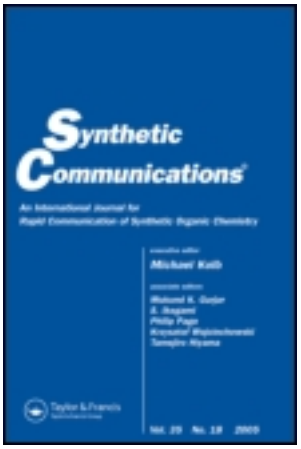

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SIMPLE AND EFFICIENT SYNTHESIS OF BELINOSTAT

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A novel synthesis of belinostat (1) starting from 3-nitrobenzaldehyde has been developed. The key step in this sequence involves the conversion of (2E)-3-(3-aminophenyl)acrylic acid methyl ester to (2E)-3-(3-chlorosulfonylphenyl)acrylic acid methyl ester via diazotization and sulfonylation.

Keywords: Belinostat; sulfonylation; synthesis

Belinostat (PXD101, **1**, Fig. 1), a new histone deacetylase (HDAC) inhibitor developed by CuraGen/TopoTarget, is currently undergoing clinical trials as an anticancer drug.[1,2] As a potent histone deacetylase inhibitor, belinostat has shown great promise for the treatment of solid tumors and haematological malignancies, used alone or in combination with other chemotherapeutics.[2,3] Bearing a sulfonamide–hydroxamide structure, belinostat belongs to the hydroxamic acid class of HDAC inhibitors. Although its structure is rather simple, the reported synthetic methods are limited. To the best of our knowledge, only one method (developed by Kalvinsh and coworkers) is available for the preparation of belinostat.[4,5] In this method, benzaldehyde was used as starting material and first sulfonylated with oleum, followed by Horner–Wadsworth–Emmons olefination with methyl (dimethoxyphosphinyl) acetate and chlorination with $SOCl_2$ to afford methyl (2E)-3-(3-chlorosulfonyl-phenyl)prop-2-enoate as the key intermediate. This key intermediate was then reacted with aniline, followed by hydrolysis, chlorination, and amidation to provide belinostat with a 12% total yield. We report an improved synthesis of belinostat with the following advantages. First, our synthesis avoids the use of the extremely corrosive oleum and $SOCl_2$ and therefore is possibly better for scaled-up production. Second, our synthetic steps do not involve tedious separations and give a better overall yield.

Scheme 1 delineates the novel synthesis of belinostat developed in our laboratories. This route emphasized the introduction of a chlorosulfonyl group into the benzene ring via diazotization and thus avoids the use of extremely corrosive oleum

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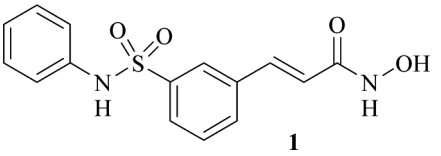

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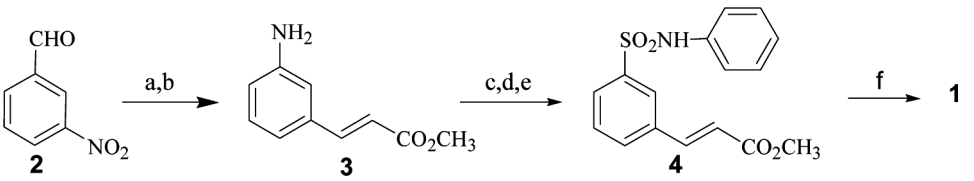
Figure 1. Structure of belinostat (**1**).



Scheme 1. Reagents and conditions: (a) $(MeO)_2P(O)CH_2CO_2CH_3/K_2CO_3$, rt, 0.5 h; (b) $SnCl_2 \cdot 2H_2O$, reflux, 2.5 h, 95% for two steps; (c) $NaNO_2/HCl/HOAc$, $-5\,^{\circ}C$ to $10\,^{\circ}C$, 0.75 h; (d) $SO_2/CuCl/HCl/HOAc$; (e) aniline, rt, 2 h, 41% for three steps; (f) $NH_2OH \cdot HCl/KOH$, EtOH, 1 h, 84%.

and $SOCl_2$ and tedious separation. More important, the total yield (33%) is significantly improved.

