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Controlling cyclizations of 2-pyrrolecarboxamidoacetals. Facile solvation of β-amido aldehydes and revised structure of synthetic homolongamide

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Abstract

Pyrrole N–C and C–C bond-forming cyclizations are described with 2-pyrrolecarboxamidoacetals **1**–**3** under standard acetal deprotection conditions (pTsOH/H_2O) and with methanesulfonic acid. Under the former, N–C cyclization provided fused bi- and tricyclic systems bearing five- or six-membered rings, while the latter produced six- and seven-membered C–C cyclized products. Furthermore, an alternative structure for homolongamide **10** is proposed and is based on the facile solvation of β-amido aldehyde **7**.

Keywords: longamide; β-amido aldehydes; oroidin.

Marine sponges are known to produce a variety of polycyclic secondary metabolites possessing a bromopyrrole moiety.[1] A common structural motif within the polycyclic framework consists of either a fused pyrrolopyrazine (N–C) or pyrroloazepine (C–C) connection. Examples of such natural products containing this structural feature can be found in agelastatin B[2] and 3-(*Z*)-bromohymenialdisine.[3] Early work by Johnson and coworkers has described the acid facilitated cyclization of 2-indolecarboxamidoacetals where N and C act as competing nucleophiles.[4] In this instance, mixtures of pyrazinoindole and pyridindole products (8:2) were observed under HCl/EtOH and H_2SO_4/Et_2O conditions. In the present communication, we report the controlled cyclizations of 2-pyrrolecarboxamidoacetals **1**–**3** for the selective synthesis of fused-bicyclic pyrrolopyrazine (N–C) and pyrroloazepine (C–C) derivatives. In addition, an alternative structure for synthetic homolongamide **10** is proposed and is based on the facile solvation of β-amido aldehyde **7**.

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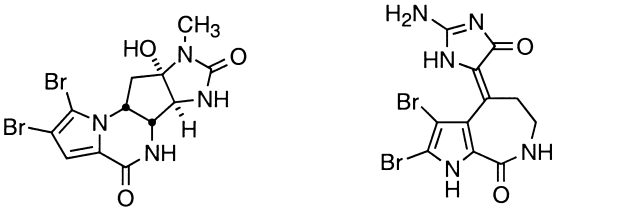
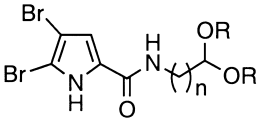
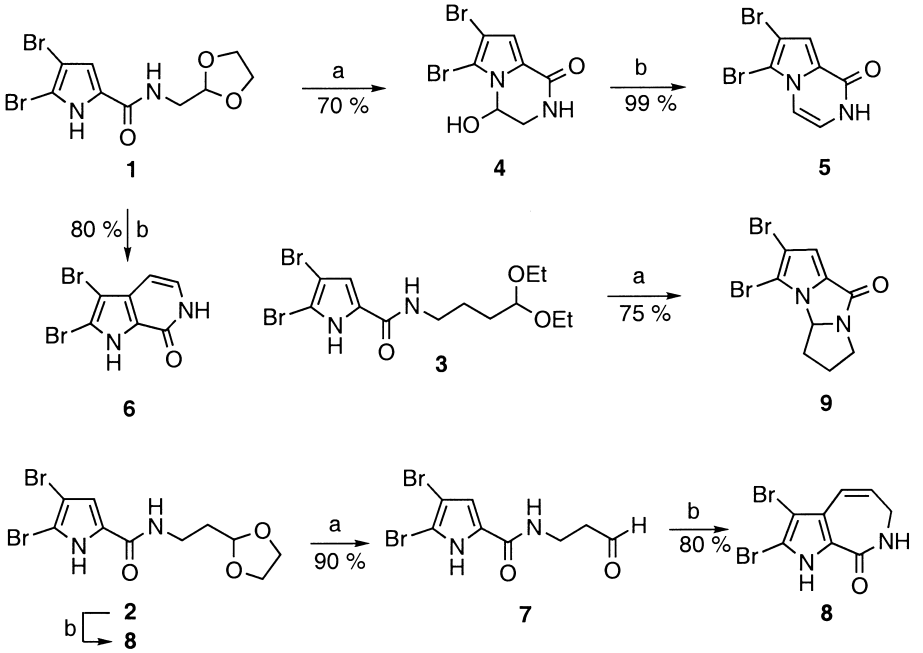




