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Synthesis of Pyrazolo[1,5-α]pyrimidinone Regioisomers

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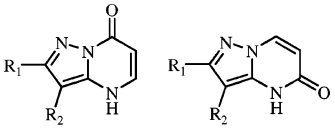


This work describes two distinct routes to prepare pyrazolo-[1,5-α]pyrimidin-7-ones and two distinct routes to prepare pyrazolo[1,5-α]pyrimidin-5-ones. Use of 1,3-dimethyluracil as the electrophile in the preparation of the pyrimidin-5-one regioisomer represents a correction of previously reported results. Also, a novel reaction to prepare this isomer was identified and the reaction mechanism elucidated. This work provides the experimentalist with complimentary synthetic pathways that afford either the pyrimidin-7-one or the pyrimidin-5-one regioisomer.

Over the past few decades, the core 4*H*-pyrazolo[1,5-α]-pyrimidin-7-one, **1**, has surfaced in a variety of biologically active molecules such as the α1*β*2*γ*2-selective ligand **2**,[1] the anti-schistosomal agent **3**,[2] and the anti-inflammatory **4**[3] (Figure 1). Moreover, core **1** may be used as a versatile synthetic intermediate and therefore has received a considerable amount of synthetic interest in recent literature.[4−10] During our investigations into the preparation of the substituted pyrazolo[1,5-α]pyrimidin-7-one intermediate, we found that altering the reaction conditions affected the regiochemical outcome of the key cyclization reaction in the synthesis. Herein, we report the results of our synthetic investigations including the correction of a previously reported regioisomeric assignment.

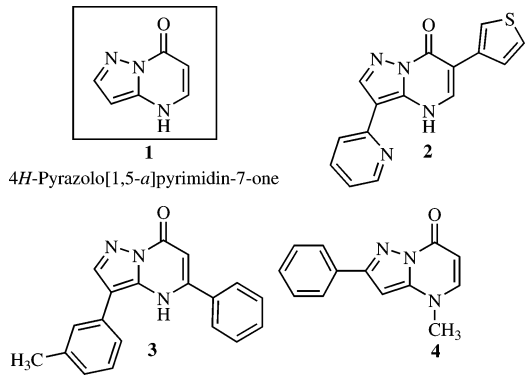
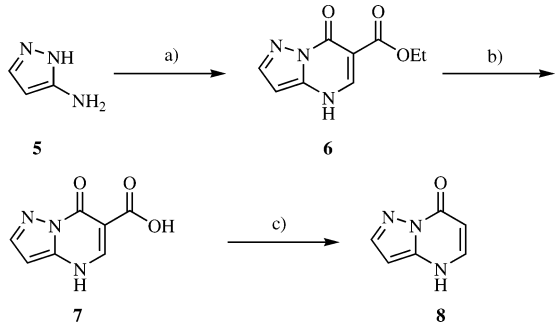


FIGURE 1. Compounds containing the pyrazolo[1,5-α]pyrimidin-7-one core.

Our initial synthesis, previously described in the literature,[6] involved condensation of an aminopyrazole and diethyl ethoxymethylenemalonate with subsequent cyclization, as shown in step 1 of Scheme 1. Starting from commercially available 2*H*-pyrazol-3-ylamine **5**, the reaction proceeded smoothly to afford ester **6** in one pot. Saponification gave the carboxylic acid **7**, which was subsequently decarboxylated yielding the desired compound **8** in 69% over the three steps.

SCHEME 1. Synthesis of the Simple Pyrazolo[1,5-α]pyrimidin-7-one Core[a]



[a] Reagents and conditions: (a) diethyl ethoxymethylenemalonate, AcOH, reflux, 16 h, 56%. (b) NaOH, EtOH, 100 °C, 3.5 h, 100%. (c) Dowtherm A, 250 °C, 2 h, 98%.

Synthesis of 5-(3-bromophenyl)-2*H*-pyrazol-3-ylamine, **11**, a key intermediate in our research, was achieved as shown in Scheme 2. Displacement of the α-bromo group with potassium cyanide was carefully developed to prevent cyanohydrin formation of the keto nitrile **10**. Condensation with hydrazine afforded the desired and novel pyrazole **11**, which reacted smoothly with

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(1) Selleri, S.; Bruni, F.; Costagli, C.; Costanzo, A.; Guerrini, G.; Ciciani, G.; Gratteri, P.; Bonaccini, C.; Malmberg Aiello, P.; Besnard, F.; Renard, S.; Costa, B.; Martini, C. *J. Med. Chem.* **2003**, *46*, 310−313.

