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Development of the 1,2-Oxaza-Cope Rearrangement

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The Cope rearrangement is a fundamental reaction in organic synthesis with a rich history. Several variants of the parent reaction have been developed, and a prominent effect of proximal charge on the rate of the [3,3]-sigmatropic process has been investigated for the oxy-Cope[1] and 2-aza-Cope versions.[2] Several hetero-Cope rearrangement reactions have been described;[3] however, [3,3]-sigmatropic transpositions involving the nitroso group (eq 1) have not been reported.[4]

(1)

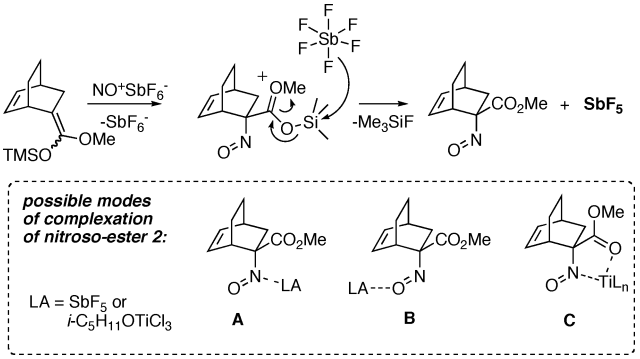
5,6-Dihydro-4*H*-[1,2]oxazines are relatively uncommon heterocycles, the full synthetic potential of which has yet to be explored.[5] In addition to their significance as pharmacologically promising heterocycles, the recent discovery of bioactive marine natural products containing oxazine rings has bolstered the need for their efficient preparation.[6] At present, we are aware of only one method that allows for a *direct* assembly of oxazine rings.[7] This method involves a highly regioselective inverse electron-demand hetero-Diels−Alder reaction of transient nitroso alkenes with olefins that are typically used in large excess. The cycloaddition reaction requires electron-rich olefins and 2,2′-unsubstituted nitroso alkenes to achieve practical yields, thus limiting its scope. Upon analysis, these requirements, along with the sense of regioselectivity observed in the hetero-Diels−Alder reaction, make it unsuitable for a direct application in the synthesis of known natural products containing oxazine rings.

In this communication, we describe another method for the direct stereoselective preparation of oxazines under mild conditions based on an unprecedented Lewis acid-promoted hetero-Cope rearrangement.

Isomerization of nitroso ester **2** to bicyclic oxazine **3** inspired by the structure of trichodermamides[6a] and penicillazine[6b] served as an excellent system for an initial study of the [3,3]-sigmatropic transposition. This type of bridged bicyclic ring system is a common template for other [3,3]-sigmatropic rearrangements[1−3] and, in this case, can be expediently accessed by nitrosation of readily available ester **1**. Thus, our approach required an efficient and diastereoselective generation of nitroso ester **2**.

While nitrosation of alkenes and carbonyl compounds is a classic reaction, nitrosation of enolates under mild conditions is much less established.[8] A preliminary investigation revealed that, while direct nitrosation of the lithium or potassium enolates of **1** was not productive, the corresponding trimethylsilyl and *tert*-butyldimethylsilyl ketene acetals were suitable intermediates. Nitrosonium hexafluoroantimonate and $TiCl_4$/isoamyl nitrite[9] were employed as nitrosating agents. The latter system generally provided superior results. Thus, under the optimum conditions, we obtained a 71% yield of the hetero-Cope rearrangement product **3**. The presence of a substoichiometric amount of an amine was required to prevent partial cleavage of the silyl ketene acetals to ester **1** and its diastereomer, presumably due to the presence of acid generated from the nitrosating agent in the presence of adventitious moisture. Both triethylamine and 2,6-*tert*-butyl-4-methylpyridine (DBMP) were suitable bases, although the use of the pyridine ensured cleaner and more consistent reactions.

Scheme 1. Proposed Involvement of Lewis Acid Coordination



Because we cannot expect the nitrosation of **1** to proceed with complete or even very high diastereocontrol,[10,11] the oxaza-Cope rearrangement of **2** must be rather efficient. In a control experiment, the TMS ketene acetals from **1** were treated with 1 equiv of nitrosyl chloride conveniently generated in situ from isoamyl nitrite and TMSCl.[12] The nitrosation occurred readily within 10 min at −50 °C; however, the nitroso ester did not undergo the [3,3]-sigmatropic transposition but rather slowly dimerized upon gradual warming to room temperature during 15 h. This observation indicates that the oxaza-Cope rearrangement is promoted by coordination of **2** to Lewis acid present in the reaction medium. When $TiCl_4$/isoamyl nitrite is employed, the Lewis acid is presumed to be *i*-$C_5H_{11}OTiCl_3$. With $NOSbF_6$, the Lewis acid is likely to be produced in situ as illustrated in Scheme 1.[13] Several modes of complexation of the nitroso group with metals are known.[14,15] The one represented by structure **A** is the most common, although the available information, particularly, regarding coordination to the titanium and antimony centers, is limited.

