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A novel approach to 1,2,3-triazole grafted chitosans *via* modified Wolff's cyclocondensation

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ABSTRACT

A novel synthetic strategy to afford 1,2,3-triazole grafted chitosans *via* modified Wolff's cyclocondensation was established. Subsequently, several multi-substituted 1,2,3-triazole grafted chitosans with a degree of conversion (DC) varying from 42.1% to 53.9% were synthesized and characterized. The chemical structures of the modified chitosans were confirmed by Fourier transform infrared spectroscopy (FTIR) and proton nuclear magnetic resonance spectroscopy (^{1}H NMR), and the DC of chitosan derivatives were determined by amino titration. Meanwhile, the impact of 1,2,3-triazole moieties in the chitosan on their thermal properties were characterized by thermogravimetic analysis (TGA) and differential calorimetry scanner (DSC) respectively.

1. Introduction

1,2,3-Triazole heterocyclic compounds have found numerous applications in materials science, medicinal chemistry, and pharmacology [1], since they were firstly synthesized by Pechmann [2] in the late 19th century. Among the methods for 1,2,3-triazole synthesis, Huisgen's 1,3-dipolar [3 + 2] cycloaddition between azides and alkynes is arguably the most popular and straightforward route to the five-membered heterocycles [3]. However, this methodology often requires specific catalysts such as copper [4], rhodium [5] or Pd-Cu bimetallic catalysts [6] to prevent the formation of regioisomers. Wolff's cyclocondensation between α-diazocarbonyl compounds and various amines, which was developed in 1900s [7], is another method to afford 1,2,3-triazoles. The advantages of Wolff's cyclocondensation include regioselectivity, the abundance and low cost of raw materials. However, the poor condensation efficiency has seriously hindered the practicality of this type of classic reaction. Recently, we have successfully overcome the problem of the poor condensation efficiency and developed a modified Wolff's cyclocondenstion to obtain 1,2,3-triazolesx [8]. Subsequently, we have successfully used this method for synthesis of poly (*N*-vinyl-triaozle)s [9].

In recent years, polymers with 1,2,3-triazoles have attracted considerable interests due to their unique properties including: bioactivity, thermostability, chemical stability, chelating property with metal and optical activity [10]. As the increasing requirement for the sustainable development, 1,2,3-triazole grafted biocompatible and biodegradable materials like polysaccharide have drawn extensive attention from chemists. The [3 + 2] cycloadditon of alkynyl compounds and azides, named click chemistry [11], is the major approach to accomplishing 1,2,3-triazole grafted polysaccharides. Although 1,2,3-triazoles have been introduced into numerous polysaccharides (such as cellulose, potato starch, (1,3)-β-$_D$-glucans) [12], there are only a few reports on 1,2,3-triazole grafted chitosans due to the poor solubility of chitosan and the limitation of effective synthetic strategy.

As a semi-synthetic polymer, chitosan is interesting not only because it has unique structures, multidimensional properties and highly sophisticated functionality, but because it is an abundant renewable and compatible resource [13]. It is obtained by deacetylation of chitin, a polysaccharide widely spread in nature (e.g. crustaceans, insects and certain fungi) [14]. Chitosan is a copolymer composed of *N*-acetyl-$_D$-glucosamine and $_D$-glucosamine units available in different grades depending upon the degree of acetylation [15]. There are two hydroxyl groups and one amino group in the repeating glucosidic residue. The hydroxyl groups can effect appropriate chemical modifications to enhance solubility [16]. The amino group gives rise to chemical reactions (such as acetylation, quaternization, alkylation, grafting, chelation of metals, and reactions with aldehydes and ketones,.) to provide a variety of products with antibacterial, anti-fungal, anti-viral, anti-acid, anti-ulcer, non-toxic, non-allergenic, total biocompatibility or biodegradability [17]. Chitosan and its derivatives are under extensive

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investigation and have found a broad application in coatings [18], drug delivery [19], food industry [20], wastewater treatment [21], biomedical materials [22], etc. As yet, all the reactions of 1,2,3-triazole grafted chitosans synthesis occur at the position of amino groups in chitosan *via* click chemistry. Kulbokaite and co-workers reported two methods to generate *N*-azidated chitosan: direct azidation of amino groups or chain extension of amino groups with azide compounds, followed by the synthesis of 1,2,3-triazole grafted chitosans *via* the click chemistry [23]. Lallana et al. reported a kind of polymeric nanostructures based on 1,2,3-triazole grafted chitosan *via* click chemistry [24].

