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Synthesis and Characterization of Sugar Derived Novel Bioactive Isoxazole Derivatives

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Abstract: ***This study explores the synthesis and characterization of novel isoxazole derivatives derived from sugar. We employed 1-3 dipolar cycloaddition between aldoxime dipole precursor and alkyne derivative of sugar dipolarophile in presence of weak base at 0^0C in DMF. The newly synthesized isoxazole derivatives as cycloadducts were separated from solvent and characterized by IR, 1H NMR, and ^{13}C NMR.***

Keywords: Isoxazole, Nitrile oxide, 1-3 dipolar cycloaddition, Hetero-cyclization reaction, dipolarophile

1. Introduction

The isoxazole moiety in natural and synthetic origin have broad spectrum biological activity. These are potent antiallergic, herbicidal, antifungal, anti-inflammatory [1-2] and antibacterial motifs. The synthesis of carbohydrate functionalized derivatives has given considerable attention [3-7]. The 1-3 dipolar cyclo addition is a valuable route for synthesis of five membered heterocycles including isoxazoles [8-11]. Thus 1-3 dipolar cycloaddition is a good tool for conjugate motifs, to synthesize adducts with structural diversity [12-17]. The importance of the isoxazole-sugar functionalization moiety has encouraged us to synthesize and report our results of cycloaddition of alkyne derivatives of sugar and nitrile oxide, as derivatives of isoxazole.

2. Result and Discussion

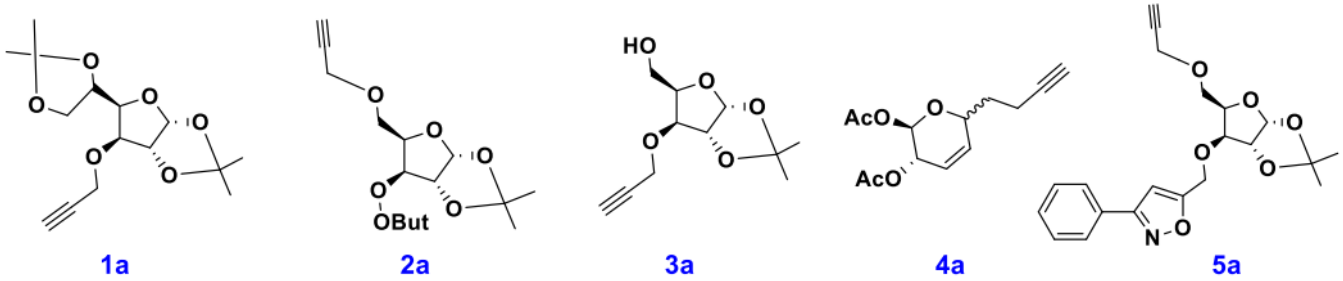


Figure: Dipolarophile (alkyne derivative of sugar)

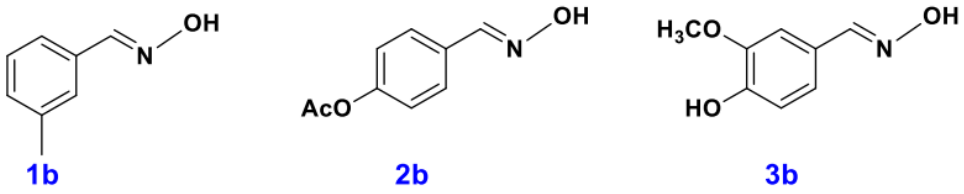
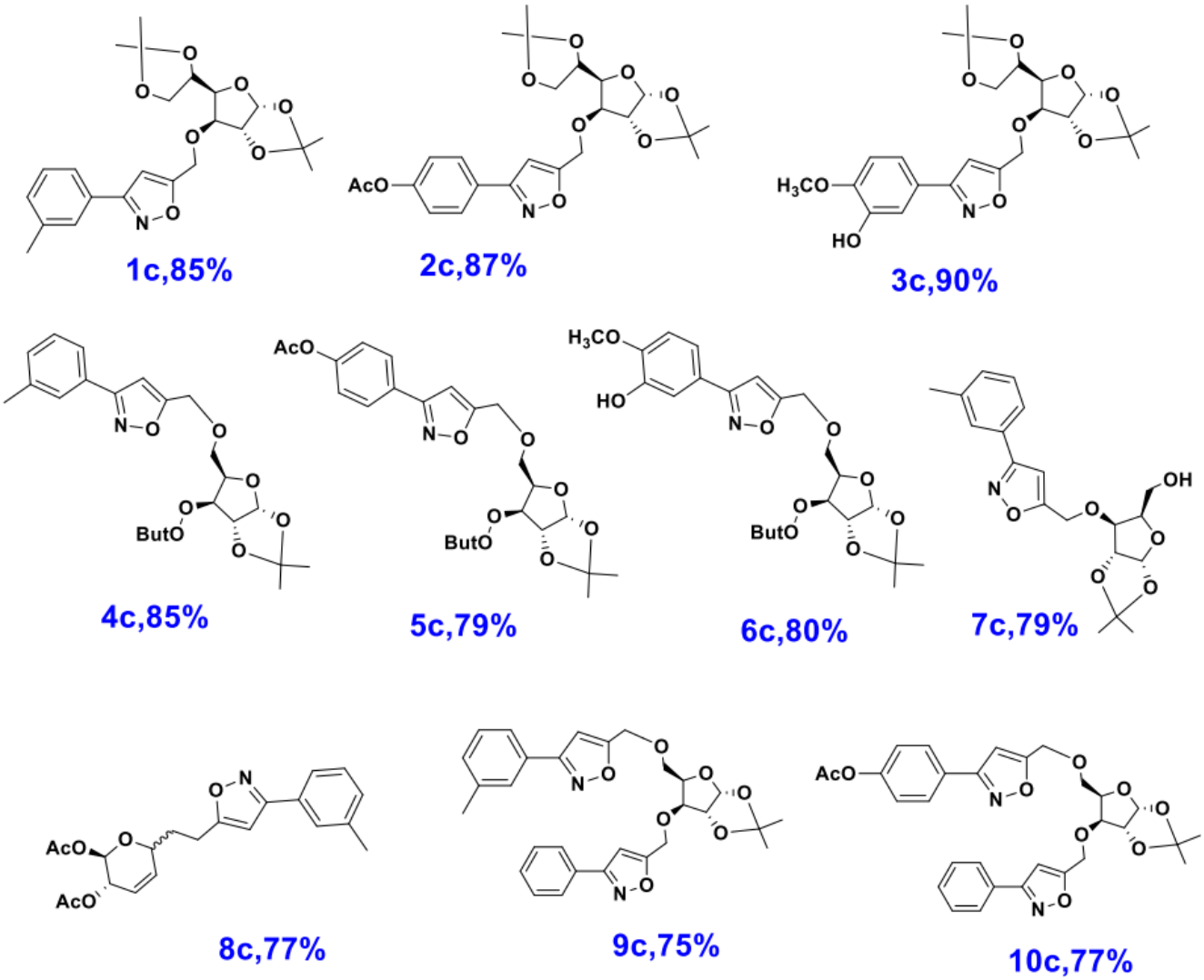


