Synthesis of isoxazole conjugates of sugars via 1,3-dipolar cycloaddition

Vipraja V. Vaidya, Karuna S. Wankhede, Manikrao M. Salunkhe, and Girish K. Trivedi

Abstract: Isoxazole conjugates of sugar have been synthesized by the aid of 1,3-dipolar cycloaddition in a click chemistry approach. The sugar-derived propargyl ethers underwent 1,3-dipolar cycloadditions smoothly with in situ generated nitrile oxides from aromatic oximes in good yields. The reaction exhibited a high degree of regioselectivity.

Key words: isoxazole conjugates, 1,3-dipolar cycloadditions, nitrile oxides.

Résumé : Faisant appel à une cycloaddition 1,3-dipolaire et une approche chimique qui marche très bien, on a réalisé la synthèse d'isoxazoles conjugués à un sucre. Les éthers propargyliques dérivés du sucre donnent lieu en douceur et avec de bons rendements à des réactions de cycloaddition 1,3-dipolaire avec les oxydes de nitrile générés in situ à partir d'oximes aromatiques. La réaction présente un degré élevé de régiosélectivité.

Mots–clés : produits conjugués de l'isoxazole, cycloadditions 1,3-dipolaires, oxydes de nitrile.

[Traduit par la Rédaction]

Introduction

Several compounds of natural and non-natural origin comprised of the isoxazole moiety possess a broad spectrum of biological properties viz., fungicidal, antibacterial, anti-inflammatory, anti-allergic, anti-tumor, herbicidal, etc. The isoxazole class of compounds are also synthetically important as 1,3-dicarbonyl equivalents (1). Among the plethora of protocols reported for the synthesis of the isoxazole skeleton, two major routes are the 1,3-dipolar cycloadditon of alkenes and alkynes with nitrile oxides and the reaction of hydroxylamine with a three-carbon atom component, such as 1,3-diketone or an α,β-unsaturated ketone. 1,3-Dipolar cycloaddition has proven particularly valuable for the construction of complex five-membered conformationally rigid heterocycles (2). Isoxazoles, also among the five-membered heterocycles, can be accessed by 1,3-dipolar cycloaddition reaction. In particular, nitrile oxides undergo cycloaddition with alkynes resulting in good yields of isoxazoles (3). A similar class of compounds, i.e., triazoles, have been synthesized via 1,3-dipolar cycloaddition of azides and alkynes. This reaction has been considered as the prototype of click chemistry (4). There are several excellent contributions from various groups in the domain of click chemistry, wherein 1,3–dipolar cycloadditions are employed as a tool to conjugate molecules of structural diversity (5). Such linkage may result in altogether new attributes and (or) an ensemble of attributes. The continuing interest in this field and the importance of the isoxazole moiety has encouraged us to report our results.

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Results and discussion

We herein report regioselective syntheses of sugar conjugates of isoxazoles (**1**–**10**) via 1,3-dipolar cycloaddition of carbohydrate derived alkynes and in situ generated nitrile oxides from oximes (Scheme 1). D-Glucose was utilized as a precursor to prepare all dipolarophiles i.e., sugar alkynes. The dipolarophiles (**1a**–**5a**) were synthesized following standard procedures. The dipoles, i.e., nitrile oxides, were generated in situ from the biphasic oxidation of the oximes with NaOCl in dichloromethane-triethyl amine (6). These dipoles underwent cycloaddition with dipolarophiles to afford cycloadducts, i.e., new isoxazole conjugates of sugars in good yields.

D-Glucose was utilized to synthesize 1,2:5,6 diisopropylidene-α-D-glucofuranose, which was subsequently subjected to etherification using propargyl bromide to yield the dipolarophile **1a**. The dipolarophile **1a** upon treatment with benzonitrile oxide, 4-methoxy benzonitrile oxide, and 3,4-dimethoxy benzonitrile oxide afforded cycloadducts (**1**–**3**) in 75%–80% yields.

