Cyclodehydration of 5-[(Carboxymethyl)amino]pyrimidines. Synthesis and Characterization of Novel Mesoionic Imidazo[1,2-c]pyrimidin-3-ones

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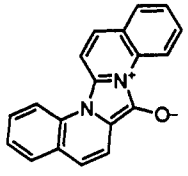
Received November 18, 1993•

The cyclodehydration of 5-(carboxymethyl)amino-substituted pyrimidines using acid anhydrides has provided a general synthesis of novel mesoionic imidazo[1,2-c]pyrimidin-3-one compounds. The complete structural characterization and chemical reactivity studies of these compounds, including X-ray crystal structures for compounds **9c** and **16a**, were determined. Compounds lacking a blocking group at N-1 were found to undergo clean alkylation at this position, under basic reaction conditions, with substituted alkyl chlorides. Imidazo[1,2-c]pyrimidin-3-ones having a benzyl group at N-1 were found to undergo substitution reactions on the pyrimidine ring in the presence of basic nucleophiles. Thus, replacement of a 5-methylthio over a 7-chloro substituent was favored, whereas the 7-chloro group was substituted in compounds where a 5-amino substituent was present. Exposure of imidazo-[1,2-c]pyrimidin-3-ones to aqueous acid results in the ring opening of the five-membered ring with subsequent loss of carbon dioxide or trifluoroacetate in an overall net reversion of the cyclodehydration reaction. Examination of the X-ray structures obtained for compounds **9c** and **16a** indicated that the five-membered ring was not aromatic, but rather a combination of a ring-opened valence tautomer and a charge-delocalized resonance hybrid structure.

Introduction

The occurrence of many heteroatomic variants of polycyclic mesoionic structures has been well established over the years.[1] Examples of mesoionic derivatives having an imidazole ring system fused to adjoining heterocyclic rings are much less common. Although the first polycyclic 1,3-diazol-4-one **1** was reported by Besthorn[2a] in 1904, it wasn't until later that Lawson and Miles[2b] characterized additional examples of ring-fused 1,3-diazol-4-ones, e.g., **2**. In these cases the imidazole ring was prepared by the anhydro-acylation of *N*-2-pyridylglycines and *N*-2-quinolylglycines using acid anhydrides. A limited number of reports involving the preparation of additional imidazole-based mesoionic like compounds have appeared over the past three decades.[3]



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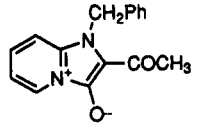

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In recent years it has been recognized that replacing the naturally occurring purine bases with isosteric purine-like systems provides new nucleotide analogues which offer much potential for use as agents in anticancer/antiviral chemotherapy, antisense oligonucleotides, and diagnostic tools.[4,5] Mesomeric and mesoionic nucleoside derivatives, which fit into this category, would be logical candidates for further biological evaluation. Mesomeric purine nucleosides were first characterized[6] as the product of guanosine methylation at N-7 and have been found to occur naturally in RNAs isolated from several sources.[7] Mesomeric betaines that mimic purine bases have received some attention in recent years,[8] however, the synthesis of mesoionic compounds which would fulfill this role have not been reported.

We have previously determined that heating of non-aromatic pyrimidine-2,4-diones in acetic anhydride cleanly affords the pyrrolo[2,3-d]pyrimidine-2,4-diones, i.e., **3** (eq 1).[9] Owing to the N-1 position being blocked by the benzyl group, ring closure is only possible at the electron-rich C-5 carbon. A similar mode of cyclization is observed for the vinylogous amide **4** leading to a tetrahydroindole (eq 2).[10]

In the next stage of development, we focused our attention to the cyclization of substrates, **5**, having an aromatic pyrimidine ring. In this case, cyclization can occur in either of two directions as depicted by the arrows

† Summer Undergraduate Participant, 1992.

• Abstract published in *Advance ACS Abstracts*, April 1, 1994.

(1) Ollis, D.; Ramsden, C. A. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Boulton, A. J., Eds.; Academic Press: New York, 1976; Vol. 19, p 3.

(2) (a) Besthorn, E.; Ibel, J. *Chem. Ber.* **1904**, *37*, 1236. (b) Lawson, A.; Miles, D. H. *J. Chem. Soc.* **1959**, 2865.

(3) (a) Roche, E. B.; Stansloski, D. W. *J. Heterocycl. Chem.* **1970**, *7*, 139. (b) Shiba, T.; Kato, H. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3941. (c) Potts, K. T.; Husain, S. *J. Org. Chem.* **1971**, *36*, 3368. (d) Steele, J. W.; Anderson, W. K.; Trager, W. F. *Can. J. Chem.* **1972**, *50*, 1026. (e) Singh, G.; Pande, P. S. *Tetrahedron Lett.* **1974**, *25*, 2169. (f) Hamaguchi, M.; Ibata, T. *Chem. Lett.* **1975**, 169.

(4) For reviews, see: (a) Hanessian, S.; Pernet, A. G. *Adv. Carbohydr. Chem.* **1976**, *33*, 111. (b) Postema, M. H. D. *Tetrahedron* **1992**, *48*, 8545.

(5) Wamhoff, H.; Berressem, R.; Nieger, M. *J. Org. Chem.* **1993**, *58*, 5181. Battacharya, B. K.; Lim, M. I.; Otter, B. A.; Klein, R. S. *Tetrahedron Lett.* **1986**, *27*, 815. Schneller, S. W.; Thompson, R. D.; Cory, J. G.; Olsson, R. A.; DeClercq, E.; Kim, I. K.; Chiang, P. K. *J. Med. Chem.* **1984**, *27*, 924. Girgis, N. S.; Michael, M. A.; Smee, D. F.; Alayhamandan, H. A.; Robins, R. K.; Cottam, H. B. *J. Med. Chem.* **1990**, *33*, 2750. Battacharya, B. K.; Otter, B. A.; Berens, R. L.; Klein, R. S. *Nucleosides Nucleotides* **1990**, *9*, 1021. Sanghvi, Y. S.; Larsson, S. B.; Smee, D. F.; Revankar, G. R.; Robins, R. K. *Nucleosides Nucleotides* **1991**, *10*, 1417.

(6) Jones, J. W.; Robins, R. K. *J. Am. Chem. Soc.* **1963**, *85*, 193.

(7) Dunn, D. B. *Biochem. J.* **1963**, *86*, 14p. Shugart, L.; Chastain, B. *Int. J. Biochem.* **1979**, *10*, 155.

(8) Coburn, R. A.; Glennon, R. A. *J. Heterocycl. Chem.* **1973**, *10*, 487. Glennon, R. A.; Rogers, M. E.; El-Said, K. *Ibid.* **1980**, *17*, 337. Glennon, R. A.; Schubert, E.; Bass, R. G. *Tetrahedron Lett.* **1981**, *22*, 2753.

(9) Edstrom, E. D.; Wei, Y. *J. Org. Chem.* **1993**, *58*, 403.

(10) For the first example of this type of pyrrole annulation to a six-membered ring enone, see: Friary, R. J.; Gilligan, J. M.; Szajewski, R. P.; Frank, R. W. *J. Org. Chem.* **1973**, *38*, 3487.

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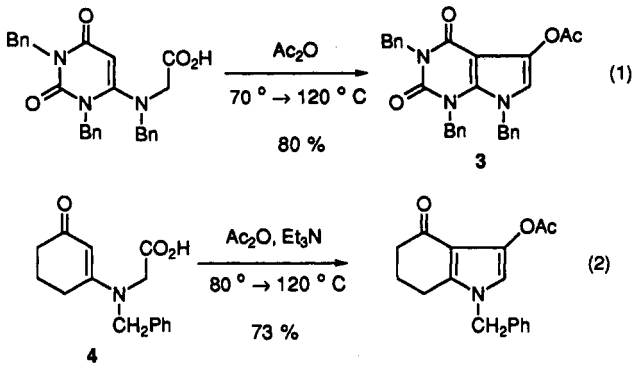
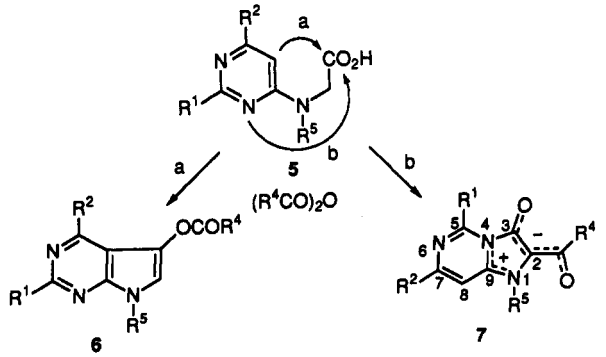


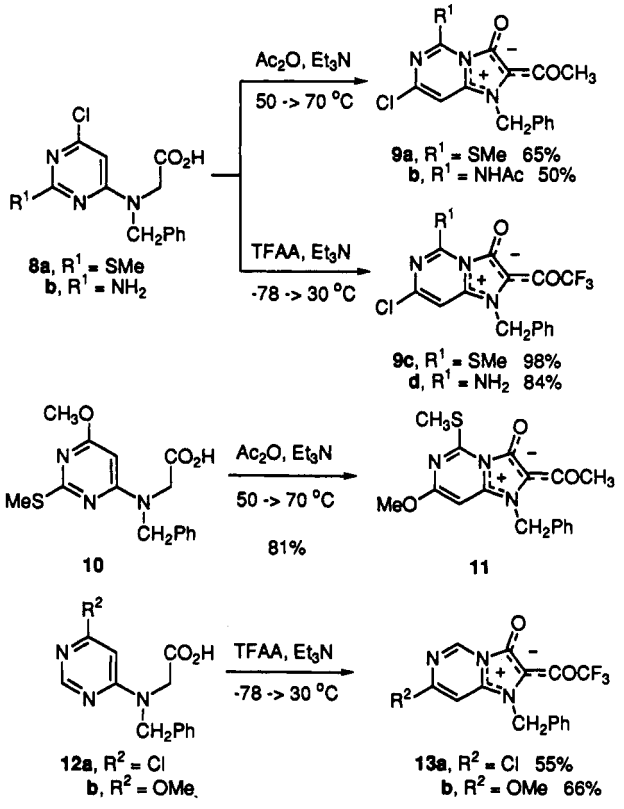
a and b, which leads to either pyrrolo[2,3-*d*]pyrimidines **6** or imidazo[1,2-*c*]pyrimidin-3-ones **7**,[11] respectively. We now disclose the full details regarding the synthesis, reactivity, and physical characterization of a novel class of mesoionic imidazo[1,2-*c*]pyrimidin-3-ones obtained through pathway b.



