Pergamon

Tetrahedron Letters 39 (1998) 8933–8934

TETRAHEDRON LETTERS

L-Selectride as a Convenient Reagent for the Selective Cleavage of Carbamates

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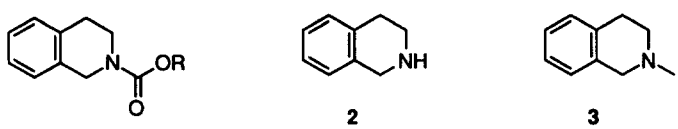
Received 6 February 1998; revised 17 July 1998; accepted 15 August 1998

Abstract: L-Selectride® was shown to selectively cleave methyl carbamates in the presence of more sterically demanding carbamates, including the selective cleavage of a methyl carbamate in the presence of an N-Boc group. Published by Elsevier Science Ltd.

Keywords: carbamates; cleavage reactions

We recently reported that L-Selectride® is an efficient reagent for the deprotection of *N*-carbomethoxy substituted opioids to the important *N*-noropioids.[1] The clean reaction under mild conditions, led us to consider the use of L-Selectride as a general reagent for the cleavage of carbamates. Traditionally, alkyl carbamates are cleaved under a variety of harsh conditions,[2] however we noted that the use of hydride sources to cleave carbamates has not been fully investigated. Although $LiAlH_4$ generally gives reduction to the *N*-methyl analogs,[3] alkali metal alkoxy aluminum hydrides have been reported to cleave certain carbamates.[4,5] In addition, it was recently shown that L-Selectride removed a benzyloxycarbonyl group from the nitrogen of an indole to give the non-basic indolic product.[6] We now wish to disclose that L-Selectride cleaves a variety of carbamates to the corresponding basic secondary amines under mild conditions, and that the difference in reaction rates allows selective carbamate cleavage.

Four carbamates of 1,2,3,4-tetrahydroisoquinoline (**1a-d**)[7,8] were treated with 3 equivalents of 1 M L-Selectride in THF at r.t. (Scheme 1).[9] In all cases, cleavage occurred to give **2**, but increased reaction times were required with increasing steric bulk. Reaction of the methyl derivative (**1a**) was complete (89%) in 24h, but after 48h the ethyl analog (**1b**) gave only 55% yield of **2**. Extending the reaction time to 5 days gave rise to 82% yield of **2**, demonstrating the slower rate of reaction. Reduction to 2-methyl-1,2,3,4-tetrahydroisoquinoline (**3**) was a very minor side reaction in three of the cases (**1a, b, c**);[10] only the phenyl derivative (**1d**) gave a significant quantity of **3** (7%).[11] Treatment of the bulky N-Boc derivative **1e** under the same conditions gave rise to a very slow reaction, yielding a mixture of **2** and **3**.[11]



2 **3**

1a	R = Me	r.t., 1 day	89%	
1b	R = Et	r.t., 2 days	55%	
1b	R = Et	r.t., 5 days	82%	
1c	R = Bn	r.t., 3 days	76%	
1d	R = Ph	r.t., 4 days	72%	7%
1e	R = ^{t}Bu	r.t., 3 days	8%	5%

Scheme 1

As the rate of reaction decreased with increasing steric bulk, it was considered that this may offer a useful method to remove a methyl carbamate in the presence of a Boc group which, to the best of our knowledge, has not been achieved to give a basic secondary amine.[12] Such a procedure would complement the use of benzyl carbamates in selective cleavage reactions,[2] as isolated double bonds and aromatic halogens are

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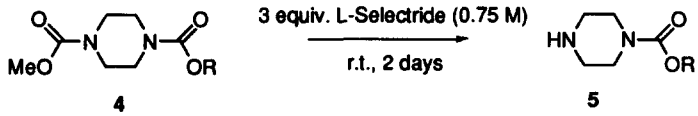
PII: S0040-4039(98)02018-8



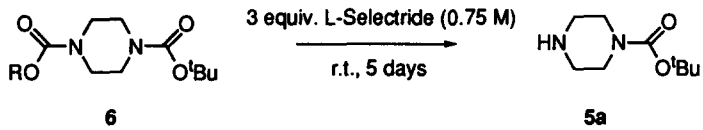
4 5

a R = ^{t}Bu 87%
b R = Bn 51%
c R = Et 69%

Scheme 2

inert to L-Selectride.[13] Indeed, treatment of dicarbamate (**4a**)[8] with 3 equivalents of L-Selectride at r.t. gave rise to cleavage of the methyl carbamate and only minor reaction with the Boc group to give **5a** (87%) (Scheme 2).[14] This order of reactivity is the opposite to that observed for the TMS-Cl/NaI cleavage system,[15] and therefore represents a reversal in the chemoselectivity which is traditionally seen. As was predicted from the results shown in Scheme 1, the selective cleavage of methyl carbamates over both benzyl (**4b**) and ethyl (**4c**) was not as efficient, due to increased reaction with the higher carbamate. However, the difference in reaction rates was still sufficient to give respectable yields of the desired products.[11]

The above work demonstrated that L-Selectride cleaves methyl carbamates more rapidly than higher carbamates. It was therefore not surprising that the cleavage of both ethyl and benzyl carbamates selectively over N-Boc required long reaction times at r.t., but the extremely low reaction rate with the N-Boc group allowed good yields of **5a** to be obtained (Scheme 3).[11]



6 5a

a R = Bn 62%
b R = Et 54%

Scheme 3

In conclusion, L-Selectride is an efficient agent for the cleavage of a variety of carbamates, and selective cleavage of methyl carbamates can be accomplished efficiently. In addition, the extremely slow reaction with an N-Boc group allows the selective removal of smaller carbamates in the presence of N-Boc.

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8. Prepared by treatment of the appropriate secondary amine with the relevant alkyl chloroformate and excess Et_3N in $CHCl_3$. All spectra of novel compounds were consistent with assigned structures.
9. A mixture of carbamate and L-Selectride (1M in THF, 3 equiv.) was stirred at r.t. The reaction was quenched with water, the THF removed, acidified to pH1 (3M HCl), and washed with CH_2Cl_2. The aqueous phase was basified (pH9, NH_4OH), extracted with CH_2Cl_2, and dried (K_2CO_3). After removal of the solvent, **2** was isolated as the oxalic acid salt from MeOH.
10. Observed as a minor product by TLC and mass spec.
11. Isolated by column chromatography (silica, $CHCl_3$:MeOH:NH_4OH 95:5:0.5).
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14. A mixture of **4a** and L-Selectride (0.75M in THF, 3 equiv.) was stirred at r.t. for 2 days. The reaction was quenched with water, the THF removed, acidified (10% citric acid, 0-5°C), and washed with CH_2Cl_2. The cold aqueous phase was basified (pH9, NH_4OH), extracted with $CHCl_3$, and dried (K_2CO_3). After removal of the solvent, **5a** was isolated as the oxalic acid salt from EtOH.
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