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# A cascade reaction sequence en route to 7-substituted 2-aminopyrrolo[1,2-*a*]pyrimidine-4,6-diones and the corresponding acrylic acid derivatives

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**Abstract**—Reaction of α-bromo ketones with 6-amino-2-methylpyrimidin-4(3*H*)-one under basic conditions and in the presence of atmospheric oxygen affords novel 7-substituted 2-amino-pyrrolo[1,2-*a*]pyrimidine-4,6-diones that are readily hydrolyzed to afford the corresponding acrylic acid derivatives. The reaction sequence consists of an initial alkylation, followed by an unexpected condensation, elimination, and oxidation sequence to afford the products. This cascade reaction sequence represents a rapid and unprecedented route to the described small molecules.


In the course of an ongoing effort to identify small molecules for the treatment of metabolic disorders, we desired access to substituted β-keto pyrimidinones. The initial synthetic route for the desired compounds (Scheme 1) consisted of a base-mediated alkylation of 6-amino-2-methylpyrimidin-4(3*H*)-one with 2-bromo acetophenone. Because several possible sites for alkylation existed within the pyrimidinone core,[1] multiple bases and solvents were screened in order to optimize the formation of the N-alkylated products. While bases such as cesium carbonate in DMF afforded mixtures of products that could be separated, the use of lithium hydroxide in DMF led to an unexpected intermediate that quickly converted to a second upon exposure to atmospheric oxygen. Subsequent investigation and optimization of this reaction sequence ultimately afforded a novel multi-step route to a class of bicyclic imides[2] and the corresponding acrylic acid derivatives that have not been reported to date.

Initial efforts to access N-alkylated pyrimidinones involved the use of cesium carbonate in DMF at room temperature. These conditions afforded a nearly 1:1 mixture of the N- and O-alkylated products **3** and **4**, respectively, which were separable by reverse phase as well as normal phase chromatography. Although this route was sufficient for providing material, we screened additional bases and solvents in an attempt to optimize the formation of **3**. While bases such as sodium hydroxide and potassium *tert*-butoxide afforded complex mixtures in either THF or DMF,[3] treatment of starting materials **1** and **2a** with lithium hydroxide in DMF afforded an unexpected product that was distinct in structure from either of the alkylated pyrimidinones **3** and **4** (Scheme 2).

In order to derive the molecular construction of this product, two-dimensional NMR analysis was performed, with the spectra being consistent with bicyclic imide **5**.[4] However, the planarity of the molecule and the dearth of protons on the bicyclic system did not allow for an unambiguous structure to be discerned by this method. Furthermore, high resolution mass spectroscopy revealed ions that were consistent with both compound **5** as well as a hydrated analog. This result indicated that hydrolysis could have occurred during the ionization process to afford the putative acrylic acid **6** (Scheme 3). In order to substantiate this observation, we then subjected the product of the reaction to mild acid conditions. Indeed, within 2 h, a distinct product

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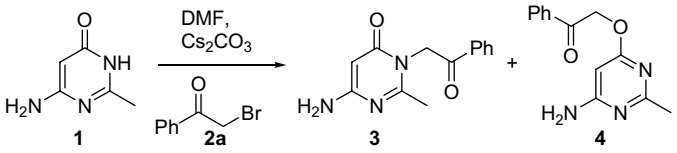
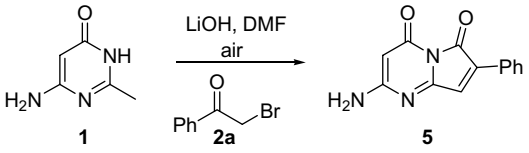