The dipolarophile **2a** was also treated with the three previously mentioned nitrile oxides separately to generate corresponding cycloadducts (**4**–**6**) in 69%–75% yields. The dipolarophile **3a** was treated with benzonitrile oxide to yield cycloadduct **7** in 74% yield. The dipolarophile **4a** was accessed by Ferrier *O*-glycosylation of 3,4,6-tri-*O*-acetyl-D-glucal with propargyl alcohol. It was further subjected to 1,3-dipolar cycloaddition with benzonitrile oxide to yield cycloadduct **8** in 67% yield.

Our next objective was to synthesize bis-isoxazole derivatives, and in that direction we carried out the propargylation of the cycloadduct **7** to have one more site for cycloaddition

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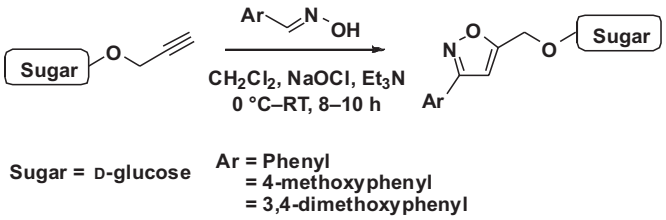
Scheme 1. Synthesis of isoxazole conjugates of sugars.



to yield the dipolarophile **5a**. The compound **5a** was subjected to cycloaddition with benzonitrile oxide and 4-methoxy benzonitrile oxide to afford bisisoxazole **9** and mixed bis-isoxazole **10**, in 65% and 67% yields, respectively. All gummy products (Table 1) were purified by silica gel column chromatography. The reaction exhibited a high degree of regioselectivity, which was confirmed from ^{1}H NMR spectra of the products. The signals in the range of δ 6.5–6.7, as singlet for vinylic proton, indicated only 5-substituted products were formed. Furthermore, all these isoxazole conjugates possess a protected furanoside ring that is accessible for elaboration after deprotection. The isoxazole moiety present can be cleaved to yield 1,3-functionalized compounds that can serve as handles for further manipulation.

In conclusion, we successfully employed a 1,3-dipolar cycloaddition strategy to conjugate sugar molecules with isoxazoles, which resulted in compounds bearing an appendage of aromatic moieties on sugar molecules. Thus, the biological profile of isoxazole coupled with sugar through C-O linkage was diversified. In the near future, we will continue our efforts to synthesize novel hybrid entities using the 1,3-dipolar cycloaddition reaction of nitrile oxides as a key step.

Experimental

General procedure for the preparation of isoxazole conjugates

A solution of the aldoxime (dipole precursor) (1 mmol), sugar alkyne (dipolarophile) (1 mmol), and triethylamine (2 to 3 drops) in dichloromethane (10 mL) was cooled to 0 °C. To this solution, sodium hypochlorite (4%, 10 mL) was added dropwise with stirring at 0 °C. The reaction mixture was warmed to RT and stirred for 8–10 h. On the disappearance of the starting material (TLC), the reaction phases were separated and the aqueous phase was extracted with dichloromethane. The combined layers were washed with brine, dried with sodium sulphate, and the solvent evaporated under reduced pressure to yield the crude cycloadduct. The crude product was chromatographed on a silica gel column. The purified products were characterized.

Characterization data

Cycloadduct 1

$[\alpha]_D^{27}$ –34.62 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 3037, 1525, 1383, 1232, 1082. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.80 (dd, 2H, *J* = 2.8, 6.4 Hz), 7.47–7.45 (m, 3H), 6.69 (s, 1H), 5.91 (d, 1H, *J* = 3.6 Hz), 4.82 (s, 2H), 4.60 (d, 1H, *J* = 3.6 Hz), 4.36 (dd, 1H, *J* = 5.5, 12.7 Hz), 4.16–4.10 (m, 3H), 4.02 (dd, 1H, *J* = 5.2, 8.5 Hz), 1.49 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 169.09, 162.35, 130.04, 128.87, 128.80, 126.72, 111.96, 109.18, 105.18, 101.10, 82.66, 82.26, 81.06, 72.14, 67.47, 63.37, 26.84, 26.72, 26.15, 25.33.

