Preparation of (2-Methyl-propane-2-sulfonylimino) Acetic Acid Ethyl Ester

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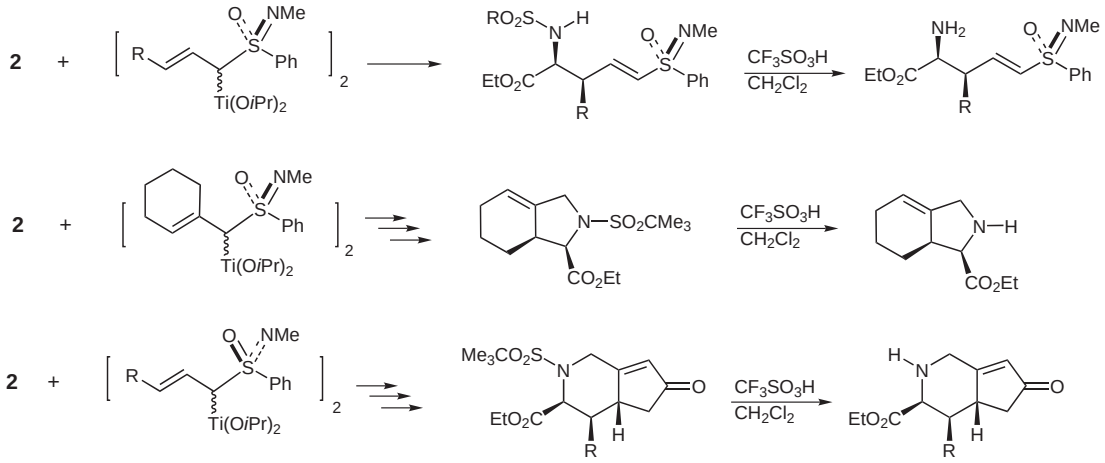
Abstract: Synthesis of (2-methyl-propane-2-sulfonylimino) acetic acid ethyl ester from *tert*-butylsulfonamide, thionyl chloride and ethyl glyoxylate is described. The *N*-*tert*-butylsulfonyl imino ester has served as a substitute of the corresponding *N*-toluenesulfonyl imino ester in allylation reactions.

Key words: imino ester, allylation, amino acids



Scheme 1 Asymmetric synthesis of α-amino acid derivatives from *N*-*tert*-butylsulfonyl imino ester and titanated allylic sulfoximines.

The *N*-toluenesulfonyl α-imino ester **1**,[1,2] (Figure 1) has found numerous applications in asymmetric synthesis through, for example ene,[3] Diels–Alder,[4] alkylation,[5] Mannich,[6] arylation,[7] aziridination,[8] and [2+2]-cycloaddition[9] reactions. However, a major drawback associated frequently with the utilization of the imino ester **1** has been that the *N*-tosyl group of the amine derivatives formed thereof is difficult to remove.[10–12] Recently we have described the utilization of the *N*-*tert*-butylsulfonyl α-imino ester **2** in the asymmetric synthesis of mono- and bicyclic α-amino acid derivatives, the key step of which is a highly diastereoselective allylation of **2** with titanated allylic sulfoximines (Scheme 1).[13–15] Aminoalkylations of titanated allylic sulfoximines with **1** and **2** revealed no differences in the reactivity of the two *N*-sulfonyl imino esters. A ready deprotection of the *N*-*tert*-butylsulfonyl protected amino acid derivatives was achieved according to the method described by Weinreb et al.[16] through treatment with CF_3SO_3H in anhydrous CH_2Cl_2. Here the use of anisole as cation scavenger was not required.[16]

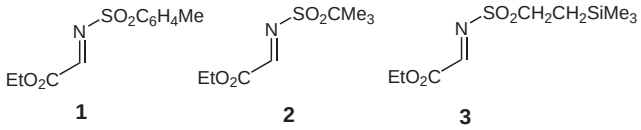


Figure 1 *N*-Sulfonyl imino esters.