**Scheme 1.** Alkylation of 6-amino-2-methylpyrimidin-4(3*H*)-one.

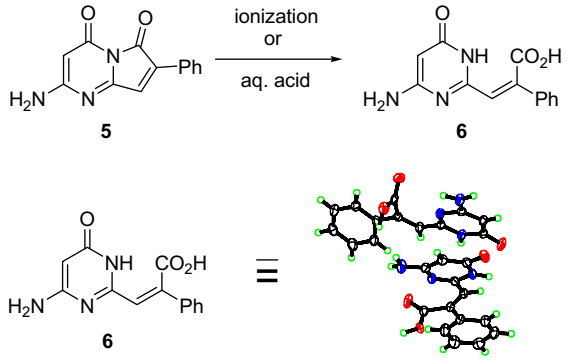



**Scheme 2.** Putative products of the alkylation reaction.

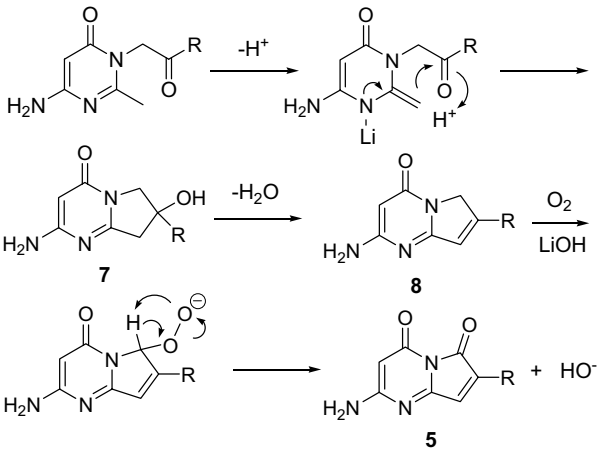
was formed. Subsequent two-dimensional NMR analysis was consistent with acrylic acid derivative **6**, and the structure was unambiguously determined via X-ray crystallography.[5]

Because of the requirement for oxygen to render the final product, we reasoned that the initial alkylation reaction was followed by an intramolecular condensation between the methyl group and the phenylketone moiety[6] as demonstrated in Scheme 4 (structure **7**). Elimination of water afforded the putative 4 pi electron-containing 5-membered bicycle **8**,[7] which then underwent oxidation[8] to afford heterocycle **5**. This bicyclic imide appears to be electronically strained, which is consistent with the observed rapid hydrolysis to the acrylic acid upon treatment with acidic water.

Given the facility of the final oxidative step, we reasoned that the execution of the entire sequence could be carried out by simply exposing the reaction mixture to air from the initiation. Gratifyingly, reacting the starting materials **1** and **2a** in DMF and with lithium hydroxide in an open vessel afforded the desired product in 47% isolated yield after 16 h. Further investigation involved the scaling of the reaction by ten fold. Although the transformation was slower with the increased scale, comparable yields were obtained by bubbling air into the reaction vessel while heating to 80 °C.



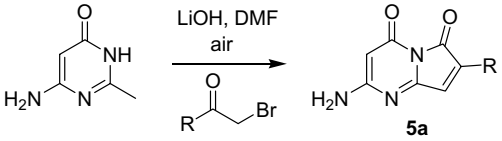

**Scheme 3.** Formation of (*E*)-acrylic acid derivative **6** and ORTEP plot of the molecular structure.




**Scheme 4.** Mechanistic proposal for the formation of **5**.

The generality of the reaction sequence was then probed by reacting the pyrimidinone core with a panel of substituted 2-bromoacetophenones as well as both enolizeable and non-enolizeable alkyl substrates. As shown in Table 1, reaction of 6-amino-2-methylpyrimidin-4(3*H*)-one with substrates **2a**, **2b** and **2e** in DMF with lithium hydroxide and with no vessel closure afforded the desired products in reasonable isolated yields. The reaction with ethyl substrate **2d** afforded a poor yield of the corresponding product, a partial result of byproduct

**Table 1.** Reaction of 6-amino-2-methylpyrimidin-4(3*H*)-one with α-bromo ketones[a]




| Entry | 2 | R | Yield[b] (%) |
|---|---|---|---|
| 1 | **a** | Phenyl | 47 |
| 2 | **b** | *tert*-Butyl | 49 |
| 3 | **c** | Adamantyl | 35[c] |
| 4 | **d** | Ethyl | 10 |
| 5 | **e** | 4-Chlorophenyl | 48 |
| 6 | **f** | *p*-Methoxyphenyl | 38[c] |
| 7 | **g** | *m*-Methoxyphenyl | 39[c] |
| 8 | **h** | *p*-Diethylaniline | 35[c] |

