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Aza-Conjugate Addition Methodology for the Synthesis of *N*-Hydroxy-isoindolin-1-ones

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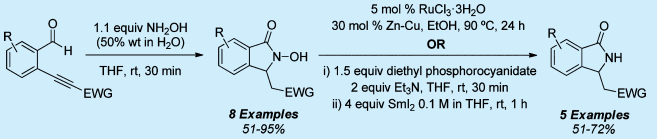
Supporting Information

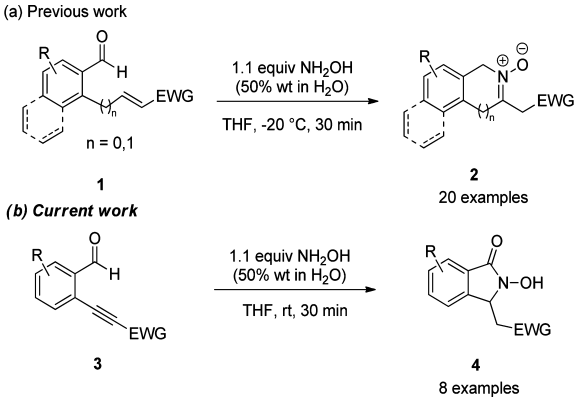
ABSTRACT: Aryl-aldehydes containing *ortho*-substituted propiolate fragments react with hydroxylamine to afford carbinolamine intermediates that undergo intramolecular *aza*-conjugate addition reactions to afford *N*-hydroxy-2.3-dihydro-isoindolin-1-ones that can be reduced to their corresponding isoindolin-1-ones and isoindoles.



Cyclic hydroxamic acids are an important class of compounds that possess a wide range of biological activity, including compounds that exhibit potent antimalarial,[1] prolyl-4-hydroxylase,[2] α-glucosidase, and *N*-methyl-aspartate inhibitory actions.[3] The biological activity of cyclic hydroxamic acids is often due to their ability to chelate to metal ions such as iron and zinc,[2,4] which has enabled ion transport and HIV-1 integrase inhibitors to be developed.[4a,c] There are a number of routes available for the synthesis of these cyclic hydroxamic acids, including zinc/palladium catalyzed reduction of nitro groups to afford hydroxylamine intermediates that cyclize onto acid derivatives.[3b,c,5] A number of nonreductive methods for their synthesis have also been developed, including approaches based on photorearrangement of nitronate anions,[6] ring-expansion reactions of acyloxy nitroso compounds derived from cyclic ketones,[7] ene cyclization reactions of unsaturated *N*-acyl-nitroso species,[8] intramolecular cyclization of enolates onto *N*-benzyloxy-carbamates fragments,[9] base catalyzed cyclization reactions of 2-alkynylphenylhydroxamic acids,[10] conjugate addition of hydroxylamine derivatives to α,β-unsaturated acid derivatives,[11] and selenium-mediated cyclization of acyclic unsaturated hydroxamic acids.[12] Given their synthetic utility and wide ranging biological activity, we now report efficient *aza*-conjugate addition methodology for the synthesis of *N*-hydroxy-isoindolinones and their conversion into their corresponding isoindolin-1-one and isoindole skeletons.

We have previously reported that treatment of aryl-aldehydes **1** containing *ortho*-substituted α,β-unsaturated carboxylic acid derivatives with hydroxylamine affords reactive *N*-hydroxy-carbinolamine intermediates that undergo intramolecular *aza*-conjugate addition reactions to afford isoindole and 3,4-dihydroisoquinoline nitrones **2** in good yield (Scheme 1a).[13] Consequently, we decided to investigate what would occur if these cyclization conditions were applied to the corresponding propiolate esters **3** and now report herein that their reaction with hydroxylamine affords *N*-hydroxy-isoindolin-1-ones **4** in good yield (Scheme 1b).

