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# Synthesis of isoindolinones: Intramolecular [4+2] cycloaddition/retro [4+2] of pyridone propiolamides

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ABSTRACT

A new synthesis of isoindolinones was discovered during a screening campaign aimed at the development of novel methods for the synthesis of pyridone-EZH2 inhibitor analogues. The reaction proceeds via an intramolecular [4+2] cycloaddition of a pyridone with a tethered propiolamide moiety followed by extrusion of isocyanic acid. The discovery, optimization, and scope of the methodology are described.



Isoindolinones are a heterocycle found in a variety of bioactive compounds with an array of activities including calcium channel antagonism (Falipamil) [1], potassium channel opening (Celikalim) [2], PARP-inhibition (NMS-P118) [3], metabotropic glutamate receptor potentiation (AZD8529) [4], anti-inflammation (Indoprofen) [5], immunomodulation (Lenalidomide and CC-220) [6,7], and $GABA_A$-agonism (Pagoclone) [8]. Additionally, the isoindolinone scaffold is present in some natural products such as hericerin and porritoxin [9,10].

In the course of a synthetic effort aimed at the synthesis of pyridone EZH2 inhibitor analogues related to CPI-1205, we inadvertently discovered a novel reaction that produces highly substituted isoindolinones from substituted N-((2-oxo-1,2-dihydropyridin-3-yl)methyl)propiolamides. Pyridone-propiolamide intermediates such as **1**, were designed to enable the development of novel methods for the synthesis of a subclass of EZH2 inhibitors containing highly substituted 3-indole carboxylic acid side-chains (see Fig. 1).

The process that we had set out to develop was a domino reaction consisting of a heteroconjugate addition reaction of an aniline to **1** followed by an intramolecular palladium catalyzed-coupling of intermediate **2** to form the indole C-3-arene bond of **3**. Processes of this nature would provide access to a wide variety of EZH2 inhibitors from readily accessible substituted anilines (Scheme 1).

We began our studies by preparing **4** via a two-step protocol consisting of a reductive amination of para-methoxybenzaldehyde with 3-(aminomethyl)-4,6-dimethyl-pyridin-2(1H)-one followed by an amide coupling with butynoic acid. We then surveyed a wide range of conditions to induce a heteroconjugate addition reaction of *N*-cyclohexylaniline or 2-halo-*N*-cyclohexylanilines to **4**. Although in certain instances we observed trace amounts of the heteroconjugate addition intermediate **5** and the desired 3-indole-amide product **6**, in instances where metal catalysts were used, we consistently generated side-product with a mass 43 amu less than the mass of the starting material **4**. This change in mass corresponds to loss of isocyanic acid. Based on this observation, we hypothesized that isoindolinone **8** was formed by extrusion of isocyanic acid from an azabicyclo[2.2.2]octadienone intermediate **7** which was generated from an intramolecular [4+2] cycloaddition reaction of the butynamide moiety and the diene embedded in the pyridone ring system of **4** (Scheme 2).

Our initial hypothesis was supported by $^1H$ and $^{13}C$ NMR of **8** that were consistent with a product derived from the reaction mechanism outlined in Scheme 2. Additionally, the product was substantially less polar than the starting material **4** which is in agreement with the conversion of the polar amide moiety of the pyridone starting material to the nonpolar benzene moiety of the isoindolinone product.

We further confirmed our mechanistic hypothesis through independent preparation of 2-benzyl-7-phenylisoindolin-1-one via the intramolecular [4+2] cycloaddition/isocyanic acid extrusion reaction and via a two-step sequence, consisting of alkylation of 7-bromoisoindolin-1-one (CAS no.: 200049-46-3) with benzylbromide and subsequent Suzuki coupling with phenylboronic acid. The products derived from these two sequences yielded products with identical LCMS retention times and $^1H$ NMR spectra (Scheme 3).

