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Report

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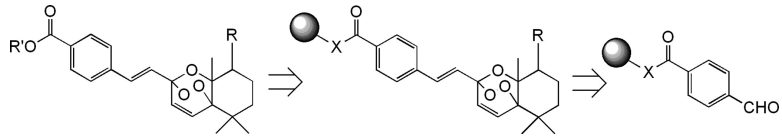

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Photoinduced Oxygen Capture on Immobilized Dienone Systems. First Solid-Phase Synthesis of Trioxane Scaffolds

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Solid-phase synthesis has developed to become a key tool in many aspects of chemistry in general and in drug discovery process in particular. The solid-supported synthesis of cyclic, nonoligomeric structures has been the focus of recent investigations with application toward a variety of natural product scaffolds and drug-like molecules.[1] Particularly, heterocyclic compounds continue to be attractive targets because they often exhibit diverse and important biological properties.[2] Thus, the library concept has been extended to hetero- and polycyclic structures, and it has stimulated the adaptation to solid support of many procedures for carbon−carbon and carbon−heteroatom bond formation.

Identification of a rare 1,2,4-trioxane element as the pharmacophore unit within the potent antimalarial natural product artemisinin has led to intensive interest in this unusual moiety extending the attention to all kind of cyclic peroxides.[3] In recent times, these substances have been investigated as antifungal,[4] antiproliferative,[5] antitumor,[5] and immunosuppressive,[6] among other interesting biological activities.[7] In addition, an increasing number of peroxide-containing natural products are being isolated, rendering peroxidic compounds as a prominent family worthy of investigation. In this context, the integration of methods for the incorporation of oxygen−oxygen units to organic compounds into the pool of reactions used in solid-phase organic synthesis will increase the potential of this chemistry for preparing large and diverse compound libraries.

Compared with other covalent bonds, peroxy bonds are quite fragile and incompatible with a range of reactions conditions, as well as reagents commonly used in organic synthesis.[8] Thus, the existing methodologies for introducing peroxy bonds into organic molecules are quite limited being a rather challenging field that requires the preparation of appropriate substrates. A methodology of great synthetic importance and with wide application in solution-phase chemistry is the photosensitized oxygenations.[9] However, these methods have remained substantially at the margin of solid phase. Moreover, examples of photochemical processes on solid support are still scarce[10] and often limited to the reactions with photolabile linkers.[11] As part of our studies on the chemistry of peroxidic compounds[12] and the application of solid-phase techniques to biologically interesting molecules,[13] we describe herein the first example of light-mediated oxygenation on solid support for the synthesis of 1,2,4-trioxane compounds.

After selection of polystyrene polymer as the solid support[14] and Wang and Rink resins as linkers, our synthetic sequence started with the preparation of the resin-bound *p*-carboxybenzaldehydes (**1a** and **b**) to employ them for anchoring the photooxygenation precursor (Scheme 1). Thus, aldol condensation between **1a** and **b** and an excess of β-ionone derivatives **2a** and **b** and LiOH in DME, led to the immobilized dienones **3a**−**c**. Irradiation with UV light (354 nm) of a toluene suspension containing **3a** in the presence of oxygen was monitored by gel-phase ^{13}C NMR. After 45 min at room temperature, formation of the photooxigenated product **4a** was evident from the presence of peaks at 82.4 and 94.4 ppm corresponding to the peroxy-bearing carbon (C-1) and peroxyketal carbon (C-8) of the trioxane system, respectively.[12a]

The time of the reaction was finally established in 2 h, according to the disappearance of the peaks corresponding to the starting material **3a** at the gel-phase ^{13}C NMR. Similar results were obtained with the Wang resin-bound dienone **3b**.

After synthesis of the solid-supported 1,2,4-trioxane **4a** was achieved, release from the resin was not trivial. Conventional acid treatment, such as 20% TFA in DCM led to the triketone **5a** as the only detectable product, albeit in low overall yield (9%) (Scheme 2). Formation of **5a** can be explained by a cleavage of the peroxy bond, followed by subsequent β-scission reactions, analogous to metal-promoted rearrangement of the 1,2,4-trioxane system.[12b] Different concentrations of TFA and other acids, including Lewis acids, were tested with similar results; the rearranged product **5a** was achieved in variable yields. As expected, Wang resin-bound trioxane **4b** yields the corresponding triketone **5b**.