Results

Cyclization of substituted aromatic 5-[(carboxymethyl)-amino]pyrimidines **8a,b**, **10**, and **12a,b** occurred exclusively at the pyrimidine N-1 position to afford 2-acylimidazo-[1,2-*c*]pyrimidin-3-ones (Scheme 1). To obtain the required cyclization precursors, treatment of commercially available 4,6-dichloropyrimidines with sodium glycinate or *N*-benzylglycinate in refluxing ethanol affords the 6-amino substitution products **8a,b** and **12a** in generally high yield (67–92%). Upon exposure of **8a** to acetic anhydride with added base catalyst[12] and gentle heating, the 1-benzyl-5-(methylthio)-2-acetylimidazo[1,2-*c*]pyrimidin-3-one (**9a**) is obtained in good yield, whereas **8b** affords the 5-acetylamino system **9b** in a lower 50% yield. By replacing the 4-chloro substituent in **8b** with an electron-releasing substituent such as methoxy, the cyclization yield of **10** to **11** is noticeably improved. On the other hand, cyclization of the C-2 unsubstituted systems **12a,b** using acetic anhydride and base afforded low yields (<15%) of products. It was later discovered that more reactive anhydrides, i.e., trifluoroacetic or trichloroacetic

Scheme 1



anhydride,[13] effect cyclizations at lower temperatures and in improved yields. For example, using TFAA, 2-(trifluoroacetoxy)imidazo[1,2-*c*]pyrimidin-3-ones **9c,d** were provided in high yields. These reaction conditions allow the less reactive 2-unsubstituted systems **12a,b** to be cyclized to **13a,b** in reasonable yields.

The spectroscopic features for compound **9c** reveal the following key features. In the IR, two absorptions at 1719 and 1614 cm^{-1} were noted. By way of comparison, compound **9a** showed similar absorptions at 1703 and 1630 cm^{-1}. The ^1H NMR spectrum for **9c** revealed three singlets at 2.57, 5.64, and 6.76 ppm along with a 5H multiplet centered at 7.26 ppm. The ^{13}C spectra contained two C–F coupled carbons at 116.9 ppm (q), J = 288.6 Hz, and 166.9 ppm (q), J = 37.4 Hz. A single crystal of **9c** was analyzed by X-ray crystallography and generated the ORTEP diagram shown in Figure 1.[14,24] A list of selected bond distances is provided in Table 1.[15] All of the imidazo-[1,2-*c*]pyrimidin-3-ones obtained in this study had an intense yellow color and revealed long wavelength ab-

(11) All of the imidazo[1,2-*c*]pyrimidin-3-ones drawn are shown to reflect the most important resonance hybrid structure as determined by the X-ray structural analysis provided in the Discussion section. This is an effort to better reflect the actual structure for these compounds and does not imply aromatic character for the five-membered imidazole ring. Therefore, we do not use the preferred resonance hybrid structure for mesoionic compounds since it implies aromatic delocalization, or localized resonance structures, i.e., **1** and **2**, ref 1. See also, Discussion section.

(12) Other bases such as pyridine and collidine also improve cyclization yields and lower the temperature required for reaction. Triethylamine is preferred due its ease of removal by evaporation.

(13) With these anhydrides the cyclization reaction will proceed slowly at −78 °C as evidenced by the appearance of a deep yellow color characteristic of the product. The reaction of compound **8a** with trichloroacetic anhydride (−78 → 25 °C) affords a compound analogous to **9c** in 98% yield (experimental details not reported).

(14) X-ray crystal data for **9c**: $C_{16}H_{11}ClF_3N_3O_2S$, M_r = 401.8, yellow needle, crystal dimensions 0.10 × 0.15 × 0.55 mm, crystallized from ethyl acetate/hexanes; monoclinic, space group $C2/c$, a = 37.809(7) Å, b = 4.988-(2) Å, c = 18.233(4) Å, β = 96.62 (2)°, V = 3415.6(11) Å^3, Z = 8, d_{calc} = 1.563 g/cm^3, λ(Mo Kα) = 0.71073 Å, μ(Mo Kα) = 0.393 mm^{-1}, F(000) = 1632. A total of 5311 symmetry-independent reflections were measured on a Siemens P4/Series II diffractometer at 25 °C ($2\theta_{max}$ = 46°), scans, scan range (1.20° pulse Kα separation), 1388 reflections with $|F| > 3\sigma(F)$ used for structure solution (direct methods) and refinement (full-matrix least squares, 205 parameters), non-hydrogen atoms refined anisotropically, H atoms localized by difference electron density determination and localized by means of a "riding" model; R = 0.054 (R_w = 0.072; $w^{-1} = \sigma^2(F) + 0.0024F^2$), largest peak in final difference Fourier map 0.44 e$^-$ Å^{-3}. The structure was solved and refined with SHELXTL-Plus.

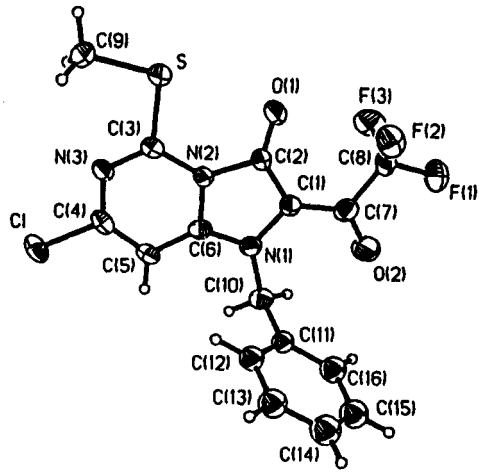
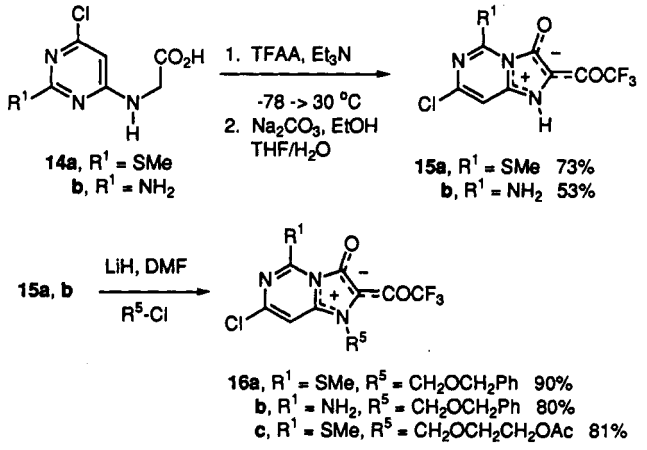


Figure 1. ORTEP plot and atom labeling of **9c** (50% probability thermal ellipsoids).

Table 1. Selected Bond Distances (Å) for 9c

O(1)–C(2)	1.219(8)	C(3)–N(3)	1.297(8)
O(2)–C(7)	1.222(9)	C(4)–N(3)	1.340(8)
C(1)–C(2)	1.408(8)	C(4)–C(5)	1.359(9)
C(1)–C(7)	1.413(9)	C(5)–C(6)	1.407(9)
C(1)–N(1)	1.422(8)	C(6)–N(1)	1.326(7)
C(2)–N(2)	1.457(8)	C(6)–N(2)	1.376(8)
C(3)–N(2)	1.397(7)	S–C(3)	1.729(6)

Scheme 2



sorption(s) in their UV–vis spectrum around 400 nm.[16] In the case of **9c**, major bands at λ_{max} of 466, 420, 330, and 292 nm were recorded.