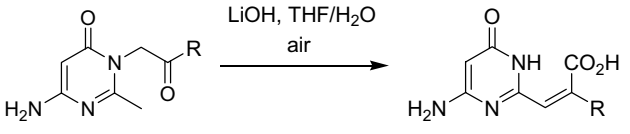
[a] General method: The desired α-bromo ketone (0.5 mmol) was added to 6-amino-2-methylpyrimidin-4(3*H*)-one (0.5 mmol) in a mixed solvent (4 mL of DMF, 0.5 mL of $H_2O$) at rt followed by the addition of LiOH·$H_2O$ (2 mmol) in an open vessel.
[b] Isolated yield after chromatography.
[c] Reaction temperature 80 °C.

formation. Not surprisingly, the sterically hindered adamantyl substrate **2c**, in addition to the electron donating substituent-containing derivatives **2e**–**h**, were slow to react at room temperature. However, subjection of the corresponding reaction mixtures to elevated temperatures afforded the desired products in yields comparable to those observed with the initial substrates in each case. Interestingly, the putative 4 pi electron 5-membered ring-containing intermediates (Scheme 4, structure **8**) corresponding to substrates **2f** and **2g** showed greater relative stability compared to the other reaction substrates, and could be observed via HPLC–MS analysis for several hours.

That the combination of DMF and lithium hydroxide was a competent system for driving the multi-step sequence while others were not presented a fascinating question. In order to further probe the requirements of the reaction, the purified alkylated product of the DMF/cesium carbonate reaction (compound **3**, Scheme 1) was subjected to the DMF/lithium hydroxide conditions. As expected, imide **5** was obtained within 12 h and in 80% yield. Subjection of **3** to otherwise identical conditions but with THF[9,10] as the solvent, however, afforded a product that was identical to the crystallographically determined structure **6** in an 85% isolated yield. This result was surprising in that the bicyclic imide was never observed or isolated when THF was used as the reaction solvent, while the use of DMF somehow retarded the hydrolysis step and afforded the bicyclic imide.

To probe the generality of this observation, several 2-bromoketone substrates were reacted with 6-amino-2-methylpyrimidin-4(3*H*)-one under the DMF/cesium carbonate conditions, and the desired products of N-alkylation were isolated (see Supplementary data). Exposure of these intermediates to lithium hydroxide in THF afforded the ring opened acrylic acid derivatives in good to excellent yields for substrates **3a**, **b**, and **3d**,**e**,

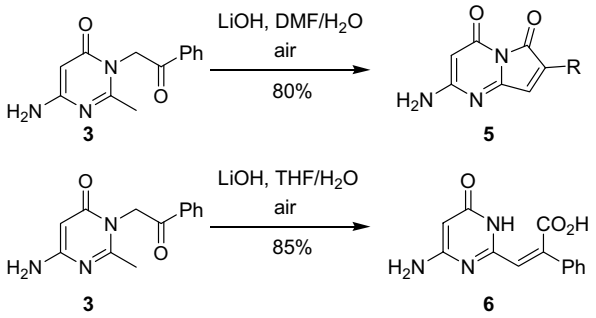
**Table 2.** Reaction of N-alkylated 6-amino-2-methylpyrimidin-4(3*H*)-one with LiOH[a]




**3** **6**

| Entry | 3 | R | Yield[b] |
|---|---|---|---|
| 1 | **a** | Phenyl | 85 |
| 2 | **b** | *tert*-Butyl | 90 |
| 3 | **c** | Adamantyl | 5 |
| 4 | **d** | Ethyl | 83 |
| 5 | **e** | 4-Chlorophenyl | 60 |
| 6 | **f** | *p*-Methoxyphenyl | 8 |
| 7 | **g** | *m*-Methoxyphenyl | 5 |
| 8 | **h** | *p*-Diethylaniline | [c] |

[a] General method: $LiOH{\cdot}H_2O$ (0.33 mmol) was added to **3a**–**g** (0.082 mmol) in a mixed solvent (3 mL of THF, 1 mL of $H_2O$) at rt in an open vessel.
[b] Isolated yield after chromatography.
[c] No reaction was observed.




