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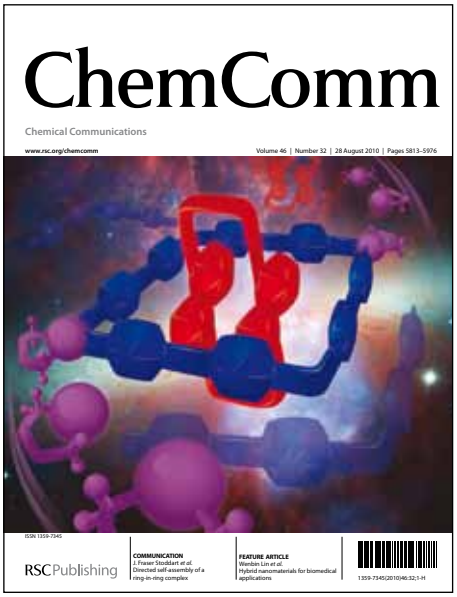

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ARTICLE TYPE

Facile Synthesis of 2-Pyrazolines and α,β-Diamino Ketones via Regioselective Ring-Opening of Hydrazone-tethered Aziridines

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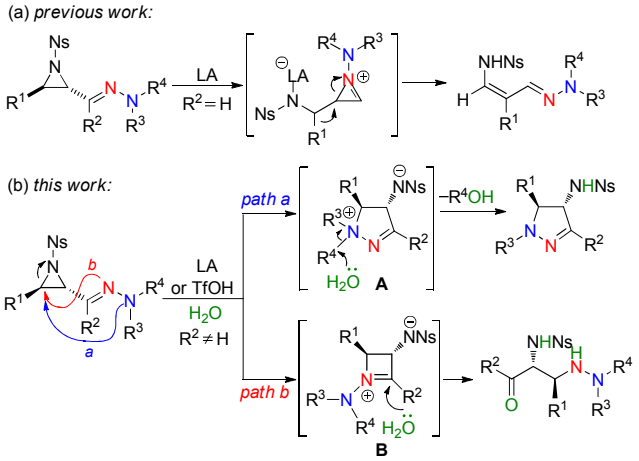
A facile strategy to access 2-pyrazolines and α,β-diamino ketones via SN_2-type ring-opening of *N*-(aziridin-2-ylethylidene)hydrazines or *N*-(aziridin-2-ylbutylidene)hydrazines in the presence of Lewis acid or trifluoromethanesulfonic acid (TfOH) is described in this context.

2-Pyrazolines have received considerable attention because of their potential bioactivities.[1] The traditional strategies for the synthesis of racemic and nonracemic 2-pyrazolines basically rely on the 1,3-dipolar cycloaddition reactions.[2] Due to the limited substrate scope of the cycloaddition reactions,[2g] the strategy for the construction of enantioenriched pyrazoline derivatives with functional diversity is still highly desirable. For instance, amino pyrazolines, exhibiting biological and pharmacological activities,[3] have no efficient strategies for their synthesis until recently. Only a few examples have been reported by using functionalized aziridines.[4]

Functionalized aziridines have shown a broad utility in organic chemistry due to their highly strained ring and the presence of the particular substitution which feature noticeable unique reactivities.[5] Recently, we have reported Lewis acid catalyzed ring-opening of *N*-(aziridin-2-ylmethylene)hydrazines to provide enamine derivatives and a mechnism was proposed via azirinium salt intermediate to rationalize the unprecedented 1,2-migration of the substituent R^1 (Scheme 1a).[6] During our ongoing investigation on these functionalized aziridines, we found that *N*-(aziridin-2-ylethylidene)hydrazines and *N*-(aziridin-2-ylbutylidene)hydrazines failed to give enamines but gave 2-pyrazolines and α,β-diamino ketones as products. It is noteworthy that α,β-diamino ketones have been found to possess mild avian antimalarial activity and no examples of synthesis of α,β-diamino ketones from aziridines have been reported.[7,8] The regio- and stereochemical outcomes of the ring-opening are sigificantly dependent on the nature of the aziridine substitution pattern,[5c] as shown in Scheme 1b, we assumed the activated aziridine could undergo intramolecular nucleophilic attack by nitrogen atom of the hydrazon moiety in an SN_2 fashion via path a or path b to provide 4,5-dihydro-1H-pyrazol-1-ium salt intermediate **A** or 2,3-dihydroazetium salt intermediate **B**, respectively.[9] In the presence of water, intermediate **A** undergoes release of the sulfonyl group (R^4) to give 2-pyrazoline and intermediate **B** undergoes hydrolysis to give α,β-diamino ketone. All the reactions proceed with excellent stereoselectivity with no isomeric products detcted by means of NMR analysis. In addition, the S_N2 pathways have been firmly established by using chiral aziridines to generate nonracemic products.[10]



Scheme 1. Ring-opening reactions of hydrazone-tethered aziridines .

