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SOLID-PHASE SYNTHESIS OF BENZISOTHIAZOLONES AS SERINE PROTEASE INHIBITORS

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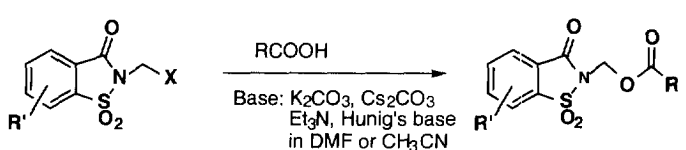
Abstract: An efficient solid-phase synthesis of benzisothiazolone-1,1-dioxide-based serine protease inhibitors involving alkylation of carboxylic acids with N-(bromomethyl)benzisothiazolone-1,1-dioxide has been developed. An example using this procedure for preparation of a library of human mast cell tryptase inhibitors is described.

The discovery and development of inhibitors of serine proteases such as elastase and tryptase have attracted considerable attention in the pharmaceutical industry in recent years.[1] One such series of compounds, benzisothiazolone-1,1-dioxides (saccharins), **2**, has been developed as inhibitors of human leukocyte elastase (HLE) for the treatment of emphysema, cystic fibrosis, and other pulmonary diseases.[2–4] As part of a program to examine the broader potential of mechanism-based inhibitors of serine proteases, we were interested in preparing a library using the benzisothiazolone-1,1-dioxide core structure. However, the chemical reactivity inherent in **2**, which is responsible for serine protease inhibitory activity, posed several problems of a practical nature. In order to minimize exposure of the fully elaborated target compounds **2** to multiple reaction events, a key element of our strategy was to build a series of structurally diverse carboxylic acid derivatives on solid phase and then introduce the heterocycle as the final step in the sequence. This has the advantage that compounds **2** need only to be able to survive their installation and subsequent cleavage from the resin and, in addition, removes a reliance on commercially available carboxylic acids as coupling partners. A survey of the literature indicated that compounds **2** can be prepared in solution by coupling the readily prepared N-(halomethyl)-benzisothiazolone **1**[4] with carboxylic acids in the presence of K_2CO_3, Cs_2CO_3 or *i*-Pr_2NEt (Hunig's base) in DMF or CH_3CN.[2–4] However, in an initial investigation of this procedure we discovered that although the reaction generally gave a pure product, the yields varied significantly, largely due to the instability of **2** under the reaction conditions. This circumstance is unsuitable for the synthesis of a combinatorial library and prompted the development of a reliable and effective solution to this problem. Here we describe a modified procedure for the alkylation of a carboxylic acid with **1**, which gives a high reaction yield of **2** under both solution- and solid-phase synthesis conditions, and



1 X = Cl, Br

2

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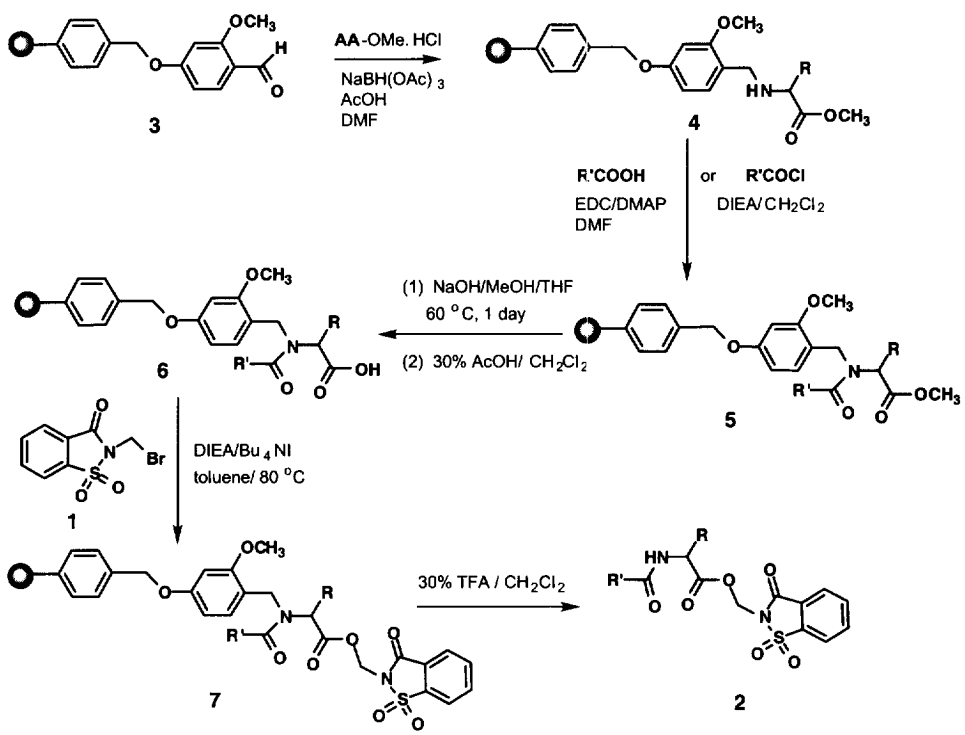
its application to the synthesis of a library of **2** on the solid phase.