Cycloadduct 2

$[\alpha]_D^{27}$ –19.84 (*c* 2.5, $CHCl_3$). IR (cm^{-1}): 3037, 1520, 1379, 1227, 1082. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.74 (d, 2H, *J* = 8.7 Hz), 6.97 (d, 2H, *J* = 8.7 Hz), 6.63 (s, 1H), 5.90 (d, 1H, *J* = 3.6 Hz), 4.80 (s, 2H), 4.59 (d, 1H, *J* = 3.6 Hz), 4.35 (dd, 1H, *J* = 5.8, 13.3 Hz), 4.16–4.10 (m, 3H), 4.02 (dd, 1H, *J* = 5.2, 8.5 Hz), 3.85 (s, 3H), 1.49 (s, 3H), 1.43 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 168.87, 162.02, 161.07, 128.22, 121.38, 114.33, 112.03, 110.81, 109.24, 105.26, 100.94, 82.77, 82.34, 81.15, 72.24, 67.54, 63.46, 55.36, 26.91, 26.82, 26.22, 25.41.

Cycloadduct 3

$[\alpha]_D^{27}$ –15.05 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 3121, 1528, 1376, 1082, 853. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.42 (d, 1H, *J* = 1.8 Hz), 7.28 (dd, 1H, *J* = 1.8, 8.1 Hz), 6.93 (d, 1H, *J* = 8.1 Hz), 6.63 (s, 1H), 5.91 (d, 1H, *J* = 3.9 Hz), 4.80 (s, 2H), 4.59 (d, 1H, *J* = 3.6 Hz), 4.35 (dd, 1H, *J* = 6.4, 13.3 Hz), 4.16–4.10 (m, 3H), 4.04–3.93 (overlapping peaks, 7H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 168.99, 162.17, 150.78, 149.44, 121.67, 119.99, 112.06, 111.13, 109.41, 105.30, 101.00, 82.82, 82.46, 81.20, 72.30, 67.58, 63.53, 56.08, 55.99, 26.92, 28.82, 26.26, 25.45. HRMS calcd. for $C_{24}H_{32}NO_9$ (M+H): 478.2077; found 478.2081.

Cycloadduct 4

$[\alpha]_D^{27}$ –30.8 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 3038, 2946, 1384, 1228, 1081, 1024. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.77 (d, 2H, *J* = 3.9 Hz), 7.44 (m, 3H), 7.30 (m, 5H), 6.56 (s,1H), 5.95 (d, 1H, *J* = 3.6 Hz), 4.76–4.61 (m, 4H), 4.49 (d, 1H, *J* = 12 Hz), 4.43–4.38 (m, 1H), 3.97 (d, 1H, *J* = 2.7 Hz), 3.83 (d, 2H, *J* = 6.0 Hz), 1.48 (s, 3H), 1.31 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 169.58, 162.36, 137.31, 130.00, 128.90, 128.51, 127.99, 127.66, 126.81, 111.78, 105.17, 101.17, 82.16, 81.69, 79.12, 71.94, 68.79, 64.28, 26.80, 26.28.

