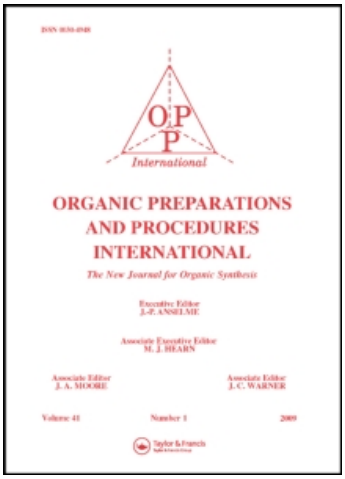

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A NEW FACILE AND EXPEDITIOUS SYNTHESIS OF N-HYDROXY-N'-PHENYLOCTANEDIAMJDE, A POTENT INDUCER OF TERMINAL CYTODIFFERECNTIATION

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A NEW FACILE AND EXPEDITIOUS SYNTHESIS OF *N*-HYDROXY-*N'*-PHENYLOCTANEDIAMIDE, A POTENT INDUCER OF TERMINAL CYTODIFFERENTIATION

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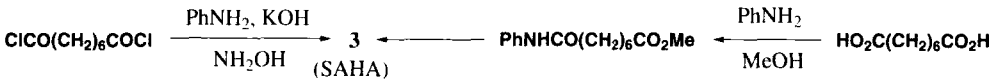
In recent years the development of cytodifferentiating agents blazed a trail in cancer therapy. The rationale presented is the evidence that many neoplastic cells do not respond to normal regulators of proliferation and suffer from a blockage of differentiation.[1,2] The use of cytodifferentiating agents can remove this blockage allowing the malignant cells to progress to more differentiated cell types with less proliferative activity. A variety of cytodifferentiating agents, including some derivatives of vitamins and steroides,[3-6] proteases,[7] tumor promoters,[8] growth factors,[9] inhibitors of nucleic acid synthesis have been reported. Among these are hybrid polar compounds (HPCs), whose prototype is hexamethylene bisacetamide (HMBA); they represent a new class of compounds which induce terminal differentiation and/or apoptosis in various transformed cells.[10-12]

N-Hydroxy-*N'*-phenyloctanediamide (suberoylanilide hydroxamic acid, SAHA), belonging to the second-generation HPCs, is a potent cytodifferentiating agent toward leukemia cells.[12] At 10^{-5} M concentration SAHA shows a potent inhibitory effect on proliferation of AXC rat prostate cancer cells,[13] and as dietary supplement is reported to inhibit *N*-methylnitrosourea-induced mammary tumors in rats.[14] Indeed, clinical Phase I trials of SAHA are about to begin for the treatment of human cancers.

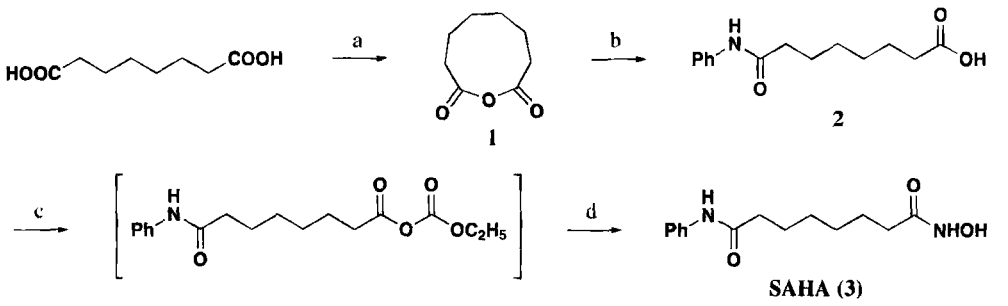
Up to date two synthetic routes for the preparation of SAHA have been reported, the first[15] involving a one-pot reaction[16] and the latter describing a three-step procedure[13] (Fig. 1). The patented, low-yielding (15-30%) method[15] suffers from the formation of by-products difficult to remove. The more recent approach[13] overcomes this difficulty but furnishes SAHA in only 36% overall yield. Here we report a new simple, high yielding method for the synthesis of SAHA, which affords the desired compound in 58% overall yield and does not produce by-products.



Known procedures for the synthesis of SAHA

Fig 1.

Accordingly, suberoyl anhydride (**1**),[17] easily obtained by heating suberic acid in acetic anhydride, was treated with aniline to give suberanilic acid **2** in 94% yield. The acid intermediate **2** was in turn converted, under neutral pH conditions, into the corresponding *N*-hydroxyamide **3** by a one-step reaction involving the use of ethyl chloroformate/triethylamine system and hydroxylamine (Scheme 1). Physical, chemical and spectral data for the compounds **2** and **3** were consistent with the literature values (see Experimental Section).



a) $(CH_3CO)_2O$, reflux; b) Aniline, THF, rt; c) ClCOOEt, Et_3N, THF, 0°; d) NH_2OH, MeOH, rt

Scheme 1

EXPERIMENTAL SECTION

Melting points (mp) were determined on a Büchi 530 melting point apparatus and are uncorrected. Infrared (FT-IR) spectra (KBr) were recorded on a Perkin-Elmer 1800 FT instrument. ^{1}H NMR spectra were recorded at 200 MHz on a Bruker AC 200 spectrometer; chemical shifts are reported in δ (ppm) units relative to the internal reference tetramethylsilane (Me_4Si). All compounds were routinely checked by TLC and ^{1}H NMR. TLC was performed on aluminum-backed silica gel plates (Merck DC-Alufolien Kieselgel 60 F_{254}) with spots visualized by UV light. All solvents were reagent grade and, when necessary, were purified and dried by standards methods. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator operating at a reduced pressure of ca. 20 Torr. Organic solutions were dried over anhydrous sodium sulfate. Analytical results are within ±0.30% of the theoretical values.

