CHEMISTRY LETTERS, pp. 2135-2138, 1992.

Stereoselective Allylation of 3-Oxo Amides

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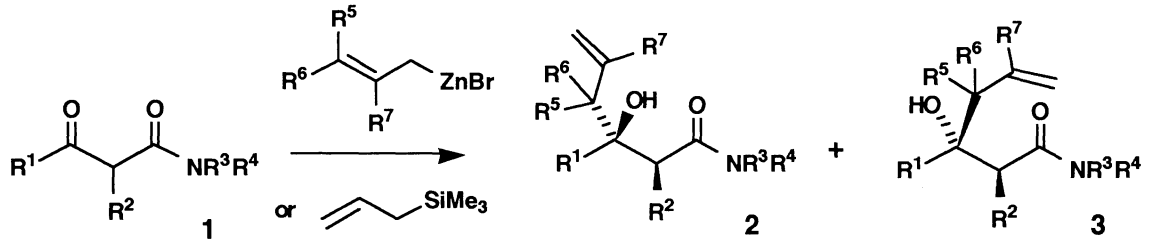
Allylation of 2-methyl-3-oxo amides with allylzinc bromide or allylsilane in the presence of $TiCl_4$ or *n*-Bu_4NF provided both threo and erythro 3-allyl-3-hydroxy-2-methyl amides with high stereoselectivity.

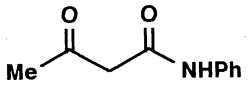
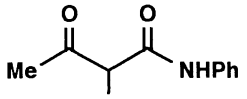
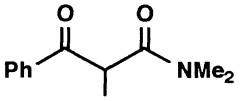
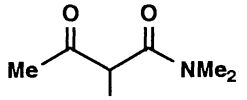
Recently we have reported stereoselective reduction[1] and stereoselective alkylation[2] of 2-methyl-3-oxo amides. Treatment of 3-oxo amide ($PhCOCH(Me)CONMe_2$, **1c**) with Me_3Al or MeMnCl gave erythro 3-hydroxy-2-methyl-3-phenylbutanamide exclusively. However, various attempts to obtain an opposite stereoisomer, threo hydroxy amide, from **1c** resulted in failure. In this paper, we describe stereoselective allylation of 2-methyl-3-oxo amides. Whereas treatment of **1c** with allylzinc bromide provided erythro 3-hydroxy-2-methyl-3-phenyl-5-hexenamide with high stereoselectivity, allylation with allylsilane in the presence of a catalytic amount of *n*-Bu_4NF afforded stereoisomeric threo hydroxy amide exclusively.

A THF solution of allyl bromide (0.24 g, 2.0 mmol) was added to a suspension of zinc dust (0.13 g, 2.0 mg atom) in THF at 25 °C. Exothermic reaction took place and the reaction mixture turned pale gray.[3] After stirring for 30 min, a THF solution of 3-oxo amide **1c** (0.21 g, 1.0 mmol) was added to the resulting allylzinc bromide at 25 °C. The mixture was stirred for another 30 min and poured into sat. aqueous ammonium chloride and extracted with ethyl acetate (20 ml x 3). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residual oil was purified by silica-gel column chromatography to give allylated product, erythro[4] 3-hydroxy-2-methyl-3-phenyl-5-hexenamide (**2c**[5,6] 0.22 g) in 91% yield.

The representative results are shown in Table 1. Reaction of allylmagnesium chloride with **1a** or **1c** provided the corresponding allylated hydroxy amide in poor yield and low stereoselectivity. In contrast, N-phenyl amides (**1a** and **1b**) as well as N,N-dimethyl amides (**1c** and **1d**) reacted readily with allylic zinc reagents, however, excess reagents were needed to complete the reaction of **1a**. It is worth noting that allylation of 2-methyl-3-oxo amides **1b**, **1c**, and **1d** with allylzinc bromide proceeded with high stereoselectivity. The selective formation of the product **2** can be attributed to selective attack of allyl group from the opposite side of the 2-methyl group of **1b**, **1c**, or **1d** in a six-membered metal chelation in a similar fashion as shown in the reduction[1] or alkylation[2] of **1c** or **1d**. Not only allylzinc bromide but also 2-methyl-2-propenylzinc bromide or 2-butenylzinc bromide added to 3-oxo amides **1a**-**1d** easily to give the corresponding 3-hydroxy amide **2** in good to excellent yields under high stereocontrol (Entries 7, 10, 11, 19, and 20). On the other hand, the reaction of 3-methyl-2-butenylzinc bromide with **1a** or **1c** proceeded sluggishly to afford the corresponding hydroxy amides in poor to fair yields (Entries 4 and 12). The allylic zinc reagents such as 2-butenylzinc bromide or 3-methyl-2-butenylzinc bromide reacted regioselectively at the secondary or tertiary carbon. No regioisomer, which may form via an alternative S_E2 reaction pathway, was detected in the reaction mixture. In the reaction

