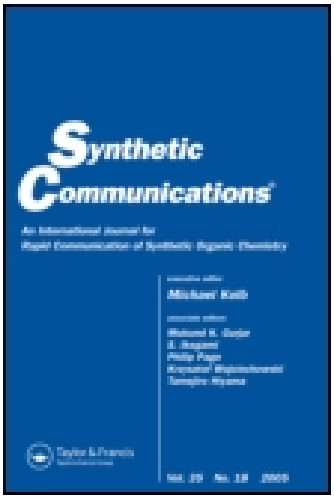

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Efficient Synthesis of Sivelestat Sodium Hydrate

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Efficient Synthesis of Sivelestat Sodium Hydrate

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Abstract: An efficient and scaleable synthesis of sivelestat sodium hydrate has been developed.

Keywords: Glycine ethyl ester, isatoic anhydride, pivaloyloxy benzene sulfonyl chloride, trimethyl silyl chloride

INTRODUCTION

Sivelestat sodium hydrate (Ono-5046, Elaspol™) is an injectable selective inhibitor of human neutrophil elastase jointly developed by Lilly and Ono for the treatment of acute lung injury associated with systemic inflammatory response syndrome (SIRS). Treatment with this agent has been shown to improve respiratory function, which facilitates the early removal of patients from mechanical ventilation and which could reduce the development of ventilator-associated pneumonia and patient stay in intensive care. A new application of elastase inhibitors has been reported[1] in the preparation of antiwrinkle cosmetic composition, which includes sivelestat. The antiwrinkle activity is believed to be the result of effective elastase inhibition, reduced hydrolytic

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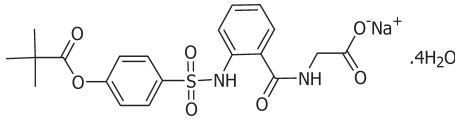

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Figure 1. Sivelestat sodium hydrate.

rate, and the increased content of elastin in derma cortex by the elastase inhibitors.

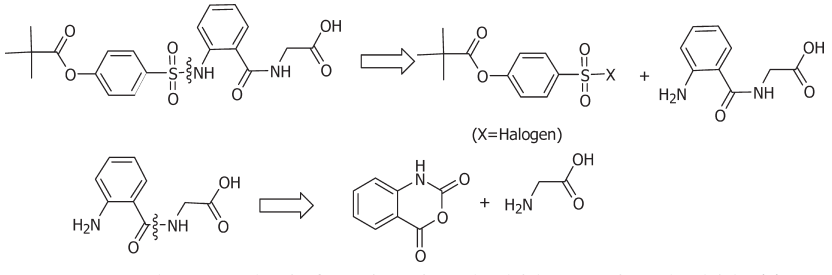
Sivelestat sodium hydrate is chemically known as N-[2-[4-(pivaloyloxy) phenylsulfonamido] benzoyl] glycine sodium salt tetrahydrate **1** (Fig. 1).

A synthesis of sivelestat sodium has been reported by Imaki et al.[2,3] The synthesis has started from o-nitro benzoic acid **2**. o-Nitro benzoic acid was converted to o-Nitrobenzoyl chloride and treated with glycine benzyl ester **3** to get (2-amino benzoyl amino) glycine benzyl ester **5**. Condensation of 4-(pivaloyloxy) benzene sulfonyl chloride **6** with (2-aminobenzoyl) glycine benzyl ester **5** in pyridine furnished N-[2-[4-(pivaloyloxy) phenylsulfonamido] benzoyl] glycine benzyl ester **7**, which on hydrogenation followed by treatment with sodium hydroxide furnished sivelestat sodium **1** (Scheme 1).

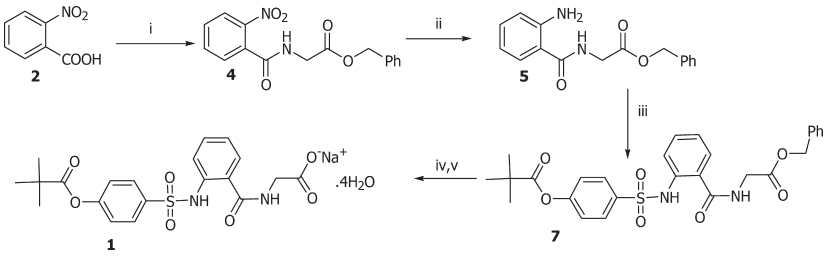
Wakatsuka et al.[4] has reported the synthesis of sivelestat sodium **1** by condensing anthranillic acid **9** with 4-(pivaloyloxy) benzene sulfonyl chloride **6** to get O-(p-pivaloyloxybenzenesulfonylamino)benzoic acid **8**, which on further reaction with trimethylsilyl glycine furnished sivelestat **10** (Scheme 2).