For the purpose of subsequent alkylation at N-1, the unprotected 6-[(carboxymethyl)amino]pyrimidines **14a,b** were cyclized using the more reactive mixed trifluoroacetic anhydride intermediates (Scheme 2). Respectable yields of 2-(trifluoroacetyl)imidazo[1,2-c]pyrimidin-3-ones **15a,b** having a free imidazole nitrogen were isolated. A mild base treatment was required in order to cleave an additional trifluoroacetate residue which was attached at N-1. The applicability of these derivatives as possible nucleoside analogues was demonstrated by representative alkylations of the anions derived from **15a** and **15b** using benzyloxymethyl chloride or (2-acetoxyethoxy)methyl

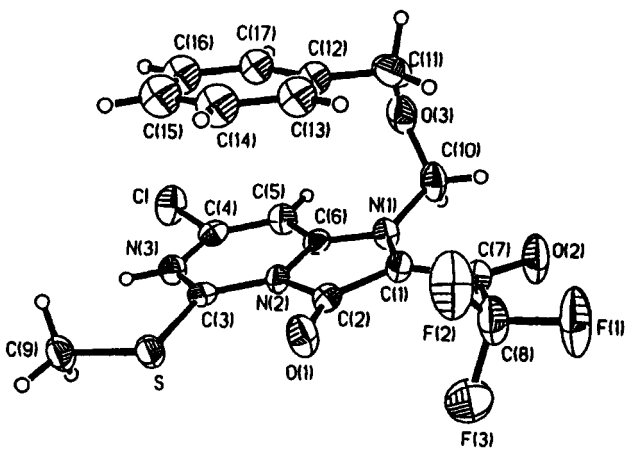


Figure 2. ORTEP plot and atom labeling of **16a** (50% probability thermal ellipsoids).

chloride[17] as electrophiles. High yields of N-1 alkylated products **16a–c** were obtained as the exclusive products. A single crystal of compound **16a** was analyzed by X-ray crystallography, the results of which are shown in Figure 2.[18,24]

Substitution Reactions. A study on the substitution chemistry of imidazo[1,2-c]pyrimidin-3-one ring systems **9a,b,d**, **11**, and **15a** was undertaken (Scheme 3). With the N-1 benzyl group in place, the 2-(methylthio)imidazo[1,2-c]pyrimidin-3-one **9a** underwent nucleophilic attack at C-5 with ammonia or methoxide ion and resulted in high yields of substitution products **17a,b**. The related 7-methoxy-substituted imidazo[1,2-c]pyrimidin-3-one **11** reacted in a similar manner by substitution of the 2-methylthio group to afford **18a,b**. The 5-amino systems **9b** and **9d** reacted with methanol and base to afford 7-methoxyimidazo[1,2-c]pyrimidin-3-ones **18a** and **19** resulting from displacement of the C-7 chloro substituent. It should be noted that prolonged exposure of **17a,b**, **18a,b**, and **19** under basic reactions conditions results in the loss of the yellow color diagnostic of their fused-ring systems and the production of polar by products which were not further characterized. The methoxy substituent in compound **11** could be readily cleaved to the 7-hydroxyimidazo[1,2-c]-pyrimidin-3-one **20** using iodotrimethylsilane.

In contrast to their N-1 benzyl counterparts, the reaction of the free imidazoles **15a,b** with these nucleophiles was very sluggish. Under more vigorous reaction conditions, involving heating at higher temperatures for extended periods, either low yields of impure substitution products or multicomponent mixtures were obtained. For example, the reaction of **15a** with sodium methoxide under reflux afforded a low yield of product resulting from displacement of the 2-methylthio group.

(15) The atom numbering scheme for the X-ray structures shown for compounds **9c** and **16a** is different that the numbering scheme used to assign the chemical names for these compounds. The correct chemical numbering scheme is shown for the general structure **7** and is used throughout the text except for discussions concerning the X-ray structures.

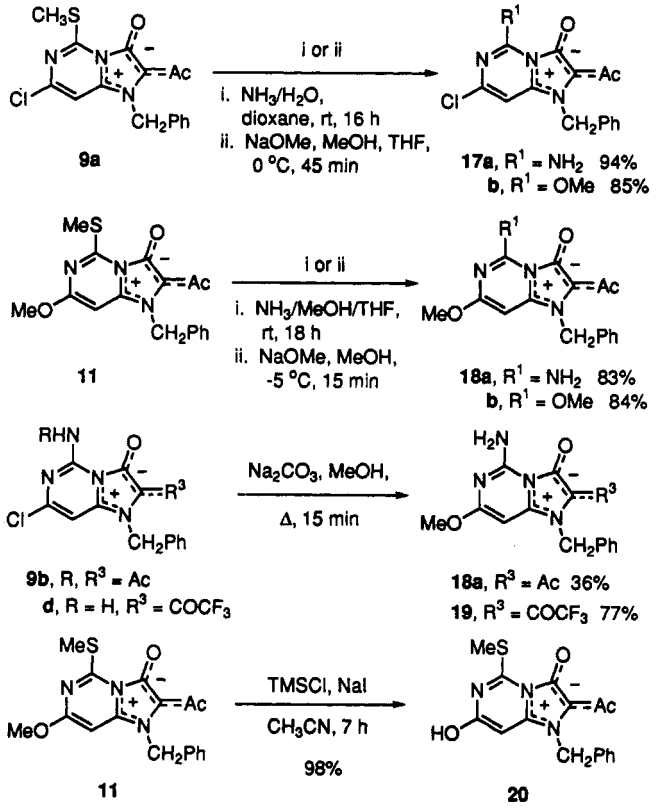
(16) The intense yellow color and a visible absorption around 400 nm is a characteristic feature of 1,3-diazol-4-one inner salts, ref 3.

(17) Robins, M. J.; Hatfield, P. W. *Can. J. Chem.* **1982**, *60*, 547.

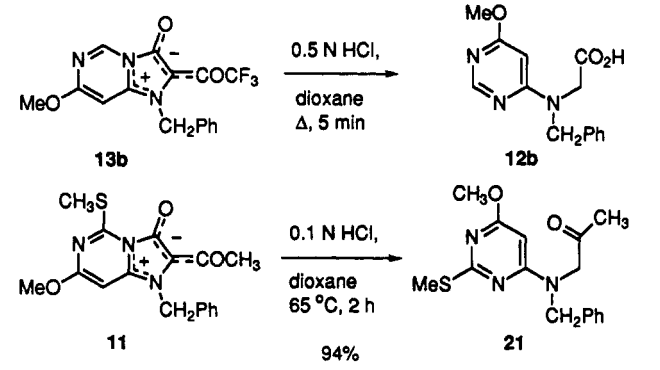
(18) X-ray crystal data for **16a**: $C_{17}H_{13}ClF_3N_3O_3S$, M_r = 431.8, yellow plate, crystal dimensions 0.15 × 0.30 × 0.60 mm, crystallized from ethyl acetate/hexanes; monoclinic, space group $P2_1/c$, a = 7.260(2) Å, b = 19.237(4) Å, c = 13.295(2) Å, β = 101.0(2)°, V = 1822.6(5) Å^3, Z = 4, d_{calc} = 1.550 g/cm^3, λ(Mo Kα) = 0.71073 Å, μ(Mo Kα) = 0.378 mm^{-1}, F(000) = 880. A total of 2765 symmetry-independent reflections were measured on a Siemens P4/Series II diffractometer at 25 °C ($2\theta_{max}$ = 46°), scans, scan range (1.20° plus Kα separation), 1619 reflections with $|F| > 3\sigma(F)$ used for structure solution (direct methods) and refinement (full-matrix least squares, 223 parameters), non-hydrogen atoms refined anisotropically, H atoms localized by difference electron density determination and localized by means of a "riding" model; R = 0.0635 (R_w = 0.0499, $w^{-1} = \sigma^2(F) + 0.0002F^2$), largest peak in final difference Fourier map 0.77 e$^-$ Å^{-3}. The structure was solved and refined with SHELXTL-Plus.

(19) Talukdar, P. B.; Sengupta, S. K.; Datta, A. K. *Ind. J. Chem.* **1984**, *23B*, 316; **1983**, *22B*, 2430; **1981**, *20B*, 538.

Scheme 3



Scheme 4



The reactivity of representative imidazo[1,2-*c*]pyrimidin-3-ones under aqueous acidic conditions was determined (Scheme 4). Whereas the imidazo[1,2-*c*]pyrimidin-3-one products reported in Scheme 3 were found to be stable for short periods of time in basic media, treatment of **13b** with refluxing aqueous acid resulted in immediate loss of color from the yellow reaction solution and the isolation of ring-opened cyclization precursor **12b**, as determined by comparison with an authentic sample. Similar behavior was also observed for other compounds in this series having a trifluoroacetyl substituent at C-2. On the other hand, the C-2 acetyl substituted system **11** cleanly affords the ring-opened methyl ketone **21**.

Discussion

In general, the anhydro-acylation of aromatic 5-[(carboxymethyl)amino]pyrimidines affords bicyclic imidazo-[1,2-*c*]pyrimidin-3-ones resulting from exclusive attack at the N-1 position of the pyrimidine ring. No evidence for attack at the potentially nucleophilic C-5 position leading to pyrrolo[2,3-*d*]pyrimidines was observed. This preferred reaction pathway is not surprising when compared with the cyclodehydration of 2-(carboxymethyl)-thio ring fused pyrimidone derivatives where N-1 of the pyrimidine ring is attacked by a mixed anhydride intermediate.[18] Competition between cyclo-acylation on carbon versus nitrogen in *N*-2-pyridylglycines results in exclusive attack on the pyridine nitrogen atom to afford mesoionic products.[2b] Our results present the first cases were a potential competition between two cyclization directions is possible on a pyrimidine ring. The more electron rich substrates **10** and **12b** are seen to facilitate the cyclization at N-1.

A mechanistic rational accounting for the formation of the observed imidazo[1,2-*c*]pyrimidin-3-one ring systems having either an acetyl or trifluoroacetyl group at C-2 can be explained by analogy to related anhydro-acylation reactions reported in previous studies.[2b,3a,c] Thus, initial formation of a mixed anhydride intermediate and then cyclization would likely produce the 3-keto salt which undergoes rapid proton loss to form a C-2 unsubstituted intermediate. This species would then undergo rapid acylation at C-2 followed by proton loss to afford the isolated products. Attempts by other workers[3a] to isolate simple C-2 unsubstituted 1,3-diazol-4-ones proved futile, suggesting that an electron-withdrawing acyl group or a phenyl ring at this position is required to stabilize the five-membered ring. In an attempt to look for a C-2 unsubstituted species in solution, **8a** was exposed to 1.0 equiv of TFAA at −78 °C in $CDCl_3$. After 5 min an aliquot was removed, warmed to ambient temperature,[20] and examined by ^1H NMR. The spectrum revealed the presence of **9c** along with several signals belonging to at least two species which could not be readily assigned. Addition of more TFAA in 0.25-equiv portions afforded spectra containing greater amounts of **9c** until a completely clean spectra of **9c** was obtained after the addition of a total of 2.0 equiv of reagent.

