

Photosensitization of *trans*-Vitamin D₃ to *cis*-Vitamin D₃ in Heterogeneous System

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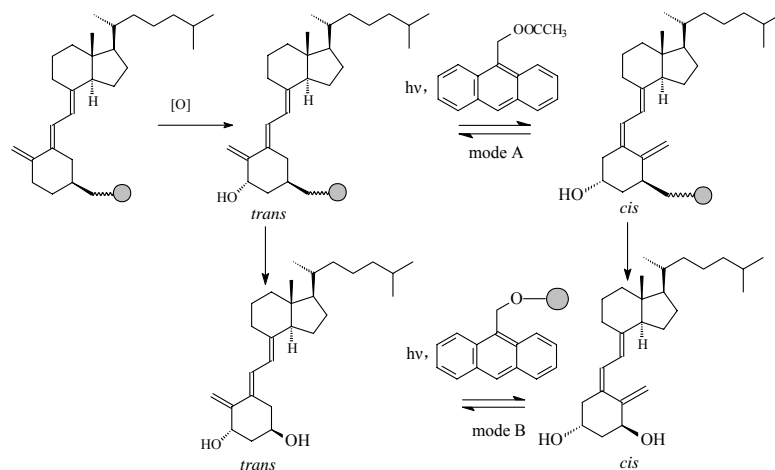
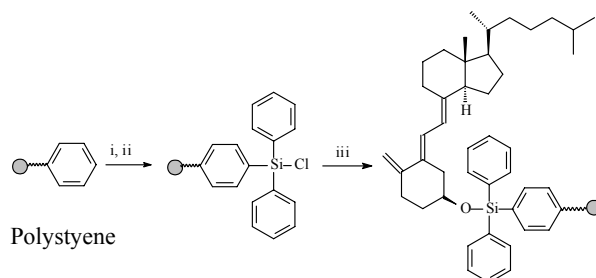
Abstract: Two modes of heterogeneous photoisomerization of *trans*-vitamin D₃ to *cis*-vitamin D₃ are described. The occurrence of isomerization on the substrate bounded to the polymeric support gives us the possibility in succession synthesis of 1 α -hydroxyvitamin D₃. The polymer-bound anthracene can sensitize isomerization of *trans*-vitamin D₃ to *cis*-vitamin D₃ efficiently and ease the separation process.

Keywords: Heterogeneous photoisomerization, vitamin D₃, solid phase.

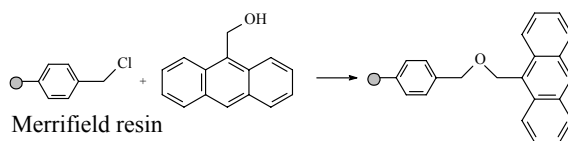
Recently the chemical and biochemical studies on 1 α -hydroxyvitamin D₃, the hormonally active metabolite of vitamin D₃ (VD₃), have rapidly expanded due to its broader spectrum of biologic activities¹⁻³. In order to synthesize 1 α -hydroxyvitamin D₃ and its analogues, several strategies in homogenous phase have been developed⁴⁻⁷. However time-consuming purification and separation of the product from the reaction mixtures are headachy problems.

To simplify the procedure and improve the yield of the synthesis of 1 α -hydroxyvitaminD₃ and its derivatives we consider the application of solid phase organic synthesis (SPOS) method by using the benefits of SPOS, such as ease of processing^{8,9}. The *cis/trans* isomerization is one of the key steps in the synthesis of hydroxylated vitamin D metabolites so we mainly discuss the results of photoisomerization here. It is well known that the conversion of *trans*- into *cis*-isomer is conducted by irradiation with appropriated UV light in the presence of photosensitizers, such as anthracene, 9-fluorenone, benzanthrone *etc.*¹⁰⁻¹². In this paper two modes of heterogeneous reactions are studied. One is that the substrate bounded to the polymeric support conducts several consecutive reaction steps (Mode A, **Scheme 1**) which takes the advantage of the stereochemistry controlled oxidation by using solid phase resin support (it has been discussed elsewhere¹³). The other is that the dissolved substrate reacts with polymer-bound reagent (Mode B, **Scheme 1**).

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Scheme 1**Scheme 2** Preparation of polymer bound *trans*-VD₃

(i) ⁿBuLi, TMEDA, cyclohexane, 60 °C, 12h; (ii) diphenyldichlorosilane, benzene, rt., overnight; (iii) imidazole, CH₂Cl₂, rt., overnight

Scheme 3 Preparation of polymer bound sensitizer

DMF/NaH, 80 °C, 48h

Experimental

The procedures for preparation of polymer bound *trans*-VD₃ and polymer bound sensitizer are showed in **Scheme 2**¹⁴ and **Scheme 3**¹⁵ respectively. The photochemical reactions were carried out by using a 450W medium pressure Hanovia lamp in a water-cooled quartz immersion well. All the samples were in glass reactors to cut off the wavelength below 300 nm and were bubbled with argon prior to and during irradiation.

