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Corey-Chaykovsky Epoxidation of Twisted Amides: Synthesis and Reactivity of Bridged Spiro-epoxyamines

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The epoxide is one of the most useful functional groups in all of organic chemistry due to its easy formation and ready ring opening, often with a high level of stereo- and regiochemical control.[1] Numerous investigators have sought to leverage the utility of epoxides in synthesis by preparing α-heteroatom substituted versions. Alkoxy-substituted epoxides[2] are especially useful as intermediates in carbohydrate synthesis; they can be made from enol ethers using oxidants, like Oxone®, which lack an interfering nucleophilic component. However, the analogous aminoepoxides have received much less attention in this regard as their existence is compromised by nitrogen-assisted ring opening and polymerization. Very few examples of stable epoxyamines are known, and those that are tend to be highly substituted (Figure 1).[3] In this communication, we report a new strategy for the synthesis and stabilization of aminoepoxides and some preliminary studies of the chemistry of this class of compounds.

Since the decomposition pathways of aminoepoxides entail ring opening of the epoxide, it should be possible to stabilize the functional group by limiting the ability of the amino group to stabilize cations resulting from such pathways. One strategy to accomplish this would be to limit overlap between n_N and $\sigma^*_{C\text{-}O}$ through some sort of structural modification. This phenomenon is likely responsible for the stability of aziridine-containing aminoepoxides, due to the effect of ring strain on the n_N orbital (Figure 1a, first two examples). A different approach would utilize geometrical constraints that limit overlap between the nitrogen lone pair and the $\sigma^*_{C\text{-}O}$ of the epoxide. Herein, we report the realization of this strategy, demonstrating that bridged amides[4] can provide direct access to stable aminoepoxides. We also show that, as predicted and demonstrated by Stevens in the study with aziridine-derived epoxyamines,[3a-c] epoxyamines so obtained have a rich chemistry leading to a variety of useful and unusual structures.

Our investigations began with amide **1a**, readily available from an intramolecular Schmidt reaction (eq 1).[5a] We found that when **1a** was exposed to dimethylsulfonium methylide under Corey-Chaykovsky conditions,[6] the spiro-epoxyamine **2a** was formed in excellent yield, following chromatography. Importantly, the resulting aminoepoxide was stable to the reaction and isolation conditions, and could be stored over long periods of time without detectable decomposition. To the best of our knowledge, such a direct amide epoxidation reaction is without precedent. This transformation is evidence for the increased reactivity of the twisted amide carbonyl group, which arises from limited overlap of the lone pair of electrons of the amide nitrogen and the carbonyl systems.[4] In a similar vein, the decreased n_N-$\sigma^*_{C–O}$ delocalization is responsible for the stability of the aminoepoxide **2a**.

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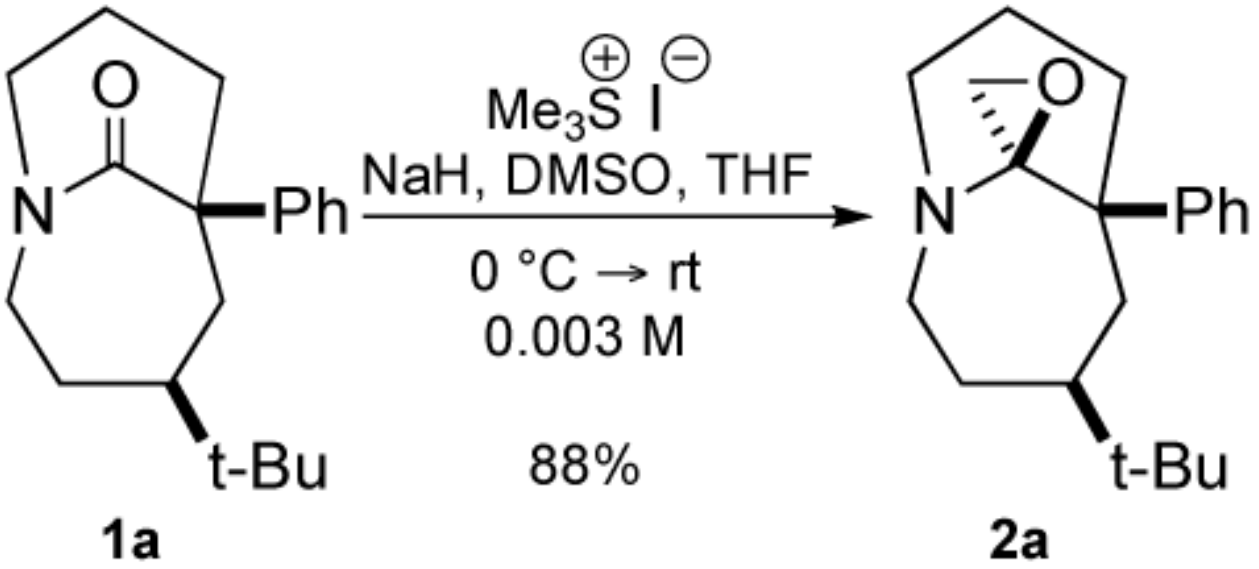
Supporting Information Available: Experimental details and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.