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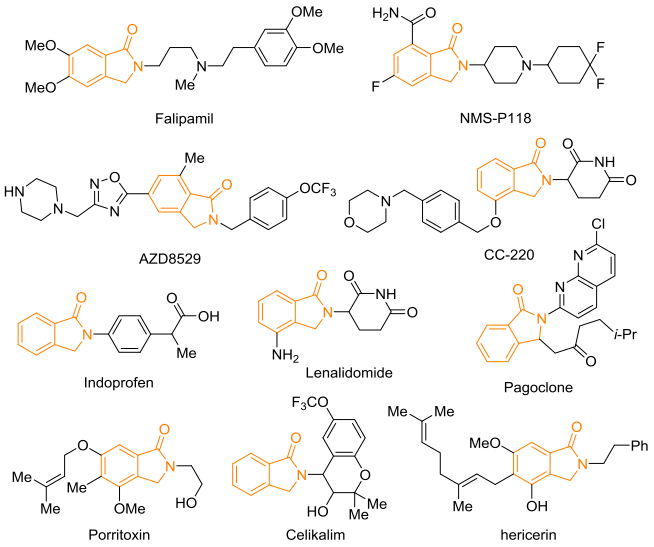
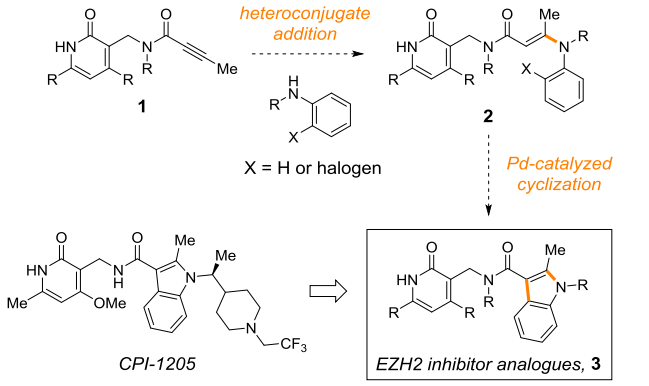
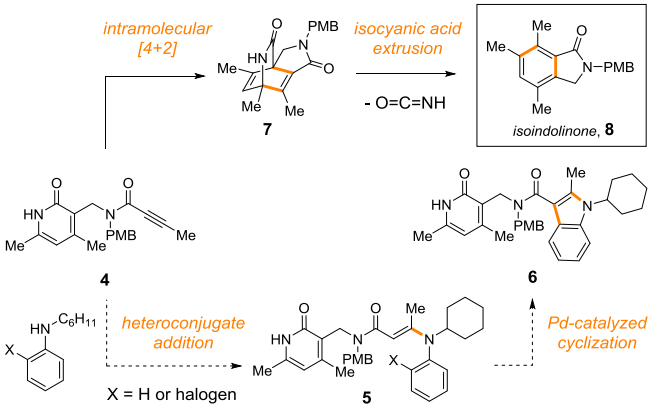



**Fig. 1.** Structures of isoindolinone drug candidates and natural products.

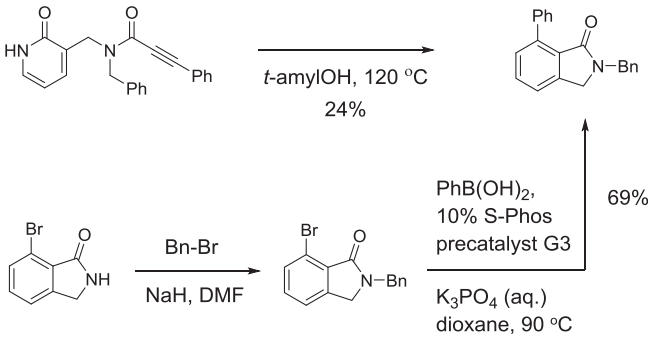



**Scheme 1.** Proposal for a domino reaction to access 3-indolecarboxamide-pyridone EZH2 inhibitors.




**Scheme 2.** Mechanism for the formation of isoindolinone byproduct.

The process outlined above is akin to the more well-known 2-pyrone [4+2] cycloaddition/$CO_2$ extrusion reaction [11–15]. While intermolecular variants of the pyridone-alkyne [4+2]/isocyanate extrusion process outlined in scheme 2 have been documented and reviewed in the literature, the intramolecular variant resulting in the formation of isoindolinones has not been described [16–43]. The optimization and scope of this process is detailed herein.




**Scheme 3.** Synthesis of 2-benzyl-7-phenylisoindolin-1-one via the [4+2] cycloaddition/isocyanic acid extrusion reaction and from 7-bromoisoindolin-1-one.

