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First Synthesis of Medium-Sized Ring Allenyl Lactams

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Dedicated to Prof. Dr. Horst Kunz on the occasion of his 70th birthday

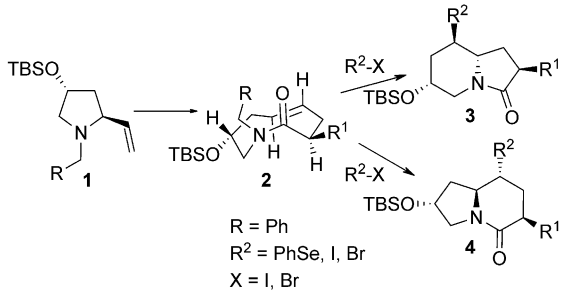
Keywords: Allenes / Rearrangement / Heterocycles / Lactams / Ring expansion

Medium-sized lactams bearing an axially chiral allene unit have been synthesized by using an aza-ketene Claisen rearrangement. Starting from 2-alkynylpiperidines or 2-alkynylazepines, ring enlargement enabled the highly diastereoselective formation of 10- or 11-membered lactams with a 4,5-allene subunit. X-ray analysis of the allenylazecinone showed the presence of a strained cumulated olefin system with a defined arrangement of the functional groups. The cyclic allenes were found to be stable upon heating up to 50 °C.

Introduction

Medium-sized unsaturated heterocycles with a defined configuration are useful key intermediates in the syntheses of natural and biologically active products. Earlier investigations from our laboratory indicated that zwitterionic aza-Claisen rearrangement enables the reaction of 2-vinylpyrrolidines **1** (Scheme 1) and Lewis acid activated ketenes to generate unsaturated azoninones **2**. A complete 1,3-chirality transfer gave rise to the formation of nine-membered ring lactams with defined stereogenic centers and *E* double bonds with defined planar chiral arrangements. Diastereospecific and regioselective transannular ring contractions delivered indolizidinones **3** and **4** with high selectivity and yields, which serve as key intermediates in natural product syntheses.[1]

The efficient generation and transformation of planar chiral cyclic olefins suggested that axially chiral cyclic allenes might be synthesized and transformed in a similar manner. We wondered whether we could rearrange a phenylethynyl-substituted pyrrolidine, piperidine, and azepane to build up 9-, 10-, and 11-membered ring model systems, respectively, bearing axially chiral allene units. In analogy to the planar chiral olefins of the azoninones, one face of each allene double bond should be shielded by the ring that could potentially undergo highly selective proceeding conversions. Focusing for example on 10-membered allenyl lactams, regio- and diastereoselective ring contractions should allow the formation of substituted 1-azabicyclo-



Scheme 1. Aza-Claisen rearrangement and regio- and diastereoselective ring contraction for the synthesis of indolizidinones with a defined configuration.[1]

[5.3.0]decanes and quinolizidines, respectively, which should serve as versatile key intermediates in the total syntheses of the alkaloids homoerythrina and lycopodium.[2]

Upon planning the syntheses of medium-sized ring allenyl lactams, the minimal ring size had to be explored. The smallest isolable cyclic allene is 1,2-cyclononadiene **7** (Figure 1), which is stable at room temperature and which dimerizes only upon heating.[3] As expected, smaller congener 1,2-cyclooctadiene **9** is too strained and undergoes rapid dimerization at room temperature.[4] In contrast, 1,2,5-cyclononatriene **8** and 1,2,5-cyclodecatriene **6** have been isolated and show thermal stability.[5] 1,2-Cyclodecadiene **5** is known to behave like a noncyclic 1,3-dialkylallene.[6] Re-

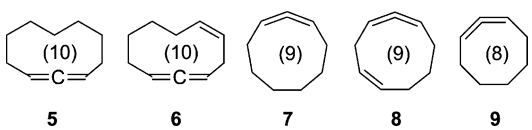


Figure 1. Eight- to 10-membered carbocyclic allenes.

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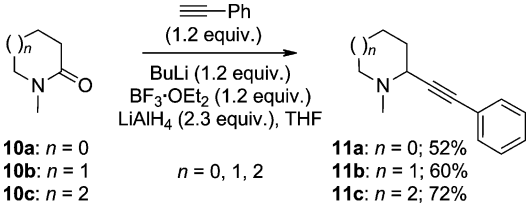
garding heterocyclic medium-sized rings, Tsuchiya reported the synthesis of an aza-nonadiene in moderate yield by using a Wittig-type 2,3-sigmatropic rearrangement of a 2-alkynylpiperidine.[7] The so-formed allene was reported to be unstable, suffering from rapid decomposition upon column chromatography. Until now, azadecadienes and undecadienes incorporating allenes are unknown.

