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SYNTHESIS OF A PRECURSOR OF *M*-IODO SAHA FOR RADIO IMAGING

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ABSTRACT
We have developed a practical synthesis of *N*-hydroxy-*N'*-(3-iodo)phenyloctanediamide (3-iodoSAHA) as well as *m*-aminophenyltributylstannane for the precursor of radio-imaging *m*-iodo SAHA. All these compounds are obtained in high yield and purity. The monoethyl ester of subaryl chloride was prepared *in situ* from subaryl chloride in presence of triethyl amine. A treatment with methanolic hydroxylamine hydrochloride and sodium methoxide produced the 3-iododiamide. The other starting material *m*-aminophenyltributylstannane was prepared using a palladium-catalyzed reaction of hexabutylditin with *m*-bromoaniline using microwave in 82% yield. The *m*-aminophenyltributylstannane was condensed with monoethylester of suberoyl chloride in the presence of base to generate the 3-tributylstannylanilide of monoethyl suberate in 48% yield. On further treatment with methanolic hydroxylamine hydrochloride and sodium methoxide, monoethylester compound gave 3-tributylstannyl suberanilohydroxamic acid in 90% yield.

KEY WORDS: Iodine-3-iodo SAHA, Histone deacetylase, HDAC, SAHA.

INTRODUCTION
Suberoylanilide hydroxamic acid (SAHA) belongs to a class of histone deacetylase (HDAC) inhibitors capable of inducing terminal differentiation, cell growth arrest and/or apoptosis of tumor cells.[1-6] The reversible acetylation of histones, mediated by histone acetyl transferases (HATs) and histone deacetylase (HDACs), plays an important role in chromatin architecture, and hence in the regulation of gene expression.[7,8] Acetylation of cationic lysine tails in nucleosome-associated histones neutralizes charge and promotes relaxation of chromatin, leading to transcriptional activation. Conversely, deacetylation of these lysine residues promotes formation of condensed chromatin, and transcription is repressed. In some tumor cells excessive hypocetylation of histones results in the under expression of growth regulatory factors such as the cyclin dependent kinase inhibitor p21Wafl and thus contributes to the development of cancer.[4-6] Histone hyperacetylation caused by HDAC inhibitors such as trichostatin and Suberoylanilide hydroxamic acid (SAHA) can cause growth arrest in a wide range of transformed cells and can inhibit the growth of human tumor xenografts.[7-11]

RESULTS AND DISCUSSION

We have developed an efficient synthesis of *N*-hydroxy-*N*-(3-iodo)phenyloctanediamide **5** (*m*-iodoSAHA) (**Scheme 1**) by modifying a synthetic procedure by Stowell *et al.* Our synthesis started with condensation of 3-iodoaniline and monoethyl ester of subaryl chloride derived in situ from subaryl chloride with dry ethyl alcohol in presence of triethylamine to afford the anilide **4**. Compound **3** treated with methanolic hydroxylamine hydrochloride and sodium methoxide provided 3-iodo-SAHA in 93% yield.

The other starting material *m*-aminophenyltributylstannane was prepared[2] (**Scheme 2**) using a palladium-catalyzed reaction of hexabutylditin with *m*-bromoaniline by microwave in 82% yield. The *m*-aminophenyltributylstannane was condensed with monoethylester of suberoyl chloride in presence of a base to yield the 3-tributylstannylanilide of monoethyl suberate in 48% overall yield. On further treatment with methanolic hydroxylamine hydrochloride and sodium methoxide, monoethylester compound generated 3-tributylstannyl suberanilohydroxamic acid in 90% yield.

