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Two-Step Synthesis of 3,4-Dihydropyrrolopyrazinones from Ketones and Piperazin-2-ones

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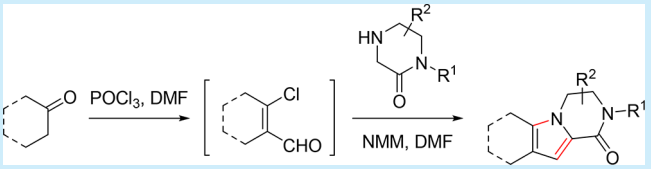
Supporting Information

ABSTRACT: An expedient two-step synthesis of 3,4-dihydropyrrolopyrazinones has been achieved via a Vilsmeier−Haack reaction of ketones, followed by an annulation of the corresponding chloroaldehydes with commercially available piperazin-2-ones. A variety of cyclic and acyclic ketones and piperazin-2-ones participated in this two-step chemistry, affording the desired 3,4-dihydropyrrolopyrazinones in up to 78% yield.



3,4-Dihydropyrrolopyrazinones are unique structural motifs found in numerous biologically active natural products and medicinally relevant compounds and thus have received much attention in the organic and medicinal communities.[1−7] For example, highly complex natural alkaloids such as immunosuppressive palau'amine,[2] antimetastatic agelastatin A−F,[3] cyclooroidin,[4] phakellin,[5] and anti-HIV investigational compound MK-2048[6] and aldose reductase inhibitor ranirestat[7] all possess a 3,4-dihydropyrrolopyrazinone heterocyclic core (Figure 1).

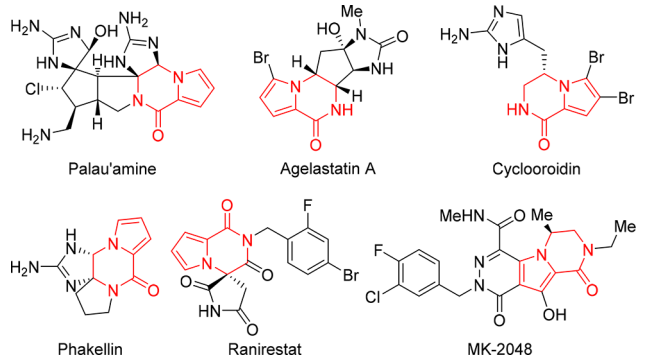
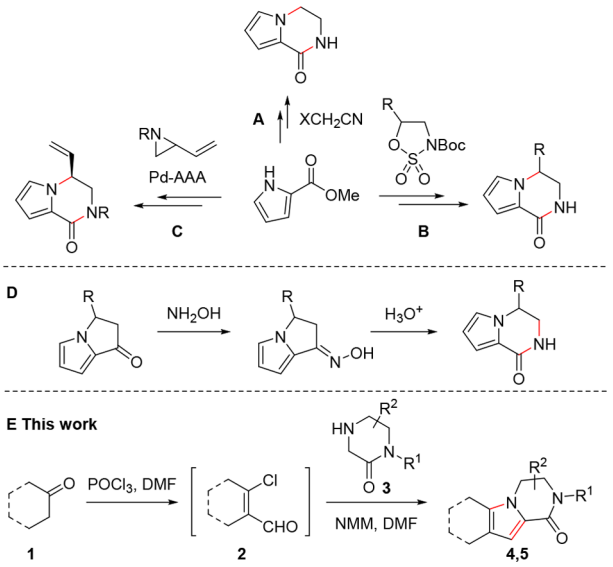


Figure 1. Selected biologically active compounds containing a 3,4-dihydropyrrolopyrazinone core.

Despite the biological and medicinal interests in 3,4-dihydropyrrolopyrazinones, there are surprisingly few synthetic approaches reported in the literature.[4e,8−11] The conventional syntheses involve the functionalization of pyrrole-2-carboxylates, followed by further functional group manipulation to construct the piperazinone ring (Scheme 1, **A** and **B**).[8,9] Unfortunately, these methods often suffer from multiple-step operations in low yields and/or the use of the toxic reagent haloacetonitrile. Trost has reported an elegant palladium-catalyzed transformation of vinyl aziridines with pyrrole-2-carboxylates to access enantioenriched vinyl-functionalized 3,4-dihydropyrrolopyrazinones[4e,10]

Scheme 1. Synthetic Approaches to 3,4-Dihydropyrrolopyrazinones



(Scheme 1, **C**). A Beckmann rearrangement[12] approach also affords substituted 3,4-dihydropyrrolopyrazinones, but the synthesis of the starting material 2,3-dihydropyrrolizin-1-one is tedious and the scope of this approach is very limited (Scheme 1, **D**).[11] Moreover, all of these strategies are initiated with pyrrole derivatives, and the substitution on the pyrrole ring has not been adequately explored. Therefore, the development of a more direct and efficient synthesis of substituted 3,4-dihydropyrrolopyrazinones with functionalization at both the pyrrole and piperazinone moieties is highly desirable.