Although mesoionic heterocycles are well-characterized species, examples of structures having the five-membered ring fused to an adjacent six-membered ring are much less common. To our knowledge the imidazo[1,2-*c*]pyrimidin-3-ones represented by **9a–d**, **11**, **13a,b**, **15a,b**, and **16a,b** are new examples of bicyclic type A[1] mesoionic-like structures. Their structural assignments were confirmed by comparisons with the X-ray crystal structures obtained for compounds **9c** and **16a**.

Inspection of the geometry and bonding in the structure for **9c** in regard to the aromatic character of such a system deserves comment. It was noticed that certain bond lengths and angles about the five-membered ring in **9c** were very close to those reported for the structures of 3-substituted 1,2,3-oxadiazol-5-ones (syndones).[21] Thus, bond angles for C(1)–C(2)–O(1) of 135.3° and N(2)–C(2)–O(1) of 121.4° coupled with the N(2)–C(2) bond length of 1.457 Å (nearly that of a C–N single bond at 1.47 Å) and the short C(2)–O(1) bond of 1.219 Å (comparable to a typical C=O double bond of 1.20 Å) suggested a significant contribution from the ring-opened ketene-like valence tautomer **A** as a canonical form to the overall structure

(20) Upon warming to room temperature, the yellow color indicative of **9c** appeared.

(21) Thiessen, W. E.; Hope, H. *J. Am. Chem. Soc.* **1967**, *89*, 5977. In comparison, the syndone ring in this paper had a CCO_{exo} bond angle of 135.5° and a OCO_{exo} bond angle of 121.2°. The exo C–O bond was 1.215 Å and the related endo C–O bond was 1.407 Å, close to a typical C–O single bond of 1.43 Å.

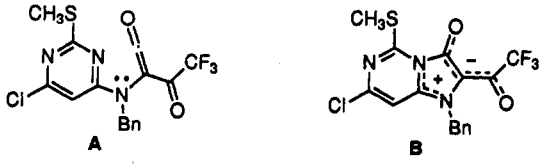


Figure 3. Major valence tautomer and resonance forms for structure **9c**.

of **9c** (Figure 3). The most important resonance contributors for **9c** can be best represented by the resonance hybrid shown in structure **B**. This conclusion is supported by noting the following bond lengths. The C-2 to O-1 bond distance of 1.219 Å was nearly identical with the C-7 to O-2 bond distance of 1.222 Å along with the C(2)–C(1) bond of 1.408 Å being nearly the same as the C(1)–C(7) bond of 1.413 Å. Also, the single C–O absorption in the IR centered at 1719 cm^{-1} can be assigned to the C(2)–O(1) and C(7)–O(2) stretching bands. This suggests a high degree of charge delocalization of the unit negative charge in **B** from O(1) through O(2) and is further supported by the coplanar arrangement of the atoms from O(1) through O(2). The N(1)–C(6) bond at 1.326 Å has much more double-bond character than the N(1)–C(1) bond at 1.422 Å and compares with the slightly longer N(2)–C(6) bond at 1.376 Å. The localization of bonds from C(3) through C(5) is indicated by the high degree of double-bond character in C(3)–N(3) (1.297 Å) and C(4)–C(5) (1.359 Å) versus the greater portion of singlehbond character in bonds N(2)–C(3) (1.397 Å), N(3)–C(4) (1.340 Å), and C(5)–C(6) (1.407 Å).

The structural features of **16a** were nearly identical with the structure obtained for **9c** in regard to the imidazo-[1,2-c]pyrimidin-3-one ring portion, i.e., the C-7 carbonyl group is coplaner and oriented anti to the C-2 oxy group. A key feature in the structure for **16a** shows the phenyl ring from the benzyloxymethyl substituent oriented over the plane of the imidazo[1,2-c]pyrimidin-3-one ring system, which can be attributed to favorable π-stacking.

From the structural analysis for **9c** and **16a**, the question of the mesoionic versus aromatic description of these systems comes into question. Based on the arguments forwarded in the case of syndone structures,[21] it can be said that the compounds described in this study do not have an aromatic five-membered ring but rather possess structures which are a combination of the valence tautomer **A** and the resonance hybrid **B** as shown in Figure 3. On the other hand, it is appropriate to consider these compounds as mesoionic since they are five-membered ring heterocycles with a sextet of electrons which can be correctly represented by more than one covalent structure.[1]

Representative alkylations of the conjugate bases derived from unprotected imidazo[1,2-c]pyrimidin-3-ones **15a,b** allow ready access to N-1 alkyl substituted compounds. By choice of the appropriate acyclic carbohydrate mimic, ribosyl, or 2-deoxyribosyl derivative, a new class of 5-aza-3,7-dideaza-3-oxypurine nucleoside analogues are available.[22]

The reaction of imidazo[1,2-c]pyrimidin-3-ones with nucleophiles demonstrated that, in order to obtain clean substitution on the pyrimidine ring at C-5 or C-7, an alkyl group attached to N-1 of the parent imidazo[1,2-c]-pyrimidin-3-one is required. The unsubstituted systems having a free NH react sluggishly with basic nucleophiles, most likely due to the deprotonation at N-1 under the reaction conditions. The conjugate bases derived from **15a,b** would predictably exhibit diminished reactivity with nucleophiles.[23]

It was reported that other imidazo[3,2-a]pyridines are quite stable and unreactive toward aqueous acid, aqueous alkali, and amines.[2b] In contrast, our systems are more sensitive to these reaction conditions. In general, heating of imidazo[1,2-c]pyrimidin-3-ones in aqueous HCl results in opening of the imidazole ring (Scheme 4). In the case of the intermediate β-trifluoroacetyl carboxylic acids derived from 2-(trifluoroacetyl)imidazo[1,2-c]pyrimidin-3-ones, water attacks at the more electron deficient trifluoroacetyl group, which is then lost through subsequent cleavage in an overall reversion of the anhydro-acylation reaction. The (carboxymethyl)amino cyclization precursors are obtained as a result. In contrast, the favored reaction pathway with ring-opened β-acetyl carboxylic acid intermediates is decarboxylation and methyl ketones are isolated as a result. This reaction process can be reviewed as an overall acylation–decarboxylation of *N*-pyrimidinyl amino acids via the intermediacy of imidazo[1,2-c]-pyrimidines. By variation of the acid anhydride, different acyl groups can, in principle, be substituted for the carboxylate group.

The characterization and chemical reactivity of a series of novel imidazo[1,2-c]pyrimidin-3-ones is provided. Compounds lacking a blocking group at N-1 were found to undergo clean alkylation at this position, under basic reaction conditions, with substituted alkyl halides. Compound **16c** can be viewed as a structural analog of the known antiviral agent acyclovir in which the guanine base portion is replaced with an unusual 5-aza-3,7-dideaza-3-oxypurine residue. The synthesis of novel mesoionic nucleoside analogues containing various acyclic carbohydrate mimics and ribosyl groups, and the biological properties of these compounds as potential diagnostic tools and/or antiviral agents, will be pursued in due course.

Experimental Section

General. The following solvents and reagents were distilled from calcium hydride under a nitrogen atmosphere: dichloromethane, acetonitrile, triethylamine, tripropylamine, and chlorotrimethylsilane. THF was distilled from potassium under a nitrogen atmosphere. DMF (0.034% of water) was purchased from EM Industries, Inc., and used without further purification. Melting points were recorded on a Thomas-Hoover apparatus and are uncorrected. IR spectra were determined with an FTIR instrument. ^1H NMR spectra were recorded at 270 or 300 MHz with tetramethylsilane or DMSO (δ 2.49) used as the internal reference. ^{13}C NMR were recorded at 67.9 MHz; $CDCl_3$ (δ 77.0) or DMSO (δ 39.5) was used as the internal reference. Elemental analyses were performed by Atlantic Microlab, Inc. Mass spectra were recorded in the electron impact mode using a potential of 70 eV. Column chromatography was performed with silica gel

(22) For example, we have also prepared the N-1,2′-deoxy-3′,5′-di-*O*-*p*-toluoyl-D-ribosyl (α:β, 1:3), and (1,3-bis(benzyloxy)-2-propoxy)methyl derivatives of **15a** and **15b**. Kazimierczuk, K.; Cottam, H. B.; Revankar, G. R.; Robins, R. K. *J. Am. Chem. Soc.* **1984**, *106*, 6379. Martin, J. C.; Dvorak, C. A.; Smee, D. F.; Matthews, T. R.; Verheyden, J. P. H. *J. Med. Chem.* **1983**, *26*, 759. These results will be reported in due course.

(23) Similar results were observed for the reaction of 4,6-dichloro-1*H*-pyrrolo[3,2-c]pyrimidine with ammonia in methanol. Schneller, S. W.; Hosmane, R. S. *J. Heterocycl. Chem.* **1978**, *15*, 325.

(24) The authors have deposited atomic coordinates for structures **9c** and **16a** with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(Merck 60 Å, 230–400 mesh). The final product solution were dried over Na_2SO_4 and concentrated on a rotary evaporator.