Scheme 1. (a) Reaction of Aryl Aldehydes 1 with Hydroxylamine Affords Cyclic Nitrones 2; (b) Reaction of Aryl Aldehydes 3 with Hydroxylamine Affords *N*-Hydroxy-isoindolin-1-ones 4



A robust five-step synthesis of 2-propiolate benzaldehydes **3a−g** and **8** was first devised, commencing with copper-free Sonogashira coupling reactions between 2-bromobenzaldehydes **5a−g** and (triisopropylsilyl)acetylene to afford the TIPS protected 2-alkynyl benzaldehydes **6a−g** in 83−91% yield. Acetal protection of aldehydes **6a−g** with 1,3-propanediol, followed by silyl deprotection using tetrabutylammonium fluoride (TBAF), resulted in a series of alkynes **7a−g** in 81−99% yield. These alkynes were then deprotonated with *n*-BuLi in THF at −78 °C to afford their corresponding alkynyl anions that were reacted with methyl chloroformate, followed by acid catalyzed acetal deprotection to afford the desired 2-propiolate benzaldehydes **3a−g** in 45−59% yield over the five steps (Scheme 2). Reaction of the propargylic alkynyl anion of **7c** with methyl chloroformate, followed by base-catalyzed ester hydrolysis, gave its parent acid. This acid then underwent

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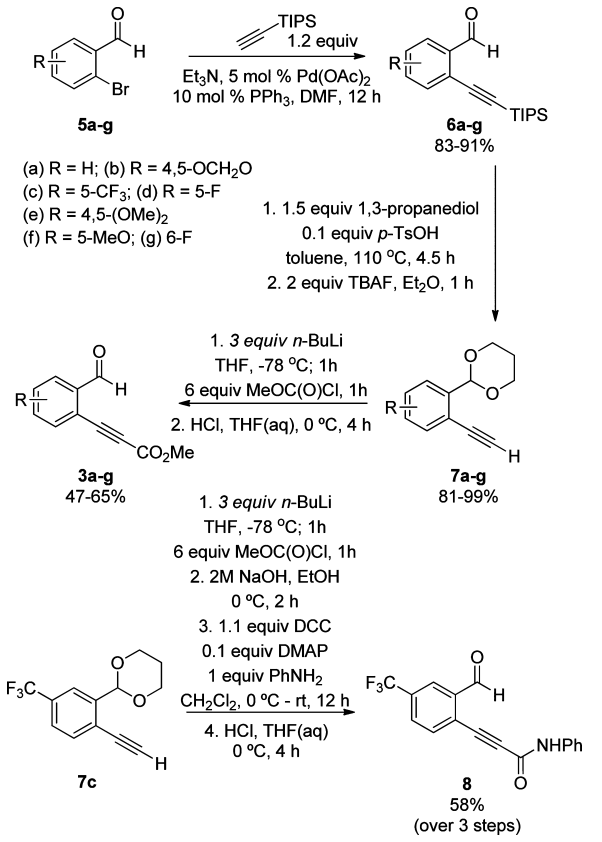
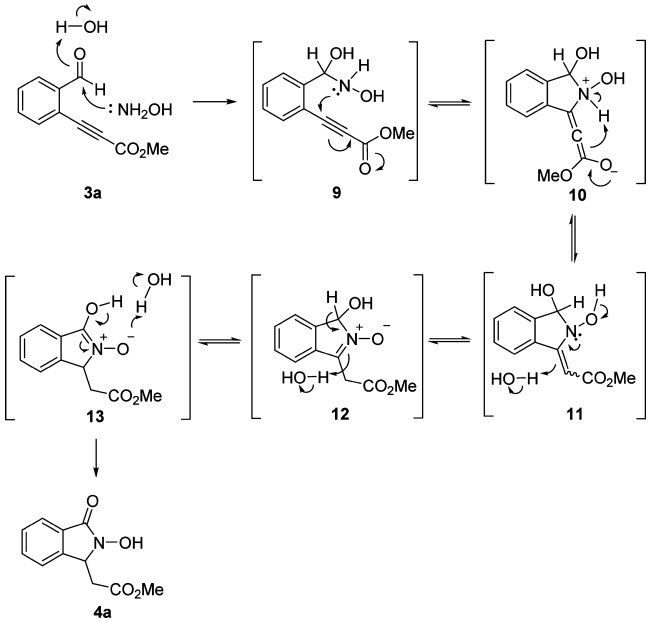
Scheme 2. Synthesis of Cyclization Substrates 3a–g and 8