(2) Senga, K.; Novinson, T.; Wilson, H. R. *J. Med. Chem.* **1981**, *24*, 610−613.

(3) Pirisino, R.; Mangano, G.; Ceppatelli, P.; Corrias, M.; Ignesti, G.; Carla, V. *Farmaco-Ed. Sci.* **1981**, *56* (8), 682−691.

(4) Senga, K.; Novinson, T.; Springer, R. H.; Rao, R. P.; O'Brien, D. E.; Robins, R. K.; Wilson, H. R. *J. Med. Chem.*, **1975**, *18* (3), 312−314.

(5) Koren, B.; Kovac, F.; Petric, A.; Stanovinik, B.; Tisler, M. *Tetrahedron* **1976**, *32*, 493−497.

(6) Nagahara, K.; Kawano, H.; Sasaoka, S.; Ukawa, C.; Hirama, T.; Takada, A. *J. Heterocycl. Chem.* **1994**, *31*, 239−243.

(7) Al-Mousawi, S. M.; Mohammad, M. A.; Elnagdi, M. H. *J. Heterocycl. Chem.* **2001**, *38*, 989−991.

(8) Jakse, R.; Svete, J.; Stanovnik, B.; Golobic, A. *Tetrahedron* **2004**, *60*, 4601−4608.

(9) Lager, E.; Andersson, P.; Nilsson, J.; Pettersson, I.; Nielsen, E. O.; Nielsen, M.; Sterner, O.; Liljefors, T. *J. Med. Chem.* **2006**, *49*, 2526−2533.

(10) Vettori, L. P.; Cecchi, L.; Costanzo, A. *Farmaco−Ed. Sci.* **1981**, *36* (6), 441−448.

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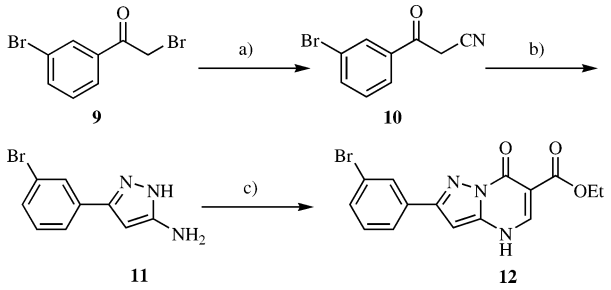
diethyl ethoxymethylenemalonate in glacial acetic acid to give the cyclized ester **12**.

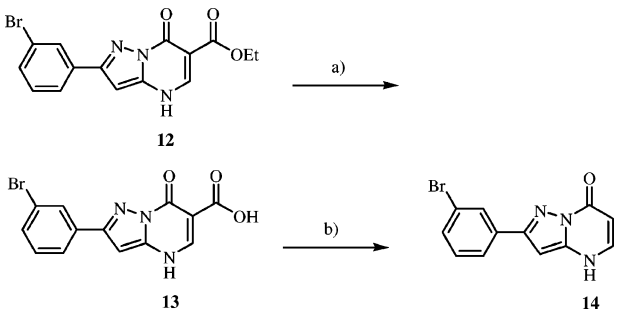
SCHEME 2. Synthesis of the Optimally Substituted Pyrazolo[1,5-α]pyrimidin-7-one Core[a]



[a] Reagents and conditions: (a) KCN, MeOH, H_2O, room temperature, 0.5 h, 65%. (b) Hydrazine hydrate, EtOH, 100 °C, 2 h, 69%. (c) Diethyl ethoxymethylenemalonate, AcOH, reflux, 16 h, 85%.

However, our desired intermediate did not have the ester moiety in the molecule. Therefore, in the same fashion as shown above, saponification and decarboxylation provided the desired intermediate **14**, as shown in Scheme 3.

