Pyrrolodiazines. 5. Synthesis, Structure, and Chemistry of Pyrrolo[1,2-*c*]pyrimidine. Dipolar Cycloaddition of Pyrrolo[1,2-*c*]pyrimidinium Ylides

José M. Minguez,[†] Juan J. Vaquero,[†] Julio Alvarez-Builla,*[,†] and Obis Castaño[‡]

Departamento de Química Orgánica and Quimica Fisica, Universidad de Alcalá, 28871-Alcalá de Henares, Madrid, Spain

José L. Andrés

Vapor Universitario, Facultad de Ciencias, Universidad Nacional de Educación a Distancia (UNED), C/Colón, 114, 0822-Tarrasa, Spain.

Received April 27, 1999

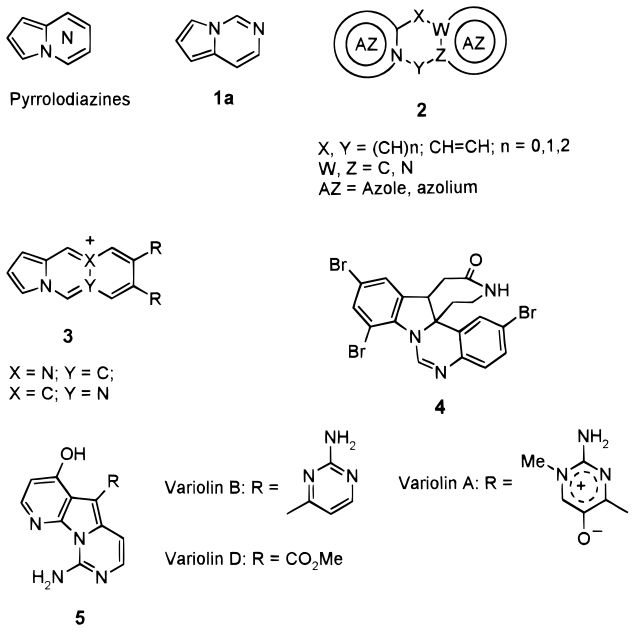
An improved synthesis of pyrrolo[1,2-*c*]pyrimidines, including the parent system, was accomplished via sequential condensation of substituted pyrrole-2-carboxaldehydes with tosylmethyl isocyanide (TOSMIC), followed by desulfonylation of the formed tosylpyrrolo[1,2-*c*]pyrimidines. Based on the ab initio calculations performed on the pyrrolo[1,2-*c*]pyrimidine **1a**, some of the basic chemistry was investigated, including electrophilic substitution, addition of organolithium reagents, metalation with lithium diisopropylamide (LDA) and subsequent reaction with electrophiles, and formation of salts by quaternization of the nonbridgehead nitrogen. Azomethine ylides generated from pyrrolo-[1,2-*c*]pyrimidinium salts undergo 1,3-dipolar cycloaddition with suitable dipolarophiles to give new dipyrrolo[1,2-*a*;1′,2′-*c*]pyrimidine derivatives, with high regio- and stereoselectivity.

Introduction

Pyrrolodiazines[1] can be potentially used as intermediates in the synthesis of novel 2,2-biazole derivatives **2**[2], and more recently, as starting heterocycles in the preparation of heteroaromatic polycyclic cations **3**, with a quaternary nitrogen, which are currently being studied as antitumor agents due to their ability to intercalate DNA[3] (Chart 1). As stated in a previous paper,[4] the systems with a bridgehead nitrogen atom can be formally considered as aza analogues of indolizines whose relevance is well documented.[5] The chemistry of all these bicyclic heterocycles, however, remains unexplored, due to a lack of efficient synthetic routes, and this led to the exploration of new synthetic strategies. As a result, the preparation of pyrrolo[1,2-*a*]pyrazine[4] was achieved by oxidation of the 3,4-dihydropyrrolo[1,2-*a*]pyrazine,[2] and this synthesis clearly improved the only reported procedure.[6] The structure and basic chemistry of these systems was also reported.[2,4,7]

Recently, a novel approach to the synthesis of the pyrrolo[1,2-*c*]pyrimidine **1a** and some derivatives was

Chart 1



---

* To whom correspondence should be addressed. E-mail: jalvarez@quimor.alcala.es. Fax: 34-91-8854660.

[†] Departamento de Química Orgánica.

[‡] Departamento de Química Física.

(1) For reviews of azaindolizines, see: (a) Amarnath, V.; Madhav, R. *Synthesis*, **1974**, 837.(b) Kuhla, D. E.; Lombardino, J. G. *Adv. Heterocycl. Chem*. **1977**, *21*, 1. (c) Blewit, H. L. *Chem. Heterocycl. Compd* **1977**, *30*, 117. (d) Maury, G. *Chem. Heterocycl.c Compd* **1977**, *30*, 179. (e) Terenin, V. I.; Kabanova, E. V.; Feoktistova, G. S. *Khim. Getertsikl. Soedin* **1991**, *10*, 1299; *Chem. Abstr*. **1992**, *117*, 48361e.

(2) De Pablo, M. S.; Gandásegui, T.; Vaquero, J. J.; García-Navío, J. L.; Alvarez-Builla, J. *Tetrahedron* **1992**, *48*, 8793.

(3) (a) Díaz, A.; Matia, M. P.; García Navío, J. L.; Vaquero, J. J., Alvarez-Builla, J. *J. Org. Chem*. **1994**, *59*, 8294. (b) Santiesteban, I.; Vaquero, J. J.; Siro, J. G.; García Navío, J. L.; Alvarez-Builla, J.; Castaño, O. *J. Org. Chem*. **1995**, *60*, 5667. (c) Molina, A.; Vaquero, J. J.; García Navío, J. L.; Alvarez-Builla, J.; Pascual-Teresa, B.; Gago, F.; Rodrigo, M. M.; Ballesteros, M. *J. Org. Chem*. **1996**, *61*, 5587. (d) Pastor, J.; Vaquero, J J.; García Navío, J. L.; Alvarez-Builla, J.; Gago, F.; de Pascual-Teresa, B.; Pastor, M.; Rodrigo, M. M. *J. Org. Chem*. **1997**, *62*, 5476. (e) Molina, A.; Vaquero, J. J.; García Navío, J. L.; Alvarez-Builla, J.; Gago, F.; de Pascual-Teresa, B.; Rodrigo, M. M. *J. Org. Chem*., in press.

(4) Mínguez, J. M.; Castellote, M. I.; Vaquero, J. J.; García Navío, J. L.; Alvarez-Builla, J.; Castaño, O.; Andrés, J. L. *J. Org. Chem*. **1996**, *61*, 1655.

(5) Flitsch, W. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; 1984; Vol. 4, pp 443−495.

(6) Skoldinov, A.; Peresada, V.; Likhosherstov, A. *Zh. Org. Khim*. **1983**, *19*, 450; *Chem. Abstr*. **1983**, *98*, 198162 u.

(7) Mínguez, J. M.; Castellote, M. I.; Vaquero, J. J.; García Navío, J. L.; Alvarez-Builla, J.; Castaño, O.; Andrés, J. L. *Tetrahedron* **1997**, *53*, 9341.

10.1021/jo9907080 CCC: $18.00
Published on Web 09/23/1999

also reported, based on the reaction of tosylmethyl isocyanide (TOSMIC) with 2-pyrrolecarboxaldehydes.[8] This method provides a simple and efficient route to the system, which can now be obtained in 40% overall yield (compared to 1% for the previously reported procedure[9]). This system, although rare in nature, is present in hinckdentine (**4**), an unusual marine alkaloid with some of its analogues having cataleptogenic activity.[10] It is also present in the variolins **5**, a family of alkaloids isolated from the antarctic sponge *Kirkpatrickia varialosa*, which have antitumor and antiviral activity.[11]

Following our studies on the chemistry of pyrrolodiazines, the present report describes the details of the synthesis of **1a** and some simple derivatives. The structure of this system was also determined by ab initio calculations, along with a study of the chemistry of the system, which included electrophilic substitutions, metalation reactions, generation of pyrrolo[1,2-*c*]pyrimidinium ylides, and trapping them with suitable dipolarophiles to give new tri- and tetracyclic adducts.

Computational Methods

The electronic structures of the pyrrolo[1,2-*c*]pyrimidine **1a** and the N-protonated species were studied using ab initio molecular orbital (MO) techniques. Molecular structures were obtained by geometric optimization using the Schlegel's algorithm.[12] All theoretical calculations were performed at the closed-shell self-consistent field level (RHF), and the electron correlation effect was introduced through the second-order Möller Plesset (MP2) theory, using the frozen core approach. Gas-phase basicities (GB) and proton affinities (PA) are defined as the standard Gibbs energy and enthalpy charges, respectively, for the following process in gas phase:

$$BH^+(g) \rightarrow B(g) + H^+(g)$$

The 6-31G* basis set[13] was used for the thermodynamic analysis, and the energy was corrected using the MP2 theory. Harmonic vibrational frequencies were computed at the RHF/6-31G* level (without exception, all values used were real) and the zero-point vibrational energies (ZPE) were obtained from the scaled level (multiplied by the factor 0.8929). Thermal corrections and entropies for **1a** were corrected with the HF/6-31G* frequencies. All calculations were performed using the GAUSSIAN-94[14] suite of programs.

Results and Discussion

The only synthesis of pyrrolo[1,2-*c*]pyrimidine that appears in the literature was reported by Rapoport *et al*. starting from 4-methylpyrimidine.[9] After a sequence of seven steps, which included initial condensation with butyl glyoxalate, synthesis of 3-(4-pyrimidyl)-1-propanol **6** from the condensation product (three steps), formation of the 6,7-dihydro-5*H*-pyrrolo[1,2-*c*]pyrimidinium salt **7**, and final oxidation, the overall yield obtained was less than 1%, mainly because the last step produced a yield of 9% (Scheme 1). As an alternative, we designed a strategy whereby condensation of pyrrole-2-carboxaldehyde **8a** (R^1 = H) with ethyl isocyanoacetate[15] leads to the 3-ethoxycarbonylpyrrolo[1,2-*c*]pyrimidine **9a** that could then be transformed into the corresponding carboxylic acid **10a**, which upon decarboxylation would generate the desired pyrrolo[1,2-*c*]pyrimidine (Scheme 1).

As expected, the ester **9a** was hydrolyzed (80%) under standard conditions to the acid **10a**, but the acid proved to be highly resistant to decarboxylation under various conditions. Thus, the attempts of decarboxylation with Cu/quinoline at reflux temperature,[16] by heating at 300 °C in the absence of solvent, by heating in a sealed tube, or by microwave irradiation were all unsuccessful, with **9a** being recovered unaltered. Similar results were obtained in the attempted decarboxylation under Burton

Scheme 1

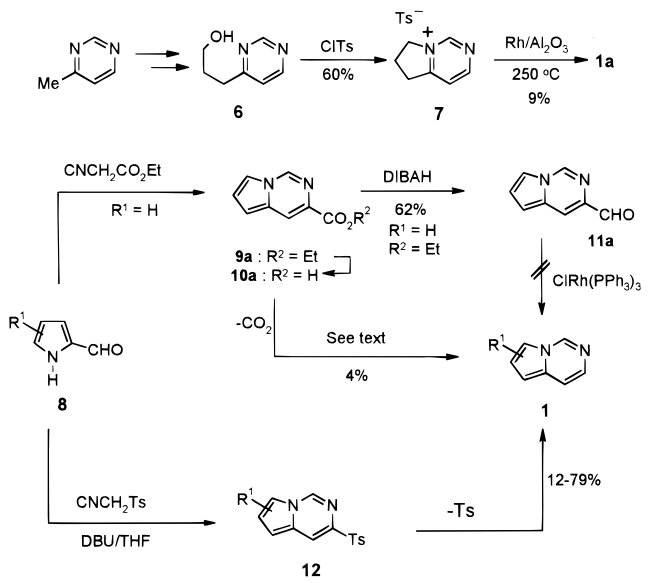
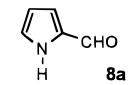
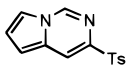
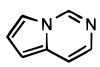
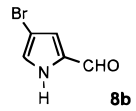
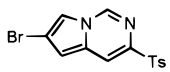
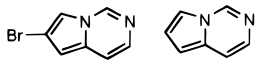
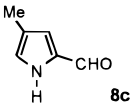
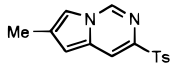
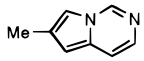
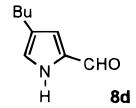
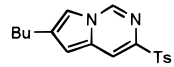
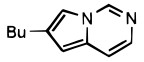
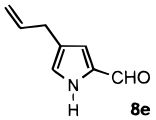
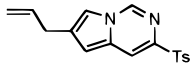
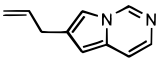
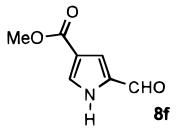
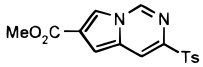
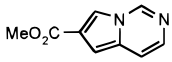
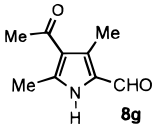
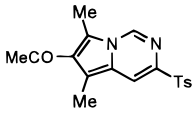
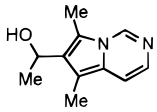
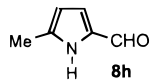
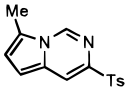
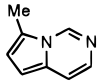
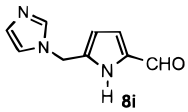
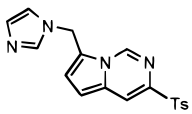
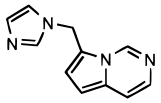
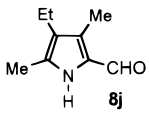
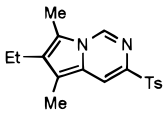
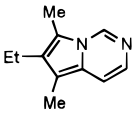


