Lewis Acid Promoted Rearrangements of 1,3-Dioxolanyl-Substituted 1,2-Oxazines into Novel Products with 1,3,6-Trioxa-7-azacyclopenta[*cd*]indene Skeletons

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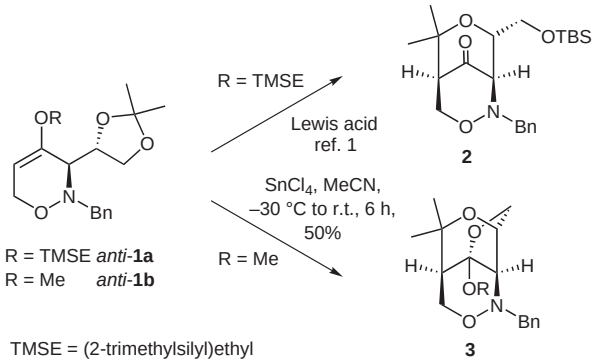
Abstract: Lewis acid promoted rearrangements of 4-methoxy- and 4-benzyloxy-substituted 1,2-oxazines *syn*-**1b** and *syn*-**1c** furnished novel tricyclic products **5** and **6**. A mechanistic rationale is suggested for the different rearrangement pathways depending on the configuration and the nature of the 4-alkoxy groups of the precursor 1,2-oxazines. Short period hydrogenolyses of these rearrangement products afforded tetrahydrofuranyl-annulated 5,6-dihydro-4*H*-1,2-oxazines **10** and **11**, whereas longer reduction times led to formation of tetrahydrofuran derivatives **14**, **15** and **16**, **17** in good yields.

Key words: heterocycles, 1,2-oxazines, furans, Lewis acids, rearrangements, 1,2-alkyl shifts, hydrogenations

We recently reported that enantiopure 4-(2-trimethylsilyl)ethoxy-substituted 1,2-oxazines such as *anti*-**1a** or *syn*-**1a** smoothly undergo Lewis acid promoted rearrangements providing bicyclic ketones **2** or **4** (Scheme 1 and Scheme 2).[1] These bicyclic 1,2-oxazine derivatives are versatile precursors for the synthesis of highly substituted tetrahydropyrans which can be regarded as carbohydrate mimetics. We now present the results of experiments involving related 1,2-oxazines with other 4-alkoxy substituents, which led to different types of rearrangement products.



Scheme 1 Lewis acid promoted rearrangement of 1,2-oxazines *anti*-**1a** and *anti*-**1b** leading to bi- or tricyclic 1,2-oxazine derivatives **2** and **3**.

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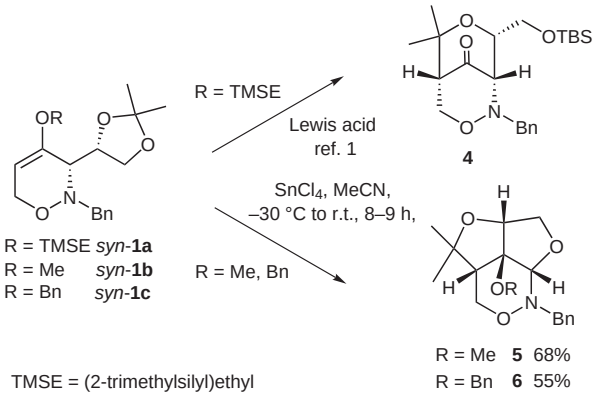
1,2-Oxazines *anti*-**1** and *syn*-**1** are easily available in a stereodivergent manner by reaction of lithiated alkoxyallenes with a D-glyceraldehyde-derived nitrone.[2] When 4-methoxy-substituted 1,2-oxazine *anti*-**1b** was exposed to tin tetrachloride the tricyclic acetal **3** was obtained in 50% yield rather than the expected product **2** (Scheme 1). Compound **3** can be regarded as an internally protected derivative of bicyclic 1,2-oxazin-4-one **2**. Constitution and configuration of **3** were proven by X-ray crystallographic analysis.[3]

