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Facile Rearrangement of *O*-Silylated Oximes on Reduction with Boron Trifluoride/Borane

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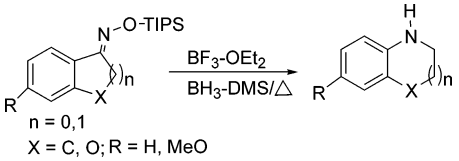
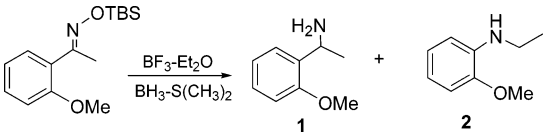


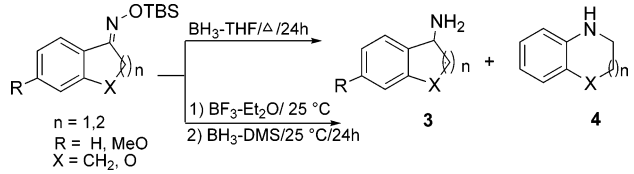
Aromatic *O*-triisopropylsilyl ketoximes were efficiently rearranged to cyclic and acyclic aniline derivatives on reduction with BF_3-ethearate /borane. The bulk of the substituents on the silicon atom, the size of the aliphatic ring, and the presence of alkoxy substituents on the aryl group all play an important role in the aniline.

Cyclic and acyclic anilines are very important organic compounds used as intermediates for the synthesis of a variety of pharmaceutical products.[1] The reduction of aromatic oxime alkyl and aryl ethers with borane and organoboron reagents has been known to afford hydroxylamines or amines, depending on their structure and the reaction conditions.[2] In earlier studies, we reported the formation of *N*-alkyl anilines in the reduction of aromatic *O*-silylated oximes with borane in THF under reflux conditions. The yield of the primary aryl alkylamines with respect to the formation of the secondary aniline depended strongly on the electronic effects of the aromatic ring substituents and on the bulk of the silicon substituents.[3,4] We describe here a new and efficient method for the selective synthesis of secondary alkyl anilines and heterocyclic anilines including tetrahydroquinolines, benzazepines, and benzoxazines in good yield, via a BF_3-Et_2O/BH_3 reductive rearrangement of *O*-silylated oximes.

SCHEME 1



SCHEME 2



Initially, we explored the borane reduction of 1.8 mmol of *O-tert*-butyldimethylsilyl-2-methoxyacetophenone oxime as a model compound, using BF_3-Et_2O as a Lewis catalyst to optimize the yield of 2-methoxy-*N*-ethylaniline **2**, shown in Scheme 1.

By the addition of 2 equiv of BF_3-Et_2O followed by 3 equiv of borane-dimethyl sulfide (DMS) to the *O*-TBS oxime at room temperature, the reaction was complete within 24 h, favoring **2** in 62% with only 16% of 2-methoxy-α-methylbenzylamine (**1**). The reaction was complete within 1 h by refluxing the oxime with 3 equiv of BF_3-Et_2O and 2 equiv of borane-THF, improving the yield of **2** to 80%. For comparison, when the reaction was carry out in the absence of BF_3-Et_2O, a mixture of 23% primary amine **1**, 70% aniline **2**, and 7% starting material was obtained. The type of borane complex (THF or dimethyl sulfide) and more than 1 equiv of boron trifluoride have a little effect on the primary and secondary amine ratios or on the rate of reduction. More important in determining the outcome of the reaction was the use of freshly distilled BF_3-Et_2O over calcium hydride to remove HF and the sequence of steps in which the BF_3-Et_2O and borane were added. The reduction time was increased to 2 h when borane was first added to the *O*-TBS oxime. On the other hand, when the silyloxime was initially treated with 3 equiv of BF_3-OEt_2 in THF at 55 °C for 1 h, followed by reduction with borane-THF under refluxing conditions, a mixture of 33% primary amine **1** and 67% aniline **2** was obtained. In addition, a significant amount of unknown side products was also observed, due possibly to the decomposition of the silylated oxime.

