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LAH aryl alkyl ether cleavage of BINOL derivatives

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Abstract—Herein we report the cleaving of aryl alkyl ethers on BINOL derivatives, using the common reducing agent LAH. The cleavage of the alkyl oxygen bond is observed when the BINOL derivative is treated with LAH, in refluxing dioxane, for 60 h. The resulting BINOL derivative can then be re-alkylated using a standard Williamson ether synthesis. The same procedure was tested on 6-hydroxy-2-naphthoic acid derivatives and cleavage was not observed, thus suggesting a chelating mechanism for the BINOL ether cleavage.

1. Introduction

Lithium aluminum hydride (LAH) is a well-known reducing agent, used frequently for the reduction of a variety of functional groups.[1] However, ethers are not considered sensitive to LAH.[1] This is not surprising as ethers are not base sensitive and are usually cleaved by reaction with strong acid. Ethers are not reduced by common reducing agents; a literature search yielded no references to ether cleavage by LAH alone, only in the presence of $AlCl_3$.[2]

In performing an amide reduction of a BINOL derivative **1**, we discovered that two ether groups were cleaved, yielding the binaphthol **3** (Fig. 1). This is the first example of this type of reaction. In order to study the generality of this reaction, we synthesized three other BINOL derivatives, and naphthalene analogues, and subjected each of them to the LAH reducing conditions.

2. Results and discussion

The ether cleavage was first noticed while trying to reduce the diamide **1** shown below in Figure 1. Treatment of diamide **1** with LAH in refluxing dioxane for 16 h gave diamine **2**; however if the reaction mixture was allowed to reflux 60 h, cleavage of the alkyl oxygen bond was observed, giving the diol **3**. ^{1}H NMR was fairly conclusive about the absence of the ether, as signature resonances at δ 4.0 (OCH_2) and δ 0.8 (CH_3) were missing. The spectroscopic analysis of ether cleavage was confirmed upon regeneration of the ether via standard Williamson ether synthesis.

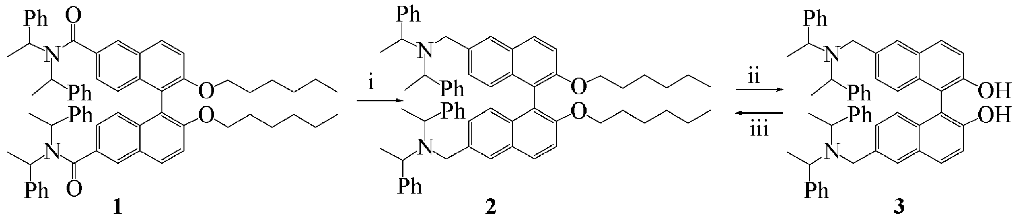

Figure 1. Reduction and ether cleavage of BINOL diamide diether followed by reformation of the ether. Reagents and conditions: (i) LAH, dioxane, reflux 16 h; (ii) LAH, dioxane, reflux 60 h; (iii) 1-bromohexane, acetone, NaOH.

Keyword: Ether cleavage.

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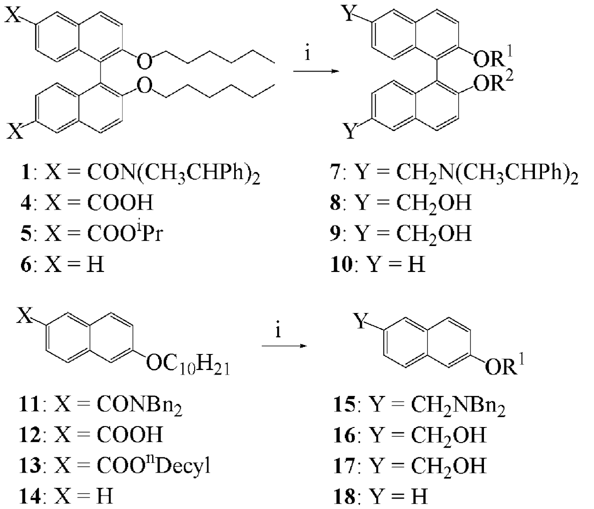

1: $X = CON(CH_3CHPh)_2$
4: $X = COOH$
5: $X = COO^iPr$
6: $X = H$

7: $Y = CH_2N(CH_3CHPh)_2$
8: $Y = CH_2OH$
9: $Y = CH_2OH$
10: $Y = H$

11: $X = CONBn_2$
12: $X = COOH$
13: $X = COO^nDecyl$
14: $X = H$

15: $Y = CH_2NBn_2$
16: $Y = CH_2OH$
17: $Y = CH_2OH$
18: $Y = H$

Figure 2. General reduction/cleavage scheme for BINOL and naphthol ethers derivatives. Reagents and conditions: (i) LAH, dioxane, reflux 60 h.

Such an unusual reaction required further study. Two questions were of particular interest: (1) is the reaction general to reduction of other carbonyls? and (2) is the reaction general to other, non-BINOL ethers? We designed and synthesized two sets of ether-reduction potential substrates. For both the BINOL and naphthalene cases, we tested three carbonyls (an amide, acid, and ester), and a 'control' with no carbonyl (Fig. 2). To test if the BINOL was acting as a chelate, we synthesized ether derivatives of 2-hydroxy-6-naphthoic acid. These naphthalene analogues have the same electronic state in the aromatic ring, and the same ether to be cleaved, but cannot chelate a metal.

