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Stereoselective Addition of Organoaluminium or Organomanganese Reagents to 2-Methyl-3–oxo Amides (or Esters) Providing erythro or threo 2-Methyl-3-hydroxy Amides (or Esters)

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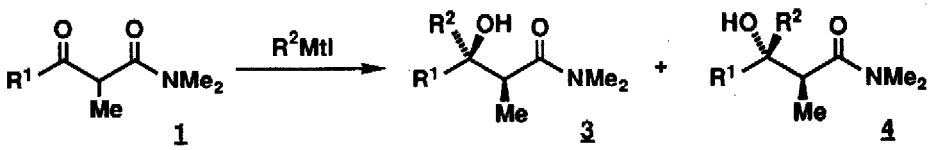
Abstract: Treatment of 2-methyl-3-oxo amides or 2-methyl-3-oxo esters with trialkylaluminium or alkylmanganese halide provided the corresponding erythro (or threo) 3-hydroxy-2-methyl amides or 3-hydroxy-2-methyl esters with high stereoselectivity.

Recently we have reported that erythro-3-hydroxy-2-methyl amides or erythro-3-hydroxy-2-methyl esters were prepared with high stereoselectivity by $NaBH_4$ reduction of the corresponding 3-oxo amides or 3-oxo esters in the presence of a catalytic amount of $MnCl_2$.[1] Here we wish to report an extension of the method for the stereoselective addition of organometallic reagent to 3-oxo amides or 3-oxo esters.

The methine proton of 3-oxo amides **1** or 3-oxo esters **2** is appreciably acidic and **1** or **2** yield highly stabilized enolate ions upon treatment with a base. In fact, MeLi mainly attacked methine proton of **1a** to generate the lithium enolate which gave the starting 3-oxo amide **1a** (51 %) upon workup and the desired hydroxy amide was obtained as a stereoisomeric mixture (**3a**:**4a** = 22:78) in only 37% combined yield along with unidentified complex products. The use of MeMgI resulted in a formation of **3a** (**3a**:**4a** = 99:1) in poor yield (51%). We expected that an addition of less basic organomanganese reagent[2] such as MeMnCl or *n*-BuMnCl to **1a** would provide the corresponding erythro-3-methyl (or 3-butyl)-3-hydroxy-2-methyl amide **3a** (or **3c**) stereoselectively in good yield. This was indeed the case and treatment of **1a** with MeMnCl (or *n*-BuMnCl) gave erythro-3-phenyl-3-hydroxy-2-methylbutanamide **3a**[3] (or erythro-3-phenyl-3-hydroxy-2-methylheptanamide **3c**) exclusively. The selective formation of erythro product **3a** or **3c** can be attributed to the selective attack of methyl group or butyl group from the opposite side of the 2-methyl group of **1a** in a six-membered metal chelate[4] in a similar fashion as shown in the reduction of **1a** with $MnCl_2$-$NaBH_4$ system.[1] Meantime, the reaction of **1b** with PhMnCl provided the opposite stereoisomer, threo-3-phenyl-3-hydroxy-2-methylbutanamide **4a**[5] stereoselectively (Table 1, Entry 10). Thus, both stereoisomers **3a** and **4a** could be obtained with high selectivity.[6]

As shown in Table 1, the stereoselectivities are high for all of the substrates **1a**-**1d** with an exception of the reaction of **1b** with *n*-BuMnCl. Organoaluminium reagents proved to be as effective as organo-

Table 1. Addition of Organometallic Reagents to 2–Methyl-3-oxo Amides[a]