Our studies were initiated by treating aziridine **1a** with various Lewis acids. To our delight, 2-pyrazoline **2a** could be obtained in moderate to good yields (68–90%) in dichloromethane using various metal-containing Lewis acid (5 mol%), such as $Sc(OTf)_3$, $Eu(OTf)_3$, $Cu(OTf)_2$ and $Bi(OTf)_3$, as catalyst and two equiv water as additive (Table 1, entries 1–5). Only a small amount of **3a** was produced along with the formation of **2a**. Aziridine **1a** was recovered when treating $BF_3{\cdot}Et_2O$ (10 mol%) (Table 1, entry 6). When catalytic amount of trifluoromethanesulfonic acid (TfOH) (20 mol%) was used, **2a** was formed as the major product (69%) along with the isolation of product **3a** (29%) (Table 1, entry 7). However, **3a** was obtained in 76% yield as sole product in the

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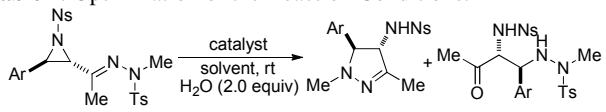
presence of 1.2 equiv TfOH (Table 1, entry 7). Further optimization of solvents revealed that dichloromethane was the best solvent for the formation of **2a** (Table 1, entries 10 and 11). Increasing the amount of water didn't improve the yield of **2a** (Table 1, entry 12). Thus, the use of $In(OTf)_3$ (5 mol%) as the catalyst in dichloromethane at 20 °C with 2.0 equiv water added was found to be the most efficient condition for the formation of **2a** and the use of 1.2 equiv TfOH and 2.0 equiv water was the best condition for the synthesis of **3a**.

Table 1. Optimization of the Reaction Conditions.



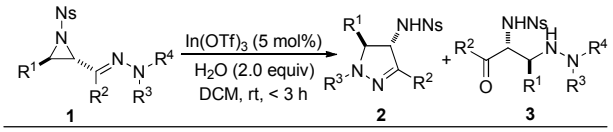
Ar = 4-ClC$_6$H$_4$ **1a** **2a** **3a**

entry	catalyst (mol%)	solvent	time	yield (%)[a] 2a	3a
1	$Sc(OTf)_3$ (5)	DCM	2 h	90	10
2	$Eu(OTf)_3$ (5)	DCM	2 h	81	18
3	$In(OTf)_3$ (5)	DCM	1 h	90	10
4	$Cu(OTf)_2$ (5)	DCM	3 h	76	18
5	$Bi(OTf)_3$ (5)	DCM	1 h	68	32
6[b]	BF_3•Et_2O (10)	DCM	1 h	0	0
7	TfOH (20)	DCM	5 min	69	29
8	TfOH (120)	DCM	5 min	trace	76
9	$FeCl_3$ (20)	DCM	3 h	trace	65
10	$In(OTf)_3$ (5)	toluene	1 h	64	< 10
11	$In(OTf)_3$ (5)	CH_3CN	1 h	59	< 10
12[c]	$In(OTf)_3$ (5)	DCM	2 h	82	< 10

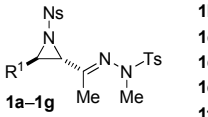
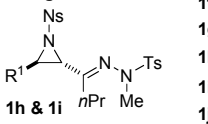
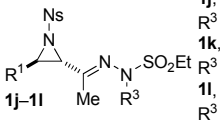
[a] Isolated yield. [b] No reaction. Ns = 4-NO_2PhSO_2, [c] 5.0 equiv H_2O was used.

