Communication

Solid Phase Synthesis of 3-Toluenesulfonylglutarimides

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A novel route for the synthesis of 3-toluenesulfonylglutarimides on a solid support is described. The cyclization step involves stepwise [3+3] strategy of Rink Amide resin bound onto an α-toluenesulfonyl group with various α,β-unsaturated esters.

Keywords: Solid-phase reaction; Stepwise [3+3] strategy; Rink Amide resin; Glutarimides; Thalidomide.

INTRODUCTION

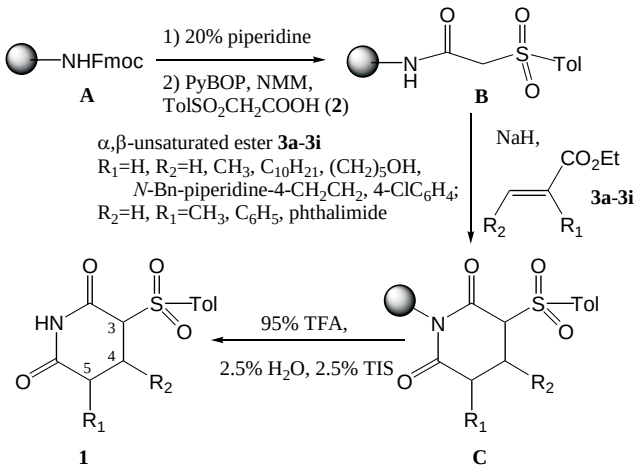
Solid-phase combinatorial and parallel synthesis methods have become a major tool for preparing small organic molecule libraries to discover new lead compounds in the pharmaceutical industry. A number of pharmaceutically useful heterocyclic compounds have been prepared recently by this solid phase methodology.[1] Here, we use a solid-phase reaction strategy to attach the α-toluenesulfonylacetic acid onto Rink Amide resin[2] for reaction with various α,β-unsaturated esters having various α-substituents (R_1) or β-substituents (R_2) to yield diverse substituents on the 3-toluenesulfonylglutarimides skeleton.

Glutarimides possess various biological activities,[3] therefore, the synthesis of these cyclic imides have attracted considerable attention.[4-5] Glutarimides are in most cases obtained by heating δ-dinitriles *via* cyclization in an acidic solution[4b] or by cyclization of monoamides with acid in the presence of thionyl chloride[4e] or BOP.[4d] Due to the harsh classical conditions, some milder methods have been proposed, such as the condensation of a diacidic compound with amine.[4a,g-i] Recently, we have developed an efficient synthesis for unsymmetrical glutarimides with a toluenesulfonyl group at the 3-position and have proposed its applications for clinical drugs and the mechanism of this reaction.[5] These 3-toluenesulfonylglutarimides **1** can be prepared by known procedures in the solution phase.[5]

RESULTS AND DISCUSSION

The attached α-toluenesulfonylacetic acid **2** was prepared in two steps from the substitution of α-bromo *t*-butylacetate with 4-toluenesulfinic acid sodium salt in a solution mixture of water and 1,4-dioxane (reflux, 10 h) and the hydrolysis of the corresponding α-toluenesulfonyl *t*-butyl ester using trifluoroacetic acid (rt, 5 h). The synthetic scheme adopted for the solid-phase synthesis is illustrated in Scheme I.

Scheme I Solid phase synthesis of 3-toluenesulfonylglutarimides **1**



Fmoc groups on the resin **A** were deprotected by 20% piperidine/DMF (rt, 20 min) to provide free amine groups on the Rink Amide resin in DMF. The loading of α-toluenesulfonylacetic acid onto the resin was achieved completely *in situ* with PyBOP[6] and *N*-methylmophorine (NMM) in DMF (0.4 M, rt, 20 min). When the synthesis of the desired resin **B** with the α-toluenesulfonylacetamide group was finished, as

Table 1. Facile Annulation of Resin **B** with Various α,β-Unsaturated Esters **3a-i**[a-b]

No.	**1**	R_1, R_2	Yield[a]
1	**1a**	H, H	66
2	**1b**	H, CH_3	56
3	**1c**	H, $C_{10}H_{21}$	53
4	**1d**	H, $(CH_2)_5OH$	43
5	**1e**	H, *N*-Bn-piperidine-4-CH_2CH_2	50
6	**1f**	H, 4-ClC_6H_4	45
7	**1g**	CH_3, H	59
8	**1h**	C_6H_5, H	41
9	**1i**	phthalimide, H	32

[a] The yields of isolated products based on the initial loading of the resin.