In previous work,[4] we found that the borane reduction of *O*-TBS indanone oxime without BF_3-Et_2O under reflux yielded only the tetrahydroquinoline. It was of interest to investigate the reduction of other cyclic aromatic silylated oximes with and without BF_3-Et_2O, as indicated in Scheme 2. Though the reduction of the tetralone analogue with only borane provided a mixture of both

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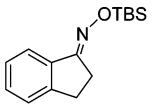
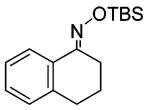
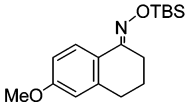
TABLE 1. Reduction of Aromatic*O*-TBS Oximes Using BH_3-THF or BH_3-DMS/BF_3-Et_2O

entry	oxime	BF_3 (equiv)	borane (equiv.)	**3:4**[a]	yield %[b]
1		-	3 (THF)	0:100	88[c]
2		3	2 (DMS)	40:60	84
3		-	3 (THF)	59:41[d]	51
4		2	2 (DMS)	[e]	58
5		-	3 (THF)	50:50	88
6		3	2 (DMS)	0:100	72[c]

[a] Determined by GC−MS analysis of crude products. [b] Yield of isolated crude products. [c] Isolated pure compound characterized by spectroscopic methods. [d] Ratio of pure compounds isolated by column chromatography. [e] Unresolved peaks by GC−MS.

amines in about equal amounts, as shown in Table 1, it seems that on heating, the rearrangement of the five-membered ring was preferred, perhaps to relieve the angular ring strain. On the contrary, reduction of 1-indanone *O*-TBS oximes with borane and BF_3-Et_2O at room temperature (entry 2) produced both, a mixture of primary and secondary amines in a 2:3 ratio, respectively. In the case of the tetralone oxime, BF_3-Et_2O influenced only the reduction rate, affording similar amounts of the amine products (entry 4). Noteworthy is the fact that the BF_3/borane reduction of 6-methoxy-1-tetralone oxime favored completely the formation of 7-methoxy-1-benzazepine, as shown in Table 1.

The influence of the triisopropylsilyl (TIPS) groups in directing the reaction pathway toward the rearranged product was previously observed in the borane reduction of 4-methoxy acetophenone *O*-silylated oximes.[4] For this reason we initiated a study of the effect of the triisopropyl silyl group on the product distribution of boron trifluoride/borane reduction of (*E*)-2-methoxy acetophenone *O*-TIPS oxime.[5] Using 1 equiv of boron trifluoride etherate and 3 equiv of borane-DMS at room temperature, the reduction was completed within 24 h, producing 85% *N*-ethyl-4-methoxyaniline and 15% 2-methoxy-α-methylbenzylamine. However, by heating the reaction mixture under reflux for 4 h, only the secondary aniline was detected by GC/MS. Thus, the *O*-TIPS oximes, indicated in Table 2, were prepared in more that 98% of the (*E*)-stereoisomer (entry 1−6) and reduced with the optimized BH_3/BF_3 system.

Our previous results suggest that the change in product distribution and reactivity of the silylated oximes depends on the size of the silicon substituents, the reaction conditions, and more significantly, if the borane reduction is carried out in the presence of boron trifluoride. This may be due to possible different reaction mechanisms. The reductive rearrangement of *O*-silylated oximes by borane without boron trifluoride was previously proposed to occur via a hydroxylamine intermediary.[3] Reduction of these oximes in the presence of boron trifluoride may involve a rearrangement via a hydroxylamine intermediary, as was postulated for the $LiAlH_4$/$AlCl_3$ reduction of aromatic oximes.[6] Further more, similar intermediates have been proposed in the rearrangement of aliphatic hydroxylamine carbonates by trialkylaluminum compounds by Yamamoto and coworkers.[7] Recently, a mechanism involving an initial heterolytic N−O cleavage of the oxygen complexed with Lewis acids such as $AlCl_3$ and $ZrCl_4$ was proposed by Kikugawa et al.[8] for the intramolecular imino migration of *O*-arylketoximes. Reduction with sodium bis(2-methoxyethoxy)aluminum hydride (Red Al) gave *o*-aminophenols. However, the high anti stereoselectivity observed in the reductive rearrangement of (*E*)-*O*-TIPS oximes in the presence of BF_3 indicates that the mechanism may be related to the concerted anti migration of the aryl group of the well-known Beckmann rearrangement of oxime ethers or esters, mediated by strong Bronsted or Lewis acids, to obtain amides/lactams.[9] Moreover, the reduction of *O*-silylated oximes may be closer to the proposed Yamamoto's mechanism[10] for the reduction of oximes using diisobutylaluminum hydride and was also proposed in the alkylation-reduction of oxime sulfonates with organoaluminum reagents. On the other hand, the large triisopropyl group on the silicon atom may hinder the initial coordination of boron trifluoride on the oxygen of the of *O*-TIPS oximes in the BF_3/BH_3 system. Therefore, a more complex mechanism may be involved.