The Lewis acid induced reaction of 4-methoxy-substituted 1,2-oxazine *syn*-**1b** followed a different, even more surprising pathway giving the novel product **5** with three annulated heterocycles (hexahydro-2*H*,4*H*-1,3,6-trioxa-7-azacyclopenta[*cd*]indene derivative) in good yield (Scheme 2).[4] This transformation was also performed with 4-benzyloxy-substituted precursor *syn*-**1c** which furnished the analogous tricyclic product **6** in 55% yield.



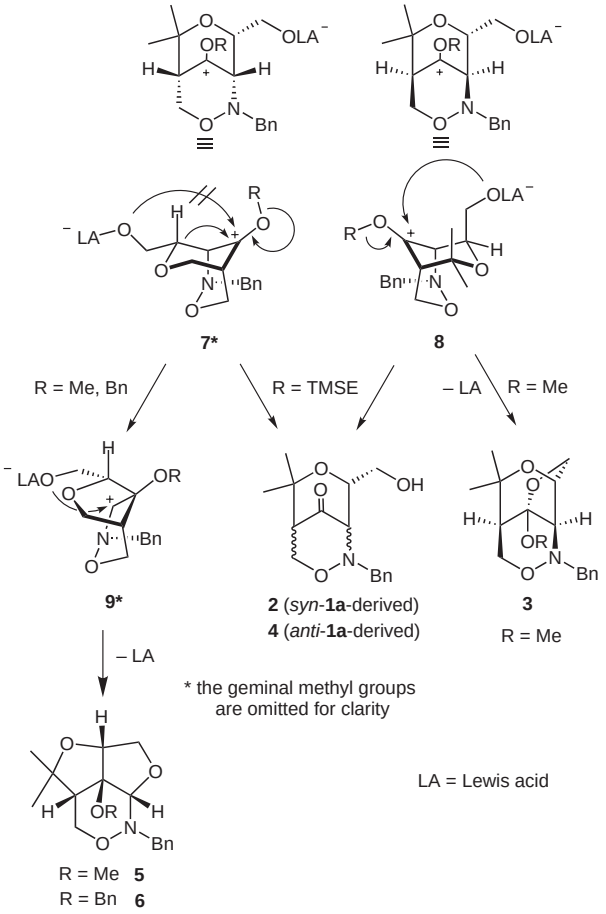
Scheme 2 Lewis acid promoted rearrangements of 1,2-oxazines *syn*-**1a**, *syn*-**1b**, and *syn*-**1c** leading to bicyclic product **4** and novel tricyclic compounds **5** or **6**.

The formation of the tricyclic products **3**, **5** and **6** can be rationalized by the following mechanisms. Coordination of the Lewis acid to the 'outer' dioxolane oxygen of *syn*-**1** or *anti*-**1**, subsequent ring opening of the ketal and intramolecular attack of the resulting stabilized carbenium ion onto the enol ether moiety of the 1,2-oxazine ring lead to stabilized carbenium ions **7** and **8** as crucial intermediates (Scheme 3). Depending on the nature of the 4-alkoxy group different pathways are possible. With 4-(2-trimethylsilyl)ethoxy substitution the bicyclic products **2** and **4**