The amine **3** was prepared from 3-nitrobenzaldehyde (**2**) using a two-step procedure carried out successively without purification in 95% overall yield. In the first stage of the transformation, the Horner reaction of **2** with $(MeO)_2P(O)CH_2CO_2CH_3$[6] in the presence of K_2CO_3 in water provided methyl (2E)-3-(3-nitrophenyl)prop-2-enoate. The resulting crude was reduced with $SnCl_2$[7] in anhydrous alcohol to yield methyl (2E)-3-(3-aminophenyl)prop-2-enoate (**3**). With amine **3** in hand, a three-step procedure was performed successively to convert **3** into sulfonamide **4**. Diazotization of **3** with $NaNO_2$ in dilute HCl, followed by substitution with dilute SO_2 in HCl and HOAc mixed solution,[8] provided the key intermediate methyl (2E)-3-(3-chlorosulfonylphenyl) prop-2-enoate. Amination of the sulfonylchloride with aniline in the presence of $NaHCO_3$ afforded methyl (2E)-3-{3-[(phenylamino)sulfonyl]phenyl}prop-2-enoate (**4**) with a overall yield of 41% for three steps. The product **1** was finally obtained by oximation of **4** with $NH_2OH \cdot HCl$ in 84% yield.[9] The melting point and ^1H NMR spectrum of **1** were identical to those described in literature.[4]

In summary, we have successfully developed a novel synthetic route to prepare belinostat from easily available 3-nitrobenzaldehyde with a considerable yield, and the route has convenient and economic advantages.

EXPERIMENTAL

Reagents were purchased from commercial sources and used without further purification unless otherwise indicated. Melting points were determined with a XT4 melting-point apparatus and are uncorrected. ^1H NMR spectra were recorded on a Bruker AV-300 instrument (300 MHz) with $CDCl_3$ and dimethylsulfoxide

(DMSO-d_6) as the solvents, and mass spectra (MS) were performed on Agilent G1956B and Shimadzu GCMS-QP2010 instruments.

Methyl (2E)-3-(3-Aminophenyl)prop-2-enoate (3)

Methyl (2E)-3-(3-aminophenyl)prop-2-enoate (**3**) was prepared by a modified literature method. m-Nitrobenzadehyde (26.2 g, 174 mmol) was added to a mixture of methyl (dimethoxyphosphinyl) acetate (34.6 g, 208 mmol) and K_2CO_3 solution (48 g of K_2CO_3 in 80 ml of water). The formed mixture was stirred at room temperature for 0.5 h. The precipitate was filtered, washed with 1N HCl and water, and dried to yield 35.9 g of methyl (2E)-3-(3-nitrophenyl)prop-2-enoate as a yellowish powder. It was used for the next step without further purification.

A mixture of methyl (2E)-3-(3-nitrophenyl)prop-2-enoate (16.6 g, 80 mmol) and $SnCl_2 \cdot 2H_2O$ (62.1 g, 275 mmol) in anhydrous EtOH (200 ml) was heated at 80 °C for 2.5 h. The mixture was allowed to cool to rt, and then the solvent was half evaporated under reduced pressure. The residue was poured into ice water and neutralized (pH ca. 7) with saturated Na_2CO_3 solution, and the resulting mixture was extracted with ethyl acetate. The organic extract was washed with saturated NaCl solution and dried over Na_2SO_4. The solvent was then evaporated under reduced pressure to provide **3** (13.4 g, 95%) as a light yellowish solid. Mp 80–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.69–3.79 (br, 5H), 6.37 (d, $J = 15.9$ Hz, 1H), 6.69 (dd, $J = 1.8$, 7.8 Hz, 1H), 6.80 (s, 1H), 6.91 (d, $J = 7.5$ Hz, 1H), 7.15 (dd, $J = 7.5$, 7.8 Hz, 1H), 7.60 (d, $J = 15.9$ Hz, 1H); MS: $m/z = 178.1$ $(M + H)^+$. The ^{1}H NMR spectrum was in good agreement with the reported data.[4]