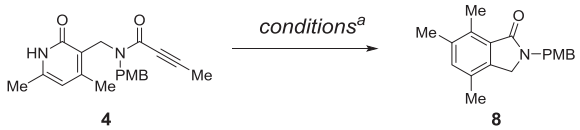
A range of solvents, temperatures, and concentrations were surveyed to optimize the efficiency and yield of the model reaction where **4** is transformed into **8** (Table 1). A range of solvents were suitable for the reaction. While reactions in toluene generated multiple unidentified decomposition products, those performed in *t*-amylalcohol and dioxane were generally very clean by LCMS. Dimethylacetamide was also a good solvent for the process but an unidentified byproduct with a LCMS retention time close to that of **8** was formed, complicating purification of the product. While reactions in dioxane were very similar to those in *t*-amylalcohol, we selected *t*-amylalcohol for further studies as it solubilized the starting materials more effectively than dioxane. Decreasing the concentration of the reaction from 0.1 M to 0.03 M had little effect on the outcome but increasing the concentration to 0.3 M led to the formation of unidentified side products. The reaction proceeds slowly or not at all at temperatures below 100 °C. Although extended reaction times were required to drive the reaction of **4** to **8** to completion, we found later that the rate of the reaction is affected by the substitution pattern of the starting material. Simple heating of a 0.1 M solution of **4** in *t*-amylalcohol in a sealed tube at 120 °C for 96 h proved to be the optimal set of conditions to induce the desired [4+2] cycloaddition/isocyanic acid extrusion reaction that yields **8** (Table 1).

With a set of effective reaction conditions in hand, we set out to explore the substrate scope of the methodology. A broad range of substituents at $R^3$ are tolerated including hydrogen, methyl, 1°-alkyl, 2°-alkyl, and aromatic (Table 2, entries 1–5). Disubstituted or unsubstituted pyridone moieties were also viable substrates in the reaction. As noted above, the rate of the reaction is affected by the substitution pattern of the substrate. With respect to the propiolamide substituent $R^3$, the rate of the reaction appears to increase in the following order: 2°-alkyl < 1°-alkyl < methyl < aromatic. In general, substituted pyridones are more reactive than unsubstituted pyridones.

The scope of the amide *N*-substituent was also examined. A wide variety of groups were tolerated including 1°-alkyl, 2°-alkyl, aromatic and hydrogen. In general, amides substituted with 2°-alkyl groups are more reactive than 1°-alkyl-substituted amides and N–H amides. The reactivity trends with respect to the $R^4$ substituent and the pyridone moiety were consistent with those outlined for the examples in Table 1. Additionally, several different functional groups were well tolerated, including an ester, a protected amine, and an acetal (Table 3).

We have also demonstrated that the reaction can be run directly on a crude material from the amide coupling reaction mixture used for the substrate synthesis to directly provide the desired isoindolinone product from an amine precursor. While we have only attempted this two-step, one-pot procedure for the single example shown in Eq. (1), we expect that this variation of the reac-

**Table 1**
Optimization of pyridone-propiolamide [4+2]/isocyanic acid-extrusion reaction.

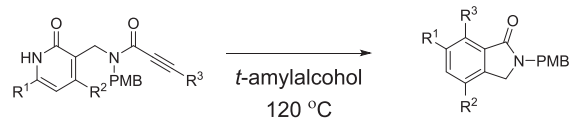



**4** **8**

| Entry[a] | Solvent | Temp (°C) | Time (h) | Ratio[b] (SM/IS) | Ratio[c] (P/IS) |
|---|---|---|---|---|---|
| 1 | toluene | 120 | 24 | 0.94 | 0.57 |
| 2 | *t*-amylOH | 120 | 24 | 1.23 | 0.62 |
| 3 | dioxane | 120 | 24 | 1.28 | 0.85 |
| 4 | DMA | 120 | 24 | 0.75 | 1.74 |
| 5[d] | *t*-amylOH | 120 | 24 | 1.35 | 0.56 |
| 6[e] | *t*-amylOH | 120 | 24 | 0.66 | 1.01 |
| 7 | *t*-amylOH | 100 | 24 | 1.57 | 0.12 |
| 8 | *t*-amylOH | 80 | 24 | 2.07 | 0.01 |
| 9 | *t*-amylOH | 60 | 24 | 2.10 | 0.00 |
| 10 | *t*-amylOH | 120 | 48 | 1.14 | 1.00 |
| 11 | *t*-amylOH | 120 | 96 | 0.55 | 1.65 |

[a] All reactions were run on a 0.5 mmol scale at a concentration of 0.1 M unless otherwise noted.
[b] Ratio of LCMS area at 254 nm of N-((2-oxo-1,2-dihydropyridin-3-yl)methyl)propiolamide to an internal standard of α-tetralone.
[c] Ratio of LCMS area of 254 nM of 2-(4-methoxybenzyl)-4,6,7-trimethylisoindolin-1-one to an internal standard of α-tetralone. See the experimental section for additional information.
[d] The reaction concentration was 0.03 M.
[e] The reaction concentration was 0.3 M.

