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Synthesis of hybrid 1,2,3-triazolo-δ-lactams/lactones using Huisgen [3+2] cycloaddition 'click-chemistry' in water

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ABSTRACT

The synthesis of a new class of hybrid 1,2,3-triazozlo-δ-lactams/lactones has been achieved using the Huisgen [3+2] dipolar cycloaddition 'click-chemistry' reaction of various organic azides with an activated alkyne in water, followed by cyclization.

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1. Introduction

Nitrogen heterocycles containing amine and related functionality are very common in natural and synthetic compounds of biological importance. The role of nitrogen in biological system can largely be attributed to the participation of nitrogen and nitrogen containing group in ionic and hydrogen bonding interactions.[1] 1,2,3-Triazole moieties exist in a large number of compounds showing anti-HIV,[2] and anti-bacterial activity,[3] and also are emerging as powerful pharmacophores.[4] Huisgen 1,3-dipolar cycloaddition involves the reaction between an alkyne and an azide[5] and has been the most popular reaction used to prepare substituted 1,2,3-triazole compounds having a wide range applications as anticorrosive agents, dyes, photostabilizer and agrochemicals.[6] The extraordinary stability towards metabolic transformation, aromatic nature of the triazole ring, along with its high dipole moment and H-bonding capability, make it a functional group of great potential utility as a connecting group.[7] This cycloaddition is typically carried out at higher temperature which usually gives a mixture of 1,4- and 1,5-substituted regioisomeric triazole products. The rate of Huisgen cycloaddition reaction can be increased due to electron-withdrawing groups on the alkyne substrate which has been also termed as 'click-chemistry'.[8]

Structurally new triazoles fused with pyranoses/furanoses **3** were synthesized and studied as inhibitors of various glycosidases.[9] A number of 1,2,3-triazolo-fused bicyclic carbohydrate-derived compounds **4**, new chiral triazolo-piperazine compounds **5** and other similar compounds were also synthesized using an inter- and intramolecular Huisgen 1,3-dipolar cycloaddition reaction (Fig. 1).[10] Our research group has been engaged in developing different strategies for the synthesis of various natural/synthetic intermediates and products of biological importance.[11] Recently, we reported the synthesis of various fused 1,2,3-triazolo-δ-lactams and the covalent functionalization of CNTs using 'click-chemistry' under different conditions.[12]

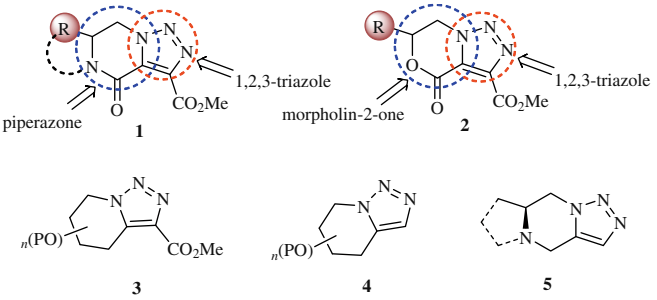

Figure 1.

2. Results and discussion

In a continuation of our study in this direction, herein we report the synthesis of various 1,2,3-triazolo-δ-lactams/lactones using a Huisgen 1,3-dipolar cycloaddition reaction between an activated alkyne and different azides in water as a 'click-chemistry' reaction. The reterosynthetic analysis of our strategy is shown in Scheme 1, in which new fused triazolo-systems **1/2** can be transformed into simple 1,2-amino alcohol/1,2-diol units **8**. Initially, we prepared various azido compounds **7** starting from different amino acids and synthesized a few hybrid 1,2,3-triazolo-δ-lactams, which we have already published in our recent communication paper.[12a]

After this successful demonstration of our methodology for the synthesis of fused 1,2,3-triazolo-δ-lactams, we further extended this work to the synthesis of fused 1,2,3-triazolo-δ-lactones from various simple 1,2-diol units. In order to do that, we initially took a very simple 1-phenylethane-1,2-diol **9**, and transformed it into