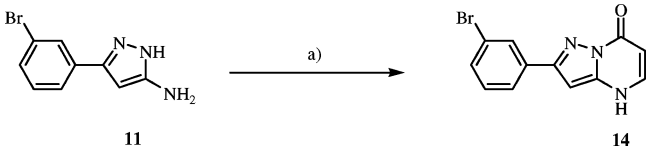
SCHEME 3. Saponification and Decarboxylation[a]



[a] Reagents and conditions: (a) NaOH, EtOH, 100 °C, 3 h, 91%. (b) Dowtherm A, 250 °C, 2 h, 91%.

In the end, synthesis of the desired pyrazolo[1,5-α]pyrimidin-7-one intermediate, **14**, was achieved in five synthetic steps and 31.5% overall yield. We thus sought alternative more efficient synthetic routes which would eliminate the need for ester group removal. One such route is shown in Scheme 4, where intermediate **14** is prepared in one step by addition of 5-(3-bromo-phenyl)-2*H*-pyrazol-3-ylamine, **11**, to a solution of the sodium salt of ethyl formylacetate[2] prepared in situ. The sodium salt of ethyl formylacetate was prepared by addition of ethyl acetate to a dispersion of sodium in toluene followed by dropwise addition of ethyl formate. This mixture was stirred for 15 h prior to addition of **11**.[11] It is worth mentioning that if the sodium was not a fine suspension, no product was detected. Also worthy of mention is that although the yield of this reaction

SCHEME 4. One-Step Synthesis of the Substituted Pyrazolo[1,5-α]pyrimidin-7-one Core[a]

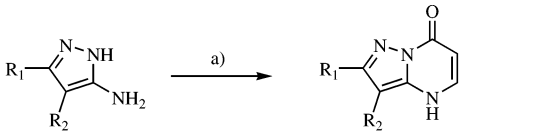


[a] Reagents and conditions: (a) (i) Na, EtOAc, EtOH, ethyl formate, 16 h. (ii) **11**, 80 °C, 4 h, 47%.

is low (47%), **14** is the only regioisomer detected. The crude reaction mixture shows 15% unreacted starting material, and the low recovery is assumed to be due to unoptimized workup/purification conditions.

Similarly, reaction of other available aminopyrazoles (**15**,[12] **5**, and **16**) with the sodium salt of ethyl formyl acetate afforded optimally substituted pyrazolo[1,5-α]pyrimidin-7-one scaffolds, as shown in Scheme 5. In all cases, exclusively one regioisomer was detected via TLC or crude NMR.

SCHEME 5. General Utility of the Reaction Using Formyl Acetate as Electrophile[a]



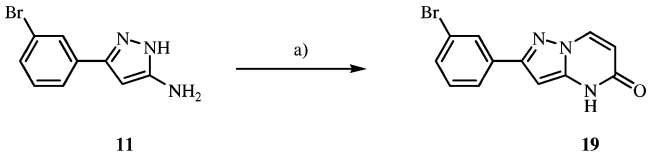
15 R_1 = 3'-BrC_6H_4, R_2 = CH_3
5 R_1 = H, R_2 = H
16 R_1 = H, R_2 = CO_2Et

17 R_1 = 3'-BrC_6H_4, R_2 = CH_3
8 R_1 = H, R_2 = H
18 R_1 = H, R_2 = CO_2Et

[a] Reagents and conditions: (a) (i) Na, EtOAc, EtOH, ethyl formate, 16 h, room temperature. (ii) **11**, 80 °C, 4 h, 42−76%.

Another appealing one-step/one-pot synthesis for intermediate **14** using a commercially available synthon was reported by Chu.[13] This work employed 1,3-dimethyluracil as the electrophile in the pyrazole addition−elimination reaction sequence. However, when we reacted 5-(3-bromophenyl)-2*H*-pyrazol-3-ylamine, **11**, with 1,3-dimethyluracil the expected product **14** (R_f ethyl acetate = 0.07) was not obtained; instead, exclusive formation of the regioisomer, **19** (R_f ethyl acetate = 0.56), was observed (Scheme 6).

SCHEME 6. One-Step Synthesis of the Substituted Pyrazolo[1,5-α]pyrimidin-5-one Core[a]



[a] Reagents and conditions: (a) 1,3-dimethyluracil, NaOEt, EtOH, 90 °C, 3 h, 75%.