[b] Each product showed satisfactory ^{1}H NMR and MS data.

determined by the ninhydrin test, deprotonation using sodium hydride in anhydrous THF led to the dianions intermediate state (rt~67 °C, 1~5 h). Stepwise [3+3] reactions of the resulting dianions with various α,β-unsaturated esters **3** proceeded to yield diverse substituents on the α-toluenesulfonylglutarimide skeleton **C**. Presumably, the reaction proceeded by 1,4-addition and intramolecular ring-closure to yield the cyclized six-member glutarimide ring.

Finally, cleavage of α-toluenesulfonylglutarimides **1** from the resin was carried out with 95% trifluoroacetic acid (TFA), 2.5% triisopropylsilane (TIS) and 2.5% water (ice bath, 1 h). As summarized in Table 1, various functional alkyl or aryl substitutents on α-toluenesulfonylglutarimides **1** were produced in moderate yields using this protocol. The reactions yielded purified products in the range of 32~66%.[7] More significantly, the stereochemistry of compounds **1** at C-3 and C-4 retained its *trans* form (reactions No. 2~6) and at the relative positions of C-3 and C-5 (reactions 7~9) maintained the mixed isomer forms. It is a short, simple, efficient and reproducible solid-state approach for synthesizing various glutarimides.

The results are presented herein along with an application to thalidomide using the resulting product **1i**. The interest in the immuno-suppressor racemate thalidomide is related to its current use for treatment of AIDS.[3a,8a] Its activity against angiogenesis has been recently discovered.[8b] Compound **1i** was desulfonated with 6% sodium amalgam (Na/Hg) to give thalidomide at rt for 4 h in 72% yield.[9] Following the same approach, attempts for desufonation step onto the resin **C** under a variety of basic conditions were unsuccessful.

CONCLUSION

In conclusion, we explored a facile stepwise [3+3] solid phase strategy that is synthetically useful for constructing 4- or 5-substituted 3-toluenesulfonylglutarimides. The procedure provided an efficient improvement over existing solution-phase methods for the high-throughput combinatorial synthesis, but the overall efficiency of this methodology only turned out to be a quite moderate yield on a small scale. The scale-up of the cycloaddition reaction to 0.5 mmole or greater creates many other complex products in disproportionate ratios, thus making it difficult to efficiently synthesize various glutarimides in large quantities. This solid phase strategy was used in a new synthetic method for thalidomide. We are currently studying the scope of this methodology for the synthesis of alkaloid analogs.

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7. Typical experimental procedure for preparation of **1a**: 4-(2′,4′-dimethoxyphenyl-Fmoc-aminomethyl)phenoxy resin (Rink amide resin) (loading 0.62 mmole/g, 0.2 g, 0.124 mmol) was suspended in 20% piperidine/DMF (2 × 3 mL). The mixture was stirred for 20 min then filtered. The resin was washed with DMF (2 × 5 mL) and this step was repeated once. A 0.4 M NMM/DMF solution (1 mL) of acid **2** (107 mg, 0.5 mmol) and PyBOP (260 mg, 0.5 mmol) were added to the suspension of the resulting resin in DMF (3 mL) at rt. After stirring 20 min the coupling was completed by negative ninhydride test. The resin was filtered, washed with CH_2Cl_2, MeOH and THF, and dried under reduced pressure. Sodium hydride (60%, 40 mg, 1.0 mmol) was added to a suspension of the resin in THF (10 mL) at rt for 5 min then ethyl acrylate (50 mg, 0.5 mmol) was added. After stirring 2 h at rt, the reaction mixture was quenched with $NH_4Cl_{(aq)}$ solution (0.5 mL), filtered, washed with THF (2 × 10 mL). A 95% TFA/2.5% TIS/2.5% water solution (10 mL) was added to the resulting resin at ice bath temperature for 1 h. The reaction mixture was then concentrated under reduced pressure. The resulting resin was washed well with MeOH or CH_2Cl_2. The filtrate was evaporated under reduced pressure and purified on silica gel (hexane/ethyl acetate = 4/1~2/1) to produce product **1a** (22 mg, 0.08 mmol, 66%): mp = 166-168 °C; EI-MS: $C_{12}H_{13}NO_4S$ *m/z* (%) = 91 (100), 155 (50), 203 (52), 268 (M^++1, 1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.06 (br s, 1H), 7.75 (d, *J* = 8.3 Hz, 2H), 7.37 (d, *J* = 8.3 Hz, 2H), 4.00 (dd, *J* = 3.4, 5.7 Hz, 1H), 3.18-3.10 (m, 1H), 2.86-2.81 (m, 1H), 2.70-2.64 (m, 1H), 2.45 (s, 3H), 2.40-2.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.84, 164.64, 146.06, 134.74, 130.01 (2×), 129.15 (2×), 64.85, 28.47, 21.80, 18.87.
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