Because of these unsuccessful results, we decided to test a nucleophilic cleavage of the Wang resin-immobilized trioxane **4b**. Therefore, treatment of **4b** with 1 equiv of NaOMe in THF/MeOH[15] led to the methyl ester **6b** in 32% overall isolated yield (Scheme 3). In addition to the methyl ester **6b**, a small amount of the trioxane **7** was isolated (2%). Although epoxides are not ordinary products from this type of reactions, there are some reports on the photosensitized epoxidation of olefins.[16] These results have been interpreted as a consequence of the deoxygenation of the intermediate peroxirane caused by either the singlet oxygen or the alkene.[17] Interestingly, a similar

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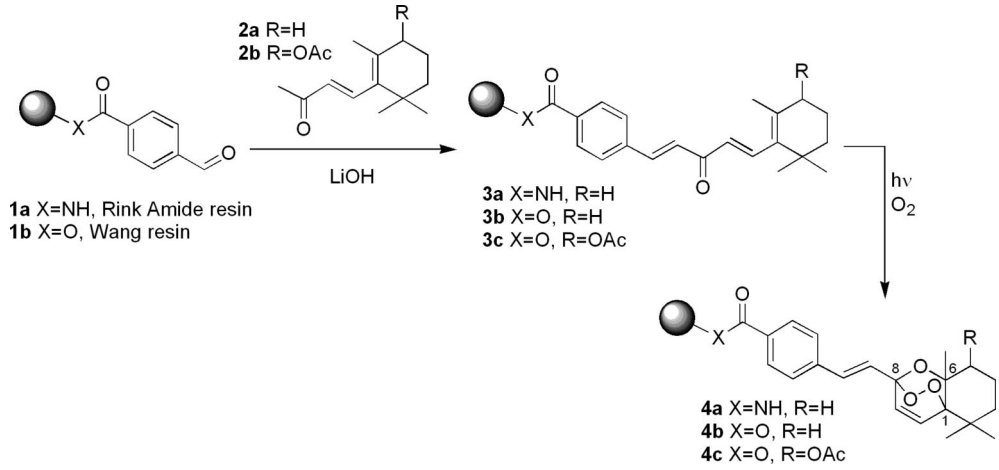
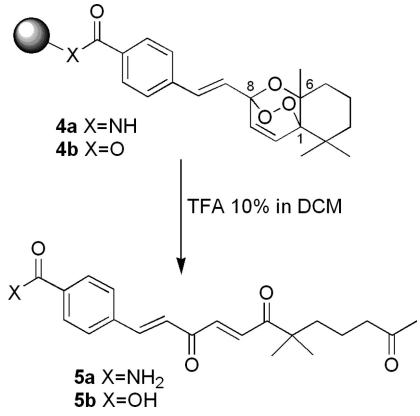
Scheme 1

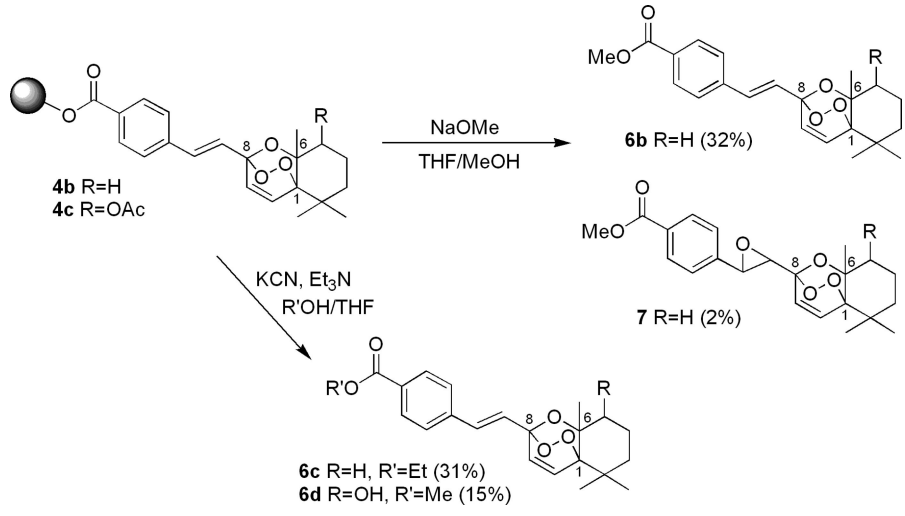


Scheme 2



reaction sequence performed in homogeneous phase gave a very low overall yield (11%) of an impure ester **6b**, being the photooxigenation step particularly inefficient. In an alternative cleavage strategy, using ethyl alcohol and KCN as activating agent,[18] the corresponding ester **6c** were obtained in 31% yield.[19] Synthesis of C-5 substituted trioxane derivatives were also tested; thus, irradiation of the 5-acetyl dienone **3c** under conditions mentioned above, gave the trioxane **4c** that was then treated with KCN in the presence of methanol to generate **6d** in 15% overall isolated yield (Scheme 3).