Each of the BINOL carbonyls was cleanly reduced, and in each case some ether cleavage was observed (Table 1). Even in the 'control' no carbonyl case, ether cleavage was observed. Only the amide gave complete cleavage of both BINOL ethers. All the other cases (acid, ester, control) gave monoether–mononaphthol as the major product, with some binaphthol observed as well. Why the different functional groups give cleavage to different extents is unclear.

For each of the naphthoic acid derivative ethers **11**–**13**, reduction of the carbonyl was clean, but no ether cleavage was observed (Table 2). No cleavage was observed for the naphthalene 'control' **14** as well, with only starting material recovered. Thus, we propose that cleavage involves a chelate of the BINOL ether oxygens. Chelating BINOL complexes of aluminum are known, though they are considered four coordinate.[3]

Our initial hypothesis was that a byproduct of the carbonyl reduction (AlH_3 perhaps?) that was coordinatively unsaturated could chelate to the BINOL oxygens, then transfer a hydride to give an aluminum complex. This is not consistent with the observation of ether cleavage in the case with no carbonyl, however, as the byproduct is not generated without a reducible substrate. We also considered the possibility that an impurity in the LAH was catalyzing cleavage, but the absence of cleavage in the naphthalene examples is not consistent with this possibility, as the impurity would be present in all cases.

It is possible that aluminum could become six coordinate (four hydrides and the chelating oxygens), which would circumvent the need for prereaction of the LAH. Six-coordinate aluminum hydride complexes are known,[4] though for hydride alkoxy complexes, it is the five-coordinate $AlH_3(OR)_2$ complexes that are reported.[5] It is also possible that at the elevated reaction temperature, the AlH_4^- degrades into AlH_3. Thus, the geometries required for BINOL–LAH chelation are known and reasonable for either five or six-coordinate chelation. In either case, the aluminum could act as a Lewis acid and lead to nucleophilic hydride attack on the alkyl.

In each of the BINOL cases, cleavage of some or all of the ethers was observed. Thus, the cleavage did not depend on the group being reduced (X = acid, ester, or amide), or even on the presence of a reducible group (X = H). This last case was most interesting to us because no alcohol– or amine–aluminum complex could be present to facilitate the ether cleavage.

3. Experimental

3.1. Reduction procedure

LAH (6 equiv) per carbonyl to be reduced were placed in a round bottom flask with a minimal amount of freshly distilled dioxane (15–20 mL). The dioxane was allowed to reflux while stirring for approximately an hour until a homogenous slurry was obtained. The reac-

Table 2. Results of LAH reduction/cleavage of naphthol derivatives (determined by GC/MS)

Reaction	X	Y	$R^1 = H$ %	R^1 = decyl %
11→**15**	$CONBn_2$	CH_2NBn_2	0	100
12→**16**	COOH	CH_2OH	0	100
13→**17**	COO^ndecyl	CH_2OH	0	100
14→**18**	H	H	0	100

Table 1. Results of LAH reduction/cleavage of BINOL derivatives (determined by GC/MS)

Reaction	X	Y	$R^1 = R^2 = H$ %	$R^1 = H$, R^2 = hex %	$R^1 = R^2$ = hex %
1→**7**	$CON(CH_3CHPh)_2$	$CH_2N(CH_3CHPh)_2$	100	0	0
4→**8**	COOH	CH_2OH	58	42	0
5→**9**	COO^iPr	CH_2OH	0	90	10
6→**10**	H	H	26	53	21

tion mixture was allowed to cool below boiling. The compound to be reduced was dissolved in warm freshly distilled dioxane and added to the LAH slurry. The reaction mixture was then brought back to reflux and allowed to reflux for 60 h at which point the reaction mixture was allowed to cool. The reaction slurry was placed on ice, and the LAH was quenched with 50 mL of stock THF followed by x mL H_2O, x mL 3 M NaOH, and $3x$ mL H_2O, in that order, where x equals the grams of LAH. Once the reaction mixture reached a milky white color 1 M HCl was added to acidify the slurry, with the exception of the amide reductions. The slurry was filtered and the filtrate was dried with $MgSO_4$, and concentrated under vacuum. Thus, for reduction of diamide **1** to diamine **7**, LAH pellets (1.00 g, 26.4 mmol) were ground, placed in 10 mL freshly distilled dioxane, and allowed to reflux while stirring until a homogenous suspension was obtained. Diamide **1** (2.12 g, 2.21 mmol) was dissolved in 5 mL of the freshly distilled dioxane and added to the LAH suspension. The reaction mixture was allowed to reflux 60 h with stirring. The reaction mixture was quenched with 50 mL of stock THF, followed by 1 mL water, 1 mL 3 M NaOH, and 3 mL water, in that order. Once the reaction mixture became milky white it was filtered through a pad of Celite. The solvent was removed from the filtrate under vacuum resulting in a highly viscous oil (1.090 g, 52.9% yield from diacid **4**). Analysis of the crude mixture was performed by GC/MS, and product ratios were determined by integration of the GC peaks.

4. Conclusion

Ether cleavage by LAH is reported in the absence of a Lewis acid catalyst for the first time. Observation of ether cleavage on the BINOL derivatives but not on the 6-hydroxy-2-naphthoic acid derivatives leads us to conclude that the cleavage takes place through an aluminum oxygen chelate complex. The aluminum must chelate to the two oxygens in order to allow a hydride to cleave the alkyl chain.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2004.11.091. The supplementary data is available online with the paper in ScienceDirect. Included within the supplemental data are detailed procedures and spectroscopic data.

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