In summary, we have achieved a highly efficient, mild, and facile method for the synthesis of secondary acyclic

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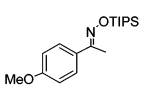
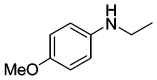
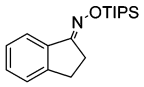
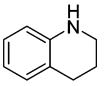
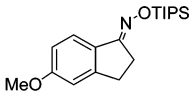
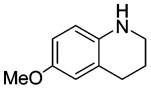
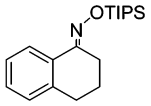
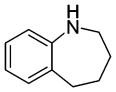
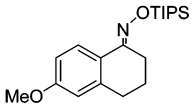
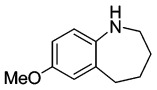
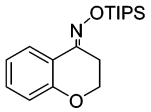
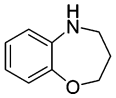
TABLE 2. Synthesis and Reduction of Aromatic (E)-*O*-TIPS Oximes Using BH_3-DMS/BF_3-Et_2O/THF under Reflux Conditions

entry	silyloxime	yield (%)	E/Z	product **4**	BF_3 (equiv)	(**3**/**4**) [a]	yield (%) [b]
1		80	98/2		1	l /100	67 [c]
					2	/100	64 [d]
2		80	>99		1	3/97	62
					2	/100	98 [d]
3		80	>99		1	2/98	66
					2	/100	58 [d]
4		86	>99		1	/100	(96) [c] 68
					2	/100	(89) [c] 81 [d]
5		95	>99		1	/100	48
					2	1/99	(85) [c] 93 [d]
6		99	>99		1	8/92	59 [c]
					2	1/99	62 [d]

[a] Composition of both amines determined by GC−MS analysis of crude products. [b] Pure products isolated by column chromatography and characterized by spectroscopic methods. [c] Isolated crude compounds characterized by spectroscopic methods. [d] Isolated as the pure hydrochloride salt.

and cyclic anilines by the reductive rearrangement of triisopropyl silylated oximes. This new procedure represents a useful method for the preparation of important biologically active acyclic and heterocyclic anilines employing user-friendly conditions and less toxic reagents.

Experimental Section

6-Methoxy-1,2,3,4-tetrahydroquinoline.[11] To a stirred solution of 5-methoxy-1-indanone *O*-triisopropylsilyl oxime (2.5 g, 7.5 mmol) in ether (2.5 mL) under nitrogen was added, via syringe, a freshly distilled boron trifluoride ethearate (0.93 mL, 7.5 mmol). Immediately following the addition, a solution of borane dimethyl sulfide in THF (7.5 mL, 2 M, 15 mmol) was added dropwise to the reaction flask at room temperature. The reaction mixture was refluxed for 5 h (or until a GC analysis indicated the complete formation of the product). At this time the solution was cooled to −30 °C, and the reaction mixture cautiously quenched by addition of distilled water (2.4 mL). To complete the hydrolysis, a solution of hydrochloric acid (6 mL, 6 M) was slowly added, and the reaction mixture was refluxed at 70 °C for 1 h. After the organic solvent was removed under reduced pressure, the solution was basified (pH >10) with aqueous NaOH, extracted with ether (2 × 7 mL), washed with brine, and dried (K_2CO_3). The solution was concentrated at reduced pressure (20 mmHg) and then under high vacuum (0.01 mmHg). The crude product (0.92 g, 75%) was analyzed by GC and purified by flash chromatography on a silica gel column (28.5 cm length × 3.0 cm diameter, 81 g) with hexane/ethyl acetate (80/20 v/v). The product, 6-methoxy-1,2,3,4-tetrahydroquinoline, was obtained as a clear yellow oil. Yield: 66% (0.81 g). IR (neat) ν cm^{-1}: 3366 (NH). ^1H NMR ($CDCl_3$) (δ ppm): 1.91 (m, J = 6.8, 2H), 2.74 (m, J = 6.4 Hz, 2H), 3.23 (t, J = 5.6 2H), 3.29(bs, 1H), 3.71(s, 3H), 6.43 (d, J = 8.4, 1H), 6.55 (dd, J = 8.4, and 2.4 Hz, 1H), 6.59 (d, J = 2.8 Hz, 1H). ^{13}C NMR: 150.8, 137.8, 121.8, 114.5, 114, 113.9, 54.8, 41.3, 26.1, 21.4. MS *m/z*: 163 ($M^{\cdot+}$, 100). Hydrochloride salt (0.46 g, 77%): mp 145−148 °C. The reaction was repeated with 2 equiv of boron trifluoride, obtaining 76% of the desired amine, which was purified as the hydrochloride salt in 58% yield.

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Supporting Information Available: Representative procedure for the synthesis of all new *O*-TBS and *O*-TIPS oximes, the synthesis of anilines, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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