After some experimentation, we found that the reaction of **1** with carboxylic acids using Et_3N or Hunig's base in toluene at 80 °C gave excellent yields of **2** (>90%) and that the inclusion of phase transfer catalysts such as *n*-Bu_4NI or *n*-Bu_4NHSO_4 increased the reaction rate.[3] To prepare libraries, we applied split/pool methodology using IRORI Microkan® and AccuTag® transmitter technology.[5] The synthesis began with Wang resin to which was attached an aldehyde anchor to afford **3**.[6] For the first library, summarized in Scheme 1, reductive amination[7] of an amino acid ester was followed by acylation of the resulting amine **4** with a carboxylic acid or acid chloride and subsequent hydrolysis of the ester moiety to give a series of acids **6**.

Scheme 1



Amino Acid Methyl Ester.HCl

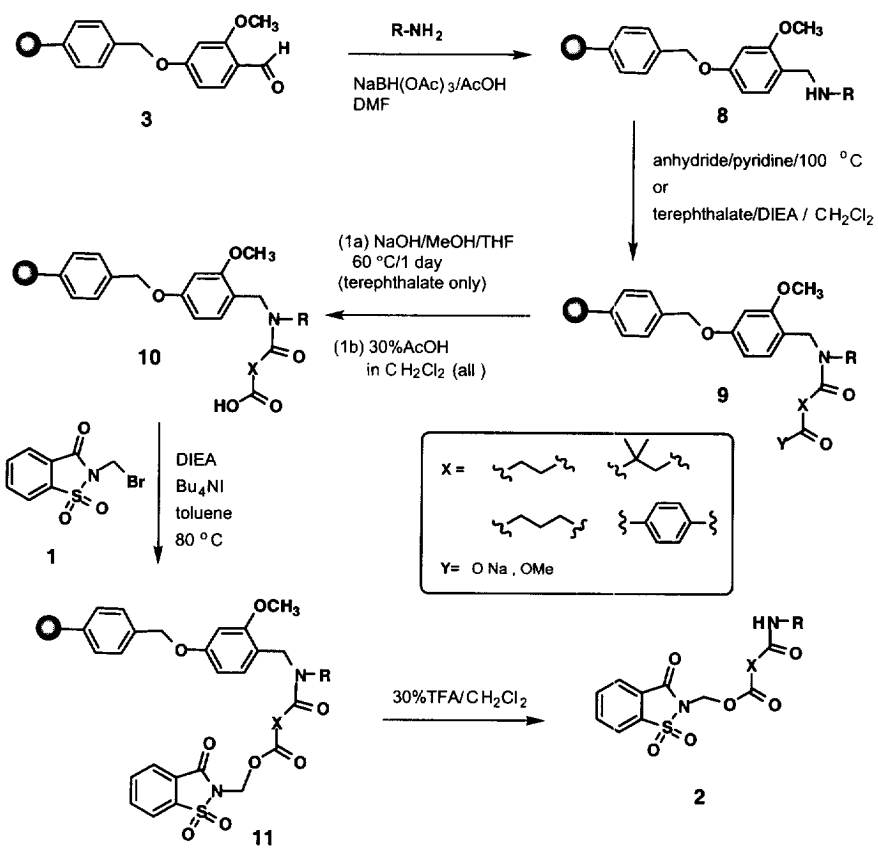
(1) Glycine
(2) DL-Valine
(3) DL-Phenylalanine
(4) DL-Methionine
(5) (S)-Phenylglycine
(6) ß-Alanine
(7) ß-Cyclohexyl-Alanine