RESULTS AND DISCUSSION

A retrosynthetic analysis has been carried out, and we identified isatoic anhydride as the key starting material. The synthesis was designed to eliminate the catalytic hydrogenation as well as the dissolving metal reduction reported in earlier syntheses.



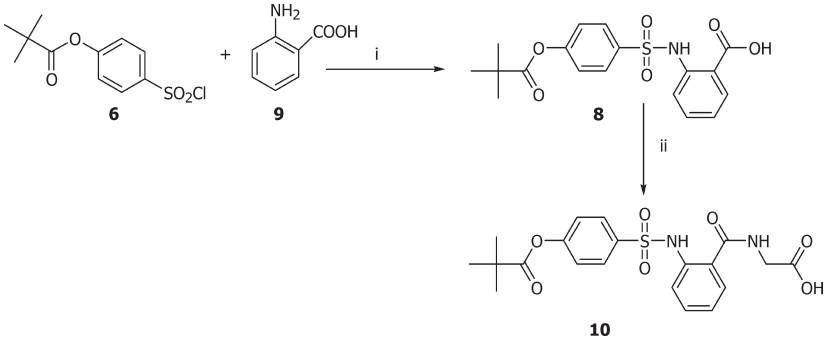
We started our synthesis from isatoic anhydride. Isatoic anhydride **11** was treated with glycine ethyl ester hydrochloride to get (2-Aminobenzoylamino) acetic acid ethyl ester **12**. (2-Aminobenzoylamino) acetic acid ethyl ester was



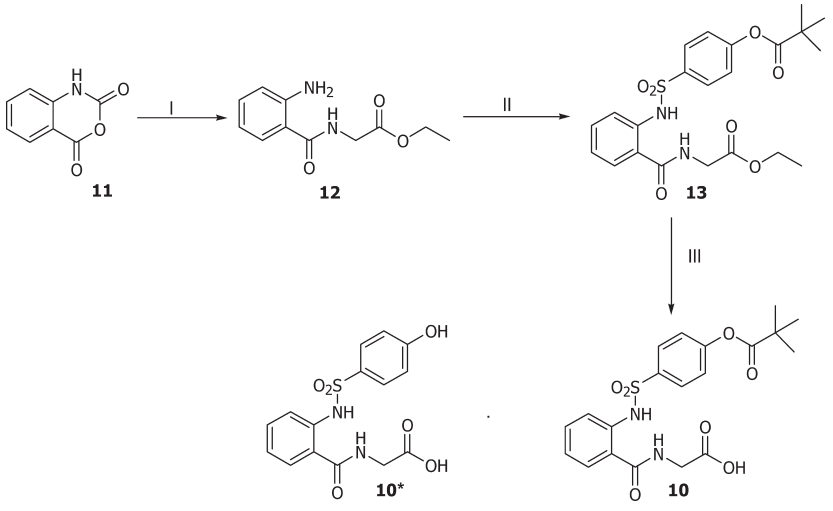
Scheme 1. (i) Thionyl chloride, glycine benzylester; (ii) Fe/HCl; (iii) pivaloyloxybenzene sulfonylchloride, sodium hydroxide; (iv) Pd-C/H_2 gas; (v) sodium hydroxide.

reacted with **6** to furnish N-[2,4-(pivaloyloxy) phenylsulfonamido] benzoyl] glycine ethyl ester **13**. Lam et al.[5] reported that aryl pivaloates are highly stable in comparison with alkanoate esters for hydrolysis. Based on this finding, we tried to selectively hydrolyze the ethyl ester in the presence of aryl pivaloate ester. Compound **13** was subjected to hydrolysis with aqueous sodium hydroxide, but in our hands the hydrolysis was not found to be selective, and mixtures of products such as sivelestat **10** and 2-(4-hydroxy benzenesulfonylamino)-benzoylamino) acetic acid **10*** were obtained (Scheme 3). Other milder bases such as sodium carbonate and sodium bicarbonate were employed for the hydrolysis, and we found that none of the reagents could selectively hydrolyze the ethyl ester in the presence of aryl pivaloate ester.