Herein we describe a practical procedure for the synthesis of **2**, which may find widespread application as a substitute for **1** in organic synthesis. The *N*-*tert*-butylsulfonyl imino ester **2** was prepared from amide **4** according to the method of Kresze (Scheme 2).[2] Thus amide **4**[17] was treated with $SOCl_2$ at reflux temperature in toluene to afford the *tert*-butylsulfonyl isothiocyanate (**5**), which was not isolated[18] but treated with freshly distilled ethyl glyoxylate at reflux temperature to give the imino ester **2** as a yellow oil in 63% yield, based on amide **4**. The overall yield of the α-imino ester **2** compares favorably with the one reported for the synthesis of **1**.[1,2] Similarly the (trimethylsilylethyl)sulfonyl imino ester **3** can be prepared from the corresponding sulfonyl amide according to the procedure used for the synthesis of **2**.[13]

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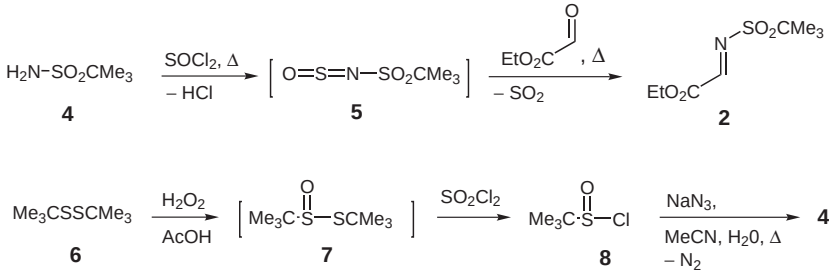

Scheme 2 Synthesis of *N*-*tert*-butylsulfonyl imino ester.

The amide **4** was prepared from the disulfide **6** on a 1 mol scale in 82% overall yield as outlined in Scheme 2 following known procedures. Thus oxidation of **6** with H_2O_2 gave the sulfinate **7**[19] which was not isolated but treated with $SOCl_2$[17] to afford the sulfinyl chloride **8**[17,19] in 92% yield. Treatment of **8** with NaN_3 in MeCN in the presence of a small amount of H_2O at elevated temperatures by the slow addition of the sulfinyl chloride to a suspension of the azide gave the amide **4**[17] in 89% yield.

2-Methylpropane-2-sulfinyl Chloride (8); Typical Procedure

The sulfinyl chloride **8** was prepared from the disulfide **6** on a 1 mol scale in 93% yield in two steps by the procedures described previously.[17,19] For the first step, the oxidation of the disulfide **6**, the procedure reported by Prinzbach et al.[19] was followed while for the second step, the chlorination of the sulfinate **7**, the procedure of Sharpless et al.[17] by using $SOCl_2$ was used.

2-Methyl-propane-2-sulfonic Acid Amide (4); Typical Procedure

The amide **4** was prepared from the sulfinyl chloride **8** on a 1 mol scale in 89% yield by the procedure described by Sharpless et al.[17] except that the purification was done by washing of the crude material with Et_2O instead of recrystallization.

(2-Methyl-propane-2-sulfonylimino) Acetic Acid Ethyl Ester (2); Typical Procedure

A dry, argon flushed 500 mL four necked round bottomed flask, equipped with an efficient reflux condenser, a magnetic stirring bar, a thermometer and an argon inlet on top of the condenser, was filled with the amide **4** (12.20 g, 89.00 mmol) and anhyd toluene (200 mL). Freshly distilled $SOCl_2$ (9.0 mL, 123.36 mmol) was added and the slightly yellow turbid mixture was heated first for 2 h at 80 °C and then at reflux temperature for 8 h. Then, the mixture was allowed to cool to approximately 80 °C and freshly distilled (vide infra) ethyl glyoxylate[20] (7.80 g, 89.00 mmol) was added. The reaction mixture was heated at reflux for 3 d. Then the reflux condenser was replaced by a downward distillation condenser and toluene was removed under atmospheric pressure. A brown and highly viscous oil remained, which was dissolved in absolute THF (50 mL). The solution was transferred to a distillation flask, THF was evaporated under reduced pressure and the flask was connected to a vacuum distillation apparatus. High vacuum distillation gave 13.2 g (63%) of the pure imino ester **2** as a pale yellow oil; bp 95–105 °C/0.2 mbar. Occasionally small amounts of amide **4** were isolated, which crystallized in the condenser.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 1.40 (t, *J* = 7.1 Hz, 3 H, CH_3CH_2), 1.49 [s, 9 H, $C(CH_3)_3$], 4.41 (q, *J* = 7.1 Hz, 2 H, CH_3CH_2), 8.38 (s, 1 H, CH).

^{13}C NMR ($CDCl_3$, 100 MHz): δ = 13.93 (d, CH_3CH_2), 23.63 [d, $C(CH_3)_3$], 58.98 [u, $C(CH_3)_3$], 63.00 (u, CH_3CH_2), 160.88 (u, C=O), 163.40 (d, CH).

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