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Facile synthesis of 4,5-disubstituted-3(2*H*)-pyridazinones

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ABSTRACT

4,5-Disubstituted-3(2*H*)-pyridazinones were initially synthesized via sodium alkoxide additions to an advanced bromide intermediate. A small parallel chemistry effort resulted in a poor success rate, and we thus increased the reactivity of the reaction partner by performing a copper-catalyzed Finkelstein reaction. Copper-catalyzed coupling of a diverse set of alcohols with the resulting iodide resulted in a more successful effort. A number of alternative syntheses of this series of compounds are also described and these methods proved to be versatile, efficient, and amenable to parallel synthesis.

Pyridazines and their 3-oxo derivatives, the pyridazinones, are widely recognized as versatile scaffolds with a diverse set of biological activities.[1] As part of an ongoing drug discovery program in our laboratories, compound **1** was identified from high-throughput screening (HTS) and possessed attractive pharmacological properties as well as structural features amenable to optimization by rapid parallel synthesis (Fig. 1).

Unfortunately, **1** was highly cleared in vitro (human hepatocytes and liver microsomes). Metabolite ID studies revealed that metabolism was occurring exclusively on the 4-alkoxy portion of the molecule. Our strategy was thus to dramatically reduce the lipophilicity (ELog*D* = 5.1) of this hit, whilst improving the ligand efficiency (LE = 0.29).[2] More specifically, we wished to expediently and efficiently vary the 4-alkoxy portion of the molecule.

The initial route to these targets was via the formation of bromo intermediate **5**. This intermediate was accessed in a straightforward fashion following the three step protocol shown in Scheme 1.[3] Mucobromic acid **2** was treated with hydrazine sulfate to afford 4,5-dibromo-3(2*H*)-pyridazinone **3**.[4] Deprotonation of **3** followed by addition of cyclopropylmethyl bromide afforded **4** in moderate yield. Reaction of **4** with 1-(2-pyrimidyl)piperazine at elevated temperatures yielded intermediate **5** only in a moderate yield once again.[5]

Due to the need to synthesize intermediate **5** on large scale, we were unsatisfied by the yield of the last two steps. Inversion of the sequence of these last two steps allowed access to intermediate **5** in a more efficient manner (Scheme 2).[6,7] Deprotonation of 2-cyclopentylethanol, followed by addition to bromide **5** afforded target compound **1** in 90% yield.[1b] This final S_NAr reaction was also performed on a variety of diverse alkyl alcohols (~280) to afford target compounds **7** with a success rate of 40%.

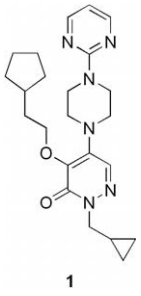

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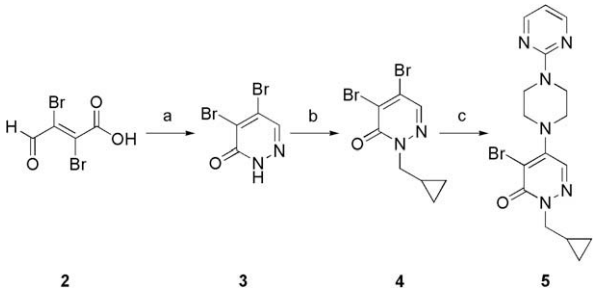
Figure 1. Initial hit **1** from high-throughput screening.



2 **3** **4** **5**

Scheme 1. Reagents and conditions: (a) $N_2H_4{\cdot}H_2SO_4$, NaOAc, H_2O, EtOH, 60 °C, 1 h then reflux, 4 h, 90%; (b) KO^{t}Bu, *c*-$C_3H_5CH_2Br$, DMA, 80 °C, 16 h, 42%; (c) DIEA, 1-(2-pyrimidyl)piperazine, DMA, 100 °C, 16 h, 50%.

Disappointed by the low success rate in the above library, we proceeded to increase the reactivity of the pyridazinone coupling partner (Scheme 3). To this end, bromide **5** underwent a copper-catalyzed Finkelstein reaction to afford iodide **8** in good yield.[8] Copper-catalyzed coupling of iodide **8** with 2-cyclopentylethanol

