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9-BBN Triflate Mediated Stereoselective Alkylation of 2-alkyl Imidazolines with Tetrahydrofurans

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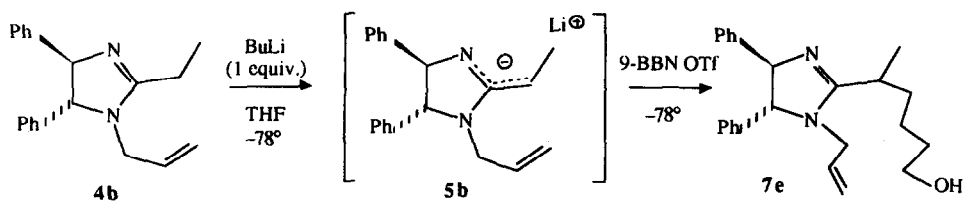
Abstract : Nucleophilic attack of deprotonated imidazolines **3** or **4** on tetrahydrofuran derivatives in the presence of 9-BBN triflate can afford the corresponding alkylated products **7** with moderate to good stereoselectivities.

During the course of a study concerning the stereoselective alkylation of azaenolate **5b**, obtained by deprotonation of the corresponding imidazoline **4b**, we were surprised to observe that, in the presence of 9-BBN triflate and before the introduction of any electrophile, a new species was formed whose spectral data were in accord with structure **7e** (Scheme 1).



4b **5b** **7e**

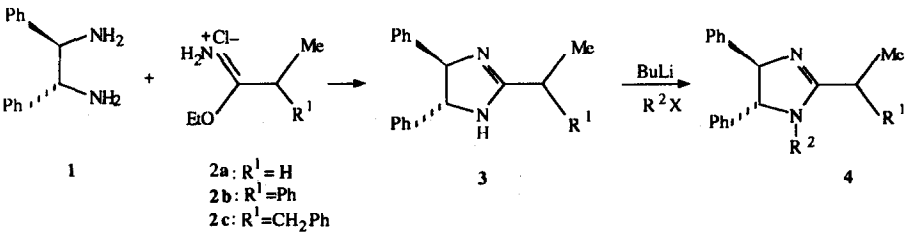
Scheme 1

It would appeared that imidazoline **7e** is the result of a nucleophilic attack of anion **5b** on the THF used as solvent after activation with 9-BBN triflate. This observation prompted us to embark on a systematic study of this unexpected reaction.

Two series of N-unsubstituted **3a** - **3c** and N-substituted **4a** - **4d** 2-alkyl imidazolines were prepared. Classical condensation[1] of diamine **1** [2-3] with the appropriate iminoether **2a** - **2c**[4] afforded imidazolines **3a** - **3c**. Further deprotonation with butyllithium (1 equiv., -78°C, THF) and quenching with iodomethane or various allylic bromides led to the N-substituted imidazolines **4a** - **4d** in good yields (Scheme 2 - Table 1).

In order to study the scope and limitation of the alkylation depicted in scheme 1, two sets of experiments were undertaken with imidazolines **3a** - **3c** and **4a**, **4b** and **4d** (Scheme 3, Table 2).

Thus, N-unsubstituted imidazolines **3a** - **3c** were deprotonated with butyllithium (2 equiv., 0°C) in either tetrahydrofuran or 2-methyltetrahydrofuran and then treated with 9-BBN OTf (1 equiv.) either at 0°C (entry 1) or at -78°C (entries 2-5). Similarly, the N-substituted imidazolines[5] **4** were sequentially treated with butyllithium (1 equiv., -78°C) and 9-BBN OTf at 0°C (entry 6) or at -78°C (entries 7, 9, 10).



