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An efficient synthesis of δ-glyconolactams by intramolecular Schmidt–Boyer reaction under microwave radiation

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ABSTRACT

δ-Glyconolactams were first synthesized by the intramolecular Schmidt–Boyer reaction using corresponding δ-azidosugars as starting material. The reaction could be efficiently performed in good yields of 61–69% under microwave radiation in acid condition, providing an alternative protocol to iminosugar δ-lactam.

Iminosugars, which exhibit effective inhibition against carbohydrate-processing enzymes, have aroused great interest for their potential clinical applications as anti-HIV, anti-diabetic, and anticancer agents in past decades.[1] δ-Glyconolactams, a special kind of iminosugar analogs, have also brought attention due to their prominence as glycosidase inhibitor and their potential application in the preparation of nojirimycin derivatives.[2] The δ-glycono lactams were commonly synthesized by the condensation of a γ-amino carboxylic acid generated from the reduction of the azido glyconic γ-lactone.[3] However, the alternative approach to synthesizing δ-glyconolactams is of continuing interest.

The Schmidt–Boyer reaction of aldehydes or ketones with hydrazoic acid or alkyl azide under acid conditions provided a very convenient method to construct an amide bond.[4] It has been successfully applied to prepare amide by the intermolecular reaction, and lactam and formyl cyclo amine derivatives by the intramolecular reaction, respectively.[5] However, the intramolecular Schmidt–Boyer reaction of the δ-azidoalkyl aldehyde was rarely reported to form the δ-lactam. To the best of our knowledge, only one example[6a] has been demonstrated that the δ-lactam was obtained from δ-azidoalkyl aldehyde as a minor product (8–22% yields), possibly via hydride migration or E2 elimination through the hydroxyimine tautomer (Scheme 1, unfavored routes b and c). Preferentially the major formamide product was formed through the migration of a C–C bond antiperiplanar to a favorably disposed N_2^+ moiety (Scheme 1, favored route a: CH_2 migration). Especially,[6b] the antiperiplanar alkyl migration only afforded the formamide products either from δ- or ε-azido aldehyde, although the reason was unclear. Very interestingly, we occasionally obtained the δ-glyconolactam as a predominant product from δ-azidosugar in acid conditions during our approach to new iminosugar,[7] which inspired us to explore the potential application of the intramolecular Schmidt–Boyer reaction in preparing δ-glyconolactam directly from the corresponding δ-azidosugar rather than the γ-lactone.

The requisite azidosugars (**1a–d**) were readily prepared according to the literatures[8] starting from D-ribose and D-mannose. The intramolecular Schmidt–Boyer reaction (Scheme 2) was first investigated using azidosugar **1a** as the starting material at room temperature catalyzed by a variety of protic (Table 1, entries 1–4, 12, and 13) or Lewis acids (entries 5–11). The intramolecular reaction was carried out successfully, accompanied with the removal of the protecting groups of TBDMS and isopropylidene, and directly afforded the corresponding product of δ-glyconolactam **2a** as the predominant product. As shown in Table 1, under the conditions of protic acid 80% TFA (entry 3) and Lewis acid BF_3 (entry 9) the reaction proceeded efficiently with the good yields of 68% and 74%, respectively. Subsequently, the exploratory study of the intramolecular reaction was further carried out under microwave radiation[9] using 80% TFA and BF_3 as acid catalyst, respectively. As expected, the reaction could be dramatically accelerated under microwave radiation within 5–10 min at the tolerable temperature of 40–50 °C (entries 10–13), and especially, in 80% TFA the reaction afforded δ-glyconolactam **2a** in a yield of 69% within 5 min at 50 °C (entry 13). Furthermore, the reaction in 80% TFA (entries 12 and 13) gave higher yields than in BF_3 (entries 10 and 11), indicating that the microwave-assisted reaction was more effective in protic acid and polar solvent than in Lewis acid and nonpolar solvent.