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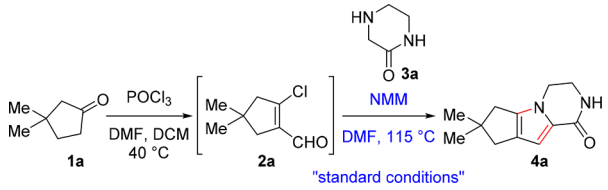
To support an internal drug research and development program in our laboratories, we were tasked to develop an efficient synthesis of a variety of 3,4-dihydropyrrolopyrazinones for structure−activity relationship studies and further process development. We decided to focus on a synthetic strategy involving an annulation reaction of Vilsmeier−Haack[13] products **2** (from ketones **1**) and piperazin-2-ones **3**. Herein, we report a facile two-step synthesis of 3,4-dihydropyrrolopyrazinones via a Vilsmeier−Haack reaction of ketones, followed by an annulation of the chloroaldehyde products with commercially available piperazin-2-ones (Scheme 1, **E**).

We initiated our studies by examining the Vilsmeier−Haack reaction of 3,3-dimethylcyclopentan-1-one (**1a**) to produce 2-chloro-4,4-dimethylcyclopent-1-ene-1-carbaldehyde (**2a**) and the annulation reaction of chloroaldehyde **2a** with commercially available piperazin-2-one (**3a**) to form tricyclic dihydropyrrolopyrazinone **4a** (Table 1). The Vilsmeier−Haack reaction could

Table 1. Optimization of 4a Formation[a]



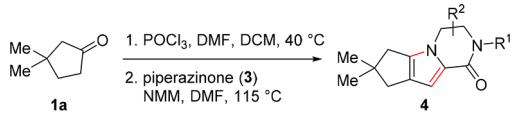
entry	variation from the "standard conditions"	assay yield[b] (%)
1	none	69 (61)[c]
2	80 °C instead of 115 °C	56
3	*i*-Pr_2NEt as base	67
4	DBU as base	14
5	2,6-lutidine as base	52
6	K_2CO_3 as base	7
7	DMA as solvent	47
8	NMP as solvent	19
9	PhMe as solvent	59

[a]Reaction conditions: **1a** (0.75 mmol, 84.0 mg), $POCl_3$ (1.58 mmol, 242 mg), DMF (1.88 mmol, 138 mg), DCM (1.5 mL), 40 °C, 18 h; **3a** (0.50 mmol, 50.0 mg), base (0.75 mmol), DMF (1.0 mL), 115 °C, 5 h. [b]Assay yields were obtained by quantitative HPLC analysis. [c]Isolated yield.

be readily achieved in full conversion employing 2.1 equiv of $POCl_3$ and 2.5 equiv of DMF in DCM at 40 °C. It is worth noting that product **2a** is not stable on silica gel column or upon storage and, therefore, was directly used in the subsequent annulation after aqueous workup. Under the best annulation conditions described in Table 1, the reaction afforded 69% HPLC assay yield and 61% isolated yield by employing 0.5 mmol of **3a**, 1.5 equiv of **2a**, and 1.5 equiv of *N*-methylmorpholine (NMM) as the base in DMF at 115 °C for 5 h (Table 1, entry 1). Performing the reaction at a lower temperature of 80 °C generated slightly lower 56% assay yield (Table 1, entry 2). The reaction using *i*-Pr_2NEt as the base afforded a similar assay yield of 67% (Table 1, entry 3), whereas other bases such as DBU, 2,6-lutidine, and K_2CO_3 all resulted in inferior assay yields (Table 1, entries 4−6). A test of solvents such as DMA, NMP, and toluene did not afford any advantage over the solvent of choice, DMF (Table 1, entries 7−9).