Based on this result, we modified the route of synthesis. Isatoic anhydride **11** was treated with glycine ethyl ester hydrochloride to get (2-aminobenzoylamino) glycine ethyl ester **12**, which on hydrolysis with aqueous sodium hydroxide furnished (2-aminobenzoylamino) acetic acid **14**. (2-Aminobenzoylamino) acetic acid was treated with 4-(pivaloyloxy) benzene sulfonyl chloride **5** in the presence of trimethyl silyl chloride to yield sivelestat. It is reported[3] that **5** on reaction with

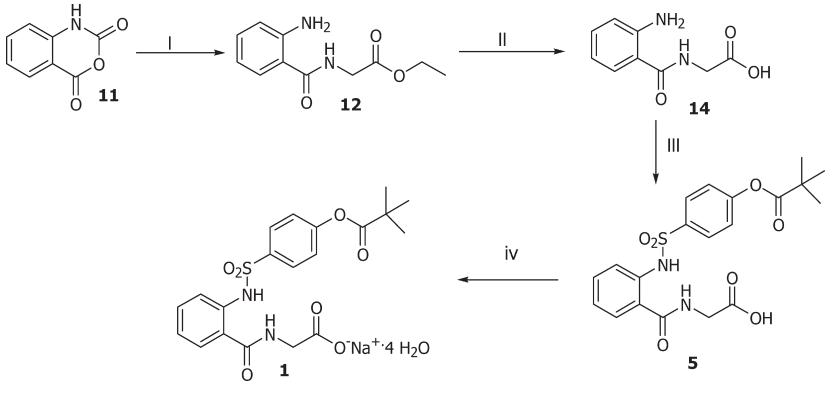


Scheme 2. (i) Sodium hydroxide and (ii) α-picoline, trimethylsilyl glycine.



Scheme 3. (i) Glycine ethyl ester, triethyl amine; (ii) pivaloyloxy benzene sulfonyl chloride; (iii) aq. sodium hydroxide or aq. sodium carbonate or aq. sodium bicarbonate.

(2-Aminobenzoylamino) acetic acid **14** will react not only with an amino group in **14** but also with the carboxyl group, because of the fairly weak nucleophilicity of the amino group, leading to formation of impurities. To avoid the formation of impurities, the carboxyl group in **14** was protected in situ as a trimethylsilyl derivative and treated with pivaloyloxy benzene sulfonyl chloride to get the sivelestat in sufficiently pure form (Scheme 4), which was converted to sivelestat sodium **1**. In short, an efficient synthesis of sivelestat sodium has been developed.



Scheme 4. (i) Glycine ethyl ester, triethyl amine; (ii) aq. sodium hydroxide; (iii) trimethylsilyl chloride, pyridine, pivaloyloxy benzene sulfonyl chloride; (iv) aq. sodium hydroxide.

EXPERIMENTAL SECTION

General Procedures

All reagents were commercially obtained and used as received unless otherwise noted. All nonaqueous reactions were performed in dry glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated by rotary evaporation at ~80.0 mm Hg at less than 60 °C except where noted. Thin-layer chromatography (TLC) was performed on Merck precoated silica-gel $60F_{254}$ plates. Visualization of the developed chromatogram was performed by fluorescence quenching or phosphomolybdic acid stain or 50% sulfuric acid char. ^{1}H NMR spectra were measured on a Varian-Gemini 300-MHz spectrometer.

N-(2-Aminobenzoyl) Glycine Ethyl Ester (12)

Isatoic anhydride (250 g, 1.53 mol) was added to a solution of glycine ethyl ester hydrochloride (213.9 g, 1.53 mol) and triethylamine (162.8 g, 1.61 mol) in acetonitrile (1.25 L). The reaction mass was heated under reflux for 3 h. After completion of the reaction (by TLC), the reaction mass was concentrated under reduced pressure at 40–45 °C to get a slurry. The slurry was dissolved in ethyl acetate (1.0 L) and washed with water (2 × 1.0 L). The layers were separated, and the organic layer was concentrated to ~400 ml to get a slurry, which was treated with n-hexane (1.0 L) under stirring at 10–15 °C to separate the solids. The separated solids were filtered and dried at 50–55 °C to get the title compound (250 g, 73.4%). Melting point: 78–81 °C; IR (KBr) ($\nu_{cm^{-1}}$): 3436, 3355, 2985, 1735, 1639, 1577, 1539, 1450, 1404, 1377, 1265, 1218, 1164, 1029, 995, 867, 744; ^{1}H NMR ($CDCl_3$) (δ ppm): 7.43 (1H, q), 7.24 (1H, m), 6.66 (2H, m), 6.60 (1H, bs), 5.50 (2H, bs), 4.28 (2H, q), 4.19 (2H, d), 1.31 (3H, t); MS (m/z): 223 [M + 1].

