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LETTERS

A mild chemospecific reductive dehalogenation of ethylaminobenzamides with lithium aluminum hydride

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Abstract

A mild reduction of *ortho*-fluoro benzamides was discovered using LAH. The reaction proceeds cleanly and in moderate yields. The scope of the reaction is explored and a mechanism is proposed. A two carbon spacer between the amide and a 3° amine is optimal for this chelation controlled reaction. © 1999 Elsevier Science Ltd. All rights reserved.

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The reduction of aryl halides with lithium aluminum hydride (LAH) is well documented and is generally believed to occur via a radical mechanism.[1] It has long been known that the order of reactivity is ArI>ArBr>ArCl>ArF.[2] The reduction of aryl fluorides are not usually achieved with LAH under mild conditions.[3] When aryl halides are reduced in the presence of amides, the amide carbonyl is reduced as well.[4] Recently, however, we discovered a mild, chemospecific reduction of *ortho*-fluoro secondary benzamides that occurred without concomitant reduction of the amide carbonyl group at room temperature.[5]

The reaction was discovered while reducing a series of benzamides to benzylamines. While reducing an *o*-fluoro benzamide, we observed the loss of starting material after a few minutes at room temperature and discovered that the *o*-fluoro group was gone yet the benzamide was untouched. To understand the scope and possible mechanistic implications of this surprising reaction we performed a series of reductions designed to determine the role of the tethered amine moiety, benzamide substituents, the carbonyl group and amide nitrogen.

We initially wanted to learn what role, if any, the tethered heteroatoms had on the course of the reaction. To this end we synthesized the simple secondary amides with and without tethered heteroatoms. We found that tethered amines all gave the desired aryl-fluoride reduction in clean, spot-to-spot, reactions. However, when the amine is replaced by simple alkyl or ether group, the reduction of an

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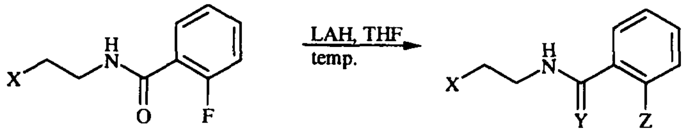
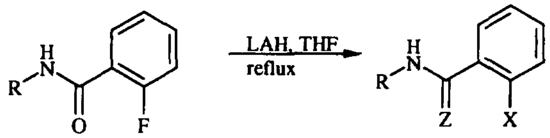
Table 1
Tethered groups

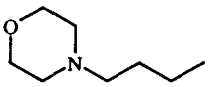
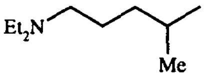
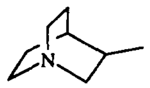


X	Temp. (°C)	Time (hours)	% Yield (Y=O, Z=H)	% Yield (Y= H_2, Z=H)	% Yield (Y= H_2, Z=F)
N-Morpholino-	25	0.5	77		
N-Morpholino-	65	8		100	
N-Piperdinyl-	25	0.5	78		
Me_2N-	25	0.5	59		
Me_2CH-	65	9.5			18[a]
MeO-	65	18			82

[a] A mixture of products formed was in this reaction. Only the major product and its yield is shown.

Table 2
Chain length



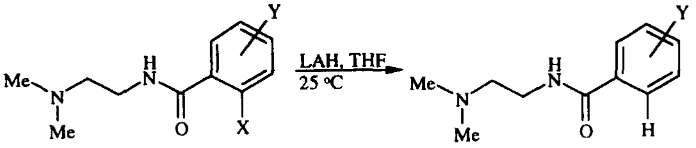
R	Time (hours)	% Yield (X=F, Z=H_2)	% Yield (X=H, Z=O)
	5	75	3
	4	10	22
	24	69	
	36	77	

o-fluorobenzamide failed at room temperature. Heating these reactions resulted in the reduction of the amide without reduction of the aryl-fluoride (Table 1). Thus, the presence of the amine in the side chain is vital for the success of the reaction.

The distance between the amide and amine nitrogen also plays a key role in the success of the reaction. A two-carbon spacer appears to be optimal for the reaction (Table 1). A three-carbon spacer failed at room temperature, however upon heating, a mixture of products were observed with the des-fluorinated product among them. A four-carbon spacer failed at both room temperature and under reflux. Under reflux, the four-carbon spacer cleanly yields *o*-fluorobenzyl amines. A hindered amine that has a two-carbon spacer, quinuclidine, also failed to yield the reduction of the fluoride at room temperature (Table 2). It appears that there is an amino–aluminum complexation prior to reduction. Chelation effects on aluminum species are not unknown in LAH reductions.[6]

A variety of substituents on the aromatic ring were subjected to these reaction conditions. The *o*-

Table 3
Benzamide substitutions

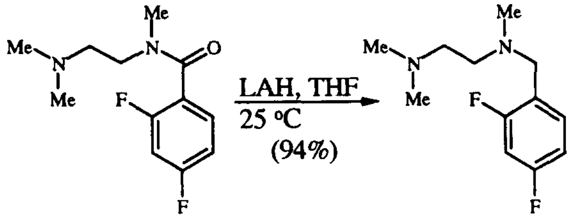


X	Y	% Yield
F	4-F	50
Cl	4-F	49
Cl	4-Cl	48
F	4-CF$_3$	56
F	3-F	50
Br	H	22
I	H	48
H	4-I	36[b]

[b] The 4-iodo group was reduced (Y=H in the product).