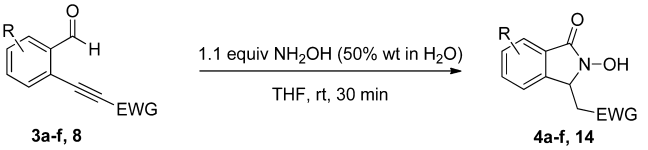
Scheme 3. Proposed Reaction of the Aldehyde Functionality of Methyl Propiolate 3a with Hydroxylamine To Afford Hydroxamic Acid 4a

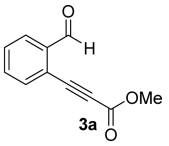
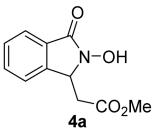
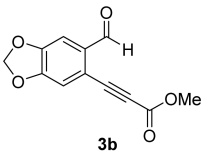
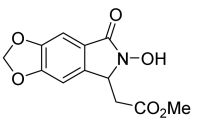
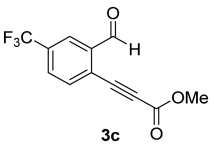
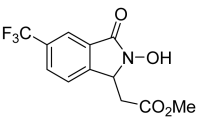
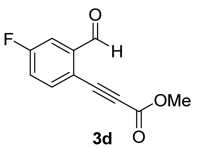
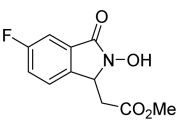
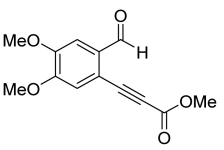
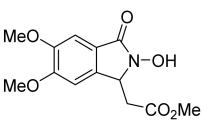
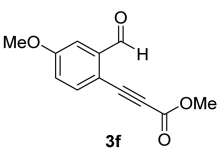
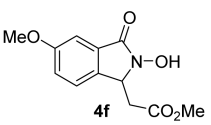
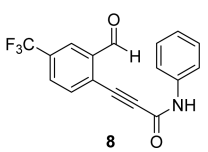
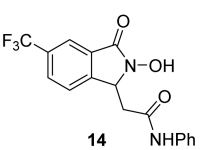


DCC-mediated amide bond coupling with aniline, followed by acid-catalyzed acetal hydrolysis to afford amide **8**.

Reaction of the aldehyde functionality of methyl-propiolate **3a** with 1.1 equiv of a 50% aqueous solution of hydroxylamine at room temperature resulted in an unexpected cyclization reaction to afford *N*-hydroxy-isoindolin-1-one **4a**. A reasonable

Table 1. Synthesis of *N*-Hydroxy-isoindolin-1-ones 3a–g and 8



entry	propiolate	hydroxamic Acid	yield (%)
1	 **3a**	 **4a**	70
2[a]	 **3b**	 **4b**	63
3	 **3c**	 **4c**	91
4	 **3d**	 **4d**	95
5	 **3e**	 **4e**	51
6	 **3f**	 **4f**	51
7	 **8**	 **14**	85

[a]5 equiv of Cs_2CO_3 added to facilitate cyclization.

mechanism to explain the formation of **4a** involves initial reversible addition of hydroxylamine to its aldehyde functionality to afford *N*-hydroxy-carbinolamine **9** that then undergoes an *aza*-conjugate addition reaction to afford a bicyclic allenyl enolate intermediate **10**. Enolate protonation of **10** then occurs to afford a *N*-hydroxy-enamine intermediate **11**, which is then protonated to afford nitrone **12** that undergoes water-mediated tautomerization (via oxime **13**) to afford the hydroxamic acid functionality of *N*-hydroxy-isoindolin-1-one **4a** (Scheme 3).