Table 1. Isolated Yields of Pyrrolo[1,2-*c*]pyrimidine 1a by Desulfonylation of Tosylderivative 12a

reagent	equiv	conditions	time (h)	yield of **1a** (%)
$LiAlH_4-NiCl_2$	6	THF, Na_2CO_3, rt	24	7
$Na_2S_2O_4$	3	$EtOH-H_2O$, heat	15	18
Na/Hg 6%	4	THF, rt	12	31
Na/Hg 10%	4	THF, rt	10	30
Na/Hg 6%	8	THF, rt	4	29
Na/Hg 6%	4	THF−MeOH, rt	4	37
Na/Hg 6%	8	Na_2HPO_4/THF−MeOH, rt	3	51

(8) Mínguez, J. M.; Vaquero, J. J.; García Navío, J. L.; Alvarez-Builla, J. *Tetrahedron Lett*. **1996**, *37*, 4263.
(9) Wong, J. L.; Brown, M. J.; Rapoport, H. *J. Org. Chem*. **1965**, *30*, 2398.
(10) (a) Blackman, A. J.; Hambley, T. W.; Picker, R.; Taylor, W. C.; Thirasana, N. *Tetrahedron Lett*. **1987**, *28*, 5561. (b) Billimoria, A. D.; Cava, M. P. *J. Org. Chem*. **1994**, 59, 6777.
(11) (a) Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Parkin, S.; Hope, H. *Tetrahedron* **1994**, *50*, 3987. (b) Trimurtuhu, G.; Faulkner, D. J.; Perry, N. B.; Ettouati, L.; Litaudon, M.; Blunt, J. W.; Munro, M. H. G.; Jameson, G. B. *Tetrahedron* **1994**, *50*, 3993.
(12) Schlegel, H. B. *J. Comput. Chem*. **1982**, *3*, 214.
(13) Hehre, W. J.; Ditchfield, R.; Pople, J. A. *J. Chem. Phys*. **1972**, *56*, 2257. (b) Frisch, M. J.; Pople, J. A.; Binkley, J. S. *J. Chem. Phys*. **1984**, *80*, 3265. (c) Clark, T.; Chandrasekhar, J.; Spitznagel, G. W.; Schleyer, P. v. R. *J. Comput. Chem*. **1983**, *4*, 294.
(14) GAUSSIAN-94: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Gill, P. M. W.; Johnson, B. G.; Wong, M. W.; Robb, M. A.; Cheesemen, T.; Keith, T.; Petersson, J. A.; Montgomery, J. A.; Raghavachari, K.; Al-Laham, M. A.; Zakrzewsky, V. G.; Ortiz, J. V.; Foresman, J. B.; Peng, C. Y.; Ayala, P. Y.; Chen W.; Wong, M, W.; Andrés, J. L.; Replogle, E. S.; Gomperts, G.; Martin, R. L.; Fox, D. J.; Binkey, J. S.; DeFrees, D. J.; Baker, J.; Stewart, J. P.; Head-Gordon, C.; González, C.; Pople, J. A. Gaussian Inc., Pittsburgh, PA, 1995.
(15) Suzuki, M.; Yoneda, N. *J. Org. Chem*. **1976**, *41*, 1482.
(16) Nagasaka, S.; Ohki, S. *Chem. Pharm. Bull*. **1977**, *25*, 3023. (b) Toussant, O.; Capdeville, P.; Maumy, M. *Tetrahedron* **1984**, *40*, 3229.

Table 2. 3-Tosylpyrrolo[1,2-*c*]pyrimidines 12 and pyrrolo[1,2-*c*]pyrimidine derivatives 1

Entry	Aldehyde (**8**)	Cyclocondensation product (**12**) [Yield %]	Pyrrolo[1,2-*c*]pyrimidine Derivatives (**1**) [Yield %]
1	 **8a**	 **12a** [82]	 **1a** [51]
2	 **8b**	 **12b** [79]	 **1b** [15] **1a** [45]
3	 **8c**	 **12c** [58]	 **1c** [77]
4	 **8d**	 **12d** [73]	 **1d** [54]
5	 **8e**	 **12e** [61]	 **1e** [46]
6	 **8f**	 **12f** [69]	 **1f** [12]
7	 **8g**	 **12g** [75]	 **1g** [58]
8	 **8h**	 **12h** [76]	 **1h** [74]
9	 **8i**	 **12i** [80]	 **1i** [55]
10	 **8j**	 **12j** [69]	 **1j** [83]

conditions.[17] Moreover, **1a** was formed only when **9a** was refluxed in diphenyl ether,[18] but in only a 5% yield. Finally, the ester was reduced to the corresponding aldehyde **11a** (DIBALH, −78 °C, 62%), and the aldehyde was treated with Wilkinson's catalysts,[19] but this attempt of decarbonylation was also unsuccessful.

Consequently, cyclocondensation of the pyrrole-2-carboxaldehyde was attempted with tosylmethyl isocyanide (TOSMIC)[20] in the assumption that the resulting sulfone **12a** would be more easily transformed into **1a** by reductive displacement of the tosyl group. The reaction of **8a** with TOSMIC in tetrahydrofuran (THF)/1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) gave the expected cyclocondensation product in high yield (82%), but subsequent removal of the tosyl moiety was also problematic. For example, attempts to desulfonylate **12a** with $H_4LiAl-NiCl_2$[21] gave **1a** in only a 7% yield, whereas treatment with $Na_2S_2O_4$[22] gave **1a** in an 18% yield. When we used amalgam, the yield was improved in the best case to 51%, after using a carefully controlled amount of sodium amalgam and Na_2HPO_4 in THF−MeOH.[23] Under these conditions, pyrrolo[1,2-*c*]pyrimidine **1a** is obtained in an

(17) Burton, D. H. R.; Hervé, Y.; Potier, P.; Thierry, J. *Tetrahedron* **1988**, *44*, 5479. (b) Newmann, W. P. *Synthesis* **1987**, 665.

(18) Wade, J. J.; Hegel, R. F.; Toso, C. B. *J. Org. Chem.* **1979**, *44*, 1811.

(19) Tsugi, J.; Ohno, K. *Synthesis* **1969**, *1*, 157. (b) Meyer, M. D.; Kruse, L. I. *J. Org. Chem.* **1984**, *49*, 3195.

(20) (a) Saikachi, H.; Kitigawa, T.; Sasaki, H.; Van Leusen, A. M. *Chem. Pharm. Bull.* **1979**, *27*, 793. (b) Saikachi, H.; Kitigawa, T.; Sasaki, H.; Van Leusen, A. M. *Chem. Pharm. Bull.* **1982**, *30*, 4199.

(21) Ho, K. M.; Lam, C. H.; Luh, T. Y. *J. Org. Chem.* **1989**, *54*, 4474.

(22) Bremmer, J.; Julia, M.; Launay, M.; Stacino, J. P. *Tetrahedron Lett.* **1982**, *23*, 3265.

Table 3. Optimized Geometrical Parameters for Pyrrolo[1,2-*c*]pyrimidine 1a

	RHF/6-31G*	MP2/6-31G*
bond lengths[a]		
C1−N2	1.268	1.302
N2−C3	1.381	1.379
C3−C4	1.341	1.373
C4−C4a	1.432	1.412
C4a−C5	1.365	1.394
C5−C6	1.422	1.407
C6−C7	1.356	1.390
C7−N8	1.357	1.372
N8−C1	1.363	1.379
bond angles[b]		
C1−N2−C3	117.7	117.7
N2−C3−C4	123.5	123.0
N2−C3−H	114.9	115.4
C3−C4−H	121.7	121.0
C3−C4−C4a	118.5	119.3
C4−C4a−C5	136.7	137.1
C4−C4a−N8	115.5	116.1
C4a−C5−C6	106.9	107.4
C4a−C4−H	119.9	119.7
C4a−C5−H	126.0	125.5
C5−C6−C7	108.6	109.0
C5−C6−H	126.2	126.2
C6−C5−H	127.0	127.1
C6−C7−H	131.4	131.6
C7−C6−H	125.2	124.8

[a] Bond lengths in angstroms. [b] Bond angles in degrees.

overall 40% yield, in a two-step sequence. The conditions employed and yields obtained are summarized in Table 1.

To further explore the scope of the above procedure, we applied the method to the synthesis of some substituted pyrrolo[1,2-*c*]pyrimidine derivatives. Thus, the cyclocondensation of substituted pyrrole-2-carboxaldehydes with TOSMIC afforded the 3-tosyl derivatives **12b**−**j** in high yields (Table 2). The subsequent desulfonylation of these derivatives under the optimized conditions used for **12a** afforded the desired compounds in moderate to high yields for most substituents (Table 2, entries 3−5, 8−10), while other functions were not compatible with the conditions employed in this step. Thus, reductive desulfonylation of 3-tosyl-7-bromopyrrolo[1,2-*c*]pyrimidine (Table 2, entry 2) was accompanied by extensive debromination, with **1b** obtained in only a 15% yield. Similarly, only a 12% yield was obtained in the conversion of **12f** into **1f** with a complex mixture being produced (Table 2, entry 6). In the acyl derivative **12g** (Table 2, entry 7) the carbonyl group was extensively reduced to the corresponding alcohol.

Complementary to the synthesis, molecular structures of **1a** and its N(2)-protonated form (a model of either protonated or *N*-alkyl derivatives) were studied at the RHF and MP2 levels using several basis sets. Bond lengths and angles of these structures are listed in Tables 3 and 4, respectively. Figure 1 shows the calculated MP2/6-31G* Mulliken charges on the heavy atoms of both systems. Nitrogen atoms of these two species have negative charges, with N-8 being larger for **1a** and N-2 larger for the N(2)-protonated form. The highest occupied molecular orbitals (HOMO) and the lowest unoccupied molecular orbitals (LUMO) and the orbital energies for both structures are presented in Figure 2. Only atomic orbitals with coefficients larger than 0.1 are shown.

Table 4. Optimized Geometrical Parameters for the N-protonated Form of Pyrrolo[1,2-*c*]pyrimidine 1a

	RHF/6-31G*	MP2/6-31G*
bond lengths[a]		
C1−N2	1.303	1.327
N2−C3	1.404	1.382
C3−C4	1.330	1.371
C4−C4a	1.437	1.404
C4a−C5	1.396	1.384
C5−C6	1.343	1.411
C6−C7	1.438	1.386
C7−N8	1.345	1.375
N8−C1	1.310	1.341
bond angles[b]		
C1−N2−C3	122.5	124.2
N2−C3−C4	119.4	118.2
N2−C3−H	115.3	116.3
C3−C4−H	120.7	119.8
C3−C4−C4a	119.6	120.4
C4−C4a−C5	136.7	136.9
C4−C4a−N8	116.0	116.9
C4a−C5−C6	107.5	107.8
C4a−C5−H	126.0	125.3
C5−C6−H	125.7	126.0
C6−C7−H	131.8	131.4
C7−C6−H	121.1	124.2
C1−N2−H	118.4	117.1
N2−C1−H	119.7	120.2

[a] Bond lengths in angstroms. [b] Bond angles in degrees.

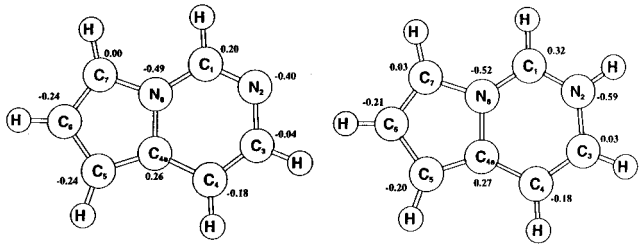


Figure 1. Mulliken atomic charges for pyrrolo[1,2-*c*]pyrimidine **1a** (right) and its N(2)-protonated form (left) obtained at the MP2/6-31G* level.

