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Synthesis of unsaturated [1,2]oxazines by using sigmatropic rearrangements and the ring-closing metathesis reaction

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Abstract—Various substituted unsaturated [1,2]oxazines have been synthesized by using a [2,3]- or a [3,3]-sigmatropic rearrangement and a ring-closing metathesis reaction as key steps.

Due to the development of the well-defined and stable ruthenium catalysts **1** and **2** which exhibit high functional group tolerance,[1] the ring-closing metathesis reaction (RCM) has found a wide range of synthetic applications and has been extensively used to generate unsaturated carbocycles and heterocycles from readily available acyclic precursors (Fig. 1).[2]

During the course of our studies concerning the preparation and the evaluation of the synthetic potential of unsaturated cyclic compounds containing two heteroatoms,[3,4] the possibility of generating structures containing a nitrogen-oxygen linkage and in particular 3,6-dihydro[1,2]oxazines by RCM was considered. These compounds have been traditionally obtained by [4+2] cycloadditions of nitroso derivatives with conjugated dienes, although alternative routes have also been developed.[5] Thus, RCM was used for the synthesis of unsaturated heterocycles bearing the N–O linkage. The requisite dienic precursors were invariably prepared starting from the appropriate substituted hydroxylamine derivatives and the introduction of the ethylenic moieties was carried out according to three different methods. The first one involves sequential Mitsunobu reactions with allylic and homoallylic alcohols which enabled the introduction of one substituent α to both the oxygen and nitrogen atoms.[6] A second method relied on the addition of *N*-Boc hydroxylamine to π-allyl complexes of Ir(I) and Pd(0).[7] Finally, the third method involves sequential *N*,*O*-alkylations with unsaturated halides (S_N2 reactions) to prepare six- to ten-membered ring heterocycles bearing the N–O linkage, but no substituents were introduced α to the heteroatoms.[8]

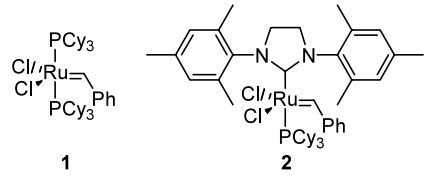
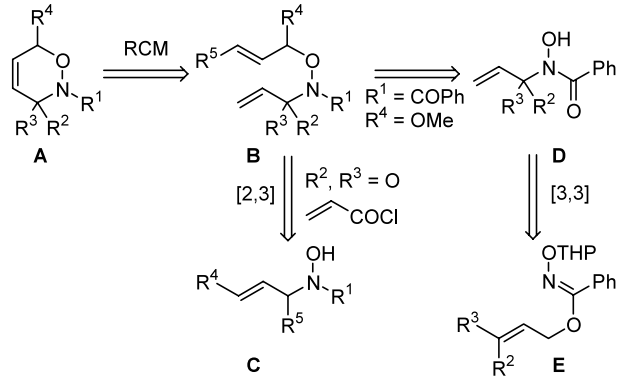


Figure 1. Ring-closing metathesis catalysts.

Due to these results, we would like to report here the synthesis of substituted unsaturated [1,2]oxazines of type **A** substituted by one and/or two substituents α to



Scheme 1.

Keywords: ring-closing metathesis; sigmatropic rearrangements; [1,2]oxazines.

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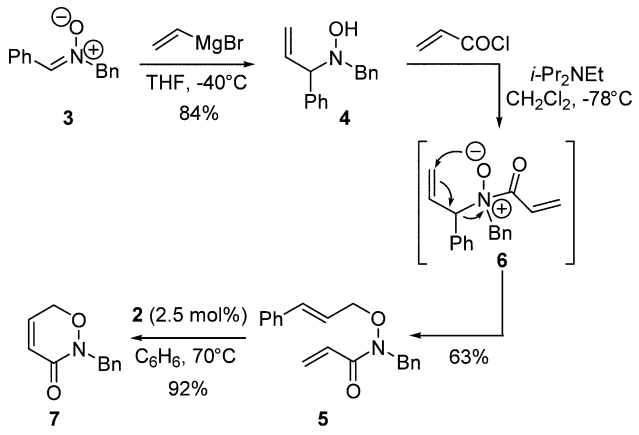
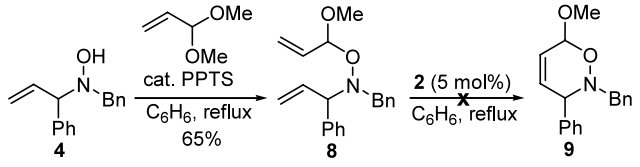
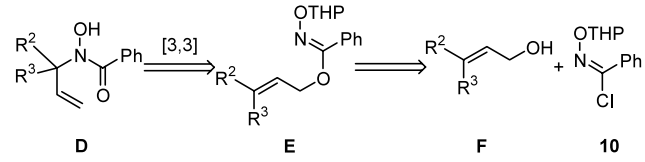


Scheme 2.