There is a dramatic difference in the chemical shift of the β proton of the vinylogous amide moiety. In the pyrimidin-7-one isomer, this proton appears at 7.96 ppm, while in the pyrimidin-5-one isomer, the chemical shift of this proton is shifted further downfield to 8.52 ppm, Figure 2.

The reaction was repeated using pyrazoles **15**, **5**, and **16** and found to give exclusive formation of the pyrazolo[1,5-α]-pyrimidin-**5**-one products, as shown in Scheme 7. This is in contrast to the Chu paper in which two of these pyrazoles (**5** and **16**) were reported to give the pyrazolo[1,5-α]pyrimidin-**7**-one products. Upon rigorous examination of the crude NMR spectrum of these compounds, no other regioisomers were detected in any case. As highlighted above, in Figure 2, there is a large difference in the chemical shift observed between the

(11) Wheeler, H. L.; Merriam, H. F. *Am. Chem. J.* **1903**, *29*, 478−480.
(12) 5-(3-Bromo-phenyl)-2*H*-pyrazol-3-ylamine was prepared by the alkylation of **10** with methyl iodide followed by pyrazole cyclization.
(13) Chu, C. K.; Suh, J. J.; Mesbah, M.; Cutler, S. J. *J. Heterocycl. Chem.* **1986**, *23*, 349−352.

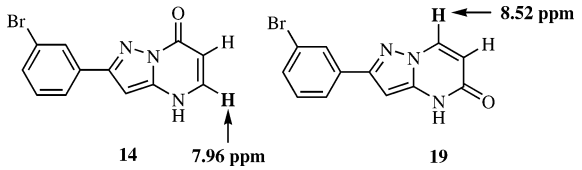
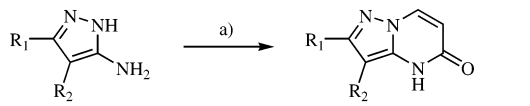


FIGURE 2. Difference in chemical shift of the vinylogous amide β-proton.

β proton of the vinylogous amides for each isomer. This trend continued for each of the novel pyrazolo[1,5-α]pyrimidin-5-one products formed (i.e., β-H chemical shift of **8** = 7.86 ppm and the β-H chemical shift in **21** = 8.47 ppm).

SCHEME 7. General Utility of the Reaction Using 1,3-Dimethyluracil as Electrophile[a]



15 R_1 = 3'-BrC_6H_4, R_2 = CH_3
5 R_1 = H, R_2 = H
16 R_1 = H, R_2 = CO_2Et
20 R_1 = 3'-BrC_6H_4, R_2 = CH_3
21 R_1 = H, R_2 = H
22 R_1 = H, R_2 = CO_2Et

[a] Reagents and conditions: (a) 1,3-dimethyluracil, NaOEt, EtOH, 90 °C, 3 h, 11−84%.

The structures of pyrazoles **8** (Schemes 1 and 5) and **21** (Scheme 7) were unambiguously determined by NMR NOE experiments of the N-methyl derivatives. The observed carbon chemical shifts of the methyl carbons of 35−40 ppm for both **23** and **24** are consistent with methylation of the pyrimidinone ring nitrogen, not oxygen. The N-methyl derivative **23** afforded two NOEs, one to a proton on the pyrimidinone ring and a second to a proton on the pyrazole ring, while the N-methyl analog, **24**, gave a single large NOE to a proton on the pyrazole ring, as depicted in Figure 3.

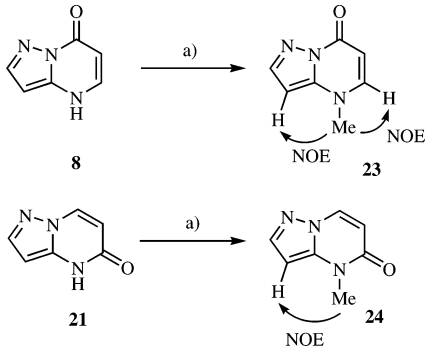
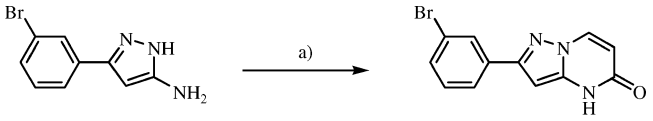


FIGURE 3. NOE experiments of the N-methyl regioisomers. Reagents and conditions: (a) (i) NaH, MeI, DMF, RT, 0.5 h, 84−89%.

