The Synthesis of Pyrazole Derivatives Based on Glucose

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Abstract—Heterocyclic compounds and glucose derivatives play important role in organic chemistry and biological chemistry for their rich functionality. A facile and convenient protocol had been developed for the synthesis of a series of novel glucosyl pyrazole derivatives starting from D-glucose. The protected glucose by O-pivaloyl groups reacted with BTC and obtained corresponding 2-isocyanate glucose, which effectively avoid the harsh conditions and highly toxic agents compared to the traditional method. Glucosyl pyrazole derivatives were then prepared through the reaction of pyrazole and its derivatives with 2-isocyanate glucose with good yields.

Index Terms—Heterocycle, glucose, pyrazole, synthesis.

I. INTRODUCTION

Pyrazoles are chemical compounds of synthetic origin that have a five-membered heterocycle with two nitrogen atoms and three adjacent carbons. Pyrazole derivatives, several members of the pyrazoles class, have shown good pharmacological effects or have the potential biological activities, such as, anti-inflammatory [1], antiviral [2], antimicrobial [3], anticonvulsant [4], antitumor [5], fungicidal activities [6] and antihistaminic [7]. The pyrazole moiety has important role in some drugs structure, for example, some arylpyrazole derivatives have anti-HIV-1 activity [8]-[10] and some pyrazole-3-carboxamide moiety has anti-CB1 cannabinoid ability [11]. In addition, the pyrazole derivatives have many applications on crop protection chemistry. There were many herbicidally, fungicidally and insecticidally active pyrazole classes in this field (Fig. 1). So pyrazole derivatives have attracted much attention of chemists.

D-glucose is one of the most important energy sources for the survival of various organisms [12]. Organic compounds which containing glycoconjugates owing to their essential roles in a lot of physiological processes and to their potential applications as tumor receptors and antibodies. The glycoconjugates also exerted important effects on many complex biological events, including cellular recognition in the processes of immune response, inflammation, tumor metastasis, and viral infections [13]. In addition, glycosylation of proteins and lipids is a key factor in modulating their structures and functions [14]. However, there are a few reports on the synthesis and pharmacology of the pyrazole derivatives containing sugar moieties.

Fig. 1. Some pyrazole derivatives

Encouraged and enlightened by the importance of D-glucose in nature and the bioactivity of pyrazole derivatives, herein, we report a facile and efficient method of preparing the pyrazole derivatives on glucose. (Fig. 2).

Fig. 2. Synthesis of D-glucopyranose derivatives 7a-7f

II. RESULTS AND DISCUSSION

During our previous research [15], we have developed a novel route for the synthesis of (2R, 3S, 4S, 6R)-2-amino-6-(pivaloyloxymethyl)tetrahydro-2H-pyran-3,4,5-triyl tris(2,2-dimethylpropanoate) 4 starting from D-glucose. Prompted by these results and in continuation of our search for bioactive molecules, we planned to synthesize some pyrazole derivatives based on glucose by the reaction of glucosyl isocyanate 5 with the different amines 6. Generally speaking, the preparation of isocyanate was using high toxic phosgene. Here we employed the triphosene (BTC) and made it react with 4 and obtained the compound 5. Compared with conventional methods, the use of BTC allowed us to be more convenient and easier to operate in experiments with good yields. And then the synthesis of the novel compounds 7 were accomplished by the reaction of pyrazole and its derivatives 6a-6f with the 2-isocyanate glucose 5 to give the

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D-glucopyranose derivatives 7a-7f with 17% -73% yields in mild reaction conditions.

A detailed study of different substrates was performed toward the formation of glucose-based pyrazole derivatives (Table 1). To investigate the influence of stereo and electronic effect about the substrate 6 toward the formation of glucose-based pyrazole derivatives 7, methyl and phenyl groups were chosen for R substituents as representatives of alkyl and aryl group in the vicinity of the 3-NH₂ reactive centre of substrate 6. At the same time, the fully unsubstituted pyrazole ring 1H-pyrazol-3-amine 6a was also considered to be the model substrate to identify the method of choice for glycosylation.

From the experimental results, it was found that the yield is relatively high (73%) when there are no substituents on the pyrazole ring (7a, Table I). On the contrary, the yield is low when there are some substituents at pyrazole ring such as methyl group, nitrile group and phenyl group. Initially, we just want to investigate the influence of electron effect coming from different groups. While the experimental results revealed that the steric effects maybe played dominant role. Because the D-glucose which be protected by O-pivaloyl groups itself is a large steric hindrance group, and with the increases of the substituted groups at pyrazole ring, the steric hindrance on pyrazole ring increases accordingly, so the reactive activity of compound 6 decreased and the yields of 7b-7f were declining correspondingly from 64%-17%.