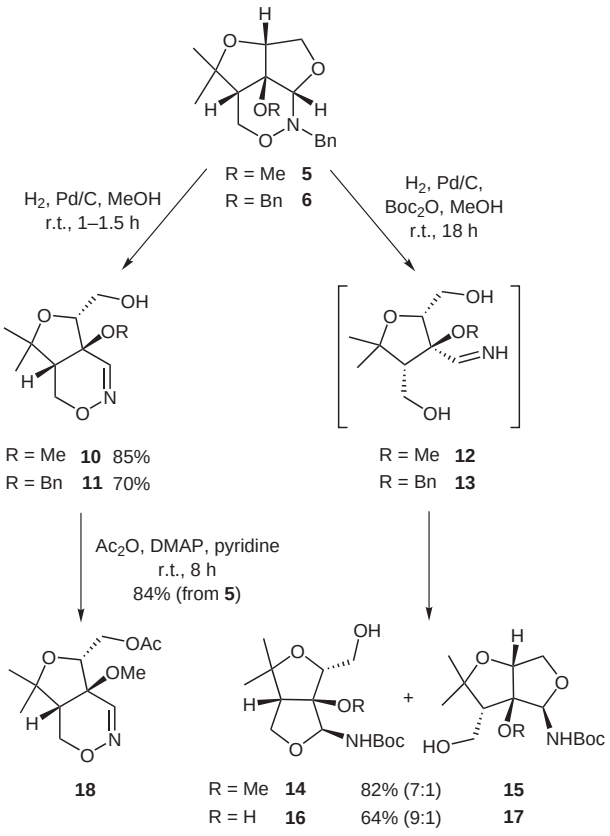
are formed, as this group allows for fast fragmentation of **7** or **8** into the carbonyl compound, ethylene and a Me_3SiX species.[1] On the other hand, the methoxy group is not capable of undergoing a similarly fast fragmentation and therefore alternative steps have to follow. In the case of carbenium ion **8** derived from *anti*-**1b** a direct cyclization under expulsion of the Lewis acid is geometrically possible and hence the observed tricyclic product **3** is formed. This pathway is not accessible in the *syn*-series for steric reasons. Instead, intermediate **7** suffers a 1,2-shift of an alkyl group[5] with retention of configuration resulting in new carbenium ion **9** which is now stabilized by the nitrogen rather than the oxygen atom. The significantly higher stability of the iminium-ion-type intermediate and possibly a steric relaxation are the driving forces for the rearrangement. Carbenium ion **9** is now able to smoothly react with the remaining oxygen under displacement of the Lewis acid, delivering compound **5** with a methoxy group at the central carbon atom of the tricyclic skeleton. The formation of compound **6** also follows this pathway, demonstrating that the 4-benzyloxy group does not undergo fragmentation into a benzyl cation at the stage of intermediate **7**.[6]

In order to prove the structure of rearrangement products **5** and **6** and to demonstrate their synthetic potential subsequent reactions were conducted. Depending on the time of a hydrogenolysis it is possible to induce debenzylation and N–O bond cleavage of 2-*N*-benzyl-protected 1,2-oxazines.[7] Hydrogenolysis of tricycles **5** and **6** first led to debenzylation at the nitrogen with subsequent ring opening of the *N*,*O*-acetal moiety affording novel 1,2-oxazines **10** and **11** with annulated furan rings in moderate to good yields (Scheme 4). Acetylation of **10** provided the corresponding 1,2-oxazine **18** which afforded suitable crystals for an X-ray crystallographic analysis.[3] This allowed not only unambiguous proof of the constitution and configuration of **18**, but also that of the structure of its precursor **5** thus supporting our mechanistic rationale as illustrated in Scheme 3.

Hydrogenolysis of **5** for a longer period in the presence of Boc-anhydride led to a 7:1 mixture of two constitutional isomers, the N-protected *N*,*O*-acetals **14** and **15** in good yield (Scheme 4). A similar result was obtained with tricyclic precursor **6**, however, now the *O*-benzyl group was also removed, which provided the two isomers **16** and **17** (ratio: 9:1) in moderate yield. Under these reaction conditions intermediate formation of **10** and **11** is followed by the cleavage of the N–O bonds to furnish dihydroxyimines **12** and **13**, respectively. These intermediates cyclize and, depending on which of the two primary hydroxyl groups is adding to the imine, either bicyclic isomers **14**, **16** or **15**, **17** are formed. The intermediates are



Scheme 3 Proposed reaction pathways for the rearrangements leading to compounds **2**, **4**, **3**, **5**, and **6**.