N-(2-Aminobenzoyl) Glycine (14)

N-(2-Aminobenzoyl) glycine ethyl ester (250.0 g, 1.12 mol) was added to a solution of sodium hydroxide (62.5 g, 1.56 mol) in 750.0 ml of water and stirred for 30 min at 25–30 °C. After completion of the reaction (by TLC), the reaction mass was washed with 2 × 100 ml of dichloromethane and separated into layers. The aqueous layer was neutralized by acetic acid (95.0 g). The clear solution was distilled under reduced pressure to ~400.0 ml at 50–55 °C to get slurry. Isopropanol (750 ml) was added to the slurry, stirred at 0–5 °C for 30 min, and filtered. The solids were dried at 50–55 °C to give the title compound (194.9 g, 89.31%). Melting

point: 164 °C (dec); IR (KBr) ($\nu_{cm^{-1}}$): 3413, 3328, 3282, 2981, 2349, 1720, 1643, 1527, 1400, 1303, 1245, 1157, 1037, 999, 933, 794, 752; ^{1}H NMR (DMSO-D_6) *(δ ppm):* 12.56 (1H, bs), 8.51 (1H, t), 7.52 (1H, q), 7.15 (1H, m), 6.7 (1H, d), 6.54 (1H, m), 6.44 (2H, bs), 3.85 (2H, t); MS (m/z): 193 [M − 1].

P-Pivaloyloxybenzenesulfonyl Chloride (6)

Sodium salt of p-pivaloyloxybenzenesulfonic acid (250 g, 0.89 mol) was charged to toluene (2.5 L), and 1.25 L of toluene was distilled out azeotropically at 110–115 °C. The resulting slurry was cooled to 0–5 °C, and phosphorus oxychloride (136.9 g, 0.89 mol) was added dropwise in 15 min. The mixture was stirred at 0–5 °C until completion (TLC). After completion of the reaction, 1.25 L of water were added to the reaction mass at 0–5 °C and stirred for 15 min. The layers were separated, and the organic layer was distilled off at 50–55 °C to get slurry, which was cooled to 0–5 °C and treated with hexane (300 ml) to separate the solids. The solids were filtered and dried to get the title compound. (210.0 g, 85.22%). Melting point: 83–87 °C; IR (KBr) ($\nu_{cm^{-1}}$): 2981, 2939, 2318, 1751, 1589, 1458, 1369, 1107, 894, 844; ^{1}H NMR ($CDCl_3$) (δ ppm): 1.37 (s, 9H), 7.34 (dd, 2H), 8.07 (dd, 2H); MS (m/z): 193 [M − 1].

N-[O-(P-Pivaloyloxybenzenesulfonyl Amino) Benzoyl] Glycine (5)

Trimethylsilyl chloride (182.5 g, 1.6 mol) was added to a slurry of N-(2-Aminobenzoyl) glycine (250 g, 1.28 mol) in pyridine (306.25 g, 3.87 mol) and methylene chloride (1.25 L) dropwise at 25–30 °C, and the reaction mass was stirred for 15 min. A solution of p-pivaloyloxy benzenesulfonyl chloride (356.25 g, 1.27 mol) in dichloromethane (1.0 L) was added dropwise to the reaction mass at 25–30 °C in 30 min. The reaction was monitored by TLC. Upon completion of the reaction, the reaction mass was distilled under reduced pressure to get a slurry. The slurry was treated with 500.0 ml of water and extracted with dichloromethane (2 × 500 ml). The layers were separated, and the organic layer was washed with 10.0% HCl solution. The organic layers were further washed with water (250.0 ml) and distilled under reduced pressure to ∼500.0 ml to get slurry. The slurry was treated with ethyl acetate (200.0 ml) and stirred at 10–15 °C for an hour and filtered to get the title compound (391.5 g, 70.0%). Melting point: 213–217 °C; IR (KBr) ($\nu_{cm^{-1}}$): 2977, 1747, 1720, 1693, 1519, 1454, 1334, 1103, 925, 759; ^{1}H NMR ($CDCl_3$ + DMSO-D_6) (δ ppm): 1.23 (9H, s), 3.87 (2H, d), 7.01 (1H, t), 7.10 (2H, d), 7.33 (1H, t), 7.52 (1H, d), 7.64 (1H, d), 7.74 (2H, d), 8.87 (1H, t), 11.39 (1H, s); MS (m/z): 434 [M].

Sivelestat Sodium Hydrate (1)

N-[O-(P-Pivaloyloxybenzenesulfonyl amino) benzoyl] glycine (250.0 g, 0.57 mol) was dissolved in tetrahydro furan (THF) (1.0 L L). The solution was cooled to 0–5 °C, and 5N aqueous solution of sodium hydroxide (121.0 ml) was added and stirred for 30 min. The solvents were concentrated under reduced pressure to 400.0 ml to get slurry, which was recrystallised from water (750.0 ml). The solids were filtered and dried under reduced pressure at 25–30 °C to obtain the product as white solid (243.5 gm, 80%). Melting point: 104–108 °C; IR (cm^{-1}): v 3498, 3440, 2977, 2873, 1755, 1504, 1446, 1392, 1110, 941, 752; ^{1}H NMR (DMSO-d_6) (δ ppm): 1.26 (s, 9H), 3.91 (s, 2H), 6.65 (t, 1H), 7.10 (m, 3H), 7.23 (d, 1H), 7.81 (m, 3H), 10.12 (s, 1H).

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