Synthesis of the pyrimidin-5-one regioisomer using 1,3-dimethyluracil has not previously been reported. In the literature, the only synthesis of this isomer reported uses ethyl propiolate as the source for the α,β-unsaturated ketone moiety.[10] Upon further investigations in our laboratory of other conditions that may preferentially react to give the pyrimidin-5-one isomer, the conditions outlined in Scheme 8 were discovered. In this case also, we carefully examined the crude NMR spectrum, and none of the pyrimidin-7-one regioisomer was observed.

(14) Scheiner, P.; Geer, A.; Bucknor, A.; Imbach, J.; Schinazi, R. *J. Med. Chem.* **1989**, *32*, 73−76.

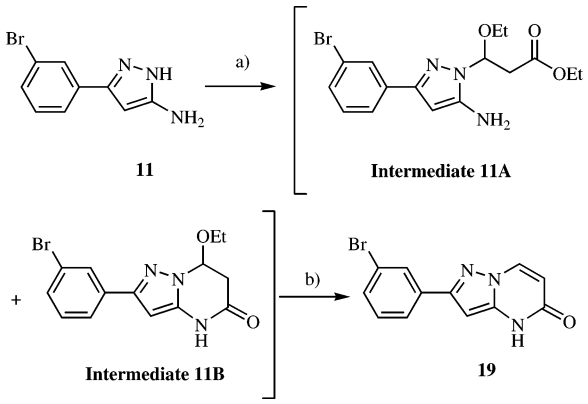
SCHEME 8. Alternate Synthesis of the Pyrazolo[1,5-α]pyrimidin-5-one Scaffold[a]



[a] Reagents and conditions: (a) ethyl 3-ethoxyacrylate, Cs_2CO_3, DMF, 110 °C, 4 h, 94%.

By lowering the temperature of the reaction from 110 °C to room temperature, we were able to isolate intermediates **11A** and **11B**, (Scheme 9) and thus elucidate the mechanism of this high-yielding cyclization reaction. Initially, there is a Michael addition of the secondary nitrogen of the pyrazole to the ethyl 3-ethoxyacrylate, which leads to formation of intermediate **11A**. Michael addition to an acrylate without elimination, although not common, has previously been documented in the literature.[14] Subsequent intramolecular lactam formation yields the bicycle **11B**, which liberates **19** following ethanol elimination.

SCHEME 9. Isolation of Intermediates: Elucidation of the Reaction Pathway[a]

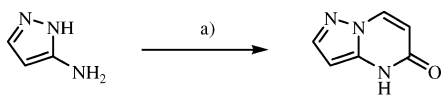


[a] Reagents and conditions: (a) ethyl 3-ethoxyacrylate, Cs_2CO_3, DMF, room temperature, 2 h, 94%. (b) 110 °C.

Additionally, it was found that intermediate **11A** can be converted to intermediate **11B** upon treatment with Cs_2CO_3 at 60 °C, and both of these intermediates can be converted into regioisomer **19** at 110 °C.

These novel reaction conditions for constructing the pyrazolo-[1,5-α]pyrimidin-5-one product were found to be reproducible and general. In another example, as shown in Scheme 10, exposure of commercially available 2*H*-pyrazol-3-ylamine **5** afforded pyrimidin-5-one **21** in moderate yield. Although reaction intermediates were not isolated in this case, we hypothesize that this reaction follows the same mechanistic pathway outlined in the formation of **19** as shown inScheme 9.

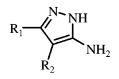
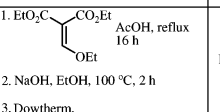
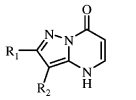
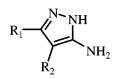
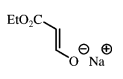
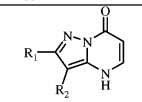
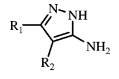
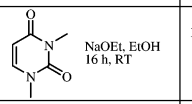
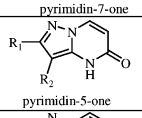
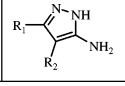
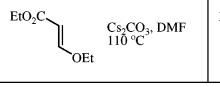
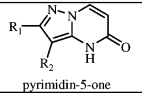
SCHEME 10. General Utility of the Reaction Using Ethyl 3-ethoxyacrylate as Electrophile[a]



[a] Reagents and conditions: (a) ethyl 3-ethoxyacrylate, Cs_2CO_3, DMF, 110 °C, 2 h, 59%.

