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Synthesis of methyl-, fluoro-, and chloro-substituted 6-hydroxyisoindolin-1-ones

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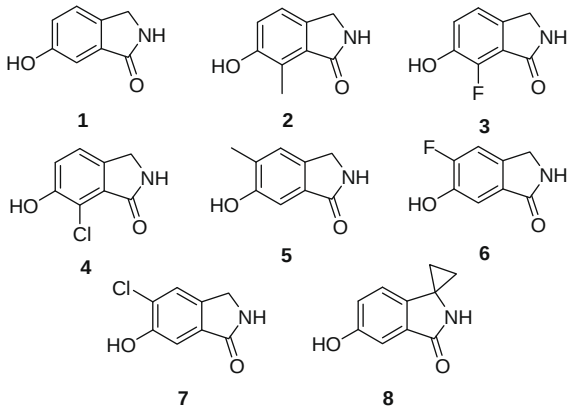
ABSTRACT

The synthesis of a series of methyl-, fluoro-, and chloro-substituted 6-hydroxyisoindolin-1-ones is described.

The importance of isoindolines has grown greatly over the last half century. Isoindolines can be found in natural products such as (±)-chilenine,[1] important anti-inflammatory agents,[2] and display properties such as high affinity toward G-protein coupled receptors such as dopamine D_4,[3] and serotonin 5-HT_{1a} and 5-HT_2.[4] Other isoindoline derivatives have been found to exhibit local anesthetic activity superior to that of procaine.[5]

There are numerous methods that have been developed to synthesize isoindolines. The more commonly used methods include from aromatic mono-carbonyl compounds,[6] from 1,2-dicarbonyl compounds,[7] transformations of heterocycles,[8] via the Diels–Alder reaction, and through the Wittig reaction.[9] Many methods for the synthesis of isoindolines proceed via chemoselective reduction of one of the carbonyls of a isoindoline-1,3-dione[10] and are therefore often suboptimal for use in the construction of substituted isoindolines.

Herein, we describe the regioselective synthesis of a series of methyl-, fluoro-, and chloro-substituted 6-hydroxyisoindolin-1-ones, all of which transpire through a common aryl ester-nitrile intermediate. With this strategy for the synthesis of 6-hydroxyisoindolin-1-ones, one just has to focus their efforts on finding a route to the appropriately substituted aryl ester-nitrile, in which a large number of methods exist.[11]



The synthesis of the parent unsubstituted 6-hydroxy-2,3-dihydroisoindol-1-one (**1**) began with cyanation of commercially available 2-bromo-5-methoxy-benzoic acid methyl ester (**9**) with CuCN as shown in Scheme 1. Alternatively, one could avoid use of stoichiometric copper by use of $K_4Fe(CN)_6{\cdot}3H_2O$ as the cyanide source and a catalytic amount $Pd(OAc)_2$ as the catalyst. The slightly lower yield of the latter could be attributed to not being optimized. Although only used in this example, we see no reason why these conditions would not be applicable to other related systems. The resultant nitrile (**10**) could be reduced with platinum oxide hydrate or sponge nickel to obtain the primary amine hydrochloride salt (**11**). In other systems one can also use 10% Pd/C/H_2. Although readily available and easy to use, the Pd/C conditions suffered from long reaction times and incomplete conversions observed on scale up. The PtO_2 or sponge nickel conditions could be used to speed up reaction times and improve conversion on scaling but had the disadvantages

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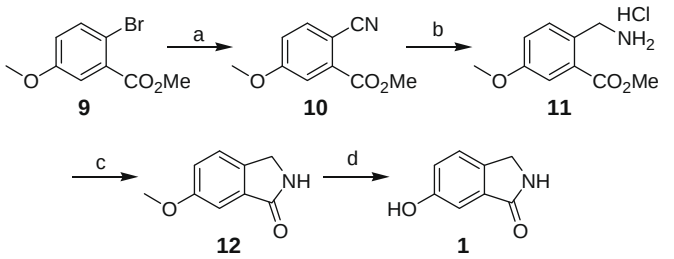