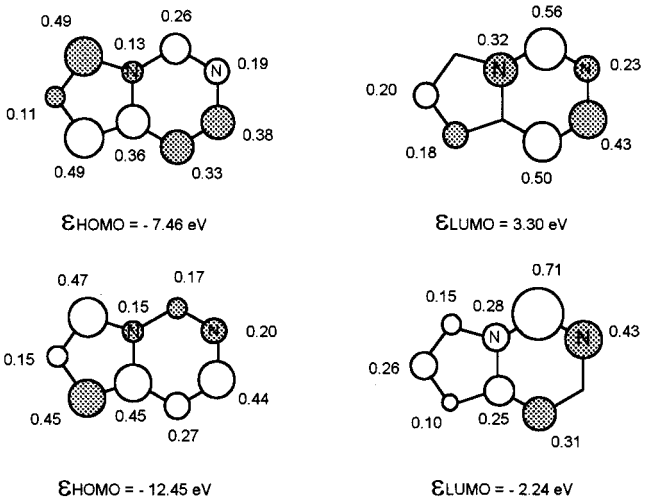


Figure 2. HOMO, LUMO, and orbital energies of the pyrrolo[1,2-*c*]pyrimidine **1a** (above) and its N(2)-protonated form (below).

(23) (a) Pascali, V.; Umani-Ronchi, A. *J. Chem. Soc., Chem. Commun.* **1973**, 351. (b) Kiddle, J. J.; Green, D. L.; Thompson, C. M. *Tetrahedron* **1995**, *51*, 2851. (c) Carr, R. V. C.; Williams, R. V.; Paquette, L. A. *J. Org. Chem.* **1983**, *48*, 4976. (d) Back, T. G.; Proudfoot, J. R.; Djerassi, C. *Tetrahedron Lett.* **1986**, *27*, 2187. (e) Trost, B. M.; Arndt, H. C.; Strege, P. E.; Verhoeven, T. R. *Tetrahedron Lett.* **1976**, *39*, 3477.

Scheme 2

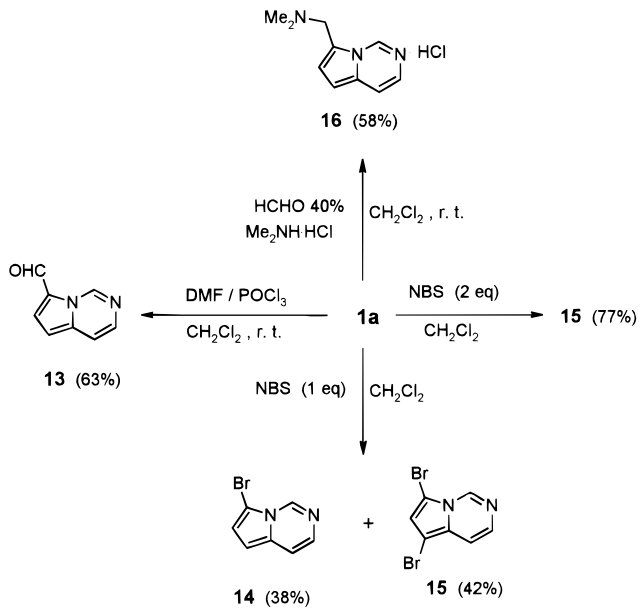


Table 5. Values for Gas-phase Basicity (GB) and Proton Affinity (PA) for Pyrrolo[1,2-*c*]pyrimidine 1a Obtained at the MP2/6-31G* Level

atom	$(PA)_{298}$[a]	$(GB)_{298}$[a]
N2	221.21	213.66
C5	217.38	191.03
C6	209.93	183.81
C7	219.75	212.30

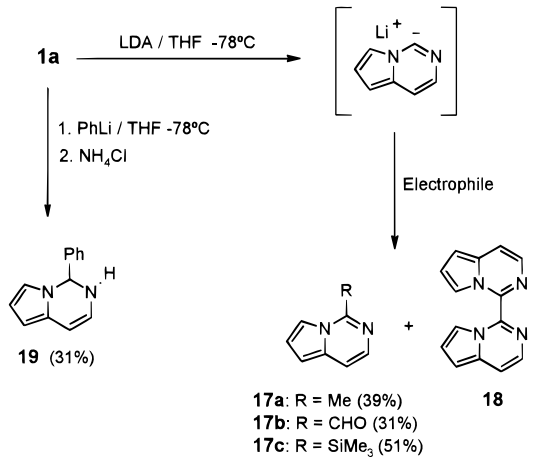
[a] Values in kcal/mol.

Electrophilic substitution of **1a** (Scheme 2) was tested by its Vilsmeier−Haak formylation with dimethylformamide and phosphorus oxychloride to give the formyl derivative **13** in moderate yield (63%). Although apparently position C-7 in **1a** corresponds to position C-2 of a simple pyrrole, theoretical calculations in a gas phase predict C-5 and C-6 to be the carbons with the greatest electron surplus in either **1a** or in its N(2)-protonated form (Figure 1). Similarly, in the bromination of **1a** with 1 equiv of NBS in CH_2Cl_2, the C-7 bromo derivative **14** was formed (38%), although in this case, the formation of **14** was accompanied by the 5,7-dibromo compound **15**, which was isolated as the main product (42%).[24] Use of 2 equiv or more of NBS gave only the dibromo compound in good yield (77%). The Mannich reaction of **1a** also produced the expected 7-dimethylaminomethyl derivative **16** in a 58% yield.

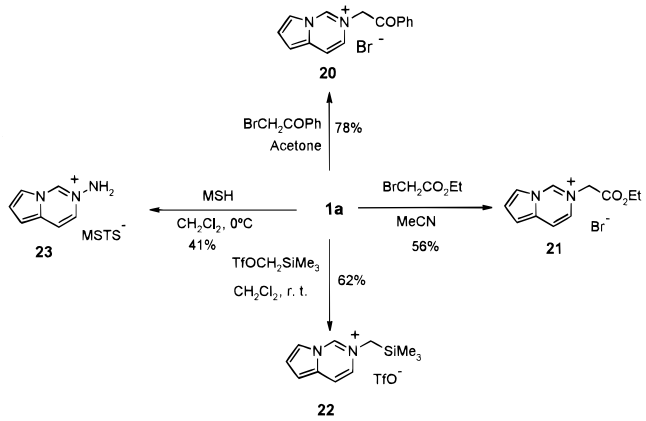
Contrary to experimental data, the C-5 and C-6 positions are preferred over the C-7 position for an electrophilic attack, according to the Mulliken charges shown in Figure 1. To elucidate this point, gas-phase basicities (GB) and proton affinities (PA) for these three positions and also for the N-2 position were calculated. Table 5 shows the calculated values, which do not change if the calculations are performed with a different basis set at the same level of theory. Although it is evident that the most stable structure is the N(2)-protonated form, values in Table 5 also show that protonation in C-7 affords a more stable form than the corresponding protonated species at C-5 and C-6. From the ranking of stabilities, and assuming the protonation as a model for electrophilic substitution, thermodynamic control can explain the experimental results.

(24) (a) Blache, Y.; Gueiffier, A.; Chavignon, J. C.; Teulade, J. C.; Milhavert, J. C.; Viols, A.; Chapat, J. P.; Dauphin, G. *J. Heterocycl. Chem.* **1994**, *31*, 161. (b) Irwin, W. J.; Wibberley, D. G.; Cooper, G. *J. Chem. Soc. C*, **1971**, 3870.

Scheme 3



Scheme 4



When **1a** was treated with 1.1 equiv of the nonnucleophilic base, lithium diisopropylamide (LDA), at −78 °C, followed by the addition of different electrophiles, 1-substituted derivatives **17a**−**c** were obtained (Scheme 3). It is noteworthy that derivatives **17** were formed along with the dimeric product **18** in all these reactions. All our attempts to improve the yields of derivatives **17** by minimizing the formation of **18**, either by using a large excess of the base or by performing the reaction with inverse addition, were unsuccessful.

The metalation at the C-1 position is consistent with theoretical calculations, which assign the lowest electronic density to this position. Nucleophilic addition also occurred at the C-1 position, as was shown in the reaction of **1a** with phenyllithium in THF at −78 °C. The 1-phenyl-1,2-dihydropyrrolo[1,2-*c*]pyrimidine **19** was formed in a 31% yield, along with decomposition products.

Following previously reported procedures,[4,7] the quaternization of **1a** (Scheme 4) with phenacyl bromide and ethoxycarbonylmethyl bromide reagents produced the corresponding salts **20** and **21** in 78% and 56% yield, respectively. Following the procedure originally described by Vedejs and Martinez,[25] the triflate salt **22** was also obtained in acceptable yield (62%) by reaction of **1a** with (trimethylsilyl)methyl triflate in CH_2Cl_2. N-Amination

(25) Vedejs, E.; Martinez, G. R. *J. Am. Chem. Soc.* **1979**, *101*, 6452.

Scheme 5

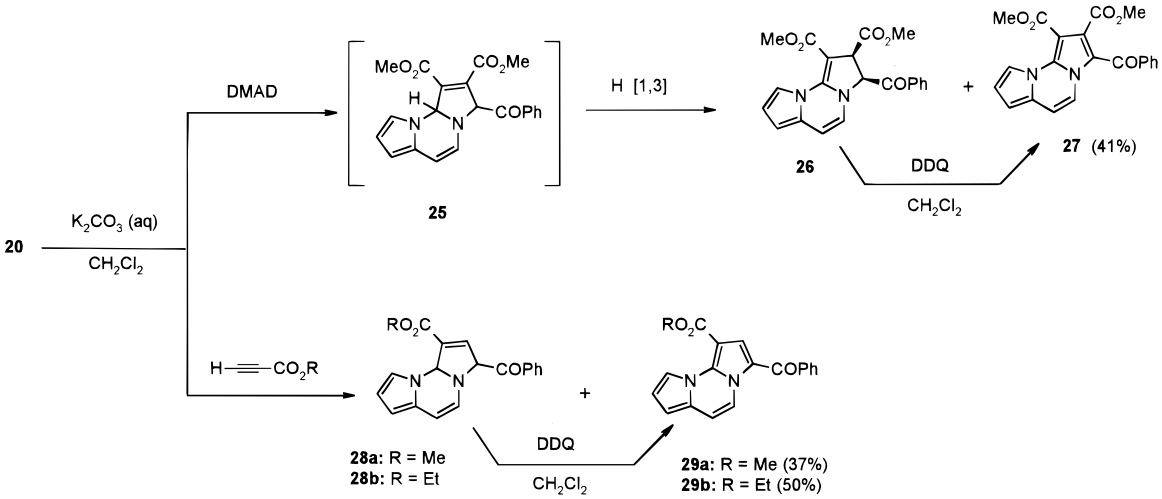
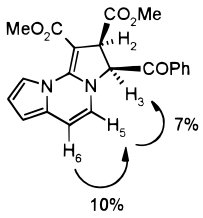


Chart 2



was accomplished by treatment of **1a** with *O*-(mesitylenesulfonyl)hydroxylamine (MSH)[26] in CH_2Cl_2 to give the *N*-amino salt **23** in moderate yield (41%).

The salt **20** reacted with the triple-bonded dipolarophile, dimethyl acetylenedicarboxylate (DMAD) in either homogeneous (THF, and Et_3N or Hünig base) or biphasic conditions. A complex mixture was obtained, with cycloadducts **26** and **27** being formed under all the conditions tested (Scheme 5). Under the more favorable conditions used, CH_2Cl_2/50% aqueous K_2CO_3, the mixture of **26** (28%) and **27** (14%) was separated using column chromatography. The dihydroderivative **26** or the whole mixture was easily and quantitatively converted into **27** by oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in CH_2Cl_2. The *cis* disposition for the C-2 methyl ester and C-3 benzoyl groups was easily established by ^{1}H NMR, which indicated a coupling constant of $J = 8.7$ Hz for the H-2 and H-3 protons. The ^{13}C NMR chemical shift of the carbonyl on the benzoyl group ($\delta =$ 197 Hz) and the NOE effect observed between H-5 and H-3 (Chart 2) support the position of a double bond on the pyrrole ring between C-10a and C-1.

The reaction with alkyl propiolates also proceeded under the same conditions and regioselectively produced the 1-alkoxycarbonyl-substituted cycloadducts **28** and **29** in moderate yields (Scheme 5). Both the dihydro derivative and the fully aromatized compound were separated by column chromatography, and **28** (or the mixture **28** and **29**) was oxidized to **29** using DDQ in CH_2Cl_2. The structure of the dihydroderivative **28**, bearing in this case the double bond between C-1 and C-2, is consistent with chemical shifts and coupling of H-10a, H-2, and H-3 protons. In both cycloadducts, but especially in **29**, the ester substitution on C-1 produces a notable deshielding of the H-9 protons that resonate at approximately δ 9.2 ppm in both **29a** and **29b** cycloadducts.

