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Studies on the preparation of unsaturated carbonyl substrates for solid-phase synthesis of peroxidic compounds

Agustina La Venia, Ernesto Mata and Mirta Mischne

Instituto de Química Orgánica de Síntesis, Universidad Nacional de Rosario, Suipacha 531, Rosario, Argentina. e-Mail mmischne@fbioyf.unr.edu.ar

Introduction

The synthesis of molecules on polymer support has become quickly and efficiently a tool of choice for the production of libraries of compounds. The benefits derived from the use of this methodology, base for Combinatorial Chemistry, with respect to chemistry in solution are well established and converge in a process that greatly accelerates the synthesis of molecular structures. Its recognized potential to be automatised, since the process only involves the incorporation of solvents and reagents, stirring and filtering, makes it one of the most significant scientific breakthroughs of recent years (Mata, 1997; Terrett, 1998).

The development of this methodology is associated with the response of the chemical community to the growing demand for new compounds for biological tests in different research areas, and primarily in the pharmaceutical field.

Recent studies on drug structure and leader compounds have shown that there is a preponderance of scaffolds from natural products. Therefore, at present strategies that combine solid-phase chemistry with the chemistry of natural products have become an area of intense research. Therefore, numerous development lines are devoted to the design and synthesis of libraries based on scaffolds of natural products. Consequently, from the beginning of the 90' different synthetic reactions used in classical chemistry in solution began to be adapted to be carried out on solid phase.

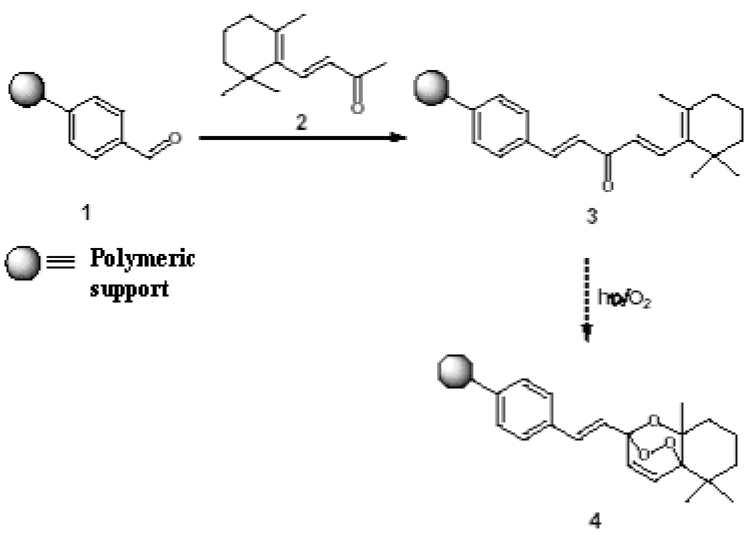
In recent years, one of the functional groups that has aroused great interest in the area of medicinal chemistry is the peroxide group, particularly the 1,2,4-trioxane system, which is considered the pharmacophore of the potent antimalarial artemisinin. In this way, the chemistry of peroxidic compounds has become an important exploration area in the development of new and effective agents for malaria control and treatment (Klayman, 1985).

Methodology

Having identified the 1,2,4-trioxane system as a scaffold of great interest derived from natural products, and based on the results obtained in our laboratory about the synthesis and reactivity of peroxidic compounds, we explored the chemistry on solid support to obtain quickly and efficiently 1,2,4-trioxane systems as a first step for further development of peroxidic compounds synthesis library.

The working methodology is based on the irradiation of dienone substrates in the presence of molecular oxygen as an oxidizing agent. The study of transfer of this process to solid-phase chemistry requires the analysis and research of previous stages.

The first of these consists in exploring the synthesis of all intermediates and target molecule in solution. In addition, substrate immobilization on the resin implies the choice of the linker as a binding point and, consequently, the structure of the substrates must include the corresponding substituent groups. One of the strategies for achieving this aim is shown in Scheme 1.