MATERIALS AND METHODS

General Methods

All chemicals and solvents were obtained from Sigma-Aldrich (Milwaukee, WI) and Fisher Scientific (Pittsburg, PA) and used without further purification. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on an IBM-Brucker Avance 600 (600 MHz for ^{1}H-NMR and 150.0 MHz for ^{13}C-NMR), spectrometers. Chemical shifts (δ) are determined relative to $CDCl_3$. Proton-proton coupling constants (*J*) are given in Hertz and spectral splitting patterns are designated as singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet or overlapped (m), and broad (br). Liquid chromatography mass spectra (ionspray, a variation of electrospray) were acquired on a Perkin-Elmer Sciex API 100 spectrometer or Applied Biosystems Q-trap 2000 LC-MS-MS. Flash chromatography was performed using Merk silica gel 60 (mesh size 230-400 ASTM) or using an Isco (Lincon, NE) combiFlash Companion or SQ16x flash chromatography system with RediSep columns (normal phase silica gel (mesh size 230-400ASTM) and Fisher Optima TM grade solvents. Thin-layer chromatography (TLC) was performed on E. Merk (Darmstadt, Germany) silica gel F-254 aluminum-backed plates with visualization under UV (254 nm) and by staining with potassium permanganate or ceric ammonium molybdate.

3-Iodoanilide of monoethyl suberate (4).

To a three-necked 500 mL round-bottomed flask was added 6 mL (7.03 g, 33.1 mmol) of suberoyl chloride and 40 mL of dry THF, and the solution was chilled to 0^{o}C. Through an addition funnel was added dropwise over a 3 hours period a solution of 40 mL THF, 1.9 mL (1.52 g, 33.1 mmol) EtOH and 4.63 mL (3.37 g, 33.1 mmol) triethylamine. Upon completion of the addition, a solution of 60 mL THF, 4.6 mL triethylamine, and 7.3 g of 3-iodoaniline (33.32 mmol) was added dropwise, and the solution was stirred overnight at room temperature.

To the solution containing white precipitate was added 50 mL of distilled water, and after concentrating, the solution was transferred to a separatory funnel with 20 mL of 1 M NaOH and 100 mL chloroform. Layers were shaken and separated. The organic layer was washed twice with 40 mL water, and was evaporated in vacuo and dried to afford 8.2 g of white solid with characteristic fragrant smell. The crude product was purified by flash column chromatography over silica gel, using polarity gradient 30-50% EtOAc in hexane to yield ester **4** (6.05 g 45 %) as a white solid: ^{1}H NMR ($CDCl_3$) δ 9.95 (s, 1H), 8.11(t, *J* = 1.8 Hz, 1H), 7.53 (dd, *J* = 0.9, 2.1 Hz, 1H), 7.50 (dd, *J* = 0.9, 2.1 Hz, 1H), 7.08 (t, *J* = 8.1 Hz, 1H), 4.03 (q, *J* = 6.9 Hz, 2H), 2.27 (p, *J* = 7.3 Hz, 4H), 1.54 (p, *J* = 6.9 Hz, 4H), 1.27 (m, 4H), 1.17

(t, *J* = 7.2 Hz, 3H); ^{13}C NMR δ 173.3, 171.9, 141.2, 131.9, 131.2, 127.6, 118.6, 94.9, 60.1, 36.8, 33.9, 28.7, 28.6, 25.3, 24.8, 14.6; MS ($C_{16}H_{22}INO_3$) Calcd. 403.0644; Found 404.4 (M+H).

***N*-Hydroxy-*N*′-[3-I]phenyloctanediamide (5).**

To a solution of hydroxylamine hydrochloride (1.38 g, 20 mmol) in MeOH (25 mL), 1 mg of phenolphthalein and then NaOMe (1.62 g, 30 mmol) was added. This mixture was stirred for 30 min at room temperature. When sodium chloride precipitated, compound **4** (4.03 g, 10 mmol) was added. The reaction mixture was stirred for an additional 16 h at room temperature and then quenched with 50 mL H_2O and glacial acetic acid (4 mL). Stirring was continued for 1 h and the resulting precipitate was filtered, and rinsed with water. The solid was dried at room temperature to yield 5 (3.63 g, 93%) as a white solid showing no impurities by thin layer chromatography or ^{1}H NMR (DMSO-d_6) δ 10.37 (s, 1H), 9.98 (s, 1H), 8.1 (s, 1H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.36 (d, *J* = 7.8 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 2.28 (t, *J* = 7.5 Hz, 2H), 1.94 (t, *J* = 7.2 Hz, 2H), 1.51 (m, 4H), 1.25 (m, 4H); ^{13}C NMR δ 172.1, 169.7, 141.2, 131.9, 131.2, 127.7, 118.7, 94.9 36.8, 32.7, 28.8 (2C), 25.5, 25.4; IR 3314, 32.74, 1660, 1620, 1600, 1530, 1442 cm^{-1}; MS ($C_{14}H_{19}IN_2O_3$) Calcd. 390.044; Found 391.4 (M+H).