1 2a: R^1 = H; 2b: R^1 = Ph; 2c: R^1 = CH_2Ph 3 4

Scheme 2

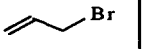
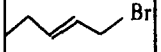
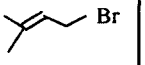
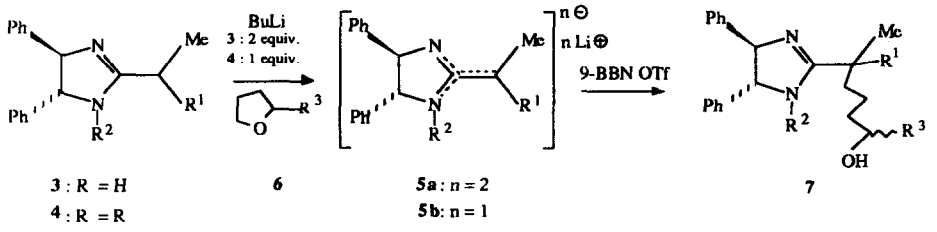
Entry	2 R^1	3 (yield %)	R^2 X	4 (yield %)
1	**2a** R^2 = H	**3a** (81)	Me I	**4a** (81)
2	"	-		**4b** (90)
3	"	-		**4c** (88)
4	"	-		**4d** (86)
5	**2b** : R^2 = Ph	**3b** (78)	-	-
6	**2c** : R^2 = CH_2Ph	**3c** (79)	-	-

Table 1 : Preparation and N-alkylation of imidazolines

These reactions were generally stereo and regioselective with the best diastereoselectivities[6] observed for N-unsubstituted imidazolines **3a** and **3b** at low temperature (entries 2-4). The difference in the selectivity between imidazolines **3** and **4** is worthnothy. This could be due to the fact that deprotonation of **3a** and **3b** gives rise to a single dianion intermediate, owing to the C-2 symetry of the starting material[7]. Whereas deprotonation of imidazolines **4** could lead to the formation of a mixture of Z or E azaenolates. In both cases increasing the temperature cause complete loss of stereocontrol (entries 1 and 6).

Three experiments deserve special comments. Excess potassium hydride can be used as a base (entry 8), but a mixture of two diastereomers at C-1 was obtained. This is probably due to further deprotonation after alkylation. With imidazoline **3c** (entry 5), a peculiar regioselectivity was observed. Deprotonation occured in α to the phenyl ring in the side chain affording imidazoline **8** as a 50:50 mixture of two diastereomers. Examination of ^1H and ^{13}C NMR spectra lead us to assume that these compounds were epimeric at C-1. When 2-methyl tetrahydrofuran was used as solvent instead of tetrahydrofuran itself (entry 3), a regioselective opening of the ring was observed.

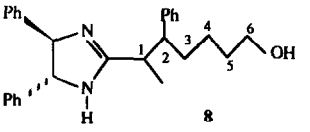


3 : R = H
4 : R = R

6

5a : n = 2
5b : n = 1

7



8

Scheme 3

Entry	Starting material	THF derivative R^3	Temperature for 9-BBN OTf [a] introduction (°C)	Product (yield %)	d.e %[b]
1	3a	H	0	7a (89)	0
2	"	"	- 78	" (87)	>95
3	"	Me	"	7b (87)	>95 [c]
4	3b	H	"	7c (67)	>95
5	3c	"	"	8 (81)	>95 [d]
6	4a	"	- 78	7d (22)	0
7	"	"	"	" (30)	67
8	"	"	"	" (79)	0 [e]
9	4b	"	"	7e (48)	64
10	4d	"	"	7f (36)	40

(a) After addition of 9-BBN OTf the reaction was generally complete within 5 minutes.

(b) See reference [6].

(c) This product is a 50:50 mixture of diastereomers at C-5.

(d) Mixture of diastereomers at C-1 (see text).

(e) This experiment was performed with an excess of potassium hydride (see text).

Table 2 : Alkylation of imidazolines **3** and **4** in the presence of 9-BBN OTf.

This is in accord with the selectivity described for the cleavage of unsymmetrical aliphatic ethers with 9-BBN Br [8-9]. Finally it is worthy of note that this reaction can afford quaternary centers[10] with a good stereocontrol (entry 4).

Further investigations concerning the use of this stereoselective reaction in synthesis with enantiomerically pure imidazolines as well as the determination of the direction of the asymmetric induction are underway in our laboratory.

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10. For a review concerning the construction of quaternary carbon centers, see : Martin, S.F., *Tetrahedron*, **1980**, 36 419-460.

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