With a set of optimized conditions in hand, we next examined the scope and limitations of this two-step approach by employing 3,3-dimethylcyclopentan-1-one (**1a**) and various substituted piperazin-2-ones **3** (Table 2). As shown in Table 2, piperazin-2-

Table 2. Scope of Piperazin-2-ones (3)[a]



entry	piperazinones	product	yield[b] (%)
	R =		
1	Me, **3b**	**4b**	55
2	Bn, **3c**	**4c**	68
3	*t*-Bu, **3d**	**4d**	47
4	Ph, **3e**	**4e**	78
5	4-ClC_6H_4, **3f**	**4f**	77
6	**3g**	**4g**	62
7	**3h**	**4h**	52
8	**3i**	**4i**	40

[a]Reaction conditions: **1a** (1.50 mmol, 168 mg), $POCl_3$ (3.15 mmol, 483 mg), DMF (3.75 mmol, 275 mg), DCM (3.0 mL), 40 °C, 18 h; **3** (1.00 mmol), NMM (1.50 mmol, 152 mg), DMF (2.0 mL), 115 °C, 5 h. [b]Isolated yield.

ones **3b−f** substituted with alkyl, benzyl, and aryl groups at the 1-position readily participated in the annulation reactions, generating the desired tricyclic dihydropyrrolopyrazinone products **4b−f** in moderate to good yields (Table 2, entries 1−5). Furthermore, 6-methylpiperazin-2-one **3g** and bicyclic 4,7-diazaspiro[2.5]octan-5-one **3h** afforded the target products **4g** and **4h** smoothly in 62 and 52% yield, respectively (Table 2, entries 6 and 7). Finally, 1,5-dimethylpiperazin-2-one produced the desired tricyclic product **4i** in 40% yield (Table 2, entries 8). The relatively low yield of this reaction was presumably caused by the increased steric hindrance introduced by the 5-methyl substituent.

We also investigated the scope of the ketones in the Vilsmeier−Haack/annulation chemistry by employing piperazin-2-one (**3a**) as the reaction partner (Table 3). Cyclopentanone (**1b**) underwent the two-step protocol and generated the desired product **5b** in 60% yield (Table 3, entry 1). 2-Methylcyclopentanone (**1c**) only gave 39% yield of product **5c** (Table 3, entry 2). The lower yield was presumably caused by the steric effect introduced by the 2-methyl group. Interestingly, cyclohexanone (**1d**), cyclopentanone (**1e**), and cyclooctanone (**1f**) produced the desired tricyclic products **5d−f**, albeit in only 30−44% yields, and 29−40% yields of the isomeric dihydropyrrolopyrazinone products **5d′−f′** (Table 3, entries 3−5, and Figure 2). Acyclic ketone 3-pentanone (**1g**) similarly formed a mixture of two isomers **5g** and **5g′** in 20 and 34% yields,

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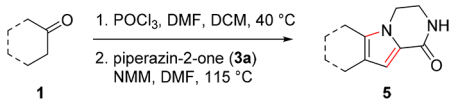
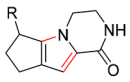
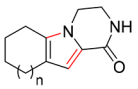
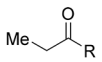
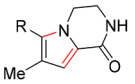
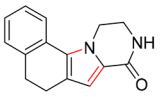
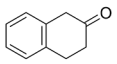
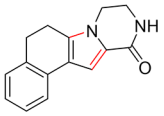
Table 3. Scope of Ketones[a]



entry	ketones	product	yield[b] (%)
			
1	R = H, **1b**	**5b**	60
2	R = Me, **1c**	**5c**	39
	 n =		
3	1, **1d**	**5d**	30(31)
4	2, **1e**	**5e**	44(29)
5	3, **1f**	**5f**	34(40)
			
6	R = Et, **1g**	**5g**	20(34)
7	R = Ph, **1h**	**5h**	<5(71)
8	 **1i**	 **5i**	61(16)
9	 **1j**	 **5j**	50

[a]Reaction conditions: **1** (1.50 mmol), $POCl_3$ (3.15 mmol, 483 mg), DMF (3.75 mmol, 275 mg), DCM (3.0 mL), 40 °C, 18 h; **3a** (1.0 mmol, 100 mg), NMM (1.50 mmol, 152 mg), DMF (2.0 mL), 115 °C, 5 h. [b]Isolated yield. The number in parentheses is the yield of the undesired isomer.