To the best of our knowledge, there were no reports dealing with the synthesis of 1,2,3-triazole grafted chitosans by Wolff's cyclocondensation. In this work, for the first time, we report the synthesis of 1,2,3-triazole grafted chitosans with high grafting ratio through the modified Wolff's cyclocondensation between the amino group on the chitosan and *α*-diazo-*β*-oxoamides. The structures of 1,2,3-triazole grafted chitosans were confirmed by NMR and FTIR, and the DC of the polymers were calculated by amino titration.

2. Experimental section

2.1. Materials

Chitosan (degree of deacetylation 95%), aniline (98%), ethyl acetoacetate (98%), ethyl benzoylacetate (98%), and 4-dodecylaniline (98%) were purchased from Aladdin. All the other chemicals were purchased from J&K Chemical. All the reagents were of analytical grade and used as received unless specified.

2.2. Measurements

FTIR spectra were performed on a Bio-Rad Digilab Division FTS-80 spectrometer Instrument (Hercules, California, USA). Carbon-13 (^{13}C) and proton (^{1}H) NMR spectra were recorded on a Bruker DRX 400 spectrometer (Billerica, Massachusetts, USA) operating at 400 MHz using deuterated chloroform ($CDCl_3$) or deuterated dimethyl sulfoxide (DMSO-d_6) as the solvents and tetramethylsilane as the internal reference. Thermogravimetric analysis (TGA) was measured with a Perkin-Elmer TGA 2 analysis system (Waltham, Massachusetts, USA) at a heating rate of 10 °C min^{-1} under nitrogen atmosphere. DSC was measured with a TA instrument Q 2000 at a heating rate of 10 °C min^{-1} under nitrogen atmosphere. The content of primary amino in the products was measured with the titration [25].

2.3. Synthesis of α-diazo-β-oxoamides

*General procedure for the synthesis of α-diazo-β-oxoamides (Scheme 1). Synthesis of 2-diazo-3-oxo-N-(4-(trifluoromethyl)phenyl)butanamide (compound **2a**).* Aniline (9.31 g, 100 mmol), ethyl acetoacetate (13.01 g, 100 mmol) and toluene (100 mL) were placed into a 500 mL round-bottom flask with a magnetic stirrer. The mixture was stirred at reflux for 3 h. Then the toluene was removed by distillation. The residue was washed with petroleum ether (50 mL × 3) to afford 3-oxo-*N*-phenylbutanamide (**1a**) as a white solid (16.66 g, 94%), mp 84–86 °C. **^{1}HNMR** ($CDCl_3$, 400 MHz) *δ* 9.16 (s, 1H), 7.56 (d, *J* = 8.0 Hz, 2H), 7.34 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 1H), 3.60 (s, 2H), 2.34 (s, 3H). **^{13}CNMR** ($CDCl_3$, 100 Hz) *δ* 205.2, 163.6, 137.5, 129.0, 124.6, 120.2, 49.9, 31.2.

Sodium azide (0.95 g, 30 mmol), tosyl chloride (5.71 g, 30 mmol), tetrabutylammonium bromide (0.97 g, 3 mmol), dichloromethane (90 mL) and water (5 mL) were placed into a 250 mL round-bottom flask with a magnetic stirrer. The mixture was stirred at room temperature for 1 h. Then the compound **1a** (5.32 g, 30 mmol) and sodium hydroxide (2.40 g, 60 mmol) were added to the mixture and the reaction system was stirred at room temperature. After 6 h, the reaction system was filtrated and the residue was dissolved into water (200 mL). Dilute hydrochloride acid was added to the solution till the pH = 3–4. The mixture was filtrated, and the residue was recrystallized with ethyl acetate to give a yellow solid as 2-diazo-3-oxo-*N*-phenylbutanamide (**2a**, 5.30 g, overall yield: 82%), mp 118–120 °C. **^{1}HNMR** ($CDCl_3$, 400 MHz) *δ* 10.17 (s, 1H), 7.57–7.60 (m, 2H), 7.30–7.36 (m, 2H), 7.09–7.14 (m, 1H), 2.42 (s, 3H). **^{13}CNMR** ($CDCl_3$, 100 Hz) *δ* 189.8, 158.0, 137.8, 128.9, 124.3, 119.9, 78.3, 26.6.

2-Diazo-3-oxo-*N*,3-diphenylpropanamide **2b**, yellowish solid (overall yield: 73%), mp 95–98 °C. **^{1}HNMR** ($CDCl_3$, 400 MHz) *δ* 10.46 (s, 1H), 7.59–7.68 (m, 5H), 7.53 (t, *J* = 8.0 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.14 (t, *J* = 8.0 Hz, 1H). **^{13}CNMR** ($CDCl_3$, 100 Hz) *δ* 187.9, 158.5, 137.8, 136.5, 132.7, 129.0, 127.0, 124.4, 120.0, 77.6.