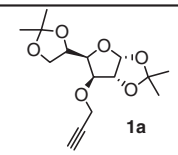
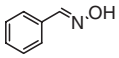
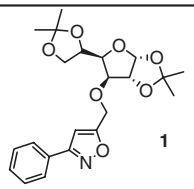
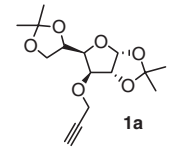
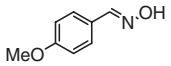
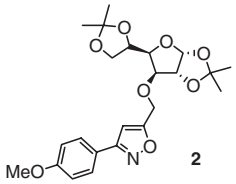
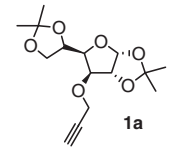
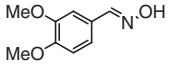
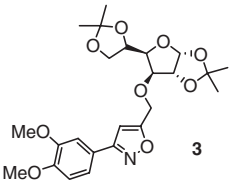
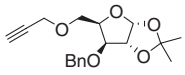
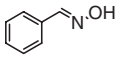
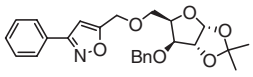
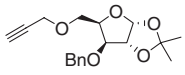
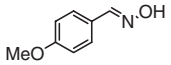
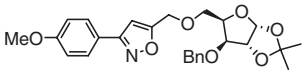
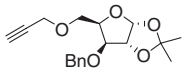
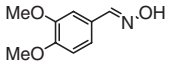
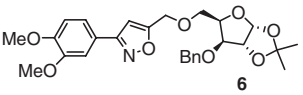
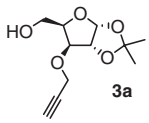
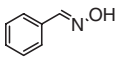
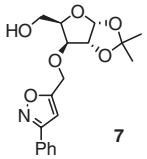
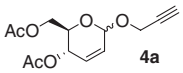
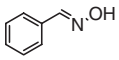
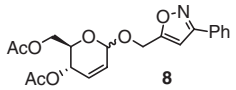
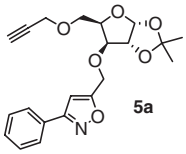
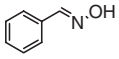
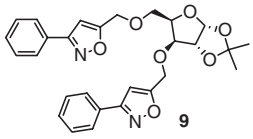
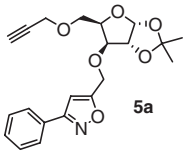
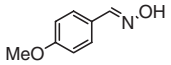
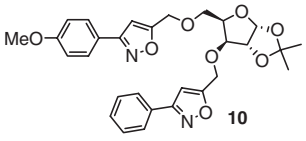
Cycloadduct 5

$[\alpha]_D^{27}$ –28.89 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 3038, 2956, 1384, 1261, 1086. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.72 (d, 2H, *J* = 8.7 Hz), 7.36–7.21 (m, 5H), 6.96 (d, 2H, *J* = 8.7 Hz), 6.50 (s, 1H), 5.95 (d, 1H, *J* = 3.9 Hz), 4.73–4.59 (m, 4H), 4.49 (d, *J* = 12 Hz, 1H), 4.43–4.38 (m, 1H), 3.97 (d, 1H, *J* = 3.3 Hz), 3.83 (overlapping peaks, 5H), 1.48 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 169.30, 161.96, 160.99, 137.33, 129.46, 128.51, 128.21, 128.10, 127.98, 127.69, 127.66, 121.44, 114.28, 111.78, 105.13, 100.94, 82.19, 81.71, 79.13, 71.96, 68.75, 64.25, 55.33, 26.80, 26.29.

Cycloadduct 6

$[\alpha]_D^{27}$ –22.7 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 3037, 2922, 1258, 1023. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.41 (d, 1H, *J* = 1.8 Hz), 7.31 (overlapping peaks, 6H), 6.93 (d, 1H, *J* = 8.4 Hz), 6.53 (s, 1H), 5.95 (d, 1H, *J* = 3.6 Hz), 4.75–4.61 (m, 4H), 4.49 (d, 1H, *J* = 12 Hz), 4.43–4.38 (m, 1H), 3.97–3.93 (overlapping peaks, 7H), 3.83 (d, 2H, *J* = 6 Hz), 1.49

Table 1. Synthesis of isoxazole conjugates of sugars.

Entry	Dipolarophile	Dipole precursor	Cycloadduct
1.	 **1a**		 **1**
2.	 **1a**		 **2**
3.	 **1a**		 **3**
4.	 **2a**		 **4**
5.	 **2a**		 **5**
6.	 **2a**		 **6**
7.	 **3a**		 **7**
8.	 **4a**		 **8**
9.	 **5a**		 **9**
10.	 **5a**		 **10**

(s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 169.45, 162.06, 150.33, 149.22, 137.27, 128.49, 127.96, 127.64, 121.60, 119.91, 110.96, 109.21, 105.13, 100.97, 82.11, 81.65, 79.10, 71.91, 68.75, 64.29, 55.97, 55.91, 26.76, 26.25. HRMS calcd. for $C_{27}H_{32}NO_8$ (M+H): 498.2128; found 498.2140.