We next examined the substrate scope of this reaction under the optimized conditions and the results are shown in Table 2. As for aryl-substituted *N*-(aziridin-2-ylethylidene)hydrazines (R^1 = Ar) **1b**–**1f**, the reactions proceeded smoothly to furnish the desired 2-pyrazolines **2b**–**2f** in 55–88% yields, along with the formation of a small amount of products **3** when aromatic rings bearing no groups or bearing fluoride or methoxy group (Table 2, entries 1–5). Changing the aryl-substitution R^1 to alkyl group (*n*-Bu), the desired 2-pyrazoline **2g** could be obtained in 85% yield without the detection of **3g** (Table 2, entry 6). Then *N*-(aziridin-2-ylbutylidene)hydrazines **1h** and **1i** were tested in the optimized conditions. It was found only trace amount of 2-pyrazoline **2h** was formed but 54% yield of **3h** was isolated (Table 2, entry 7). However, aziridine **1i** which bearing bromide group on its benzene ring gave 2-pyrazoline **2i** as the sole product in 92% yield, indicating electron-withdrawing groups on the benzene ring (R^1) inhibited the formation of product **3** (Table 2, entry 8). When an alkylsulfonyl group was introduced to the substrate instead of the tosyl group, the reactions also proceeded smoothly to give the corresponding 2-pyrazolines in good yields (Table 2, entries 9 and 10). Introducing an isopropyl group instead of methyl group (R^3), the corresponding product **2l** was formed in 79% yield (Table 2, entry 11). For methanesulfonyl group substituted substrate **1m**, 82% yield of **3m** was isolated and only trace amount of **2c** was detected (Table 2, entry 12). Comparing with substrate **1c**, it illustrates that the substituent of hydrazone moiety (R^4) also affect the outcome of the ring-opening.

Table 2. $In(OTf)_3$-catalyzed ring-opening reaction of aziridine **1**.[a]

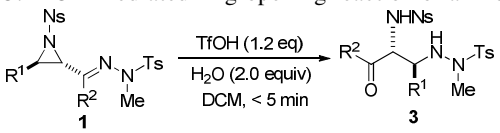


1 **2** **3**

entry	aziridine **1**		yield (%)[b] **2**	**3**
1		**1b**, R^1 = 4-$CF_3C_6H_4$	**2b**, 81	**3b**, 0
2		**1c**, R^1 = 4-FC_6H_4,	**2c**, 56	**3c**, 18
3		**1d**, R^1 = 2-BrC_6H_4	**2d**, 88	**3d**, 0
4	**1a–1g**	**1e**, R^1 = C_6H_5	**2e**, 79	**3e**, 10
5		**1f**, R^1 = 3-$MeOC_6H_4$	**2f**, 74	**3f**, 25
6		**1g**, R^1 = *n*Bu	**2g**, 85	**3g**, 0
7		**1h**, R^1 = C_6H_5	**2h**, trace	**3h**, 54
8		**1i**, R^1 = 2-BrC_6H_4	**2i**, 92	**3i**, 0
9	**1h & 1i**	**1j**, R^1 = 2-BrC_6H_4, R^3 = Me	**2d**, 98	**3j**, 0
10		**1k**, R^1 = 2,6-$Cl_2C_6H_4$, R^3 = Me	**2k**, 69	**3k**, 0
11	**1j–1l**	**1l**, R^1 = 2-BrC_6H_4, R^3 = *i*Pr	**2l**, 79	**3l**, 0
12		**1m**, R^1 = 4-FC_6H_4, R^2 = R^3 = Me, R^4 = Ms	**2c**, trace	**3m**, 82[c]

[a] Reaction conditions: $In(OTf)_3$ (5 mol%), H_2O (2.0 equiv), CH_2Cl_2, room temperature, < 3 h. [b] Isolated yield. [c] $Sc(OTf)_3$ (5 mol%) was used as catalyst.

Table 3. TfOH-mediated ring-opening reaction of aziridine **1**.[a]



1 **3**

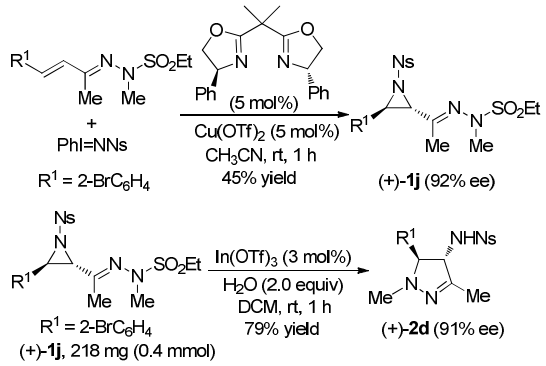
entry	**1**	product	yield (%)[b]
1	**1d**	**3d**, R^1 = 2-BrC_6H_4, R^2 = Me	52
2	**1e**	**3e**, R^1 = C_6H_5, R^2 = Me	64
3	**1f**	**3f**, R^1 = 3-$MeOC_6H_4$, R^2 = Me	60
4	**1g**	**3g**, R^1 = *n*Bu, R^2 = Me	0[c] (72)[d]
5	**1h**	**3h**, R_1 = C_6H_5, R^2 = *n*Pr	67
6	**1i**	**3i**, R^1 = 2-BrC_6H_4, R^2 = *n*Pr	0[c] (88)[d]

[a] Reaction conditions: TfOH (1.2 equiv), CH_2Cl_2, H_2O (2.0 equiv), room temperature, < 5 min. [b] Isolated yield. [c] Without detection of **3**. [d] Isolated yield of 2-pyrazoline **2**.