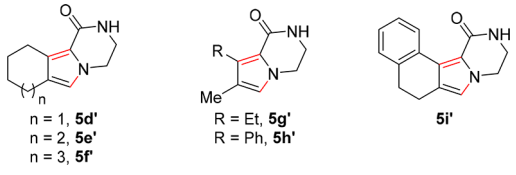
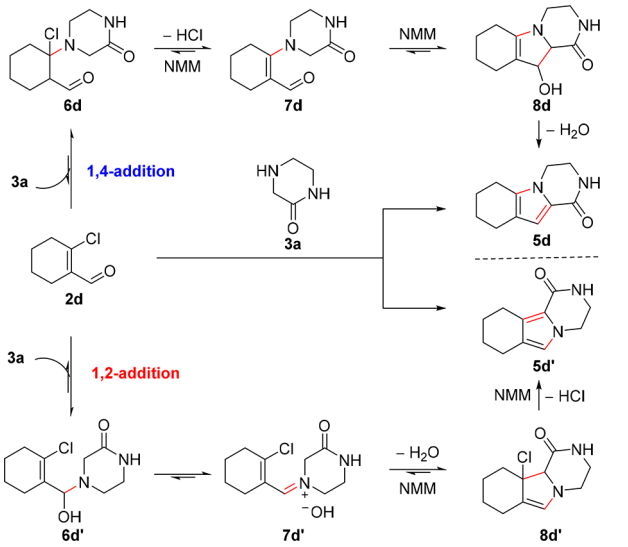


Figure 2. Undesired isomeric 3,4-dihydropyrrolopyrazinones.

respectively (Table 3, entry 6, and Figure 2), whereas propiophenone (**1h**) only afforded predominantly a single isomer **5h′** in 71% yield (Table 3, entry 7, and Figure 2). 1-Tetralone (**1i**) produced a mixture of isomers **5i** and **5i′** in 61 and 16% yields, favoring the desired product **5i** (Table 3, entry 8, and Figure 2). Interestingly, only the desired isomer **5j** was isolated in 50% yield when 2-tetralone (**1j**) was employed in this two-step reaction (Table 3, entry 9). The structures of the isomers were confirmed by NOESY spectra (see Supporting Information). It is worth noting that, although the isomeric products **5d′–i′**, which still possess medicinally relevant dihydropyrrolopyrazinone functional core, were isolated as undesired products in this chemistry, they were nevertheless very difficult to prepare by any other means.

We propose a mechanism for this annulation process exemplified by the reaction of 2-chlorocyclohex-1-ene-1-carbaldehyde (**2d**) and piperazin-2-one (**3a**) (Scheme 2). We

Scheme 2. Proposed Mechanism



believe that chloroaldehyde **2d** can undergo either a 1,4-addition or 1,2-addition pathway when reacting with piperazin-2-one (**3a**). A 1,4-aza-Michael addition[14] would lead to an amination intermediate **7d** that readily transforms to an intramolecular aldol product **8d** in the presence of base NMM. Intermediate **8d** then loses water and aromatizes to afford the desired tricyclic lactam **5d**. On the other hand, a 1,2-addition of piperazin-2-one (**3a**) to chloroaldehyde **2d** leads to the formation of an iminium species **7d′**. Intermediate **7d′** then undergoes an intramolecular cyclization followed by loss of HCl in the presence of base NMM to generate the isomeric tricyclic lactam **5d′**.

It is not entirely clear why certain substrates, for example, cyclopentanones **1a–c**, only produced a single isomer arising from the 1,4-addition pathway while other ketones such as **1d–f** afforded a mixture of isomers. One plausible explanation, taking cyclopentanone (**1b**), for example, is that 1,4-addition of piperazin-2-one (**3a**) to the Vilsmeier–Haack product **2b** releases the ring strain of the cyclopentene core of **2b** more than that of the cyclohexene, cycloheptene, or cyclooctene core of **2d–f**, thus rendering a more facile and predominant 1,4-addition. The primary formation of isomer **5h′** from propiophenone (**1h**) is presumably attributed to the steric effect introduced by the phenyl group that disfavors the 1,4-addition. In the case of 1-tetralone (**1i**), the steric element on the phenyl ring possibly slows down the 1,4-addition reaction, resulting in the formation of the 1,2-addition product **5i′** as the minor product, whereas 2-tetralone (**1j**), without any steric interference of the phenyl ring, only afforded 1,4-addition product **5j** in 50% yield.

In conclusion, we have developed an expedient two-step synthesis of 3,4-dihydropyrrolopyrazinones via a Vilsmeier–Haack reaction of ketones, followed by an annulation of the resulting products with commercially available piperazin-2-ones. A variety of cyclic and acyclic ketones and piperazin-2-ones participated in this two-step chemistry, affording the desired 3,4-dihydropyrrolopyrazinones in moderate to good yields. We anticipate that this practical method will provide rapid access to

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useful quantities of versatile dihydropyrrolopyrazinones to support our drug discovery programs.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00197.

General experimental procedures, characterization of new compounds, and copies of ^{1}H NMR, ^{13}C NMR, and NOESY spectra (PDF)

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Notes

The authors declare no competing financial interest.

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