Scheme 3.



Scheme 4.

the oxygen and nitrogen atoms, involving a [2,3]- or a [3,3]-sigmatropic rearrangement to elaborate the dienic compounds and a RCM to build the heterocycles.

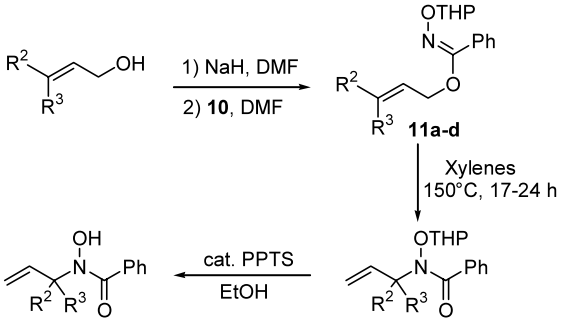
Oxazines of type **A** were seen as arising from a RCM applied to *N*,*O*-substituted unsaturated hydroxylamines of type **B** which could be synthesized following two strategies depending on their substitution pattern. A [2,3]-sigmatropic rearrangement of allylic hydroxylamines of type **C** induced by the presence of acryloyl chloride could provide access to monosubstituted hydroxylamines of type **B**. The formation of mixed acetals of allylic hydroxamic acids of type **D**, which could be obtained by a [3,3]-sigmatropic rearrangement of benzimidoates of type **E**, was proposed for preparing mono- or disubstituted oxazines (Scheme 1).

According to the first strategy, the addition of vinylmagnesium bromide to the *N*-benzylnitrone of benzaldehyde **3** afforded the corresponding allylic hydroxylamine **4** (84%). The acylation of the hydroxyl group of **4** with acryloyl chloride did not provide the *O*-acylated hydroxylamine compound but the *N*-acylated product **5** was obtained (63%). Its formation was ascribed to a [2,3]-sigmatropic rearrangement (related to the Meisenheimer rearrangement)[9] of the intermediate *N*-acryloyl-*N*-oxide **6** generated by treatment of **4** with acryloyl chloride in the presence of Hünig's base (*i*-Pr_2NEt). The [1,2]oxazin-3-one **7** was finally obtained in 92% yield when a RCM reaction catalyzed by Grubbs' catalyst **2** was applied to **5** (Scheme 2).

However, generalization of the [2,3]-sigmatropic rearrangement with other acylating reagents and various substrates did not give the desired products. Nor was the formation of the *O*-acylated product observed. In order to avoid the use of an acylating agent, the allylic hydroxylamine **4** was subjected to transacetalization with acrolein dimethyl acetal in the presence of a catalytic amount of PPTS in benzene. The mixed acetal **8** was obtained in 65% yield but this compound did not undergo a subsequent RCM reaction. Therefore, it was concluded that the nitrogen substituent of the hydroxylamine should be necessarily an electron-withdrawing group by analogy with the reported examples of RCM involving amines (Scheme 3).[2d]

As a carbonyl-containing electron-withdrawing group such as benzoyl ($R^1 = Bz$) was selected for the nitrogen atom of the hydroxylamines, it was therefore proposed to prepare the corresponding hydroxamic acids of type **D** by using the [3,3]-sigmatropic rearrangement[10] of the benzimidoates of type **E** which can be elaborated by condensation of various allylic alcohols of type **F** with the known benziminoyl chloride **10**[11] (Scheme 4). Moreover, this attractive approach towards the RCM hydroxylamine precursors would be complementary to those reported in the literature[6–8] which employ allylic alkylations or S_N2-type reactions and cannot accommodate the presence of two substituents α to the nitrogen atom.

Accordingly, various allylic alcohols were converted to their sodium alkoxides and condensed with the benziminoyl chloride **10** to afford the corresponding allylic benzimidoates **11a–d**. The [3,3]-sigmatropic rearrangement of these substrates was carried out in refluxing



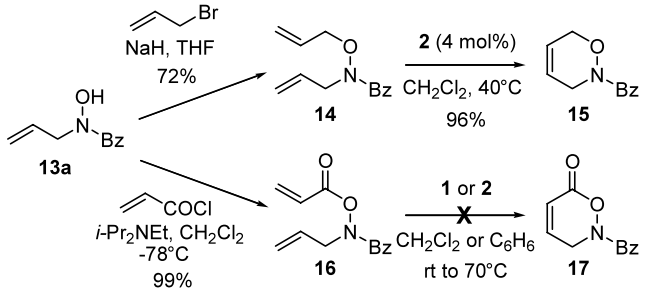
R^2	R^3		Overall Yield (%)
H	H	**13a**	79
Ph	H	**13b**	20
CH_2OBn	H	**13c**	51
CH_3	CH_3	**13d**	35

Scheme 5.