1 n = 1; R = -CH_2CH_2-
2 n = 2; R = -CH_2CH_2-
3 n = 3; R = -CH_2CH_3

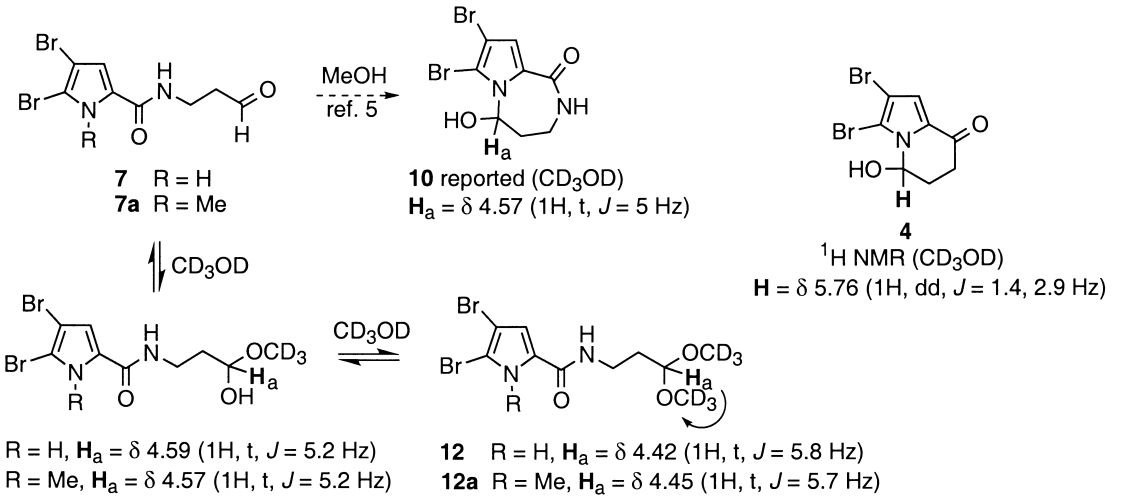
Pyrrolecarboxamidoacetals **1**–**3** were prepared by acylation of the corresponding amino acetals using 4,5-dibromopyrrolo-2-yl trichloromethyl ketone[6] in good yields. Deprotection of the acetal moiety of **1** under standard deprotection conditions (*p*TsOH, acetone/H_2O) produced longamide **4**, a metabolite from the Caribbean sponge *Agelas longissima*.[7] Under no circumstances could the corresponding aldehyde be isolated. Exposure of longamide **4** to methanesulfonic acid produced the dehydration product, pyrrolopyrazine **5**, in nearly quantitative yield (Scheme 1).



Scheme 1.

On the other hand, similar deprotection of acetal **2** under standard deprotection conditions (*p*TsOH, acetone/H_2O) produced aldehyde **7**[8] as the sole product. Unlike **1**, the corresponding N–C cyclization product of **2** was not observed under these conditions (vide infra). Upon treatment of acetals **1** and **2** with strong acid (methanesulfonic acid), cyclodehydration to the corresponding pyrrolopyridine **6** and pyrroloazepine **8**[8] was observed, respectively. From these results, it is evident that an important factor in the formation of the N–C bond is the ring size of the product formed. While cyclization to form the six-membered pyrrolopyrazine **4** readily occurs, the corresponding seven-membered ring closure is not observed. These results parallel related studies involving reactions of amines with aldehydes and ketones.[9] In the case of cyclic amines having ring sizes 7 to 9, ring opening is favored under conditions that permit equilibration between opened and closed forms. Treatment of acetal **3** under standard deprotection conditions produced tricyclic pyrrole **9**.[10] Finally, a complex mixture of compounds resulted when acetal **3** was subjected to methanesulfonic acid. Preliminary calculations on the heat of formation of isomeric N–C and C–C cyclized structures (e.g. **5** and **6**) reveal the latter to be approximately 10–18 kcal mol^{-1} more stable.[11]