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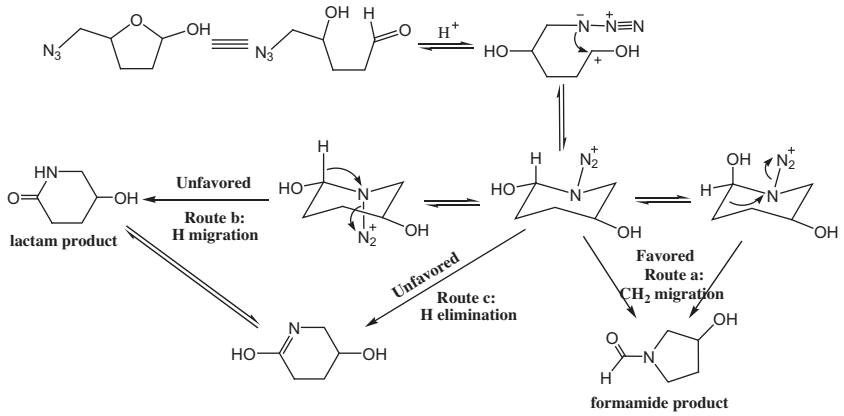
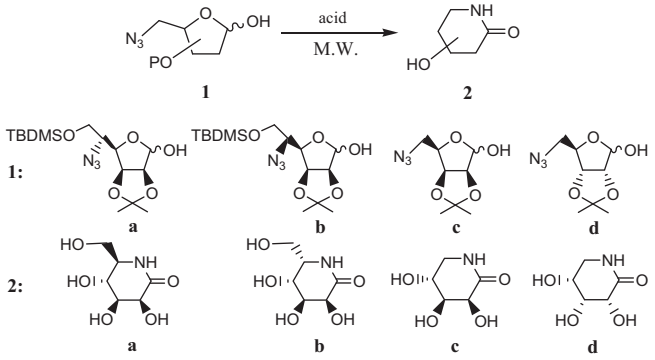


Scheme 1. The proposed mechanisms of the intramolecular Schmidt–Boyer reaction.



Scheme 2. Synthesis of δ-glyconolactams by the intramolecular Schmidt–Boyer reaction. Reagents and conditions: 80% CF_3COOH, 50 °C, M.W., 5 min, 61–69%.

Table 1
The exploratory study of the intramolecular reaction using **1a**

Entry	Acid	Solvent	Temp (°C)	Reaction time[a]	Yield[b] (%)
1	1N-HCl	Dioxane	rt	9 h	54
2	CF_3COOH	—[c]	rt	15 h	64
3	80% CF_3COOH	—[c]	rt	26 h	68
4	50% CF_3COOH	—[c]	rt	48 h	56
5	$AlCl_3$	CH_2Cl_2	rt	12 h	61
6	$FeCl_3$	CH_2Cl_2	rt	12 h	50
7	$ZnCl_2$	CH_2Cl_2	rt	12 h	20
8	$TiCl_4$	CH_2Cl_2	rt	15 h	43
9	BF_3	CH_2Cl_2	rt	10 h	74
10	BF_3	CH_2Cl_2	M.W. 40	10 min	32
11	BF_3	CH_2Cl_2	M.W. 50	5 min	30
12	80% CF_3COOH	—[c]	M.W. 40	10 min	60
13	80% CF_3COOH	—[c]	M.W. 50	5 min	69

[a] Compound **1a** disappeared on TLC.
[b] Isolated yield.
[c] CF_3COOH as solvent.

Under the same conditions as described in entry 13, the δ-glyconolactams **2b–d** were conveniently synthesized in good yields of 61–69% from the corresponding azidosugars **1b–d**.[10] It should be mentioned that, although we could not absolutely rule out small (<5%, determined by ^1H NMR) amounts of the formamide products from these reactions, their presence was not evident from examination of the crude reaction mixtures. The results indicated that the intramolecular Schmidt–Boyer reaction would take place preferentially via the unfavored route of b or c as shown in Scheme 1. It was likely that the presence of the hydroxyl group (an electron-withdrawing substituent) on the C-2 position led to diminish the C–C migration.[11]

In conclusion, δ-glyconolactams were conveniently synthesized from the corresponding δ-azido sugars by the microwave-assisted intramolecular Schmidt–Boyer reaction in good yields, providing an alternative protocol to construct the iminosugar like δ-lactam. Although it was unclear why the results of the intra-molecular reaction were different from those reported,[6] our findings would be an important supplement for the potential application of the Schmidt–Boyer reaction.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.10.098.