The salt **20** also reacted with 1,2-disubstituted double-bond dipolarophiles in MeCN/K_2CO_3 to give the corresponding cycloadducts (Scheme 6). The reaction with dimethyl fumarate produced two stereoisomers, **30** and **31**, in 29% and 17% yields, respectively, and the reaction with *N*-methylmaleimide stereoselectively produced the *endo* adduct **32** in a 52% yield. The stereochemical assignment for compounds **30** to **32** was made on the basis of ^{1}H NMR, ^{13}C NMR, and ^{1}H−^{13}C HETCOR data. In the *endo* product **30**, the H-10a proton resonates as a doublet with a coupling constant of $J = 8.1$ Hz, whereas the corresponding value of the coupling constant for the *exo* cycloadduct **31** is $J = 6.6$ Hz, thus supporting the *cis* and *trans* disposition for H-10a and H-1 in **30** and **31**, respectively. Whereas in both stereoisomers the coupling constants between H-1 and H-2 have the same value of $J = 5.7$ Hz, confirming the *trans* disposition of these hydrogens in both tetrahydroderivatives, H-3 appears coupled with H-2 with a coupling constant of $J = 6.1$ Hz in **30** while the same coupling in **31** gave a value of $J =$ 3.4 Hz, also confirming the *cis* and *trans* disposition of these hydrogens in **30** and **31**, respectively. The ^{1}H and ^{13}C HETCOR experiments allowed, for assignment of the chemical shift for C-10a in both stereoisomers, a value of δ 73.54 ppm for **30** and δ 74.05 ppm for **31**, consistent with previously reported data[27] establishing that, in similar fused pentagonal systems, the bridgehead carbon (C-10a) resonates at a higher field when H-10a and H-1 adopts a *cis* (**30**) rather than a *trans* orientation (**31**).

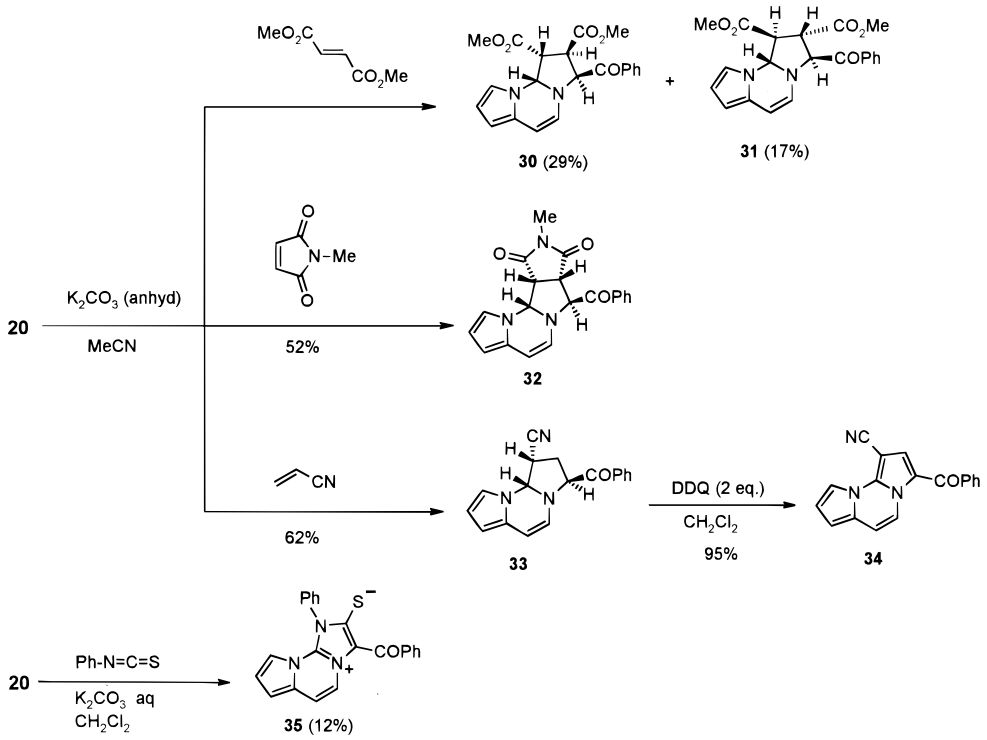
The stereochemistry for the endo cycloadduct **32** was established on the basis of coupling constants between H-11a and H-11b ($J = 7.3$ Hz), H-11b and H-3a ($J = 8.0$ Hz), and H-3a and H-4 ($J = 1.4$ Hz), which easily allowed for assignment of the *trans* disposition for H-3a/H-4 and the *cis* orientation of H-3a with respect to H-11b and H-11b with respect to H-11a.

The reaction with monosubstituted olefinic dipolarophiles, such as acrylonitrile, produced the *endo* regioisomer **33** in a 62% yield, under the same conditions, which was also easily transformed into the fully aromatic compound **34**, as described, in almost quantitative yield.

(26) Tamura, Y.; Minamikawa, J.; Ikeda, M. *Synthesis* **1977**, 1.

(27) (a) Toth, G.; Frank, J.; Bende, Z.; Weber, L.; Simon, K. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1961. (b) Chiu, I.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2857.

Scheme 6



The *exo* isomer was also detected with ^{1}H NMR, but chromatographic attempts to isolate and purify this adduct failed. The regio- and stereochemistry of the initial cycloadduct **33** was also determined by ^{1}H NMR on the basis of couplings (H-10a resonates as a doublet and H-3 hydrogen as a triplet) and the constant coupling between H-10a and H-1 (J = 7.0 Hz), which supports the *cis* orientation for these hydrogens.

With respect to the stereoselectivity observed, the reaction of **20** with mono- and disubstituted olefinic dipolarophiles preferred the *endo* approach[28] of the dipolarophile and the ylide, which seems to react through the *anti* form[29] in all cases. The exclusive participation of the *anti* form **24** of the ylide is related to the well-established higher stability of this form over the *syn* one, when ylides are stabilized by a carbonyl group.[29]

The stereoselectivity can be explained in terms of the transition states coming from the *endo* and *exo* approaches. As can be seen in Scheme 7, the *endo* approach is clearly favored over the *exo* in the case of *N*-methylmaleimide, because both the steric interaction between the benzoyl moiety of the ylide and the carbonyl of the dipolarophile and the interaction working between the heterocyclic nucleus and the carbonyl group of the maleimide are more favorable in the transition state, leading to the *endo* cycloadduct. In the case of the dimethyl fumarate, the attractive secondary interaction in the *endo* approach seems partially compensated by the unfavorable steric interaction working in this approach, when compared with the *exo* one. As a result, both the *endo* and *exo* cycloadducts are formed in the reaction of dimethyl fumarate with **20**.

The reaction of **20** with heterocumulenes, such as methyl isothiocyanate, produced complex mixtures of compounds under all conditions used, and the attempts to isolate the presumable cycloadducts were all unsuccessful. Only from the reaction of phenyl isothiocyanate in aqueous K_2CO_3/CH_2Cl_2 could the corresponding cycloadduct **35** (as heterobetainic form) be isolated, albeit in low yield (12%) (Scheme 6).

The formation of the corresponding azomethine ylides from salts **21**−**23** and its trapping with dipolarophiles was also investigated (Scheme 8). The reaction of **21** with acetylenic dipolarophiles, such as DMAD and methyl propiolate, afforded complex mixtures under the same conditions used for salt **20**, with the hydroxy derivative **38** being the only isolated product, with yields ranging from 40% to 63%, depending on the reaction times. The use of anhydrous K_2CO_3 in acetonitrile allowed isolation of the cycloadducts **37** and **39**, although only in 10% and 12% yields, respectively. In both reactions, the derivative **38** was also formed as the main product (50% and 37% yields, respectively). Similar results were obtained under homogeneous conditions (dry THF, Hünig's base). Analogous formation of hydroxy derivatives has been described for pyrimidines bearing electron-withdrawing substituents either in basic or acid media.[30] The treatment of **22** with cesium fluoride and subsequent attempts to trap the ylide thus generated were all unsuccessful with DMAD as dipolarophile. In contrast, the regioisomer **41** was isolated in a 15% yield with methyl propiolate.

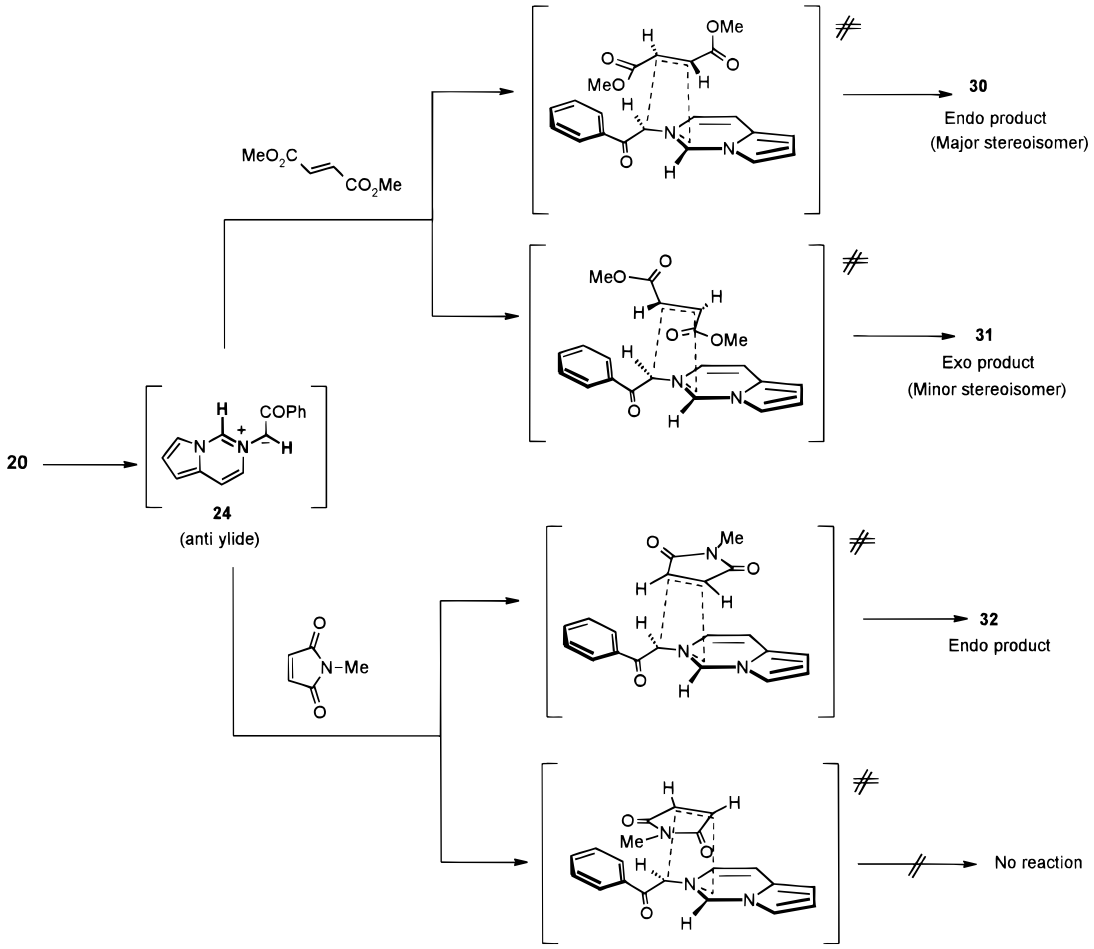
Finally, all of our attempts to generate the corresponding ylides from the *N*-amino salt **23** in the presence of

(28) (a) Tsuge, O.; Kanemasa, S.; Takenaka, S.; Kuraoka, S. *Chem. Lett.* **1984**, 465. (b) Tsuge, O.; Kanemasa, S.; Takenaka, S.*Bull. Chem. Soc. Jpn.* **1986**, *59*, 3631. (c) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1489. (d) Lakhlifi, T.; Sedqui, A.; Fathi, T.; Laude, B.; Robert, J. F. *Can. J. Chem.* **1994**, *72*, 1417.

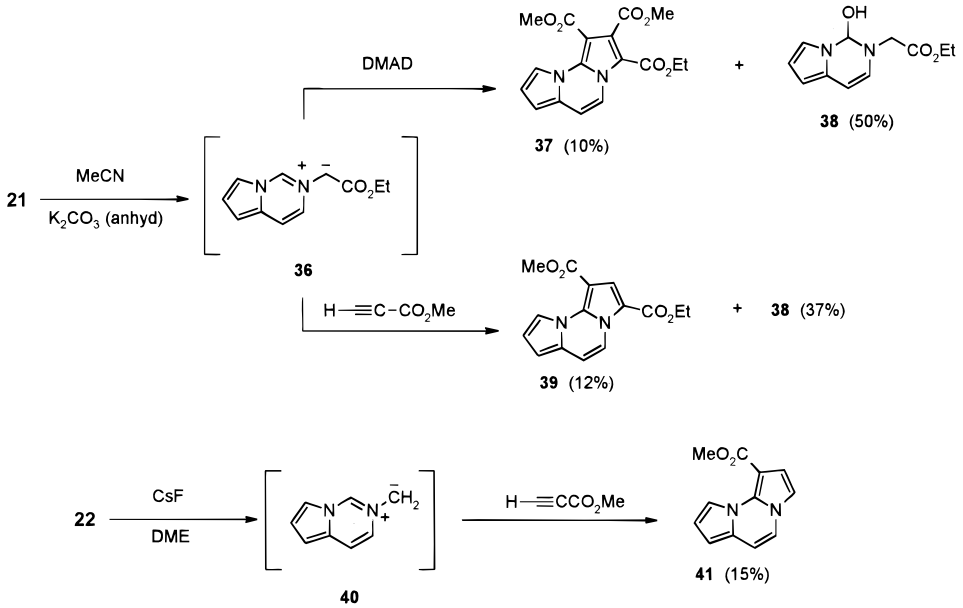
(29) (a) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3137. (b) Tsuge, O.; Kanemasa, S.; Takenaka, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 3320.(c) Jones, R.; Howard, K.; Snaith, J. S.; *Tetrahedron Lett.* **1996**, 37, 1707.