Scheme 4 Hydrogenolyses of rearrangement products **5** and **6** leading to 1,2-oxazine derivatives **10** and **11** or to tetrahydrofuryl annulated tetrahydrofurans **14**, **15** and **16**, **17**.

then in situ protected to generate the NHBoc moiety. In the case of 4-benzyloxy-substituted 1,2-oxazine **6** the benzyl group was also reductively removed giving compounds **16**, **17** with a free tertiary hydroxyl group.

In summary, a novel stereoselective Lewis acid promoted rearrangement of 1,3-dioxolanyl-substituted 1,2-oxazines was discovered, which led to enantiopure heterocyclic compounds with a complex skeleton. The resulting tricyclic products **5** and **6** are suitable precursors for further transformations as demonstrated by their reductive transformations into compounds such as **10**, **11** and **14**–**17**. Easily accessible intermediates such as 5,6-dihydro-4*H*-1,2-oxazines **10** and **11** should be excellent starting materials for addition reactions to the C=N double bond, thus leading to new enantiopure heterocycles. All these options will enhance the synthetic utility of 1,2-oxazines, which has already been demonstrated in several reports.[8]

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(4) **Typical Procedure, Conversion of *syn*-1b into 5.** $SnCl_4$ (0.78 mL) was added to a solution of *syn*-**1b** (0.65 g, 2.13 mmol) in MeCN (18 mL) at –30 °C. The mixture was allowed to warm up to 0 °C within 3 h, then stirred for an additional 5 h at r.t., H_2O (32 mL) was added and the mixture was extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4) and concentrated. The residue was purified by column chromatography (silica gel, hexane–EtOAc, 2:1) to give **5** (0.44 g, 68%) as a colorless oil.

Analytical Data for (4a*R*,7a*S*,7b*S*)-7-Benzyl-7b-methoxy-4,4-dimethylhexahydro-2*H*,4*H*-1,3,6-trioxa-7-azacyclopenta[*cd*]indene.
$[\alpha]_D^{22}$ +4.8 (*c* 0.42, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.35, 1.41 (2 s, 3 H each, Me), 2.15 (dd, *J* = 1.1, 5.1 Hz, 1 H, 4a-H), 3.42 (s, 3 H, OMe), 3.85 (dd, *J* = 4.6, 10.4 Hz, 1 H, 2-H), 3.99 (dd, *J* = 1.1, 12.3 Hz, 1 H, 5-H), 4.00 (dd, *J* = 1.0, 10.4 Hz, 1 H, 2-H), 4.01 (d, *J* = 14.2 Hz, 1 H, NCH_2), 4.08 (dd, *J* = 5.1, 12.3 Hz, 1 H, 5-H), 4.22 (d, *J* = 14.2 Hz, 1 H, NCH_2), 4.49 (dd, *J* = 1.0, 4.6 Hz, 1 H, 2a-H), 4.50 (s, 1 H, 7a-H), 7.24–7.40 (m, 5 H, Ph) ppm. IR (film): ν = 3055–3030 cm^{-1} (=C–H), 2970–2870 (C–H), 1605 (C=C). MS (EI, 80 eV, 150 °C): *m/z* (%) = 305 (44) $[M]^+$, 244 (100) $[M – OCH_3 – CH_2O]^+$, 214 (3) $[M – C_7H_7]^+$, 91 (57) $[C_7H_7]^+$. Anal. Calcd for $C_{17}H_{23}NO_4$ (305.4): C, 66.86; H, 7.59; N, 4.59. Found: C, 66.51; H, 7.27; N, 4.54. HRMS (EI, 80 eV, 150 °C): *m/z* calcd for $C_{17}H_{23}NO_4$: 305.16272; found: 305.16366.

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