The Claisen rearrangement of propargyl vinyl ethers are well-known reactions that allow the synthesis of allenes even in highly complex substrates.[8] Rearrangements of propargyl esters often involve in situ generated ester enolates. In most cases, an additional driving force is required to induce the reaction; thus, steric repulsions force the reaction towards the allene product.[9] To the best of our knowledge, allenes obtained from Claisen rearrangements are linear, unstrained systems. Upon synthesizing ring systems with constrained allene subunits, the zwitterionic aza-ketene Claisen reaction potentially offers enough driving force (charge neutralization) to form the allenyl lactam products in acceptable yield.

Results and Discussion

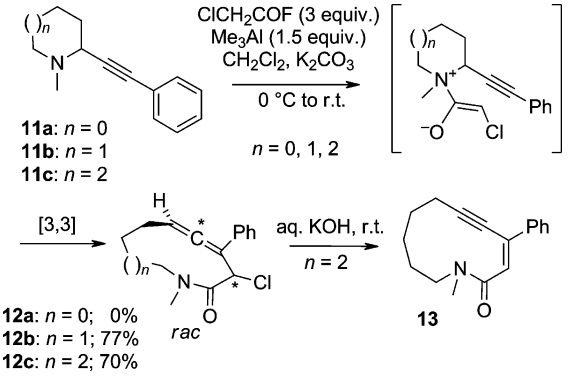
Initial investigations required simple and efficient access to cyclic 2-(2-arylpropargyl)amines.[10] Focusing on *N*-methyl heterocycles, most literature procedures used thiolactams as starting materials.[11] Initially, the thioamide function had to be activated in situ by *S*-methylation or -acylation. Then, a sequence of alkynyl anion addition and subsequent $LiAlH_4$ reduction allowed the generation of the *N*-methyl-2-alkynyl heterocycles in 67–80% yield. Without thioamide activation, the results had been reported to be poor.

In 1983, M. Yamaguchi and I. Hirao published a communication using lactams as starting materials to avoid the use of thiolactam congeners.[12] One-pot reactions of simple magnesium and lithium acetylide additions and subsequent $LiAlH_4$ reductions failed. In contrast, the use of preformed $BF_3{\cdot}OEt_2$-mediated alkynyl anions enabled the synthesis of the propargylamine products after a final aluminum hydride reduction. Careful optimization of the reaction conditions gave satisfactory results. Starting from pyrrolidone **10a** (n = 0), piperidone **10b** (n = 1), or azepinone **10c** (n = 2), phenylethynyllithium addition in the presence of $BF_3{\cdot}OEt_2$ delivered the intermediate iminium salt, which was immediately reduced with $LiAlH_4$ to give propargylamine product **11a**, **11b**, or **11c** in 52–72% yield overall (Scheme 2).[13] In several runs, *N*-methylpyrrolidine, -piperidine, or -azepine was formed as the major side product, indicating incomplete or reversible alkyne addition.



Scheme 2. Synthesis of propargylamines.

First ring expansion reactions of these propargylamines were carried out by using the in situ formed Lewis acid activated chloroketene. Treatment of 2-alkynylpiperidine **11b** and -azepane **11c** with chloroacetyl fluoride[14,15] and trimethylaluminum[16] in the presence of solid potassium carbonate smoothly delivered allenyl lactams **12b** and **12c** in 77 and 70% yield, respectively (Scheme 3). The NMR spectra of the products always displayed at least a double set of peaks because of the slow interconversion of the amide mesomers.[17] Because HPLC analyses always gave predominating peaks, the formation of one diastereomer with high selectivity seemed reasonable. In contrast, the ring expansion of 2-alkynylpyrrolidine **11a** failed, and no corresponding nine-membered ring lactam was found to form despite the complete consumption of the starting material. Ring strain of the product might have caused a low stability of the lactam, inducing rapid decomposition.



Scheme 3. Synthesis of allenyl lactams by zwitterionic aza-Claisen rearrangement.

