# <u>Cramic</u> LETTERS

# Synthesis of Fused 3-Aminoazepinones via Trapping of a New Class of Cyclic Seven-Membered Allenamides with Furan

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**(5)** Supporting Information

**ABSTRACT:** Novel tricyclic tetrahydroazepinones were synthesized via an *in situ* Diels—Alder reaction of furan with cyclic allenamides. These reactive intermediates are the first examples of cyclic seven-membered allenamides and were prepared starting from N-(2-chloroallyl)-2-allylglycine derivatives via ring-closing metathesis followed by dehydrochlorination. The trapping of the intermediate cycloallene with furan occurred *endo*- and regioselectively and provided a convenient



entry into new building blocks for medicinal chemistry. The diastereoselectivity of the cycloaddition was confirmed using quantum chemical computations.

A llenamides have emerged in recent years as versatile and polyvalent building blocks in organic synthesis.<sup>1</sup> Since their discovery by Dickinson in 1967,<sup>2</sup> acyclic allenamides have gained attention as a more stable form of allenamines, which are prone to hydrolysis, polymerization, and isomerization.<sup>1</sup> Allenamides are attractive building blocks for the preparation of bioactive compounds and have been used in the synthesis of a variety of heterocycles such as pyrroles,<sup>3</sup> imidazolidines,<sup>4</sup> bicyclic guanidines,<sup>5</sup> furans,<sup>6</sup> benzazepines,<sup>7</sup> and cephams.<sup>8</sup> In addition, by introduction of chiral or directing substituents at the N-atom, regio- and stereoselective transformations have been described.<sup>9,10</sup> Regarding the use of the cumulene bond of allenamides as substrate for cycloaddition reactions, thermal [2 + 2]-cycloadditions,<sup>11</sup> Pauson–Khand-type [2 + 2 + 1]cycloadditions,<sup>12</sup> and [4 + 3]-cycloadditions after epoxidation of the allenamide have been described.<sup>13</sup> Allenamides are generally prepared via base-induced isomerization of propargylamides,<sup>2,14–16</sup> aminocyclization,<sup>17,18</sup> copper-catalyzed Nallenylation of amides,<sup>19</sup> and elimination reactions.<sup>20,21</sup>

In contrast to allenamides in which only the amide moiety is part of a heterocyclic ring system, analogous derivatives characterized by a cyclic *N*-allene system in small- to medium-sized rings have not been studied to date.<sup>22</sup> It is however known that allenes can be accommodated in smalland medium-sized ring systems, as demonstrated by various experiments where generated 1,2-cyclohexadienes are trapped or dimerized *in situ*.<sup>23</sup> The nine-membered and higher ring homologues are stable and can be isolated, while smaller ring systems are unstable at room temperature and spontaneously dimerize or decompose in the absence of trapping agents because of their high ring strain.<sup>24</sup> The combination of an allene and an amide group in a cyclic system has to our knowledge been described only for unconjugated systems.<sup>25</sup> In the present study, the generation of a new class of sevenmembered cyclic *N*-allenamides as starting material for new azepane derivatives was evaluated.

Because of our interest in new 3-amino-1,3,4,7-tetrahydro-2H-azepin-2-ones bearing fused (carbo- or heteroaromatic) rings for use in peptidomimetic chemistry,<sup>26</sup> a synthetic route toward related new nonplanar 3-aminoazepinones was envisaged by making use of cycloaddition reactions with seven-membered cyclic allenamides. Indeed, the synthesis of new nonplanar heterocyclic core structures with a considerable number of tetrahedral centers is of upcoming importance in medicinal chemistry.<sup>27</sup> In order to evaluate the possible formation of seven-membered allenamides via dehydrohalogenation,<sup>20,21</sup> a model study to efficiently synthesize the corresponding halogenated tetrahydroazepinones 4 (Scheme 1) was performed. N-Protected racemic allylglycine derivatives 1a were synthesized via a Claisen rearrangement of O-allyl-N-Cbz-glycinate<sup>28</sup> or by allylation of N-benzophenonimine-Oethylglycinate followed by imine hydrolysis, protection of the nitrogen with Boc<sub>2</sub>O, and hydrolysis of the ethyl ester.<sup>29</sup> While the amidation of pentenoic acid 1a with secondary amines is well described and proceeded uneventfully to give a mide  $\mathbf{5,}^{30}$ the coupling of the corresponding amino acid derivatives 1b