TABLE I: CHEMICAL STRUCTURE OF THE TITLE COMPOUNDS

Compd	R	Product	Yield ^a
7a			73%
7b			64%
7c			57%
7d			21%
7e			17%
7f			45%

^a Isolated yield

All the products were confirmed by IR, ¹H NMR, ¹³C NMR and MS. The IR spectrum exhibited absorption bands at 3435 cm⁻¹ and 2950 cm⁻¹, indicating the presence of N-H and C-H groups of the pyrazole ring, while absorption at 1740 cm⁻¹ indicated the presence of carbonyl of the sugar ketone groups. In the ¹H NMR spectrum hydrogen of pyrazole ring and multiplet of the glucose ring were observed at about δ 7.3 ppm and δ 4.89 ppm, respectively. The typical

signals on ¹³C NMR spectrum of carbonyl group in acetyl showed from δ 178.20 ppm to 153.06 ppm and the shift values from about δ 140 ppm to 70 ppm proved the existence of pyrazole ring. The biological screen of these compounds will be performed in next research work.

A. Experimental

All the reagents used without any further purification. The solvents were purified according to the standard methods. Analytical TLC was performed on a Merck precoated TLC (Silica Gel 60 F254) plate. Melting points were recorded on an X₄-Data microscopic melting point apparatus and are uncorrected. IR spectra were recorded on a Bruker Equinox-55 spectrophotometer using KBr discs in the 4000-400 cm⁻¹ region. MS were acquired on a Bruker Esquire 3000 plus spectrometer. ¹H and ¹³C NMR were recorded on a Bruker Avance 400 spectrometer in CDCl₃ using TMS as internal standard.

B. General Procedure for the D-glucosepyranose Derivatives

A typical experimental procedure for D-glucosepyranose derivatives 7a was as follows. A mixture of 3-aminopyrazole 6a (0.0415 g, 0.5 mmol) and D-pyranoid glucose isocyanate 5 (0.2750 g) in 5 mL anhydrous THF solution was incubated in the round bottomed flask, then reflux for 4h. The reaction was further stirred until the disappearance of starting material. The residue was evaporated and the product 7a was purified using column chromatography ((10:1 ethyl acetate/MeOH).

(2R, 3S, 4S, 6R)-2-(3-(1H-pyrazol-3-yl)ureido)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyltris(2,2-dimethylpropanoate) (7a): yield 73%; IR (KBr, cm⁻¹): 3435, 2950, 1740, 1455, 1300, 1150, 1050; MS (ESI): m/z (%): 624.72 [M+1]⁺; ¹H NMR (CDCl₃): δ 7.93-7.95 (m, 1H), 7.43 (d, J = 10.0Hz, 1H), 7.28-7.30 (m, 1H), 5.81 (d, J = 3.2Hz, 1H), 5.44 (t, J = 6.4Hz, 2H), 5.28 (t, J = 6.3Hz, 1H), 5.19 (t, J = 6.3Hz, 1H), 5.13 (t, J = 6.4Hz, 1H), 4.15-4.19 (m, 2H), 3.89 (d, J = 10.0Hz, 2H), 1.12-1.20 (m, 36H); ¹³C NMR (CDCl₃): δ 178.10, 177.76, 176.99, 176.31, 156.43, 149.53, 130.13, 99.68, 79.58, 74.13, 72.25, 70.16, 67.45, 61.56, 38.89, 39.77, 27.14, 26.84.

(2R, 3S, 4S, 6R)-2-(3-(4-cyano-1H-pyrazol-3-yl)ureido)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl-tris(2,2-dimethylpropanoate) (7b): yield: 64%; IR (KBr, cm⁻¹): 3435, 2950, 2210, 1740, 1455, 1300, 1150, 1050, 950; MS(ESI): m/z (%) : 649.73 [M+1]⁺; ¹H NMR (CDCl₃): δ 7.50-7.52 (m, 1H), 7.43-7.45 (m, 1H), 7.00-7.22 (m, 1H), 6.13-6.17 (m, 1H), 5.44-5.46 (m, 1H), 5.39 (t, J = 9.2Hz, 1H), 5.18 (t, J = 6.3Hz, 1H), 5.13 (t, J = 10.0Hz, 1H), 4.88-4.91 (m, 2H), 4.10-4.13 (m, 2H), 2.29-2.30 (m, 1H), 1.10-1.20 (m, 36H); ¹³C NMR (CDCl₃): δ 178.20, 178.05, 176.86, 176.46, 153.40, 149.53, 145.34, 138.45, 137.90, 135.00, 129.45, 90.74, 79.82, 73.84, 72.12, 70.48, 67.54, 70.16, 61.66, 38.91, 39.99, 26.89.

(2R, 3S, 4S, 6R)-2-(3-(5-phenyl-1H-pyrazol-3-yl)ureido)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl-tris(2,2-dimethylpropanoate) (7c): yield: 57%; IR (KBr, cm⁻¹): 3435, 2950, 1740, 1530, 1455, 1300, 1150, 1050, 950; MS(ESI): m/z (%) : 701.00 [M+1]⁺; ¹H NMR (CDCl₃): δ 9.15-9.16 (m, , 1H), 8.01 (d, J = 8.4Hz, 2H), 7.83 (d, J =

7.2Hz, 2H), 7.42-7.44 (*m*, 1H), 6.72 (*s*, 1H), 5.48-5.50 (*m*, 2H), 5.41-5.42 (*m*, 1H), 5.25-5.27 (*m*, 1H), 5.23-5.25 (*m*, 1H), 5.27-5.29 (*m*, 1H), 4.18-4.20 (*m*, 2H), 3.93 (*d*, *J* = 10.0Hz, 2H), 1.12-1.22 (*m*, 36H); ^{13}C NMR (CDCl_3): δ 178.13, 177.92, 177.03, 176.37, 153.06, 152.55, 150.20, 132.03, 128.99, 128.57, 126.10, 86.39, 70.42, 74.11, 72.18, 70.10, 67.52, 67.45, 61.50, 47.54, 38.48, 28.63.