Table 1. Allylation of 3-Oxo Amides[a)]



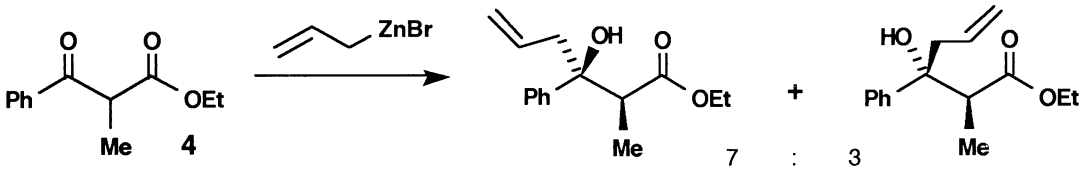
Entry	Keto amide	Allylic metal / mmol	Yield / %	Ratio of **2** : **3**
1		CH_2=$CHCH_2MgCl$ (5.0)[b)]	42	——
2		CH_2=$CHCH_2ZnBr$ (5.0)	91	——
3		CH_2=$C(Me)CH_2ZnBr$ (5.0)	84	——
4		Me_2C=$CHCH_2ZnBr$ (5.0)	75	——
5	**1a**	CH≡CCH_2ZnBr (4.0)[c)]	73[d)]	——
6		CH_2=$CHCH_2ZnBr$ (2.0)	99	>99 (**2a**) : <1 (**3a**)
7	**1b**	CH_2=$C(Me)CH_2ZnBr$ (2.0)	93	>99 (**2b**) : <1 (**3b**)
8		CH_2=$CHCH_2MgCl$ (1.1)[b)]	90	80 (**2c**) : 20 (**3c**)
9		CH_2=$CHCH_2ZnBr$[e)] (2.0)	91	>99 (**2c**) : <1 (**3c**)
10		CH_2=$C(Me)CH_2ZnBr$ (2.0)	96	>99 (**2d**) : <1 (**3d**)
11		CH_3CH=$CHCH_2ZnBr$[e)] (4.0)	99	>99 (**2e**) : <1 (**3e**)
12		Me_2C=$CHCH_2ZnBr$ (3.0)	27[f)]	82 (**2f**) : 18 (**3f**)
13		CH≡CCH_2ZnBr (3.0)	94[g)]	
14	**1c**	CH_2=$CHCH_2SiMe_3$ / $TiCl_4$[c)]	76	>99 (**2c**) : <1 (**3c**)
15		CH_2=$CHCH_2SiMe_3$ / BF_3·Et_2O[c)]	57	>99 (**2c**) : <1 (**3c**)
16		CH_2=$CHCH_2SiMe_3$/ $MeAlCl_2$[c)]	80	96 (**2c**) : 4 (**3c**)
17		CH_2=$CHCH_2SiMe_3$ / n-Bu_4NF[b)]	84	<1 (**2c**) : >99 (**3c**)
18		CH_2=$CHCH_2ZnBr$ (2.0)	92	98 (**2g**) : 2 (**3g**)
19		CH_2=$C(Me)CH_2ZnBr$ (2.0)	93	97 (**2h**) : 3 (**3h**)
20		CH_3CH=$CHCH_2ZnBr$[e)] (2.0)	92	>99 (**2i**) : <1 (**3i**)
21		CH_2=$CHCH_2SiMe_3$ / $TiCl_4$[c)]	65	>99 (**2g**) : <1(**3g**)
22	**1d**	CH_2=$CHCH_2SiMe_3$ / $MeAlCl_2$[c)]	76	>99 (**2g**) : <1(**3g**)
23		CH_2=$CHCH_2SiMe_3$ / n-Bu_4NF[b)]	61	17 (**2g**) : 83 (**3g**)

a) Reactions were performed at 25 °C unless otherwise noted. b) Reaction was performed at 0 °C. c) Reaction was performed at -78 °C. d) Propargylated product : allenylated product = 7:1. e) Prepared from a mixture of 1-bromo-3-butene and 3-bromo-1-butene (purchased from Aldrich Chemical Co.) f) Starting material was recovered (48%) and unidentified complex products were also obtained. g) Propargylated product : allenylated product = 1: 1. The ratio was not affected by the reaction temperature. Each product is a single stereoisomer corresponding to **2**.