(30) (a) Biffin, M. E.; Brown, D. J.; Lee, T. C. *J. Chem. Soc. C* **1967**, 573. (b) Brown, D. J.; Ford, B. W.; Pudden-Row: M. N. *J. Chem. Soc. C* **1968**, 1452. (c) Keilen, G.; Undheim, K. *Acta Chem. Scand. Ser. B* **1988**, *42*, 362.

Scheme 7



Scheme 8



typical acetylenic or olefinic dipolarophiles led to complex reaction mixtures from which the expected cycloadducts were not easily isolated. More than likely, the low stability of this salt under basic conditions precluded the formation of cycloadducts even under mild conditions.

In conclusion, this work describes a new and efficient synthetic method for the pyrrolo[1,2-*c*]pyrimidine system and some of its derivatives, together with the more significant structural features of this poorly studied heterocycle. The study also includes some relevant aspects of the basic chemistry of the system, with emphasis on electrophilic substitution, nucleophilic addition, metalation, and N-alkylation reactions. The cycloaddition reactions of the azomethine ylides generated

from pyrrolo[1,2-*c*]pyrimidinium salts afforded new dipyrrolo[1,2-*a*;1′,2′-*c*]pyrimidine derivatives, although yields of cycloaddition products were relatively low with ethoxycarbonyl-stabilized and nonstabilized ylides. Cycloadducts from the reaction of 2-phenacylpyrrolo[1,2-*c*]-pyrimidinium salt **20** and acetylenic and olefinic dipolarophiles such as DMAD, alkyl propiolates, *N*-methylmaleimide, dimethyl fumarate, and acrylonitrile were obtained in better overall yields, with high regio- and stereoselectivity.

Experimental Section

General experimental conditions were as described previously.[4] 4-Bromopyrrolo-2-carboxaldehyde[31] (**8b**), 4-methylpyrrolo-2-carboxaldehyde[32] (**8c**), 4-butylpyrrolo-2-carboxaldehyde[32] (**8d**), 4-allylpyrrolo-2-carboxaldehyde[32] (**8e**), 4-methoxycarbonylpyrrolo-2-carboxaldehyde[33] (**8f**), 4-acetyl-3,5-dimethylpyrrolo-2-carboxaldehyde[34] (**8g**), 5-methylpyrrolo-2-carboxaldehyde[35] (**8h**), 5-(imidazol-1-ylmethyl)pyrrolo-2-carboxaldehyde[36] (**8i**), and 4-ethyl-3,5-dimethylpyrrolo-2-carboxaldehyde[37] (**8j**) were prepared following previously published methods.

3-(Ethoxycarbonyl)pyrrolo[1,2-*c*]pyrimidine (9a). 2-Pyrrolocarboxaldehyde (1 g, 10.5 mmol) in 10 mL of THF was added, under argon atmosphere, to ethyl isocyanoacetate (1.19 g, 10.5 mmol) and DBU (1.6 g, 10.5 mmol) in 15 mL of dry THF. The reaction mixture was stirred at room temperature for 5 h and then neutralized with 10% acetic acid. The solvent was removed under reduced pressure, and the residue was extracted with EtOAc and washed with H_2O and brine. The organic extracts were dried over Na_2SO_4, removed, and purified by silica gel chromatography using hexane/EtOAc (3:7) as the eluent. The title compound (1.47 g, 71%) was obtained as a white solid: mp 69−71 °C (Hex/EtOAc); IR (KBr) 1598, 1435, 1187; ^{1}H NMR (300 MHz, $CDCl_3$) 8.91 (s, 1H), 8.21 (s, 1H), 7.53 (dd, 1H, J = 2.5, 1.1 Hz), 6.98 (dd, 1H, J = 4.0, 2.5 Hz), 6.76 (dd, 1H, J = 4.0, 1.1 Hz), 4.43 (q, 2H, J = 7.2 Hz), 1.42 (t, 3H, J = 7.2 Hz). Anal. Calcd for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 63.29; H, 5.44; N, 14.89.

3-(Pyrrolo[1,2-*c*]pyrimidine)carboxylic Acid (10a). 9a (0.9 g, 4.7 mmol) in 30 mL of 6 N HCl was refluxed for 18 h. The solvent was then removed under reduced pressure, and the precipitate was filtered off and washed with Et_2O to give **10a** as a green solid (0.61 g, 80%): mp 246−248 °C (EtOH); IR (KBr) 1725, 1590, 1210, 1047 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.20 (s, 1H), 8.18 (s, 1H), 7.87 (d, 1H, J = 1.4 Hz), 7.04−7.02 (m, 1H), 6.83 (d, 1H, J = 3.4 Hz), 3.90 (bs, 1H). Anal. Calcd for $C_8H_6N_2O_2$: C, 65.26; H, 3.73; N, 17.28. Found: C, 65.50; H, 3.61; N, 17.21.

3-(Pyrrolo[1,2-*c*]pyrimidine)carboxaldehyde (11a). A solution of DIBAL 1.0 M in hexane (1.44 mL) was added dropwise to a stirred solution of ester **9a** (0.25 g, 1.31 mmol) in 8 mL of dry THF at −78 °C. The mixture was stirred for 3 h at −78 °C and then allowed to rise gradually to room temperature and stirred overnight. The reaction was quenched with a saturated solution of ammonium chloride. The mixture was extracted with EtOAc, and the organic extracts were washed with water and brine and dried over Na_2SO_4. Removal of the solvent gave a residue that was purified by chromatography (hex/EtOAc, 7:3) to yield the formyl derivative **11a** (108 mg, 62%) as a green powder: mp 104−107 °C (EtOH); IR (KBr) 1684, 1521, 1073 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.89 (s, 1H), 8.85 (s, 1H), 7.99 (s, 1H), 7.58−7.55 (m, 1H), 7.04−7.01 (m, 1H), 6.89 (d, 1H, J = 3.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 190.2, 138.4, 132.2, 123.1, 118.4, 114.2, 112.8, 107.3. Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.98; H, 4.11; N, 19.13.

Synthesis of 3-Tosylpyrrolo[1,2-*c*]pyrimidine Derivatives 12. General Procedure. The corresponding pyrrolo-2-carboxaldehyde **8** (1 mmol) in 5 mL of dry THF was added to a mixture of TOSMIC (214 mg, 1.1 mmol) and DBU (167 mg, 1.1 mmol) in 3 mL of dry THF under argon. The mixture was stirred at room temperature and then neutralized with acetic acid. The solvent was removed under reduced pressure, and the residue was purified with a silica gel column to yield **12**, which was recrystallized from the appropriate solvent.

3-Tosylpyrrolo[1,2-*c*]pyrimidine (12a). After the mixture was stirred for 2 h, chromatography (hexanes−EtOAc 7:3) produced 223 mg of **12a** (82%): mp 200−202 °C (white powder, MeCN); IR (KBr) 1594, 1301, 1147 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.25 (s, 1H), 7.94 (d, 2H, J = 8.2 Hz), 7.49 (d, 1H, J = 2.9 Hz), 7.31 (d, 2H, J = 8.2 Hz), 7.02 (dd, 1H, J = 4.0, 2.9 Hz), 6.82 (d, 1H, J = 4.0 Hz), 2.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.4, 140.9, 138.7, 136.4, 129.6, 129.4, 128.5, 118.4, 115.2, 113.9, 106.0, 21.6; MS *m*/*z* (rel int) 272 (M^+, 29), 207 (18), 139 (18), 106 (100). Anal. Calcd for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.44; N, 10.29. Found: C, 61.50; H, 4.58; N, 10.58.

6-Bromo-3-tosylpyrrolo[1,2-*c*]pyrimidine (12b). After the mixture was stirred for 5 h and the usual workup occurred, chromatography (hexanes−EtOAc 7:3) produced 0.55 g (79%) of **12b**: mp 223−224 °C (white powder, hexanes−EtOAc); IR (KBr) 1595, 1293, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.15 (s, 1H), 7.91 (d, 2H, J = 8.1 Hz), 7.49 (s, 1H), 7.30 (d, 2H, J = 8.1 Hz), 6.82 (s, 1H), 2.40 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.8, 142.5, 137.5, 130.1, 129.9, 128.8,113.8, 113.6, 109.0, 108.3, 21.7. Anal. Calcd for $C_{14}H_{11}BrN_2O_2S$: C, 47.88; H, 3.16; N, 7.98. Found: C, 48.15; H, 3.25; N, 8.22.

6-Methyl-3-tosylpyrrolo[1,2-*c*]pyrimidine (12c). After the mixture was stirred for 3 h and the usual workup occurred, chromatography (hexanes−EtOAc 8:2) produced 0.83 g (58%) of **12c**: mp 180−181 °C (yellow prisms, MeCN); IR (KBr) 2928, 1595, 1306, 1145 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.60 (s, 1H), 8.12 (s, 1H), 7.91 (d, 2H, J = 7.7 Hz), 7.30 (d, 2H, J = 7.7 Hz), 7.28 (s, 1H), 6.62 (s, 1H), 2.39 (s, 3H), 2.33 (s, 3H). Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found: C, 63.21; H, 4.88; N, 9.89.

6-Butyl-3-tosylpyrrolo[1,2-*c*]pyrimidine (12d). After the mixture was stirred for 15 h and the usual workup occurred, chromatography (hexanes−EtOAc 8:2) produced 0.48 g (73%) of **12d**: mp 100−102 °C (gray powder, MeCN,); IR (KBr) 2928, 1596, 1360, 1149 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 8.13 (s, 1H), 7.92 (d, 2H, J = 8.1 Hz), 7.30 (d, 2H, J = 8.1 Hz), 7.28 (s, 1H), 6.64 (s, 1H), 2.67 (t, 2H, J = 7.3 Hz), 2.39 (s, 3H), 1.67−1.57 (m, 2H), 1.39−1.32 (m, 2H), 0.92 (t, 3H, J = 7.3 Hz). Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 66.01; H, 6.23; N, 8.67.

6-(2-Propenyl)-3-tosylpyrrolo[1,2-*c*]pyrimidine (12e). After the mixture was stirred for 5 h and the usual workup occurred, chromatography (hexane/EtOAc 7:3) produced 341 mg (61%) of **12e**: mp 237−238 °C (white powder, MeCN); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.64 (s, 1H), 8.15 (s, 1H), 7.91 (d, 2H, J = 8.1 Hz), 7.31 (s, 1H), 7.29 (d, 2H, J = 8.1 Hz), 6.65 (s, 1H), 6.01−5.89 (m, 1H), 5.13 (dd, 1H, J = 7.5, 1.3 Hz), 5.09 (s, 1H), 3.44 (d, 2H, J = 6.6 Hz), 2.39 (s, 3H). Anal. Calcd for $C_{17}H_{16}N_2O_2S$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.30; H, 5.31; N, 8.78.

6-Methoxycarbonyl-3-tosylpyrrolo[1,2-*c*]pyrimidine (12f). After the mixture was stirred for 3 h and the usual workup occurred, chromatography (hexanes−EtOAc,1:1) produced 0.45 g (69%) of **12f**: mp 210−212 °C (white powder, MeCN); IR (KBr)1705, 1523, 1324, 1151 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.72 (s, 1H), 8.25 (s, 1H), 7.97 (d, 1H, J = 0.8 Hz), 7.93 (d, 2H, J = 8.2 Hz), 7.33 (d, 2H, J = 8.2 Hz), 7.18 (d,1H, J = 0.8 Hz), 3.91 (s, 3H), 2.41 (s,3H). Anal. Calcd for

(31) Sonnet, P. *J. Org. Chem.* **1971**, *36*, 1005.
(32) Muchowski, J. M.; Hess, P. *Tetrahedron Lett.* **1988**, *29*, 3215.
(33) Anderson, H.; Loader, C.; Foster, A. *Can. J. Chem.* **1980**, *58*, 2527.
(34) Chong, R.; Clezy, P. S.; Liepa, A. J.; Nichol, A. W. *Aust. J. Chem.* **1969**, *22*, 229.
(35) Pale-Grosdemange, C.; Chuchue, J. *Tetrahedron* **1989**, *45*, 3397.
(36) Martinez, G. R.; Walker, K. A.; Hirschfeld, D. R.; Maloney, P. J.; Yang, D. S.; Rosenkranz, R. P. *J. Med. Chem.* **1989**, *32*, 890.
(37) Woodward, R.; Ayer, W.; Beaton, J.; Bonnett, Closs, G. L.; Dutler, H.; Leimbruger, W.; Sauer, J.; Volz, H. *Tetrahedron* **1990**, *46*, 7599.