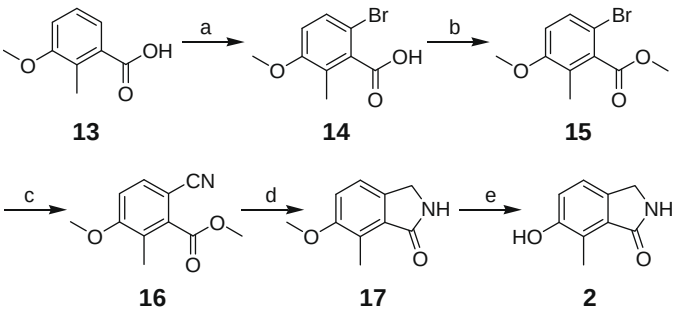
Scheme 1. Reagents and conditions: (a) CuCN, DMF, 140 °C, 91% or $K_4Fe(CN)_6{\cdot}3H_2O$, $Pd(OAc)_2$, Na_2CO_3, 140 °C 72%; (b) $PtO_2{\cdot}H_2O$, EtOH/$CHCl_3$, H_2, 48 h, used crude; or sponge Ni, MeOH, H_2, 58 °C, 84%; (c) 1 M NaOH (aq), adjust to pH 9, 80% two steps; (d) BBr_3, DCM, 0 °C, 39% or methionine, MsOH, 85 °C, 79%.

of cost (PtO_2) or flammability (Ni). Basification of this salt to pH 9 effects ring closure to provide isoindol-1-one (**12**). The 6-methoxy-2,3-dihydro-isoindol-1-one could be demethylated using BBr_3 in DCM or the milder conditions of methionine and methanesulfonic acid to obtain 6-hydroxy-2,3-dihydro-isoindol-1-one (**1**).

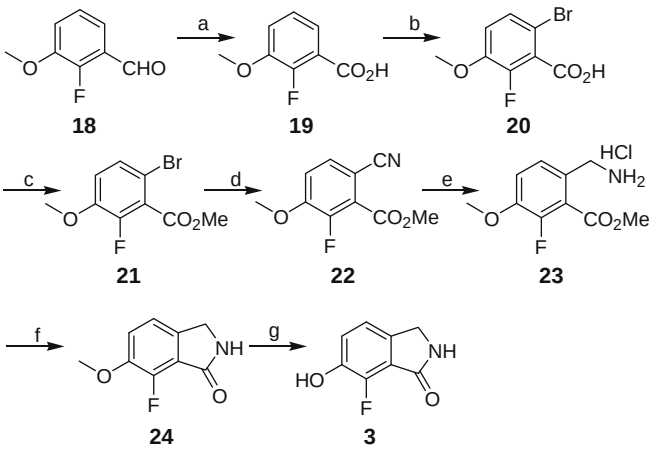
The synthesis of previously unreported 6-hydroxy-7-methyl-2,3-dihydro-isoindol-1-one (**2**) was carried out in similar fashion to the synthesis of 6-hydroxy-2,3-dihydro-isoindol-1-one (**1**) (Scheme 2). Commercially available 3-methoxy-2-methyl-benzoic acid (**13**) was regioselectively brominated using Br_2/AcOH in water to obtain **14**. The bromo acid was dissolved in a mixture of benzene and methanol and treated with trimethylsilyldiazomethane to obtain the bromoester (**15**). Cyanation with CuCN provided nitrile **16**. This nitrile was reduced with 10% Pd/C to afford the free amine, which cyclizes under the reaction conditions to obtain the isoindol-1-one (**17**) in 88% yield. Treatment of **17** with boron tribromide in DCM afforded 6-hydroxy-7-methyl-2,3-dihydro-isoindol-1-one (**2**) in 94% yield.

The synthesis of previously unreported 7-fluoro-6-hydroxy-2,3-dihydro-isoindol-1-one (**3**) is shown in Scheme 3. Commercially available 2-fluoro-3-methoxy-benzaldehyde (**18**) was oxidized to its corresponding acid **19** in 92% yield. The resulting acid was regioselectively brominated using a bromine/AcOH mixture in water to obtain the bromofluoro acid **20**. Treatment of **20** with a solution of trimethylsilyldiazomethane gave ester **21** in 88% yield. The bromo ester was then treated with CuCN in DMF to obtain the nitrile product **22**. Reduction of the nitrile with 10% Pd/C followed by acidification yielded the hydrochloride **23**. When the hydrochloride was suspended in toluene and treated with diisopropylethylamine, the cyclized product **24** was obtained. This was treated with boron tribromide in DCM to obtain 7-fluoro-6-hydroxy-2,3-dihydro-isoindol-1-one (**3**) in 80% yield.