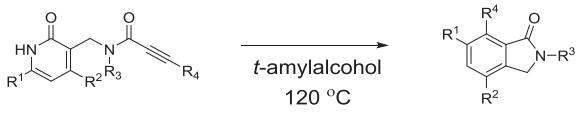
**Table 2**
Propiolamide and pyridone scope in the pyridone-propiolamide [4+2]/isocyanic acid extrusion reaction.

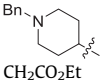
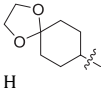



| Entry[a] | $R^1$ | $R^2$ | $R^3$ | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | Me | Me | H | 24 | 39 |
| 2 | Me | Me | Me | 72 | 60 |
| 3 | Me | Me | $CH_2OH$ | 48 | 57 |
| 4 | Me | Me | $CH_2OTBS$ | 24 | 60 |
| 5 | Me | Me | $C_6H_{11}$ | 168 | 80 |
| 6 | Me | Me | Ph | 140 | 71 |
| 7 | H | H | Ph | 72 | 30 |
| 8 | Me | OMe | Ph | 24 | 77 |
| 9 | Me | OMe | *n*-$C_3H_7$ | 48 | 22 |
| 10 | Me | SMe | Me | 72 | 97 |
| 11 | Me | SMe | *n*-$C_3H_7$ | 72 | 54 |

[a] All reactions were run at a concentration of 0.1 M in *t*-amylalcohol at 120 °C for the time indicated in the table.
[b] Isolated yield of purified isoindolinone. See the experimental section for further details.

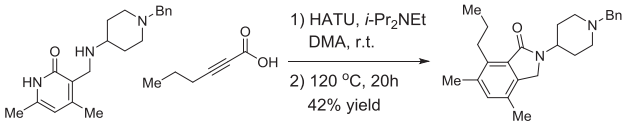
**Table 3**
Amide *N*-substituent and pyridone scope in the pyridone-propiolamide [4+2]/isocyanic acid extrusion reaction.




| Entry[a] | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Time (h) | Yield (%)[b] |
|---|---|---|---|---|---|---|
| 1 | Me | Me | $(CH_2)_3Ph$ | Me | 60 | 94 |
| 2 | Me | Me | $(CH_2)_3Ph$ | Ph | 24 | 88 |
| 3 | Me | Me |  | Ph | 24 | 91 |
| 4 | Me | Me | $CH_2CO_2Et$ | Ph | 72 | 83 |
| 5 | Me | Me |  | Ph | 16 | 92 |
| 6 | Me | Me | H | Ph | 96 | 34 |
| 7 | H | H | 4-Et-Ph | Ph | 96 | 44 |
| 8 | Me | Cl | $C_6H_{11}$ | Ph | 24 | 81 |
| 9 | H | H | Bn | Ph | 72 | 24 |

[a] All reactions were run at a concentration of 0.1 M in *t*-amylalcohol at 120 °C for the time indicated in the table.
[b] Isolated yield of purified isoindolinone.

tion could be applied to the examples demonstrated in Tables 2 and 3.




In conclusion, we have developed a novel synthesis of isoindolinones that proceeds by an intramolecular [4+2] cycloaddition reaction of a pyridone-propiolamide followed by extrusion of isocyanic acid. The scope of the reaction is broad and proceeds well for a range of substitution patterns on both the pyridone and propiolamide moieties. We anticipate that this methodology will be useful for the synthesis of complex isoindolinone analogues.

## Appendix A. Supplementary data

Supplementary data (A document containing representative procedures for the synthesis of starting materials and characterization of a selection of the compounds reported in the manuscript has been supplied.) to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151105.

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*See references 12–15 for select examples of intramolecular [4+2] cycloaddition/CO2 extrusion reactions in synthesis*

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*See references 16-43 for select methods of isoindolinone synthesis.*

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