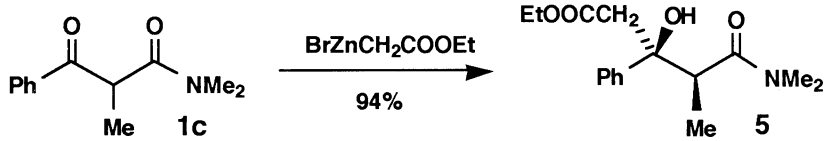
of 2-butenylzinc bromide with **1c** or **1d**, the corresponding allylated product **2e** or **2i** was obtained as a 1:1 diastereomeric mixture of (3R*,4R*) and (3R*,4S*) (Entries 11 and 20).[7] Propargylzinc bromide reacted with **1a** at 25 °C to give a mixture of a propargyl product (MeC($CH_2C{\equiv}CH$)$OHCH_2CONHPh$) and an allenyl product (MeC($CH{=}C{=}CH_2$)$OHCH_2CONHPh$) in a 2.7:1 ratio in 65% combined yield. The distribution of the products depended on the reaction temperature. Reaction at -78 °C provided a mixture of propargyl adduct and allenyl adduct in a 7:1 ratio (Entry 5).

Allylation of **1c** or **1d** (1.0 mmol) with allyltrimethylsilane (1.5 mmol)[8] in the presence of titanium tetrachloride (2.0 mmol) proceeded smoothly to give the same stereoisomeric 3-hydroxy amide **2c** or **2g** as allylation with allylzinc reagent. Boron trifluoride or methylaluminium dichloride proved to be as effective as titanium tetrachloride. In contrast, the reaction of **1c** or **1d** with allyltrimethylsilane in the presence of a catalytic amount of tetrabutylammonium fluoride[9] afforded an opposite stereoisomer **3c** or **3g** selectively. For instance, treatment of a THF solution of **1c** (1.0 mmol) and allyltrimethylsilane (2.0 mmol) with *n*-Bu_4NF (0.1 mmol) at 0 °C provided threo 3-hydroxy-2-methyl-3-phenyl-5-hexenamide **3c**[10] in 84% yield. The results are also shown in Table 1.

An addition of allylzinc bromide to a 3-oxo ester instead of a 3-oxo amide was examined. Exposure of ethyl acetoacetate to allylzinc bromide at -78 °C afforded ethyl 3-hydroxy-3-methyl-5-hexenoate in 84% yield. Treatment of $PhC(O)CH(CH_3)COOEt$ (**4**) with allylzinc bromide afforded 3-hydroxy ester as a stereoisomeric mixture (erythro:threo = 7:3) in 90% yield.



Reformatsky reaction also proceeded stereoselectively as shown below. Treatment of **1c** (1.0 mmol) with the reagent generated from ethyl bromoacetate (2.0 mmol) and zinc dust (2.0 mg atom) gave the corresponding adduct **5**[11,12] as a single stereoisomer in good yield.



Financial support by Asahi Glass Foundation for Industrial Technology is acknowledged.

References

1) H. Fujii, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, **32**, 6147 (1991).

2) M. Taniguchi, H. Fujii, K. Oshima, and K. Utimoto, *Tetrahedron Lett.*, in press.

3) 3-Methyl-2-butenylzinc bromide was prepared as follows. A suspension of zinc dust containing 1,2-dibromoethane was heated to reflux for a few minutes, and cooled to 25 °C, and 1-bromo-3-methyl-2-butene was added. A. Yanagisawa, S. Habaue, and H. Yamamoto, *J. Am. Chem. Soc.*, **111**, 366 (1989).

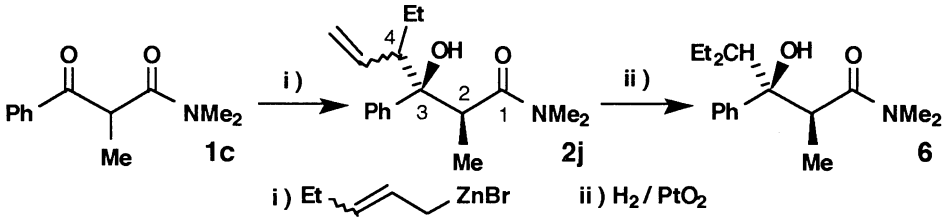
4) For nomenclature of threo and erythro, see: R. Noyori and Nishida, *J. Am. Chem. Soc.*, **103**, 2106 (1981).

5) **2c:** Mp 104.0-104.5 °C; IR ($CHCl_3$) 3344, 3008, 1617, 1497, 1451, 1418, 1401 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.89 (d, *J* = 7.1 Hz, 3H), 2.58 (d, *J* = 7.1 Hz, 2H), 3.04 (s, 3H), 3.07 (q, *J* = 7.0 Hz, 1H), 3.15 (s, 3H),

4.88 -5.05 (m, 2H), 5.46-5.67 (m, 1H), 5.80 (bs, 1H), 6.95-7.28 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.53, 35.56, 37.62, 42.45, 46.76, 77.26, 117.2, 125.5, 126.4, 128.0, 134.1, 143.6, 177.7. Found: C, 72.64; H, 8.75%. Calcd for $C_{15}H_{21}NO_2$: C, 72.85; H, 8.56%.