Figure: Dipole precursor (aldoxime),

Here we are reporting 1,3 dipolar cycloaddition of carbohydrate derivatives of alkynes and nitrile oxide (oxime), this regioselective synthesis Yields D- glucose derivatives of isoxazole (1- 10, Scheme 1). The sugar-alkyne derivatives (dipolarophiles) utilized as precursors and synthesized by following method. The 1,2,5,6 di-isopropylidene, α-D-glucofuranose was synthesized by using α, D-glucopyranose and propyne derivatives by fusion reaction, subsequently followed by esterification, yields dipolarophiles **(a).** The dipoles, i.e., nitrile oxides, were generated in situ from the biphasic oxidation of the oximes**(b)** with NaOCl in dichloromethane-triethyl amine.

Scope of the reaction between dipole precursor and dipolarophile



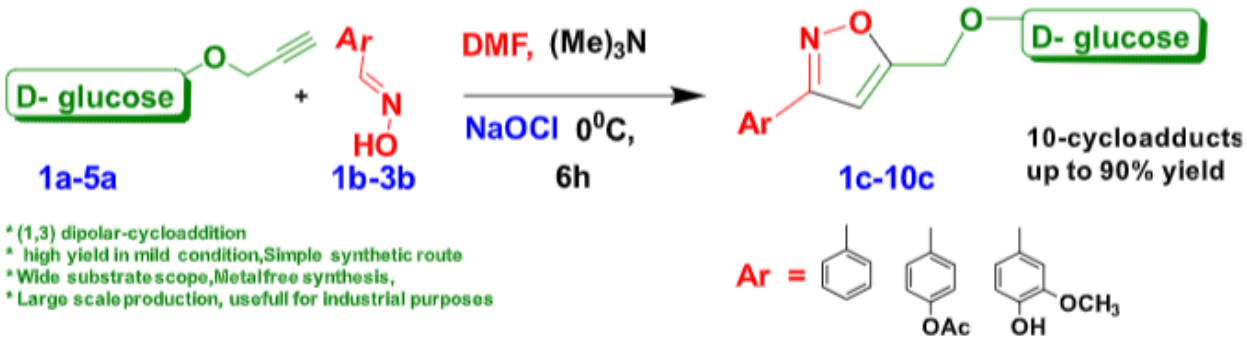
These dipoles and dipolarophiles undergo 1-3 dipolar cycloaddition to afford cycloadducts, i.e., new isoxazole conjugates of sugars in good yields. The dipolarophile 1a upon treatment with benzonitrile oxide, 4-acetyl benzonitrile oxide, and 3-hydroxy 4- methoxy benzonitrile oxide afforded cycloadducts (**1C–3C**) in 85%–90% yields.

