

Short Note

2-Bromophenyl Salicylate

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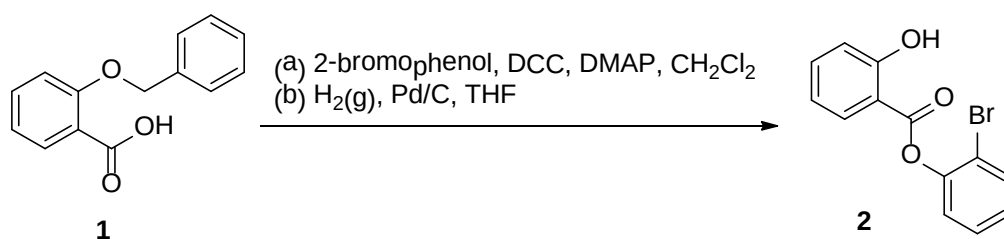
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Abstract: 2-Bromophenyl salicylate is synthesized from 2-benzyloxybenzoic acid in two steps. The final compound has been characterized by IR, ^1H -NMR, ^{13}C -NMR and HRMS. The melting point for 2-bromophenyl salicylate is provided.

Keywords: esterification; debenzoylation; salicylate ester

Derivatives of salicylic acids can be of great biological importance. Salicylate derivatives have been probed for their potential to mimic or exceed the effects of salicylic acid in its anti-inflammatory [1,2] and anti-thrombotic activities [3,4]. In addition, researchers have studied the derivatives' anti-malarial [5], antifungal [6] and herbicidal activities [7,8] and the ability of salicylates to induce immunity to disease in plants [9,10]. Here in we report the synthesis of a new salicylate ester, 2-bromophenyl salicylate **2**, in two steps beginning with commercially available 2-benzyloxybenzoic acid **1** (Scheme 1). The first step of the synthesis is a Steglich esterification with **1** and 2-bromophenol. This is followed by debenzoylation of the resulting product with hydrogen gas and palladium catalyst to provide **2**.

Scheme 1. Synthesis of 2-bromophenyl salicylate **2**.



Experimental

General

Unless noted, all reactions were performed under an atmosphere of argon in oven-dried glassware. Solvents for the reaction were obtained from commercial sources and purified with MBraun Manual Solvent Purification System prior to use. All other chemicals were obtained from commercial sources without further purification. Chromatography was performed with Selecto Scientific Si-gel (particle size 100–200 microns) and the chromatography solvents were purchased from commercial sources and used without further purification. All IR spectra were recorded on a Thermo Nicolet Avatar 370-FTIR. NMR spectra were recorded on a Bruker Multi-Nuclear NMR instrument, ^1H -NMR: 250 MHz and ^{13}C -NMR: 63MHz; the solvent was CDCl_3 . The NMR signals are reported in parts per million (ppm) relative to the residual CHCl_3 in the solvent. Signals are described with multiplicity, singlet (s), doublet (d), triplet (t), triplet of doublet (td) and multiplet (m); coupling constants (Hz) and integration. The melting point was measured with the Vernier Melt Station using Vernier LabQuest 2 and is uncorrected. High Resolution Mass Spectrometry was performed using **Waters Micromass Q-ToF micro Mass Spectrometer**, ESI, positive ion mode.

2-Bromophenyl Salicylate (2)

(a) An oven dried, round-bottom flask equipped with a stir bar and an argon inlet was charged with dichloromethane (50 mL), 2-bromophenol (0.59 mL, 5.05 mmol), *N,N'*-dicyclohexylcarbodiimide (DCC) (1.14 g, 5.50 mmol), 4-(*N,N*-dimethylamino)pyridine (DMAP) (122 mg, 1.00 mmol) and 2-benzyloxybenzoic acid (1.14 g, 5.00 mmol). After stirring for 12 hours at room temperature, the resulting white precipitate was removed by vacuum filtration. The clear filtrate was concentrated under vacuum and the crude, yellow oil was purified by flash column chromatography (5% ethyl acetate in petroleum ether) to provide a colorless oil (1.86 g, 97%) [11].