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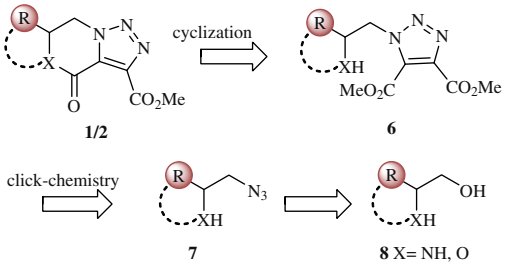
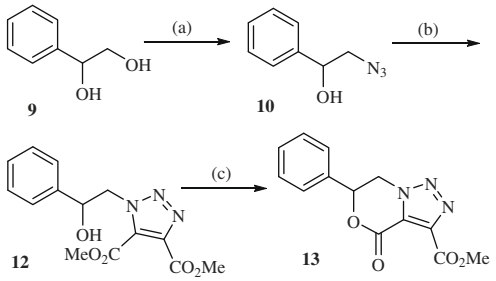


Scheme 1. Reterosynthetic analysis of fused 1,2,3-triazolo-δ-lactams/lactones.

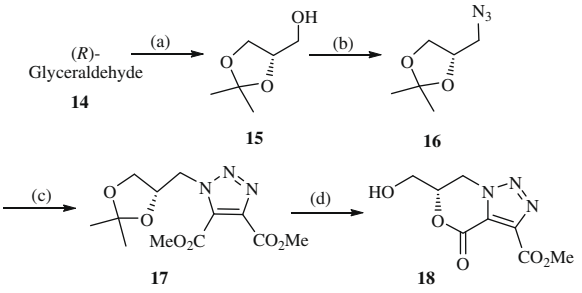
the corresponding azido-alcohol **10** in 79% yield. The 'click' 1,3-dipolar cycloaddition reaction of **10** with dimethylacetylene dicarboxylate **11** (1.1 equiv) in water (8 mL) at 70 °C for 1 h provided triazolo cycloadduct **12** as a slight yellowish solid in 86% yield. Next, **12** was treated with 1.2 mol equiv of NaH (55% on paraffin oil) in dry THF under reflux condition for 12 h to provide hybrid 1,2,3-triazolo-δ-lactone **13** in 67% isolated yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) (i) TsCl (1.1 equiv), Et_3N (1.2 equiv), dry CH_2Cl_2, 0 °C, 4 h; (ii) NaN_3 (2.2 equiv), 1,4-dioxane/DMSO (10:1), 65 °C, 6 h, 79% over two steps; (b) dimethylacetylene dicarboxylate **11** (1.1 equiv), H_2O (8 mL), 70 °C, 1 h, 86% yield; (c) NaH (1.2 equiv, 55% in paraffin oil), dry THF, reflux, 12 h, 67% yield.

In order to prepare some chiral 1,2,3-triazolo-δ-lactones, alcohol **15** was prepared by $NaBH_4$ reduction of (*R*)-glyceraldehyde **14**. This alcohol **15** was transformed into the corresponding azido compound **16** through a sequence of tosyl protection/substitution with NaN_3 in an excellent yield. Compound **16** (1 mmol) underwent smooth cycloaddition with **11** (1.1 mol equiv) in water to provide an adduct **17** in almost quantitative yield. Further, deprotection of the acetonide moiety and lactonization was performed in one-pot procedure by treating with 1 M HCl/MeOH followed by heating in benzene to provide fused 1,2,3-triazolo-δ-lactone **18** in 61% yield after two steps as shown in Scheme 3.