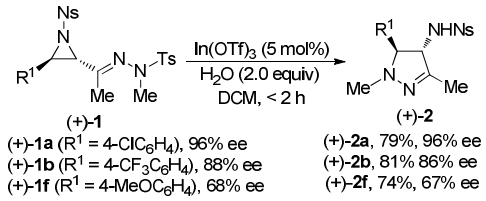
Furthermore, we investigated TfOH-mediated ring-opening of aziridines **1** and the results are summarized in Table 3. For aryl-substituted *N*-(aziridin-2-ylethylidene)hydrazines, the expected products **3d**, **3e** and **3f** were obtained in 52–64% yields under the standard conditions no matter electron-withdrawing or electron-donating groups on the aryl ring (R^1) (Table 3, entries 1–3). When R^1 was an alkyl group, no desired product **3g** was detected but 2-pyrazoline **2g** was isolated in 72% yield (Table 2, entries 4). For *N*-(aziridin-2-ylbutylidene)hydrazines **1h** and **1i**, the results were similar to the outcomes of $In(OTf)_3$-catalyzed ring-opening of **1h** and **1i** (Table 3, entries 5 and 6). These results further imply that the regiochemical outcomes of the ring-opening of aziridine **1** are significantly dependent on the aziridine substitution pattern and the hydrazon substitution pattern.

To make our strategy more attractive as a synthetic methodology, the protocol for the synthesis of chiral 2-pyrazolines via Lewis-acid catalyzed ring-opening of chrial aziridines was explored. Chiral *N*-(aziridin-2-ylmethylene)hydrazines could be easily synthesized with good enantioselectivities by copper bis(oxazoline) complex-catalysed aziridination of *N*-substituted hydrazones (e.g. (+)-**1j**, see: Scheme 2).[11] To our delight, aziridine (+)-**1j** was converted to 2-pyrazoline (+)-**2d** in 79% yield with 91% ee

even if the reaction was performed in an enlarged scale (0.4 mmol) (Scheme 2). Its absolute configuration has been determinde by X-ray diffraction (see Supporting Information). Other chiral aziridines (+)-**1a**, (+)-**1b** and (+)-**1f** were also tested in the reaction and the corresponding chiral 2-pyrazolines were obtained in good stereoselectivity (up to 96% ee) and good yields (up to 81%) (Scheme 3). In addition, the transformation of chiral aziridine (+)-**1f** to α,β-diamino ketone (–)-**3f** was also examined and the process had no variation on ee value (Scheme 4).



Scheme 2. Synthesis of chiral pyrazoline (+)-**2d**.



Scheme 3. Synthesis of chiral pyrazolines (+)-**2a**, (+)-**2b** and (+)-**2f**.

Scheme 4. Synthesis of chiral α,β-diamino ketone (-)-**3f**.

In conclusion, we have developed a simple protocol for the synthesis of substituted racemic and nonracemic 2-pyrazolines and α,β-diamino ketones through a SN_2-type ring-opening of *N*-(aziridin-2-ylethylidene)hydrazines or *N*-(aziridin-2-ylbutylidene)hydrazines. We found the electronic effects of the substrates govern the reactivity and thus the ring-opening process. Further applications of this novel type of functionalized aziridines are under way in our laboratory.

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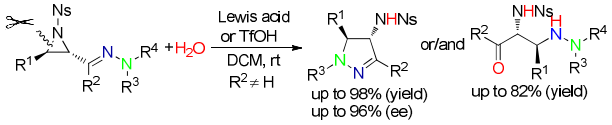
Facile Synthesis of 2-Pyrazolines and α,β-Diamino Ketones via Regioselective Ring-Opening of Hydrazone-tethered Aziridines



Lewis acid-catalyzed or trifluoromethanesulfonic acid-mediated SN_2-type ring-opening of *N*-(aziridin-2-ylethylidene)hydrazines or *N*-(aziridin-2-ylbutylidene)hydrazines forming 2-pyrazolines and α,β-diamino ketones

*Zhen Zhang, De Wang, Yin Wei and Min Shi**