In summary, we have shown two distinct routes to prepare pyrazolo[1,5-α]pyrimidin-7-ones, such as **14** (Schemes 3 and 4). Both of these routes are applicable to a variety of pyrazole substrates, offering products with optimal substitution patterns. Alternatively, we have shown two distinct routes for the preparation of pyrazolo[1,5-α]pyrimidin-5-ones, such as **19** (Schemes 6 and 8). Table 1 summarizes these findings.

TABLE 1. Summary of Results

Method	Starting Material	Reagents	Product
A		 1. EtO_2C, CO_2Et, AcOH, reflux 16 h, OEt; 2. NaOH, EtOH, 100 °C, 2 h; 3. Dowtherm, 250 °C, 2 h	 pyrimidin-7-one
B		 EtO_2C, O, Na	 pyrimidin-7-one
C		 NaOEt, EtOH 16 h, RT	 pyrimidin-5-one
D		 EtO_2C, Cs_2CO_3, DMF 110 °C, OEt	 pyrimidin-5-one

Further experimentation and mechanistic studies are required to fully understand the differences in regioisomer selectivity. It seems that both the conditions (acidic vs basic) and the electrophile play important roles in determining the course of the cyclization reaction.

Both routes for formation of the pyrimidin-5-ones are noteworthy. First, use of 1,3-dimethyluracil as the electrophile in the preparation of regioisomers **21** and **22** represents a correction from previously reported results.[13] This one-step procedure can be used to prepare a variety of novel compounds. Also, we report here for the first time that reaction of an aminopyrazole with ethyl 3-ethoxyacrylate in the presence of cesium carbonate affords the pyrimidin-5-one regioisomer. Furthermore, the mechanism of formation of **19** was revealed by isolation of intermediates within the reaction pathway. This work provides the experimentalist with a variety of synthetic pathways that will afford either the pyrimidin-7-one or the pyrimidin-5-one regioisomer.

Experimental Section

Method A: Ethyl 7-Oxo-4,7-dihydropyrazolo[1,5-α]pyrimidine-6-carboxylate (6). To a solution of 2*H*-pyrazol-3-ylamine (4.15 g, 50 mmol, 1 equiv) in glacial acetic acid (60 mL) at room temperature was added diethyl ethoxymethylenemalonate (11.89 g, 55 mmol, 1.1 equiv). The mixture was heated at 120 °C for 4.5 h. The suspension was filtered warm, then washed several times with EtOH, and dried to yield ethyl 7-oxo-4,7-dihydropyrazolo-[1,5-α]pyrimidine-6-carboxylate (5.76 g, 28 mmol, 56%) as a white powder.

Method A: 7-Oxo-4,7-dihydropyrazolo[1,5-α]pyrimidine-6-carboxylic Acid (7). To a suspension of ethyl 7-oxo-4,7-dihydro-pyrazolo[1,5-α]pyrimidine-6-carboxylate, **6**, (2.07 g, 10 mmol) in EtOH (10 mL) at room temperature was added 2.5 N NaOH (10 mL). The resulting suspension was heated to 100 °C for 3.5 h. The suspension was cooled to room temperature and diluted with H_2O (300 mL) and citric acid (5.78 g, 30 mmol). The white suspension was stirred an additional 30 min, filtered, and washed with water. The wet solid was azeotroped to dryness by refluxing in toluene (150 mL). The suspension was cooled to room temperature, filtered, and dried to yield 7-oxo-4,7-dihydropyrazolo[1,5-α]pyrimidine-6-carboxylic acid (1.80 g, 10 mmol, 100%) as a white solid.