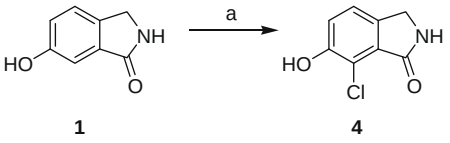
The synthesis of previously unreported 7-chloro-6-hydroxy-2,3-dihydro-isoindol-1-one (**4**) is shown in Scheme 4. Previously synthesized 6-hydroxy-2,3-dihydro-isoindol-1-one (**1**) could be



Scheme 2. Reagents and conditions: (a) Br_2 /AcOH, 60 °C, 95%; (b) MeOH/benzene, trimethylsilyldiazomethane, 0 °C, quant; (c) CuCN, DMF, 150 °C (4 h), 43%; (d) 10% Pd/C, EtOH, H_2 (55 psi), 72 h, 88%; (e) BBr_3, DCM, 0 °C, 94%.



Scheme 3. Reagents and conditions: (a) NaH_2PO_4, H_2O_2, $NaClO_2$, 0 °C, 92%; (b) Br_2/AcOH, 60 °C, 86%; (c) trimethylsilyl diazomethane in hexane, MeOH, 88%; (d) CuCN, DMF, 150 °C, 84%; (e) 10% Pd/C, THF/EtOH/MeOH (15:60:40), 4 M HCl/dioxane, H_2 (55 psi), quant; (f) diisopropylamine, Δ, 85 %; (g) BBr_3, DCM, −78 °C to 0 °C, 80%.

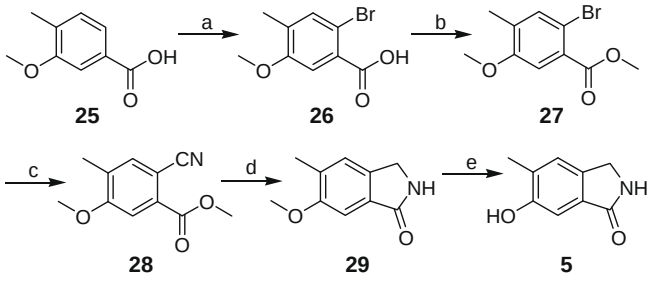


Scheme 4. Reagents and conditions; (a) NCS (1.1 equiv), ACN, 60 °C, 61%.

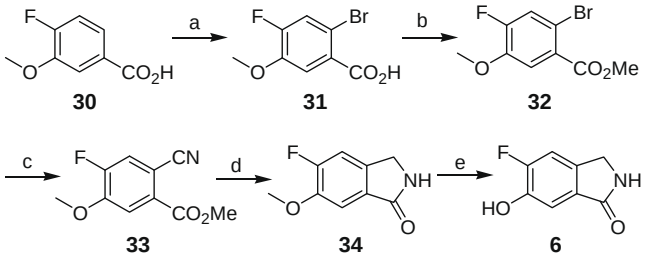
regioselectively chlorinated with NCS in acetonitrile to obtain 7-chloro-6-hydroxy-2,3-dihydro-isoindol-1-one (**4**) in 61% yield.

The synthesis of previously unreported 6-hydroxy-5-methyl-2,3-dihydro-isoindol-1-one (**5**) can be found in Scheme 5. Commercially available 3-methoxy-4-methyl-benzoic acid (**25**) was regioselectively brominated using a bromine/AcOH mixture in water to obtain **26**. The acid was esterified using sulfuric acid in methanol to obtain **27** in 89% yield. Treatment of the ester with CuCN in DMF afforded the nitrile **28**. Reduction of the nitrile with Pd/C in ethanol gave the ring-closed 6-methoxy-5-methyl-2,3-dihydro-isoindol-1-one (**29**). This was treated with boron tribromide in DCM to obtain 6-hydroxy-5-methyl-2,3-dihydro-isoindol-1-one (**5**) in 88% yield.