The 10- and 11-membered allenyl lactams **12b** and **12c** were found to be stable at room temperature, and up to 50 °C no dimerization was observed. The major diastereomer (*rac*-3*R*,a*R*) of 10-membered allenyl lactam **12b** crystallized (Figure 2). X-ray data showed a slightly deformed allene (angle of 173.4°), which is in good accord-

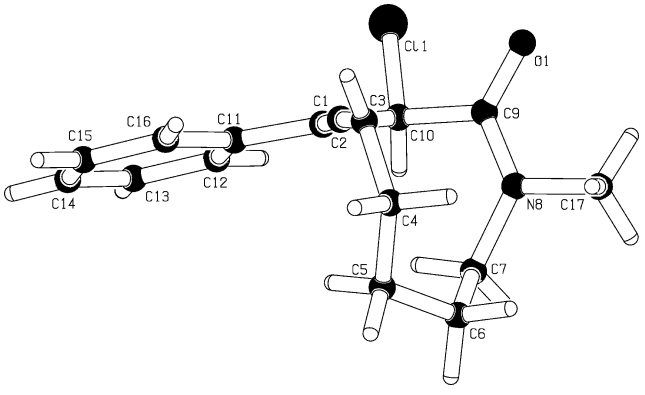


Figure 2. Crystal structure of *rac*-(3*R*,a*R*)-1-methyl-3-chloro-1-aza-deca-4,5-diene-2-one **12b**.

ance with the ring strain expected. The planes of the double bond π systems are almost rectangular (89.3°), whereas C3 suffered from a 4.5° distortion out of the C1–C2–C10 plane.

The nearly ideal coplanar arrangement of the vinyl C–H bond, the π orbital of the C4–C5 double bond, and the C–Cl bond caused some sensitivity towards bases. Upon washing the 11-membered lactam with an aqueous solution of KOH, 1,4-HCl elimination gave enyne lactam **13** in high yield.

Conclusions

In summary, treatment of 2-alkynylpiperidines and 2-alkynylazepines with chloroacetyl fluoride resulted in ring expansion to form 10- and 11-membered 3-chloro-4,5-allenyl lactams in >70% yield. Further investigations into the synthesis of optically active propargylamine derivatives, the application of the zwitterionic aza-Claisen rearrangement to generate enantiomerically pure allenyl lactams (via 1,3-chirality transfer), and the exploration of the scope and limitations concerning the substitution pattern of the compounds involved are in progress.[18]

Experimental Section

General Remarks: Reaction solvents were dried by standard procedures prior to use when necessary. All reactions containing moisture- or air-sensitive reagents were carried out under an argon atmosphere. ^{1}H NMR, ^{13}C NMR, and 2D (COSY, HSQC) spectra were recorded at room temperature with a Bruker ARX400 or AV400 spectrometer in $CDCl_3$ using the signal of residual $CHCl_3$ as an internal standard. IR spectra were recorded with a FTIR-400 plus spectrometer. High-resolution mass spectra (HRMS) were recorded with a Waters Q TOF Ultima 3 Micromasses spectrometer. Optical rotation were recorded with a Perkin–Elmer P 241 polarimeter using dichloromethane (Uvasol) as solvent. Column chromatography was performed on MN silica gel 60M from Macherey–Nagel (grain size: 0.040–0.063 mm). Progress of the reaction was monitored by thin-layer chromatography (TLC) performed on aluminum sheets precoated with 60F254 silica gel from Merck.

Synthesis of 2-(2-Phenylethynyl)pyrrolidine, -piperidine, and -azepane 11a–c: Under an atmosphere of argon, phenylethyne (5.76 g, 56.4 mmol, 1.2 equiv.) and dry THF (50 mL) were placed in a 500-mL, three-necked flask equipped with a mechanical stirrer. At –78 °C, *n*BuLi (1.6 M in toluene, 35.3 mL, 56.4 mmol) was added by syringe. The solution was kept at this temperature for 3 h until a white milky solution was obtained. $BF_3{\cdot}OEt_2$ (7.15 mL, 56.4 mmol, 1.2 equiv.) was injected, and after another 10 min lactam **10** (1 equiv.) was added. After raising the temperature to 0 °C, $LiAlH_4$ (4.1 g, 108 mmol, 2.3 equiv.) was added portionwise. The reaction mixture was diluted with diethyl ether to maintain an easily stirred suspension. After about 3 h, the reaction was found to be complete (careful TLC monitoring). Then, water (20 mL) was added dropwise to precipitate the aluminum salts. The mixture was extracted with diethyl ether (8 × 100 mL). The combined organics were extracted with aq. HCl (5 × 100 mL, 1 M). Then, the combined aqueous solutions were re-extracted with diethyl ether. With cooling, the remaining aqueous solution was neutralized by adding NaOH (s) until pH >8. After extraction with diethyl ether (150 mL, 2 × 50 mL, vigorous stirring) the combined organic phases were washed with water (2 × 50 mL) and dried ($MgSO_4$). Evaporation of the solvent gave propargylamines **11** (52–70%) pure enough for ring expansion studies. For spectroscopic data see ref.[10–12] and the Supporting Information