6) The assignment of the products was performed as follows. Hydrogenation of **2c** (H_2, PtO_2) gave 3-hydroxy-2-methyl-3-phenylhexanamide which was identical with a sample derived from the reaction of **1c** with *n*-PrMnCl.

7) The products **2e** and **2i** consisted of two stereoisomers. The stereochemistry was confirmed by the following experiments. The addition of 2-pentenylzinc bromide to **1c** gave an adduct **2j** as a 1 : 1 stereoisomeric mixture of (3R*,4R*) and (3R*,4S*). Hydrogenation of **2j** afforded erythro-4-ethyl-3-hydroxy-2-methyl-3-phenylhexanamide **6** as a single product.



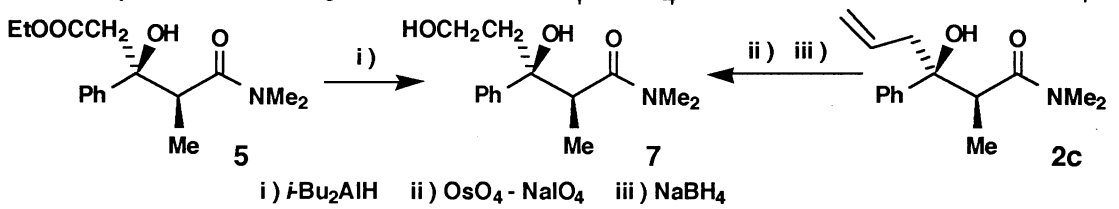
8) T. H. Chan and I. Fleming, *Synthesis*, **1979**, 761; P. D. Magnus, *Aldrichimica Acta.*, **13**, 43 (1980); H. Sakurai, *Pure Appl. Chem.*, **54**, 1 (1982).

9) A. Hosomi, A. Shirata, H. Sakurai, *Tetrahedron Lett.*, **1978**, 3043; T. K. Sarkar and N. H. Andersen *ibid.*, **1978**, 3513; B. M. Trost and J. E. Vincent, *J. Am. Chem. Soc.*, **102**, 5680 (1980).

10) **3c**: Mp 98.0-99.0 °C; IR ($CHCl_3$) 3336, 3006, 1616, 1493, 1416, 1399, 1160 cm^{-1}; ^{1}NMR ($CDCl_3$) δ 1.36 (d, *J* = 7.0 Hz, 3H), 2.47 (dd, *J* = 13.9, 7.3 Hz, 1H), 2.66 (s, 3H), 2.68 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.88 (s, 3H), 3.26 (q, *J* = 7.0 Hz, 1H), 4.91-5.03 (m, 2H), 5.51 (ddd, *J* = 17.2, 10.1, 7.1 Hz, 1H), 6.20 (bs, 1H), 7.15-7.40 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 11.88, 35.11, 37.26, 41.96, 43.82, 117.6, 125.3, 126.5, 127.8, 133.4, 146.4, 176.9. Found: C, 72.95; H, 8.76%. Calcd for $C_{15}H_{21}NO_2$: C, 72.85; H, 8.56%.

11) **5**: Mp 57.5-58.0 °C; IR ($CHCl_3$) 3308, 3014, 1713, 1618, 1451, 1419, 1401, 1210 cm^{-1}; ^{1}NMR ($CDCl_3$) δ 1.02 (d, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.1 Hz, 3H), 2.79 (d, *J* = 14.4 Hz, 1H), 2.97 (s, 3H), 3.03 (s, 3H), 3.05 (d, *J* = 14.5 Hz, 1H), 3.47 (q, *J* = 7.0 Hz, 1H), 3.95 (q, *J* = 7.2 Hz, 2H), 6.20 (bs, 1H), 7.25-7.55 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 12.51, 13.91, 35.55, 37.41, 41.72, 43.31, 60.25, 75.95, 125.1, 126.9, 128.0, 143.6, 171.4, 176.8. Found: C, 65.27; H, 8.00%. Calcd for $C_{16}H_{23}NO_4$: C, 65.51; H, 7.90%.

12) Stereochemistry of **5** was determined as follows. Reduction of **5** with *i*-Bu_2AlH gave the erythro 3-hydroxy-2-methyl-3,5-dihydroxypentanamide **7** which was identical with a sample derived from the adduct **2c** by oxidative cleavage of C=C bond (OsO_4, $NaIO_4$) and successsive reduction ($NaBH_4$).



(Received July 15, 1992)