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Diastereoselectivity in the Reduction of α-Oxy- and α-Amino-Substituted Acyclic Ketones by Polymethylhydrosiloxane

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Abstract: Diastereoselectivity in the reduction of α-alkoxy-, α-acyloxy-, and α-alkylamino-substituted ketones with polymethylhydrosiloxane (PMHS) in the presence of fluoride ion catalysis was investigated. High syn-selectivity was observed in the reduction of α-alkoxy, α-acyloxy, and α-dialkylamino ketones. Reduction of α-monoalkylamino ketone proceeded in anti-selective manner with moderate selectivity. The observed selectivity is explained based on Felkin-Anh and Cram-chelate models.

Significant progress has been made in recent years in controlling the diastereoselectivity during reduction of α-substituted acyclic carbonyl compounds. It is commonly recognized that reduction of α-hydroxy and α-amino ketones with common metal hydrides is generally anti-selective.[1] This has been explained based on Cram's cyclic chelate model. Syn-selectivity in ketone reductions is observed if chelation cannot occur, either due to the absence of chelating metal cations in the reducing agent or due to the preferred conformation of ketones (Felkin-Anh model).[2] In addition, the degree of diastereoselectivity has been found to be dependent on several factors such as reaction temperature, solvent, steric bulk of the reducing agent, and the steric and stereoelectronic environment around carbonyl group.[1,3,5]

In connection with our studies aimed at improving syn-selectivity in the reduction of pharmaceutical intermediates of the general structure $Ar-CO-CH(NR_2)-CH_3$ **(I)** we examined the diastereoselectivity of reduction of **I** with several silyl hydride reducing agents. High syn-selectivity was observed in the reduction of **I** with polymethylhydrosiloxane (PMHS) in the presence of fluoride ion catalysis. Syn-selective reductions for substrates similar to **I** have been reported in the literature using bulky alkyl hydrides of boron, tin, or aluminum.[3,4]

TABLE 1. Diastereoselective Reduction of α-Amino and α-Oxy Ketones by the PMHS/F^- Reducing System

entry	ketone **1**	% yield[a]	syn:anti[b] **2:3**
1	R^1 = Ph, R^2 = piperidine (**1a**)	80	100:0
2	R^1 = Ph, R^2 = $N(C_2H_5)_2$ (**1b**)	76	100:0
3	R^1 = Ph, R^2 = $N(CH_3)CH_2Ph$ (**1c**)	87	100:0
4	R^1 = Ph, R^2 = N $CH_2Ph)_2$ (**1d**)	95	100:0
5	R^1 = Ph, R^2 = $NHCH_2Ph$ (**1e**)	88	26:74
6	R^1 = Ph, R^2 = $OCOCH_3$ (**1f**)	76[c]	97:3
7	R^1 = Ph, R^2 = OCOPh (**1g**)	71[c]	97:3
8	R^1 = Ph, R^2 = OCH_3 (**1h**)	77	87:13
9	R^1 = CH_3, R^2 = OCH_2Ph (**1i**)[d]	79	73:27
10	R^1 = CH_3, R^2 = $N(CH_2Ph)_2$ (**1j**)	90	95:5

[a] Total isolated yield. [b] Ratio determined by ^1H NMR of crude product. [c] Yield as diol after ester hydrolysis. [d] *S* enantiomer.

Use of these reagents for synthesis on a large scale can be hampered by their limited availability in bulk, pyrophoric nature, and high cost.[5] Also often sub-zero temperatures are required for good selectivity.[3a,5] Silyl hydrides on the other hand are generally air-stable liquids, inexpensive, and amenable to scale-up. Hydrosilanes can be used as reducing agents in the presence of transition metal catalysts, acids, bases, or fluoride ions.[6] Hiyama and Fujita have reported high diastereoselectivities for the reduction of α-oxy and α-amino ketones using trialkyl- or triarylalkylsilanes in the presence of fluoride ion catalysis.[7] The applicability of this methodology is limited by the need to use a coordinating solvent such as HMPA. Use of such a high boiling and toxic solvent is impractical for large-scale synthesis. PMHS is an inexpensive nontoxic liquid that is readily available in bulk.[8] Polymeric hydrosiloxanes reduce carbonyl compounds rapidly under mild conditions with catalysis by fluoride ions.[9] The rate enhancement during reactions with PMHS/F^- has been explained by what is called as "zipper catalysis" mechanism.[10] Herein we report the extension of our results observed for **I** with PMHS to diastereoselective reduction of several ketones substituted at the α position with alkoxy, acyloxy, and alkylamino substituents.

Exceptionally high syn-selectivities were observed in the reduction of ketones substituted with dialkylamino substituents at the α position under mild conditions with PMHS/cat. F^- (Table 1, entries **1a**−**d**). We chose commercially available tetrabutylammonium fluoride (TBAF) as the source of fluoride. With monoalkylamino-substituted ketone **1e** the reduction proceeded in anti-selective manner with moderate selectivity. It is noteworthy that reduction of the above ketones with commonly used reducing agents such as sodium borohydride proceeds in only moderate to poor selectivity.[11]

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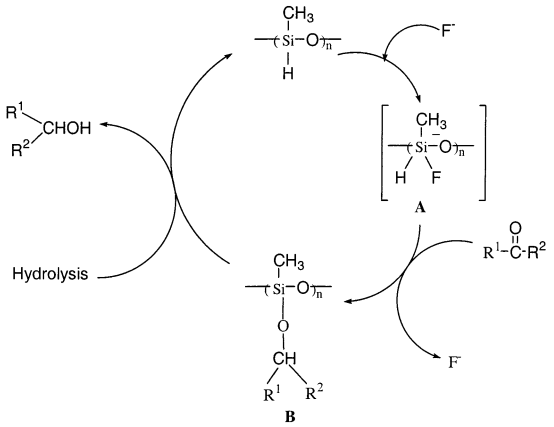
SCHEME 1



