-dicyclohexylsulfamoyl-D-isoborneol in this reaction.



Oppolzer's auxiliary

The chiral β-keto esters **1a,b** were prepared (80% and 57% yields, respectively) by refluxing either ethyl benzoylacetate or acetoacetate with the chiral auxiliary in DMAP/ toluene (*Table*).[9,10] As expected, a lack of stereoselectivity was observed for the reaction with $NaBH_4$ in the absence of coordinating agents.[8] The reductions of **1a** and **1b** with $NaBH_4$ in the presence of $MnCl_2$ are faster,[6d] cleaner, easier to handle and show better chemical yields than reactions in $Zn(BH_4)_2$-$ZnCl_2$.[6b,c] Surprisingly, the use of $NaBH_4$-$ZnCl_2$ in the reductions of **1a** and **1b** led to mixture of products.

In contrast to the $Zn(BH_4)_2$-$ZnCl_2$ protocol, the crude diastereoisomeric mixtures of the β-hydroxy esters **2a,b** and **3a,b** were easily obtained in excellent purities by flash chromatography on silica gel from the reductions using $NaBH_4$-$MnCl_2$. Similar selectivities of **2a,b** and **3a,b** were obtained in all procedures and attempts of increasing the % d. e. of **2a,b** by recrystallization failed.

TABLE. Improved Reduction of **1a,b** with $NaBH_4$-$MnCl_2$.

Cmpd	Reducing system	T(°C)	Yield(%)[a]	**2:3**[b]
1a	$NaBH_4$, $MnCl_2$, MeOH, 20 min.	0	96	73:27
1a	$Zn(BH_4)_2$, $ZnCl_2$, Et_2O, 2 h	-78	75	74:26
1b	$NaBH_4$, $MnCl_2$, MeOH, 20 min.	0	94	73:27
1b	$Zn(BH_4)_2$, $ZnCl_2$, Et_2O, 2 h	-78	70	72:28

a) For mixtures of isomers **2** and **3** after flash chromatography on silica gel. b) Determined from the signals of the carbonyls in the crude ^{13}C NMR spectra.

The stereoselectivities were determined from the signals of the carbonyl groups in quantitative ^{13}C NMR spectra of the mixtures of these isomers using the 'gated decoupled' procedure. The

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absolute configurations of the newly created asymmetric centers in the main isomers **2a** and **2b** were determined by comparison of the optical rotations of the products obtained either by hydrolysis of to the known (-)-3-hydroxy-3-phenylpropanoic acid[11] or by reduction with $LiAlH_4$ in dry diethyl ether to the known (-)-butane-1,3-diol.[6d]

In summary, the use of $NaBH_4$ in the presence of $MnCl_2$ as complexating additive is more efficient and attractive than the classic system $Zn(BH_4)_2$-$ZnCl_2$ in the reduction of β-keto esters attached to chiral auxiliaries, since better yields and similar stereoselectivities can be obtained through more convenient conditions reactions.

EXPERIMENTAL SECTION

Mps are uncorrected. Flash column chromatography was performed on silica gel 60 (230-400 mesh). IR spectra were measured with a Perkin-Elmer 1420 spectrometer and NMR in $CDCl_3$ on a Varian Unityplus (300 MHz) instrument. Chemical shifts are expressed in δ (ppm) downfield from TMS and coupling constant in Hertz. Low Resolution Mass Spectra (LRMS) were measured on a V.G. Auto Spec. Q and the optical rotations were obtained with a Perkin-Elmer 243-B polarimeter. Elemental analyses were determined with a Carlo Erba 1104 apparatus. $MnCl_2$ was refluxed with excess $SOCl_2$, the excess of which was then distilled off.

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General Procedure for Ketoesters 1a and 1b.- A mixture of the Oppolzer's auxiliary (0.76 g; 1.92 mmol), DMAP (0.07 g; 0.58 mmol) and toluene (10 mL) was stirred under a nitrogen atmosphere until the solids dissolved. To the resulting solution was added either ethyl benzoylacetate or ethyl acetoacetate (5.8 mmol) and the mixture was refluxed for 48 hours. The solution was cooled to 0° and the reaction was quenched by addition of sat. NH_4Cl (20 mL). The mixture was extracted with dichloromethane (3 x 10 mL) and the combined organic layers were dried over anhydrous Na_2SO_4. Solvent removal in vacuum was followed by flash chromatography on silica gel using 3% EtOAc in hexane as eluant.