Results and Discussion

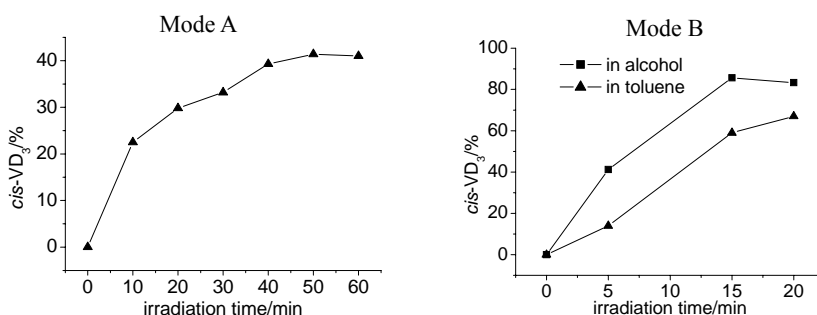
The preparation of polymer bound sensitizer was described in the experimental section. The active silyl chloride content of the polymer was determined by hydrolysis followed by acid-base titration to be 8.2×10^{-4} mol/g resin. The amount of the sensitizer in the Merrifield resin backbone was determined by UV absorption intensity of the 9-anthracene derivative which was cleaved by Schaap's¹⁶ cleavage procedure with SnCl₄¹⁵ as cleaving agent. The loading was found to be 2.0×10^{-5} mol/g. The samples were taken during the reaction and cleaved by using tetrabutylammonium fluoride (TBAF) as cleaving agent for mode A. The amounts of *cis*-VD₃ were analyzed by HPLC.

Figure 1 shows the change of concentration of *cis*-VD₃ during irradiation by mode A and mode B. In mode A, after 40 min irradiation the yield of *cis*-VD₃ was 40% and no obvious increase by prolonging the reaction time. On the other hand, about 85% *trans*-VD₃ was converted into *cis*-VD₃ in alcohol and 67% in toluene after 20min irradiation for mode B. The formation of *cis*-VD₃ was almost 100% based on the consumption of *trans*-VD₃. The efficiency of mode A is much lower than that of mode B. This result can be explained by light scattering of the resin because a relative large amount of the resin was used in mode A than mode B and the yield of *cis*-VD₃ can be increased when large amount of the solvent is used. The other reason for this could be that *trans*-VD₃ was wrapped by resin and part of them could not absorb light.

The photoisomerizations through mode A with different amount of sensitizer were also investigated. To avoid over irradiation, the reaction time was fixed at 20 minutes. The results are shown in **Table 1**. As expected, the reaction is faster when higher concentration sensitizer is used within our experiment scale. The similar tendency can be observed in mode B.

Furthermore, the recycle property of polymer-bound sensitizer was investigated and the results are shown in **Table 2**. After three cycles the sensitizer still shows reasonable sensitization efficiency.

Figure 1 The change of the concentration of *cis*-VD₃ as a function of irradiation time



In toluene and concentration of sensitizer: 0.10 mol/L; initial concentration of *trans*-VD₃ moiety: 1.2×10^{-2} mol/L

Concentration of sensitizer moiety: 4×10^{-5} mol/L; initial concentration of *trans*-VD₃: 8.0×10^{-4} mol/L

Table 1 The yield of *cis*-VD₃ in toluene with different concentration of sensitizer after 20 min irradiation with mode A

Concentration of sensitizer/(mol/L)	0.02	0.04	0.06	0.08	0.10
<i>cis</i> -VD ₃ /%	12.5	16.1	20.3	31.0	35.5

initial concentration of *trans*-VD₃ moiety: 1.2×10^{-2} mol/L.

Table 2 Recycle results of the polymer-bound sensitizer

Cycle	<i>cis</i> -VD ₃ /%
1	88.0
2	87.8
3	80.2

8.0×10^{-3} mol/L polymer-bound sensitizer, 8×10^{-4} mol/L *trans*-VD₃ in alcohol.

Conclusion

The results presented in this paper indicate that the polymer-bound anthracene can sensitize *trans*-VD₃ to isomerize to *cis*-VD₃ efficiently and this heterogeneous photosensitizer may be feasible to the industrial production because of its easy separation from the reaction mixture. The occurrence of isomerization on the substrate bounded to the polymeric support shows us the possibility in succession synthesis of 1 α -hydroxy-vitamin D₃ by using SPOS.

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