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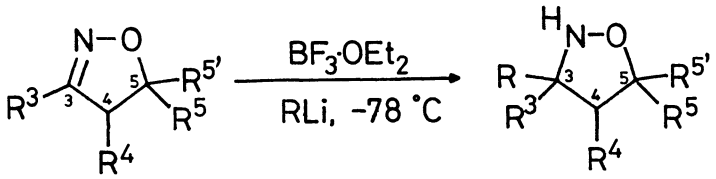
Boron Trifluoride-Assisted Alkylation of 2-Isoxazolines. A Novel Route to N-Unsubstituted Isoxazolidines

Hidemitsu UNO,* Tetsuya TERAKAWA, and Hitomi SUZUKI*
Advanced Instrumentation Center for Chemical Analysis,
Department of Chemistry, Faculty of Science,
Ehime University, Matsuyama 790

In the presence of boron trifluoride, 2-isoxazolines undergo the addition of organolithiums to afford N-unsubstituted isoxazolidines in moderate to good yields.

1,3-Dipolar cycloaddition reaction of nitrones with olefins is a useful, conventional method for the preparation of 1,2-oxazolidines (isoxazolidines).[1] This method is, however, of limited use for the preparation of N-unsubstituted isoxazolidines, although some successes based on the thermal isomerization of oximes into nitrones have been reported.[2] Nucleophilic conversion of 2-isoxazolines into isoxazolidines seems to be an attractive alternative, because the starting isoxazolines are readily available from the reaction of nitrile oxides with olefins.[3] A leaving group at the azomethine carbon of 2-isoxazolines is known to be subject to nucleophilic displacement with various nucleophiles.[4] Nevertheless, no good examples of such conversion have been known except for the reductions with $NaBH_3CN$ or $NaBH_4$,[5] since 2-isoxazolines are readily deprotonated by a strong base such as alkyllithium or lithium amide at C-3 side chain or C-4.[6] The recent report on the BF_3-promoted addition of aryllithium to oxime ethers[7] prompted us to report our own results which involve the boron trifluoride-assisted reaction of 2-isoxazoline with organolithiums.[8] In this communication we describe the first example of an efficient alkylative conversion of 2-isoxazolines into N-unsubstituted isoxazolidines in the presence of $BF_3 \cdot OEt_2$ (Eq. 1).



(1)

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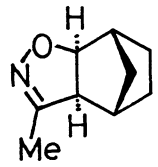
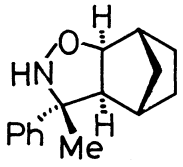
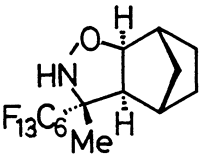
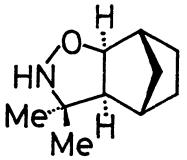
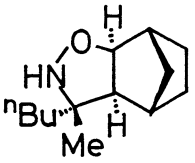
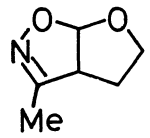
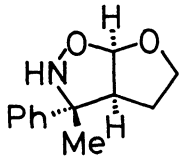
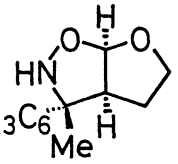
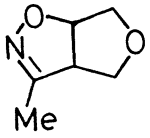
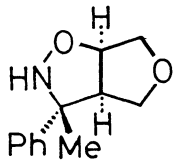
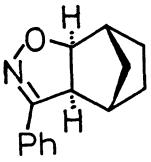
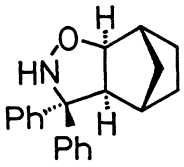
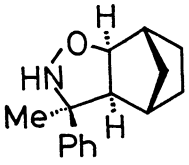
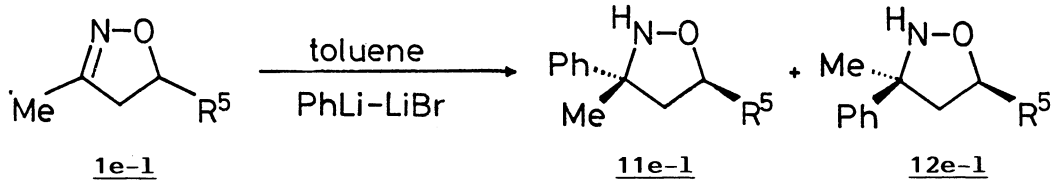
Table 1. BF_3-Assisted addition of organolithiums to 4,5-disubstituted 2-isoxazolines