6-[*N*-Benzyl-*N*-(carboxymethyl)amino]-4-chloro-2-(methylthio)pyrimidine (8a). A mixture of 4,6-dichloro-2-(methylthio)pyrimidine (10.00 g, 51.28 mmol) and sodium *N*-benzylglycinate (14.38 g, 76.90 mmol) in 100 mL of 80% EtOH was refluxed for 1 h. $NaHCO_3$ (5.00 g, 59.52 mmol) was added in portions. The resulting mixture was refluxed for 4 h. The reaction was monitored by TLC until all the starting material had been consumed. The mixture was cooled to room temperature and concentrated under reduced pressure. The residue was dissolved in 150 mL of water, washed with CH_2Cl_2 (50 mL), acidified with concentrated HCl to pH 2–3, and extracted with EtOAc (200 mL). The organic layer was dried and concentrated to afford 16.1 g (96.9%) of **8a** as a white solid (this material was used in the next step without further purification): mp 176 °C dec; IR (KBr) 3090, 1708, 1589, 1557, 1539 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.20 (5 H, m), 6.23 (1 H, br s), 4.68 (2 H, br s), 4.28 (2 H, br s), 2.47 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 174.8, 172.1, 162.5, 159.9, 135.2, 129.1, 128.1, 126.9, 97.2, 52.8, 49.4, 14.1; HRMS calcd for $C_{14}H_{14}ClN_3O_2S$ 323.0495, found 323.0521.

2-Amino-6-[*N*-benzyl-*N*-(carboxymethyl)amino]-4-chloropyrimidine (8b). A mixture of 2-amino-4,6-dichloropyrimidine (0.70 g, 4.27 mmol) and sodium *N*-benzylglycinate (1.00 g, 5.35 mmol) in 15 mL of 66% EtOH was refluxed for 1 h. $Na_2CO_3·H_2O$ (0.53 g, 4.27 mmol) was added. The resulting mixture was refluxed for 3 h and then cooled to room temperature. The solvent was removed under reduced pressure. The residue was treated with 70 mL of water and extracted with $CHCl_3$ (50 mL). The aqueous layer was acidified with concentrated HCl to pH 3 and was extracted with EtOAc (150 mL). The organic layer was dried and concentrated to afford 1.07 g (85.5%) of **8b** as light yellow powder (this material was used for the next reaction without further purification): mp 172–173 °C; IR (KBr) 3483, 3337, 3131, 1736, 1699, 1631, 1597, 1543, 1507 cm^{-1}; ^1H (DMSO, 270 MHz) δ 7.32–7.22 (5 H, m), 6.55 (2 H, s), 5.89 (2 H, s), 4.60 (2 H, br s), 4.28 (2 H, br s); ^{13}C NMR (DMSO, 67.9 MHz) δ 171.0, 163.4, 162.4, 159.1, 137.5, 128.5, 127.1, 126.8, 90.8, 52.1, 49.0; HRMS calcd for $C_{13}H_{13}ClN_4O_2$ 292.0727, found 292.0729.

6-[*N*-Benzyl-*N*-(carboxymethyl)amino]-4-methoxy-2-(methylthio)pyrimidine (10). Compound **8a** (3.00 g, 9.26 mmol) was dissolved in 30 mL of MeOH to which sodium metal (0.75 g, 32.61 mmol) had previously been added. The mixture was heated in a sealed vessel at 120 °C for 3.5 h. After the solution was cooled to room temperature, the solvent was removed under reduced pressure. The residue was treated with 50 mL of water, acidified with concentrated HCl to pH 3, and extracted with EtOAc (200 mL). The organic layer was dried and concentration gave 2.80 g (95%) of **10** as white solid (this material was used for the next step reaction without further purification): mp 167–168 °C; IR (KBr) 3118, 1728, 1576, 1548 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.20 (5 H, m), 5.54 (1 H, s), 4.66 (2 H, s), 4.27 (2 H, s), 3.88 (3 H, s), 2.48 (3 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 171.2, 169.4, 169.3, 137.6, 128.5, 127.1, 127.0, 81.1, 53.4, 52.6, 50.2, 13.3; HRMS calcd for $C_{15}H_{17}N_3O_3S$ 319.0991, found 319.0953.

6-[*N*-Benzyl-*N*-(carboxymethyl)amino]-4-chloropyrimidine (12a). A mixture of 4,6-dichloropyrimidine (2.00 g, 13.42 mmol) and sodium *N*-benzylglycinate (3.86 g, 20.64 mmol) in 80% EtOH was refluxed overnight. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was treated with 50 mL of 3% NaOH and extracted with $CHCl_3$ (30 mL). The aqueous layer was acidified to pH 3 and extracted with EtOAc (100 mL). The organic layer was dried and concentrated to afford 3.70 g (99.2%) of **12a** as white solid (this material was used for next step reaction without further purification): mp 161 °C dec; IR (KBr) 3115, 1714, 1592, 1537 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.47 (1 H, s), 7.38–7.21 (5 H, m), 6.53 (1 H, s), 4.72 (2 H, br s), 4.35 (2 H, br s); ^{13}C NMR (DMSO, 67.9 MHz) δ 170.4, 162.7, 158.8, 157.8, 136.5, 128.6, 127.3, 126.9, 101.9, 52.2, 49.9; HRMS calcd for $C_{13}H_{12}ClN_3O_2$ 277.0618, found 277.0593.

6-[*N*-Benzyl-*N*-(carboxymethyl)amino]-4-methoxypyrimidine (12b). A mixture of **12a** (350 mg, 1.26 mmol) and NaOMe (525 mg, 9.72 mmol) in 7 mL of anhydrous MeOH was refluxed for 24 h. The mixture was cooled to room temperature and the solvent was removed under reduced pressure. The residue was treated with 20 mL of water, acidified with concentrated HCl to pH 3, and extracted with EtOAc (100 mL). The organic layer was dried and concentrated to provide 325 mg (94.6%) of **12b** as a viscous oil which solidified on standing at room temperature (this material was used for the following step reaction without further purification): mp 120–122 °C; IR (KBr) 3117, 1728, 1614, 1546, 1508 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 8.38 (1 H, s), 7.34–7.20 (5 H, m), 5.82 (1 H, s), 4.68 (2 H, s), 4.31 (2 H, s), 3.88 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 173.8, 170.1, 163.7, 157.0, 136.1, 128.8, 127.6, 126.9, 85.6, 54.0, 52.8, 49.7; HRMS calcd for $C_{14}H_{15}N_3O_3$ 273.1113, found 273.1081.

6-[*N*-(Carboxymethyl)amino]-4-chloro-2-(methylthio)pyrimidine (14a). A mixture of glycine (1.16 g, 15.38 mmol) and NaOH (0.62 g, 15.38 mmol) in 5 mL of water was stirred for 5 min. To this solution was added 4,6-dichloro-2-(methylthio)-pyrimidine (2.00 g, 10.27 mmol) dissolved in 15 mL of ethanol. The reaction mixture was refluxed for 4 h. The progress of the reaction was monitored by TLC until all the starting material had been consumed. The mixture was cooled to room temperature and treated with 25 mL of water. The solution was acidified with concentrated HCl to pH 3 and extracted with EtOAc (2 × 40 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to provide 2.20 g (92%) of **14a** as white solid (this material was used for the next step reaction without further purification): mp 172–173 °C; IR (KBr) 3382, 3139, 1575, 1488, 1446, 1266, 1211 cm^{-1}; ^1H NMR (DMSO, 300 MHz) δ 8.09 (1 H, br), 6.36 (1 H, s), 4.01 (2 H, d, J = 5.6 Hz), 2.39 (3 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 171.3, 170.2, 162.5, 156.8, 99.4, 42.2, 13.4; HRMS calcd for $C_7H_8ClN_3O_2S$ 233.0026, found 233.0026.

2-Amino-6-[*N*-(carboxymethyl)amino]-4-chloropyrimidine (14b). A mixture of sodium glycinate (1.45 g, 8.79 mmol), 1-amino-4,6-dichloropyrimidine (1.28 g, 13.20 mmol), and $Na_2CO_3·H_2O$ (1.09 g, 8.79 mmol) in 15 mL of 67% ethanol was refluxed for 6 h. The reaction mixture was cooled to room temperature and treated with 50 mL of water. The solution was extracted with 50 mL of EtOAc–hexanes (1:1). The aqueous layer was acidified with concentrated HCl to pH 3. The solid was collected by filtration, washed with water, and dried to give 1.55 g (86.9%) of **14b** as light yellow powder (this material was used for the next reaction without further purification): mp 214–215 °C; IR (KBr) 3329, 3152, 2667, 2589, 2402, 1280 cm^{-1}; ^1H NMR (DMSO, 300 MHz) δ 7.43 (1 H, d, J = 4.8 Hz); 6.45 (2 H, s), 5.84 (1 H, s), 3.94 (2 H, d, J = 4.8 Hz); ^{13}C NMR (DMSO, 67.9 MHz) δ 171.8, 164.1, 162.8, 157.5, 93.0, 41.7; HMRS calcd for $C_6H_7ClN_4O_2$ 202.0258, found 202.0251.

General Procedure for Cyclodehydrations in Acetic Anhydride. A mixture of the [(carboxymethyl)amino]pyrimidine (4–10 mmol) and triethylamine (4 equiv) in 20 mL of acetic anhydride was stirred at room temperature for 45 min under N_2 and then at 50 °C for 10 min. The reaction mixture was cooled to 0 °C with an ice bath. The precipitate which had formed was collected by filtration, washed with 10 mL of EtOAc/hexanes (1:4), and dried in vacuo to furnish the product as a yellow solid. The product purity, as determined by TLC and ^1H NMR analysis, was above 95% and sufficient for further use. An additional portion of product was obtained by concentration of the filtrate and then flash chromatography of the resulting residue (solvents specified for each case). Analytical samples were obtained by recrystallization from EtOAc/hexanes.