(2R, 3S, 4S, 6R)-2-(3-(1,5-dimethyl-3-oxo-2-phenyl-2,3-dihydro-1H-pyrazol-4-yl)ureido)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl(tris(2,2-dimethylpropanoate) (7d): yield: 21%; IR (KBr, cm^{-1}): 3435, 2950, 1740, 1513, 1488, 1462, 1321, 1236, 1088, 950; MS(ESI): *m/z* (%): 744.87 [*M*+1] $^{+}$; ^1H NMR (CDCl_3): δ 7.93-7.94 (*m*, 1H), 7.43 (*d*, *J* = 10.0Hz, 1H), 7.28-7.31 (*m*, 1H), 5.81 (*d*, *J* = 3.2Hz, 1H), 5.44 (*t*, *J* = 6.4Hz, 2H), 5.28 (*t*, *J* = 6.3Hz, 1H), 5.19 (*t*, *J* = 6.3Hz, 1H), 5.13 (*t*, *J* = 6.4Hz, 1H), 4.15-4.17 (*m*, 2H), 3.89 (*d*, *J* = 10.0Hz, 2H), 1.19-1.25 (*m*, 36H); ^{13}C NMR (CDCl_3): δ 178.10, 177.76, 176.99, 176.31, 156.43, 149.53, 130.13, 99.68, 79.58, 74.13, 72.25, 70.16, 67.45, 61.56, 39.92, 29.67.

(2R, 3S, 4S, 6R)-2-(3-(3-methyl-1-phenyl-1H-pyrazol-5-yl)ureido)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyltris(2,2-dimethylpropanoate) (7e): yield: 17%; IR (KBr, cm^{-1}): 3435, 2950, 1741, 1513, 1498, 1463, 1321, 1236, 1088, 950. MS(ESI): *m/z* (%): 714.85 [*M*+1] $^{+}$; ^1H NMR (CDCl_3): δ 7.84-7.86 (*m*, 1H), 7.45-7.47 (*m*, 2H), 7.29-7.31 (*m*, 2H), 6.42 (*s*, 1H), 6.10-6.13 (*m*, 1H), 5.40-5.42 (*m*, 1H), 5.19 (*t*, 1H), 5.10-5.13 (*m*, 1H), 5.19-5.21 (*m*, 2H), 4.81 (*t*, *J* = 9.6Hz, 1H), 4.10-4.12 (*m*, 1H), 3.85 (*s*, 1H), 2.41-2.42 (*m*, 1H), 2.25-2.27 (*m*, 1H), 2.18(*s*, 3H), 1.17-1.20 (*m*, 36H); ^{13}C NMR (CDCl_3): δ 178.07, 177.03, 176.85, 176.45, 153.68, 149.55, 149.37, 145.53, 138.35, 137.94, 129.12, 129.17, 124.55, 123.81, 90.55, 79.70, 73.77, 72.37, 70.45, 67.53, 61.74, 39.93, 28.69.

(2R, 3S, 4S, 6R)-2-(3-(1-methyl-1H-pyrazol-3-yl)ureido)-6-((pivaloyloxy)methyl)tetrahydro-2H-pyran-3,4,5-triyl-tris(2,2-dimethylpropanoate) (7f): yield: 45%; IR (KBr, cm^{-1}): 3435, 2950, 1741, 1513, 1498, 1463, 1321, 1236, 1083, 953; MS(ESI): *m/z* (%): 638.75 [*M*+1] $^{+}$; ^1H NMR (CDCl_3): δ 7.80-7.82 (*m*, 1H), 7.43 (*d*, *J* = 10.0Hz, 1H), 7.29-7.31 (*m*, 1H), 5.03-5.05 (*m*, *J* = 3.2Hz, 1H), 5.44-5.45 (*m*, 1H), 5.28-5.29 (*m*, 1H), 5.19-5.21 (*m*, 1H), 5.13-5.15 (*m*, 1H), 4.15-4.16 (*m*, 2H), 3.91-3.93 (*m*, 1H), 1.16-1.25 (*m*, 36H); ^{13}C NMR (CDCl_3): δ 178.09, 177.74, 176.85, 176.35, 176.15, 149.55, 130.43, 99.78, 79.58, 74.13, 72.25, 70.16, 67.45, 61.56, 40.22, 29.92.

III. CONCLUSION

In conclusion, we developed a facile and convenient protocol for the synthesis of glucosyl pyrazole derivatives starting from D-glucose. This method avoids using the harsh reaction

conditions and highly toxic agents compared to the traditional method, which provides an effective method to synthesize the sugar-heterocyclic derivatives.

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