Tetrahedron Letters, Vol.22, No.35, pp 3331 - 3334, 1981
Printed in Great Britain

0040-4039/81/353331-04$02.00/0

REDUCTION OF O-ACYL OXIMES

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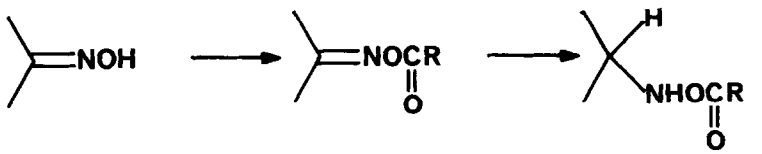
Abstract: $NaCNBH_3$/AcOH and Et_3SiH/CF_3CO_2H were found to be excellent reducing reagents for oxime benzoates without cleaving the N-O bond.

During the course of some synthetic work we needed a method for obtaining O-acyl hydroxylamines. Scanning the literature revealed that few general methods for the formation of this species were available, therefore we decided to explore some new routes. Since acylation of hydroxylamines usually leads to the thermodynamically more stable N-acyl compounds (hydroxamic acids), an acylation route would requre nitrogen protection. One attractive alternative seemed to be the reduction of O-acyl oximes which in turn are readily accessible by acylation (Equation 1). When we started our work



Equation 1

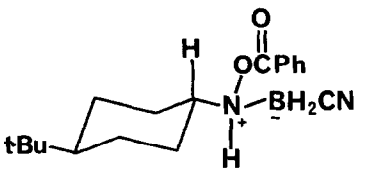
only one method had been reported [2], which required the use of one equivalent of BH_3 (excess BH_3 leads to over reduction to the amine[3]). In this procedure the O-acyl hydroxylamines were not isolated but rather induced to undergo acyl migration to form hydroxamic acids. After we began our work, Kikugawa [4] reported the use of pyridine-borane complex under acidic conditions for the reduction of O-acyl oximes. We would like to report two new complementary methods for this transformation. Both methods employ acidic conditions (previously used in the reduction of C=N[5] or C=C[6]) and afford hydroxylamine derivatives free from over reduction products.

Contrary to a previous report[2] we have found that $NaCNBH_3$ reduces ketoximes rapidly at room temperature in good yields (Table I). The reaction is performed by simply dissolving the oxime benzoate in acetic acid and adding to this one molar equivalent of $NaCNBH_3$ as a solid. The reactions were usually over within 6 hours (sometimes as soon as 1/2 hour). The workup involves dilution with ether and basification with aqueous bicarbonate or KOH followed by normal extraction procedures. In one case, t-butylcyclohexanoneoxime benzoate, a small amount of the intermediate boron containing species survived the workup and was identified as 1 (exact mass, NMR, IR) [7]. Aromatic ketoximebenzoates are not reduced under these conditions.

TABLE I Reduction of O-benzyl Oximes

R^1	R^2	% yield method A[a]	% yield method B[a]	mp.°C	NMR ($CDCl_3$, 100MHz) H^a
- $(CH_2)_4$-		85%	70%	oil[4]	3.60 - 3.92 (m)[f]
- $(CH_2)_5$-		95%	86%	oil[8]	2.90 - 3.22 (m)[f]
-$(CH_2)_2$CH$(CH_2)_2$-		85%	90%	axial 89-91°[e]	3.30 - 3.46 (m)[f]
tBu		ax.:eq.=5:1	ax.:eq.=1:4	equat. 31-33°[e]	2.91 (br. t)[d]
-$(CH_2)_{11}$-		73%	82%	waxy solid[e]	3.10 - 3.42 (m)[f]
PhCH	CH_3	90%	92%	oil[e]	3.61 (apparent q J = 9 Hz)
pMePh	H	54%[b]	--[c]	--	4.23 (s)
Ph	CH_3	no reaction	no reaction		

(a) Method A:Et_3SiH/TFA; method B: $NaCNBH_3$ /AcOH. (b) This compound was always produced with a trace amount of impurity. (c) This reaction was slow and contained numerous side products. (d) A 250 MHz spectrum showed this absorption as a t x t, J = 11 Hz and J = 3.7 Hz. (e) All new compounds were characterized by spectroscopic means as well as combustion analysis.(f) This absorption was an unresolved multiplet.