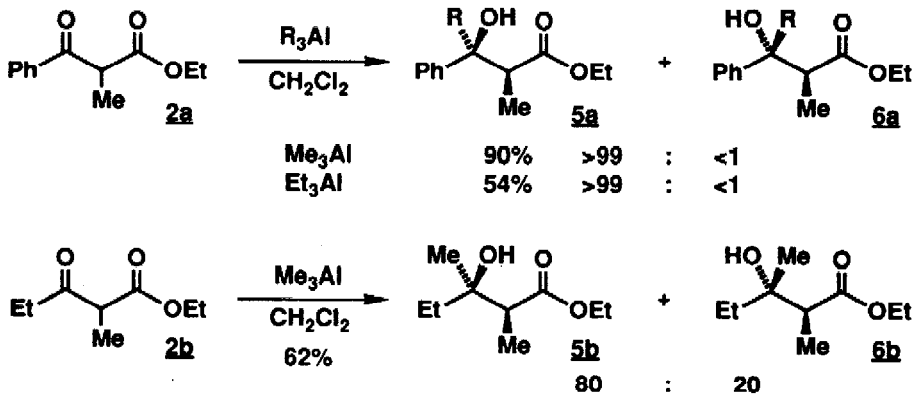


Entry	Keto Amide	R^2Mtl	Solvent	Yield (%)	Ratio of 3 : 4
1		MeMnCl	THF	93	>99 (**3a**) : <1 (**4a**)
2		Me_3Al	CH_2Cl_2	90	>99 (**3a**) : <1 (**4a**)
3		$MeTiCl_3$	ether	80	>99 (**3a**) : <1 (**4a**)
4	Ph, NMe2, Me **1a**	Et_2AlCl	CH_2Cl_2	88	>99 (**3b**) : <1 (**4b**)
5		*n*-BuMnCl	THF	98	>99 (**3c**) : <1 (**4c**)
6		$(n\text{-BuC}\equiv\text{C})_3Al$[b]	ether	84	>99 (**3d**) : <1 (**4d**)
7		CH_2=CHMnI	ether	83	>99 (**3e**) : <1 (**4e**)
8		Et_2AlCl	CH_2Cl_2	76	>99 (**3f**) : <1 (**4f**)
9		*n*-BuMnCl	THF	74	83 (**3g**) : 17 (**4g**)
10	Me, NMe2, Me **1b**	PhMnCl	THF	83	>99 (**4a**) : <1 (**3a**)
11		CH_2=CHMnI	ether	66	90 (**3h**) : 10 (**4h**)
12		Me_3Al	CH_2Cl_2	81	>99 (**4f**) : <1 (**3f**)
13	Et, NMe2, Me **1c**	PhMnI	ether	52	93 (**4b**) : 7 (**3b**)
14		Me_3Al	CH_2Cl_2	87	>99 (**3i**) : <1 (**4i**)
13	t-Bu, NMe2, Me **1d**	$MeTiCl_3$	ether	58	>99 (**3i**) : <1 (**4i**)

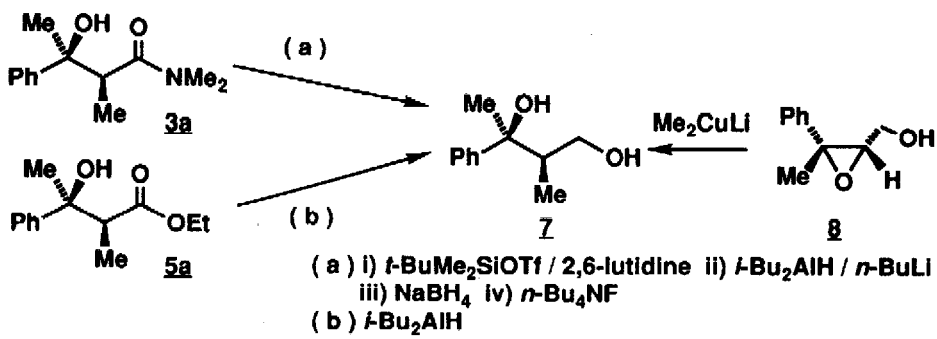
a) 3-Oxo amide (1.0 mmol) and organometallic reagent (2.0 mmol)[7] were employed. The reactions were performed at 0 °C. b) Prepared from $AlCl_3$ and three equivalents of lithium acetylide.

manganese reagents for the stereoselective formation of 3-hydroxy-2-methyl amides. Not only alkyl group but also alkynyl group could be introduced stereoselectively. Organotitanium reagent ($MeTiCl_3$) gave the same stereoisomeric products as trimethylaluminium.

An addition of organometallic reagents to 3-oxo ester **2a** or **2b** instead of 3-oxo amides **1** was examined. In this case, organoaluminium reagents proved to be superior to the corresponding organomanganese reagents. For instance, treatment of **2a** with Me_3Al gave the desired hydroxy ester **5a** selectively in 90% yield. On the other hand, an addition of MeMnCl to **2a** gave a complex mixture[8] and no trace of **5a** was observed in the reaction mixture.



The assignment of stereochemistry of the products **3** or **5** was performed as follows. Reduction of erythro-amide **3a** with *n*-BuLi-*i*-Bu_2AlH followed by $NaBH_4$[9] gave erythro diol **7**[10,11] which was identical with a sample derived from epoxy alcohol **8** upon treatment with Me_2CuLi.[12] Reduction of hydroxy ester **5a** with *i*-Bu_2AlH afforded the same diol **7**.



