

## Synthesis of Silica-anchored Sensitizer and its Application in the Preparation of Previtamin D<sub>3</sub> from Tachysterol

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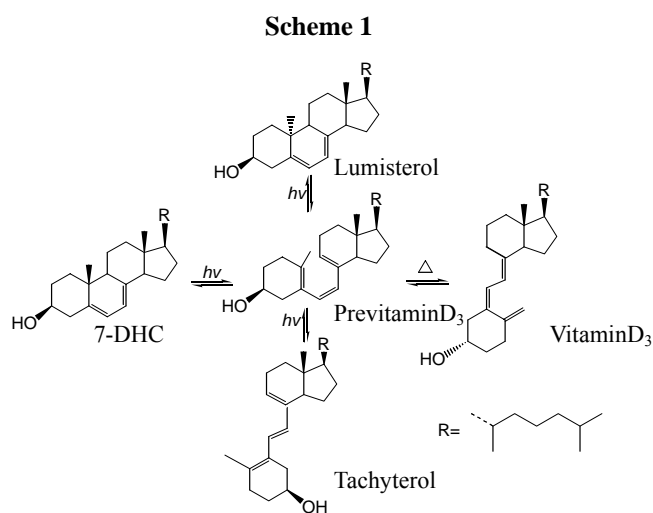
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**Abstract:** A silica gel-anchored photosensitizer was synthesized with anthracene as sensitizer moiety. The photoisomerization of tachysterol to previtamin D<sub>3</sub> was carried out with this heterogeneous photosensitizer in ethanol. The experiment results demonstrate that this solid phase photosensitizer is efficient for the photoisomerization and can be simply separated from the reaction mixture by filtration.

**Keywords:** Solid phase photosensitizer, photoisomerization, tachysterol, vitamin D<sub>3</sub>.

The photochemistry of 7-dehydrocholesterol (7-DHC) has been studied extensively in many years<sup>1-3</sup>. As shown in **Scheme 1**, irradiation of 7-dehydrocholesterol (7-DHC) in



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organic solvent results in its photoisomerization to previtamin D<sub>3</sub> (Pre). Previtamin D<sub>3</sub> can be thermally transferred into vitamin D<sub>3</sub> (VD<sub>3</sub>), which is of commercial interest. However, previtamin D<sub>3</sub> will further undergo photoisomerization resulting in the undesired toxic tachysterol (Tachy)<sup>4</sup>. Even when the irradiation conditions are well controlled there is still about 15% formation of tachysterol that lowers the yield of previtamin D<sub>3</sub> (and hence of the vitamin D<sub>3</sub>) during the production process.

It is well known that photochemical conversion of tachysterol to previtamin D<sub>3</sub> can be conducted by irradiation with appropriate UV light in the presence of triplet photosensitizers, such as anthracene, 9-fluorenone, benzanthrone, *etc*<sup>4,5</sup>. All these sensitizers can only be separated from the reaction mixtures by column chromatography. This procedure is not feasible for the large scale production of vitamin D. To overcome this difficulty, water-soluble<sup>6</sup> and non-crosslinked polymeric photosensitizers<sup>7-9</sup> were used in these reactions. Although column chromatography is not necessary in these methods, the process is not environment friendly and not economic for manufacture. The separation of the sensitizer will produce a large amount of waste water or mixed solvents. In this paper, we synthesize a silica-anchored anthracene for photoisomerizing tachysterol into previtamin D<sub>3</sub>. This sensitizer can be simply separated from the reaction mixture by filtration.

## Experimental

The silica-anchored anthracene was synthesized in the following procedure. To a slurry of silica gel H in dry THF, malonic acid, N, N'-dicyclohexylcarbodiimide (DCC) and dimethylaminopyridine (DMAP) were added. After being stirred for 3 days at room temperature, the reaction mixture was filtered and washed and the residue was heated in the vacuum oven at 80 °C for 12 hours. The obtained silica was then reacted with 9-anthracenemethanol in THF using DCC and DMAP as catalysts at room temperature for 2 days. After filtration and washing, the silica-anchored anthracene (Silica-An) was dried in the vacuum oven.

The photochemical reactions were carried out using a 450W medium pressure Hanovia lamp in a water-cooled quartz immersion well. The first irradiation (a solution of 7-DHC) was performed in a quartz reactor for 30 minutes and the second irradiation (photosensitization) was carried out in the glass reactor to cut off the light with wavelength below 300 nm. Argon was bubbled *prior to* and during the irradiation. In the recycle experiments, the solid phase photosensitizer was filtered from the reaction mixture and washed by THF and methanol. After being dried in vacuum, it was reused directly in the next irradiation.