3-Aminophenyltributylstannane (7).

In a microwave tube containing 0.63 g (3.65 mmol) of m-bromoaniline was placed 50.0 mg (0.0443 mmol) of $Pd(PPh_3)_4$ the tube was then sealed and flushed with argon. To the tube was then added 3 mL of toluene and 1.5 mL (1.71 g, 2.93 mmol) of $(SnBu_3)_2$ (2.6 g, 4.45 mmol). The tube was then placed in the microwave and heated to 155^{o}C for 14 min. The resulting black mixture was filtered through celite, and the filtrate obtained was evaporated to dryness under reduced pressure. The residue obtained was dissolved in hexane and the solution was applied to a flash column chromatography eluting with hexane/EtOAc (98:2) to yield the pure m-aminophenyltributylstannane **7** in 82% yield. ^{1}H NMR ($CDCl_3$): δ 7.11 (t, *J* = 7.5 Hz, 1H), 6.84 (d, *J* = 7.0 Hz, 1H), 6.79 (d, *J* = 2.5 Hz, 1H), 6.61 (m, 1H), 3.56 (s, 2H), 1.53 (m, 6H), 1.32 (m, 6H), 1.03 (m, 6H), 0.88 (t, *J* = 7.3 Hz, 9H); ^{13}C NMR ($CDCl_3$) δ 146.1, 143.3, 129.0, 127.1, 123.4, 115.4, 29.5(3C), 27.8(3C), 14.1(3C), 9.9(3C); MS ($C_{18}H_{33}NSn$); Calcd. 383.1635; Found 384.3 (M+H).

3-Tributylstannylanilide of monoethyl suberate (8).

To a three-necked 500 mL round-bottomed flask was added 6 mL (7.03 g, 33.1 mmol) of suberoyl chloride and 40 mL of dry THF, and the solution was chilled to 0^{o}C. Through an addition funnel was added dropwise over a 3 hours period a solution of 40 mL THF, 1.9 mL (1.52 g, 33.1 mmol) EtOH and 4.63 mL (3.37 g, 33.1 mmol) triethylamine. Upon completion of the addition, a solution of 60 mL THF, 4.6 mL triethylamine, and 12.8 g of aminophenyltributylstannane (33.32 mmol) was added dropwise, and the solution was stirred overnight at room temperature.

To the solution containing white precipitate was added 50 mL of distilled water, and after concentrating, the solution was transferred to a separatory funnel with 20 mL of 1 M NaOH and 100 mL chloroform. The layers were separated. The organic layer was washed twice with 40 mL water, and was evaporated in vacuo. The crude product was then purified by flash column chromatography over silica gel, using polarity gradient 25-40% EtOAc in hexane to yield the pure ester 8 (9.07 g, 48%) as a liquid: ^{1}H NMR (DMSO-d_6) δ 9.74 (s, 1H), 7.61 (m, 2H), 7.22 (t, *J* = 7.5 Hz 1H), 7.04 (d, *J* = 6.9 Hz, 1H), 4.03 (dq, *J* = 6.9, 1.8 Hz, 2H), 2.25 (m, 4H), 1.55 (m, 10 H), 1.30 (m, 10H), 1.06 (m, 3H), 0.99 (m, 6H), 0.83 (m, 9H); ^{13}C NMR (DMSO-d_6) 173.2, 171.5, 141.7, 139.5, 131.0, 128.5, 126.9, 119.3, 60.0, 36.8, 33.8, 29.0 (3C), 28.8, 28.7, 27.1 (3C), 25.4, 24.8, 24.7, 14.5, 13.9 (3C), 9.5 (3C); MS ($C_{28}H_{49}NO_3Sn$); Calcd. 567.2734; Found 568.5 (M+H).

3-Tributylstannyl suberanilohydroxamic acid. (9).