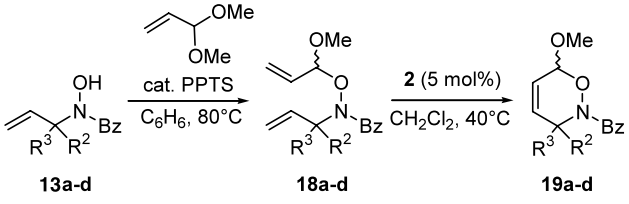
xylenes to afford the rearranged compounds **12a–d**. Deprotection of the hydroxyl group was readily achieved by treatment with a catalytic amount of PPTS in ethanol and the benzhydroxamic acids **13a–d** were obtained in modest to excellent overall yields (20–79%) (Scheme 5).

Whereas the allylic ether **14** readily obtained from **13a** was efficiently converted to the 3,6-dihydro[1,2]oxazine **15** (96%) upon treatment with catalyst **2**, the α,β-unsaturated ester **16** failed to cyclize to **17** whatever the catalyst or the conditions used (**1** or **2**, CH_2Cl_2 or C_6H_6, room temperature to 70°C). The presence of $Ti(O\textit{i}\text{-}Pr)_4$ as an additive did not bring about any improvement (Scheme 6).[12]

This problem was therefore circumvented by the formation of the mixed acetals[13] **18a–d** which were generated by transacetalization of the benzhydroxamic acids **13a–d** with an excess of acrolein dimethyl acetal in the presence of a catalytic amount of PPTS in benzene



Scheme 6.

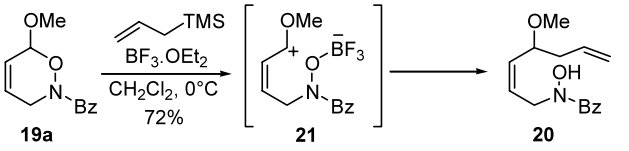


	R^2	R^3	Yield (%)	Yield (%)
a	H	H	82	97 (92)[a]
b	Ph	H	58	93
c	CH_2OBn	H	80	84
d	CH_3	CH_3	58	58 (80)[b]

[a] Yields in parentheses refer to the use of catalyst **1**

[b] Yields in parentheses refer to the use of C_6H_6 at 70°C

Scheme 7.



Scheme 8.

(58–82%). Indeed, the RCM of acetals **18a–d** proceeded smoothly and afforded the desired 6-alkoxy-3,6-dihydro[1,2]oxazines **19a–d** in satisfactory yields (58–97%) by treatment with catalyst **2** in dichloromethane at 40°C. Worthy of note is the fact that catalyst **1** was also efficient in the case of compound **18a** with no substituents α to the nitrogen atom. A much better yield was observed in the case of compound **18d** when the RCM was carried out in benzene at 70°C, due to the steric bulk of the *gem*-dimethyl group adjacent to the nitrogen atom (Scheme 7).

Although compounds of type **A** such as **19a–d** have been synthesized by other routes and subjected to a variety of subsequent transformations,[14] an unexplored possibility of functionalization involves the nucleophilic displacement of the methoxy group of the acetal moiety by nucleophiles in the presence of Lewis acids.[13] Contrary to our expectations, when **19a** was treated with allyltrimethylsilane in the presence of $BF_3{\cdot}OEt_2$ in dichloromethane at 0°C, the benzhydroxamic acid **20** was obtained in 72% yield. Its formation can be explained by the formation of the intermediate oxycarbenium ion **21** involving the cleavage of the endocyclic C–O bond,[15] which reacts with allylsilane to give **20**. Neither regioisomers, nor stereoisomers were detected in the crude reaction mixture (Scheme 8).

In conclusion, efficient syntheses of various substituted unsaturated [1,2]oxazines have been developed involving a [2,3]- or [3,3]-sigmatropic rearrangement and a RCM reaction as key steps. These strategies provided access to substituted unsaturated [1,2]oxazines which are complementary to and more versatile than the previously reported ones. Other subsequent transformations of this class of compounds are currently being investigated in order to expand the scope of this methodology in organic synthesis.

Acknowledgements

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