The representative group of substrates that have been subjected to our 1,2-oxaza-Cope rearrangement protocol under optimized reaction conditions is presented in Table 2. Generally, the nitrosation/[3.3]-shift sequence proceeds well with a variety of functionalized substrates, which are readily accessible by Diels−Alder methodology.[16] The results with the bicyclo[2.2.1]hept-2-ene system (entries 4 and 5) are particularly remarkable because (1) the diastereoselectivity of the nitrosation step was expected to be opposite to that desired for our process,[17] and (2) we observed that the rearrangement with these substrates occurred at significantly higher rates since the reactions were complete within 1 h at −78 °C. Notably, no epimerization at the C3 position in the potentially sensitive rearrangement product **3e** was observed. A methoxy group at the ring junction as in trichodermamides[6a] can be readily introduced (entry 3). In another example, the methyl enol ether

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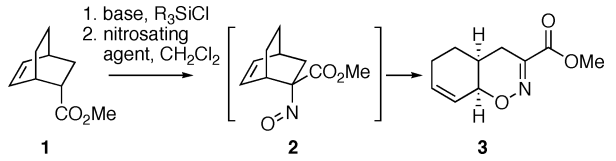
Table 1. Preliminary Screening of the Reaction Conditions[a]

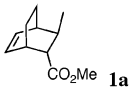
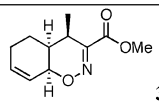
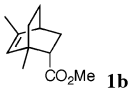
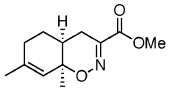
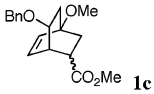
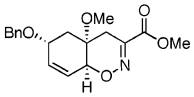
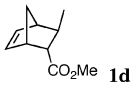
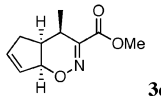
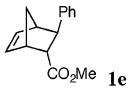
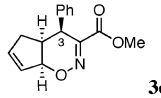
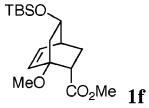
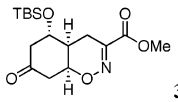
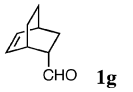
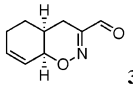


1 2 3

entry	R_3Si	nitrosating agent (equiv)	additive (equiv)	yield[b] (%)
1	TMS	$NOSbF_6/MeNO_2$ (1.2)	none	11
2	TMS	$NOSbF_6/MeNO_2$ (1.2)	Et_3N (2.0)	30
3	TMS	$NOSbF_6/MeNO_2$ (5)	Et_3N (5)	28
4	TBS	$NOSbF_6/MeNO_2$ (1.2)	Et_3N (2.0)	17
5	TBS	$NOSbF_6$/MeCN (1.2)	Et_3N (2.0)	19
6	TBS	$NOSbF_6$/MeCN (1.2)	propylene oxide (5) Et_3N (5)	5
7	TBS	*i*-$C_5H_{11}ONO/TiCl_4$ (1.0)	none	57
8	TBS	*i*-$C_5H_{11}ONO/TiCl_4$ (2.0)	none	50
9	TBS	*i*-$C_5H_{11}ONO/TiCl_4$ (1.0)	Et_3N (0.3)	64
10	TBS	*i*-$C_5H_{11}ONO/TiCl_4$ (1.0)	DBMP[c] (0.3)	68
11	**TMS**	***i*-$C_5H_{11}ONO/TiCl_4$ (1.0)**	**DBMP[c] (0.3)**	**71**
12	TMS	NOCl	DBMP[c] (0.3)	0

[a] All nitrosation reactions were performed at −45 to −15 °C, 1.5 h, ~0.15 M in CH_2Cl_2; 1.2 equiv of isoamyl nitrite was employed with $TiCl_4$ in all cases. [b] Isolated yield. [c] 2,6-Di-*tert*-butyl-4-methylpyridine.

Table 2. Tandem Nitrosation/1,2-Oxaza-Cope Sequence for Compounds **1a**−**g**[a]

entry	starting material[b]	product	yield,[c] %
1	 **1a**	 **3a**	80
2	 **1b**	 **3b**	75
3	 **1c**	 **3c**	62
4	 **1d**	 **3d**	50
5	 **1e**	 **3e**	67
6	 **1f**	 **3f**	60
7	 **1g**	 **3g**	35[d]

[a] See Supporting Information for experimental details. [b] Preparation of the substrates is described in Supporting Information. [c] Isolated yields. [d] Preliminary result, not optimized.

produced initially upon nitrosation/rearrangement of **1f** underwent hydrolysis under the reaction conditions to afford ketone **3f** as the isolated product. A preliminary study revealed that aldehydes can also be used as the substrates (entry 7).

In conclusion, we have developed a tandem nitrosation/oxaza-Cope rearrangement sequence that allows for a rapid construction of functionalized oxazine rings. The described process features the first examples of the [3,3]-sigmatropic rearrangement involving the nitroso group promoted by Lewis acid coordination. Further studies to determine the details of the mechanism of the rearrangement, especially the role of Lewis acids, and to expand the scope of the reaction are underway in our laboratory.

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

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