Next, L-(+)-tartaric acid **19** was transformed into its corresponding protected diol **20** easily by following the reported procedure.[13] The azido-alcohol **21** was prepared by using NaH (1.0 equiv) and TsCl (1.1 equiv) followed by nucleophilic substitution with NaN_3 in 79% yield from **22**. Similarly, the diazido compound **22** was prepared using 2 equiv of NaH and TsCl followed by nucleophilic substitution with NaN_3 with 83% yield from **20**. The 1,3-dipolar cycloaddition 'click' reaction of these azides proceeded smoothly with **11** (1.1 equiv) for **21** and **11** (2.2 equiv) for **22** in water at 70 °C for 1 h to provide cycloadducts **23** and **24** in excellent yields as shown in Scheme 4. In order to obtain the corresponding mono- and di-hybrid triazolo lactones of the **23** and **24**, cyclization of these cycloadducts was attempted first under the standard conditions using 1 M HCl/MeOH in benzene under reflux conditions. However, it resulted into the formation of a complex reaction mixture. Hence we attempted the cyclization under different acidic conditions, but all these trials gave a complex reactions mixture,



Scheme 3. Reagents and conditions: (a) $NaBH_4$, MeOH, rt, quantitative; (b) (i) TsCl (1.1 equiv), Et_3N (1.2 equiv), dry CH_2Cl_2, 0 °C, 4 h; (ii) NaN_3 (2.2 equiv), 1,4-dioxane/DMSO (10:1), 65 °C, 6 h, 86% after two steps; (c) dimethylacetylene dicarboxylate **11** (1.1 equiv), H_2O (8 mL), 70 °C, 1 h, quantitative; (d) 1 M HCl, MeOH, benzene, reflux, 4 h, 61%.

from which the desired lactones could not be isolated. Nevertheless, our study demonstrated the successful synthesis of hybrid triazolo lactams/lactones following the 'click-chemistry' approach. All the new compounds were fully characterized by spectroscopic means.

3. Conclusion

In conclusion, we have demonstrated the Huisgen 1,3-dipolar cycloaddition 'click' reaction of various chiral azides derived from 1,2-amino alcohols/diols with dimethylacetylene dicarboxylate as an activated alkyne in water. This approach was found to be useful for the synthesis of a new class of hybrid 1,2,3-triazolo-δ-lactams/lactones after the intramolecular cyclization of the corresponding cycloadducts. The synthesis of these hybrid compounds containing biologically important moieties and an ester group on the triazole ring can provide access to a variety of new compounds with different biological significances.

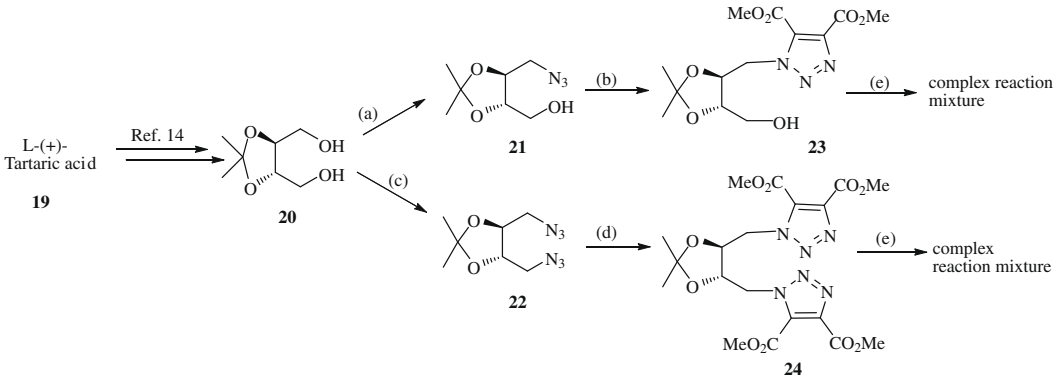
4. Experimental

4.1. General methods

All the reagents were used as supplied. The reactions involving hygroscopic reagents were carried out under an argon atmosphere using oven-dried glassware. THF was distilled from sodium-benzophenone ketyl prior to use. Reactions were followed by TLC using 0.25 mm Merck silica gel plates (60F-254). Optical rotation values were measured using JASCO P-1020 digital polarimeter using Na light. IR spectra were recorded on Perkin–Elmer FT-IR 16 PC spectrometer. The NMR spectra were recorded on a Bruker system (200 MHz for ^1H and 75 MHz for ^{13}C). The chemical shifts are reported using the δ (delta) scale for ^1H and ^{13}C spectra. Choices of deuterated solvents ($CDCl_3$, D_2O) are indicated below. LC–MS was recorded using the electrospray ionization technique. All the organic extracts were dried over sodium sulfate and concentrated under aspirator vacuum at room temperature. Column chromatography was performed using (100–200 and 230–400 mesh) silica gel obtained from M/s Spectrochem India Ltd. Room temperature is referred as rt.

