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Direct Access to Tetrahydro[1,2]diazepinones from α,β-Epoxy-*N*-aziridinylimines via Anionic Rearrangement

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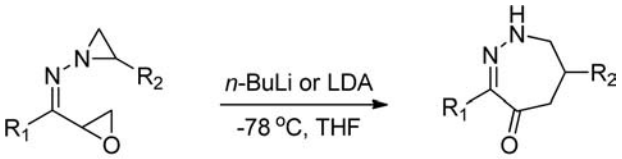
ABSTRACT



A novel one-step synthetic approach to tetrahydro[1,2]diazepinones via base-promoted rearrangement of α,β-epoxy-*N*-aziridinylimines, derived from α,β-epoxyketones and *N*-aminoaziridines, has been developed.

Aziridinylimines (**1a**) have emerged as a class of attractive and versatile chemical entities in modern organic synthesis. For instance, these compounds have been employed as the precursors of many reactive intermediates such as diazoalkanes, carbenes, and carbocations.[1] In addition, *N*-aziridinylimines have been used in a catalytic Shapiro reaction[2] and to produce geminal methylene radicals[3a−e] and trimethylenemethane (TMM) biradical intermediates,[3f] to effect further radical cyclizations. The TMM biradical chemistry resulted in facile construction of triquinanes and was applied to an elegant total synthesis of hirsutene.[3f] In addition, the conversion of α,β-epoxy-*N*-aziridinylimines (**1b**) into carbonyl compounds, alkynes, and nitrogen through fragmentation of diazo intermediates was discovered by Eschenmoser[4] and, almost simultaneously, by Tanabe.[5] Furthermore, anionic cyclization

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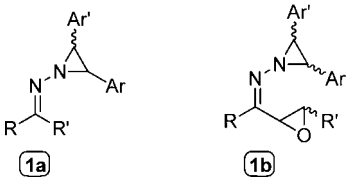
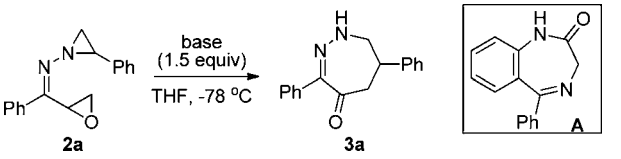
of *N*-aziridinylimines can be used to construct consecutive carbon−carbon bonds.[6]



Epoxyaziridinylimine **2a** was synthesized by dehydrative condensation[7] of the corresponding α,β-epoxyketone[8] and 1-amino-2-phenylaziridine.[9] During the course of our investigations related to the Shapiro reaction, we discovered that, upon treatment with 1.5 equiv of MeLi, *n*-BuLi, or lithium diisopropylamide (LDA) at −78 °C, **2a** underwent an unprecedented rearrangement to afford **3a** in a good to excellent yield (entries 6−8, Table 1). Compound **3a** features a novel and potentially biologically significant[10] 1,5,6,7-tetrahydro[1,2]diazepin-4-one core structure. *n*-BuLi and LDA seemed to be slightly better than MeLi as the base since they led to higher yields of the product. Neither anionic addition to the hydrazone moiety nor Shairo-type reaction took place under the reaction conditions. Note that the structural resemblance of **3a** to benzodiazepine[11] (**A**, Table 1) might endow the novel heterocyclic molecule **3a** with attractive pharmacological properties. Benzodiazepine derivatives are widely used as anticonvulsant, antianxiety, hypnotic, and anti-inflammatory agents.[12] Some benzodiazepines have been applied in photography as dyes for acrylic fibers.[9] In addition, pyrrolodiazepines are known as a family of substances with pronounced analgesic, anxiolytic, sedative, antiepileptic, antibacterial, and antifungal activities.[13] In contrast to the above-mentioned bases, employment of K_2CO_3, *t*-BuOK, LHMDS, or KHMDS resulted in no rearrangement reaction at all (entries 1−4, Table 1). In the case of NaOMe (entry 5) as the base, the starting material was completely consumed, while no isolable products were formed.

In order to explore the scope of the current method, epoxyaziridinylimines with various substituents attached to the benzene ring adjacent to the imino group (**2b**−**e**) or to that connected to the aziridine moiety (**2f**, **g**) were screened (Table 2). In addition, **2h** features a bulky ^{t}Bu group adjacent to the imino carbon. All substrates were treated with *n*-BuLi (method A) and LDA (method B), respectively. As for method A, regular addition has to be adopted; otherwise, the desired rearrangement products cannot be obtained at all. In contrast, the addition order is not significant for method B. In general, the rearrangement reaction takes place smoothly to afford the corresponding diazepinones **3** under the reaction conditions. However, for the brominated reactant **2e**, both debromination and

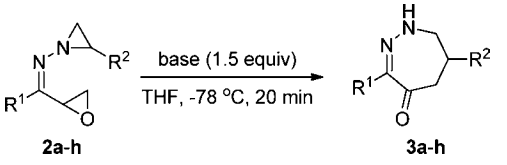
Table 1. Effect of the Base on the Rearrangement



entry	base	time (min)	yield[a] (%)
1	K_2CO_3	40	NR
2	*t*-BuOK	40	NR
3	LHMDS	40	NR
4	KHMDS	40	NR
5	NaOMe	20	complex
6	MeLi	20	86
7	*n*-BuLi	20	96
8	LDA	20	94

[a] Isolated yield.