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Scheme 1



with secondary amines 2 proved to be more difficult. After screening a wide variety of coupling reagents, including DCC, EDC, DIC, PyBOP, TBTU, PyBrop EDC/HOAt, and DIC/ HOAt, the best results to give 3a-i were obtained by using HATU ((1-[bis(dimethylamino)methylene]-1H-1,2,3-triazolo-[4,5-b]pyridinium-3-oxide hexafluorophosphate) in CH<sub>2</sub>Cl<sub>2</sub>. Having in hand a variety of diene substrates 3a-i and 5, ring-closing metathesis, to give tetrahydroazepinones 4, was investigated. Because of the ease of synthesis, first metathesis experiments were performed using 4-pentenamide 5 as a substrate. However, in no case could the envisaged ring structure be obtained in good yields, and mainly starting material and decomposition products were observed. It is known that the introduction of extra substituents in the aliphatic part increases the viability for ring closure during  $\hat{RCM}^{31}$  Therefore, further studies were evaluated on  $\alpha$ -amino acid derivatives 3a-i. Unfortunately, metathesis reactions of 2bromoallylated derivative 3a using Grubbs' II catalyst or the related Umicore catalyst M2 did not result in acceptable yields of the corresponding brominated tetrahydroazepinone 4a.<sup>32</sup> However, when the same reactions were performed using nonhalogenated<sup>33</sup> or 2-chlorinated substrates, compounds 4 were obtained in good yields (Scheme 1). 6-Chloro-3-amino-1,3,4,7-tetrahydro-2*H*-azepinones 4d-i are a new class of easily available chlorinated azepinone derivatives that can be used as building blocks for further transformations.

The obtained chlorinated tetrahydroazepinone 4d was subjected to deprotonation reactions with t-BuOK in order to effect a dehydrochlorination. While no reaction was observed at 0 °C or below, even after 1 h, the reaction at room temperature gave rise to a complex reaction mixture. HPLC and LC-MS analysis of the obtained mixture revealed the presence of three major compounds (almost equimolar), of which the molar mass corresponded to dimeric compounds, probably formed via [2 + 2]-cycloaddition of an intermediate allene. Unfortunately, the isolation and separation of the obtained dimers were not successful via preparative HPLC. It is known that reactive allenes can dimerize easily to form a mixture of regioisomeric cyclobutane derivatives.<sup>23b</sup> To further study the plausible formation of intermediate allenamides, the deprotonation reaction was performed in deuterated THF and followed by NMR at different temperatures. Also in this case, it was observed that no reaction occurred at 0 °C, while after raising

the temperature to 25 °C, the starting compound was completely consumed within 30 min. Because no intermediate allenamide could be detected in the complex mixture at different stages during the reaction, high reactivity and rapid dimerization can be suggested. In the following experiments, the dehydrohalogenation reaction was performed in furan as a solvent. Although normal demand Diels–Alder reactions of allenamides with furans are quite rare, successful regioselective intramolecular examples have been described recently.<sup>34</sup>

We were pleased to observe the clean formation of only two cycloadducts in a 3:2 ratio after treatment of 4d with 4 equiv of *t*-BuOK in furan at room temperature during 18 h.<sup>35</sup> The possibility of a formation of the cycloadducts 7a via initial cycloaddition of furan to 4d followed by dehydrochlorination was excluded since no reaction occurred when 4d was treated with furan when no *t*-BuOK was present, even at elevated temperatures. It should be noted that also the nonhalogenated azepinone 4c did not give cycloadducts when treated with furan, with or without *t*-BuOK, and only starting material was recovered. X-ray analysis revealed unambiguously the relative stereochemistry of the obtained major and minor cycloadducts 7a and 7a' (see Supporting Information). The selectivity in formation of both regioisomers 7 and 7' via a normal electrondemand [4 + 2]-cycloaddition of allenes 6 (Scheme 2) with the





"Notes: (a) Ratio determined by HPLC. (b) Isolated yield after preparative HPLC. (c) Isolated yield of 7a-e after column chromatography.

electron-rich furan corresponds well with the difference in the electron-rich N-C=C bond and the more electron poor C=  $C-CH_2$  bond in 6. It should be noted that in addition to the novelty of the cyclic allene structure, the observed regioselectivity is another example of the very few reported normal Diels-Alder reactions with allenamides. In a first reaction of an intermolecular<sup>36</sup> and one recent intramolecular example,<sup>34</sup> an analogous regioselectivity is described. Next to the abovedescribed regioselectivity, the formation of only one racemic diastereomer of both regioisomers is remarkable. In theory, two diastereomers can be formed upon dehydrochlorination of 4d because of the axial chirality of the allene group. When taking diastereomer  $6a_{isomer 1}$  (Scheme 3) into account, four different approaches of furan can be considered (Figure 1). The structures depicted in Figure 1 are drawn according to DFT calculations (vide infra) performed on two related substrates 6x  $(R^1 = Moc, R^2 = Me)$  and **6**y  $(R^1 = Cbz, R^2 = Bn)$ . For both substrates 6x and 6y the allene  $C_5-C_6-C_7$  bending angle and





the  $H-C_5-C_6-C_7$  twist angle correspond well with literature values (see Supporting Information).<sup>24</sup> While approaches **A** and **D** (Figure 1) are not plausible because of steric hindrance, both an *endo-* and *exo*-cycloaddition (approaches **B** and **C**, respectively) seem probable. One might even suggest the *exo*-approach to be more favored because of steric reasons. However, it was surprising to observe only the *endo* adduct **7a** (via **B**) in which  $H_a$  and  $H_b$  adopt a *trans* configuration. An analogous stereochemical consideration can be made for the minor regioisomer (see Supporting Information). Despite the assumed higher steric hindrance, related *endo*-selectivity was observed by Hsung in an intramolecular acyclic allene furan cycloaddition.<sup>15</sup>