Preparation of Lactams 12b and 12c by Aza-Claisen Rearrangement: Under an atmosphere of argon, amine **11** (2 mmol) was dissolved in a suspension of K_2CO_3 (0.3 g, 2.2 mmol, 1.1 equiv.) in dry CH_2Cl_2 (20 mL). After cooling to 0 °C, freshly prepared chloroacetyl fluoride (0.42 mL, 6 mmol, 3 equiv.) was added, and the mixture was stirred at 0 °C. Then, trimethylaluminum (2 M in toluene, 3 mL, 6 mmol, 3 equiv.) was injected, and the mixture was stirred for 16 h, allowing the temperature to reach 20 °C (TLC monitoring). The reaction was stopped by quenching with water (0.5 mL). After dilution with additional CH_2Cl_2, drying was achieved by addition of $MgSO_4$. Then, the solvent was evaporated, and the crude lactams were purified by column chromatography on silica gel to give the products in 70–77% yield as mixtures of diastereomers (>6:1).

1-Methyl-3-chloro-1-aza-deca-4,5-diene-2-one (12b): Green crystals (light petroleum ether/EtOAc); m.p. 130–132 °C (decomp.). Double signal set due to *cis*/*trans* amide isomers (1:0.7) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.56–7.46 (m, 3.4 H), 7.41–7.32 (m, 3.4 H), 7.28–7.22 (m, 2 H), 5.96–5.76 (m, 2.5 H), 5.72–5.68 (dd, $^3J_{HH}$ = 6.8 Hz, $^3J_{HH}$ = 10.5 Hz, 0.8 H), 4.39–4.29 (0.6 H), 3.41–3.13 (1.5 H), 2.95 (s, 2 H), 2.92 (s, 3 H), 2.65–2.59 (m, 0.7 H), 2.54–2.41 (m, 1 H), 2.33–2.25 (m, 0.7 H), 2.21–2.09 (m, 0.7 H), 2.09–2.01 (m, 0.7 H) 1.99–1.90 (m, 1 H), 1.87–1.67 (m, 2.7 H), 1.67–1.52 (m, 2.4 H), 1.48–1.34 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 204.9 (C-sp), 167.2 (CO), 133.3 (C), 128.8 (CH), 128.6 (CH), 127.6 (CH), 126.4 (CH), 126.0 (CH), 107.2 (C), 104.9 (C), 99.4 (CH), 98.9 (CH), 60.4 (CH), 59.6 (CH), 50.7 (CH_2), 49.7 (CH_2), 37.1 (CH_3), 33.1 (CH_3), 28.5 (CH_2), 28.2 (CH_2), 27.8 (CH_2), 25.6 (CH_2), 25.3 (CH_2) ppm. HRMS (ESI): calcd. for $C_{16}H_{18}NONaCl$ $[M]^+$ 298.0975; found 298.0977. IR: $\tilde{\nu}$ = 3056, 2924, 2855, 1948 (w), 1660 (s, br.), 1596, 1577, 1495 (m), 1440 (m), 1399 (m), 800 (m), 773 (m), 693 (m), 611 (m) cm^{-1}.

CCDC-743967 (for **12b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1-Methyl-3-chloro-1-aza-undeca-4,5-dien-2-one (12c): Containing approximately 5–10% of the minor diastereomer/conformer. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.38 (m, 2 H), 7.40–7.33 (m, 2 H), 7.32–7.25 (m, 1 H), 5.91–5.85 (m, 1 H), 5.79–5.75 (d, $^3J_{HH}$ = 3.2 Hz, 1 H), 4.16–4.00 (m, 1 H), 3.33–3.14 (m, 1 H), 2.93 (s, 3 H), 2.60–2.44 (m, 1 H) 2.01–1.87 (m, 1 H), 1.81–1.64 (m, 4 H), 1.64–1.51 (m, 1 H), 1.49–1.30 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 203.6 (C-sp), 167.5 (CO), 134.2 (C), 128.5 (CH), 127.6 (CH), 126.7 (CH), 105.4 (C), 98.1 (CH), 60.0 (CH), 47.5 (CH_2), 32.4 (CH_3), 26.4 (CH_2), 25.2 (CH_2), 23.8 (CH_2), 23.2 (CH_2) ppm. HRMS (ESI): calcd. for $C_{17}H_{21}ClNO$ 290.1312; found 290.1323. IR: $\tilde{\nu}$ = 3056, 2930, 2862, 2242 (w), 1945 (w), 1715, 1636 (s, br.), 1493, 1444, 1400, 909 (m), 727 (s), 692 (s), 607 (s) cm^{-1}.

Supporting Information (see footnote on the first page of this article): Spectral data for known compounds and copies of the ^{1}H and ^{13}C NMR spectra.

Acknowledgments

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