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Synthesis of Novel Chitosan Derivatives

R.C. LI

Department of Chemistry, Dezhou University, Dezhou, P.R. China

Corresponding author: Fax: +86 534 8985835; Tel: +86 534 8985835; E-mail: lirc78@126.com

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Novel chitosan derivatives 2-[4-(2-fluorobenzylideneamino)pyridyl]acetyl chitosan chloride (FBPACS), 2-[4-(2-chlorobenzylideneamino)-pyridyl]acetyl chitosan chloride (CBPACS), 2-[4-(2-bromobenzylideneamino)pyridyl]acetyl chitosan chloride (BBPACS), 2-[4-(2,4-dichlorobenzylideneamino)pyridyl]acetyl chitosan chloride (DCBPACS) and 2-[4-(2,4-difluorobenzylideneamino)pyridyl]acetyl chitosan chloride (DFBPACS) were prepared. The structures of the derivatives were confirmed by Fourier transform infrared and ^{13}C nuclear magnetic resonance. These novel chitosan derivatives were expected to have potent biological activities due to the halo-benzaldehyde condensation 4-aminopyridine Schiff base structure in their molecules.

Key Words: Synthesis, Chitosan derivative, Halo benzaldehyde, 4-Aminopyridine.

INTRODUCTION

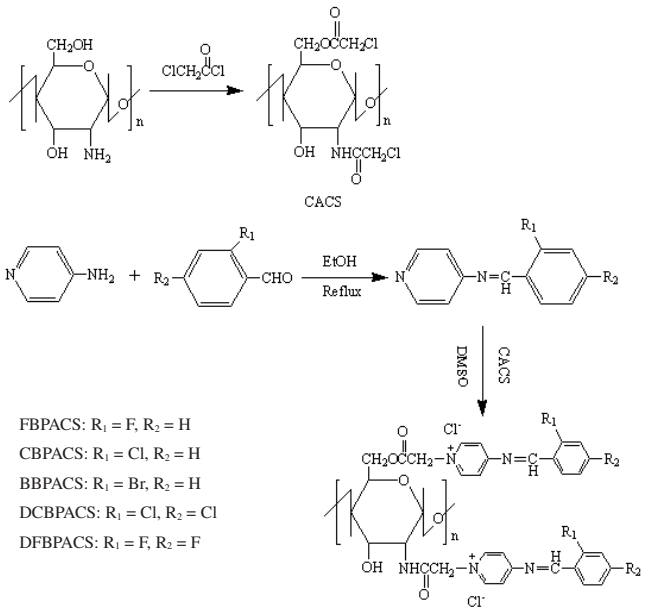
Recently synthetic fungicides have been used to control the plant fungus. However, in several studies it has been shown that the compounds used in these fungicides caused strain resistance representing a potential risk for the environment and human health[1,2]. The search of natural alternatives has been improved and option such as chitosan has been evaluated[3].

Chitosan is a copolymer of glucosamine and N-acetyl-glucosamine units linked by 1,4-glucosidic bonds, obtained by N-deacetylation of chitin[4]. It has a number of interesting properties such as a good biodegradability and a low toxicity for mammalian cells[5,6]. In addition, its antimicrobial activity has received considerable attention due to problems associated with fungicidal and bactericidal agents[7,8]. At present, it has been commonly recognized that the biological activity of chitosan depends on its molecular weight, degree of deacetylation, chemical modification, degree of substitution, pH, length and position of a substituent on the glucosamine units of chitosan and, of course, the target organism[9,10]. Therefore, several research groups have started to modify a chitosan molecule to produce derivatives with a high antimicrobial activity such as N-(sulfonated) and N-(sulfobenzoyl)chitosans[11], N,N,N-trimethyl chitosan[12], N,O-(acyl)chitosans[13], O-(acyl)chitosans[14], hydroxyethylacryl chitosan[15], dimethylpiperazine and trimethylpiperazine chitosans[16], carboxymethyl chitosans[17], acyl thiourea chitosans[18], chitosan N-betainates[19], N-succinoyl chitosans[20] and N-heterocyclic chitosans[21].