2-Diazo-3-oxo-*N*-(4-(trifluoromethyl)phenyl)butanamide **2c**, yellow solid (overall yield: 84%), mp 137–139 °C. **^{1}HNMR** ($CDCl_3$, 400 MHz) *δ* 10.41 (s, 1H), 7.72 (d, *J* = 12.0 Hz, 2H), 7.58 (d, *J* = 12.0 Hz, 2H), 2.44 (s, 3H). **^{13}CNMR** ($CDCl_3$, 100 Hz) *δ* 189.9, 158.6, 140.8, 129.6, 126.2, 125.4, 122.7, 119.6, 78.4, 26.6.

2-Diazo-3-oxo-3-phenyl-*N*-(4-(trifluoromethyl)phenyl)propanamide **2d**, yellow solid (overall yield: 70%), mp 148–150 °C. **^{1}HNMR** (DMSO-d_6, 400 MHz) *δ* 10.67 (s, 1H), 7.89 (d, *J* = 8.0 Hz, 2H), 7.82–7.84 (m, 2H), 7.74 (d, *J* = 8.0 Hz, 2H), 7.65–7.69 (m, 1H), 7.58 (t, *J* = 8.0 Hz, 2H). **^{13}CNMR** (DMSO-d_6, 100 Hz) *δ* 187.4, 159.2, 141.3, 136.3, 132.7, 127.2, 126.2, 125.5, 124.3, 124.0, 122.8, 119.7, 78.1.

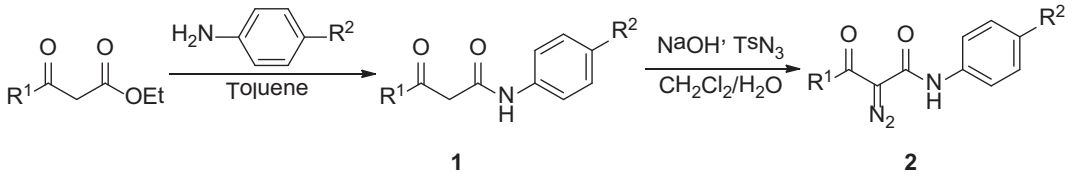
2-Diazo-*N*-(4-dodecylphenyl)-3-oxobutanamide **2e**, yellow solid (overall yield: 78%), mp 81–84 °C. **^{1}HNMR** (DMSO-d_6, 400 MHz) *δ* 10.15 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 9.0 Hz, 2H), 3.31–3.32 (m, 2H), 2.41 (s, 3H), 1.50–1.56 (s, 2H), 1.20–1.30 (s, 18H), 0.85 (t, *J* = 8.0 Hz, 3H). **^{13}CNMR** (DMSO-d_6, 100 Hz) *δ* 191.1, 158.3, 138.1, 135.5, 128.7, 119.5, 77.9, 34.5, 31.2, 30.9, 28.9, 28.8, 28.6, 28.5, 26.9, 22.0, 13.9.

2-Diazo-*N*-(4-dodecylphenyl)-3-oxo-3-phenylpropanamide **2f**, yellow solid (overall yield: 69%), mp 82–84 °C. **^{1}HNMR** (DMSO-d_6, 400 MHz) *δ* 10.35 (s, 1H), 7.81(d, *J* = 8.0 Hz, 2H), 7.66 (t, *J* = 8.0 Hz, 1H), 7.53–7.59 (m, 4H), 7.18 (d, *J* = 8.0 Hz, 2H), 3.31–3.32 (m, 2H), 1.50–1.56 (s, 2H), 1.20–1.30 (s, 18H), 0.85 (t, *J* = 8.0 Hz, 3H). **^{13}CNMR** ($CDCl_3$, 100 Hz) *δ* 188.1, 158.4, 139.3, 136.7, 135.5, 132.8, 129.1, 128.9, 127.1, 120.2, 35.4, 31.9, 31.5, 29.7, 29.5, 29.4, 29.3, 22.7, 14.1.

2.4. Synthesis of 1,2,3-triazole grafted chitosans

All the grafting reactions were carried out under a nitrogen atmosphere in a three-necked round-bottom flask. Dimethylsulfoxide (DMSO) was used as the solvent and $PdCl_2$ (1 mol%) was used as the catalyst.

A typical procedure for the grafting reaction of chitosan with polymer 3a



Scheme 1. Synthesis of *α*-diazo-*β*-oxoamides.