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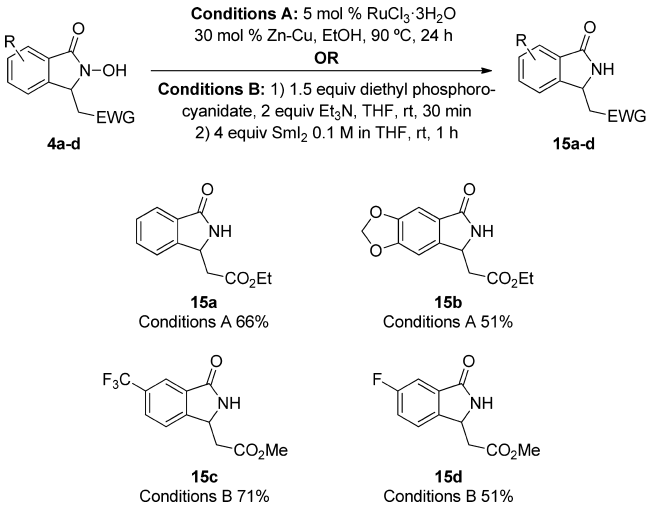
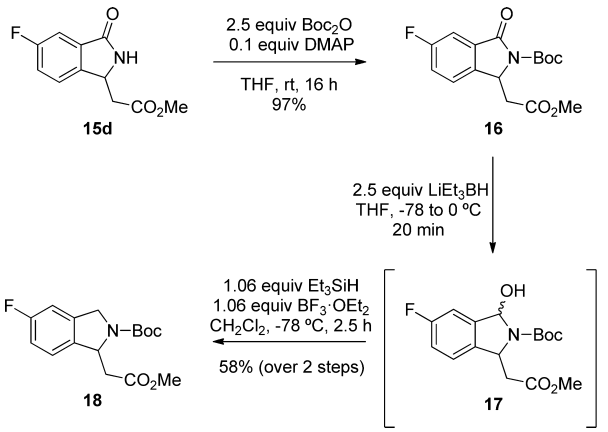
Scheme 4. Synthesis of Isoindolin-1-ones 15a−d



Scheme 5. Synthesis of 5-Fluoro-isoindole 18

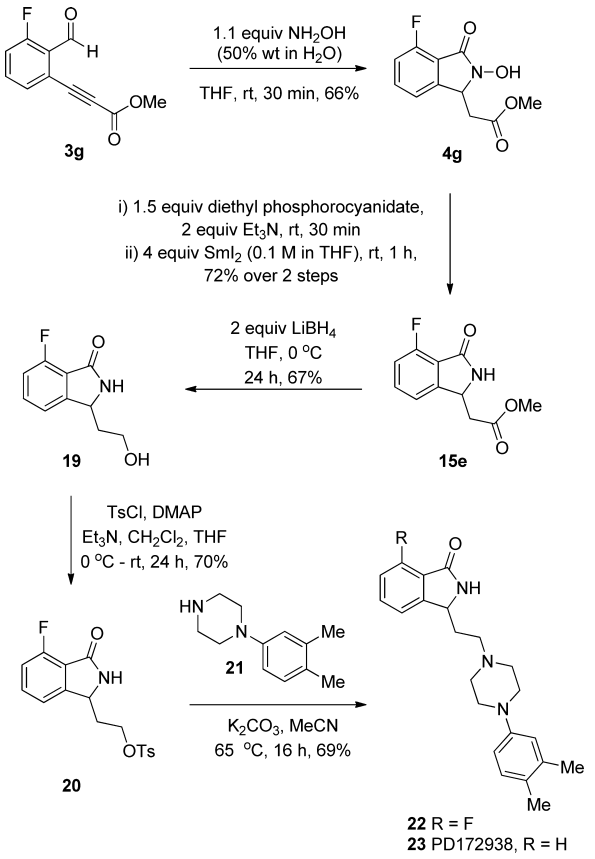


Repeating the cyclization reaction of methyl-propiolate **3a** with hydroxylamine at −20 °C resulted in precipitation of a crystalline product that was isolated and found to have spectroscopic data consistent with the structure of nitrone intermediate **12**, which decomposed on standing to afford *N*-hydroxy-isoindolin-1-one **4a**.