Scheme 3



In summary, a new cascade process involving a self-sensitized oxidation of dienone systems has been developed for the solid-phase synthesis of 1,2,4-trioxane scaffolds. Our results show that the reactivity of the electronic excited states of immobilized ionone derivatives is as good or even better than the corresponding transformation in solution, allowing for an easy approach to the target heterocycles. This study has become a starting point for a more general application of photochemical procedures on solid support including singlet oxygen oxidation reactions.

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Supporting Information Available. Experimental procedures, spectroscopic data, ^{1}H and ^{13}C NMR spectra of new compounds, and ^{13}C NMR gel-phase spectra of trioxane **4b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) Typical procedure: A solution of *p*-carboxybenzaldehyde (99.1 mg, 0.66 mmol, 3 equiv), DIC (0.10 mL, 0.66 mmol, 3 equiv), and DMAP (cat.) in anhydrous DCM (7 mL) was added to Wang resin (200 mg, 1.1 mmol/g) under nitrogen atmosphere. The mixture was stirred for 18 h at room temperature. After filtration, the resulting resin **1b** was washed with MeOH (3 × 3 mL), DMF (3 × 3 mL), and DCM (3 × 3 mL) and dried under high vacuum. A solution of β-ionone **2a** (0.90 mL, 4.4 mmol, 20 equiv) in anhydrous DME (2 mL) was added to resin **1b** (0.22 mmol) under nitrogen atmosphere. Then, LiOH (105.4 mg, 4.4 mmol, 20 equiv.) was added with stirring. The mixture was stirred for 18 h under nitrogen atmosphere at room temperature, after which the resin was filtered, washed with AcOH (3 × 3 mL), H_2O (2 × 3 mL), MeOH (2 × 3 mL), DMF (3 × 3 mL), MeOH (3 × 3 mL), and DCM (3 × 3 mL), and finally dried in high vacuum. The resin was then resubjected to the same reaction conditions to ensure the formation of the product (**3b**). After that, a suspension of the resin **3b** (0.22 mmol) in toluene (60 mL) contained in a transparent Pyrex vessel was irradiated at $\lambda = 354$ nm, while a stream of oxygen was passed through this suspension. After 2 h the resin was filtered, washed with DCM (3 × 3 mL), and dried under high vacuum to give the resin-bound trioxane **4b**. For the release of trioxanes from the solid support, two general protocols were used: (a) Resin **4b** (131.1 mg, 0.10 mmol) was swelled in anhydrous THF/MeOH (4:1) (3.5 mL) at room temperature for 1 h. Then, a solution of freshly prepared MeONa 0.5 N in anhydrous MeOH (0.20 mL, 0.10 mmol, 1 equiv) was added by syringe, and the mixture was kept at room temperature for 50 min. The resin was filtered into a separating funnel containing a saturated NH_4Cl solution and washed with AcOEt (3 × 5 mL) and DCM (1 × 3 mL). After it was dried in vacuo, the resin was subjected once more to the same reaction conditions. The collected phases were separated, and the organic phase was washed with saturated aqueous NH_4Cl, brine, and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded the crude material, which was purified by column chromatography to give 12 mg of 4-[2-(2,2,6-trimethyl-7,9,10-trioxa-tricyclo[6.2.2.0^{1,6}]dodec-11-en-8-yl)vinyl]-benzoic acid methyl ester (**6b**) (32% overall yield, based on the initial loading level of the Wang resin) and 1 mg of 4-[3-(2,2,6-Trimethyl-7,9,10-trioxa-tricyclo-[6.2.2.0^{1,6}]dodec-11-en-8-yl)-oxiranyl]-benzoic acid methyl ester (**7**) (2% overall yield, based on the initial loading level of the Wang resin). (b) KCN (30 mg) and Et_3N were added to a suspension of the resin **4b** (147.0 mg, 0.11 mmol) in THF/EtOH (1:3) (12 mL). The mixture was stirred at 50 °C for 26 h, after which the resin was filtered and washed with MeOH (4 × 5 mL), DCM (4 × 5 mL), and saturated aqueous $NaHCO_3/H_2O$ (1:1) (1 × 5 mL). The phases were separated, and the organic phase was washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent afforded the crude material, which was purified by column chromatography to give 14.0 mg of 4-[2-(2,2,6-trimethyl-7,9,10-trioxa-tricyclo[6.2.2.0^{1,6}]dodec-11-en-8-yl)vinyl]-benzoic acid ethyl ester (**6c**) (31% overall yield, based on the initial loading level of the Wang resin).

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