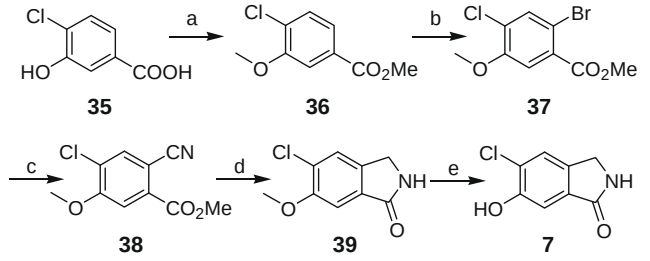
In a similar fashion to **5**, the synthesis of previously unreported 5-fluoro-6-hydroxy-2,3-dihydro-isoindol-1-one (**6**) can be found in Scheme 6. Commercially available 4-fluoro-3-methoxy-benzoic acid (**30**) was brominated in water with Br_2/AcOH to afford **31**. This was then converted to the ester by treating the acid with concentrated sulfuric acid in methanol to provide **32** in 93% yield. Cyanation of **32** with CuCN in DMF resulted in **33**. The reduction of the



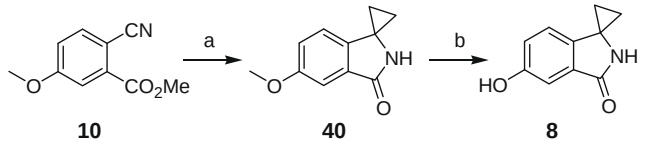
Scheme 5. Reagents and conditions: (a) Br_2/AcOH, 60 °C, quant; (b) H_2SO_4/MeOH, Δ, 89%; (c) CuCN, DMF, 155 °C (2 h), 75%; (d) 10% Pd/C, EtOH, 4 M HCl/dioxane, H_2 (55 psi), 72 h, 88%; (e) BBr_3, DCM, 0 °C, 88%.



Scheme 6. Reagents and conditions: (a) Br_2/AcOH, 60 °C, 85%; b) H_2SO_4/MeOH Δ, 93%; (c) CuCN, DMF, 150 °C (3 h), 68%; (d) 10% Pd/C, EtOH, H_2 (55 psi), 80%; (e) BBr_3 (5.0 equiv), DCM, −78 °C, 80%.



Scheme 7. Reagents and conditions: (a) trimethylsilyl diazomethane, benzene, 0 °C, 80%; (b) Br_2/AcOH, 60 °C, 95%; (c) CuCN, DMF, 160 °C, 60%; (d) Raney Ni, MeOH/EtOAc/NH_4OH (40:10:1.0), H_2 (45 psi), 76%; (e) BBr_3, DCM, 77%.



Scheme 8. Reagents and conditions: (a) $Ti(OCH(CH_3)_2)_4$, 3 M EtMgBr/diethyl ether, 0 °C, 38% (b) BBr_3, DCM, 0 °C, 41%.

nitrile and cyclization to afford **34** was accomplished using 10% Pd/C in ethanol. Finally, the removal of the methoxy group was accomplished using boron tribromide in DCM to generate 5-fluoro-6-hydroxy-2,3-dihydro-isoindol-1-one (**6**) in 80% yield.

In a similar manner as **5** and **6**, the synthesis of previously unreported 5-chloro-6-hydroxy-2,3-dihydro-isoindol-1-one (**7**) is found in Scheme 7. Commercially available **35** was treated with trimethylsilyldiazomethane in benzene to form the ester **36**. Bromination of the ester with bromine/AcOH in water afforded **37** in 95% yield. The nitrile **38** was formed by reacting the bromide with CuCN in DMF. Reduction of the nitrile with Raney Nickel in a MeOH/EtOAc/NH_4OH mixture yielded **39**. 5-Chloro-6-hydroxy-2,3-dihydro-isoindol-1-one (**7**) was obtained in 77% yield by treatment of **39** with boron tribromide in DCM.

Alkylation of these 6-hydroxyisoindolin-1-ones can occur using the common cyano ester intermediate. This is exemplified by the synthesis of previously unreported 5′-hydroxy-spiro[cyclopropane-1,1′-isoindol]-3′(2′H)-one (**8**, Scheme 8). Following a previously reported procedure,[12] the 2-cyano-5-methoxy-benzoic acid methyl ester (**10**) was treated with titanium(IV) isopropoxide in ether followed by the addition of 3 M ethyl magnesium bromide in diethyl ether at 0 °C to obtain the ring-closed 5′-methoxy-spiro[cyclopropane-11′-isoindol]-3′(2′H)-one (**40**) in 38% yield. This was then treated with boron tribromide in DCM at 0 °C to obtain 5′-hydroxy-spiro[cyclopropane-1,1′-isoindol]-3′(2′H)-one (**8**) in 41% yield.

In summary, a collection of methyl-, fluoro-, and chloro-substituted 6-hydroxyisoindolin-1-ones were prepared as templates for drug discovery from a common aryl nitrile-ester intermediate.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.12.099.

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