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Novel triethylsilane mediated reductive *N*-alkylation of amines: improved synthesis of 1-(4-imidazolyl)methyl-4-sulfonylbenzodiazepines, new farnesyltransferase inhibitors

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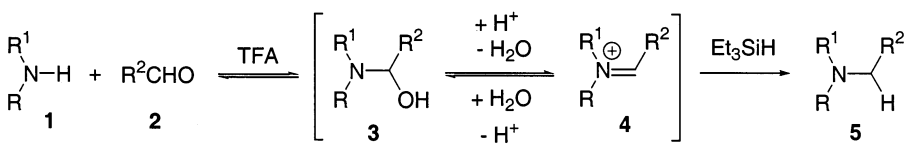
Abstract—An improved synthesis of 1-(imidazolyl)methyl-4-sulfonylbenzodiazapines, new farnesyltransferase inhibitors, was achieved using a novel reductive *N*-alkylation method. The new method involves reaction of a secondary amine with an aldehyde using triethylsilane in the presence of trifluoroacetic acid, giving a tertiary amine in 90–95% isolated yields. © 2001 Elsevier Science Ltd. All rights reserved.

1-(4-Imidazolyl)methyl-4-sulfonylbenzodiazepines are a novel class of farnesyltransferase inhibitors.[1] They were previously prepared from isatoic anhydride with the last step being reductive *N*-alkylation of 1-unsubstituted 4-sulfonylbenzodiazepines with 4-formylimidazole using sodium triacetoxyborohydride.[1,2] While the desired *N*-alkylated products were obtained, large excess (sometime >10 equivalents) of the expensive 4-formylimidazole and sodium triacetoxyborohydride were used in order to compete with the unwanted side reaction, i.e. aldehyde reduction by sodium triacetoxyborohydride. Since this reaction was carried out under relatively harsh conditions (high temperature and the presence of a large excess of reducing reagent), it did not work well with some substrates, especially with those having a reducible functional group in the molecule. In this communication, we report an improved synthesis of 1-(4-imidazolyl)methyl-4-sulfonylbenzodiazepine farnesyltransferase inhibitors, which involves a novel reductive *N*-alkylation method.

Hydrosilanes such as triethylsilane in the presence of Lewis acid are mild and useful reducing reagents in organic synthesis.[3–8] They are especially useful for the reduction of benzylic alcohols to the corresponding hydrocarbons.[4] They have also been used in the reduction of imines to secondary amines,[5] in the reductive *N*-methylation of amino acids via oxazolidines,[6] in the *N*-alkylation of anthranilamides via quinazolinones,[7] and more recently in the *N*-alkylation of amides, carbamates and ureas.[8] We envisioned that a secondary amine **1** would react with an aldehyde **2** to give a hemiaminal **3** (Scheme 1). This in situ formed hemiaminal **3** may undergo reduction with triethylsilane and trifluoroacetic acid through an iminium ion **4**, affording the *N*-alkylated product **5**.

Indeed, when triethylsilane (2.0 equiv.) was added to a solution containing 3-benzyl-4-(*n*-propyl)sulfonyl-7-cyanobenzodiazepine **6a** and 4-formylimidazole **7** (2.0 equiv.) in methylene chloride/trifluoroacetic acid (1:1), 1-(4-imidazolyl)methyl-3-benzyl-4-(*n*-propyl)sulfonyl-7-cyanobenzodiazepine **8a** was formed smoothly (Scheme 2). In 2 h at room temperature, the



Scheme 1.

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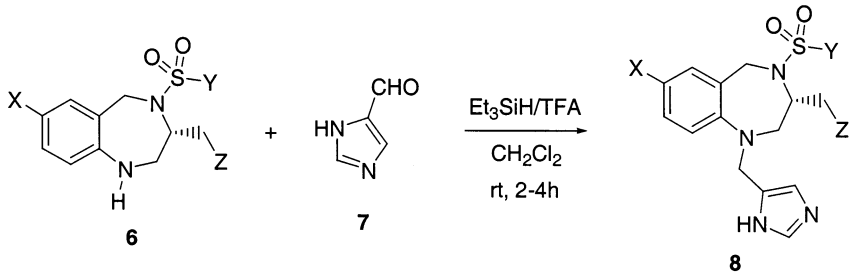

Scheme 2.

Table 1. Preparation of 1-(imidazolyl)methyl-4-sulfonylbenzodiazapines **8** using triethylsilane

Entry	**6**/**8**	X	Y	Z	Time (h)	Yield (%)
1	**a**	CN	*n*-Pr	Ph	2	90
2	**b**	CN	4-$MeOC_6H_4$	Ph	4	94
3	**c**	CN	2-Thienyl	Ph	4	93
4	**d**	CN	Ph	4-FC_6H_4	4	95
5	**e**	Ph	2-Thienyl	3-Pyridinyl	4	93
6	**f**	Ph	3-$(Me_2N)C_3H_6$	Ph	4	90

reaction was complete and the product **8a** was isolated in 90% yield.[1] A number of other benzodiazepines **6b–f** were tested with this new method (Table 1). In all cases, the corresponding *N*-alkylated products **8b–f** were obtained similarly in high yields (90–95%).[1]

In summary, an improved method for the synthesis of 1-(imidazolyl)methyl-4-sulfonylbenzodiazapines, new farnesyltransferase inhibitors, was developed. The new method involves the reaction of a secondary amine with an aldehyde using triethylsilane in the presence of trifluoroacetic acid, giving a tertiary amine in 90–95% isolated yields. With the convenience and high yield associated with this method, it is expected that the new method will find other applications in organic synthesis, especially in the preparation of medicinally important molecules.

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