Highly Stereoselective Reduction of β-Keto Amides: The First General and Efficient Approach to N-mono- and non-Substituted *anti*-α-Alkyl β-Hydroxy Amides

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Abstract: The first general protocol for the *anti*-selective reduction of α-alkyl-β-keto amides is described. This simple and efficient methodology based on an open-chain Felkin–Anh model pathway, allows the isolation of N-mono- and non-substituted *anti*-α-substituted β-hydroxy amides in good yields and with high diastereoselectivity.

Key words: stereoselectivity, β-keto amides, reduction, *anti*-β-hydroxy amides, Felkin–Anh model

Although seminal research has recognized the aldol reaction[1] as the more appropriate chemical tool for the stereocontrolled construction of acyclic β-hydroxy carbonylic systems,[2] an efficient alternative approach[3] can be offered by the stereoselective reduction of α-substituted β-keto acid derivatives having adjacent stereogenic centers.

In the course of our program to develop new methodologies for the reductions of β-functionalized carbonyl compounds with an asymmetric α-carbon in their racemic form, we have found that the correct choice of hydride, solvent and Lewis acid allows the highly selective preparation of *syn*- or *anti*-α-substituted β-hydroxy derivatives.[4] Accordingly, two strategies – chelation and non-chelation – have been accomplished that enabled the achievement of an opposite diastereoselectivity by choosing the appropriate reducing system. These approaches have been reported to be useful in the synthesis of various natural products including β-lactam[5] and β-lactone antibiotics.[6]

The stereoselective synthesis of α-substituted β-hydroxy amides is a challenging problem for synthetic organic chemists since these moieties repeatedly appear in the framework of natural products.[7] In this context the development of an efficient protocol for the *anti*-selective reduction of β-keto amides of type **1** (see Scheme 1) to N-mono- and non-substituted β-hydroxy amides (*anti*-**2**)[8] appears particularly important because, at present, a general and efficient approach to these compounds is still lacking.

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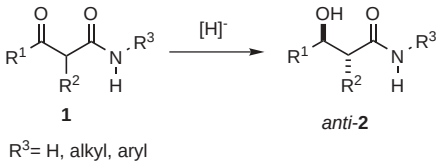
In fact, the *anti*-reduction with $KBEt_3H$[9] and $HSiMe_2Ph$[10] as reducing agents works well only in the case of N-disubstituted compounds. In addition, the latter method fails when the group bound to the ketone moiety is an alkyl chain.

Moreover, compounds *anti*-**2** are not directly available from an aldol approach: in fact, the addition of amide enolates to aldehydes requires the use of tertiary amides.[11]

In this communication we report the first general and highly selective method for the reduction of N-mono- and non-substituted α-alkyl-β-keto amides **1** to the corresponding *anti*-β-hydroxy derivatives **2**.

The *anti*-reduction of 1,3-dicarbonyl compounds of type **1** should require a pathway proceeding through an open-chain mechanism[12] (see Scheme 2) according to the Felkin–Anh model.[13,14]



1 *anti*-**2**

R^3= H, alkyl, aryl

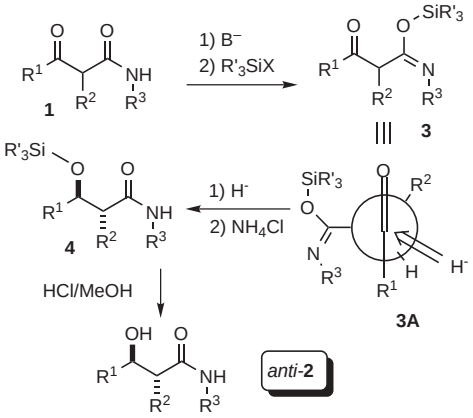
Scheme 1

However, the accomplishment of such a protocol presents some problems; for example, the $CeCl_3$-mediated reduction, which has been proved to be very useful in the case of β-keto phospine oxides and related systems,[15] affords a poor selectivity in the present case. Probably, the high charge density on the oxygen of the amide group promotes the formation of a cyclic complex even in the presence of a Lewis acid with a low tendency to undergo chelation phenomena.

Thus, in order to avoid the formation of a metal chelate, it is essential to drastically reduce the electron density on the amide moiety. With this in mind, we planned to convert the β-keto amide **1** into the corresponding silyl derivative **3** by deprotonation of the amide hydrogen with an appropriate base and subsequent silylation of the oxygen. According to the Felkin–Anh rules, the acyclic compound **3** should preferentially assume the most stable conforma-

tion **3A**. Thus, the in situ addition of a hydride ion source should afford the O-silylated compound **4**, which can be ultimately converted into the desired *anti*-β-hydroxy amide **2** in good yield and very high selectivity, (Scheme 2).