Cycloadduct 7

$[\alpha]_D^{27}$ –39.1 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 3431, 2929, 1612, 1373, 1214, 1078, 1019, 853. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.80 (d, 2H, *J* = 6.6 Hz), 7.6–7.36 (m, 3H), 6.61 (s, 1H), 5.97 (d, 1H, *J* = 3.6 Hz), 4.83–4.65 (m, 3H), 4.40–4.21 (m, 1H), 4.10 (d, 1H, *J* = 2.7 Hz), 3.98–3.85 (m, 2H), 2.26 (bs, 1H), 1.50 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 168.54, 162.42, 130.13, 128.90, 128.52, 126.74, 111.91, 104.90, 101.42, 83.15, 82.32, 80.11, 62.79, 60.21, 26.66, 26.20.

Cycloadduct 8

$[\alpha]_D^{27}$ +44.9 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 3038, 2951, 1754, 1369, 1232, 1043. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.80 (d, 2H, *J* = 3.6 Hz), 7.46–7.44 (m, 3H), 6.60 (s, 1H), 6.04–5.88 (m, 2H), 5.35 (d, 1H, *J* = 9 Hz), 5.19 (s, 1H), 4.96–4.75 (m, 2H), 4.29–4.13 (m, 3H), 2.094 (s, 3H), 2.09 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.74, 170.23, 169.12, 162.46, 130.11, 130.05, 129.51, 129.09, 128.96, 128.84, 128.39, 126.93, 126.82, 126.28, 101.39, 94.11, 67.39, 65.14, 63.93, 62.75, 60.65, 20.94, 20.77. HRMS calcd. for $C_{20}H_{21}NO_7$ Na (M+Na): 410.1216; found 410.1213.

Cycloadduct 9

$[\alpha]_D^{27}$ –27.10 (*c* 2.0, $CHCl_3$). IR (cm^{-1}): 3042, 2954, 1609, 1234, 1099, 1028. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.8–7.76 (m, 4H), 7.51–7.37 (m, 6H), 6.59 (s, 1H), 6.58 (s, 1H), 5.95 (d, 1H, *J* = 3.6 Hz), 4.79–4.62 (m, 5H), 4.46–4.41 (m, 1H), 4.06 (d, 1H, *J* = 2.7 Hz), 3.90–3.79 (m, 2H), 1.49 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 169.29, 168.57, 162.41, 130.13, 130.01, 129.09, 128.93, 128.89, 128.62, 128.38, 126.78, 126.25, 112.00, 105.07, 101.57, 101.41, 82.45, 82.71, 78.64, 68.03, 64.20, 62.85, 26.75, 26.26. HRMS calcd. for $C_{28}H_{29}N_2O_7$ Na (M+H): 505.1975; found 505.1988.

Cycloadduct 10

$[\alpha]_D^{27}$ –20.74 (*c* 1.0, $CHCl_3$). IR (cm^{-1}): 3042, 2956, 1609, 1251, 1074, 1023. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ: 7.75–7.68 (m, 4H); 7.42 (s, 3H), 6.92 (d, 2H, *J* = 8.7 Hz), 6.57 (s, 1H), 6.53 (s, 1H), 5.95 (d, 1H, *J* = 3.3 Hz), 4.79–4.61 (m, 5H), 4.46–4.41 (m, 1H), 4.06 (d, 1H, *J* = 3.3 Hz), 3.83 (overlapping peaks, 5H), 1.49 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ: 168.99, 168.60, 162.41, 161.97, 160.98, 130.11, 128.93, 128.65, 128.19, 126.78, 121.33, 114.28, 113.63, 112.00, 105.06, 101.53, 101.20, 82.46, 82.21, 78.63, 67.94, 64.20, 62.90, 55.32, 26.75, 26.27.

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