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10. *General procedure for the synthesis of δ-glyconolactams* ***2***: Azidosugar **1** (1.0 mmol) was dissolved in 3 mL 80% CF_3COOH and was stirred in sealed tube at 50 °C under microwave irradiation in a CEM Discover S-Class Synthesizer for 5 min. After the reaction complete, the solvent was evaporated under reduced pressure to get a crude product that was purified using flash column chromatography (ethyl acetate–methanol V/V = 7:1–3:1) to get δ-glyconolactams **2**. **(3*S*,4*S*,5*R*,6*R*)-3,4,5-***Trihydroxy-6-(hydroxymethyl) piperidin-2-one (**2a**)*: White solid, yield 69%; mp 164–165 °C (lit. mp 163–168 °C[2b]), ^{1}H NMR (600 MHz, MeOD) δ_H (ppm): 4.26 (d, *J* = 3.6 Hz, 1H, CH), 3.96 (t, *J* = 3.6 Hz, 1H, CH), 3.80 (t, *J* = 4.8 Hz, 1H, CH), 3.77 (dd, *J* = 10.8 Hz, 4.2 Hz, 1H, CH), 3.62 (dd, *J* = 10.8 Hz, 7.2 Hz, 1H, CH_2), 3.31–3.33 (m, 1H, CH_2); ^{13}C NMR (150 MHz, MeOD) δ_C (ppm): 174.2, 74.3, 69.8, 69.6, 64.0, 60.5; HRESIMS: calcd for $C_6H_{11}NO_5Na$ ($[M+Na]^+$) 200.0535, found: 200.0541. *(3S,4S,5R,6S)-3,4,5-Trihydroxy-6-(hydroxymethyl) piperidin-2-one (**2b**)*: White solid, yield 67%, mp 172–173 °C; $[\alpha]_D^{32}$ +27.1 (c 1.0, MeOH); ^{1}H NMR (600 MHz, MeOD) δ_H (ppm): 4.30 (d, *J* = 3.0 Hz, 1H, CH), 4.14 (t, *J* = 3.6 Hz, 1H, CH), 4.07–4.08 (m, 1H, CH), 3.73–3.77 (m, 2H, CH, CH_2), 3.69 (dd, *J* = 10.2 Hz, 4.2 Hz, 1H, CH_2); ^{13}C NMR (150 MHz, MeOD) δ_C (ppm): 173.9, 70.9, 67.5, 67.1, 61.4, 54.3; HRESIMS: calcd for $C_6H_{11}NO_5Na$ ($[M+Na]^+$) 200.0535, found: 200.0523. *(3S,4S,5R)-3,4,5-Trihydroxy piperidin-2-one (2c)*: White solid, yield 61%, mp 196–198 °C; $[\alpha]_D^{32}$ −18.6 (c 1.0, MeOH); ^{1}H NMR (600 MHz, MeOD) δ_H (ppm): 4.32 (d, *J* = 3.0 Hz, 1H, CH), 4.09 (t, *J* = 4.2 Hz, 1H, CH), 4.03 (t, *J* = 4.2 Hz, 1H, CH), 3.66 (dd, *J* = 13.2 Hz, 3.6 Hz, 1H, CH_2), 3.16 (dd, *J* = 13.2 Hz, 2.4 Hz, 1H, CH_2); ^{13}C NMR (150 MHz, MeOD) δ_C (ppm): 173.6, 74.9, 71.0, 67.3, 44.8; HRESIMS: calcd for $C_5H_9NO_4Na$ ($[M+Na]^+$) 170.0429, found: 170.0433. *(3R,4R,5R)-3,4,5-trihydroxy piperidin-2-one (2d)*: White solid, yield 63%, mp 147–148 °C; $[\alpha]_D^{32}$ +35.3 (c 1.0, MeOH); ^{1}H NMR (600 MHz, D_2O) δ_H (ppm): 4.11–4.16 (m, 3H, 3CH), 3.34 (dd, *J* = 12 Hz, 6.6 Hz, 1H, CH_2), 3.22 (t, *J* = 10.2 Hz, 1H, CH_2); ^{13}C NMR (150 MHz, D_2O) δ_C (ppm): 173.3, 70.9, 68.2, 64.7, 42.5; HRESIMS: calcd for $C_5H_9NO_4Na$ ($[M+Na]^+$)170.0429, found:170.0421.
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