The dipolarophile (2a) when reacted with mentioned nitrile oxides separately to generate corresponding cycloadducts (4C–6C) in 79%–85% yields. Then our afford for other derivatives on reaction of 2a with benzonitrile oxide to yield cycloadduct (7C) in 79% yield. Then (4a) was accessed by *O*-glycosylation of 3,4,6-tri-*O*-acetyl derivative with propargyl alcohol. Its 1,3- dipolar cycloaddition with benzonitrile oxide to gives (8C) in 77% yield.

Now due to our next interest to synthesize bis-isoxazole derivatives, the cycloadduct 7C was subjected for propargylation to give dipolarophile (5a), then it was subjected to cycloaddition with benzonitrile oxide and 4-methoxy benzonitrile oxide to affords (9Cand 10C) 75% and 77% yields, (Table 1). The reaction was with high degree of regioselectivity, confirmed from ^{1}H NMR spectra of the products. The signals are obtained in the range of δ 6.5–6.7. All isoxazoles have protected protected furanoside ring which becomes accessible for elaboration after deprotection. When isoxazole moiety decomposed it yield 1,3-functionalized cycloadducts, were purified by silica gel column chromatography, which can serve as handles for next manipulation.

3. Experimental

Procedure for the preparation of sugar derived isoxazole:



Scheme 1: Systhesis of isoxazole derivatives of sugar

1 mol of dipole precursor (aldoxime), and 1 mol of dipolarophile (alkyne derivative of sugar), two to three drops of trimethyl amine in 10 ml of in DMF cooled at 0^0C, 5% 20 ml of sodium hypochlorite was added dropwise with constant stirring. Then reaction mixture allowed to stay at room temperature for 6 h. The reaction was monitored with TLC, and separated from organic layer by using separating. Then obtained layer was washed with brine and dried with calcium chloride, solvent was allowed for evaporation. Then we get crude cycloaddition product. Then obtained crude adduct was farther purified by using silica gel chromatography, and purified product ware characterized by IR (cm^{-1}),1H NMR (300 MHz, $CDCl_3$, ppm) and ^{13}C NMR (75 MHz, $CDCl_3$, ppm).

Characterization data: Cycloadduct 1C:
[α]D –34.62 (c 2.0, $CHCl_3$). IR (cm): 3037, 1525,1383, 1232, 1082. H NMR (300 MHz, $CDCl_3$, ppm) : 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): 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. 1.43 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) : 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 2C:
[α]D –22.7 (c 1.0, $CHCl_3$). IR (cm): 3037, 2922, 1258,1023. H NMR (300 MHz, $CDCl_3$, ppm) : 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– s3.93 (overlapping peaks, 7H), 3.83 (d, 2H, J = 6 Hz), 1.49(s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) : 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

Cycloadduct 3C:
[α]D –15.05 (c 2.0, $CHCl_3$). IR (cm): 3121, 1528, 1376, 1082, 853. H NMR (300 MHz, $CDCl_3$, ppm) : 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) 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.

Cycloadduct 4C:
[α]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): 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) : 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 5C:
[α]D –28.89 (c 2.0, $CHCl_3$). IR (cm): 3038, 2956, 1384, 1261, 1086. H NMR (300 MHz, $CDCl_3$, ppm) : 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), 3.9(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)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 6C:
[α]D –22.7 (c 1.0, $CHCl_3$). IR (cm): 3037, 2922, 1258,1023. H NMR (300 MHz, $CDCl_3$, ppm) : 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– s3.93 (overlapping peaks, 7H), 3.83 (d, 2H, J = 6 Hz), 1.49(s, 3H), 1.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) : 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.

Cycloadduct 7C:
[α]D –39.1 (c 2.0, CHCl3). IR (cm): 3431, 2929, 1612,1373, 1214, 1078, 1019, 853. H NMR (300 MHz, CDCl3,ppm) : 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,CDCl3, ppm) : 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 8C:
[α]D +44.9 (c 2.0, CHCl3). IR (cm): 3038, 2951, 1754, 1369, 1232, 1043. H NMR (300 MHz,
CDCl3, ppm): 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}CNMR (75 MHz, CDCl3) : 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.

Cycloadduct 9C:
[α]D^{27} –27.10 (c 2.0, CHCl3). IR (cm^{-1}): 3042, 2954, 1609, 1234, 1099, 1028. ^{1}H NMR (300 MHz, CDCl3, ppm) 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, CDCl3, ppm) : 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.

Cycloadduct 10C:
[α]D^{27} –20.74 (c 1.0, CHCl3). IR (cm^{-1}): 3042, 2956, 1609, 1251, 1074, 1023. ^{1}H NMR (300 MHz, CDCl3, ppm) : 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}CNMR (75 MHz, CDCl3, ppm) : 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

4. Conclusion

Here we have developed well planned procedure for 1,3-dipolar cycloaddition strategy for cyclization of conjugate sugar molecules with isoxazoles. The isoxazole derivatives of sugar were obtained in moderate to good yield with high degree of regioselectivity. The aromatic moieties on sugar molecules support high yield. Here the bio logical profile of isoxazole derivatives coupled with sugar through C-O linkage was diversified.

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