Suberic Anhydride (**1**).- A solution of suberic acid (5.0 g, 28.7 mmol) in acetic anhydride (10 mL) was heated at reflux while stirring for 1 h. After cooling to room temperature, the solvent was evaporated under reduced pressure and the pale-yellow solid residue was recrystallized from acetonitrile. Pure **1** (4.3 g, 96% yield) was obtained as a white solid, mp 51-52°. FT-IR (KBr): 2910, 1801, 1741, 1705, 1473, 1415, 1333, 1218, 1078, 910, 726 cm^{-1}; 200 MHz ^{1}H NMR ($CDCl_3$): δ 1.34 (m, 4H, $C_{4,5}$-H), 1.62 (m, 4H, $C_{3,6}$-H), 2.41 (m, 4H, $C_{2,7}$-H).

Anal. Calcd for $C_8H_{12}O_3$: C, 61.52; H, 7.74. Found: C, 61.64; H, 7.76

Suberanilic Acid (**2**).- Aniline (0.6 g, 6.4 mmol) was added to a stirred solution of the anhydride **1** (1.0 g, 6.4 mmol) in anhydrous tetrahydrofuran (10 mL). After stirring at room temperature for 30 min, the resulting mixture was diluted with water (100 mL) and the formed white solid was filtered

and collected. Recrystallization from water gave **2** as a pure solid (1.5 g, 94% yield), mp 122-123°, *lit.*[13] mp 126-128°. FT-IR (KBr): 3308, 2938, 1693, 1661, 1598, 1529, 1442, 1252, 1180, 756, 690 cm^{-1}; 200 MHz ^1H NMR (DMSO-d_6): δ 1.24 (m, 4H, $C_{4,5}$-H), 1.45 (m, 4H, $C_{3,6}$-H), 2.13 (m, 2H, $C_{2,7}$-H), 2.23 (m, 2H, $C_{2,7}$-H), 6.94 (t, 1H, Ar_4-H), 7.21 (t, 2H, $Ar_{3,5}$-H), 7.51 (d, 2H, $Ar_{2,6}$-H), 9.77 (s, 1H, NH), 11.92 (s, 1H, OH).

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.45; H, 7.68; N, 5.62. Found: C, 67.74; H, 7.70; N, 5.39

***N*-Hydroxy-*N'*-phenyloctanediamide (3).**- To a 0° cooled solution of suberanilic acid **2** (0.47 g, 1.89 mmol) in anhydrous tetrahydrofuran (10 mL), ethyl chloroformate (0.25 mL, 2.52 mmol) and triethylamine (0.40 mL, 2.73 mmol) were added and the mixture was stirred for 10 min. The solid was filtered off and the filtrate was added to freshly prepared hydroxylamine[18] (0.1 g, 3.15 mmol) in methanol. The resulting mixture was stirred at room temperature for 15 min, then was evaporated and the residue was recrystallized from acetonitrile to give pure **3** as white solid (0.32 g, 64% yield), mp 159.5-160°, *lit.*[13] mp 159-160.5°. FT-IR (KBr): 3312, 3269, 2943, 1662, 1617, 1599, 1530, 1443, 1395, 1317, 1186, 977, 762, 704, 573 cm^{-1}; 200 MHz ^1H NMR (DMF-d_7): δ 1.45 (m, 4H, $C_{4,5}$-H), 1.72 (m, 4H, $C_{3,6}$-H), 2.18 (m, 2H, $C_{2,7}$-H), 2.48 (m, 2H, $C_{2,7}$-H), 7.16 (t, 1H, Ar_4-H), 7.42 (t, 2H, $Ar_{3,5}$-H), 7.81 (d, 2H, $Ar_{2,6}$-H), 9.05 (s, 1H, OH), 10.09 (s, 1H, NH), 10.63 (s, 1H, NH).

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16. In the patent, Breslow *et al.*[15] report four general procedures (A-D) for the synthesis of compounds of general formula R-CO-$(CH_2)_n$-CONHOH, the simplest of which (A) is the one-pot reaction cited by us (yields 15-30%). The other procedures are rather elaborate and give hydroxamide products in low yields again (B: 35-65%, C: 20-35%, D: 20-33% yields).

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18. J. P. Devlin, W. D. Ollis, J. E. Thorpe, *J. Chem. Soc. Perkin 1*, 846 (**1975**). A solution of hydroxylamine hydrochloride (0.22 g, 3.15 mmol) in methanol (5 mL) was added to a stirred solution of potassium hydroxide (0.18 g, 3.15 mmol) in methanol (5 mL) at 0°. After stirring for 15 min, the precipitate was removed and the filtrate was used as such.

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