(1)

The epoxidation proved to be very dependent on reaction concentration (see Supporting Information (SI) for details). Even slight increases in the concentration led to the complete decomposition of the reaction components. In addition, monitoring of the reaction by NMR revealed a $t_{1/2}$ of ~ 5 h (cf. a $t_{1/2}$ of minutes for the ylide at rt[6a]). This is consistent with initial fast addition of the methylide to the amide carbonyl. We think that the resulting zwitterion exists in equilibrium with the ring-opened 9-membered heterocycle, which is destabilized due to a transannular interaction between the amine and ketone groups (Scheme 1).[5b] Notably, no monocyclic compounds or a reasonable alternative product from the ring-opened intermediate having a [4.3.2] ring system were observed.

We next examined the scope of this Corey-Chaykovsky reaction by varying the substituents and the ring systems of bridged amides (Table 1). Substitution with a heteroatom in the α position, and removal of the bulky *tert*-butyl group also permits isolation of the desired spiro-epoxyamine in very good yield (entry 2). Remarkably, even the sensitive α-unsubstituted bridged amide **1c**[5b] could be used to deliver isolable aminoepoxide (entry 3). Although the thiomethyl analogue was incompatible with the polar solvent system, resulting in the polymerization of the aminoepoxide product, we found that the use of modified conditions allowed for isolation of the sensitive epoxide **1d** (entry 4, SI). However, a 1-carbon-higher homologue of **1d** ([5.3.1] ring system) did not undergo the epoxidation reaction under these conditions (SI). Tricyclic amides could also be employed to access spiro-epoxyamines (entries 5-8). Importantly, increased steric hindrance close to the reactive amide bond did not diminish the facility of aminoepoxide formation (entry 8).[7]

Having established a general route to bridged spiro-epoxyamines, we probed the reactivity of this new class of compounds using epoxide **2a** as a test substrate (Scheme 2). In particular, we were curious how the reactivity of these bridged aminoepoxides would compare to that of traditional epoxides. Among the most synthetically useful reactions of epoxides are ring opening under acidic and reductive conditions.[1] Thus, exposure of **2a** to hydrochloric acid

resulted in the selective epoxide opening at the less substituted carbon, however in the case of aminoepoxide the ensuing collapse of the bicyclic ring system affords a chloromethyl ketone (**3a**). The reduction of **2a** resembled the opening under acidic conditions, involving the final collapse of the bicyclic aminal to the ketoamine **3b**. In this case, it is likely that the initially formed reduction product persists in the reaction mixture prior to workup, since no alcohol corresponding to **3b** was observed. We have determined that aminoepoxides also undergo reactions at nitrogen with preservation of the epoxide structure as exemplified by *N*-protonation with *p*-TsOH (**3c**).

We established that bridged spiro-epoxyamines participate in a number of Lewis acid catalyzed reactions not typical to traditional epoxides. For example, upon exposure of **2a** to Et_2AlCl conversion to aldehyde and subsequent alkyl transfer is observed (**3d**, see SI for more examples). This contrasts with traditional epoxides, which typically undergo direct alkyl transfer when exposed to alkylaluminum compounds.[8] Interestingly, although BF_3 is the most common Lewis acid used for the transformation of epoxides into carbonyl groups[9] (it has even been suggested[9a] that that "no epoxide is insensitive" to this reagent), **2a** was found to be inert to BF_3.