The conditions used to carry out the cyclization reaction of aldehyde **1a** were then optimized by screening different bases, solvents, and sources of hydroxylamine, which enabled us to identify that use of 1.1 equiv of hydroxylamine (50% solution in water) in THF at rt for 30 min could be employed to afford *N*-hydroxy-isoindolin-1-one **4a** in 70% yield. These optimal conditions were then applied to the cyclization of six further propiolate derivatives **3b−f** and **8** that contain both electron-donating and -withdrawing substituents, which all cyclized cleanly to give their corresponding cyclic hydroxamic acids **4b−f** and **14** in 51−95% yields (Table 1).

The parent isoindolin-2-one and isoindole ring systems occur as fragments of many natural products.[14] Therefore, they may be considered to be privileged structures for drug discovery applications.[14c,d] Consequently, investigation was initiated to identify conditions that would enable cleavage of the N−O bond of our *N*-hydroxyisoindolin-1-ones. A range of known N−O bond cleavage conditions were screened for this purpose,[15] with the best results being obtained for electron-rich *N*-hydroxy-isoindolin-1-one **4a** and **4b** using 5 mol %

Scheme 6. Synthesis of 6-Fluoro Analogue of PD172938



$RuCl_3·3H_2O$ and 30 mol % Zn−Cu couple in EtOH at 90 °C for 24 h,[16] which gave the transesterified ethyl esters of isoindolin-1-ones **15a** and **15b** in acceptable 51−66% yields, respectively. Alternatively, stepwise treatment of electron-poor *N*-hydroxy-isoindolin-1-ones **4c−d** with 1.5 equiv of diethyl phosphorocyanidate and 2 equiv of Et_3N in THF for 30 min at room temperature gave their corresponding phosphate diester, which were immediately reduced with 4 equiv of samarium iodide in THF for 1 h,[17] to give isoindolin-1-ones **15c−e** in acceptable 51−71% yields (Scheme 4). Finally, treatment of 5-fluoro-isoindolin-1-one **15d** with $(Boc)_2O$ and DMAP afforded *N*-Boc-5-fluoro-isoindolin-1-one **16** that was reduced via treatment with $LiEt_3BH$ to give a *N*-Boc-carbinolamine intermediate **17** that was treated with $BF_3·OEt_3$ and Et_3SiH,[18] to afford the desired 5-fluoro-isoindole skeleton of *N*-Boc-*β*-amino ester **18** in 58% yield over two steps (Scheme 5).

Isoindoline-2-ones such as PD172938 **23** (R = H) have been shown to be potent antagonists for dopamine D_4 receptors, and their use as potential treatments for schizophrenia has been investigated.[19] Consequently, it was decided to employ our cyclization methodology to prepare a 6-fluoro-isoindolin-1-one analogue **22** (R = F) using the protocol shown in Scheme 6. Therefore, aldehyde **3g** was treated with hydroxylamine under our standard conditions to afford *N*-hydroxy-6-fluoro-isoindolin-1-one **4g** in 66% yield, whose phosphate ester was then reduced using samarium iodide to afford 6-fluoro-isoindolin-1-one **15e** in 72% yield. Ester **15e** was then reduced to its corresponding alcohol **19** using $LiBH_4$ in 67% yield that was then reacted with Et_3N, DMAP, and tosyl chloride to afford *O*-tosyl-6-fluoro-isoindolinone **20** in 70% yield. Nucleophilic substitution of tosylate **20** using *N*-aryl-piperidine **21** under

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basic conditions successfully gave the 6-fluoro analogue **22** of PD172938 in 69% yield (Scheme 6).

In conclusion, we have shown that aryl-aldehydes **3** containing *ortho*-substituted propiolate fragments react with hydroxylamine via a nucleophilic addition-*aza*-conjugate addition pathway to afford a series of cyclic *N*-hydroxy-isoindolin-1-ones **4** that may be reduced to their parent isoindolin-1-one or isoindole skeletons as required.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00261.

Experimental procedures and spectral data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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