(-)-10-Dicyclohexylsulfamoyl-D-isobornyl Benzoylacetate (1a), yield 80%, white solid mp. 75°, $[a]_D^{25}$ –32.4 (c 1.05; CH_2Cl_2). IR: (KBr): 2921, 2848, 1737, 1682, 1633, 1447, 1321, 1259, 1188 and 1135 cm^{-1}. ^1H NMR: ($CDCl_3$, COSY): δ 12.66 (s, OH of enol), 7.96-7.37 (m, 5H, H_{19}-H_{21}), 5.58 (s, 1H, H_{16} of enol), 5.19 (dd, 1H, J = 7.8 and 3.3 Hz, H_1 of enol), 5.00 (dd, 1H, J = 7.8 and 3.6 Hz, H_1 of keto), 4.09 (d, 1H, J = 15.3 Hz, H_{16} of keto), 3.82 (d, 1H, J = 15.3 Hz, H_{16} of keto), 3.37-3.16 (m, 2H, H_{11}), 3.30 (d, 1H, J = 13.2 Hz, H_{10} of enol), 3.21 (d, 1H, J = 13.2 Hz, H_{10} of keto), 2.70 (d, 1H, J = 13.2 Hz, H_{10} of enol), 2.63 (d, 1H, J = 13.2 Hz, H_{10} of keto), 2.06-1.88 (m, 2H, H_6 of enol), 1.85-1.08 (m, 16H, H_3-H_5, H_6 of keto and H_{12}-H_{14}), 1.03 (s, 3H, CH_3 of enol), 0.91 (s, 3H, CH_3 of enol), 0.82 (s, 3H, CH_3 of keto), 0.72 (s, 3H, CH_3 of keto) ppm; ^{13}C NMR: ($CDCl_3$, DEPT, HETCOR): δ 192.2 (C_{17} of keto), 171.7 (C_{18} of enol), 171.2 (C_{18} of keto), 166.0 (C_{15}), 135.9 (C_{17} of enol), 131.0 (C_{16} of enol), 133.6, 128.7, 128.3 and 125.7 (C_{19}-C_{21}), 79.5 (C_1 of keto) 78.1 (C_1 of enol), 57.4 (C_{11} of keto), 57.3 (C_{11} of enol), 53.6 (C_{10} of keto), 53.4 (C_{10} of enol), 49.4 (C_7 of enol), 49.3 (C_7 of keto), 49.1 (C_2 of enol), 49.0 (C_2 of keto), 46.3 (C_{16} of keto), 44.5 (C_5 of enol), 44.3 (C_5 of keto), 39.3, 39.0, 32.8, 32.6,

30.2, 29.7, 26.9, 26.8, 26.4, 26.3, 25.1 and 24.9 (C_3, C_4, C_6 and C_{12}-C_{14}), 20.4 (CH_3 of enol), 20.2 (CH_3 of keto), 20.0 (CH_3 of enol), 19.4 (CH_3 of keto) ppm.

Anal. Calcd for $C_{31}H_{45}NO_5S$: C, 68.47; H, 8.34; N, 2.57. Found: C, 68.36; H, 8.22; N, 2.74

(-)-10-Dicyclohexylsulfamoyl-D-isobornyl Acetoacetate (1b), yield 57%, white solid, mp. 133°. IR: (KBr): 2939, 2864, 1749, 1731, 1658, 1332, 1251, 1173 and 1147 cm^{-1}. ^1H NMR: ($CDCl_3$, COSY): δ 12.17 (s, OH of enol), 5.30 (s, 1H, H_{16} of enol), 5.18 (dd, 1H, J = 8.0 and 2.7 Hz, H_1 of enol), 5.01 (dd, 1H, J = 8.0 and 2.7 Hz, H_1 of keto), 3.43 (d, 1H, J = 15.0 Hz, H_{16} of keto), 3.37 (d, 1H, J = 15.0 Hz, H_{16} of keto), 3.30-3.20 (m, 2H, H_{11}), 3.20 (d,1H, J = 13.2 Hz, H_{10}), 2.65 (d,1H, J = 13.2 Hz, H_{10}), 2.29 (s, 3H, H_{18}), 2.04-1.90 (m, 2H, H_6), 1.88-1.06 (m, 16H, H_3-H_5, H_7 and H_{12}-H_{14}), 0.98 (s, 3H, CH_3 of enol), 0.96 (s, 3H, CH_3 of keto), 0.89 (s, 3H, CH_3 of enol), 0.88 (s, 3H, CH_3 of keto) ppm. ^{13}C NMR: (DEPT, HETCOR): δ 201.1 (C_{17}), 165.8 (C_{15}), 90.0 (C_{16} of enol), 79.5 (C_1), 57.4 (C_{11} of keto), 57.3 (C_{11} of enol), 53.7 (C_{10}), 50.4 (C_{16} of keto), 49.4 (C_2 of keto), 49.1 (C_2 of enol), 44.4 (C_7), 39.3, 32.6, 26.9, 26.4 and 25.1 (C_3, C_4 and C_{12}-C_{14}), 30.4 (C_6), 29.9 (C_5), 20.3 and 19.8 (C_8, C_9) ppm. LRMS m/z (relative intensity): 483 (M^+, 22), 380 (24), 298 (69), 244 (68), 194 (32), 181 (70), 180 (81), 179 (46), 135 (100), 83 (66), 55 (94).

