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Synthesis and characterization of novel silyl derivatives of curcumin

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Abstract

Turmeric which is a member of the ginger family (Zingiberacea) is extensively used as a spice, food preservative and colouring material. Curcumin is a main bioactive natural compound derived from the rhizome of this plant. Curcumin can exist in several tautomeric forms, such as keto and enol. The keto form is more stable than enol form. Silyl ethers have proven to be versatile substrates for a wide variety of organic reactions and they can be prepared by the reaction of alcohol and silicon halide using a base such as triethylamine in stoichiometric quantity. Curcumin-silyl ether derivatives were prepared under mild conditions. The stability of products decreases when the size of the silyl substitutions increases.

Keywords: Turmeric, Curcuma Longa, curcumin, silyl ethers, silicon halide.

Introduction

Turmeric (curcuma longa) which is a member of the ginger family (Zingiberaceae) can be extensively used as a spice, food preservative and colouring material in China, India and South East Asia. Although most usages of turmeric are in the form of root powder

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[1-3], Curcumin is a main bioactive natural compound derived from the rhizome of Curcuma Longa [2]. It has anti-tumor [4,5], anti-HIV protease activity [6], anti-inflammatory [7], alzheimer's disease [8] and other functions. Curciminoids are responsible for the yellow colour of turmeric powder [9]. Curcumin is a pH indicator. Moreover, it turns yellow in acidic solutions, whereas in basic solutions it turns bright red [10-13]. Curcumin can exist in several tautomeric forms, e.g. keto and enol. The keto form is more stable in solid phase and enol form is energetically stable in solution [1]. Silyl ethers have proven to be versatile substrates for a wide variety of organic reactions and they are prepared by alcohol and silicon halide reaction using a base such as triethylamine in stoichiometric quantity [14-22]. Curcumin, due to the hydroxyl groups in its molecular structure, has a hydrophilic property, besides, replacement of the hydroxyl groups' hydrogen with silicon groups increases the lipophilic state of curcumin which is due to the structure of silicon. Whereas, body cell membranes are made of phospholipid and have lipophilic properties, silyl derivatives crosses cell membranes, hydrolize intracellular and curcumin releases. In the aqueous environment of the cell, hydrophilic curcumin case will help to show its own effect.

Experimental

All silylation reactions were carried out under dry argon gas to exclude oxygen and moisture from the system because chlorosilanes are highly moisture sensitive reagents [20]. The solvents and regents were purchased from Merck Company. All the solvents were distilled and stored over a drying agent. Tetrahydrofuran (THF) was dried by a standard method and $^{t}BuMe_2SiCl$, Et_3SiCl and Me_3SiCl were used as received. IR spectra were recorded with a Shimadzu FTIR-408 spectrophotometer as KBr pells. ^1H NMR spectra were recorded on a Brucker 400 AC spectrometer in $CDCl_3$ as a solvent at room temperature. TLC

was performed by the use of Merck's silica gel.

Synthesis of trimethylsilyl derivative of curcumin

The trimethylsilyl derivative was prepared by the treatment of 1.1 g (3 mmol) curcumin with 1.2 mL (9 mmol) trimethylchlorosilane and 0.9 mL (9 mmol) triethylamine at room temperature in dried THF under dry argon gas. After 24 h stirring the reaction mixture was filtered. The product (Scheme 1) was chromatographed over silicagel by CH_2Cl_2: n-hexane: ethyl acetate in a ratio of 10:1:5 to good yield. IR (neat, cm^{-1}): 1704 (stretching conjugated carbonyl), 1276 and 1261 (stretching Si-C) and 1083 (stretching Si-O). ^{1}H-NMR (FT-400 MHz, $CDCl_3$): δ; 1.58 (s, $3H_i$ and $9H_b$), 3.98 (s, $3H_a$), 5.33 (s, $1H_h$), 5.83 (s, $1H_k$), 5.88 (s, $1H_j$), 6.51 (d, $1H_g$), 6.96 (d, $1H_d$), 7.08 (s, $1H_c$), 7.15 (d, $1H_e$) and 7.62 (d, $1H_f$).

Synthesis of triethylsilyl derivative of curcumin

The triethylsilyl derivative (Scheme 2) was prepared by the treatment of 1.1 g (3 mmol) curcumin with 1.5 mL (9 mmol) triethylchlorosilane and 0.9 mL (9 mmol) triethylamine at room temperature in dried THF under dry argon gas. After 24 h of stirring, the reaction mixture was filtered. The product was chromatographed over silica gel by CH_2Cl_2: n-hexane in a ratio of 10:1 to good yield. IR (neat, cm^{-1}): 1742 (stretching C=O), 1232 (stretching Si-C), 1083 (stretching Si-O) and 848 (bending Si-C). The compound was unstable due to bulky ethyl groups and its tendency to form a ring at the place of carbonyl groups; it was destroyed after 6 hours. The destruction of product was determined with the appearance of a broad peak due to the fact that hydroxyl groups were in 3424 cm^{-1} and the shift in stretching vibrations peak of the carbonyl

group were from 1742 cm^{-1} to 1692 cm^{-1} at IR spectrum.