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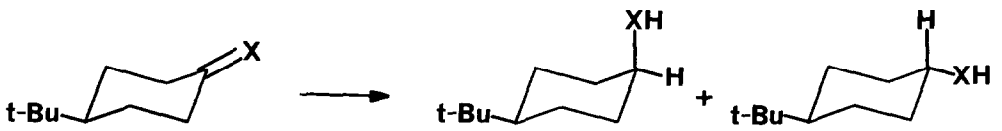
The other method employs Et_3SiH as a hydride source and CF_3CO_2H as the acid. Although the conditions here are somewhat more acidic then in the first method, the products are formed quite cleanly in most cases (Table I). The reaction is performed quite simply by stirring the oxime benzoate with two equivalents of Et_3SiH in a minimum amount of CF_3CO_2H as a solvent (a cosolvent such as CH_2Cl_2 may be used). The reaction times are similar to those in the first method (tlc was used to monitor product formation). The aromatic ketoximebenzoate was not reduced under these conditions and, not unexpectedly, forcing the reaction by heating resulted in a Beckmann rearrangement.

It should be mentioned that aromatic aldoxime benzoates are reduced albeit slower with Et_3SiH and the product is always contaminated with a trace amount of an unidentified side product. The same reduction with $NaCNBH_3$ is not feasible since the reducing reagent reacts faster with the solvent (AcOH) than with the oxime benzoate. Addition of more $NaCNBH_3$ after one day and again after two days failed to consume all the starting material. Some of the desired product was formed in this reaction but it was contaminated by numerous side products (NMR evidence).

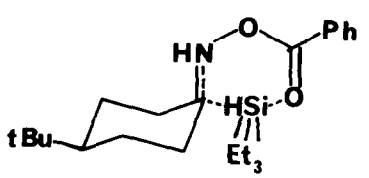
To probe the stereochemistry of these reductions t-butylcyclohexanoneoxime benzoate was reduced (third entry in Table I). Surprisingly the two reagents showed complementary stereospecificity. Et_3SiH afforded a 5-fold excess of axial product (equatorial attack of hydride) while $NaCNBH_3$ produced a 4-fold excess of equatorial product. These results are particularly surprising in light of the work published by Doyle[6], where 4-t-butylmethylene cyclohexane was reduced with

Fig. 1



X = NOCOPh	Et_3SiH	5	1
	$NaCNBH_3$	1	4
X = CH_2	Et_3SiH	1	9

Et_3SiH to yield predominantly the equatorial reduction product (Fig. 1). Doyle reports that in his example CF_3CO_2H adds to the double bond much more rapidly than the reduction occurs. In



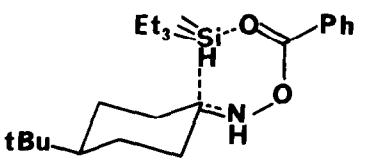


Fig. 2

our case there was no evidence (NMR) for prior addition of CF_3CO_2H to the oxime benzoate. Doyle also suggests that hydride donation from silicon is facilitated by neighboring nucleophiles. In our case this hypothesis may be used to explain the increased amount of equatorial hydride attack by invoking the participation of the benzoyl carbonyl as an intramolecular nucleophile (Fig. 2). Axial hydride attack with nucleophilic participation of the benzoyl carbonyl would require the Et_3SiH to be positioned directly over the cyclohexane ring while equatorial attack would require the sterically unhindered transition state depicted in Fig. 2. Failure of the reduction of cyclohexanone oxime under the same conditions as used for the O-benzoyl oximes lends further support to the hypothesis that the benzoyl carbonyl is involved in the reaction.

Further reactions of these O-acylhydroxylamines will be reported in the near future.

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7). The IR spectrum (KBr) showed the characteristic strong B-H stretch at 2410 cm^{-1} as well as a weak C N stretch at 2210 cm^{-1}. NMR (250 MHz, $CDCl_3$) RRC (H)N-, 3.468 (t x t, J = 11.76 Hz, J = 3.68 Hz).

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(Received in USA 27 April 1981)