Method A: Pyrazolo[1,5-α]pyrimidin-7(4*H*)-one (8). To 7-oxo-4,7-dihydropyrazolo[1,5-α]pyrimidine-6-carboxylic acid, **7**, (12.10 g, 68 mmol) was added Dowtherm A (100 mL). The suspension was heated to 250 °C for 2 h. The reaction mixture was cooled to room temperature, then diluted with hexanes (300 mL), stirred vigorously, filtered, and dried to afford pyrazolo[1,5-α]pyrimidin-7(4*H*)-one (8.90 g, 66 mmol, 98%) as a pink solid.

Method B: 2-(3-Bromophenyl)pyrazolo[1,5-α]pyrimidin-7(4*H*)-one (14). Sodium, prewashed with hexanes (0.13 g, 5.6 mmol, 2.8 equiv), was added to a scintillation vial (20 mL) to which toluene (2 mL) was added. The vial was heated in a 120 °C oil bath until the sodium became molten. The vial was shook vigorously to produce a fine suspension of sodium as the mixture cooled. To the suspension at room temperature under N_2 was added ethyl acetate (430 μL, 4.4 mmol, 2.2 equiv) followed by EtOH (3 drops). Ethyl formate (355 μL, 4.4 mmol, 2.2 equiv) was added in portions over 20 min. The suspension was allowed to stir for 16 h at room temperature under N_2. A solution of 3-(3-bromophenyl)-1*H*-pyrazol-5-amine, **11** (0.43 g, 2 mmol, 1 equiv), in EtOH (2 mL) was added to the suspension and then heated to 80 °C for 4 h. The solvent was removed, H_2O (50 mL) was added, and the crude product was heated to boiling, filtered through Celite, cooled, and brought to pH 1 by addition of 6 N HCl. The precipitate was filtered and washed with H_2O. The wet solid was triturated with EtOH, filtered, and dried to yield 2-(3-bromophenyl)pyrazolo[1,5-α]pyrimidin-7(4*H*)-one (0.27 g, 0.93 mmol, 47%) as a pale yellow solid.

Method C: 2-(3-Bromophenyl)pyrazolo[1,5-α]pyrimidin-5(4*H*)-one (19). To 3-(3-bromophenyl)-1*H*-pyrazol-5-amine, **11** (1.19 g, 5 mmol, 1 equiv), under a N_2 atmosphere was added a solution of sodium ethoxide in EtOH (1 N, 17.5 mL). Solid 1,3-dimethyluracil (0.77 g, 5.5 mmol, 1.1 equiv) was added, and the mixture was heated to 90 °C for 3 h. The reaction mixture was then cooled in an ice−water bath. The resulting amber precipitate was filtered off and dissolved in water (20 mL) and neutralized with acetic acid. The solid was then washed with H_2O and azeotroped to dryness by refluxing in toluene (100 mL) to give 2-(3-bromophenyl)pyrazolo[1,5-α]pyrimidin-5(4*H*)-one (1.09 g, 3.8 mmol, 75%) as a cream-colored solid.

Method D: 2-(3-Bromophenyl)pyrazolo[1,5-α]pyrimidin-5(4*H*)-one (19). To a solution of 3-(3-bromophenyl)-1*H*-pyrazol-5-amine, **11** (0.238 g, 1.0 mmol), and ethyl 3-ethoxyacrylate (220 μL, 1.5 mmol) in DMF (15 mL) was added cesium carbonate (480 mg, 1.5 mmol). The reaction mixture was heated to 110 °C for 4 h. The mixture was then allowed to cool, and acetic acid (3 mL) was added. The solvent was evaporated, and the product was partitioned between H_2O and ethyl acetate. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to give crude product. The resultant material was purified by trituration with ethyl acetate:EtOH to give 2-(3-bromophenyl)pyrazolo[1,5-α]pyrimidin-5(4*H*)-one (0.273 g, 0.94 mmol, 94%) as a white solid.

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Supporting Information Available: Full characterization and purity data for compounds **6**, **7**, **8**, **14**, and **19**. Experimentals, characterization and purity data for compounds **10**, **11**, **11A**, **11B**, **12**, **13**, **15**, **17**, **18**, **20**, **21**, **22**, **23**, and **24**. NOE experimental details and data for compounds **23** and **24**. This material is available free of charge via the Internet at http://pubs.acs.org.

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