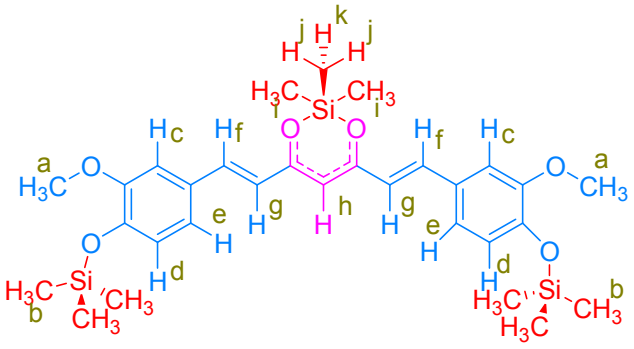
Synthesis of tert-butyldimethylsilyl derivative of curcumin

The tert-butyldimethylsilyl derivative of curcumin (Scheme 3) was prepared by the treatment of 1.1 g (3 mmole) curcumin with 1.4 mL (9 mmol) tert-butyldimethylchlorosilane and 0.9 mL (9 mmol) triethylamine at room temperature in dried THF under dry argon gas. After 48 h of stirring, the reaction mixture was filtered. Then the product was chromatographed over silicagel by CH_2Cl_2: $CHCl_3$: n-hexane in a ratio of 5:10:1 to good yield. IR (neat, cm^{-1}): 1731 (stretching C=O), 1229 (stretching Si-C), 1020 (stretching Si-O) and 800 (bending Si-C). The compound was unstable due to bulky tert-butyl group and its tendency to form a ring at the place of carbonyl groups; it was destroyed after 2 hours.The destruction of product was determined with the appearance of a broad peak which was due to the notion that hydroxyl groups were in 3421 cm^{-1} and the shift in stretching vibrations peak of the carbonyl group was from 1731 cm^{-1} to 1702 cm^{-1} at IR spectrum.

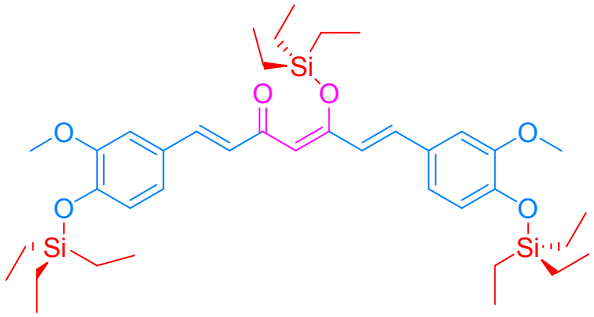
Results and discussion

Silyl ethers are very interesting fields in organic synthesis; they can be used as protective group of alcohols, phenols and carboxylic acids. The reaction mechanism is simple for the silyl ethers synthesis. Triethylamine as a moderate base abstract acidic hydrogen of all hydroxyl groups of curcumin, then the resulting alkoxy groups attack silyl reagents by SN_2 mechanism, then as a result, the chloride ions are altered by mentioned groups [24]. The curcumin interacted with $^tBuMe_2SiCl$, Et_3SiCl and Me_3SiCl and the hindrance effects of silicon halides on the stability of resulting compounds were investigated. All reactions were carried out with high yields approximately above 90 percent. In trimethylsilyl derivative, the silyl group can compose sextet ring with two carbonyl groups of curcumin in enol state,

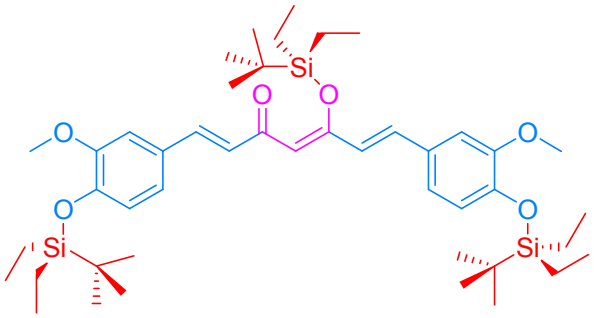
because trimethylsilyl branches are small and the resulting sextet ring is stable. But, in other two products, the silyl groups can't compose sextet ring with curcumin because the branches of silyl reagents (ethyl and tert-butyl) are large and the sextet rings are very unstable, then only one carbonyl group of curcumin participates with enol form in the products. Due to the complex ring structure and for space reasons, the stability of complex rings decreases with increasing size of the substituted and the products will be unstable.



Scheme 1. Structure of trimethylsilyl derivative of curcumin



Scheme 2. Structure of triethylsilyl derivative of curcumin



Scheme 3. Structure of tert-butyldimethylsilyl derivative of curcumin

In this study, we synthesized the silyl derivatives of curcumin with SN_2 mechanism with a moderate base at room temperature. After synthesis of silyl derivatives, we saw that the stability of products decreases with increasing size of the silyl substitutions and the products will become unstable.

Acknowledgments

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