Entry	Isoxazoline 1	Organolithium (solvent)	Product (yield/%)
1	 **1a**	PhLi-LiBr[a] (ether)	 **2** (38)
2	**1a**	PhLi-LiBr[a] (CH_2Cl_2)	**2** (92)
3	**1a**	PhLi-LiBr[a] (toluene)	**2** (89)
4	**1a**	$^nC_6F_{13}Li$[b] (ether)	 **3** (91)
5	**1a**	MeLi-LiBr[c] (CH_2Cl_2)	 **4** (47)
6	**1a**	^nBuLi[c] (CH_2Cl_2)	 **5** (14)
7	 **1b**	PhLi-LiBr[a] (CH_2Cl_2)	 **6** (94)
8	**1b**	$^nC_6F_{13}Li$[b] (toluene)	 **7** (76)
9	 **1c**	PhLi-LiBr[a] (toluene)	 **8** (89)
10	 **1d**	PhLi-LiBr[a] (toluene)	 **9** (80)
11	**1d**	MeLi-LiBr[c] (toluene)	 **10** (7)

a) Purchased from Kanto Chemical Co. Ltd. b) The perfluoroalkyllithium was generated in situ from the reaction of the perfluoroalkyl iodide with methyllithium. See Ref. 8. c) Purchased from Aldrich Chem. Co. Inc.

The reaction was carried out at -78 °C in ether, CH_2Cl_2 or toluene. Best results were obtained when an organolithium reagent (1.2 equiv.) was added to a mixture of an isoxazoline (1 equiv.) and $BF_3 \cdot OEt_2$ (1.2 equiv.) (Table 1). Toluene and CH_2Cl_2 were the solvents of choice (entries 1-3), but the latter was not suitable in the case of perfluoroalkylation because of low solubility of perfluoroalkyl iodide used for in situ generation of the lithium reagent. In one case, phenyllithium reacted with **1a** in toluene without the assistance of $BF_3 \cdot OEt_2$ to give **2**, although the yield was slightly less (70%). t-Butyllithium, lithium phenylacetylide, phenylmagnesium bromide, and n-butylmagnesium bromide failed to react with **1a** even in the presence of $BF_3 \cdot OEt_2$.

In each case, the alkylation of a 4,5-disubstituted isoxazoline occurred from the opposite side of the substituent at C-4 to form one diastereomer, stereochemistry of which was assigned by the diagnosis of NOESY spectra. On the other hand, the addition of phenyllithium to 5-monosubstituted 2-isoxazolines in toluene proceeded in a less stereoselective manner, similar to the reduction of isoxazolines with lithium aluminiumhydride leading to γ-hydroxy amines[9] (Eq. 2, Table 2). An interesting stereochemical outcome was obtained from the reaction of isoxazolines **1i** and **1j**, bearing oxygen atom or atoms on the C-5 side chain (entries 17-23). In the presence of $BF_3 \cdot OEt_2$ the reaction of **1i** with phenyllithium proceeded in a nonstereoselective manner to give a diastereomeric mixture (**11i**/**12i** = 55/4-60/40), while in the absence of $BF_3 \cdot OEt_2$ the



(2)

1e-l **11e-l** **12e-l**

Table 2. Phenylation of 5-monosubstituted 2-isoxazolines

Entry	Isoxazoline 1	R^5	$BF_3 \cdot OEt_2$ equiv.	Yield/%	(ratio 11/12)
12	**1e**[a]	Ph	1.2	74	(95/5)[b]
13	**1f**[a]	CH_2Ph	1.2	70	(90/10)[c]
14	**1g**[a]	CH_2SiMe_2Ph	1.2	74	(>95/5)[c]
15	**1h**[a]	^nBu	1.2	72	(92/8)[c]
16	**1h**[a]		0	58	(92/8)[c]
17	**1i**[a]	CH_2OEt	5	79	(60/40)[b]
18	**1i**[a]		1.2	72	(55/45)[b]
19	**1i**[a]		0	19	(89/11)[b]
20	**1j**[a]	$CH_2OCH_2CH_2OMe$	2.4	48	(52/48)[b]
21	**1j**[a]		1.2	41	(41/59)[b]
22	**1j**[a]		0.9	28	(37/63)[b]
23	**1j**[a]		0	4	(61/39)[b]
24	**1k**[a]	$CONMe_2$	1.2	-	[d]
25	**1l**[a]	CO_2Me	1.2	-	[d]

a) The regioisomeric purity was estimated to be ca. >95% by NMR. See Ref. 3. b) Determined by GLC. c) Estimated by NMR. d) See text.

diastereoselectivity was remarkably improved at the expence of yields (**11i**/**12i** = 89/11). A similar trend was observed for the reaction of **1j**. The selectivity of **12j** reached the maximum in the presence of nearly one equiv of $BF_3 \cdot OEt_2$. These results may suggest that phenyllithium approaches to 2-isoxazoline ring preferentially from the coodination side of BF_3 as it forms an "ate" complex with BF_3.[10] Finally, the reactions of **1k** and **1l** with phenyllithium occurred predominantly on the carbonyl group to give 5-benzoyl-3-methyl-2-isoxazoline (<20%) together with small amounts of 5-diphenylcarbinyl isoxazoline.

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10) For the diastereoselection in the reduction of $LiAlH_4$, a coordination model of $LiAlH_4$ and 2-isoxazolines was proposed. See ref. 9.

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