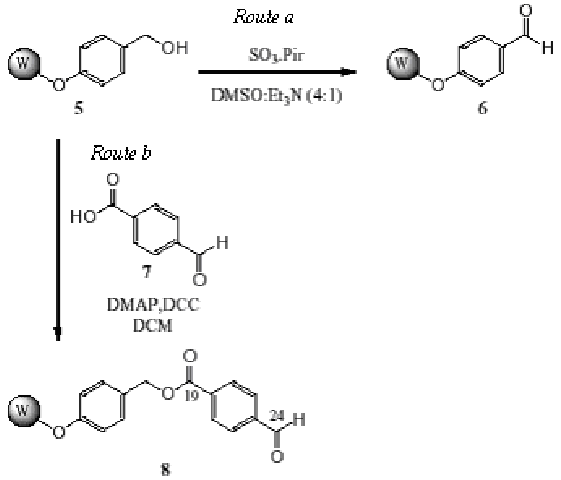


Scheme 1

Results:

According to the designed strategy, and with the aim to perform substrate immobilization on the polymer support, we have began adequacy studies of different resins in order to evaluate their behaviour as an electrophilic component (intermediate **1**, Scheme 1) in aldol condensation reactions.

Initially, the choice fell on the use of Wang resin (**5**). The first tested sequence was the oxidation of **5,** obtaining resin **6** as product (Scheme 2, route a) (Chen *et al*., 1997). A second modificatin was based on the incorporation of *p*-carboxybenzaldehyde (**7**) to yield **8** (Scheme 2, route b) (Wipf and Henninger, 1997). Substrates **6** and **8** showed in their structures different functional groups, which will be afterwards responsible for product release. In compound **6** the group is an ether function, and in **8** accounts for an ester group, having distinct lability characteristics in acid media, which will allow to evaluate its effectiveness in the sequence.



Scheme 2

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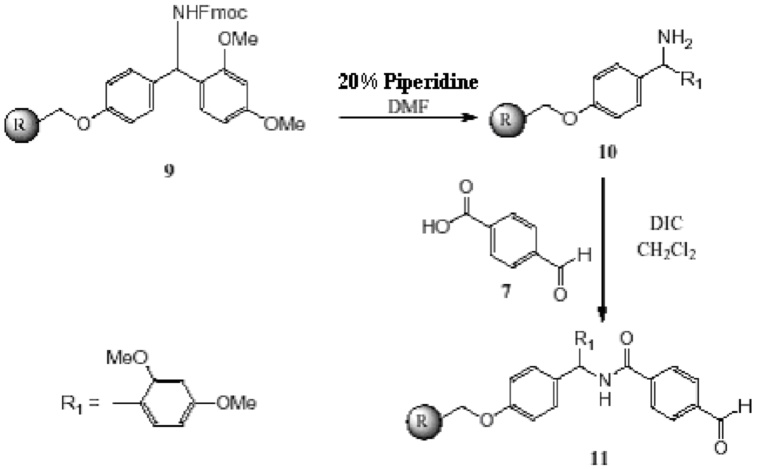
A new sequence was tested for Rink resin (**9**) (Scheme 3). After deprotection of **9** to give **10**, *p*-carboxybenzaldehyde (**7**) was added, thus obtaining resin **11** (Sensfuss, 2003), expanding in this case the moiety responsible for product release to an amide bond.



Scheme 3

The results show that the above-mentioned transformations are successfully carried out, monitoring each of them by IR and ^{13}C-NMR spectroscopy in gel phase. The characterization of the different suitable resins (**6**, **8** and **11**) by IR spectroscopy was based primarily on the aldehyde functional group identification by two typical bands: 2730 cm^{-1} (low intensity) and 1705 cm^{-1} (intense). ^{13}C-NMR spectra in gel phase allowed us to identify resin **6** by the signal of the aldehyde carbonyl carbon (δ = 190.5 ppm) and of resin **8** by the signals attributed to C_{24} aldehyde carbonyl carbon (δ = 191.3 ppm) and to C_{19} ester carbonyl carbon (δ = 165.3 ppm). Resin **11** was identified by the presence of a signal at δ = 191.3 ppm in the ^{13}C-NMR spectrum in gel phase.

Conclusions

The present work has allowed to adequate different resin sorts and the subsequent coupling with *p*-carboxybenzaldehyde used as linker, thus obtaining type **1** intermediates.

Progress in developing this sequence requires the study of aldol condensation reactions to obtain **3** (Scheme 1). In continuation of this research line we will present results about the studies on coupling of methylketones with the aldehyde group of resin substrates (**6**, **8** and **11**) in order to optimize conditions for obtaining dienone intermediates **3**.

Note: This study was presented at the "XXVI Congreso Argentino de Química" , San Luis, Argentina, 2006

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