A number of thermal manipulations were briefly examined as well (Scheme 3, only products shown). When **2a** was subjected to KCN the bridged amide **1a** was obtained. Interestingly, the use of NaI under similar conditions afforded the bicyclic **3e** (see SI for proposed intermediates). In addition, when heated to higher temperatures **2a** undergoes 1,2-hydride shift to provide aldehyde **3f**, while exposure to NaN_3 resulted in the rearrangement to the primary amide **3g**. This reaction proceeds most likely via rearrangement to aldehyde, azide addition, and Schmidt reaction.

In conclusion, the Corey-Chaykovsky reaction permits the direct epoxidation of twisted amides. This method allows for preparation and isolation of bridged aminoepoxides, compounds which, as correctly suggested by Stevens 40 years ago, display reactivity divergent from traditional epoxides. The generality of this approach was demonstrated by the application to a range of bicyclic and tricyclic bridged amide substrates. Further investigation of the scope of this reaction and the application of the products in a target oriented synthesis is currently in progress.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

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(7). We have attempted the epoxidation using a number of other sulfur ylides, however we did not observe the formation of the corresponding epoxyamines so far. See SI for details

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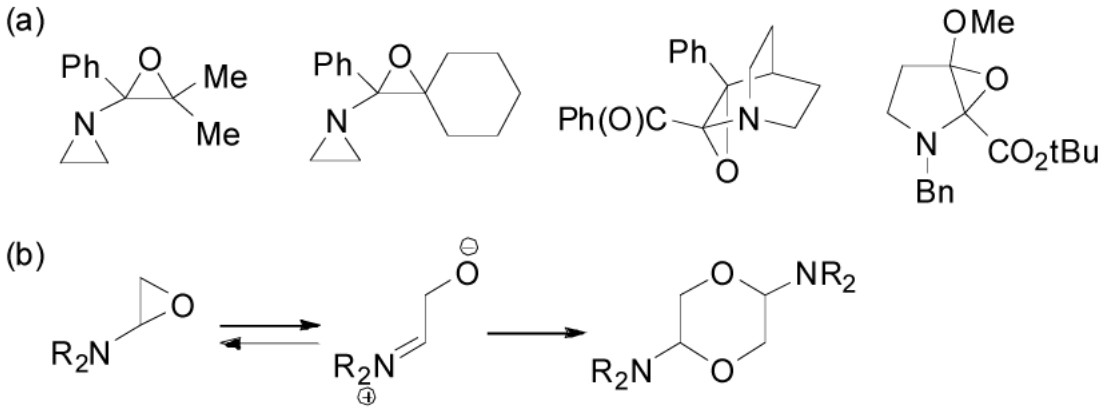
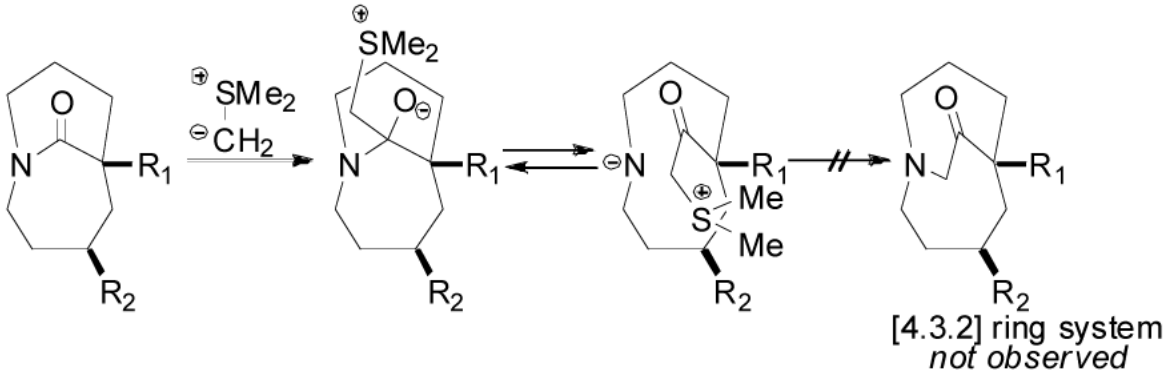
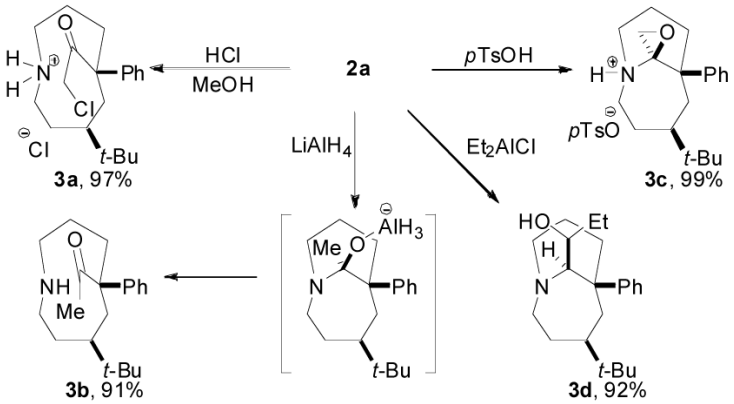