Methyl (2E)-3-{3-[(Phenylamino)sulfonyl]phenyl}prop-2-enoate (4)

Methyl (2E)-3-(3-aminophenyl)prop-2-enoate (**3**) (8.41 g, 48 mmol) was added to a mixture of concentrated HCl (40 ml) and glacial acetic acid (12 ml) under vigorous stirring. The formed mixture was then cooled to −13 °C with an ice–NaCl bath, and a solution of sodium nitrite (3.61 g of $NaNO_2$ in 12 ml of water) was added dropwise at such a rate that the temperature did not exceed −5 °C. After addition, the stirring was continued for 45 min with the temperature below −5 °C.

In another flask, sulfur dioxide was introduced to 45 ml of glacial acetic acid with vigorous stirring at 0 °C until saturation. Cuprous chloride (1.45 g, 15 mmol) was then added to the solution, and sulfur dioxide was added until the yellow-green suspension became blue-green. Sulfur dioxide solution was added to the diazotization reaction mixture in portions. After all the diazonium salt had been added, the mixture was poured into 500 ml of ice water and stirred until the ice melted, and then the crude sulfonamide was extracted with ethyl acetate. The organic extract was then washed with saturated sodium bicarbonate and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure to afford a black oil, which was used directly for the next step.

A solution of the black oil (obtained the previous step) in 40 ml of 1,4-dioxane was added dropwise to a solution of aniline (2.56 g, 28 mmol) in 1,4-dioxane (10 ml) and 10% aqueous sodium bicarbonate solution (50 ml), and the mixture was stirred at room temperature for 10 h. The solvent was then evaporated, and 80 ml of water

were added. The resulting mixture was stirred for 1 h and extracted with ethyl acetate. The organic extract was washed successively with 1N HCl solution, water, and saturated brine. After removing the solvent, the residue was purified by column chromatograph to afford **4** as a yellowish powder (4.43 g, 41% for three steps). Mp 144–146 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.81 (s, 3 H), 6.00–6.38 (br, s, 1H), 6.41 (d, $J = 15.6$ Hz, 1H), 7.09–7.15 (m, 3 H), 7.22–7.27 (m, 2 H), 7.45 (t, $J = 7.8$ Hz, 1H), 7.59–7.64 (m, 2 H), 7.77 (d, $J = 7.5$ Hz, 1H), 7.92 (s, 1H); MS: $m/z = 317$ $[M]^+$, 318 $[M+H]^+$.

(2E)-N-Hydroxy-3-{3-[(phenylamino)sulfonyl]phenyl}prop-2-enamide (Belinostat, 1)

Potassium hydroxide (2.2 g, 39.0 mmol) was added to a solution of hydroxylamine hydrochloride (2.70 g, 39.0 mmol) in dry ethanol (10 ml), and the resulting mixture was cooled to 0 °C and filtered. Potassium hydroxide (0.35 g, 6.39 mmol) and **4** (0.37 g, 1.17 mmol) were added to the filtrate, and the mixture was stirred at 0 °C for 1 h. Then 25 ml of water were added to quench the reaction, and the mixture was then neutralized with 2 N HCl solution. The precipitate was filtered and dried under vacuum to provide **1** as an off-white solid (0.31 g, 84% yield). Mp 170–172 °C; ^{1}H NMR (300 MHz, DMSO-d_6): δ 6.52 (d, $J = 15.9$ Hz, 1H), 6.81–7.12 (m, 6H), 7.33 (d, $J = 15.9$ Hz, 1H), 7.47–7.67 (m, 3 H), 7.87 (s, 1H), 9.00–11.20 (br, 3H); HRMS calcd. for $C_{15}H_{14}N_2O_4SNa$, m/z: 341.0567 $(M+Na)^+$; ; found, m/z: 341.0578.

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