Anal. Calcd for $C_{26}H_{43}NO_5S$: C, 64.88; H, 9.00; N, 2.91. Found: C, 64.61; H, 8.85; N, 3.05

General Procedure for the Reduction of the Ketoesters 1a,b with $NaBH_4$-$MnCl_2$.- To a solution of the adequate keto ester **1a,b** (1.0 mmol) in methyl alcohol (10 mL) was added $MnCl_2$ (0.22 g; 2.0 mmol) and the mixture was stirred at room temperature for 30 minutes. The resulting clear solution was cooled to 0° and $NaBH_4$ (0.04 g; 1.0 mmol) was added portionwise. After stirring for 20 minutes, the mixture was poured into 10% aqueous HCl (30 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4. Solvent removal in vacuum was followed by flash chromatography on silica gel using 5% EtOAc in hexane as eluant.

Mixture of 2a and 3a, yield 96%, white solid mp. 160°, $[a]_D^{25}$ –34 (c 1.03; CH_2Cl_2). IR: (KBr): 3620-3350, 2926, 2853, 1730, 1321, 1160, 1138 and 1047 cm^{-1}. ^1H NMR: ($CDCl_3$, COSY): δ 7.40-7.26 (m, 5H, H_{19}-H_{21}), 5.22-5.14 (m, 1H, H_1), 5.06 (dd, 1H, J = 9.3 and 4.5 Hz, H_{17} of **2a**), 5.00 (dd, 1H, J = 9.3 and 4.5 Hz, H_{17} of **3a**), 3.32-3.28 (m, 3H, H_{10} and H_{11}), 2.78-2.60 (m, 3H, H_6 and H_{10}), 2.06-1.95 (m, 1H, H_{16}), 1.95-1.00 (m, 10H, H_3, H_4, H_{12}-H_{14} and H_{16}), 0.96 (s, 3H, H_8 of **3a**), 0.94 (s, 3H, H_8 of **2a**), 0.87 (s, 3H, H_9) ppm. ^{13}C NMR: (DEPT, HETCOR): δ 171.0 (C_{15} of **2a**), 170.8 (C_{15} of **3a**), 142.5 (C_{18} of **2a**), 142.4 (C_{18} of **3a**), 128.3, 127.5, 127.4, 125.5 and 125.4 (C_{19}-C_{21}), 78.9 (C_1 of **3a**), 78.8 (C_1 of **2a**), 70.2 (C_{17} of **2a**), 69.9 (C_{17} of **3a**), 57.5 (C_{11} of **3a**), 57.4 (C_{11} of **2a**), 53.9 (C_{10} of **3a**), 53.8 (C_{10} of **2a**), 49.4 (C_2), 49.1 (C_7 of **3a**), 49.0 (C_7 of **2a**), 44.4 (C_5), 44.0 (C_6), 39.4 (C_{16} of **3a**), 39.3 (C_{16} of **2a**), 32.8 (C_3 of **3a**), 32.6 (C_3 of **2a**), 30.4 (C_4), 26.9, 26.4, 26.3 and 25.0 (C_{12}-C_{14}), 20.3 (C_9), 19.9 (C_8) ppm.