(b) An oven dried, round-bottom flask equipped with a stir bar and an argon inlet was charged with the product from (a) (766.5 mg, 2.00 mmol) in tetrahydrofuran (THF) (20 mL) and 10% Pd/C catalyst (77 mg). The argon inlet was replaced with a hydrogen inlet and the black suspension was stirred under an atmosphere of hydrogen. After 24 h, the hydrogen inlet was removed and the suspension was filtered through a silica-plug (50% ethyl acetate in hexanes). The filtrate was concentrated under vacuum and resulting crude, a yellow solid, was purified by flash column chromatography (2% ethyl acetate in petroleum ether) to provide **2**, a white solid (356 mg, 61%). M.p. 63.0–64.7 °C; FT-IR (ZnSe): 3210 (broad, OH), 1686, 1301, 1251, 1208, 1155, 1069, 755, 760, 697 cm^{-1} ; ^1H -NMR δ 10.34 (s, 1H, OH), 8.18 (dd, 1H, $J = 1.5, 7.9$ Hz), 7.71 (dd, 1H, $J = 1.2, 7.9$ Hz) 7.57 (td, 1H, $J = 1.4, 7.1$ Hz), 7.41 (td, 1H, $J = 1.4, 7.4$ Hz), 7.21–7.33 (m, 2H), 7.09 (d, 1H, $J = 8.8$ Hz), 7.02 (d, 1H, $J = 7.2$ Hz); ^{13}C -NMR δ 167.8, 162.1, 147.6, 136.7, 133.5, 130.5, 128.5, 127.7, 123.7, 119.6, 117.8, 116.1, 111.3; HRMS (ESI, positive ion mode): $[\text{M}+\text{Na}]^+$ m/z calculated: 314.9633, found: 314.9622.

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References and Notes

1. Delgado-Rivera, R.L.; Rosario-Melendez R.; Uhrich, K.E. Salicylate-based poly(anhydride-esters): A dual system delivery of fibroblast growth factor-2 and the suppression of inflammation *Polymer Prepr. (Am. Chem. Soc., Div. Polym. Chem.)* **2010**, *51*, 598–599.
2. Osman, A.; Al-Ashmawi, M.I.; Shalaby, M.A. Synthesis and Biological Activity of certain salicylic acid esters. *Egypt. J. Pharm. Sci.* **1986**, *25*, 189–194.
3. Zavodnik, I.B.; Lapshina, E.; Sudnikovich, E.; Boncler, M.; Luzak, B.; Rozalski, M. Helinska, M.; Watala, C. Structure, stability and antiplatelet activity of *O*-acyl derivatives of salicylic acid and lipophilic esters of acetylsalicylate. *Pharmacol. Rep.* **2009**, *61*, 476–489.
4. Kim, C.; Nam, S.-W.; Choi, D.-Y.; Choi, J.-H.; Park, E.-S.; Jhoo, W.-K.; Kim, H.-C. A new antithrombotic agent, aspalatone, attenuated cardiotoxicity induced by doxorubicin in the mouse; possible involvement of antioxidant mechanism. *Life Sci.* **1996**, *60*, 75–82.
5. Fritzson, I.; Bedingfield, P.T.P.; Sundin, A.P.; McConkey, G.; Nilsson, U.J. *N*-Substituted salicylamide as selective malaria parasite dihydroorotate dehydrogenase inhibitors. *MedChemComm* **2011**, *2*, 895–898.
6. Bassoli, A.; Borgonovo, G.; Caimi, S.; Farina, G.; Moretti, M. Oleoylsalicylate derivatives: Synthesis and antifungal activity. *Open Nat. Prod. J.* **2008**, *1*, 14–19.
7. Silverman, F.P.; Petracek, P.D.; Heiman, D.F.; Ju, Z.; Fledderman, C.M.; Warrior, P. Salicylate activity. 2. Potentiation of atrazine. *J. Agric. Food Chem.* **2005**, *53*, 9769–9774.
8. Nezu, Y.; Miyazaki, M.; Sugiyama, K.; Wada, N.; Kajiwara, I.; Miyazawa, T. Dimethoxypyrimidines as novel herbicides. Part 2. Synthesis and herbicidal activity of *O*-pyrimidinylsalicylates and analogues. *Pestic. Sci.* **1996**, *47*, 115–124.
9. Beber, K.; Jarosch, B.; Langen, G.; Kogel, K.-H. Expression analysis of genes induced in barley after chemical activation reveals distinct disease resistance pathways. *Mol. Plant Path.* **2000**, *1*, 277–286.
10. Hause, B.; Voros, K.; Kogel, K.-H.; Besser, K.; Wasternack, C. A jasmonate-responsive lipoxygenase of barley leaves is induced by plant activators but not by pathogens. *J. Plant Physiol.* **1999**, *154*, 459–462.
11. The product from (a) is 2-bromophenyl 2-benzyloxybenzoate: FT-IR (ZnSe): 1749, 1470, 1204, 1034, 1018, 749, 737, 695 cm^{-1} ; ^1H -NMR δ 8.21 (dd, 1H, $J = 1.6, 8.1$ Hz), 7.69 (d, 1H, $J = 7.9$ Hz), 7.54–7.61 (m, 3H), 7.27–7.42 (m, 5H), 7.20 (d, 1H, $J = 7.8$ Hz), 7.22–7.09 (m, 2H), 5.28 (s, 2H); ^{13}C -NMR δ 163.0, 158.9, 148.4, 136.4, 134.4, 133.3, 132.5, 128.5, 128.4, 127.7, 127.2, 126.8, 124.1, 120.5, 118.9, 116.4, 113.7, 70.5; HRMS (ESI, positive ion mode): $[\text{M}+\text{Na}]^+$ m/z calculated: 405.0102, found: 405.0094.