4.2. Dimethyl 1-(2-hydroxy-2-phenylethyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate 12

A mixture of compound **10** (0.21 g, 1.23 mmol) and dimethylacetylenedicarboxylate **11** (0.195 g, 1.35 mmol) in water (8.0 mL) was heated at 70 °C with constant stirring for 1 h. The resulting mixture was cooled to rt and stirred further with EtOAc (15 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated



Scheme 4. Reagents and conditions: (a) NaH (1.1 equiv), dry THF, TsCl (1.2 equiv), 0 °C, 2 h; (ii) NaN_3 (2.2 equiv), 1,4-dioxane/DMSO (10:1), 65 °C, 6 h, 81% after two steps; (b) dimethylacetylene dicarboxylate 11 (1.1 equiv), H_2O (8 mL), 70 °C, 1 h, 79%; (c) (i) NaH (2.2 equiv), TsCl (2.2 equiv), dry THF, 0 °C, 2 h; (ii) NaN_3 (3.5 equiv), 1,4-dioxane/DMSO (10:1), 65 °C, 6 h, 89%; (d) dimethylacetylene dicarboxylate 11 (2.2 equiv), H_2O (8 mL), 70 °C, 1 h, 95%; (e) (i) 1 M HCl, MeOH, benzene, reflux, 4 h; (ii) CF_3CO_2H (0.1 equiv), MeOH, reflux, 4 h; (iii) *p*-TSA (cat.), MeOH, reflux, 2 h, complex reaction mixtures in all cases.

under reduced pressure to provide a pasty mass, which was passed through a small pad of silica gel to give slightly yellowish compound **12** (solidify slowly) in 89% yield. ^{1}H NMR (200 MHz, $CDCl_3/D_2O$): δ = 3.81 (s, 3H), 3.98–4.15 (m, 5H), 4.84 (m, 1H), 7.15–7.21 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 51.17, 52.41, 62.54, 76.31, 126.89, 127.11, 128.81, 128.98, 129.23, 139.51, 161.15, 163.92. LC–MS (ESI-TOF): *m*/*z* $[M+H]^+$ 306.21, $[M+Na]^+$ 328.82.

4.3. Methyl 4-oxo-6-phenyl-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine-3-carboxylate 13

67% from **12**; For **13**: ^{1}H NMR (200 MHz, $CDCl_3/D_2O$): δ = 3.91 (s, 3H), 4.32–4.38 (m, 2H), 4.98–5.10 (m, 1H), 7.27–7.42 (m, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.43, 62.91, 79.13, 121.71, 124.83, 127.73, 128.19, 128.95, 139.94, 162.14, 168.12. Anal. Calcd for $C_{13}H_{11}N_3O_4$: C, 57.14; H, 4.06; N, 15.38. Found: C, 57.19; H, 4.11; N, 15.31.

4.4. (*S*)-Dimethyl 1-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate 17

96% from **16**; For **17**: $[\alpha]_D^{25} = +11.2$ (*c* 1.0, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.45 (s, 3H), 1.49 (s, 3H), 3.87 (s, 3H), 3.92–4.15 (m, 5H), 4.18–4.25 (m, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.38, 25.97, 52.23, 54.69, 57.42, 69.59, 78.91, 109.13, 121.23, 122.95, 154.76, 164.23. Anal. Calcd for $C_{12}H_{17}N_3O_6$: C, 48.16; H, 5.73; N, 14.04. Found: C, 48.10; H, 5.65; N, 14.12.