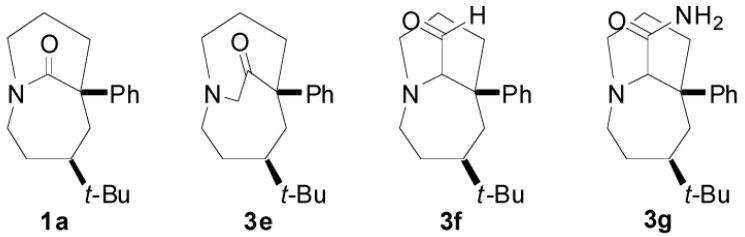
Figure 1.
(a) Examples of isolable aminoepoxides. (b) Common decomposition pathway of unmodified aminoepoxides.



Scheme 1.



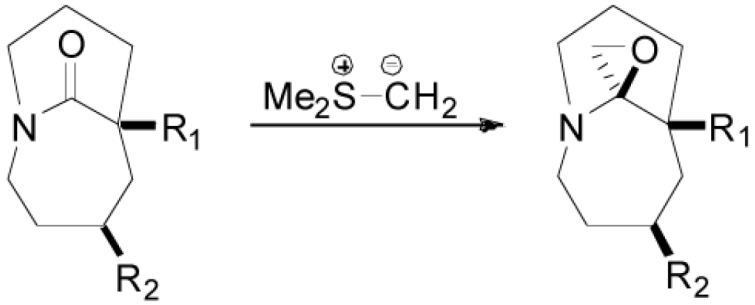
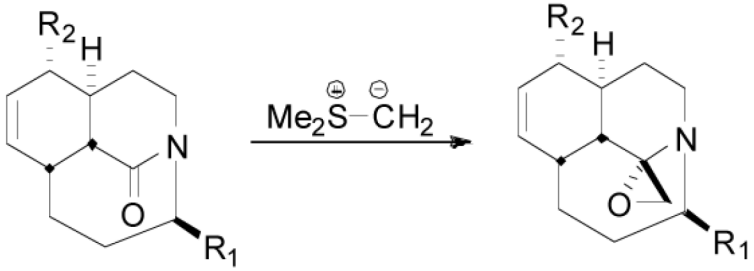
Scheme 2.
Transformations of **2a** under acidic and reductive conditions.



Scheme 3.
Transformations of **2a** under thermal conditions (only products shown).

Table 1

Scope of the Corey-Chaykovsky reaction.

entry	amide	epoxide	yield (%)
			
1	(**1a**) R_1 = Ph, R_2 = *t*-Bu	(**2a**)	88
2	(**1b**) R_1 = SPh, R_2 = H	(**2b**)	81
3	(**1c**) R_1 = H, R_2 = *t*-Bu	(**2c**)	41
4	(**1d**) R_1 = SMe, R_2 = H	(**2d**)	89
			
5	(**1e**) R_1 = H, R_2 = 4-BrC_6H_4	(**2e**)	70
6	(**1f**) R_1 = H, R_2 = $(CH_2)_2$OBn	(**2f**)	73
7	(**1g**) R_1 = H, R_2 = H[a]	(2g)[a]	77
8	(**1h**) R_1 = *i*-Pr, R_2 = H	(**2h**)	70

[a] compounds **1g** and **2g** lack the olefin.