Although no explanation of this selectivity was reported, DFT calculations by Houk and Tolbert of the reaction of furan with 1,2-cyclohexadiene at the  $BLYP/6-31G^*$  level<sup>37</sup> revealed that also in this case the endo-approach is kinetically favored. Because of the observed trans relationship of H<sub>a</sub> and H<sub>b</sub> in 7a and the cis relationship of  $H_a$  and  $H_c$  in 7a', a furan cycloaddition using the other diastereomer of  $6a_{isomer 2}$ (Scheme 3) is unlikely. Indeed, in order to obtain the observed stereochemistry, a highly hindered approach of the furan ring (related to approach A, but with inversed stereochemistry at  $C_{3}$ , Figure 1) would be necessary. This suggests the selective formation of one diastereomer  $6a_{isomer 1}$  from the reaction of 4d with t-BuOK. In all, not only is the tandem dechlorination/ cycloaddition reaction regioselective (major:minor ratio of 3:2) and completely endo-selective, the observed stereochemistry also suggests a diastereoselective dechlorination. This combination is unprecedented, and the stereochemical pathways were rationalized by computational analysis (DFT) on the two model substrates 6x and 6y. Calculations were performed at the B3LYP/6-311G\*\* level. We were pleased to find that our model was able to correctly predict the experimental outcome of the cycloaddition. The major product (approach **B**, Figure 1) is both kinetically and thermodynamically favored. The calculated energy difference of transition state B from the other transition states C, D, and A (4.80, 8.26, and 38.00 kcal/ mol, respectively, for 6y, Figure 1) corresponds with the observed selectivity (a more detailed description of the computational analysis is included in the Supporting Information).

To evaluate the scope of this transformation, derivatives 4di were treated with *t*-BuOK in furan, and the major isomer was separated from the minor regioisomer (ratio M:m varied from 2:1 to 96:4) via column chromatography (Scheme 2). In addition, an N-acetylated analogue 4k was obtained via treatment of 4e with TFA, followed by reaction with acetic anhydride, and was treated with t-BuOK in furan to give 7e. It was observed that the dehydrochlorination-cycloaddition tandem reaction did not proceed in the case of unprotected amines. In this case only side products and starting material were found in the reaction mixture. We suggest that the presence of an electron-withdrawing group on the amine is necessary to prevent it from attacking the reactive allenamide. In an attempt to reduce the amount of furan used, reactions were performed using 1 equiv of furan in THF. In this case only dimers were found in the reaction mixture. Also the use of 2,3and 2,5-dimethylfuran and N-Boc-pyrrole did not result in cycloaddition under these reaction conditions. In order to elaborate the obtained stable tricyclic compounds 7 further into additional derivatives for medicinal chemistry, hydrogenation reactions were evaluated (Scheme 4).



The reaction of 7c and 7d under  $H_2$  atmosphere (2–4 bar) over catalytic amounts of Pd–C resulted in a simultaneous reduction of the Z-double bond and N-deprotection to give 8a and 8b. The reaction of the obtained amines 8 with aldehydes followed by treatment with NaCNBH<sub>3</sub> in methanol at pH 4–5 yielded new derivatives 9a, 9b, and 9c. It is clear that the enamide functionality remained intact even after hydrogenation and reductive amination protocols.

In conclusion, we were able to synthesize a novel class of tricyclic tetrahydro-aminoazepinones via an *in situ* Diels–Alder reaction of furan with cyclic allenamides. The reactive allenamide intermediates were prepared from substituted N-(2-chloroallyl)-2-allylglycinamide derivatives via ring-closing metathesis followed by dehydrochlorination by *t*-BuOK. The intermediate allenamides reacted *in situ* with furan in a regioselective (reaction at the terminal C=C bond of the allenamide), a diastereoselective (furan addition at the opposite



Figure 1. Four possible approaches in the Diels-Alder reaction of furan with 6y ( $R^1 = Cbz$ ,  $R^2 = Bn$ ). Substituents on 6y are omitted for clarity.

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face of the 3-aminosubstituent), and an *endo*-selective manner, suggesting a diastereoselective allenamide formation. The obtained cycloadducts were hydrogenated and derivatized into novel tricyclic heterocycles of interest as new core structures for medicinal chemistry purposes. DFT calculations of the Diels–Alder reaction of furan with allenamides **6** were in accordance with the experimental outcome of the reaction. The observed *endo*-approach is kinetically (17.64 vs 22.44, 25.90, and 45.64 kcal/mol) as well as thermodynamically favored as compared to the other possible approaches. A full exploration of cyclic allenamides is under current investigation and will be reported in due time.

# ASSOCIATED CONTENT

### **Supporting Information**

Spectroscopic data (<sup>1</sup>H and <sup>13</sup>C NMR spectra) for all new compounds, LC–MS data of crude mixtures, and X-ray data (CIF) for compounds 7a and 7a'. Additional computational data regarding 6x and 6y. This material is available free of charge via the Internet at http://pubs.acs.org.

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#### Notes

The authors declare no competing financial interest.

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