Photochemical ring expansion reactions: synthesis of tetrahydrofuran derivatives and mechanism studies†

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The reaction mechanism of oxygen and sulfur ylide mediated rearrangements is even today a matter of debate. In this report, we describe ring expansion reactions of oxetane and thietane heterocycles that allow probing the underlying reaction mechanism under metal-free, photochemical conditions. This ring expansion proves highly efficient and allows the synthesis of tetrahydrofurans and thiolo heterocycles under mild and operationally simple reaction conditions. These studies reveal marked differences in the stereoselectivity of the ring expansion of oxygen or sulfur ylides, which were further investigated computationally. DFT calculations show that carbenes react under ylide formation and that the corresponding ring expansion reactions proceed via a diradical pathway. The different bond lengths in free oxygen or sulfur ylide intermediates cause the distinctive stereocchemical outcome.

Introduction

Ylides are important reaction intermediates in sigmatropic rearrangement reactions and serve as highly versatile synthons for the construction of complex molecular scaffolds. Despite significant advances over the past decades, the basic understanding of the rearrangement process of oxygen or sulfur ylides is still limited and currently available synthesis methods underpin a substantial difference of the reaction mechanism of sulfur vs. oxygen ylides: Both are typically accessed from unsymmetrically substituted (thio)ethers in the presence of a metal catalyst. The influence of the ether substitution pattern and the catalyst environment on the stereocchemical outcome of the rearrangement step can thus not be completely ruled out and both metal-bound or free ylide reaction mechanisms are currently under discussion. With the re-emergence of photochemical carbene transfer reactions in the past years, free ylides can now be efficiently accessed in a metal-free approach. However, the reaction types with these in situ generated free carbene intermediates are limited to X–H insertion, cyclopropagation, and few others. Substantially, the exploration and the development of stereoselective versions are challenging and highly desirable with this reactive species.

We envisioned that the formation of ylides starting from 4-membered ring heterocycles should provide achiral free ylide intermediates, or ylide intermediates bearing a stereocchemical information in the proximity of the ylidic bond and may thus serve as a tool to study differences in the reactivity of oxygen vs. sulfur ylides and to obtain evidence on the underlying reaction mechanism. Against this background, the rearrangement reaction of 4-membered ring heterocycles under photochemical, metal-free conditions is highly desirable as it provides an experimental probe to elucidate the reaction mechanism of rearrangement reactions. Combining these experimental findings with DFT calculations on this transformation would provide important insight into the reaction mechanism of photochemical Stevens rearrangements and allow the identification of differences between oxygen and sulfur ylides. Moreover, it opens up a pathway to selectively yield 5-membered, saturated heterocycles in an expedient fashion without over-reaction to larger ring sizes. This approach would streamline currently available multi-step protocols for tetrahydrofuran synthesis following a de novo 2-step photochemical synthetic strategy via Paterno-Büchi and consecutive ring expansion reaction (Scheme 1).

Results and discussion

We thus set out our investigations by studying the reaction of 3,3-dimethyl oxetane (4a) with methyl phenyldiazooacetate 5a under metal-free photochemical conditions and after a short optimization the tetrahydrofuran product 6a was obtained in...
complex oxetane heterocycles. The estrone derived furan 17 was obtained in good yield as a single diastereoisomer. Despite multiple ether functional groups, the PEGylated furan 16 was obtained in a diastereoselective ring expansion in good yield. This PEGylation is a common strategy to prevent drugs from entering the central nervous system and thus prevent centrally mediated side effects. We also investigated the ring expansion of a spirocyclic oxetane that allows a high-yielding, unprecedented, access to rare 6-oxa-2-azaspiro[3.4]octane building blocks (18) that find applications as herbicides\textsuperscript{1a} or S1P modulating agents. Limitations of the present methodology lie within amines (19) and free alcohols (22) that smoothly react under ylide formation and subsequent Stevens rearrangement (21) or cyclization (24).

Next, we studied the photochemical ring expansion reaction of 2-phenyl oxetane with aryl diazoesters. This reaction proceeded in good to very good yields and gave exclusive formation of the cis-2,2,3,3-tetrasubstituted furan heterocycle as the major product (d.r. > 20 : 1, Scheme 3a, 25a–i). The high diastereoselectivity of this rearrangement can be rationalized by diastereoselective ylide formation followed by a stereospecific rearrangement reaction that leads to the cis-substituted 5-membered ring heterocycle. In this context, we also studied different 2-phenyl substituted oxygen containing heterocycles, yet no ring expansion was observed when using an epoxide, tetrahydrofuran or pyran heterocycle.