The formation of the intermediate **3** requires the use of a base able to selectively deprotonate the amide proton rather than the active methine α-proton. Considering that the α-proton of a β-keto amide is assumed to exhibit a low kinetic acidity,[16] we thought to favor the formation of **3** by using a large excess of a silylating agent (5 equiv compared to β-keto amide) and a kinetic base (1.1 equiv) at room temperature. Furthermore, the use of an encumbered metal hydride having a counter cation with low O-chelating ability should ensure a highly selective *anti*-reduction.



Scheme 2

After examination of various reaction conditions, the use of $(i\text{-Pr})_3SiCl$ as the silylating agent,[17] NaH as the base, K-selectride as the reducing agent, and a coordinating solvent such as Et_2O, was the best choice. Another crucial point is the addition sequence of the silylating agent and NaH base. The optimum conditions, in fact, require the addition of $(i\text{-Pr})_3SiCl$ before NaH. Probably, this procedure avoids the deprotonation of the methine α-proton, favoring the selective formation of the intermediate **3**. Under these conditions, quenching of the reaction with an NH_4Cl aqueous solution affords the O-silyl derivative **4**. Its formation should be ascribed to an internal migration from the oxygen of the amide function to the more basic alkoxide moiety after the reduction process. We were able to isolate this compound **4a** in pure form in the reduction of **1a** (Figure 1).[18] On the other hand, compound **4** can be easily converted in the corresponding *anti*-β-hydroxy amides **2** by simple acidic treatment (6 N HCl/MeOH), without a preliminary purification.

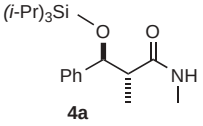
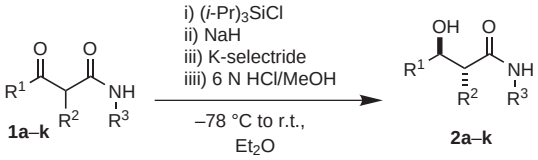
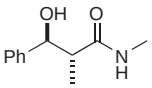
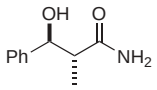
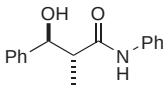
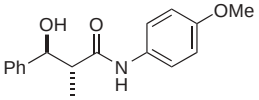
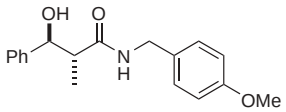
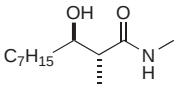
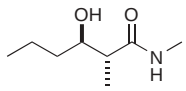
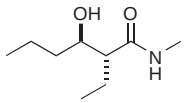
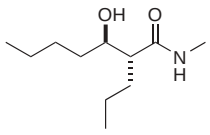
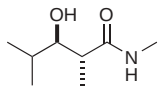
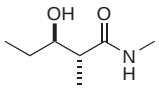


Figure 1

Table 1 Highly *anti*-Selective Reduction of N-mono- and non-Substituted α-Alkyl-β-keto Amides **1**



Entry	Hydroxy amide **2**	Yield (%)[a]	*anti*/*syn*[b]
1	 **2a**	85	>99/1
2	 **2b**	71	98/2
3	 **2c**	90	>99/1
4	 **2d**	84	>99/1
5	 **2e**	88	>99/1
6	 **2f**	75	99/1
7	 **2g**	58	99/1
8	 **2h**	77	99/1
9	 **2i**	78	>99/1
10	 **2j**	51	99/1
11	 **2k**	56	99/1

[a] Yields of pure isolated products after chromatographic purification.
[b] Determined by ^1H NMR and ^{13}C NMR.

The results are summarized in Table 1. The methodology shows its effectiveness with a significant series of N-mono- and non-substituted α-alkyl-β-keto amides **1**. Yields vary from good to high (up to 90%); diastereomeric excesses are excellent in all cases.

The best results in terms of both selectivity and reactivity were achieved with aromatic β-keto amides (R^1 = Ph, entries 1–5). It is noteworthy that the reduction of a non-substituted amide (entry 2) affords the corresponding product **2b** in good yield and high selectivity.