Chitosan and its derivatives have been considered as versatile biopolymers in agriculture applications. Nevertheless its potential uses as an antimicrobial compound need to be studied in depth[22]. Previously, we have noted that chloracetyl chitosan (CACS) was synthesized and its reactive chlorine can be used to chemically alter under mild reaction conditions. Two chitosan derivatives were prepared through the reaction of chloracetyl chitosan with 4-(5-chloro-2-hydroxybenzylideneamino)pyridine and 4-(5-bromo-2-hydroxybenzylideneamino)pyridine. The antifungal activity of the two derivatives was much better than that of the native chitosan[23]. In the present study, we further investigated this kind of chitosan derivatives and prepared five novel chitosan derivatives (**Scheme-I**): 2-[4-(2-fluorobenzylideneamino)pyridyl]-acetyl chitosan chloride (FBPACS), 2-[4-(2-chlorobenzylideneamino)pyridyl]acetyl chitosan chloride (CBPACS), 2-[4-(2-bromobenzylideneamino)pyridyl]acetyl chitosan chloride (BBPACS), 2-[4-(2,4-dichlorobenzylideneamino)-pyridyl]acetyl chitosan chloride (DCBPACS), 2-[4-(2,4-difluorobenzylideneamino)pyridyl]acetyl chitosan chloride (DFBPACS).

EXPERIMENTAL

Chitosan was purchased from Qingdao Baicheng biochemical Corp. (China). Its degree of deacetylation was 97 % and the average-molecular weight was 7.0×10^3. The other reagents were of analytical grade and used without further purification.



Scheme-I: Synthesis pathway of chitosan derivatives

Synthesis of chloracetyl chitosan[23]: 1.61 g chitosan was dispersed in 100 mL N-methyl-2-pyrrolidone (NMP) and stirred for 12 h at room temperature. Then 0.02 mol chloracetyl chloride was added. After stirring for 24 h at room temperature, the solution was precipitated in ether and the precipitate was washed with methanol and ether by turns and lyophilized.

General synthesis method of six chitosan derivatives: A solution of 0.01 mol substituent benzaldehyde and equimolar amount of 4-aminopyridine were refluxed in 30 mL ethanol for 4 h. The solvent was evaporated under reduced pressure and the product was dissolved by adding 20 mL of DMSO. After the product dissolved under stirring, 0.3 g chloracetyl chitosan was added. The solution was stirred at 60 ºC for 24 h and then precipitated with excess acetone and the precipitate was filtered. The unreacted aldehyde, amine and other outgrowth were extracted in a Soxhlet with ethanol for 2 days. The product was lyophilized.

The Fourier transform infrared (FT-IR) spectrum was measured by a JASCO FT-IR-4100 instrument using KBr disks. The ^{13}C nuclear magnetic resonance (^{13}C NMR) spectrum was measured by a Bruker AVIII-500 spectrometer.

RESULTS AND DISCUSSION

Fig. 1 presented the transmission FT-IR spectra of chitosan and its derivatives. In the FT-IR spectra of chloracetyl chitosan, the chitosan characteristic absorbance of -NH_2 at 1600 cm^{-1} disappeared. New peaks at 1750, 1666 and 787 cm^{-1} appeared in the spectra of chloracetyl chitosan, which were assigned to the C=O of -OCOR group, C=O of -NHCOR group and C-Cl group, respectively[24]. It indicated that chloracetyl chitosan was obtained by the acylated reaction between chloracetyl chloride and the groups (-NH_2, -OH) of chitosan. In the spectrum of FBPACS, new peaks appeared at 1450, 3081, 840 and 763 cm^{-1} which attributed to aromatic ring stretching vibrations, C-H stretching vibrations and benzene bending[25]. The characteristic absorbance of C-Cl at 787 cm^{-1} disappeared and the peaks of carbonyl groups of acylamide and ester were