Encouraged by the above observation, we set out to study the reaction of chiral phenyldiazoacetates to render this process diastereoselective and to enable an auxiliary-mediated stereoselective formation of the 5-membered heterocycles. In this context, we investigated chiral phenyldiazoacetates, based on (–)-borneol and (–)-menthol in the reaction with 3,3-dimethyloxetane. While only little selectivity was observed using the borneol derived phenyldiazoester (29), almost exclusive formation of furan 30 (d.r. > 20 : 1) was observed when using the (–)-menthol derived diazoester. This outcome can be rationalized by a highly diastereoselective ylide formation (33), which is a result of steric shielding of one face of the carbene by the isopropyl group of the chiral auxiliary. Similarly, 2-phenyl oxetane underwent a highly diastereoselective ring expansion reaction with (–)-menthol phenyldiazoacacetate to yield 31 essentially as a single isomer via 32 (Scheme 3c). In contrast to oxetane heterocycles, thietanes did not undergo diastereoselective ring expansion reactions. 2-Phenyl thietane underwent a chemoselective ring expansion reaction to yield the 2,2,3,3-tetrasubstituted thiolane, yet only little diastereoselectivity was observed (37, d.r. 1 : 1). Notably, in the case of 2-phenyl oxetane and 2-phenyl thietane oxidative workup procedures had to be performed to remove ring-opened by-products.

Similarly, only a minor chiral induction was detected when using (–)-menthol phenyldiazoacetate (Scheme 3d, 38).

In further studies, we examined the general applicability of this transformation and studied different 4-membered ring heterocycles as well as different diazoesters. In general, the substitution pattern of the aromatic ring of the diazoester had only little influence on the ring expansion reaction of 3,3-dimethyloxetane, oxetane and thietane and in all cases the desired products (Scheme 2, 6–18) were isolated in high yields. Investigations on different acceptor groups of the diazoalkane reaction partner revealed that the nitrile group was well tolerated (6c), while the corresponding trifluoromethyl substituted diazoalkane only underwent a decomposition reaction.

Notably, unsymmetrically substituted oxetanes gave the ring expansion product in a 1 : 1 mixture of both diastereoisomers (10–15). This 1 : 1 mixture can be explained by an unselctive ylide formation due to missing side-differentiation by the remote substituents leading to two diastereomeric ylides and thus the reaction product is generated as a 1 : 1 mixture of both diastereoisomers. To showcase the potential in functionalization of drugs or drug-like molecules, we investigated more.

excellent isolated yield; the best yield was obtained when using chloroform as solvent (Table 1, entry 2 and Table S1 in ESI). Not even trace amounts of further ring-expanded products, such as pyran or oxepane were observed. Importantly, when carrying out the reaction in the absence of light, no reaction was observed (Table 1, entry 3). When studying the parent oxetane and thietane heterocycles, the respective ring expanded products were obtained in good yields. Importantly, for the parent unsubstituted heterocycles the crude reaction mixture was treated with KMnO₄ for oxetane or Br₂ for thietane to remove ring-opened by-products resulting from ring opening reactions of the heterocycle. The importance of light mediated carbene transfer reactions is highlighted in studies using Rh₂(OAc)₄ as catalyst, which provided the ring-expansion products 6a and 8a in decreased yield, while for 7a a similar yield was observed.

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a single carbene transfer (35, 57%) when subjecting 5a with 2 eq. of 34 without formation of the double ring expanded product. In a second, consecutive ring expansion the bis-tetrahydrofuran 36 was obtained in good yield (72%). When subjecting 34 with an excess of diazoalkane (4 eq.) we could obtain exclusively the double ring expanded product 36 in 46% yield; in both cases only the meso-isomer was obtained in a highly stereoselective manner (Scheme 3b).

### Table 1  Reaction Optimization

| Entry  | Reaction conditions | Solvent | X, R | Yield\(^d\) (%) |
|--------|---------------------|---------|------|-----------------|
| 1      | 470 nm              | DCM     | O, Me (4a) | 71 (6a) |
| 2      | 470 nm              | CHCl\(_3\) | O, Me (4a) | 93 (6a) |
| 3\(^c\) | Dark reaction       | CHCl\(_3\) | No reaction |
| 4\(^d\) | 470 nm              | CHCl\(_3\) | O, Me (4a) | 68 (6a) |
| 5\(^e\) | 470 nm              | CHCl\(_3\) | O, H (4b)  | 70 (7a) |
| 6\(^f\) | 470 nm              | CHCl\(_3\) | S, H (4e)  | 73 (8a) |
| 7      | Rh\(_2\)(OAc)\(_3\) (1 mol%) | CHCl\(_3\) | O, Me (4a) | 43 (6a) |
| 8      | Rh\(_2\)(OAc)\(_3\) (1 mol%) | CHCl\(_3\) | O, H (4b)  | 61 (7a) |
| 9      | Rh\(_2\)(OAc)\(_3\) (1 mol%) | CHCl\(_3\) | S, H (4e)  | 55 (8a) |

\(^a\) Reaction conditions: 4a–c (0.4 mmol, 2.0 eq.) was dissolved in 1.0 mL of solvent and 5a (0.2 mmol, 1.0 eq.) was added by syringe pump over a period of 2 h and then stirred for another hour while irradiating with blue LEDs (3 W, 470 nm). Yields refer to isolated products. \(^b\) Reaction in the dark. \(^c\) Reaction with 1.0 eq. 4a and 2.0 eq. 5a. \(^d\) The reaction mixture was treated with aq. KMnO\(_4\) after completion of the reaction. \(^e\) The reaction mixture was treated with Br\(_2\) after completion of the reaction.

