Domino Inverse Electron-Demand Diels−Alder/Cyclopropanation Reaction of Diazines Catalyzed by a Bidentate Lewis Acid

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Supporting Information

ABSTRACT: A domino inverse electron-demand Diels−Alder (IEDDA)/cyclopropanation reaction of diazines was discovered by applying electron-rich furans in the bidentate Lewis acid catalyzed IEDDA reaction. This process produces benzonorcaradienes in excellent yields with a low loading of a bidentate Lewis acid catalyst of 2 to 5 mol %. We demonstrate the broad applicability by 20 examples with different dienophiles and a variety of dienes. A detailed mechanism is proposed supported by DFT calculations.

Currently, the efficient use of resources, as well as the minimization of waste and production costs, is more important than ever. Therefore, an organic synthesis procedure where one could form several bonds in one sequence would lead to a tremendous benefit over usual stepwise procedures. Domino reactions represent a highly potential approach to address the above-mentioned criteria.1,2 Especially the incorporation of Diels−Alder reactions into Domino sequences allows quick access to molecular complexity.3 The inverse electron-demand Diels−Alder (IEDDA) reaction emerged in recent decades4,5 as a powerful synthetic tool featured in the preparation of complex molecules.6−12 In 2010 we reported the first catalytic activation of diazines by a bidentate Lewis acid for an IEDDA reaction.13 More recently also a silver catalyzed formal IEDDA reaction of phthalazine and siloxy alkynes was published by Rawal and co-workers.14 Furthermore, we showed the broad application spectrum of the IEDDA reaction of phthalazines with a variety of dienophiles, such as enamines and dihydrofurans.15,16

During the investigations of electron-rich furans 1a in the cataytic IEDDA reaction, we discovered a novel bidentate Lewis acid catalyzed domino IEDDA/cyclopropanation reaction (Scheme 1). The application of these dienophiles did not yield the anticipated annellated ring system. Instead the cycloaddition intermediate was further transformed to the cyclopropane annellated benzonorcaradiene. In Nature the benzonorcaradiene framework is for instance found in salvipuberulin.17,18 Additionally, such highly functionalized compounds containing small rings are useful building blocks for further transformations to quickly access complex target structures especially in the context of new drugs. Lately, two transition metal catalyzed reactions19,20 and a Diels−Alder reaction21,22 of a tungsten-tetra-ene complex have been published forming benzonorcaradiene with either no or a limited range of aromatic substituents.

We started our investigation with the reaction of phthalazine and differently substituted oxyfurans 1a−e, to display the scope of dienophiles in the Lewis acid catalyzed domino reaction (Table 1). Thereby, we found that all substrates did not show any reaction in the absence of catalyst even if heated to 160 °C for 1 day. Both steric and electronic factors play an important role in the reactivity of oxyfurans. The most reactive oxy-substituent is the trimethylsilyl (TMS) moiety due to polar effects followed by the methyl substituent, and the least reactive, the trisopropylsilyl (TIPS) group due to steric reasons (Table 1, entries 1−3). Oxyfuran 1a directly yielded the free acid 3a after purification on silica gel (SiO2), while 1b and 1c gave access to stable esters 3b and 3c.

The methyl substituent on the furan core accounts for another positive inductive effect while also adding steric bulk, which counteract depending on the position of the Me group. A methyl-substituent in the 3-position as in 1d is beneficial for the reaction allowing the reaction to proceed at lower temperature in a shorter time compared to the unsubstituted analog 1a (Table 1, entry 4). If the methyl substituent is placed in position 5, it seems to sterically interfere with the reactive site resulting in permitting the reaction with only the more reactive dichlorophthalazine 2b (Table 1, entry 5). No reaction was observed with less electron-deficient phthalazine 2a. This reactivity can be explained by the steric interference of the methyl residue in furan 1e with the Lewis acid 4 in complex 6 during the IEDDA reaction (Figure 1).

To demonstrate the scope of dienes, a variety of differently substituted diazines and trimethylsilyloxyfuran 1a have been employed in the Lewis acid catalyzed domino IEDDA/
The substituted diazines can be accessed by a one-pot synthesis from aldehydes developed in our laboratory.23 Moreover, we used alkyllithium chemistry to form dichloro- and difluorophthalazine 2b and 2d, also in one pot in good yields (see Supporting Information). Since in an IEDDA reaction an electron-deficient diene is preferred over an electron-rich one, the reactivity of substituted phthalazines decreases in the following order of substituents: F > Cl > MeS > Me > MeO (Table 2). Therefore, the reaction temperature can be lowered to 80 °C in the case of dichlorophthalazine 2b and has to be increased to 160 °C with a prolonged reaction duration in the case of dimethoxyphthalazine 2h. Even pyridopyridazine 2k and benzophthalazine 2l were reactive in this transformation. The complete desilylation of the labile trimethylsilyl ester was accomplished by slightly acidic elution on silica forming the carboxylic acid.