**3** **5** **3** **6**

**Scheme 5.** Reaction of purified *N*-alkyl pyrimidinone in DMF or THF solvent systems.

as shown in Table 2. It is interesting to note the high yielding transformation with ethylated analog **3d** considering the low yield of the corresponding reaction with 1-bromobutan-2-one and 6-amino-2-methylpyrimidin-4(3*H*)-one. Similar to the previously described transformations in Table 1, starting materials **3c** and **3e** and **3g** proved to be difficult reaction substrates, and afforded low yields of the desired products. Additionally, reactions with substrate **3h** failed to proceed. In contrast, these transformations were not aided by the use of elevated temperatures, as multiple byproducts were formed, sometimes at the complete expense of the desired products as exemplified by entry 7. With these results in mind, the more operationally straight-forward reaction conditions described in Scheme 2, followed by acid mediated hydrolysis represent a superior route to access the acrylic acid products.[11] It is currently unclear as to why the purified N-alkylated pyrimidinones would render the corresponding acrylic acid derivatives when THF is used in place of DMF as a solvent given the otherwise redundant reaction conditions.

In summary, treatment of substituted 2-bromoketones with 6-amino-2-methylpyrimidin-4(3*H*)-one, lithium hydroxide, and DMF in the presence of atmospheric oxygen affords a class of bicyclic imides that can be readily transformed to the corresponding acrylic acid derivatives. Both classes of products are reported for the first time, and are generated from an unexpected and novel sequence that involves no fewer than four distinct steps. The divergent fates of reaction sequences demonstrated in Scheme 5 present a fascinating and currently unexplained phenomenon, and require further study.

## Acknowledgments

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## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.08.003.

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2. The structurally similar 2-(dimethylamino)-7,8-diphenyl-pyrrolo[1,2-*a*]pyrimidine-4,6-dione was accessed in an alternative manner. See the following: Banfield, J. E.; Fallon, D.; Gatehouse, B. M. *Aust. J. Chem.* **1987**, *40*, 1003–1009.
3. The use of sodium hydride in DMF afforded a 2:1 mixture of **3** and **4**. No products were observed when THF was used. See Ref. 1.
4. ROESY analysis demonstrated an NOE between the protons at C8 on the heterocycle and the ortho position on the phenyl ring for both structures **5** and **6**. While definitive proof of structure **5** cannot be obtained via NMR, this analysis disproves the possibility of **5** being an alkene isomer of **6**. Please see Supplementary data for details.
5. Yellow plate-like crystals of compound **6**, crystallized from methylenechloride/nitromethane, belong to the space group $P2_1/c$. Crystal data: $C_{13}H_{11}N_3O_3$, $M = 257.25$, $a = 12.567(3)$ Å, $b = 14.014(3)$ Å, $c = 13.468(3)$ Å, $\beta = 91.941(4)°$, $V = 2370.3(9)$ Å$^3$, $Z = 8$, $d = 1.442$ g/cm$^3$, $\mu = 0.106$ cm$^{-1}$. A yellow plate-like crystal of dimensions $0.5 \times 0.3 \times 0.05$ mm was used for X-ray measurements on a BrukerAXS APEX CCD area detector with graphite monochromated Mo K$\alpha$ radiation. Of the 27704 reflections that were collected 5805 were unique ($R_{int} = 0.1062$); Data were processed using Saint + (BrukerAXS). The structure was solved by direct methods and expanded using Fourier techniques. Refinement was performed using SHELXTL. Crystallographic data for the structure have been deposited in the Cambridge Crystallographic Data Centre (deposition no. CCDC657980). Copies of these data can be obtained, free of charge on application to the CCDC via the Internet at www.ccdc.com.ac.uk/conts/retrieving.html.
6. Baraldi, P. G.; Preti, D.; Tabrizi, M. A.; Fruttarolo, F.; Romagnoli, R.; Zaid, N. A.; Moorman, A. R.; Merighi, S.; Stefania, V.; Katia, B.; Borea, P. A. *J. Med. Chem.* **2005**, *14*, 4607–4701.
7. Elimination is possible at the 6 or 8 position within the five membered ring.
8. For a base-mediated oxidation using molecular oxygen see the following: Tao, Z.-F.; Sowin, T. J.; Lin, N.-H. *Tetrahedron Lett.* **2005**, *46*, 7615–7618.
9. All THF utilized in the reactions contained 250 ppm BHT. Since the formation of **5** in either THF or DMF involves an oxidative pathway, we do not suspect that the presence of BHT plays any role in the divergent pathways depicted in Scheme 5. However, further studies are required.
10. This transformation was also attempted in other solvents such as ethanol and acetonitrile; however, none of these provided the same results. This is primarily due to the limited solubility of the starting material **1** in these solvents.
11. With the exception of Entry 4, Table 2.