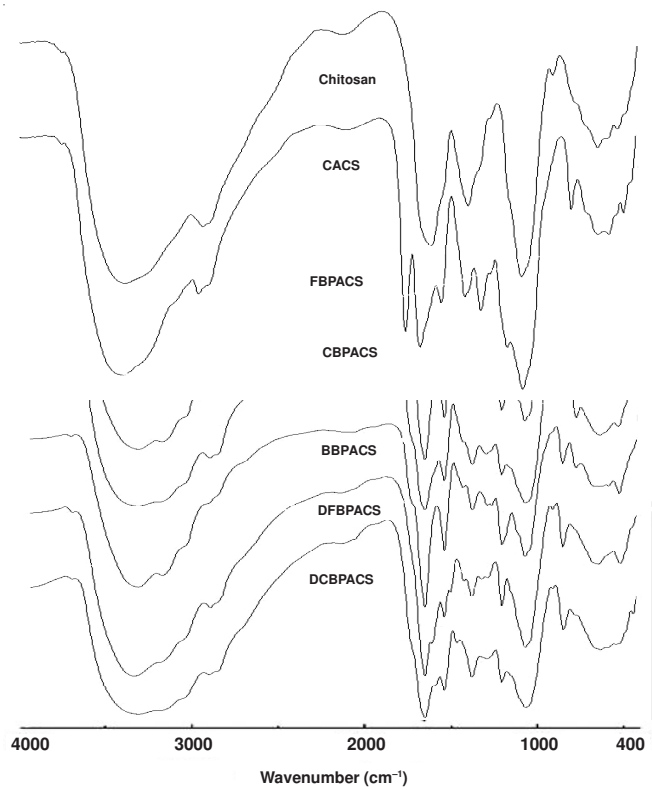


Fig. 1. FT-IR spectra of chitosan and its derivatives

bathochromic shifted to 1658 and 1727 cm^{-1}, respectively due to the graft of the 4-(2-fluoro-benzylideneamino)pyridine[26]. For the similar reason, the C-Cl characteristic absorbance at 787 cm^{-1} disappeared in the FT-IR spectra of CBPACS, BBPACS, DFBPACS and DCBPACS. New peaks due to aromatic ring appeared in the spectra of CBPACS, BBPACS, DFBPACS and DCBPACS.

Fig. 2 showed the ^{13}C NMR spectra of chitosan derivatives. The ^{13}C NMR chemical shifts of FBPACS, CBPACS, BBPACS, DFBPACS, DCBPACS signals were assigned as follows:

FBPACS/^{13}C NMR/D_2O/δ (ppm): δ 192.6 ppm (C=O of ester group), δ 168.5 ppm (C=O of acylamide), δ 143.6, 109.6 and 159.2 ppm (pyridine ring)[27], δ 159.6 ppm (carbon of N=CH-), δ 134.7, 136.1, 127.8, 131.4, 125.2, 129.7 (benzene ring carbons)[28], δ 55.8-100.6 ppm (pyranose rings). The peak of methylene carbon in -$OCOCH_2$- and that of methylene carbon in -NH_2COCH_2- was included in the peaks at about 60 ppm[29].

CBPACS/^{13}C NMR/D_2O/δ (ppm): δ 168.5 ppm (C=O of ester group), 165.7 ppm (C=O of acylamide), δ 143.6, 109.7 and 159.2 ppm (pyridine ring)[27], δ 159.2 ppm (carbon of N=CH-), δ 136.1, 137.5, 129.8, 131.7, 127.6, 130.8 (benzene ring carbons)[28], δ 55.8-97.5 ppm (pyranose rings). The peak of methylene carbon in -$OCOCH_2$- and that of methylene carbon in -NH_2COCH_2- was included in the peaks at about 60 ppm[29].

BBPACS/^{13}C NMR/DMSO/δ (ppm): δ 166.1 ppm (C=O of ester group), δ 166.1 ppm (C=O of acylamide), δ 144.5, 109.8 and 159.3 ppm (pyridine ring)[27], δ 159.9 ppm (carbon of N=CH-), δ 133.8, 138.3, 128.6, 131.2, 125.9, 130.1 (benzene ring carbons)[28], δ 56.1-101.3 ppm (pyranose rings). The peak of methylene carbon in -$OCOCH_2$- and that of methylene