2-Acetyl-1-benzyl-7-chloro-5-(methylthio)imidazo[1,2-*c*]-pyrimidin-3-one (9a). Starting with **8a** (2.00 g, 6.17 mmol), 1.13 g of **9a** was collected by filtration. An additional 265 mg of product (total yield 65.0%) was obtained from the filtrate using $CHCl_3$ and then $CHCl_3$/EtOAc (3:7) as chromatography solvents. For **9a**, as orange yellow crystals: mp 233 °C dec; IR (KBr) 1686, 1672, 1610, 1521 cm^{-1}; UV ($CHCl_2$) λ_{max} (ε) 468 (6060, shoulder to 438), 438 (9930), 424 (9940), 340 (6890), 284 (20 340); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.16 (5 H, m), 6.72 (1 H, s), 5.76 (2 H, S), 2.58 (3 H, s), 2.54 (3 H, s); ^{13}C NMR ($CDCl_3$, 69.7 MHz) δ 186.6, 160.3, 154.3, 151.7, 136.5, 134.7, 129.0, 128.3, 126.9, 105.3, 97.6, 48.9, 28.4, 143. Anal. Calcd for $C_{16}H_{14}ClN_3O_3S$: C, 55.25; H, 4.06; N, 12.18. Found: C, 55.35; H, 4.03; N, 12.14.

2-Acetyl-5-(acetylamino)-1-benzyl-7-chloroimidazo[1,2-*c*]-pyrimidin-3-one (9b). Starting with **8b** (2.00 g, 6.83 mmol), 1.04 g of **9b** was collected by filtration. An additional 180 mg of

product (total yield 50%) was obtained from the filtrate using EtOAc/hexanes (3:2) as the chromatography solvent. For **9b**, as yellow crystals: mp 244–245 °C; IR (KBr) 3106, 1738, 1684, 1624, 1559, 1517 cm^{-1}; UV λ_{max} (ϵ) 406 (11 920), 330 (5860), 268 (15 810); ^1H NMR ($CDCl_3$, 300 MHz) δ 12.57 (1 H, br s), 7.38–7.18 (5 H, m), 6.73 (1 H, s), 5.75 (2 H, s), 2.53 (3 H, s), 2.48 (3 H, s); ^{13}C NMR ($CDCl_3$, 69.7 MHz) δ 186.8, 168.2, 155.0, 153.2, 145.1, 136.9, 134.4, 129.1, 128.5, 126.9, 105.6, 96.6, 48.8, 28.6. 26.2. Anal. Calcd for $C_{17}H_{15}ClN_4O_3$: C, 56.91; H, 4.21; N, 15.62. Found: C, 57.00; H, 4.16; N, 15.69.

2-Acetyl-1-benzyl-7-methoxy-5-(methylthio)imidazo[1,2-c]pyrimidin-3-one (11). Starting with **10** (1.50 g, 4.67 mmol), 1.20 g of **11** was collected by filtration. An additional 110 mg of product (total yield 81%) was obtained from the filtrate using EtOAc/hexanes (1:1) as the chromatography solvent. For **11**, as yellow crystals: mp 207–208 °C; IR (KBr) 3090, 1703, 1630, 1577, 1548, 1495, 1263 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ϵ) 410 (6070), 330 (5580), 274 (10 380); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.19 (5 H, m), 5.88 (1 H, s), 5.69 (2 H, s), 4.00 (3 H, s), 2.58 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 185.7, 164.5, 160.5, 154.8, 140.6, 135.5, 128.8, 128.0, 127.0, 104.5, 78.6, 55.3, 48.4, 28.6, 14.1. Anal. Calcd for $C_{17}H_{17}N_3O_3S$: C, 59.46; H, 4.99; N, 12.24. Found: C, 59.32; H, 4.97; N, 12.17.

General Procedure for Cyclodehydrations in Trifluoroacetic Anhydride. A mixture of the [(carboxymethyl)amino]-pyrimidine (0.4–3 mmol) and trifluoroacetic anhydride (3.0 equiv) in 3.5–20 mL of CH_2Cl_2 was stirred at −78 °C for 5 min under N_2. Triethylamine (3.0 equiv) was added, and the mixture was stirred for 10 min and then allowed to warm to room temperature. After 20 min, the mixture was diluted with 50 mL of CH_2Cl_2, washed with water (50 mL) and brine (50 mL), dried, and then concentrated. Flash chromatography of residue using a EtOAc/hexanes mixture as the eluent afforded the purified product as a yellow solid. Analytical samples were obtained by recrystallization from EtOAc/hexanes.

1-Benzyl-7-chloro-5-(methylthio)-2-(trifluoroacetyl)imidazo[1,2-c]pyrimidin-3-one (9c). The reaction was run using **8a** (1.00 g, 3.09 mmol). The crude product was purified using EtOA/hexanes (1:1) as the chromatography solvent and afforded 1.22 g (98.3%) of **9c**. For **9c**, as yellow needles: mp 221–222 °C; IR (thin film) 1719, 1614, 1522 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ϵ) 466 (7620, shoulder to 438), 438 (13 550, shoulder to 420), 420 (14 120), 330 (7550), 292 (16 380); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.18 (5 H, m), 6.76 (1 H, s), 5.66 (2 H, s), 2.70 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 166.9 (q, J = 37.4 Hz), 161.4, 154.5, 153.2, 140.3, 129.2, 128.6, 126.8, 116.9 (q, J = 288.6 Hz), 102.3, 97.5, 49.2, 14.4. Anal. Calcd for $C_{16}H_{11}ClF_3N_3O_2S$: C, 47.83; H, 2.76; N, 10.46. Found: C, 47.94; H, 2.72; N, 10.45.

5-Amino-1-benzyl-7-chloro-2-(trifluoroacetyl)imidazo[1,2-c]pyrimidin-3-one (9d). The reaction was run using **8b** (100 mg, 0.34 mmol). The crude product was purified using EtOAc/hexanes (1.0:1.86) as the chromatography solvent and afforded 109 mg (84.5%) of **9d** as yellow solid. For **9d**, as yellow needles: mp 237 °C dec; IR (KBr) 3358, 3171, 1662, 1599, 1529, 1153 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ϵ) 424 (11 000, shoulder to 404), 402 (17 340), 386 (15 190, shoulder to 402), 290 (4930, shoulder to 274, 274 (7860); ^1H NMR (DMSO, 270 MHz) δ 9.23 (1 H, s), 8.83 (1 H, s), 7.35–7.21 (5 H, m), 7.05 (1 H, s), 5.53 (2 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 156.7, 155.2, 150.7, 143.4, 135.8, 128.5, 127.5, 126.7, 119.4, 115.2, 101.9, 90.5, 47.8. Anal. Calcd for $C_{16}H_{12}ClF_3N_4O_3$: C, 48.60; H, 2.72; N, 15.11. Found: C, 48.57; H, 2.76; N, 15.18.

1-Benzyl-7-chloro-2-(trifluoroacetyl)imidazo[1,2-c]pyrimidin-3-one (13a). The reaction was run using **12a** (0.50 g, 1.80 mmol). The crude product was purified using EtOAc/hexanes (7:3) as the chromatography solvent and afforded 0.52 g (55%) of **9a** as yellow powder. This compound decomposed upon standing at room temperature for a few hours, giving a dark brown residue. Thus, complete characterization was not carried out. For **13a**: IR (KBr) 1707, 1622, 1544, 1526 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.03 (1 H, s), 7.38–7.19 (5 H, m), 5.75 (2 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 167.7 (q, J = 38.6 Hz), 155.7, 150.7, 141.1, 138.2, 133.5, 129.3, 128.9, 126.8, 116.8 (q, J = 275 Hz), 103.7, 102.4, 49.6.

1-Benzyl-7-methoxy-2-(trifluoroacetyl)imidazo[1,2-c]pyrimidin-3-one (13b). The reaction was run using **12b** (100 mg, 0.37 mmol). The crude product was purified using EtOAc/hexanes (1:1) as the chromatography solvent and afforded 85 mg (66.1%) of **13b** as yellow solid. For **13b** as orange yellow crystals: mp 148–149 °C; IR (KBr) 3117, 1728, 1637, 1594, 1538, 1496, 1406, 1228 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ϵ) 398 (9710), 322 (11 769), 236 (12 210); ^1H NMR ($CDCl_3$, 300 MHz) δ 9.00 (1 H, s), 7.34–7.19 (5 H, m), 6.33 (1 H, s), 5.65 (2 H, s), 4.10 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 167.8, 151.3, 142.0, 141.7, 134.5, 129.0, 128.4, 127.0, 123.6, 119.3, 115.1, 110.8, 101.8, 84.0, 56.3, 48.8. Anal. Calcd for $C_{16}H_{12}F_3N_3O_3$: C, 54.71; H, 3.44; N, 11.96. Found: C, 54.7; H, 3.49; N, 11.96.

7-Chloro-5-(methylthio)-2-(trifluoroacetyl)imidazo[1,2-c]pyrimidin-3-one (15a). The reaction was run using **14a** (5.00 g, 21.36 mmol). Ethyl acetate was used as the extraction solvent. The organic layer was dried and concentrated to 70 mL. The yellow solid which precipitated was collected by filtration and then was dissolved in 200 mL of THF/EtOH/H_2O (2:1:1) and treated with 8 g of $Na_2CO_3 \cdot H_2O$. The mixture was stirred overnight at room temperature and extracted with EtOAc (2 × 200 mL). The organic layers were combined, dried, filtered, and concentrated to give 3.85 g (74.0%) of **15a** as yellow solid (this material was used for the next step reaction without further purification): mp >260 °C; IR (KBr) 3447, 3149, 1691, 1608, 1549, 1522, 1480, 1263, 1231 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 430 (7460), 418 (7320), 302 (4750, shoulder to 286), 286 (7750, shoulder to 274), 274 (12 950), 260 (13 220); ^1H NMR (CD_3CN, 270 MHz) δ 6.52 (1 H, s), 2.43 (3 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 159.5, 156.3, 142.2, 135.3, 125.0, 120.7, 116.4, 106.5, 106.2, 98.6, 12.8; HRMS calcd for $C_9H_5ClF_3N_3O_2S$ 310.9743, found 310.9774.