4.5. (*S*)-Methyl 6-(hydroxymethyl)-4-oxo-6,7-dihydro-4*H*-[1,2,3]triazolo[5,1-*c*][1,4]oxazine-3-carboxylate 18

61% from **17**; For **18**: $[\alpha]_D^{25} = +5.7$ (*c* 0.75, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3/D_2O$): δ = 3.95 (s, 3H), 4.12–4.35 (m, 4H), 4.51–4.63 (m, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 52.34, 59.81, 69.95, 80.05, 123.56, 126.93, 162.12, 167.23. LC–MS (ESI-TOF): *m*/*z* $[M+H]^+$ 228.26, $[M+Na]^+$ 150.85. Anal. Calcd for $C_8H_9N_3O_5$: C, 42.30; H, 3.99; N, 18.50. Found: C, 42.26; H, 4.89; N, 18.59.

4.6. ((4*S*,5*S*)-5-(Azidomethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol 21

81% from **20**; For **21**: $[\alpha]_D^{25} = -60.3$ (*c* 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3/D_2O$): δ = 1.40 (s, 3H), 1.43 (s, 3H), 2.33 (br s, 1H, –OH) 3.30 (dd, *J* = 4.6 Hz, 1H), 3.54 (dd, *J* = 3.8 Hz, 1H), 3.58–3.82 (m, 2H), 3.90–4.11 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.67, 26.87, 51.63, 61.62, 76.07, 78.31, 109.70. LC–MS (ESI-TOF): *m*/*z* $[M+H]^+$ 187.18, $[M+Na]^+$ 210.17.

4.7. (4*S*,5*S*)-4,5-Bis(azidomethyl)-2,4-dimethyl-1,3-dioxalane 22

89% from **20**; For **22**: $[\alpha]_D^{25} = -114.95$ (*c* 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3/D_2O$): δ = 1.44 (s, 6H), 3.31 (dd, *J* = 4.7 Hz, 2H), 3.53 (dd, *J* = 3.8 Hz, 2H), 4.00–4.05 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.81, 51.56, 76.88, 110.33. Anal. Calcd for $C_7H_{12}N_6O_2$: C, 39.62; H, 5.70; N, 39.60. Found: C, 39.59; H, 5.73; N, 39.69.

4.8. Dimethyl 1-(((4*S*,5*S*)-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-1*H*-1,2,3-triazole-4,5-dicarboxylate 23

79% from **21**; For **23**: $[\alpha]_D^{25} = -34.55$ (*c* 1, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3/D_2O$): δ = 1.41 (s, 3H), 1.45 (s, 3H), 3.61–3.68 (m, 2H), 3.72–4.02 (m, 8H), 4.35–4.55 (dd, *J* = 3.7 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.65, 26.77, 51.83, 54.29, 56.32, 61.79, 76.16, 78.28, 110.05, 129.51, 132.45, 159.19, 163.32. LC–MS (ESI-TOF): *m*/*z* $[M+H]^+$ 329.38, $[M+Na]^+$ 352.46.

4.9. Tetramethyl 1,1′-((4*S*,5*S*)-2,2-dimethyl-1,3-dioxolane-4,5-diyl)bis(methylene)bis(1*H*-1,2,3-triazole-4,5-dicarboxylate) 24

95% from **22**; For **24**: $[\alpha]_D^{25} = -46.9$ (*c* 0.5, $CHCl_3$), ^{1}H NMR (200 MHz, $CDCl_3/D_2O$): δ = 1.03 (s, 6H), 3.89 (s, 6H), 3.91 (s, 6H), 3.96 (m, 2H), 4.78 (dd, *J* = 3.9 Hz, 2H), 4.96 (dd, *J* = 3.3 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.12, 49.31, 52.53, 53.24, 74.97, 110.66, 131.66, 139.46, 158.76, 160.02. Anal. Calcd for $C_{19}H_{24}N_6O_{10}$: C, 45.97; H, 4.87; N, 16.93. Found: C, 45.91; H, 4.84; N, 16.98.

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