Diastereoselective Reduction of Acyclic *N*-Aryl-β-amino Ketones

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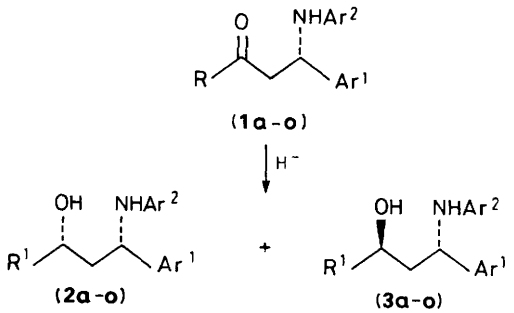
A stereoselective route to *anti*- and *syn*-*N*-aryl-γ-amino alcohols is reported featuring the reduction of the corresponding β-amino ketones with Et_3BHLi or $Zn(BH_4)_2$, respectively.

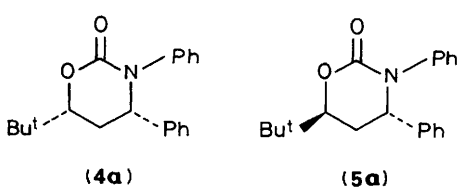
Recently, we reported a mild and efficient method for preparing *N*-aryl-β-amino ketones (**1**) through trimethylsilyl trifluoromethanesulphonate (TMSOTf) promoted addition of silyl enol ethers to Schiff bases.[1] Because of the interest in γ-amino alcohols as building blocks both in the total synthesis of natural products[2] and pharmaceuticals,[3] we have initiated a systematic study of the experimental and structural features controlling the diastereoselective reduction of acyclic *N*-aryl-β-amino ketones (**1**), (see Scheme). Our preliminary results are reported herein.



Scheme.

Earlier, the $LiAlH_4$ reduction of primary and secondary β-amino ketones unsubstituted at the α position was described as a non-stereoselective route to γ-amino alcohols while tertiary β-amino ketones showed modest diastereoselection leading preferentially to the *syn* isomer.[4] This result was rationalized through polar or cyclic models of asymmetric induction.[5]

† Reduction of (**1a**) with $LiAlH_4$ in THF at −78 °C yielded a 30:70 mixture of (**2a**):(**3a**). The major isomer showed an upfield shift for the asymmetric carbons[8] [(**2a**): δ 59.53 and 79.45; (**3a**): δ 55.21 and 76.20



ppm)] and the corresponding urethane (**5a**) showed the CHN proton at δ 5.15 (*J* 5.0 and 2.0 Hz) while in (**4a**) it appeared at δ 4.95 (*J* 12.0 and 6.0 Hz).[9]

Recently, Narasaka *et al.*[6] achieved high diastereoselection in the $LiAlH_4$–NaOMe reduction of the *O*-benzyl oximes derived from β-hydroxy ketones.

Although poor diastereoselection was expected from earlier attempts with $LiAlH_4$,† most relevant to our study was the sense of induction observed. The predominance of the *anti* configuration was not at all consistent with the reduction taking place through a cyclic intermediate.[7] Several metallic hydrides were then evaluated [*e.g.* $LiAlH_4$, $LiBH_4$, $(Bu^tO)_3AlHLi$ and Et_3BHLi] and the highest *anti* induction was observed when a bulky reducing agent less able to promote the formation of a cyclic intermediate (*e.g.* Et_3BHLi in THF–ether, at −78 °C) was employed.

As shown in the Table, the level of diastereoselection proved to be dependent on the bulkiness of the R^1 group: while a preparatively useful diastereoisomeric ratio was achieved for t-butyl and phenyl β-amino ketones (**1**), it dropped significantly when less bulky R^1 groups were employed (*e.g.* isobutyl). However, an increase in the diastereoisomeric ratio was again observed in the reduction of methyl β-amino ketones.

These results can be rationalized through conformation **A** which features the C(2)–C(3) bond perpendicular to the C=O plane and the Ar^2 group blocking either the carbonyl *Si* face (when R^1 = Bu^t, Ph, and Pr^i) or its *Re* face (when R^1 = Bu^i and Me). **B** should be a less stable conformation owing to the steric hindrance developed when Ar^1 is forced close to the R^1 group.

At this point, we reasoned that a reducing agent able to coordinate both to the carbonyl and to the secondary nitrogen would lead to the *syn* γ-amino alcohol (**2**) since hydride *Si* approach to the Zn^{2+}-chelated intermediate **C** is expected to be favoured both on steric and electronic grounds when R^1 = Bu^t, Ph, and Pr^i while the hydride *Re* approach is expected when R^1 = Bu^i and Me. This expectation was born out when $Zn(BH_4)_2$ was employed[9] and the γ-amino alcohol (**2**) was obtained as the major diastereoisomer.