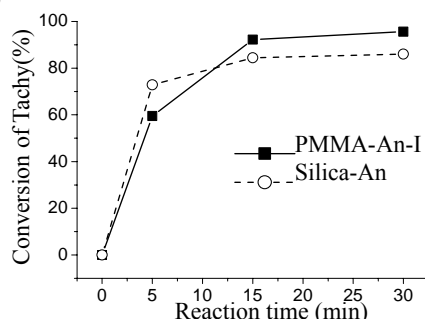
The photochemical reaction was followed by a Hitachi HPLC system, equipped with L-7110 pump and L-7420 UV/Vis detector. An Alltima LC-Si 5 μm column (4.6 mm ID, 25 cm) was used with a mobile phase of 0.3% pentanol in hexane. The samples were monitored at 254 nm with flowing rate 2 mL/min. Retention time and independent samples established peak identities. The conversion of tachysterol can be obtained by comparison the peak areas of tachysterol before and after the second irradiation.

## Results and Discussion

The preparation of silica-anchored sensitizer was described in the experimental section. The amount of the anthracene moieties was determined by UV absorption intensity of the 9-anthracene derivative that was yielded by saponification of the solid phase sensitizer with KOH as base. The loading was found to be  $5 \times 10^{-5}$  mol/g.

The photochemical reaction was followed by HPLC. **Figure 1** shows the photoisomerization results with Silica-An and PMMA-An-I as sensitizers (PMMA-An-I is cross-linked poly(methyl methacrylate)-bound anthracene with the loading of  $6 \times 10^{-5}$  mol/g). All the consumption of tachysterol was corresponding to the formation of previtamin D<sub>3</sub> and vitamin D<sub>3</sub> determined by HPLC. The same amounts of anthracene moieties were used in these experiments. In another paper<sup>10</sup> it has been shown that PMMA-An-I is efficient in the photoisomerization of tachysterol to previtamin D<sub>3</sub>. From the results shown in **Figure 1**, the photostationary state is almost reached after 15 minutes irradiation. The conversion of tachysterol with Silica-An is about 84%, a little bit lower but still compatible than that with PMMA-An-I as sensitizer. The results also show that the photoreaction rate is higher with Silica-An than PMMA-An-I.

**Figure 1** Conversion of tachysterol with different solid phase photosensitizers at ambient temperature in ethanol (concentration of anthracene moiety:  $1.0 \times 10^{-4}$  mol/L; [7-DHC] = 1 mg/mL)



**Table 1** Conversion of tachysterol with different amounts of Silica-An at ambient temperature in ethanol ([7-DHC] = 1 mg/mL)

	Concentration of anthracene moiety (mol/L)	Irradiation time (min)			
		0	5	15	30
Conversion of Tachy (%)	$5.6 \times 10^{-5}$	0	52	71	81
	$1.4 \times 10^{-4}$	0	66	80	84

The photoisomerizations with different amounts of Silica-An were also studied. The results are listed in **Table 1**. As expected, the reaction proceeds faster with more sensitizer because it will enhance the probability of the reactant encountering the anthracene moieties, but the rate increase is not proportional to the amount of

photosensitizer.

Generally the photodimerization is considered as the reason for the bleach of anthracene<sup>11</sup>. When anthracene chromophores are anchored on silica gel, the photobleaching may be suppressed, because the anthracene chromophores are separated from each other by solid phase support. The recycle experiment results of eight runs are shown in **Table 2**. The irradiation time was kept constant for each cycle. The sensitization efficiency dropped about 10% in the first recycle and 2% in the rest runs. This indicates that some anthracene chromophores anchored on silica gel may not distribute very well or have relatively high local concentration. So the solid phase photosensitizer with better recycle property may be obtained by lower loading and well dispersing of sensitizer moieties.

**Table 2** The recycle results of Silica-An

Number of cycle	1	2	3	4	5	6	7	8
Conversion of Tachy (%)	86.0	77.4	75.0	74.4	70.2	69.2	68.3	66.0

Irradiation time for each cycle: 30 minutes, concentration of anthracene moiety:  $1.0 \times 10^{-4}$  mol/L; [7-DHC] = 1 mg/mL

In conclusion, the results presented in this paper prove that the silica gel-bound anthracene is efficient in the photoisomerization of tachysterol to previtamin D<sub>3</sub> with recycle possibility and feasible to industrial production owing to its easy separation from the reaction mixture.

### Acknowledgments

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