Furthermore, we were able to synthesize other TIPS-esters 3q−3s showing good applicability of 1c in the reaction of electron-poor phthalazine 2b, 2c, and 2e (Table 3). The reaction of methoxyfuran 1b with pyridopyridazine 2k gave the methylester 3t (Table 3, entry 4). These additional examples demonstrate not only the high atom economy merely producing N₂ as a side product but also the versatility of the procedure.

In cases of nonsymmetrical phthalazine substrates the IEDDA/cyclopropanation reaction produces mostly regioisomers of both Diels−Alder adducts in similar amounts.
Substitution in the 5–8-position on the phthalazine hardly influences the ratio of the regioisomers.

Mechanistic Considerations. The proposed catalytic cycle13,15 derived from Heuschmann and co-workers24–27 starts with the complexation of phthalazine 2 by the bidentate Lewis acid 4 to activate the diazine for the following IEDDA reaction. The cycloaddition of complex 6 with methoxyfuran 1b gives intermediary complex 7. The elimination of molecular nitrogen regenerates the Lewis acid catalyst 4, and the proposed dihydronaphthalene intermediate 8 is formed. Intermediate 8 rearranges to endo-cyclopropane 3′, and endo-to-exo isomerization28–30 leads to the final product 3b (Scheme 2).13,15 By the nature of the IEDDA cycloaddition, the domino reaction is diastereoselective resulting in only the exo-cyclopropane proven by 2D-NMR as well as X-ray analysis (see Supporting Information).

The intermediary formed dihydronaphthalene 8 represents an o-quinodimethane type, which is a well-known highly reactive intermediate.31–35 Recently, we were also able to trap such an o-quinodimethane intermediate by an intramolecular Diels–Alder reaction consecutive to the Lewis acid catalyzed IEDDA reaction.16 Stable o-quinodimethanes have been unambiguously characterized and expose a substantial double bond with some biradical character indicated by calculations.36,37 Dihydronaphthalene 8 reacting as tetraketraene species undergoes the final rearrangement to form the cyclopropanaphthalene 3. The same observations were made starting from a tungsten–tetraketraene complex.21,22 From dihydronaphthalene 8 we propose the occurrence of a sigmatropic rearrangement according to the Woodward–Hoffmann rules.38,39 A σ-bond is moved from position 1 to 3 on one side and from 1′ to 9′ on the other side (Scheme 3).

Simplified 3-atom and 9-atom fragments can be divided into their topologies. On the 3-atom fragment the migration of the σ-bond occurs on the opposite face and on the nine-membered fragment on the same leading to an ‘allowed’ antara-suprafacial [3,9]-sigmatropic rearrangement involving 4n (n = 3) electrons. Alternatively, the transformation can be described by the model according to Dewar40 and Zimmerman.41 This way one phase dislocation occurs, representing a Möbius topology which in the case of 4n electrons describes an ‘allowed’ transition state.

The antarafacial [3,9]-sigmatropic rearrangement of furan 8 to cyclopropane 3′ is supported via DFT calculations on the B3LYP level with a basis set of 6-31g(d,p) (Figure 2). The transition state was located in the gas phase resulting in a free energy of activation as low as $\Delta^2G^\ddagger(298) = 11.9$ kcal/mol and a

Table 3. Domino IEDDA/Cyclopropanation Reactions Forming Isolable Esters

<table>
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<tr>
<th>entry</th>
<th>2</th>
<th>product</th>
<th>t / T / yield</th>
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<td>3</td>
<td>100</td>
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high Gibbs free energy of reaction $\Delta G^\circ (298K) = -30.3 \text{ kcal/mol}$ (Figure 2; $-39.1 \text{ kcal/mol}$ for the ester in trans-conformation). The high thermodynamic driving force of the rearrangement results from the formation of the ester resonance and the aromatic stabilization which has been lost in the dihydroxynaphthalene intermediate 8 by the elimination of molecular nitrogen springloading the molecule and easily accounting for the strain energy of the cyclopropane formation. Despite the evidence for a rearrangement, an ionic mechanism cannot be ruled out.

In conclusion, we discovered a new method to produce cyclopropanated naphthalenes in a diastereoselective fashion by a bidentate Lewis catalyzed domino process starting with an IEDDA reaction proceeding with elimination of nitrogen and concluding with an antarafacial [3,9]-sigmatropic rearrangement. A wide variety of substrituents are allowed on the diazine as well as on the oxyfuran providing a very versatile entry to substituted aromatonorcaradiene in excellent yields with a low catalyst loading of 2–5 mol%. Further studies will address the selectivity issue in the reaction with unsymmetrical phthalazines, e.g. by using diboron species with different substituents as catalysts.

**ASSOCIATED CONTENT**

Supporting Information
Experimental details and characterization data for 2b, 2d, and all products 3, as well as X-ray data for 3g, 3l are available. This material is available free of charge via the Internet at http://pubs.acs.org.

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