The results described herein are a promising entry into the stereoselective synthesis of both the *syn* and *anti* series of γ-amino alcohols and studies are underway to evaluate this methodology in the stereoselective reduction of *N*-alkyl β-amino ketones.

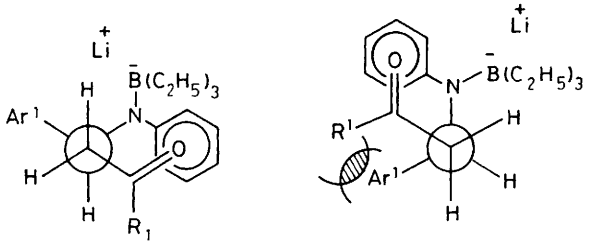
Experimental

General Procedure for the Et_3BHLi *Reduction of* β-*Amino Ketones* (**1**).—To a stirred solution of the β-amino ketone (**1**) (0.5 mmol) in THF (3 ml), at −78 °C and under nitrogen

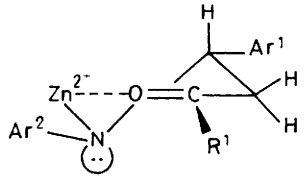
Table. 1,3-Diastereoselection in the reduction of β-amino ketones (**1**).[a,b]

β-Amino ketone (**1**)	R^1	Ar^1	Ar^2	(**2**):(**3**) $LiBH(C_2H_5)_3$	(**2**):(**3**) $Zn(BH_4)_2$
a	Bu^t	Ph	Ph	18:82	82:18
b	Bu^t	Ph	*p*-ClC_6H_4	17:83	83:17
c	Bu^t	*p*-$NO_2C_6H_4$	Ph	17:83	84:16
d	Ph	Ph	Ph	17:83	83:17
e	Ph	Ph	*p*-ClC_6H_4	13:87	86:14
f	Ph	*o*-$NO_2C_6H_4$	Ph	17:83	83:17
g	Pr^i	Ph	Ph	17:83	83:17
h	Pr^i	Ph	*p*-ClC_6H_4	20:80	83:17
i	Pr^i	*p*-$NO_2C_6H_4$	Ph	20:80	86:14
j	Bu^i	Ph	Ph	34:66	86:14
k	Bu^i	Ph	*p*-ClC_6H_4	34:66	86:14
l	Bu^i	*p*-$NO_2C_6H_4$	Ph	34:66	83:17
m	Me	Ph	Ph	25:75	70:30
n	Me	Ph	*p*-ClC_6H_4	14:86	66:34
o	Me	*p*-$NO_2C_6H_4$	Ph	20:80	75:25

[a] Diastereoisomeric ratio determined in the crude mixtures by ^1H NMR (80 MHz), except entries (**1d–f**) where it was evaluated by ^{13}C NMR (25.01 MHz). [b] Yields of the crude γ-amino alcohols >90%. Major diastereoisomer isolated by fractional recrystallization or column chromatography. Spectral and elemental analytical data are in accordance with the proposed structures.



A **B**



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atmosphere, was added dropwise a 1.0M solution of Et_3BHLi in THF (1.0 ml, 1.0 mmol). After 2 h at −78 °C, the reaction was quenched by addition of water (2 ml) and allowed to warm to room temperature.

After extraction with ether (3 × 2 ml), the combined organic phases were washed with brine (2 × 2 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Fractional crystallization of the residue from dichloromethane–hexane or column chromatography on silica and elution with hexane–ether (95:5, v/v) afforded the pure *anti*-γ-amino alcohol (**3**).

General Procedure for the $Zn(BH_4)_2$ *Reduction of the* β-*Amino Ketones* (**1**).—To a stirred solution of the β-amino ketone (**1**) (0.5 mmol) in THF (3.0 ml), at 0 °C and under a nitrogen atmosphere, was added dropwise a 0.16M ethereal solution of $Zn(BH_4)_2$ (6.25 ml, 1.0 mmol). After 2 h at 0 °C, the reaction was quenched with saturated aqueous NH_4Cl (2.0 ml). After extraction with ether (3 × 2 ml), the combined organic phases were washed with brine (2 × 2 ml), dried ($MgSO_4$), and evaporated under reduced pressure. Fractional crystallization of the residue from dichloromethane–hexane or column chromatography on silica and elution with hexane–ether (95:5, v/v) afforded the pure *syn*-γ-amino alcohol (**2**).

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