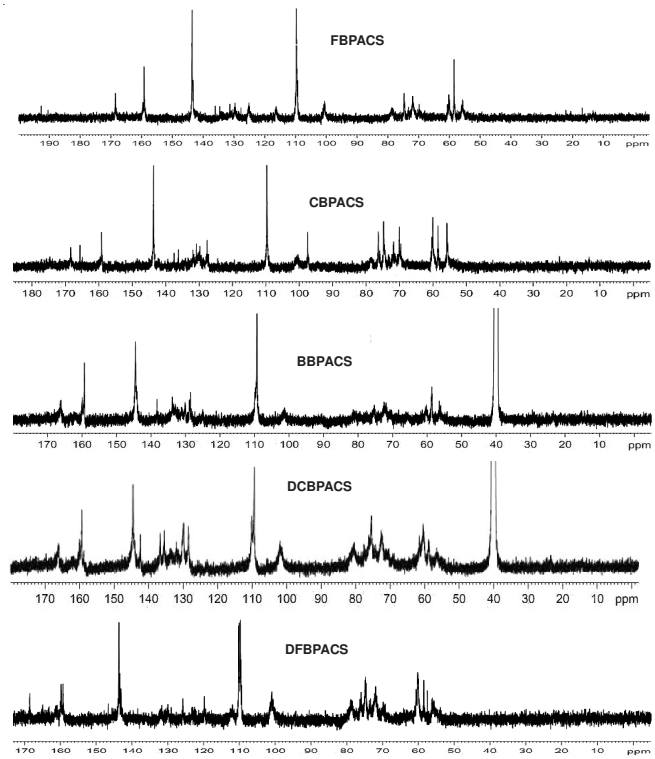


Fig. 2. ^{13}C NMR spectra of chitosan and its derivatives

carbon in -NH_2COCH_2- was included in the peaks at about 60 ppm[29].

DFBPACS/^{13}C NMR/D_2O/δ (ppm): δ 168.5 ppm (C=O of ester group), δ 168.5 ppm (C=O of acylamide), δ 143.7, 109.8 and 159.3 ppm (pyridine ring)[27], δ 159.8 ppm (carbon of N=CH-), δ 131.9, 141.7, 119.8, 130.0, 112.5, 125.8 (benzene ring carbons)[28], δ 56.1-100.9 ppm (pyranose rings). The peak of methylene carbon in -$OCOCH_2$- and that of methylene carbon in -NH_2COCH_2- was included in the peaks at about 60 ppm[29].

DCBPACS/^{13}C NMR/DMSO/δ (ppm): δ 166.0 ppm (C=O of ester group), δ 166.0 ppm (C=O of acylamide), δ 144.6, 109.4 and 159.3 ppm (pyridine ring)[27], δ 160.0 ppm (carbon of N=CH-), δ 136.6,142.4, 129.9, 135.4, 128.4, 133.7 (benzene ring carbons)[28], δ 58.9-101.9 ppm (pyranose rings). The peak of methylene carbon in -$OCOCH_2$- and that of methylene carbon in -NH_2COCH_2- was included in the peaks at about 60 ppm[29].

Conclusion

All the 5 derivatives of chitosen *i.e.*, FBPACS, CBPACS, BBPACS, DFBPACS and DCBPACS were synthesized successfully by reaction of the condensation product of 4-aminopyridine and halo-benzaldehyde with the reactive Cl of CACS. Many researchers have showed that aromatic nucleus Schiff bases have good bioactivities[30,31]. It is also reported that the aromatic ring with one or more halo-atoms showed variety of biological activities like antibacterial and antifungal activities[32]. Above novel chitosan derivatives were expected to have potent biological activities due to the halo-benzaldehyde condensation 4-aminopyridine Schiff base structure in their molecules.