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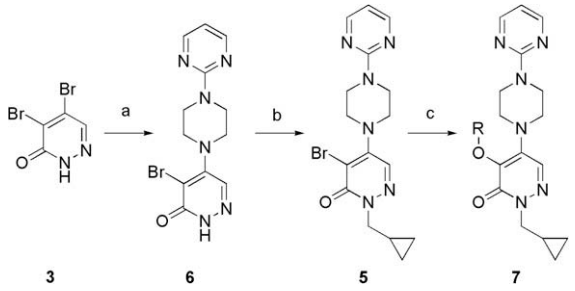
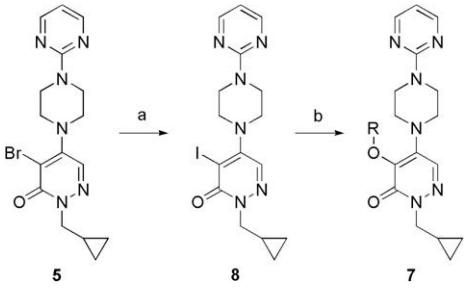


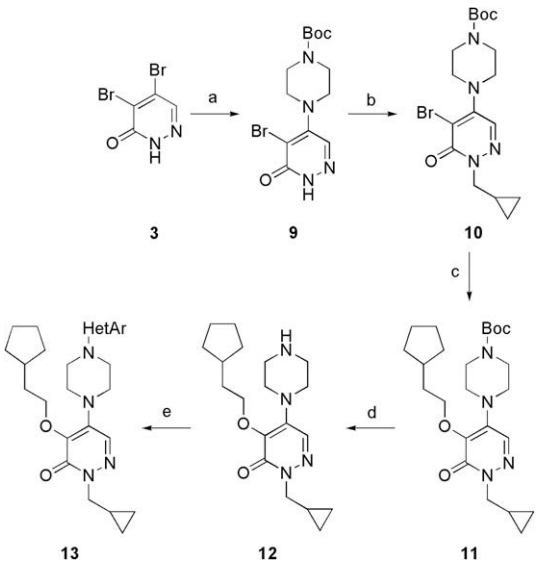
Scheme 2. Reagents and conditions: (a) DIEA, 1-(2-pyrimidyl)piperazine, DMA, 100 °C, 16 h, 71%; (b) KO^{t}Bu, c-$C_3H_5CH_2Br$, DMA, 80 °C, 16 h, 95%; (c) ROH, NaHMDS, THF, reflux, 16 h.



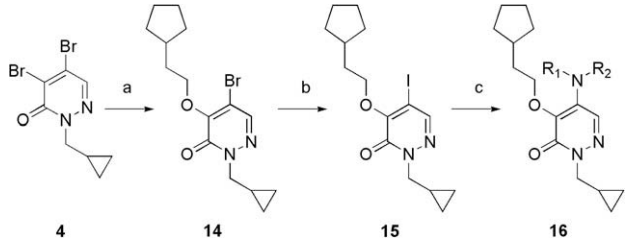
Scheme 3. Reagents and conditions: (a) $(CH_2NHMe)_2$, CuI, NaI, dioxane, 100 °C, 16 h, 80%; (b) ROH, phenanthroline, Cs_2CO_3, CuI, dioxane, 100 °C, 16 h.

once again afforded target compound **1** in 92% yield.[9] Taking a small subset (~60) of the failed alcohols from the first library attempt, we applied these new conditions to iodide **8** to yield target compounds **7** with a success rate of 61%.

In an effort to efficiently vary the pyrimidine moiety of the molecule we required access to piperazine intermediate **12** (Scheme 4). Treatment of 4,5-dibromo-3(2*H*)-pyridazi-none **3** with 1-Boc-piperazine afforded **9** in good yield.[5] Deprotonation of **9**, followed by addition of cyclopropylmethyl bromide yielded **10**. Deprotonation of 2-cyclopentylethanol, followed by addition to bromide **10** resulted in the formation of **11** in 88% yield.[1b] Deprotection of



Scheme 4. Reagents and conditions: (a) DIEA, 1-Boc-piperazine, DMA, 100 °C, 16 h, 76%; (b) KO^{t}Bu, *c*-$C_3H_5CH_2Br$, DMA, 80 °C, 16 h, 80%; (c) 2-cyclopentylethanol, NaHMDS, THF, reflux, 16 h, 88%; (d) HCl, dioxane, rt, 16 h, 79%; (e) 2-Cl-HetAr, DIEA, DMA, 100 °C, 16 h.



Scheme 5. Reagents and conditions: (a) 2-cyclopentylethanol, NaHMDS, dioxane, 50 °C, 2 h, 70%; (b) $(CH_2NHMe)_2$, CuI, NaI, dioxane, 100 °C, 16 h, 67%; (c) R_1R_2NH, Cs_2CO_3, $Pd_2(dba)_3$, Xantphos, PhMe, 120 °C, 16 h.

the piperazine afforded intermediate **12** in a concise manner. Treatment of piperazine **12** with 2-chloropyrimidine afforded target compound **1** in 55% yield. This final S_NAr reaction was also performed on a variety of diverse 2-chloroheteroaryls (~55) to yield target compounds **13** with a success rate of 89%.