5-Amino-7-chloro-2-(trifluoroacetyl)imidazo[1,2-c]pyrimidin-3-one (15b). A modified procedure was developed for the cyclization of **14b**. A mixture of **14b** (2 g, 9.85 mmol) and tripropylamine (4.23 g, 29.54 mmol) in 20 mL of CH_2Cl_2 was stirred for 0.5 h at room temperature. This solution was added dropwise to a solution of trifluoroacetic anhydride (6.20 g, 29.54 mmol) in 20 mL of CH_2Cl_2 through a dropping funnel over 15 min at −78 °C under N_2. The mixture was stirred for 20 min, warmed to room temperature, and then stirred an additional 0.5 h. Addition of 70 mL of water and 150 mL of EtOAc generated an organic layer which was separated, washed with 50 mL of brine, dried, and concentrated to about 70 mL. The yellow-green solid which precipitated was collected by filtration and then dissolved in 80 mL of THF/EtOH/H_2O (2:1:1) and treated with 3.0 g of $Na_2CO_3 \cdot H_2O$. The mixture was stirred at room temperature overnight and extracted with EtOAc (2 × 200 mL). The organic layer was dried and concentrated to give 1.47 g (53%) of **15b** as yellow solid (this material was used for next step reaction without further purification): mp >260 °C; IR (KBr) 3355, 3116, 1695, 1650, 1603, 1567, 1537 cm^{-1}; UV (MeOH) λ_{max} (ϵ) 420 (7490 shoulder to 402), 402 (11 780), 390 (10 640, shoulder to 402), 286 (4670, shoulder to 266), 266 (10 580); ^1H NMR (DMSO, 300 MHz) δ 8.37 (1 H, br s), 7.95 (1 H, br s), 6.08 (1 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 166.8 (q, J = 30.9 Hz), 161.5, 150.3, 145.7, 137.2, 118.7 (q, J = 292.0 Hz), 114.8, 98.3; HRMS calcd for $C_8H_4ClF_3N_4O_2$ 279.9985, found 280.0002.

General Procedure for the Alkylation of Imidazo[1,2-c]-pyrimidines at N-1. A mixture of the imidazo[1,2-c]pyrimidine (1–2 mmol) and LiH (2.5 equiv) in 5.0 mL of DMF was stirred at 0 °C for 20 min under N_2. The alkyl halide (2.0 equiv) was then added in one portion. After being stirred at room temperature for 2 h, the mixture was poured onto ice–water, immediately neutralized with a few drops of acetic acid, and extracted with EtOAc (100 mL). The organic layer was washed with water (2 × 50 mL) and brine (50 mL), dried, and concentrated. Flash chromatography of the residue using EtOAc/hexanes as the eluent afforded the purified product. Analytical samples were obtained by recrystallization from EtOAc/hexanes.

1-[(Benzyloxy)methyl]-5-(methylthio)-7-chloro-2-(trifluoroacetyl)imidazo[1,2-c]pyrimidin-3-one (16a). The reaction was run using **15a** (300 mg, 0.96 mmol) and benzyl chloromethyl ether (301 mg, 1.92 mmol). The crude product was purified using EtOAc/hexanes (4:1) as the chromatography solvent and afforded 376 mg (90.5%) of **16a** as yellow solid. For **16a**, as yellow needles: mp 148–149 °C; IR (KBr) 1724, 1608, 1524, 1489 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ϵ) 458 (8150, shoulder to 436), 436 (13 040, shoulder to 420), 420 (13 360), 332 (5530), 294 (14 340); ^1H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.21 (5 H, m), 6.70 (1 H, s),

6.04 (2 H, s), 4.68 (2 H, s), 2.60 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 167.0 (q, J = 37.4 Hz), 161.3, 155.1, 152.9, 155.1, 152.9, 141.8, 136.1, 128.4, 128.2, 127.8, 117.0 (q, J = 288.6 Hz), 102.2, 98.6, 75.3, 72.4. Anal. Calcd for $C_{17}H_{13}ClF_3N_3O_3S$: C, 47.28; H, 3.03; N, 9.73. Found: C, 47.35; H, 3.00; N, 9.70.

5-Amino-1-[(benzyloxy)methyl]-7-chloro-2-(trifluoroacetyl)imidazo[1,2-*c*]pyrimidin-3-one (16b). The reaction was run using **15b** (500 mg, 1.79 mmol) and benzyl chloromethyl ether (559 mg, 3.57 mmol). The crude product was purified using EtOAc/hexanes (1:1) as the chromatography solvent and afforded 575 mg (80.3%) of **16b** as yellow solid. For **16b**, as yellow crystals: mp 187–188 °C; IR (KBr) 3314, 3108, 1741, 1673, 1592, 1533 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 420 (13 440, shoulder to 402), 402 (19 960), 388 (17 950, shoulder to 402), 288 (5410, shoulder to 274), 274 (7920); ^{1}H NMR (DMSO, 300 MHz) δ 9.26 (1 H, br s), 8.82 (1 H, br s), 7.29–7.19 (5 H, m), 7.03 (q H, s), 5.84 (2 H, s), 4.56 (2 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 163.1 (q, J = 35.3 Hz), 157.3, 155.0, 150.6, 144.5, 137.3, 128.0, 127.6, 127.4, 117.4 (q, J = 289.7 Hz), 101.5, 91.0, 74.2, 70.3. Anal. Calcd for $C_{16}H_{12}ClF_3N_4O_3$: C, 47.96; H, 3.03; N, 13.98. Found: C, 48.03; H, 3.06; N, 13.90.

1-[(2-Acetoxyethoxy)methyl]-7-chloro-5-(methylthio)-2-(trifluoroacetyl)imidazo[1,2-*c*]pyrimidin-3-one (16c). The reaction was run using **15a** (200 mg, 0.64 mmol) and (2-acetoxyethoxy)methyl bromide (190 mg, 0.96 mmol). The reaction was stirred at −5 °C for 2 min prior to the addition of the bromide. The crude product was purified using EtOAc/hexanes (1:1) as the chromatography solvent and afforded 221 mg (80.5%) of **16c** as yellow solid. For **16c**, as yellow needles: mp 184–185 °C; IR (KBr) 1739, 1713, 1608, 1521 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 462 (6790, shoulder to 432), 432 (12 850), 418 (13 190), 330 (5170), 294 (14 350); ^{1}H NMR ($CDCl_3$, 270 MHz) δ 7.01 (1 H, s), 6.00 (2 H, s), 4.20 (2 H, t, J = 4.62 Hz), 3.87 (2 H, t, J = 4.62 Hz), 2.62 (3 H, s), 2.05 (3 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 170.2, 163.9 (q, J = 36.4 Hz), 160.3, 153.5, 153.4, 143.5, 117.2 (q, J = 288.6 Hz), 101.4, 99.6, 74.3, 66.4, 62.7, 20.5, 13.8. Anal. Calcd for $C_{14}H_{13}ClF_3N_3O_5S$: C, 39.31; H, 3.06; N, 9.82. Found: C, 39.43, H, 3.13, N, 9.82.

2-Acetyl-5-amino-1-benzyl-7-chloroimidazo[1,2-*c*]pyrimidin-3-one (17a). A solution of **9a** (100 mg, 0.29 mmol) in 10 mL of 1,4-dioxane and stirred for 5 min, and then 5 mL of NH_3/MeOH (saturated at 0 °C) was added. The mixture was stirred at room temperature for 70 min, and then the volatiles were removed under reduced pressure. Flash chromatography of the residue using EtOAc provided 86 mg (94.4%) of **17a** as yellow solid. An analytical sample was obtained by recrystallization from EtOAc/hexanes as yellow needles: mp 235–236 °C; IR (KBr) 3338, 3112, 1669, 1651, 1621, 1574, 1526 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 412 (12 220, shoulder to 396), 396 (15 760), 314 (4140), 268 (13 430); ^{1}H NMR (DMSO, 300 MHz) δ 9.00 (2 H, br d), 7.32–7.18 (5 H, m), 6.96 (1 H, s), 5.62 (2 H, s), 2.26 (3 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 183.1, 155.5, 153.9, 150.8, 139.2, 136.3, 128.4, 127.4, 126.8, 104.3, 90.6, 47.4, 27.5. Anal. Calcd for $C_{15}H_{13}ClN_4O_2$: C, 56.88; H, 4.14; N, 17.69. Found: C, 56.78; H, 4.10; N, 17.75.

2-Acetyl-1-benzyl-7-chloro-5-methoxyimidazo[1,2-*c*]pyrimidin-3-one (17b). A mixture of **9a** (300 mg, 0.86 mmol) and $NaOCH_3$ (600 mg, 11.1 mmol) in 20 mL of methanol was stirred at 0 °C for 45 min. The reaction was quenched with 0.60 mL of acetic acid. The mixture was treated with 100 mL of water and extracted with CH_2Cl_2 (200 mL). The organic layer was washed with brine (100 mL), dried, and concentrated. Flash chromatography of the residue first using CH_2Cl_2 and then CH_2Cl_2/EtOAc (1:1) gave 243 mg (84.9%) of **17b** as light yellow solid. An analytical sample of **17b** was obtained by recrystallization from EtOAc/hexanes as light yellow needles: mp 158 °C dec; IR (KBr) 1714, 1631, 1602, 1538 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 432 (7650, shoulder to 410), 410 (11 230), 322 (2580), 272 (6570), 264 (6710); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–717 (5 H, m), 6.70 (1 H, s), 5.78 (2 H, s), 4.24 (3 H, s), 2.53 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 186.7, 153.1, 153.0, 152.1, 137.7, 134.7, 129.0, 128.3, 126.8, 104.5, 96.8, 57.4, 49.0, 28.5. Anal. Calcd for $C_{16}H_{14}ClN_3O_3$: C, 57.93; H, 4.25; N, 12.67. Found: C, 57.85; H, 4.30; N, 12.75.