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REFERENCES

1. J.E. Adaskaveg, H. Förster and N.F. Sommer, Postharvest Technology of Horticultural Crops, Oakland, USA: University of California, pp. 163-195 (2002).
2. J. Northover and T. Zhou, *Can. J. Plant Pathol*., **24**, 144 (2002).
3. P. Tripathi and N.K. Dubey, *Postharvest Biol. Technol*., **32**, 235 (2004).
4. H.K. No and S.P. Meyers, In eds.: ed. R.A.A. Peter M.G. and A. P. Grottammare, Preparation and Production of Chitin and Chitosan, Muzzarelli Chitin Handbook, Italy, European Chitin Society, pp. 475-489 (1997).
5. Z. Guo, R. Xing, S. Liu, Z. Zhong, X. Ji, L. Wang and P. Li, *Carbohydr. Res*., **342**, 1329 (2007).
6. R.A.A. Muzzarelli, C. Muzzarelli, R. Tarsi, M. Miliani, F. Gabbanelli and M. Cartolari, *Biomacromolecules*, **2**, 165 (2001).
7. Y. Jeon and S. Kim, *Carbohydr. Polym*., **41**, 133 (2000).
8. N. Liu, X.G. Chen, H.J. Park, C.G. Liu, C.S. Liu, X.H. Meng and L.J. Yu, *Carbohydr. Polym*., **64**, 60 (2006).
9. D.V. Gerasimenko, I.D. Avdienko, G.E. Bannikova, O.Y. Zueva and V.P. Varlamov, *Appl. Biochem. Microbiol*., **40**, 253 (2004).
10. Y.J. Jeon, P.J. Park and S.K. Kim, *Carbohydr. Polym*., **44**, 71 (2001).
11. C.S. Chen, W.Y. Liau and G.J. Tsai, *J. Food Protect*., **61**, 1124 (1998).
12. Z. Jia, D. Shen and W. Xu, *Carbohydr. Res*., **333**, 1 (2001).
13. M.E.I. Badawy, E.I. Rabea, T.M. Rogge, C.V. Stevens, G. Smagghe, W. Steurbaut and M. Höfte, *Biomacromolecules*, **5**, 589 (2004).
14. M.E.I. Badawy, E.I. Rabea, T.M. Rogge, C.V. Stevens, W. Steurbaut, M. Höfte and G. Smagghe, *Polym. Bull*., **54**, 279 (2005).
15. G. Ma, D. Yang, Y. Zhou, M. Xiao, J.F. Kennedy and J. Nie, *Carbohydr. Polym*., **74**, 121 (2008).
16. M. Másson, J. Holappa, M. Hjálmarsdóttir, O.V. Rúnarsson, T. Nevalainen and T. Järvinen, *Carbohydr. Polym*., **74**, 566 (2008).
17. F. Seyfarth, S. Schliemann, P. Elsner and U.C. Hipler, *Int. J. Pharm*., **353**, 139 (2008).
18. Z. Zhong, R. Xing, S. Liu, L. Wang, S. Cai and P. Li, *Carbohydr. Res*., **343**, 566 (2008).
19. J. Holappa, M. Hjálmarsdóttir, M. Másson, Ö. Rúnarsson, T. Aaplund, P. Soininen, T. Nevalainen and T. Järvinen, *Carbohydr. Polym*., **65**, 114 (2006).
20. V.E. Tikhonov, E.A. Stepnova, V.G. Babak, I.A. Yamskov, J. Palma-Guerrero, H.B. Jansson, L.V. Lopez-LIorca, J. Salinas, D.V. Gerasimenko, I.D. Avdienko and V.P. Varlamov, *Carbohydr. Polym*., **64**, 66 (2006).
21. M.EI. Badawy, *Polym. Int*., **57**, 254 (2008).
22. E.I. Rabea, M.E.T. Badawy, C.V. Stevens, G. Smagghe and W. Steurbaut, *Biomacromolecules*, **4**, 1457 (2003).
23. R. Li and Z. Guo and P. Jiang, *Carbohydr. Res*., **345**, 1896 (2010).
24. R.H. Huang, Y.M. Du, L.S. Zheng, H. Liu and L.H. Fan, *React. Funct. Polym*., **59**, 41 (2004).
25. H. Khanmohammadi and M. Darvishpour, *Dyes Pigm*., **81**, 167 (2009).
26. L. Vachoud, T.H. Chen, G.F. Payne and R. Vazquez-Duhalt, *Enzym. Microbiol. Technol*., **29**, 380 (2001).
27. K. Chruszcz, M. Baranska, K. Czarniecki, B. Boduszek and L.M. Proniewicz, *J. Mol. Struct*., **648**, 215 (2003).
28. H. Dal, Y. Süzen and E. Sahin, *Spectrochim. Acta A*, **67**, 808 (2007).
29. A. Heras, N.M. Rodríguez, V.M. Ramos and E. Agulló, *Carbohydr. Polym*., **44**, 1 (2001).
30. C.Y. Liu, W.Y. Ge, J. Qian, Z. Li and A.H. Yu, *Chin. J. Chem. Reag*., **25**, 160 (2003).
31. M.S. Karthikeyan, D.J. Prasad, B. Poojary, K.S. Bhat, B.S. Holla and N.S. Kumari, *Bioorg. Med. Chem*., **14**, 7482 (2006).
32. L.C. Felton and J.H. Brewer, *Science*, **105**, 409 (1947).