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Lewis acid catalyzed regioselective ring opening of azetidines with alcohols and thiols

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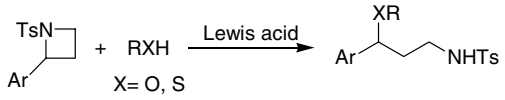
Abstract—An efficient synthesis of amino ethers and amino thioethers has been achieved via the ring cleavage of *N*-tosylazetidines with alcohols or thiols. The reactions were studied in the presence of various Lewis acids and $BF_3{\cdot}OEt_2$ was found to be the most efficient. The products were obtained in modest to good yields under very mild conditions in 5–15 min.

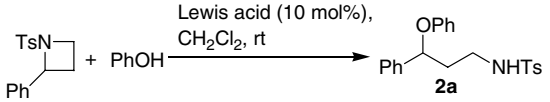
Azetidines,[1] saturated four-membered nitrogen-containing heterocycles, own a special place in organic chemistry due to their presence in many biologically active drugs and natural products.[2] Their tendency to act as masked 1,4-dipoles[3] contributes largely towards their synthetic importance. We earlier reported the application of this property of azetidines in the synthesis of tetrahydropyrimidines via cycloaddition reactions with nitriles.[4] The ring opening reaction of azetidines has, however, not been as widely explored as compared to three-membered aziridines.[5] The ability of azetidines to undergo various transformations such as cycloaddition,[3,4] ring expansion[6] and ring opening[7] makes them highly valuable in organic synthesis. We had previously carried out the ring opening of aziridines with alcohols in the presence of Lewis acids.[5f] In this paper, we extend the same methodology to the ring cleavage of azetidines (Scheme 1). The product amino ethers find varied applications in pharmaceutical,[8] polymer[9] and plastics[10] industries. The ring cleavage has also been studied using thiols as nucleophiles leading to the formation of amino thioethers. These molecules possess interesting properties and have been utilized as precursors for the synthesis of functionalized amines via sulfur–lithium exchange reactions.[11]



Scheme 1.

Azetidines were synthesized from *N*-tosylarylaldimines in two steps according to our earlier reported procedure.[4] Initially, 2-phenyl-*N*-tosylazetidine was reacted with phenol in the presence of various Lewis acids such as $BF_3{\cdot}OEt_2$, $Cu(OTf)_2$, $Zn(OTf)_2$, $Yb(OTf)_3$, $Sn(OTf)_2$ and $Sc(OTf)_3$ in dichloromethane at rt (Table 1). $BF_3{\cdot}OEt_2$ was found to be the best Lewis acid. All subsequent reactions with $BF_3{\cdot}OEt_2$ proceeded smoothly and were complete in less than 15 min (Table 2). The products, γ-amino ethers were obtained in moderate to good yields. The yields were slightly higher in the case of 3-chlorophenyl-substituted azetidines (entries 9–12). The reactions with β-naphthol were found to be faster which may be due to its higher acidity (entries 2, 6 and 10).

Table 1. Screening of Lewis acids in the reaction of an azetidine with phenol



Entry	Lewis acid	Time (min)	Yield (%)
1	$BF_3{\cdot}OEt_2$	15	54
2	$Cu(OTf)_2$	10	30
3	$Yb(OTf)_3$	20	41
4	$Zn(OTf)_2$	15	33
5	$Sn(OTf)_2$	15	36
6	$Sc(OTf)_3$	15	26

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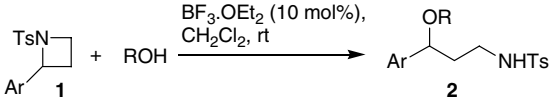
Table 2. Reactions of various azetidines with alcohols in the presence of $BF_3{\cdot}OEt_2$

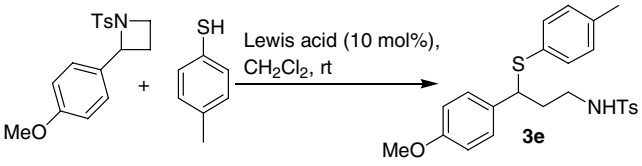


Entry	Ar	R	Product	Time (min)	Yield[a] (%)
1	C_6H_5	C_6H_5	**2a**	15	54
2	C_6H_5	β-Naphthyl	**2b**	5	66
3	C_6H_5	Et	**2c**	10	48
4	C_6H_5	^{t}Bu	**2d**	10	40
5	4-$OMeC_6H_4$	C_6H_5	**2e**	10	53
6	4-$OMeC_6H_4$	β-Naphthyl	**2f**	5	61
7	4-$OMeC_6H_4$	Et	**2g**	15	54
8	4-$OMeC_6H_4$	^{t}Bu	**2h**	15	48
9	3-ClC_6H_4	C_6H_5	**2i**	10	78
10	3-ClC_6H_4	β-Naphthyl	**2j**	5	69
11	3-ClC_6H_4	Et	**2k**	15	82
12	3-ClC_6H_4	^{t}Bu	**2l**	15	81

[a] Isolated yield.

The reaction was further extended to thiols as nucleophiles. Various Lewis acids were screened in the reaction of 4-methoxyphenyl-substituted azetidine and 4-methylbenzene thiol (Table 3). Almost all the Lewis acids gave an excellent yield of product, however, $BF_3{\cdot}OEt_2$ was found to be slightly superior in terms of yield and thus, it was used for further reactions.

Table 3. Screening of Lewis acids in the reaction of azetidine with 4-methylbenzene thiol



Entry	Lewis acid	Time (min)	Yield (%)
1	$BF_3{\cdot}OEt_2$	10	97
2	$Cu(OTf)_2$	10	95
3	$Yb(OTf)_3$	15	91
4	$Zn(OTf)_2$	15	77
5	$Sn(OTf)_2$	15	80
6	$Sc(OTf)_3$	20	85

Several azetidines were reacted with different thiols in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane at rt (Table 4). γ-Amino thioethers were isolated in high yields in almost all the cases.

In conclusion, important functionalities such as amino ethers and amino thioethers were synthesized following the general strategy of nucleophilic opening of azetidine rings with alcohols or thiols.

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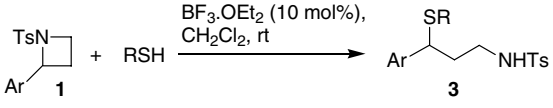
Table 4. Reactions of various azetidines with thiols in the presence of $BF_3{\cdot}OEt_2$



Entry	Ar	R	Product	Time (min)	Yield[a] (%)
1	C_6H_5	4-MeC_6H_4	**3a**	15	86
2	C_6H_5	β-Naphthyl	**3b**	20	72
3	C_6H_5	Et	**3c**	20	81
4	C_6H_5	4-ClC_6H_4	**3d**	10	88
5	4-$OMeC_6H_4$	4-MeC_6H_4	**3e**	10	97
6	4-$OMeC_6H_4$	β-Naphthyl	**3f**	15	76
7	4-$OMeC_6H_4$	Et	**3g**	15	83
8	4-$OMeC_6H_4$	4-ClC_6H_4	**3h**	20	97
9	3-ClC_6H_4	4-MeC_6H_4	**3i**	20	78
10	3-ClC_6H_4	β-Naphthyl	**3j**	15	88
11	3-ClC_6H_4	Et	**3k**	15	85
12	3-ClC_6H_4	4-ClC_6H_4	**3l**	15	93

[a] Isolated yield.

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