To a solution of hydroxylamine hydrochloride (1.73 g, 25 mmol) in MeOH (32 mL), 1 mg of phenolphthalein and then NaOMe (2.1 g, 37.5 mmol) was added. This mixture was stirred for 30 min at room temperature. When sodium chloride precipitated, compound 8 (7.08 g, 12.5 mmol) was added. The reaction mixture was stirred for an additional 16 h at room temperature and then quenched with 70 mL H_2O and glacial acetic acid (5 mL). Stirring was continued for 1 h and the resulting gummy yellow product was collected, and the residue was diluted with ethyl acetate and then was washed with water. After it was dried and concentrated, the crude product was purified by flash chromatography (2-10% methanol in dichloromethane) to give 9 (6.2 g, 90%) as a light yellow gummy product: ^{1}H NMR (DMSO-d_6) δ10.35 (s, 1H), 9.78 (s, 1H), 7.60 (m, 2H), 7.22 (t, *J* = 7.2 Hz 1H), 7.04 (d, *J* = 7.2 Hz, 1H), 2.28 (t, *J* = 7.2 Hz, 2H), 1.94 (t, *J* = 7.2 Hz, 2H) 1.53 (m, 10H), 1.29 (m, 10H), 1.01 (m, 6H), 1.01 (m, 9H), ^{13}C NMR (DMSO-d_6) 173.2, 170.9, 141.8, 138.2, 131.7, 127.8, 127.4, 119.7, 36.6, 32.3, 29.0 (3C), 28.9, 28.6, 27.0 (3C), 25.4, 25.2, 12.7 (3C), 9.0 (3C).

CONCLUSIONS

Synthesis of *N*-hydroxy-*N*-(3-iodo)phenyloctanediamide (3-iodoSAHA) and precursor for the stannyl compound have been accomplished for radiolabelling. This new compound may be useful in treatment of cancer and described method may be suitable for the preparation of other I-124 radio labeled of SAHA analogue for PET.

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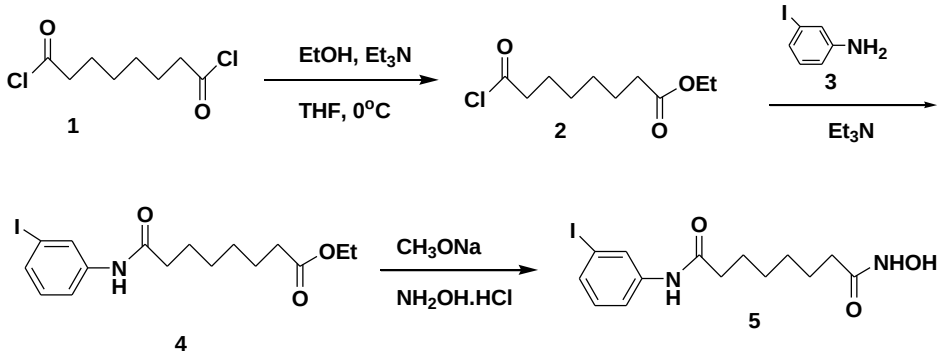
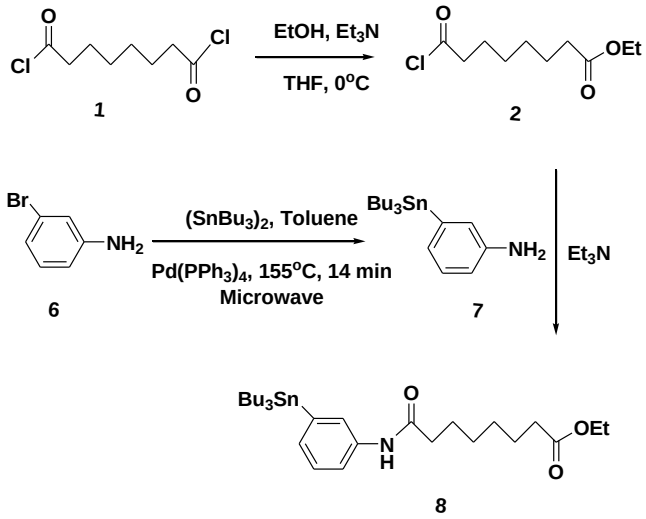


Scheme 1: Synthesis of *N*-hydroxy-*N*′-[3-I]phenyl-octanediamide



Scheme 2: Synthesis of stannyl precursor of *N*-hydroxy-*N*′-[3-I]phenyl-octanediamide