5-Amino-2-acetyl-1-benzyl-7-methoxyimidazo[1,2-*c*]pyrimidin-3-one (18a). A mixture of 11 (150 mg, 0.44 mmol) and 15 mL of NH_3/MeOH (saturated at 0 °C) in 15 mL of THF was stirred at room temperature overnight. The precipitate which had formed was collected by filtration, washed with 5 mL of EtOAc/hexanes (1:4), and dried in vacuo to provide 54 mg of **18a**. The filtrate was concentrated under reduced pressure. Flash chromatography of residue using EtOAc/$CHCl_3$ (1:1) furnished an additional 60 mg of **18a** (total yield 83.6%). An analytical sample of **18a** was obtained by recrystallization from EtOAc/hexanes as light yellow needles: mp 227–228 °C; IR (KBr) 3282, 3150, 1696, 1660, 1634, 1573, 1547 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 368 (20 032), 180 (7560), 252 (8050); ^{1}H NMR (DMSO, 300 MHz) δ 8.96 (1 H, br s), 8.76 (1 H, br s), 7.31–7.18 (5 H, m), 5.97 (1 H, s), 5.55 (2 H, s), 3.86 (3 H, s), 2.24 (3 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 182.2, 167.8, 155.9, 151.1, 142.4, 136.9, 128.4, 127.3, 127.0, 103.6, 72.1, 54.8, 46.8, 27.3. Anal. Calcd for $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94. Found: C, 61.61; H, 5.19; N, 17.99.

5-Amino-2-acetyl-1-benzyl-7-methoxyimidazo[1,2-*c*]pyrimidin-3-one (18a). A mixture of **9b** (300 mg, 0.836 mmol) and 1.20 g of Na_2CO_3 in 15 mL of MeOH was refluxed for 30 min. After being cooled to room temperature, the mixture was treated with 50 mL of water and extracted with EtOAc (150 mL). The organic layer was dried and concentrated. Flash chromatography of the residue using EtOAc/$CHCl_3$ (1:1) provided 93 mg (35.7%) of **18a**.

2-Acetyl-1-benzyl-5,7-dimethoxyimidazo[1,2-*c*]pyrimidin-3-one (18b). A mixture of 11 (100 mg, 0.29 mmol) of $NaOCH_3$ (40 mg, 0.74 mmol) in 12 mL of MeOH/THF (7:5) was stirred for 15 min at −5 °C. The reaction was quenched by adding several drops of acetic acid. The mixture was treated with 50 mL of water and extracted with EtOAc (150 mL). The organic layer was dried and concentrated. Flash chromatography of residue using MeOH/EtOAc (1:19) provided 80 mg (84%) of **18b** as yellow solid. An analytical sample was obtained by recrystallization from EtOAc/hexanes as light yellow needles: mp 175–176 °C; IR (KBr) 1718, 1651, 1579, 1557, 1533 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 376 (14 050), 330 (7240, shoulder to 376), 278 (6560), 244 (5470); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30–7.18 (5 H, m), 5.83 (1 H, s), 5.70 (2 H, s), 4.22 (3 H, s), 3.95 (3 H, s), 2.51 (3 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 180.2, 169.3, 157.2, 152.8, 145.7, 137.7, 128.4, 128.3, 127.3, 127.0, 126.9, 103.4, 79.3, 67.4, 53.1, 46.4, 27.0. Anal. Calcd for $C_{17}H_{17}N_3O_4$: C, 62.38; H, 5.23; N, 12.84. Found: C, 62.37; H, 5.23; N, 12.85.

5-Amino-1-benzyl-7-methoxy-2-(trifluoroacetyl)imidazo-[1,2-*c*]pyrimidin-3-one (19). A mixture of **9d** (500 mg, 1.35 mmol) and Na_2CO_3 (2.0 g) in 25 mL of methanol was refluxed for 12 min. The mixture was allowed to cool to room temperature, and the inorganic solids were removed by filtration. The filtrate was evaporated, and the resulting residue was treated with 50 mL of water and extracted with EtOAc (100 mL). The organic layer was dried and concentrated. Flash chromatography of residue using EtOAc/hexanes (7:3) gave 380 mg (77%) of **19** as light yellow solid. An analytical sample of **19** was obtained by recrystallization from EtOAc/hexanes as yellow needles: mp 213–214 °C; IR (KBr) 3495, 3374, 1723, 1660, 1592, 1563, 1538 cm^{-1}; UV (CH_2Cl_2) λ_{max} (ε) 384 (20 990), 298 (3990), 262 (3070); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.21 (1 H, br s), 7.35–7.21 (5 H, m), 5.84 (1 H, br s), 5.58 (1 H, s), 5.50 (2 H, s), 3.90 (3 H, s); ^{13}C NMR (DMSO, 67.9 MHz) δ 169.2, 161.8 (q, J = 35.3 Hz), 155.7, 151.4, 145.9, 136.3, 128.4, 127.4, 127.1, 126.9, 117.7 (q, J = 288.6 Hz), 101.6, 72.6, 54.9, 47.2. Anal. Calcd for $C_{16}H_{13}F_3N_4O_3$: C, 52.46; H, 3.58; N, 15.30. Found: C, 52.54; H, 3.57; N, 15.40.

2-Acetyl-1-benzyl-7-hydroxy-5-(methylthio)imidazo[1,2-*c*]pyrimidin-3-one (20). A mixture of 11 (300 mg, 0.87 mmol) and NaI (0.524 mg, 3.50 mmol) in 15 mL of acetonitrile was stirred at room temperature for 10 min. Chlorotrimethylsilane (380 mg, 3.50 mmol) was added. The mixture was stirred at 75 °C for 7 h under N_2. After being cooled to room temperature, the mixture was evaporated to dryness under reduced pressure. The residue was treated with 20 mL of water/EtOAc (1:1), and then 900 mg of $NaS_2O_3 \cdot 5H_2O$ was added. The resulting mixture was stirred vigorously at room temperature for 30 min. The yellow precipitate which had formed was collected by filtration, washed with water, and dried in vacuo to provide 281 mg (97.6%) of **20** as yellow powder: mp >250 °C; IR (KBr) 3419, 1708, 1626, 1538 cm^{-1}; UV (MeOH) λ_{max} (ε) 380 (13 470), 316 (9980), 266 (9660), 242 (10 450); ^{1}H NMR (DMSO, 300 MHz) δ 7.28–7.17 (5 H, m), 6.22 (1 H, s), 5.62 (2 H, s), 2.47 (3 H, s), 2.25 (3, H, s); ^{13}C NMR (DMSO, 67.9

MHz) δ 182.6, 165.5, 158.8, 154.6, 141.9, 136.5, 127.4, 126.9, 103.1, 77.9, 47.1, 27.1, 13.5; HRMS calcd for $C_{16}H_{15}ClN_3O_3S$ 329.0834, found 329.0856.

12b from Hydrolysis of 13b. A mixture of **13b** (100 mg, 0.28 mmol) and 6 mL of 0.5 N HCl in 6 mL of 1,4-dioxane was refluxed for 5 min. After cooling, the mixture was extracted with 50 mL of EtOAc. The organic layer was washed with brine (20 mL) and dried. Concentration of the solvent provided **12b**, which was confirmed with an authentic sample by TLC and ^1H NMR analysis.

6-[*N*-Benzyl-*N*-(2-oxopropyl)]-4-methoxy-2-(methylthio)-pyrimidine (21). A mixture of 11 (270 mg, 0.73 mmol), 10 mL of 1 N HCl, and 10 mL of 1,4-dioxane was stirred at 65–70 °C for 2 h. After being cooled to room temperature, the mixture was extracted with EtOAc (50 mL). The organic layer was washed with brine (50 mL), dried, and concentrated. Flash chromatography of the residue using EtOAc/hexanes (1:4) provided 212 mg (94.5%) of **21**. An analytical sample of **21** was obtained by recrystallization from EtOAc/hexanes as colorless crystals: mp 82–83 °C; IR (KBr) 1722, 1576, 1552 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33–7.19 (5 H, m), 5.48 (1 H, br s), 4.64 (2 H, br s), 4.27 (2 H, br s), 3.86 (3 H, s), 2.45 (3 H, s), 2.12 (3 H, s); ^{13}C NMR ($CDCl_3$, 67.9 MHz) δ 204.9, 170.1, 163.2, 136.5, 128.7, 127.5, 126.9, 81.2, 57.6, 53.5, 52.7, 27.0, 13.9. Anal. Calcd for $C_{16}H_{19}N_3O_2S$: C, 60.55; H, 6.03; N, 13.24. Found: C, 60.70; H, 6.08; N, 13.17.

Acknowledgment. This research was supported by the donors of the Petroleum Research Fund, administered by the American Chemical Society. E.D.E. is grateful for support provided by the American Cancer Society Jr. Faculty Research Award. We thank Professor John L. Hubbard for obtaining the X-ray crystal structures for compounds **9c** and **16a**. The X-ray data was obtained with equipment funded by NSF grant No. CHE-9002379.