### Scheme 2  Substrate scope, applications for drug discovery and limitations of the photochemical ring expansion reaction.

- Ethyl ester instead of methyl ester. Reaction conditions: oxetane/thietane (0.4 mmol, 2.0 eq.) was dissolved in 1.0 mL of solvent and diazoalkane (0.2 mmol, 1.0 eq.) was added by syringe pump over a period of 2 h and then stirred for another hour while irradiating with blue LEDs (3 W, 470 nm). Yields refer to isolated products. 
- Treatment with aq. KMnO\(_4\) after completion of the reaction. 
- Treatment with Br\(_2\) after completion of the reaction.
The synthesis of oxetane heterocycles might pose a challenge, for broader applications of this ring expansion reaction, due to its lengthy and tedious synthesis.\textsuperscript{17} To overcome this challenge, we studied a two-step approach towards furan heterocycles via UV-light mediated Paternò–Büchi reaction of benzaldehyde and styrene to yield in a first photochemical reaction the oxetane heterocycle \textit{A} in moderate yield. When subjecting \textit{A} to the ring expansion reaction, we obtained the tetra-substituted tetrahydropuran \textit{B} as a single diastereoisomer and could thus showcase a convenient \textit{de novo} synthesis of substituted tetrahydropuran heterocycles from cheap commodity chemicals (Scheme 3e).

For a better understanding of the underlying reaction mechanism, we explored different mechanistic pathways of this ring expansion reaction by DFT calculations at the SMD(chloroform)//\textit{U}B3LYP/6-311+G(d,p)//SMD(chloroform)//\textit{U}B3LYP/6-31G(d) level. With regards to the blue-light-induced carbene transfer reactions, a free singlet carbene should be the (U)B3LYP/6-31G(d) level. With regards to the blue-light-induced ring expansion reactions with chiral diazoesters; (d) reactions of thietanes; (e) \textit{de novo} photochemical synthesis of tetrahydropurans. \textsuperscript{2} Treatment with aq. KMnO$_4$ after completion of the reaction. \textsuperscript{b} Treatment with Br$_2$ after completion of the reaction.

Scheme 3 Diastereoselective ring expansion of 2-phenyl oxetane and 2-phenyl thietane and investigations on other oxygen-containing heterocycles: (a) substrate scope of aryldiazoacetates; (b) multi-carbene transfer reactions for the synthesis of bis-tetrahydropurans; (c) ring expansion reactions with chiral diazoesters; (d) reactions of thietanes; (e) \textit{de novo} photochemical synthesis of tetrahydropurans. \textsuperscript{2}
steric repulsion due to the longer length of C–S bonds (1.86 Å and 1.76 Å) compared to C–O bonds (1.45 Å and 1.35 Å) in TSPh3.

Conclusions

In summary, we herein report on a simple photochemical carbene transfer protocol that allows the diastereoselective synthesis of valuable tetrahydrofuran and thiolane heterocycles via ylide mediated ring expansion reactions of oxetane heterocycles, including multi-carbene transfer reactions for the synthesis of bis-oxetanes (61 examples, up to 96% yield, up to >20 : 1 d.r.). We have demonstrated a two-step, photochemical approach via Paternò–Büchi reaction and subsequent ring expansion that now enables a simple, photochemical de novo access of tetrahydrofuran heterocycles. Moreover, mechanistic studies based on DFT calculations revealed that the reaction mechanism of both oxonium and sulfur ylide mediated ring expansion reactions proceed via a diradical pathway. Based on this strategy more applications towards the synthesis of 5-membered rings, multi-carbene transfer reactions and telescoped synthetic methodology are expected.

Conflicts of interest

There are no conflicts to declare.

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12 For details, please see the ESL†.

13 Oxetane and thietane heterocycles bearing a proton in the 3-position might undergo ring opening side reactions to give minor amounts of ring-opened by-products under both photochemical and metal-catalyzed conditions. To remove the alkene by-products and for ease of purification, oxidative workup with KMnO4 or Br2 was performed. This ring opening reaction did not occur in case of 3,3-disubstituted oxetane heterocycles.

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\begin{align*}
\text{by-product from} \\
\text{ring opening reaction} \\
X = O, S
\end{align*}
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