Table 2. Base-Promoted Rearrangement of **2**



entry	R^1	R^2	method[a]	reactant/product	yield[d] (%)
1	Ph	Ph	A	**2a/3a**	96
2	Ph	Ph	B	**2a/3a**	94
3	*p*-MeC_6H_4	Ph	A	**2b/3b**	93
4	*p*-MeC_6H_4	Ph	B	**2b/3b**	98
5	*p*-$MeOC_6H_4$	Ph	A	**2c/3c**	86
6	*p*-$MeOC_6H_4$	Ph	B	**2c/3c**	94
7	*p*-PhC_6H_4	Ph	A	**2d/3d**	81
8	*p*-PhC_6H_4	Ph	B	**2d/3d**	96
9	*p*-BrC_6H_4	Ph	A	**2e/3a**[c]	57
10	*p*-BrC_6H_4	Ph	B	**2e/3e**	98
11	Ph	*p*-ClC_6H_4	A	**2f/3f**	91
12	Ph	*p*-ClC_6H_4	B	**2f/3f**	92
13	Ph	*p*-MeC_6H_4	A	**2g/3g**	75
14	Ph	*p*-MeC_6H_4	B	**2g/3g**	91
15	*t*-Bu	Ph	A	**2h/3h**	73
16	*t*-Bu	Ph	B[b]	**2h/3h**	81

[a] Method A: base = *n*-BuLi. Method B: base = LDA. [b] LDA (2 equiv), 40 min. [c] *n*-BuLi (2 equiv). [d] Isolated yield.

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rearrangement occurred and **3a** was formed in 57% yield when *n*-BuLi was used in the reaction (entry 9). In the case of **2h**, an excess amount of LDA (2 equiv) and a longer time (40 min) were necessary for the reaction to reach completion (entry 16). If *n*-BuLi was used as the base instead, **2h** behaved similar to other substrates although the yield of the product dropped to 73% (entry 15). It was noted that LDA gave higher yields of the products than *n*-BuLi for all substrates except the parent epoxyaziridinylimine **2a**, where method B proved superior due to the milder reaction conditions. The structure of **3e** was confirmed by X-ray crystallographic analysis (Figure 1).

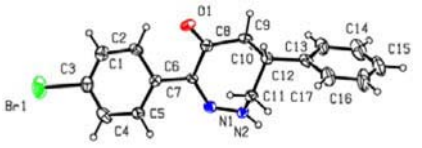
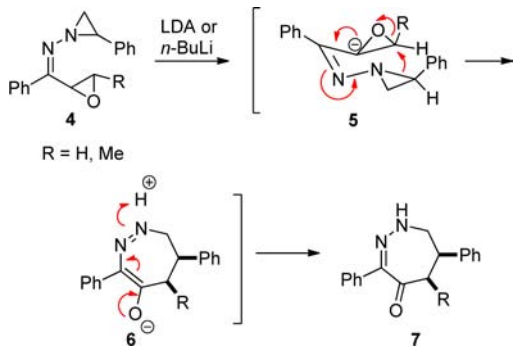


Figure 1. X-ray structure of **3e**.

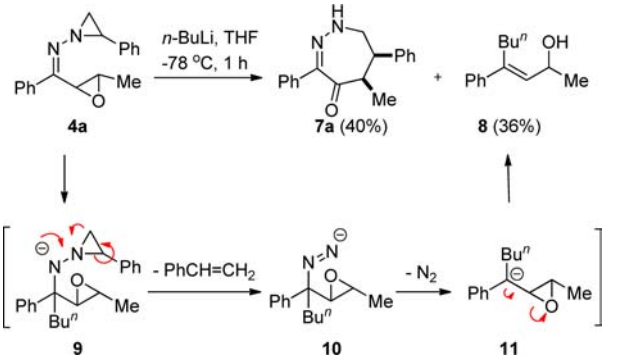
A plausible mechanism for the present transformation is proposed in Scheme 1. Epoxyaziridinylimine **4** is deprotonated to produce anion **5**,[14] which undergoes a rearrangement via a six-membered chairlike transition state (forming enolate **6**) followed by protonation, leading to the generation of ketone **7**.

Scheme 1. Proposed Mechanism



Furthermore, treatment of 1,2-disubstituted epoxide **4a** (Scheme 2) with *n*-BuLi afforded allylic alcohol **8** (36%) in addition to the seven-membered cyclic ketone **7a** (40%). The formation of **8** arises from addition of *n*-butyl anion followed by fragmentation involving loss of styrene and nitrogen gas. However, when LDA was used instead of *n*-BuLi as the base, neither **7a** nor **8** could be generated from the same substrate.

Scheme 2. Rearrangement of **4a**



The reactivity of **4** (Scheme 1) seems to be dependent upon the nature of the R substituent. With R = H, only cyclic ketone **7** is produced. When R = Me, the deprotonation/rearrangement process (Scheme 1) is dramatically retarded due to steric hindrance, allowing the formation of allylic alcohol **8** via tandem nucleophilic addition/fragmentation (Scheme 2).

In summary, we have developed a novel one-step synthetic approach to tetrahydro[1,2]diazepinones, featuring base-promoted rearrangement of α,β-epoxy-*N*-aziridinylimines. The seven-membered heterocyclic ketones thus generated may have potential pharmaceutical applications that deserve further exploration.

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Supporting Information Available. Experimental procedures, analytical data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.