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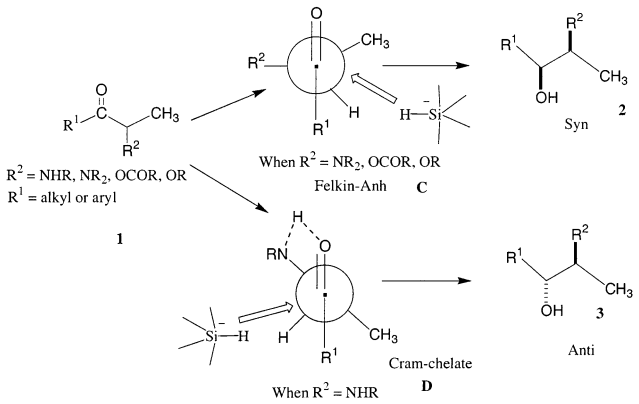

Next we investigated the applicability of the PMHS/F^- reducing system for syn-selective reduction of α-alkoxy and acyloxy ketones. It is known that the reduction of these substrates with conventional hydride reagents occurs with marginal stereoselection.[7,12] Acyloxy- and benzoyloxy-substituted arylalkyl ketones **1f** and **1g** were reduced in remarkably high syn selectivity by PMHS in the presence of a catalytic amount of TBAF under mild reaction conditions. In contrast to reported anti-selective reduction of alkoxy-substituted ketone **1h** with sodium borohydride,[12] the reduction with PMHS furnished predominantly syn alcohol **2h**. Good diastereoselectivity was observed in the reduction of alkoxy- and dialkylamino-substituted alkyl ketones **1i** and **1j**. No epimerization was observed at the 3-position of the product alcohol **2i**−**3i** during this transformation.

The proposed catalytic cycle involved during the present reduction methodology is depicted in Scheme 1. The pentacoordinate hydridosilicate **A** transfers hydride to the carbonyl compound. Prior to hydrolysis the product is attached to the polymer backbone as silyl ether **B**. The product is readily obtained by hydrolysis of the silyl ether by either aqueous (acid or base) or nonaqueous (excess TBAF) workup under mild conditions.[7,9b] The observed syn-selectivity in Table 1 for ketones lacking a proton on the heteroatom α to carbonyl can be explained by the Felkin-Anh model shown in Scheme 2. For these substrates the reducing agent attacks the carbonyl on the preferred reactive conformation **C** leading to syn alcohol **2**. Lack of metal cations in the PMHS/F^- reducing agent and absence of protons on the heteroatom in these substrates precludes formation of a chelate conformer like **D**. For substrates containing protons on the heteroatom α to carbonyl (e.g. **1e)** the reducing agent attacks the preferred Cram-chelate conformation **D** resulting in anti-alcohol **3**. It is not clear whether the observed selectivity is partially due to the polymeric nature of the reagent.[13] It is interesting to note, however, that monomeric alkoxysilanes reduce ketones with poor diastereoselectivity.[7]

In conclusion, high syn-selectivity in reductions of α-alkoxy, α-acyloxy, and α-dialkyl amino ketones can be accomplished with polymethylhydrosiloxane in the presence of fluoride ions under mild reaction conditions.

Experimental Section

All ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ solvent at 400 and 100 MHz respectively with chloroform (^{1}H, 7.26 ppm; ^{13}C, 77.0 ppm) as an internal standard. Column chromatography was performed using silica gel 60. Analytical TLC was performed on silica gel (250 μm) TLC plates. Polymethylhydrosiloxane [PMHS, $-(CH_3SiHO)_n-$, where $n \sim 35$] and tetrabutylammonium fluoride (1 M solution in THF) were purchased from commercial sources. Commercially available BHT-stabilized tetrahydrofuran (THF) was used as solvent without further purification. Compounds **1a**−**f** were prepared from 2-bromopropiophenone and appropriate amine in the presence of K_2CO_3 by previously reported procedures.[14] Ketones **1g**[7] and **1h**−**j**[14] were prepared using literature procedures.

General Procedure for Reduction of Ketones with PMHS Catalyzed by TBAF. To a clean dry flask equipped with a thermometer, a magnetic stirrer, and an addition funnel were added ketone (5 mmol, 1 equiv), THF (25 mL), and PMHS (0.2−0.3 mmol, 2−2.5 hydride equiv). The solution was cooled to 0 to −5 °C in an ice−acetone bath. The solution of tetrabutylammonium fluoride (5 mol % with respect to ketone) in THF was added to the reaction mixture slowly with a syringe over a 15-min period maintaining the temperature between 0 and 5 °C. The reaction mixture was stirred at 0−5 °C for 2 h. After TLC indicated the disappearance of starting ketone additional solution of TBAF (5 mmol, 1 equiv) was slowly added to the reaction mixture. The reaction mixture was allowed to warm to room temperature over 1 h. Solvent was evaporated to dryness on a rotary evaporator. The residue was dissolved in 25 mL of methylene chloride. The methylene chloride solution was stirred with 25 mL of water for 1 h. Layers were separated and the organic layer was washed with water (15 mL). Methylene chloride solution was dried over sodium sulfate, filtered, and evaporated to dryness to furnish crude product. All crude products were purified by column chromatography on silica gel using ethyl acetate/hexane solvent mixture. The diastereomeric ratios were determined by integration of diagnostic peaks in ^{1}H NMR spectra of the isolated crude product mixture.

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Supporting Information Available: Experimental procedures for the reduction of ketones **1a**−**j** and selected ^{1}H, ^{13}C NMR and HRMS data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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