$C_{16}H_{14}N_2O_4S$: C, 58.17; H, 4.27; N, 8.48. Found: C, 58.48; H, 4.40; N, 8.40.

6-Acetyl-5,7-dimethyl-3-tosylpyrrolo[1,2-*c*]pyrimidine (12g). After the mixture was stirred for 4 h and the usual workup occurred, chromatography (hexane/EtOAc 3:7) produced 513 mg (75%) of **12g**: mp 214−215 °C (yellow powder, MeCN); IR (KBr) 1701, 1584, 1294, 1162 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.54 (d, 1H, J = 1.4 Hz), 8.20 (d, 1H, J = 1.4 Hz), 7.92 (d, 2H, J = 8.1 Hz), 7.32 (d, 2H, J = 8.1 Hz), 2.69 (s, 3H), 2.59 (s, 3H), 2.53 (s, 3H), 2.39 (s, 3H). Anal. Calcd for $C_{18}H_{18}N_2O_3S$: C, 63.14; H, 5.30; N, 8.18. Found: C, 63.14; N, 5.42; N, 8.42.

7-Methyl-3-tosylpyrrolo[1,2-*c*]pyrimidine (12h). After the mixture was stirred for 12 h and the usual workup occurred, chromatography (hexane/EtOAc 7:3) produced 0.43 g (76%) of **12h**: mp 203−205 °C (white powder, MeCN); IR (KBr) 1592, 1312, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.56 (s, 1H), 8.20 (d, 1H, J = 1.5 Hz), 7.93 (d, 2H, J = 8.2 Hz), 7.30 (d, 2H, J = 8.2 Hz), 6.76−6.73 (m, 2H), 2.54 (s, 3H), 2.39 (s, 3H). Anal. Calcd for $C_{15}H_{14}N_2O_2S$: C, 62.92; H, 4.93; N, 9.78. Found: C, 62.79; H, 5.05; N, 10.07.

7-(Imidazo-1-ylmethyl)-3-tosylpyrrolo[1,2-*c*]pyrimidine (12i). After the mixture was stirred for 5 h and the usual workup occurred, chromatography (CH_2Cl_2/MeOH 9.5:0.5) produced 0.56 g (80%) of **12i**: mp 98−99 °C (hexanes−EtOAc, white powder); IR (KBr) 1594, 1350, 1150 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.25 (s, 1H);7.89 (d, 2H, J = 7.9 Hz), 7.46 (s, 1H), 7.28 (d, 2H, J = 7.9 Hz), 7.05−7.03 (m, 2H), 6.84−6.82 (m, 2H), 5.46 (s, 2H), 2.40 (s, 3H). Anal. Calcd for $C_{18}H_{16}N_4O_2S$: C, 61.35; H, 4.58; N, 15.90. Found: C, 59.97; H, 4.85; N, 16.32.

6-Ethyl-5,7-dimethyl-3-tosylpyrrolo[1,2-*c*]pyrimidine (12j). After the mixture was stirred for 10 h and the usual workup occurred, chromatography (hexane/EtOAc 8:2) produced 0.45 g (69%) of **12j**: mp 191−192 °C (yellow powder, MeCN); IR (KBr) 1593, 1314, 1147 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.42 (d, 1H, J = 1.4 Hz), 8.13 (d, 1H, J = 1.4 Hz), 7.92 (d, 2H, J = 8.2 Hz), 7.29 (d, 2H, J = 8.2 Hz), 2.63 (q, 2H, J = 7.6 Hz), 2.43 (s, 3H), 2.39 (s, 3H), 2.32 (s, 3H), 1.12 (t, 3H, J = 7.6 Hz). Anal. Calcd for $C_{18}H_{20}N_2O_2S$: C, 65.83; H, 6.14; N, 8.53. Found: C, 65.95; H, 6.30; N, 8.91.

Synthesis of Pyrrolo[1,2-*c*]pyrimidine Derivatives 1. General Procedure. A suspension of Na_2HPO_4 (639 mg, 4.5 mmol) in anhydrous MeOH (15 mL) and **12** (272 mg, 1 mmol) in anhydrous THF (10 mL) were successively added to 6% sodium amalgam (184 mg, 8 mmol Na) under argon. The reaction mixture was stirred at room temperature for 3 h and then diluted with water and extracted with Et_2O. The organic layer was dried over Na_2SO_4, the solvent removed under reduced pressure, and the residue separated on silica gel column chromatography (CH_2Cl_2−acetone, 9.5:0.5 unless otherwise indicated) to give the corresponding pyrrolo[1,2-*c*]-pyrimidines **1**, which in some cases were isolated as hydrobromides by addition of hydrobromic acid in EtOH.

Pyrrolo[1,2-*c*]pyrimidine (1a) was prepared according to standard procedures in a 51% yield: mp 42−44 °C (from hexanes−EtOH) (lit.[9] mp 37−39 °C); IR (KBr) 1612, 1232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H), 7.36 (d, 1H, J = 6.5 Hz), 7.34 (dd, 1H, J = 2.9, 1.5 Hz), 7.21 (dd, 1H, J = 6.5,1.5 Hz), 6.87 (dd, 1H, J = 4.0, 2.9 Hz), 6.43 (dd, 1H, J = 4.0, 1.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.5, 136.1, 130.9, 115.8, 113.1, 110.3, 99.3; MS *m*/*z* (rel int) 118 (M^+, 100), 91 (26), 80 (28).

6-Bromopyrrolo[1,2-*c*]pyrimidine hydrobromide (1b) was prepared according to standard procedures in a 15% yield and characterized as hydrobromide: mp >300 °C (from EtOH brown powder); IR (KBr) 3063,1643, 1144 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.42 (d, 1H, J = 6.4 Hz), 7.38 (s, 1H), 7.15 (dd, 1H, J = 6.4 and 1.4 Hz); 6.47 (s, 1H). Anal. Calcd for $C_7H_6Br_2N_2$: C, 30.25; H, 2.18; N, 10.08. Found: C, 30.30 H, 2.25 N, 9.74.

6-Methylpyrrolo[1,2-*c*]pyrimidine hydrobromide (1c) was prepared according to standard procedures in a 77% yield (green oil) and characterized as hydrobromide: mp 235−237 °C (EtOAc−EtOH); IR (KBr) 2654, 1646, 1203, 1137 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.76 (s, 1H),7.62 (d, 1H, J = 7.2 Hz), 7.46 (d, 1H, J = 7.2 Hz), 6.68 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.3, 130.7, 122.2, 112.9, 112.6, 107.1, 104.3, 11.8. Anal. Calcd for $C_8H_9BrN_2$: C, 45.10; H, 4.26; N, 13.15. Found: C, 44.76; H, 4.31; N, 13.08.

6-Butylpyrrolo[1,2-*c*]pyrimidine hydrobromide (1d) was prepared according to standard procedures in a 54% yield (colorless oil) and characterized as hydrobromide: mp 193−195 °C (white powder, EtOAc−EtOH); IR (KBr) 2641, 1648, 1209 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.68 (s, 1H), 7.70 (s, 1H), 7.54 (d, 1H, J = 7.0 Hz), 7.41 (d, 1H, J = 7.0 Hz), 6.63 (s, 1H), 2.67 (t, 2H, J = 7.3 Hz), 1.60 (qi, 2H, J = 7.3 Hz), 1.33 (sext, 2H, J = 7.3 Hz), 0.89 (t, 3H, J = 7.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 140.5, 135.8, 121.9, 112.7, 112.4, 103.3, 31.3, 25.8, 21.3, 13.2. Anal. Calcd for $C_{11}H_{15}BrN_2$: C, 51.78 H, 5.93; N, 10.98. Found: C, 52.03; H, 6.02; N, 11.36.

6-(2-Propenyl)pyrrolo[1,2-*c*]pyrimidine hydrobromide (1e) was prepared according to standard procedures in a 73% yield using hexane/EtOAc (7:3) as the eluent (colorless oil) and characterized as a hydrobromide: mp >300 °C (white prisms, EtOAc−EtOH); IR (KBr) 1645, 1149 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.70 (s, 1H), 7.35 (d, 1H, J = 6.5 Hz), 7.16 (s, 1H), 7.14 (dd, 1H, J = 6.5, 1.5 Hz), 6.30 (s, 1H), 6.07−5.98 (m, 1H), 5.15 (dd, 1H, J = 17, 1.5 Hz), 5.10 (dd, 1H, J = 10.3, 1.5 Hz), 3.45 (d, 2H, J = 6.5 Hz); MS *m*/*z* (rel int) 159 (M^+, 43), 158 (100), 157 (99). Anal. Calcd for $C_{10}H_{11}BrN_2$: C, 50.23; H, 4.64; N, 11.72. Found: C, 49.98; H, 4.78; N, 11.80.

6-Methoxycarbonylpyrrolo[1,2-*c*]pyrimidine (1f) was prepared according to standard procedures in a 12% yield: mp 98−99 °C (brown powder, EtOH); IR (KBr) 1720, 1668, 1220 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.76 (s, 1H, H1), 7.87 (s, 1H), 7.42 (d, 1H, J = 6.2 Hz), 7.23 (d, 1H, J = 6.2 Hz), 6.82 (s, 1H), 3.90 (s, 3H). Anal. Calcd for $C_9H_8N_2O_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.54; H, 4.40; N, 15.68.

6-(1-Hydroxyethyl)-5,7-dimethylpyrrolo[1,2-*c*]pyrimidine hydrobromide (1g) was prepared according to standard procedures in a 58% yield (orange oil) and characterized as hydrobromide: mp >300 °C (EtOH, yellow powder); IR (KBr) 3363, 1621, 1181, 1084 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 9.61 (s, 1H), 7.66 (d, 1H, J = 7.2 Hz), 7.31 (d, 1H, J = 7.2 Hz), 5.04 (q, 1H, J = 6.6 Hz), 2.57 (s, 3H), 2.31 (s, 3H), 1.36 (d, 3H, J = 6.6 Hz); MS *m*/*z* (rel int) 190 (M^+, 100), 171 (64), 147 (88). Anal. Calcd for $C_{11}H_{15}BrN_2O$: C, 48.73; H, 5.58; N, 10.33. Found: C, 48.98; H, 5.51; N, 10.08.

7-Methylpyrrolo[1,2-*c*]pyrimidine (1h) was prepared according to standard procedures in a 74% yield: mp 56−57 °C (from CH_3CN, white powder); IR (KBr) 2923, 1650, 1148 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.62 (s, 1H), 7.36 (d, 1H, J = 6.3 Hz), 7.20 (dd, 1H. H3, J = 6.4, 1.5 Hz), 6.61 (d, 1H, J = 3.6 Hz), 6.37 (d, 1H, J = 3.6 Hz), 2.55 (s, 3H). Anal. Calcd for $C_8H_9BrN_2$: C, 45.10; H, 4.26; N, 13.15. Found: C, 44.77; H, 4.21; N, 13.31.

7-(Imidazol-1-ylmethyl)pyrrolo[1,2-*c*]pyrimidine (1i) was prepared according to standard procedures in a 55% yield using CH_2Cl_2−MeOH (9:1) as the eluent: mp 147−149 °C (white powder, EtOAc); IR (KBr) 1612, 1272 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.49 (s, 1H), 7.48 (s, 1H), 7.45 (d, 1H, J = 6.4 Hz), 7.26 (dd, 1H, J = 6.4 y 1.6 Hz), 7.05 (s, 1H), 6.90 (d, 1H, J = 3.7 Hz), 6.86−6.83 (m, 1H), 6.45 (d, 1H, J = 3.7 Hz), 5.44 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.7, 135.9, 133.2, 132.1, 130.3, 118.6, 118.1, 116.4, 113.9, 99.7, 42.3; MS *m*/*z* (rel int) 198 (M^+, 16), 131 (100), 104 (93). Anal. Calcd for $C_{11}H_{10}N_4$: C, 66.65; H, 5.08; N, 28.26. Found: C, 66.38; H, 5.49; N, 27.50.

6-Ethyl-5,7-dimethylpyrrolo[1,2-*c*]pyrimidine hydrobromide (1j) was prepared according to standard procedures in an 83% yield (reddish oil) and characterized as a hydrobromide: mp 272−274 °C (yellow powder, EtOH); IR (KBr) 1645, 1227; ^1H NMR (300 MHz, DMSO-d_6) 9.61 (s, 1H), 7.65 (d, 1H, J = 7.1 Hz), 7.30 (d, 1H, J = 7.1 Hz), 2.64 (q, 2H, J = 7.5 Hz), 2.48 (s, 3H), 2.26 (s, 3H), 1.09 (t, 3H, J = 7.5 Hz); ^{13}C NMR (50 MHz, DMSO-d_6) 139.5, 135.1, 125.1, 120.8, 117.1, 112.6, 112.1, 17.3, 14.6, 8.7, 8.0. Anal. Calcd for $C_{11}H_{15}BrN_2$: C, 51.78; H, 5.93; N, 10.98. Found: C, 51.90; H, 5.80; N, 11.24.