A typical experiment is as follows. A THF solution of 3-oxo amide **1a** (0.21 g, 1.0 mmol) was added to a solution of $MeMnCl$[2] (2.0 mmol) prepared from $MnCl_2$ and MeLi in THF at 0 °C under argon atmosphere. After stirring for 1 h at 0 °C, the resulting mixture was poured into water and extracted with ethyl acetate (20 ml x 3). The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification by silica gel column chromatography gave erythro-3-hydroxy-2-methyl amide **3a** (0.21 g) in 93% yield.[13]

References and Notes

1. Fujii, H.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1991**, *32*, 6147-6150.
2. Normant, J-F.; Cahiez, G. Organomanganous Reagents: Their use in Organic Synthesis. In *Modern Synthetic Methods, Vol. 3*; Scheffold, R. Ed.; Otto Salle Verlag GmbH & Co.; Frankfurt am Main, 1983; pp.173-216.
3. **3a**: Mp 130-131 °C; IR (nujol) 3252, 2920, 2852, 1611, 1499, 1459, 1421, 1377, 1309, 1255, 1202, 1146, 1120, 1066, 705, 682, 649 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (d, *J* = 7.0 Hz, 3H), 1.52 (s, 3H), 3.01 (q, *J* = 6.9 Hz, 1H), 3.04 (s, 3H), 3.15 (s, 3H), 5.91 (s, 1H), 7.2-7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.58, 29.97,

35.53, 37.67, 43.81, 74.69, 124.9, 126.4, 128.0, 146.0, 177.7. Found: C, 70.49; H, 8.85%. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65%.

4. We are tempted to assume that the first step in the reaction must be the coordination of the 3-oxo amide **1a** to form a six-membered metal chelate which is followed by the attack of second organomanganese reagent on the carbonyl carbon from the opposite side of the methyl group of **1a**. Chelation control in addition reaction of α- and β-alkoxy carbonyl compound or α-keto amide has been reported. Reetz, M. T. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 556-569; Soai, K.; Ishizaki, M. *J. Org. Chem.* **1986**, *51*, 3290-3295; Fujisawa, T.; Ukaji, Y.; Funabora, M.; Yamashita, M.; Sato, T. *Bull. Chem. Soc. Jpn.* **1990**, *63*, 1894-1897.
5. **4a**: Mp 72.0-73.0 °C; IR (nujol) 3356, 2926, 2852, 1615, 1459, 1378, 1365, 1316, 1258, 1231, 1138, 1087, 1064, 935, 770, 711, 657, 627 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.35 (d, J = 7.0 Hz, 3H), 1.47 (s, 3H), 2.65 (s, 3H), 2.80 (s, 3H), 3.19 (q, J = 7.0 Hz, 1H), 7.2-7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.14, 27.11, 35.01, 37.15, 43.16, 72.65, 124.4, 127.9, 148.7, 177.0. Found: C, 70.58; H, 8.84%. Calcd for $C_{13}H_{19}NO_2$: C, 70.56; H, 8.65%.
6. The reaction of lithium enolate ($CH_3CH(Li)CONMe_2$) with acetophenone gave a mixture of **3a** and **4a** (**3a/4a** = 72/28).
7. An addition of equimolar amount of MeMnCl to **1a** resulted in the formation of **3a** in <50% yield along with the recovered starting material. Two equivalents of organomanganese reagent was necessary for the completion of the reaction.
8. The reaction mixture contained acetophenone which might be generated by retro aldol reaction from the adduct, PhCMe(OMnCl)CH(Me)COOEt.
9. Kim, S.; Ahn, K. H. *J. Org. Chem.* **1984**, *49*, 1717-1724.
10. **7**: Bp 90-93 °C (0.3 Torr, bath temp); IR (neat) 3324, 2970, 2926, 2884, 1495, 1459, 1447, 1375, 1140, 1105, 1069, 1057, 1026, 927, 763, 701 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.81 (d, J = 7.1 Hz, 3H), 1.66 (s, 3H), 1.98-2.15 (m, 1H), 2.98 (bs, 2H), 3.55 (dd, J = 11.0, 6.0 Hz, 1H), 3.84 (dd, J = 11.0, 3.5 Hz, 1H), 7.2-7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.70, 29.21, 44.22, 65.70, 78.13, 125.3, 126.6, 127.9, 146.0. Found: C, 73.13; H, 9.00%. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95%.
11. Treatment of an epoxy alcohol derived (E)-3-phenyl-2-buten-1-ol with Me_2CuLi afforded threo diol **9** ($PhC(OH)MeCH(Me)CH_2OH$) which was identical with a sample derived from **4a**. **9**: Mp 68.2-68.7 °C; IR (nujol) 3340, 3084, 2852, 1457, 1377, 1354, 1314, 1221, 1083, 1018, 1005, 908, 760, 722, 695, 665, 616 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (d, J = 7.1 Hz, 3H), 1.55 (s, 3H), 1.95-2.18 (m, 1H), 2.82 (bs, 2H), 3.53 (dd, J = 10.9, 3.6 Hz, 1H), 3.62 (dd, J = 10.9, 5.6 Hz, 1H), 7.2-7.6 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.29, 25.69, 43.99, 66.24, 78.16, 125.0, 126.7, 128.1, 148.2. Found: C, 73.34; H, 8.96%. Calcd for $C_{11}H_{16}O_2$: C, 73.30; H, 8.95%.
12. Johnson, M. R.; Nakata, T.; Kishi, Y. *Tetrahedron Lett.* **1979**, 4343-4346.
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