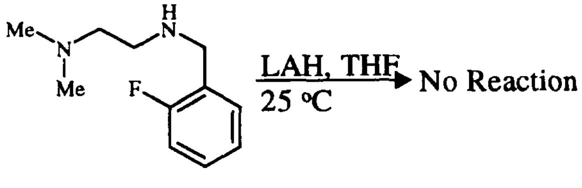
fluoro or *o*-chloro benzamides are readily reduced without touching substituents in either the *meta*- or *para*-positions. The *o*-bromide was also reduced but the reduction occurred more slowly and at a lower yield indicating that a nucleophilic aromatic substitution may be the predominate mechanism in these reactions. It is well known that aryl halides undergo nucleophilic aromatic substitution with the order of reactivity ArF»ArCl~ArBr>ArI.[7] However, the *o*- and *p*-iodo derivatives were readily reduced indicating that aryl-iodo derivatives are reduced via the well known radical mechanism[1] (Table 3).

The 2° amide also plays a role in the success of the reaction. It was observed that the 3° amide **1** quickly undergoes reduction to the 3° amine **2** without reducing the aryl-fluoride (Scheme 1). While the *o*-fluorobenzyl amine **3** is not reduced (Scheme 2). It appears that the amide nitrogen also chelates to the aluminum while the electron withdrawing amide activates the *o*-halide to nucleophilic attack.[8]



1 **2**

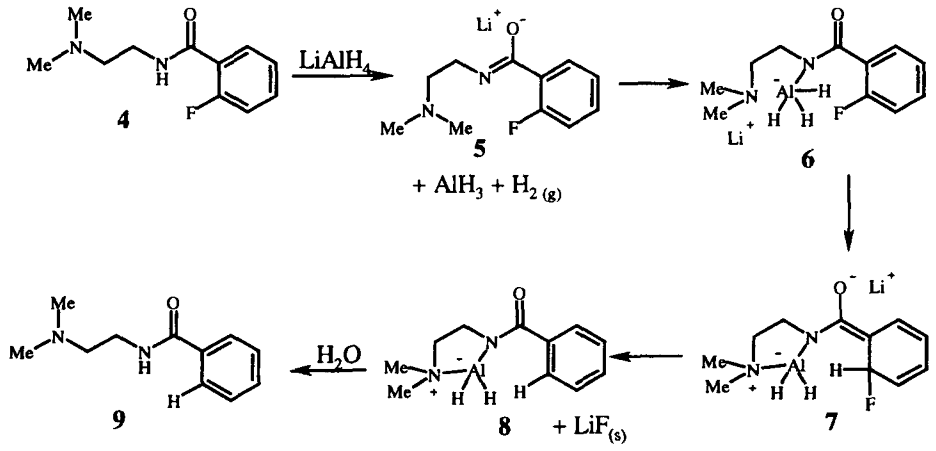
Scheme 1.



3

Scheme 2.

Our proposed mechanism involves first, the deprotonation of the amide **4** giving rise to the evolution of hydrogen gas which is observed immediately upon the addition of LAH. The formation of the conjugate base **5** would seem to retard nucleophilic attack on the ring carbon. However, coordination to the alane, a Lewis acid, offsets that effect setting the stage for nucleophilic substitution. The hydride then attacks the activated *o*-position of the benzamide while the aluminum species is stabilized by the chelation of the amine nitrogen of the side chain **7**. Cleavage of the C–F bond releases fluoride which gives rise to the lithium halide salt, a cloudy solution is observed, and rearomatization of the benzamide gives the reduced aluminum complex **8**. The aqueous quench reveals the final reduction product **9** (Scheme 3).



Scheme 3. Proposed mechanism

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5. The typical procedure for the reductive dehalogenation of benzamides: To a stirred solution of the amide (2.00 mmoles) in dry THF (75 mL) was added a solution of LAH (6.00 mmoles, 1.0 M in THF) dropwise. The resulting mixture was stirred at room temperature for 30 minutes when the reaction was quenched by the sequential addition of water (0.25 mL), 2N NaOH (0.25 mL) and water (1 mL). The resulting suspension was filtered through a plug of Celite and the aluminum salts were thoroughly washed with EtOAc. (While these reactions are very clean giving only one major product, the moderate yields are believed to be due to chelation of the product to the aluminum salts. Thus, thorough washing of the aluminum salts with EtOAc is very important for obtaining good yields.) The filtrate was dried ($MgSO_4$), filtered and evaporated yielding the product. The product was typically purified via flash column chromatography (10% MeOH in CH_2Cl_2). All compounds were characterized with ^{1}H NMR, MS and IR.
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