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Solution and Solid Phase Synthesis of 5-Alkoxyhydantoin Libraries with a Three-Fold Functional Diversity

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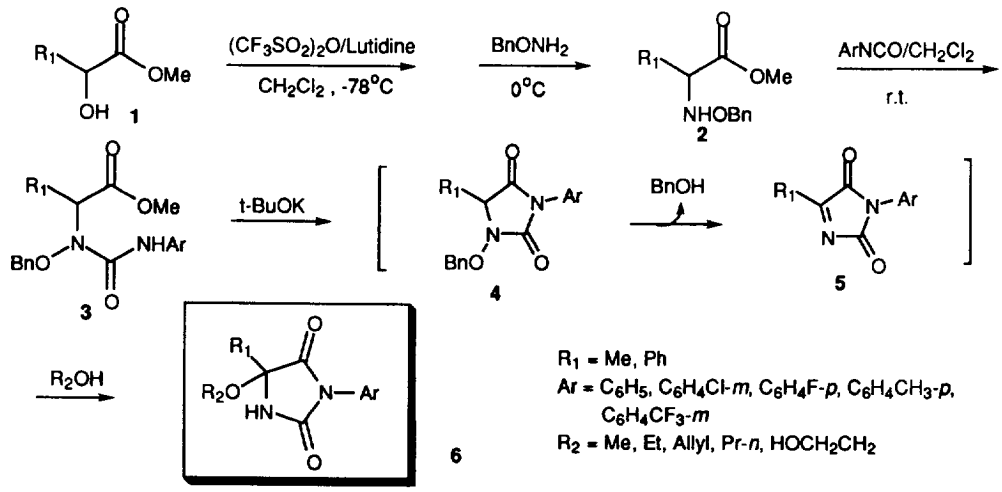
Abstract: A general method for the synthesis of 5-alkoxyhydantoins in solution and on solid support is described. A library of fifty discrete 5-alkoxyhydantoins with three functional group variations was prepared. Copyright © 1996 Elsevier Science Ltd

The generation and exploitation of chemically and functionally diverse libraries of discrete families of organic molecules is becoming a fundamental technique for the discovery and optimization of lead compounds in the pharmaceutical industry.[1] With the availability of automated techniques for high capacity synthesis and high through-put screening technologies, much interest is being focused on the generation of libraries of small drug-like molecules in solution and on polymer support.[2]

Hydantoins have been reported to possess a wide range of biological activities as anticonvulsants, antiarrythmics and antidiabetics. Herbicidal and fungicidal activities have also been noted.[3] A protocol for the synthesis of hydantoins on solid support was reported in 1993 by DeWitt and co-workers,[4] and very recently by Kaldor and coworkers.[5] To the best of our knowledge, only very few examples of 5-alkoxyhydantoin derivatives are known.[6,7] Herein we describe a general synthesis protocol for the generation of functional diversity in a 5-alkoxyhydantoin nucleus in solution and on solid support.

Our first objective was to devise a general approach to the synthesis of 5-alkoxyhydantoins in solution and to study the adaptability of the method to solid support. α-Hydroxy esters represented by structure **1** (Scheme 1) were converted to N-benzyloxy α-amino esters **2** using Ottenheijm's protocol.[8,9] Treatment of **1** with trifluoromethanesulfonic acid anhydride in the presence of lutidine in dichloromethane, followed by addition of O-benzylhydroxylamine *in situ* gave **2** in excellent yield. The α-N-benzyloxy amino acid esters were reacted with different aryl isocyanates to afford urea derivatives exemplified in expression **3**. Treatment of **3** in a variety of alcohols in the presence of two equivalents of potassium tert-butoxide gave the desired 5-alkoxyhydantoin products expressed as **6** in excellent yields. These products are formed from the intermediate N-benzyloxyhydantoins **4** via cyclization, elimination of benzyl alcohol to give imine **5**, followed by attack by the alcohol.[10] This four-step sequence produces a three-fold functional diversity encompassing the original R_1 group, the N-aryl group and the alkoxy function R_2O. The versatility of the protocol was demonstrated by the preparation of two sets of libraries, each containing 25 distinct 5-alkoxyhydantoins as shown in Figure 1. Each

Scheme 1



compound was fully characterized by ^{1}H, ^{13}C NMR, and mass spectrometric techniques. In general, yields were good to excellent, averaging 70-90%. The method shown in Scheme 1 is adaptable to the synthesis of the hydantoin nucleus in general by replacing the aryl isocyanate with chlorosulfonyl isocyanate.[11]