Anal. Calcd for $C_{31}H_{47}NO_5S$: C, 68.22; H, 8.68; N, 2.57. Found: C, 68.01; H, 8.46; N, 2.73

Mixture of 2b and 3b, yield 94%, white solid mp. 145°, $[a]_D^{25}$ –90.3 (c 0.62; CH_2Cl_2). IR: (KBr): 3580-3460, 2938, 2860, 1745, 1461, 1330, 1171, 1143 and 1052 cm^{-1}. ^1H NMR: ($CDCl_3$, COSY): δ 5.20 (dd, 1H, J = 8.6 and 4.0 Hz, H_1 of **2b**), 4.97 (dd, 1H, J = 8.6 and 4.0 Hz, H_1 of **3b**), 4.28-4.17 (m,

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1H, H_{17}), 3.32-3.18 (m, 1H, H_{11}), 3.23 (d, 1H, J = 13.2 Hz, H_{10}), 2.65 (d, 1H, J = 13.2 Hz, H_{10}), 2.48-2.34 (m, 2H, H_{16}), 2.03-1.91 (m, 2H, H_6), 1.83-1.05 (m, 16H, H_3-H_5, H_7 and H_{12}-H_{14}), 1.22 (d, 3H, J = 6.3 Hz, H_{18}), 0.99 (s, 3H, H_8), 0.88 (s, 3H, H_9) ppm. ^{13}C NMR: (DEPT, HETCOR): δ 171.4 (C_{15} of **2b**), 170.2 (C_{15} of **3b**), 78.6 (C_1), 64.1 (C_{17}), 57.5 (C_{11} of **3b**), 57.4 (C_{11} of **2b**), 53.9 (C_{11} of **2b**), 53.7 (C_{10} of **3b**), 49.3 (C_2), 49.0 (C_7), 44.3 (C_5), 43.5 (C_{16}), 39.5 (C_6), 32.8 (C_3), 30.4 (C_4), 26.4, 26.3 and 25.0 (C_{12}-C_{14}), 22.3 (C_{18}), 20.4 and 19.9 (C_8 and C_9) ppm. LRMS m/z (relative intensity): 481 (59), 298 (100), 244 (76), 221 (47), 181 (93), 180 (54), 138 (95), 135 (98), 55 (34).

Anal. Calcd for $C_{26}H_{45}NO_5S$: C, 64.56; H, 9.38; N, 2.89. Found: C, 64.29; H, 9.19; N, 3.03

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10. Compounds **1a,b** were obtained as 80-90% of the keto tautomers by ^{1}H NMR spectra. These selectivities were measured from the signals of the acidic methylene H_{16} and those due to the vinylic hydrogens of the corresponding enol forms.

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A FACILE AND EFFICIENT ZINC-PROMOTED ALLYLATION OF CARBONYL COMPOUNDS

Submitted by (11/13/00) Chinpiao Chen*†, Wen-Chin Dai and Han-Gen Chang

Department of Medical Technology, Tzu Chi University
Hualien, 970, Taiwan, Republic of CHINA

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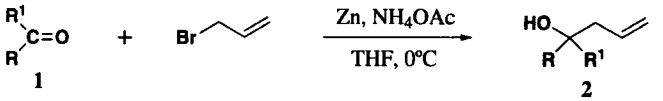
The synthesis of homoallylic alcohols by allylation of carbonyl compounds is an important process[1] because these alcohols can be easily converted into many essential functional groups for natural product synthesis.[2] By the use of a variety of metals such as manganese,[3] tin,[4] and zinc,[5] different homoallylic alcohols are generally prepared *via* the Barbier-type reaction of allylic halides and carbonyl compounds with metal powder. Such reactions are typically performed in anhydrous organic solvents under an inert atmosphere.[5a-5f] The feasibility of performing organometallic reactions in an aqueous media has been of considerable recent interest.[5g-5k] Luche has demonstrated that the Barbier-type reaction could be performed in a mixture of organic solvent with water, particularly when the metal surface was activated by ultrasound[5k] or with ammonium salts. The present work describes a study of the Barbier-type reaction of allyl bromide and carbonyl compounds in the presence of zinc powder and ammonium chloride in an aqueous media.



1 2

a) R = C_6H_5, R^1 = H b) R = C_5H_{11}, R^1 = H c) R = *p*-$MeOC_6H_4$, R^1 = H
d) R = CH_3, R^1 = C_4H_9 e) R = R^1 = $(CH_2)_5$ f) R = CH_3, R^1 = C_6H_5
g) R = CH_3, R^1 = 2-furyl h) R = CH_3, R^1 = 2-pyridyl i) R = R^1 = C_6H_5