When R^1 is an alkyl chain, the reduction is still very efficient in term of stereoselectivity. In the presence of a short alkyl chain (entries 7, 10 and 11) the decrease in chemical yield is ascribed to a difficult isolation of the hydrophilic products. Varying the alkyl group in the α-position, an increase in yield with very high *anti*-selectivity was observed (entries 8 and 9).

In conclusion, we have developed the first general methodology for a highly *anti*-selective reduction of N-mono- and non-substituted α-alkyl-β-keto amides.

The observed *anti*-selectivity is explained in terms of an open-chain Felkin–Anh model pathway. The key role for such stereochemical outcome is ascribed to the formation of the intermediate **3**, generated by selective abstraction of the amide proton with NaH in the presence of $(i\text{-Pr})_3SiCl$ as the silylating agent.

Typical Procedure

To a dry Et_2O (10 mL) solution of β-keto amide **1** (1 mmol), $(i\text{-Pr})_3SiCl$ (5 equiv) was added at r.t., followed by NaH (1.1 equiv). The resulting mixture was stirred for 15 min and then cooled at –78 °C. K-selectride (2.5 equiv, 1 M THF solution) was added drop wise. After being stirred for 3 h at –78 °C, the reaction mixture was allowed to rise to r.t. Then the reaction was quenched with sat. NH_4Cl and extracted with EtOAc. After evaporation of the solvent under reduced pressure, the crude residue was dissolved in MeOH (5 mL/mmol) and conc. HCl (1 mL/mmol) and stirred at r.t. for 1 h or until the disappearance of silylated product (checked by TLC). After evaporation of MeOH, the mixture was poured into a separation funnel together with 10 mL H_2O and extracted with EtOAc. Chromatographic purification afforded the *anti*-α-substituted β-hydroxy amides **2**.[19]

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(17) The use of a less hindered silylating agent results in a reduced *anti*-selectivity of the process. This is consistent with a Felkin–Anh model in which the presence of a bulky group on the oxygen of the intermediate **3** (Scheme 2) promotes the selective approach of the hydride anion to the β-carbonyl from the opposite side. For the importance of using bulky silylated reagents to effectively prevent chelation, see: Chen, X.; Hortelano, E. R.; Eliel, E. L. *J. Am Chem. Soc.* **1990**, *112*, 6130.
(18) Compound **4a** was isolated by chromatography (pentane/Et_2O) in 87% yield, *anti*/*syn*>99/1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.86 (d, 3 H, J_{HH} = 7.2 Hz), 0.90–1.00 (m, 21 H), 2.45–2.50 (m, 1 H), 2.79 (d, 3 H, J_{HH} = 4.8 Hz), 4.91 (d, 1 H, J_{HH} = 7.8 Hz), 5.80 (br s, 1 H, NH), 7.20–7.35 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.3 (CH), 14.1 (CH_3), 17.7 (CH_3), 17.8 (CH_3), 26.0 (CH_3), 50.5 (CH), 77.4 (CH), 126.9 (CH), 127.5 (CH), 127.8 (CH), 142.7 (C), 175.1 (C).
(19) A typical case is reported: **(*R**,*S**)-2-ethyl-3-hydroxy-*N*-methylhexanamide (2h).**[20] The title compound was isolated by column chromatography (CH_2Cl_2/EtOAc) as a white solid (mp = 135–137 °C); yield 77%; *anti*/*syn* = 99/1. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–0.95 (m, 6 H, 2 × CH_3), 1.30–1.55 (m, 4 H), 1.55–1.70 (m, 1 H, CH_2), 1.70–1.85 (m, 1 H, CH_2), 1.95–2.05 (m, 1 H, CH), 2.80 (d, 3 H, CH_3, J_{HH} = 4.8 Hz), 3.00 (bs, 1 H, OH), 3.60–3.70 (m, 1 H, CH), 6.00 (br s, 1 H, NH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 12.0 (CH_3), 14.0 (CH_3), 19.2 (CH_2), 23.6 (CH_2), 25.9 (CH_3), 38.2 (CH_2), 53.5 (CH), 71.9 (CH), 176.2 (C). Anal. Calcd for $C_9H_{19}NO_2$: H, 11.05; C, 62.39; N, 8.08. Found: H, 11.36; C, 62.18; H, 7.90.
(20) Descriptors *R**, *S** indicate that diastereomeric compounds are obtained as racemates. We prefer this terminology to avoid the ambiguities that could arise from *syn–anti* descriptors.