Our final exercise was to identify a replacement for the 1-(2-pyrimidyl)piperazine moiety (Scheme 5). This effort would require access to iodo intermediate **15** in an efficient manner. The Hajós group had described methods for selective reaction at the 4- or 5-position (e.g., **4**) depending on the choice of solvent.[10] Reactions in solvents with high dielectric constant (e.g., methanol) afford 5-alkoxy products, whereas solvents with low dielectric constant (e.g., dioxane) favor formation of the 4-alkoxy regioisomer. Interestingly, elegant work by Kerdesky revealed that there is also a base effect on the regioselectivity.[11] NaHMDS and KHMDS in THF afford the 4-alkoxy product as the major regioisomer, whereas LiHMDS in THF provides a reversal of selectivity favoring the 5-alkoxy product. In our case, we deprotonated 2-cyclopentylethanol with NaHMDS in dioxane, and the resulting alkoxide was coupled with dibromide **4** to afford required intermediate **14** in good yield. At no point did we observe any 5-alkoxy regioisomer in this reaction. Bromide **14** underwent a copper-catalyzed Finkelstein reaction to afford iodide **15** in good yield.[8] Significant optimization was carried out in order to find an efficient method for accessing target compounds **16**. The optimum conditions utilized a Pd-catalyzed amination reaction with **15** and a diverse set of amines. A parallel array (~460 compounds) was performed utilizing this methodology with a success rate of 30%.

In summary, we have developed a number of efficient protocols for the facile synthesis of 4,5-disubstituted-3(2*H*)-pyridazinones. Efforts on hit compound **1** required target compounds to be synthesized via sodium alkoxide additions to an advanced bromide intermediate. Poor success rate in the parallel array required us to increase the reactivity of the reaction partner by performing a copper-catalyzed Finkelstein reaction. Copper-catalyzed coupling of a diverse set of alcohols with the resulting iodide led to a much more successful effort. A number of these methods proved to be versatile, efficient, and amenable to parallel synthesis.

Acknowledgment

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6. *Synthesis of* ***6***. To a solution of dibromide 3 (15.0 g, 59.1 mmol) in anhydrous *N*,*N*-dimethylacetamide (350 mL), under an atmosphere of nitrogen, were added 1-(2-pyrimidyl)piperazine (13.0 g, 65.0 mmol) and *N*,*N*-diisopropylethylamine (41.2 mL, 236 mmol). The resulting solution was heated to 100 °C and stirred for 16 h. The reaction mixture was allowed to cool to ambient temperature, diluted with water (500 mL), and extracted with ethyl acetate (3 × 500 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (3 × 500 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated in vacuo to afford the crude product. The residue was recrystallized from ethyl acetate to yield pure **6** (14.13 g, 71%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.94 (s, 1H), 8.38 (d, J = 4.7 Hz, 2H), 7.80 (s, 1H), 6.66 (t, J = 4.7 Hz, 1H), 3.86–3.83 (m, 4H), 3.43–3.41 (m, 4H). ESIMS (*m*/*z*): 338 (M+H).
7. *Synthesis of* ***5***. To a solution of bromide **6** (9.3 g, 28 mmol) in anhydrous *N*,*N*-dimethylacetamide (150 mL), under an atmosphere of nitrogen at 0 °C, were added potassium *tert*-butoxide (33.1 mL of a 1.0 M solution in tetrahydrofuran, 33.1 mmol) and cyclopropylmethyl bromide (2.94 mL, 30.3 mmol). The reaction was heated to 80 °C and stirred for 16 h. The solution was then allowed to cool to ambient temperature, diluted with water (250 mL) and was extracted with ethyl acetate (3 × 250 mL). The combined organic extracts were washed with saturated aqueous sodium chloride (3 × 250 mL), dried (anhydrous magnesium sulfate), filtered, and concentrated in vacuo to afford the crude product The residue was purified by flash column chromatography (40% ethyl acetate/heptane to ethyl acetate over 10 column volumes) to yield pure **5** (10.45 g, 95%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.38 (d, J = 4.8 Hz, 2H), 7.86 (s, 1H), 6.66 (t, J = 4.8 Hz, 1H), 3.90 (d, J = 7.05 Hz, 2H), 3.87–3.84 (m, 4H), 3.44–3.41 (m, 4H), 1.20 (m, 1H), 0.45 (m, 2H), 0.33 (m, 2H). ESIMS (*m*/*z*): 392 (M+H).
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