7-Pyrrolo[1,2-*c*]pyrimidinecarboxaldehyde (13). DMF (136 mg, 1.86 mmol) was added to a suspension of $POCl_3$ (286 mg, 1.86 mmol) in dry Et_2O (4 mL) and cooled to 0 °C. The reaction mixture was stirred until an insoluble oil was formed (approximately 10 min). The oil was then dissolved in CH_2Cl_2 (3 mL), and a CH_2Cl_2 solution (7 mL) containing **1a** (200 mg, 1.7 mmol) was added. The reaction mixture was then stirred for 5 h at room temperature, the solvent evaporated under reduced pressure, and the residue poured into water (15 mL). The solution was neutralized with NaOAc and extracted with EtOAc, the organic phase dried (Na_2SO_4), and the solvent removed under reduced pressure. The oily residue was chromatographed using hexane/EtOAc 8:2 to produce the formyl derivative **13**, which was recrystallized from EtOH to give 155 mg (63%) of white needles: mp 114−115 °C; IR (KBr) 1636, 1604, 1251 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.31 (d, 1H, J = 1.6 Hz), 9.79 (s, 1H), 7.87 (d, 1H, J = 6.3 Hz), 7.54 (d, 1H, J = 4.3 Hz), 7.44 (dd, 1H, J = 6.3, 1.6 Hz), 6.58 (d, 1H, J = 4.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 178.0, 140.9, 140.0, 138.5, 130.1, 128.6, 113.6, 103.1. Anal. Calcd for $C_8H_6N_2O$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.91; H, 4.06; N, 19.01.

Bromination of 1a (NBS, 1 Equiv). NBS (295 mg, 1.7 mmol) was added to a solution of **1a** (200 mg, 1.7 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. It was then poured into cold water and extracted with CH_2Cl_2. The organic phase was washed with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the residue was chromatographed using hexane/EtOAc (9.5:0.5) as the eluent to give 94 mg (38%) of **14.** Elution with hexane/EtOAc (8:2) produced the dibromo derivative **15 (**197 mg, 42%).

7-Bromopyrrolo[1,2-*c*]pyrimidine (14): mp 64−66 °C (white powder, EtOH); IR (KBr) 1615, 1280, 1030 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.84 (s, 1H), 7.46 (d, 1H, J = 6.2 Hz), 7.19 (d, 1H, J = 6.2 Hz), 6.86 (d, 1H, J = 4.0 Hz), 6.50 (d, 1H, J = 4.0 Hz). Anal. Calcd for $C_7H_5BrN_2$: C, 42.67; H, 2.56; N, 14.22. Found: C, 42.87; H, 2.64; N, 13.98.

5,7-Dibromopyrrolo[1,2-*c*]pyrimidine (15): mp 97−98 °C (white powder, EtOH); IR (KBr) 1606, 1282, 1231 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.78 (s, 1H), 7.54 (d, 1H, J = 6.5 Hz), 7.20 (dd, 1H, J = 6.5, 1.4 Hz), 6.88 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) 137.0,132.3, 119.5, 112.9, 111.3, 91.5, 87.6. Anal. Calcd for $C_7H_4Br_2N_2$: C, 30.47; H, 1.46; N, 10.15. Found: C, 30.65; H, 1.35; N, 10.34.

Bromination of 1a (NBS, 2 Equiv). NBS (0.62 g, 3.56 mmol) was added to a solution of **1a** (200 mg, 1.7 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The mixture was stirred at room temperature for 15 h, poured into cold water, and extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the crude extract was purified by chromatography, producing 360 mg (77%) of **15**.

7-Dimethylaminomethylpyrrolo[1,2-*c*]pyrimidine Hydrochloride (16). 1a (100 mg, 0.85 mmol) was added to a solution of formaldehyde (40%, 70 mg, 0.93 mmol) and dimethylamine hydrochloride (76 mg, 0.93 mmol) in 5 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 20 h. The precipitate was filtered and washed with CH_2Cl_2 to produce the title compound as a gray powder: yield 104 mg, 58%; mp 181−182 °C (EtOH); IR (KBr) 2468, 1614, 1318, 1141 cm^{-1}; ^1H NMR (300 MHz, CD_3OD) δ 9.30 (s, 1H), 7.50 (d, 1H, J = 6.2 Hz), 7.45 (d, 1H, J = 6.2 Hz), 7.20 (d, 1H, J = 4.0 Hz), 6.64 (d, 1H, J = 4.0 Hz), 4.83 (s, 2H), 2.91 (s, 6H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 138.5, 132.7, 132.0, 120.9,113.1, 113.0, 99.8, 49.4,41.1. Anal. Calcd $C_{10}H_{14}ClN_3$: C, 56.74; H, 6.67; N, 19.85. Found: C, 56.89; H, 6.82; N, 19.58.

Metalation Reactions. General Procedure. A 2 M solution of LDA in THF (0.95 mL, 1.90 mmol) was added to a solution of **1a** (200 mg, 1.7 mmol) in 10 mL of dry THF at −78 °C under argon. The corresponding electrophile (1.90 mmol) was added after stirring for 40 min at −78 °C, and the reaction mixture was stirred for the appropriate time. The reaction mixture was then quenched with a saturated solution of NH_4Cl and extracted with Et_2O. The combined organic extracts were washed with water and brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude extract was purified by chromatography.

1-Methylpyrrolo[1,2-*c*]pyrimidine (17a). Following the general method, methyl iodide (270 mg, 1.90 mmol) was added at −78 °C to the lithiated intermediate. The mixture was stirred for 14 h, and the residue was chromatographed using hexane/EtOAc 8:2 as the eluent to produce **17a** as a dark oil (87 mg, 39%): IR (KBr) 2922, 1615, 1292 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, 1H, J = 6.5 Hz), 7.25−7.22 (m, 1H), 7.18 (d, 1H, J = 6.5 Hz), 6.88 (dd, 1H, J = 3.8, 2.5 Hz), 6.47 (d, 1H, J = 3.8 Hz), 2.71 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.4, 132.3, 131.2, 115.8, 111.7, 109.9, 100.1, 21.0. Anal. Calcd for $C_8H_8N_2$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.65; H, 6.23; N, 20.95.

1-Pyrrolo[1,2-*c*]pyrimidine Carboxaldehyde (17b). DMF (140 mg, 1.90 mmol) was added following the general method, and the mixture was stirred at −78 °C for 9 h. After the usual workup, the oily crude extract was purified using silica gel chromatography with hexane/EtOAc 9:1 to give the title compound (77 mg, 31%) as a red powder and 76 mg (38%) of the dimer **18** as a yellow solid: mp 58−59 °C (EtOH); IR (KBr) 1682, 1224, 1089, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.98 (s, 1H), 8.84 (d, 1H, J = 2.2 Hz), 7.73 (d, 1H, J = 5.8 Hz), 7.58 (d, 1H, J = 5.8 Hz), 7.11 (dd, 1H, J = 4.1, 2.2 Hz), 6.76 (d, 1H, J = 4.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 188.0, 139.5, 134.4, 130.5, 118.4, 117.9, 114.2, 102.4. Anal. Calcd for $C_8H_6N_2$: C, 65.75; H, 4.14; N, 19.17. Found: C, 65.48; H, 4.19; N, 19.30.

1-(Pyrrolo[1,2-*c*]pyrimidin-1-yl)pyrrolo[1,2-*c*]pyrimidine (18): mp 137−139 °C (yellow powder, EtOH); IR (KBr) 1598, 1277, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.39 (d, 2H, J = 2.5 Hz), 7.63 (d, 2H, J = 6.2 Hz), 7.44 (d, 2H, J = 6.2 Hz), 6.97 (dd, 2H, J = 4.1, 2.5 Hz), 6.67 (d, 2H, J = 4.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 133.7, 129.3, 116.5, 115.2, 114.3, 112.9, 101.4; MS *m*/*z* (rel int) 234 (M^+, 95), 233 (100), 232 (68). Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.71; H, 4.43; N, 23.47.

1-(Trimethylsilyl)pyrrolo[1,2-*c*]pyrimidine (17c). Following the standard methods, chlorotrimethylsilane (212 mg, 1.90 mmol) was added, and the mixture was stirred for 2 h to give, after the usual workup, an oily residue. The residue was purified using silica gel chromatography with hexane/EtOAc 8:2 to produce **17c** as a brown oil (180 mg, 50%): IR (KBr) 1605, 1286, 1232 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.47 (m, 1H), 7.43 (d, 1H, J = 6.3 Hz), 7.26 (d, 1H, J = 6.3 Hz), 7.02 (dd, 1H, J = 3.9, 2.4 Hz), 6.45 (d, 1H, J = 3.9 Hz), 0.40 (s, 9H); MS *m*/*z* (rel int) 190 (M^+, 34),175 (100), 149 (57). Anal. Calcd for $C_{10}H_{14}N_2Si$: C, 63.11; H, 7.41; N, 14.72. Found: C, 63.35; H, 7.31; N, 14.75.

1-Phenyl-1,2-dihydropyrrolo[1,2-*c*]pyrimidine (19). A 2 M solution of phenyllithium in hexane (0.9 mL, 1.8 mmol) was added to a solution of **1a** (200 mg, 1.7 mmol) in 10 mL of dry THF at −78 °C under argon. After 1 h, the mixture was hydrolyzed with NH_4Cl and extracted with EtOAc. The combined organic extracts were washed with water and dried over Na_2SO_4, and the solvent was removed under reduced pressure. Chromatography of the residue using hexane/EtOAc (9.5:0.5) as eluent yielded the title compound as a yellow powder (106 mg, 31%): mp 83−85 °C (EtOH); IR (KBr) 3384, 1630, 1446,1278 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.95 (bs, 1H), 8.20 (s, 1H), 7.81−7.78 (m, 2H), 7.52−7.47 (m, 3H), 6.99 (d, 1H, J = 1.1 Hz), 6.77 (d, 1H, J = 7.8 Hz), 6.31 (d, 1H, J = 1.1 Hz), 6.25−6.22 (m, 1H), 6.16 (d, 1H, J = 7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 136.1, 135.0, 131.1, 130.9, 128.9, 128.4, 120.7, 117.5, 111.6, 108.9; MS *m*/*z* (rel int) 196 (M^+, 61), 119 (100). Anal. Calcd for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.27. Found: C, 78.92; H, 6.18; N, 14.48.

2-Phenacylpyrrolo[1,2-*c*]pyrimidinium Bromide (20). A mixture of **1a** (1 g, 8.47 mmol) and phenacyl bromide (1.68 g, 8.47 mmol) was refluxed in 20 mL of acetone for 3 h. The yellow precipitate that appeared was filtered off and washed with acetone and Et_2O to produce 2.09 g (78%) of **20** as a yellow solid, which was recrystallized from EtOH: mp 184−186 °C; IR (KBr) 1697, 1646, 1594, 1225 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.33 (s, 1H), 8.18 (d, 1H, H7, J = 2.5 Hz), 8.07

(d, 2H, J = 7.3 Hz), 7.98 (d, 1H, J = 7.7 Hz), 7.81−7.76 (m, 1H), 7.67−7.62 (m, 2H), 7.59 (d, 1H, J = 7.7 Hz), 7.42 (dd, 1H, H6, J = 3.7, 2.5 Hz), 7.05 (d, 1H, J = 3.7 Hz), 6.21 (s, 2H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 190.9, 145.7, 134.7, 133.5, 129.0, 128.3, 128.1, 124.5, 122.6, 118.1, 114.3, 105.8, 62.0. Anal. Calcd for $C_{15}H_{13}BrN_2O$: C, 56.80; H, 4.13; N, 8.83. Found: C, 56.49; H, 4.65; N, 8.60.

2-[(Ethoxycarbonyl)methyl]pyrrolo[1,2-*c*]pyrimidinium Bromide (21). Ethyl bromoacetate (1.5 g, 9.0 mmol) was added to a solution of **1a** (1.0 g, 8.47 mmol) in CH_3CN (20 mL), and the mixture was refluxed for 5 h. The resulting precipitate was filtered off, washed with Et_2O, and recrystallized from EtOH to give 1.35 g (56%) of the title salt as a brown powder: mp 165−167 °C; IR (KBr) 1742, 1647, 1231; ^{1}H NMR (300 MHz, DMSO-d_6) 10.41 (s, 1H), 8.14 (d, 1H, H7, J = 2.9 Hz), 7.94 (d, 1H, J = 7.6 Hz), 7.61 (d, 1H, J = 7.6 Hz), 7.40 (dd, 1H, J = 3.7, 2.9 Hz), 7.01 (d, 1H, J = 3.7 Hz), 5.39 (s, 2H), 4.22 (q, 2H, J = 7.2 Hz), 1.24 (t, 3H, J = 7.2 Hz); ^{13}C NMR (50 MHz, DMSO-d_6) 166.4, 145.9, 128.0, 124.2, 122.8, 118.3, 114.2, 106.0, 62.2, 56.3, 14.1. Anal. Calcd for $C_{11}H_{13}BrN_2O_2$: C, 46.34; H, 4.60; N, 9.82. Found: C, 46.21; H, 4.79; N, 9.72.