Acids or Acid Chlorides

(1) Dicyclohexylacetic acid
(2) Benzoyl chloride
(3) Nicotinic acid
(4) Hydrocinnamic acid
(5) Pivalic acid
(6) Acetyl chloride
(7) *p*-Anisoyl chloride
(8) Cyclohexanecarboxylic acid chloride

Note:
AA-OMe: amino acid methyl ester
DIEA: diisopropyethylamine
EDC: 1-(3-methylaminopropyl)-ethyl carbodiimide hydrochloride
DMAP: 4-(dimethylamino)pyridine
TFA: trifluoroacetic acid

Scheme 2



Primary Amines

(1) Cyclohexane methylamine
(2) Propylamine
(3) Isopropylamine
(4) Phenethylamine
(5) 4-Methoxybenzylamine
(6) 3,4-Dichlorobenzyl amine
(7) 4-(2-Aminoethyl)-morpholine

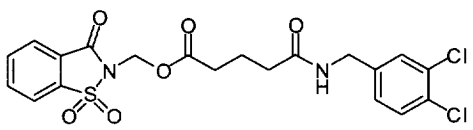
Anhydrides/Terephthalate

(1) Succinic anhydride
(2) 2,2-Dimethylsuccinic anhydride
(3) Glutaric anhydride
(4) Terephthalic acid chloride monomethyl ester

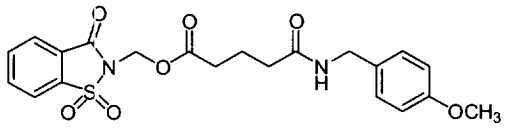
A different series of carboxylic acid **6** was prepared on solid phase for the second library as summarized in Scheme 2. The aldehyde resin **3** was first reacted with a primary amine in the presence of $NaBH(OAc)_3$ and the resulting amine **8** acylated either with an anhydride or an acid chloride ester followed by saponification of the ester gave acids **10**. Acids **6** and **10** were together treated with bromide **1** in the presence of nBuN4I in toluene at 80 °C overnight. The Microkans were deconvoluted and the compounds were cleaved from the resin separately using 30% TFA/CH_2Cl_2 solution to afford the final products **2**. From the 84 compounds attempted, 60 successfully gave the desired product in greater than 70% purity by HPLC. Analysis of the products indicated that with the exception of two Microkan reactors that lost resin during the process, the reactions that failed to give

the desired product were due to the failure of the EDC/DMAP-mediated coupling reactions of nicotinic acid and the bulky acids pivalic acid and dicyclohexyl acetic acid with resin-bound amines.

The library obtained was screened for inhibitory activity against a panel of viral and mammalian serine proteases including human mast cell tryptase.[8] Among them, 11 compounds demonstrated >80% inhibition human mast cell tryptase at a concentration of 33 μM. A more detailed evaluation revealed that compounds **2a** and **2b** had IC_{50}'s of 0.23 μM and 0.43 μM, respectively. Compound **2a** and **2b** are structurally similar to a related series of benzisothiazolone-based tryptase inhibitors.[9] These compounds are notable because they lack a basic guanidine or amidine element that is usually required for recognition by the S_1 subsite of the enzyme.



2a



2b

In conclusion, we have developed a reaction procedure for the preparation of benzisothiazolone-based serine protease inhibitors that proceeds in high yield under mild conditions. The procedure was applied to the preparation of a combinatorial library using solid phase synthesis, which resulted in discovery of compounds **2a** and **2b** that exhibited moderate inhibitory activity towards human mast cell tryptase.

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