While this work was in progress, a synthesis of longamide **4** by a route identical to ours was reported by Al Mourabit and coworkers.[5] The communication also reports the quantitative cyclization of aldehyde **7** to homolongamide **10** in methanol at room temperature. This result, however, is inconsistent with our previous studies with aldehyde **7**, which was found to readily undergo solvation in protic solvents.[12] Close examination of the chemical shift of the carbinol hydrogen reported for homolongamide **10**[5] (4.57 ppm) and longamide **4** (5.76 ppm) reveals a difference in chemical shift of approximately 1.2 ppm. This difference is significant when one considers the similarity of the two structures. Furthermore, the splitting pattern for H_a reported for homolongamide **10** (t, $J = 5$ Hz) is consistent with an acyclic structure. Upon careful examination of aldehyde **7** in CD_3OD, we found that **7** readily undergoes rapid addition of CD_3OD to give hemiacetal **11**[13] (complete conversion after ~2 min of mixing), which was followed by formation of acetal **12**.[13] This conclusion is supported by HMBC correlations in **12**, which were observed between the methine hydrogen (H_a) and the corresponding methoxymethyl carbons of



Scheme 2.

the acetal moiety. Furthermore, pyrrole N–Me aldehyde **7a** was prepared[14] and its ^{1}H NMR data obtained in CD_3OD revealed an analogous pattern. First, solvation to hemiacetal **11a**[15] was followed by conversion to acetal **12a**.[15] Since aldehyde **7a** is not expected to undergo intramolecular cyclization, these results suggest that the previously reported ^{1}H NMR data for structure **10** is in better agreement with hemiacetal **11**. It is well known that α-amido aldehydes, such as the serine protease inhibitor leupeptin, readily undergo hemiacetal formation under neutral conditions.[16] To the best of our knowledge, this is the first demonstration of the facile solvation properties of β-amido aldehydes and further studies will be reported in due course (Scheme 2).

In summary, the construction of two types of ring systems can be easily accomplished by altering the acidity of the reaction conditions. The cyclization is sensitive to ring size of the resulting product and is potentially useful for the construction of substructures within the oroidin alkaloid family. In addition, the structure reported as homolongamide **10** was found to be in better agreement with hemiacetal **11**, which is readily formed by solvation of β-amido aldehyde **7** in methanol.

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10. Compound **9**: ^{1}H NMR ($CDCl_3$) δ 1.62 (1H, dtt, J = 8.4, 12.1, 15.0 Hz), 2.13–2.40 (2H, m), 2.47–2.60 (1H, m), 3.32 (1H, ddd, J = 3.9, 8.4, 12.1 Hz), 3.76 (1H, dt, J = 8.1, 11.4 Hz), 5.48 (1H, dd, J = 5.8, 8.2 Hz); ^{13}C NMR ($CDCl_3$) δ

26.3, 30.1, 42.9, 76.4, 101.1, 104.0, 108.8, 128.9, 163. 0. IR (film) 1701, 1358, 1323 cm^{-1}; HRMS calcd for $C_9H_8Br_2N_2O$ (M^+): 317.90034; found: 317.90026. Connectivity of the ring was confirmed by ^1H–^{15}N HMBC correlations.

11. Heats of formation were calculated using AM1 Semi-Empirical model, Spartan v. 4.1, Wavefunction Inc: Irvine, CA 1995.
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13. Compound **11**: ^1H NMR (CD_3OD) δ 1.77–1.90 (2H, m), 3.37 (2H, t, $J = 7.2$ Hz), 4.59 (1H, t, $J = 5.2$ Hz), 6.75 (1H, s). Reported for **10** (Ref. 5): ^1H NMR (CD_3OD) δ 1.77–1.90 (2H, m), 3.37 (2H, t, $J = 7$ Hz), 4.57 (1H, t, $J = 5$ Hz), 6.73 (1H, s). Compound **12**: ^1H NMR (CD_3OD) δ 1.85 (2H, q, $J = 6.8$ Hz), 3.34 (2H, t, $J = 6.9$ Hz), 4.42 (1H, t, $J = 5.8$ Hz), 6.76 (1H, s).
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15. Compound **11a**: ^1H NMR (CD_3OD) δ 1.77–1.90 (2H, m), 3.36 (2H, t, $J = 7.1$ Hz), 3.90 (3H, s), 4.57 (1H, t, $J = 5.2$ Hz), 6.77 (1H, s). Compound **12a**: ^1H NMR (CD_3OD) δ 1.85 (2H, q, $J = 6.9$ Hz), 3.33 (2H, t, $J = 7.0$ Hz), 3.90 (3H, s), 4.45 (1H, t, $J = 5.7$ Hz), 6.80 (1H, s).
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