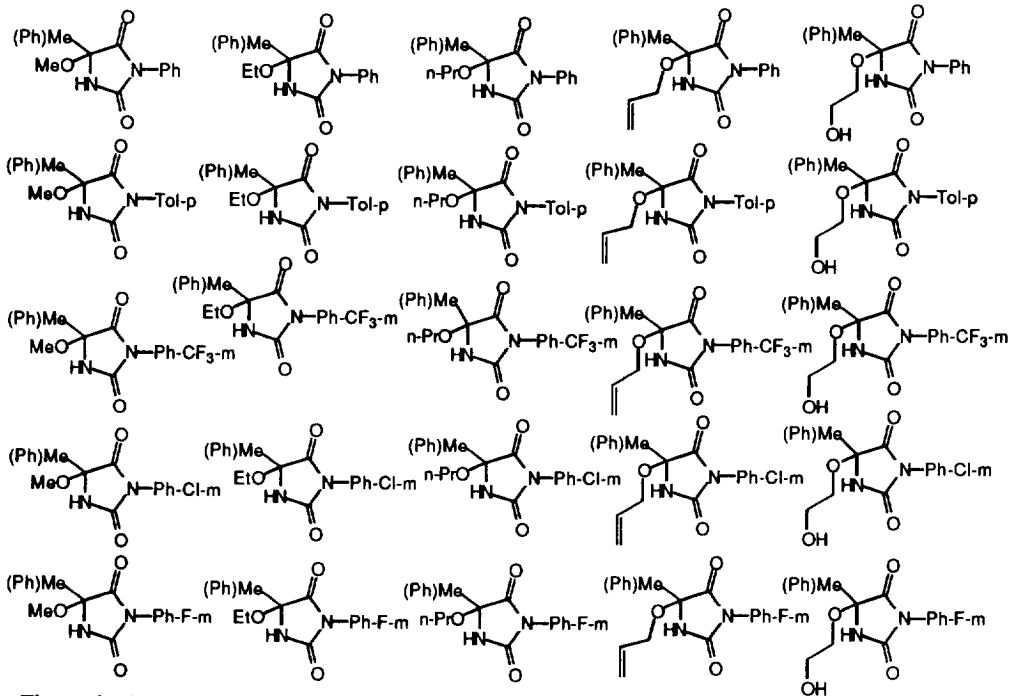
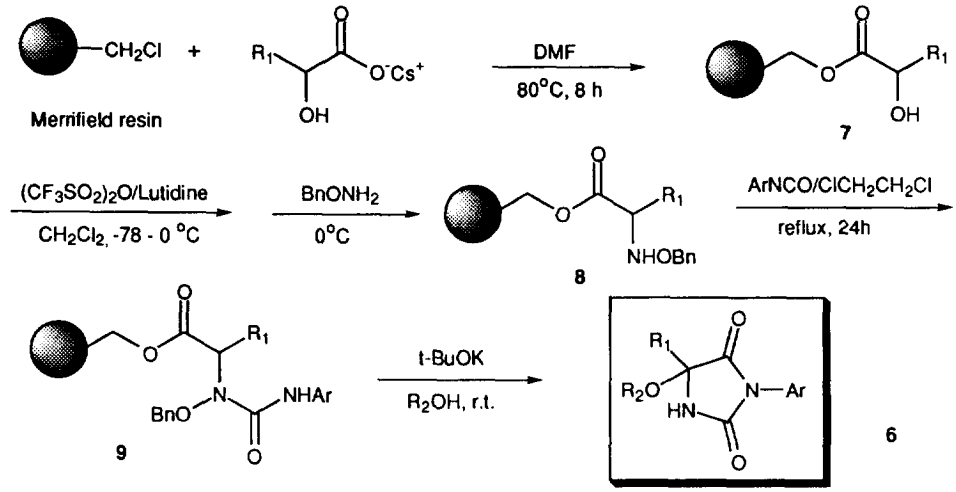


Figure 1. Fifty discrete 5-alkoxyhydantoins.

Because of the generality and high yields of the solution method, we extended this protocol to a synthesis on solid support (Scheme 2). The α-hydroxy acid was first linked to a chloromethylated polystyrene resin (1% DVB Merrifield resin, 1 mmol/g) *via* its cesium salt. Then the polymer-bound α-hydroxy ester **7**

Scheme 2



was efficiently transformed into the N-benzyloxyamino ester **8** using the same conditions as in solution phase chemistry. The resulting α-amino acid derivative **8** was subsequently condensed with individual aryl isocyanates in dichloroethane under reflux to give the polymer-bound urea derivative **9**. Treatment of **9** with potassium tert-butoxide in an alcoholic solution led to sequential cyclization and detachment from the polymer to give the desired 5-alkoxyhydantoin **6** *via* the same elimination-addition mechanism as described above.

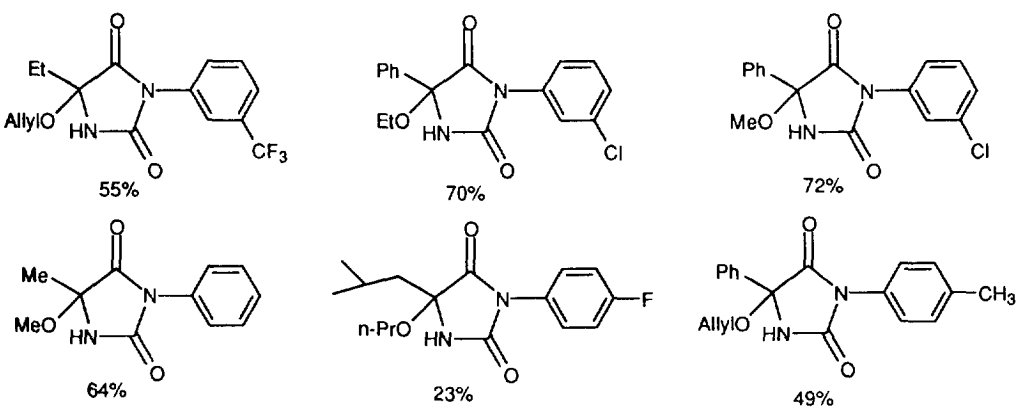


Figure 2. 5-Alkoxyhydantoins prepared on solid support

Representative products prepared on solid support by the above described protocol are shown in Figure 2. Yields correspond to purified products and they are calculated based on the chloromethyl functionality of the

original Merrifield resin. The structure and identity of the products were compared to those produced *via* solution synthesis and they exhibited satisfactory ^{1}H and ^{13}C NMR spectra. HPLC analysis of crude products cleaved from the resin showed purities ranging from 89-96%.

In summary, we have developed the first general method for the synthesis of a library of 5-alkoxyhydantoins in solution and on solid support. Three sites of functional diversities can be introduced on the hydantoin nucleus, thus providing corresponding sites of hydrophobic, hydrophilic, electronic and other interactions with appropriate biological receptors and related target sites.

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