2-[(Trimethylsilyl)methyl]pyrrolo[1,2-*c*]pyrimidinium Trifluoromethanesulfonate (22). A mixture of **1a** (0.2 g, 1.70 mmol) and (trimethylsilyl)methyl trifluoromethanesulfonate (0.44 g, 1.86 mmol) in 10 mL of dry CH_2Cl_2 was stirred at room temperature under argon for 3 h. The solvent was removed under reduced pressure, and the residue was treated with Et_2O. The solid was filtered off, washed with Et_2O, and recrystallized from EtOH to give 373 mg (62%) of **22** as a brown solid: mp 135−136 °C (EtOH); IR (KBr) 1647, 1278, 1029 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.20 (s, 1H), 8.04 (d, 1H, J = 2.7 Hz), 7.92 (d, 1H, J = 7.3 Hz), 7.46 (d, 1H, J = 7.3 Hz), 7.33 (dd, 1H, J = 4.1, 2.7 Hz), 6.97 (d, 1H, J = 4.1 Hz), 4.08 (s, 2H), 0.16 (s, 9H); ^{13}C NMR (50 MHz, DMSO-d_6) δ 142.3, 127.9, 123.9, 121.5, 117.7, 115.3, 107.6, 105.3, 48.9, −2.9. Anal. Calcd for $C_{12}H_{17}F_3N_2O_3SSi$: C, 40.67; H, 4.83; N, 7.90. Found: C, 40.93; H, 4.76; N, 7.77.

2-Aminopyrrolo[1,2-*c*]pyrimidinium Mesitylenesulfonate (23). 1a (0.25 g, 2.10 mmol) in 3 mL of dry CH_2Cl_2 was added to a solution of MSH (0.45 g, 2.10 mmol) in 5 mL of dry CH_2Cl_2 at 0 °C, and the reaction mixture was stirred for 1 h at that temperature. The precipitate that formed was filtered off and washed with Et_2O to give 290 mg (41%) of **23**: mp 151−153 °C (brown powder, EtOH); IR (KBr) 3240, 1610, 1220 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 10.27 (s, 1H), 8.00 (d, 1H, J = 2.5 Hz), 7.84 (d, 1H, J = 7.4 Hz), 7.49 (d, 1H, J = 7.4 Hz), 7.30 (dd, 1H, J = 3.7, 2.5 Hz), 6.95 (d, 1H, J = 3.7 Hz), 6.72 (s, 2H), 2.48 (s, 6H), 2.15 (s, 3H). Anal. Calcd for $C_{16}H_{19}N_3O_3S$: C, 57.64; H, 5.74; N, 12.60. Found: C, 57.78; H, 5.98; N, 12.44.

Dipolar Cycloaddition Reactions of 20. Reaction with DMAD. DMAD (0.45 g, 3.15 mmol) and 50% aqueous K_2CO_3 (13 mL) were added to a suspension of 0.4 g (1.26 mmol) of **20** in CH_2Cl_2 (25 mL). The mixture was stirred at room temperature for 12 h, and then the organic phase was separated, washed with water and brine, and dried over Na_2SO_4. After the solvent was removed under reduced pressure, the oily residue was chromatographed. Elution with hexane/EtOAc 9:1 and 8:2 allowed the separation of the dihydro derivative **26** (130 mg, 28%) as a yellowish oil and the fully aromatized **27** (66 mg, 14%) as a white solid.

Compound **27** was also obtained by treatment of the mixture of **26** and **27** (185 mg) with DDQ (120 mg, 0.51 mmol) in CH_2Cl_2 (10 mL) by stirring the mixture for 2 h at room temperature. Compound **27** (185 mg, 40% from **20**) was purified using silica gel chromatography with CH_2Cl_2 as eluent.

(2*R*,3*S*)- and (2*S*,3*R*)-3-benzoyl-1,2-dimethoxycarbonyl-2,3-dihydrodipyrrolo[1,2-*a*;1′,2′-*c*]pyrimidine (26): IR (KBr) 1732, 1680, 1633, 1217 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (d, 2H, J = 7.1 Hz), 7.66−7.63 (m, 1H), 7.56−7.49 (m, 2H), 6.86 (d, 1H, J = 2.7 Hz), 6.28 (dd, 1H, J = 3.5, 2.7 Hz), 6.18 (d, 1H, J = 8.7 Hz), 6.05 (dd, 1H, J = 3.5, 1.3 Hz), 5.99 (d, 1H, J = 7.4 Hz), 5.83 (d, 1H, J = 7.4 Hz), 4.76 (d, 1H, J = 8.7 Hz), 3.90 (s, 3H), 3.45 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 197.8, 171.8, 163.8, 134.9, 134.7, 129.2, 129.2, 127.9, 117.8, 116.9, 112.8, 110.9, 106.7, 104.3, 102.0, 53.4, 53.1, 51.3.

3-Benzoyl-1,2-dimethoxycarbonyldipyrrolo[1,2-*a*;1′,2′-*c*]pyrimidine (27): mp 171−173 °C (EtOH); IR (KBr) 1727, 1638, 1519, 1214; ^{1}H NMR (300 MHz, $CDCl_3$) 8.65 (d, 1H, J = 2.5 Hz), 8.29 (d, 1H, J = 8.0 Hz), 7.72 (d, 2H, J = 7.0 Hz), 7.58−7.53 (m, 1H), 7.46−7.41 (m, 2H), 6.94 (d, 1H, J = 8.0 Hz), 6.75 (dd, 1H, J = 4.0, 2.5 Hz), 6.56 (dd, 1H, J = 4.0, 1.1 Hz), 3.85 (s, 3H), 3.23 (s, 3H); MS *m*/*z* (rel int) 376 (M$^+$, 100), 313 (15). Anal. Calcd for $C_{21}H_{16}N_2O_5$: C, 67.02; H, 4.28; N, 7.44. Found: C, 67.42; H, 4.19; N, 7.35.

Reaction with Methyl Propiolate. A mixture of **20** (0.4 g, 1.26 mmol) and methyl propiolate (0.26 g, 3.15 mmol) in CH_2Cl_2 (25 mL) and 50% aqueous K_2CO_3 (15 mL) was stirred at room temperature for 8 h. The organic phase was then separated, and the organic layer was extracted with CH_2Cl_2. The combined organic phases were washed with H_2O and brine. The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure to yield a dark oil. Chromatography (hexane/EtOAc 8:2) allowed the separation of the dihydro derivative **28a** (64 mg, 16%) as a yellow oil and **29a** (85 mg, 21%) as a yellow solid.

3-Benzoyl-1-methoxycarbonyl-3,10a-dihydrodipyrrolo-[1,2-*a*;1′,2′-*c*]pyrimidine (28a): IR (KBr) 1722, 1702, 1640, 1260, 1236 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11−8.07 (m, 1H), 7.84 (d, 2H, J = 8.0 Hz), 7.68 (d, 1H, J = 1.7 Hz), 7.58−7.44 (m, 3H), 7.30 (d, 1H, J = 1.7 Hz), 6.81 (d, 1H, J = 8.5 Hz), 6.68 (dd, 1H, J = 4.1, 2.7 Hz), 6.38 (d, 1H, J = 8.5 Hz), 6.12 (dd, 1H, J = 6.1, 2.6 Hz), 5.93 (dd, 1H, J = 4.1, 1.5 Hz), 3.83 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.5, 163.9, 138.1, 133.2, 132.4, 129.3, 128.4, 125.2, 122.1, 120.6, 119.9, 118.1, 116.9, 111.5, 109.8, 51.5; MS *m*/*z* (rel int) 320 (M$^+$, 39), 215 (49), 105 (100). Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74. Found: C, 70.82; H, 4.93; N, 9.13.

3-Benzoyl-1-methoxycarbonyldipyrrolo[1,2-*a*;1′,2′-*c*]-pyrimidine (29a): mp 153−155 °C (EtOH); IR (KBr) 1715, 1620, 1211, 1178 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.18 (d, 1H, J = 2.8 Hz), 8.91 (d, 1H, J = 7.9 Hz), 7.82 (d, 2H, J = 7.7 Hz), 7.60−7.53 (m,3H), 7.52 (s, 1H), 6.99 (d, 1H, J = 7.9 Hz), 6.80 (dd, 1H, J = 3.7, 2.8 Hz), 6.59 (dd, 1H, J = 3.7, 1.1 Hz), 3.88 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.8, 163.8, 139.5, 131.9, 129.2, 128.5, 127.8, 127.6, 119.6, 118.1, 114.2, 113.0, 106.9, 104.2, 100.0, 51.9; MS *m*/*z* (rel int) 318 (M$^+$, 57), 105 (52), 77 (100). Anal. Calcd for $C_{19}H_{14}N_2O_3$: C, 71.69; H, 4.43; N, 8.80. Found: C, 71.56; H, 4.56; N, 8.97.

Reaction with Ethyl Propiolate. Ethyl propiolate (0.27 g; 2.84 mmol) was added to a suspension of **20** (0.3 g, 0.95 mmol) in CH_2Cl_2 (20 mL) and 50% K_2CO_3 (10 mL). The reaction mixture was stirred for 15 h, and then the organic phase was separated, washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude extract was purified by chromatography. Elution with hexane/EtOAc (8:2) allowed the separation of the dihydro derivative **28b** (60 mg, 19%) as an oil and the product **29b** as a white solid (104 mg, 33%).

3-Benzoyl-1-ethoxycarbonyl-3,10a-dihydrodipyrrolo-[1,2-*a*;1′,2′-*c*]pyrimidine (28b): IR (KBr) 1728, 1700, 1272, 1230 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07−8.03 (m, 1H), 7.83 (d, 2H, J = 7.3 Hz), 7.67 (d, 1H, J = 1.4 Hz), 7.60−7.54 (m, 1H), 7.50−7.45 (m, 2H), 7.29 (d, 1H, J = 1.4 Hz), 6.80 (d, 1H, J = 8.4 Hz), 6.68−6.65 (m, 1H), 6.38 (d, 1H, J = 8.4 Hz), 6.12 (app t, 1H, J = 2.8 Hz), 5.94−5.92 (m, 1H), 4.29 (c, 2H, J = 7.2 Hz), 1.33 (t, 3H, J = 7.2 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 185.5,163.6, 138.2, 133.1, 132.4, 129.3, 128.4, 125.3, 122.1, 120.6, 120.0, 118.2, 117.4, 111.7, 109.9, 60.5, 14.4. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.98; H, 5.49; N, 8.09.

3-Benzoyl-1-ethoxycarbonyldipyrrolo[1,2-*a*;1′,2′-*c*]-pyrimidine (29b): mp 140−142 °C; IR (KBr) 1706, 1621, 1213, 1186 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (d, 1H, J = 2.1 Hz), 8.89 (d, 1H, J = 7.7 Hz), 7.83 (d, 2H, J = 7.5 Hz), 7.60−7.52 (m, 3H), 7.51 (s, 1H), 6.96 (d, 1H, J = 7.7 Hz), 6.78 (dd, 1H, J = 3.8, 2.1 Hz), 6.56 (d, 1H, J = 3.8 Hz), 4.33 (q, 2H, J = 7.1 Hz), 1.35 (t, 3H, J = 7.1 Hz); ^{13} C NMR (50 MHz, $CDCl_3$) δ 185.7, 163.1, 139.4,131.9, 129.1, 128.4, 127.6, 121.3,

119.6, 118.0, 114.0, 112.9, 106.8, 104.1, 100.3, 60.7, 14.4. Anal. Calcd for $C_{20}H_{16}N_2O_3$: C, 72.28; H, 4.85; N, 8.43. Found: C, 71.95; H, 4.90; N, 8.78.

Reaction with Dimethyl Fumarate. A mixture of **20** (0.4 g, 1.26 mmol), dimethyl fumarate (0.27 g, 1.8 mmol), and anhydrous K_2CO_3 (0.69 g, 5.0 mmol) in 20 mL of dry CH_3CN was stirred at room temperature for 40 h. The K_2CO_3 was filtered off and washed with CH_2Cl_2. The combined organic extracts were washed with H_2O and brine and dried over Na_2SO_4. After the solvent was removed, chromatography (hexane/EtOA, 9:1) allowed the separation of the endo isomer **30** (140 mg, 29%) as a white solid and the exo isomer **31** (81 mg, 17%) as a colorless oil.

(1*R*,2*R*,3*S*,10a*R*)- and (1*S*,2*S*,3*R*,10a*S*)-3-benzoyl-1,2-dimethoxycarbonyl-1,2,3,10a-tetrahydrodipyrrolo[1,2-*a*;1′,2′-*c*]pyrimidine (±30): mp 144−146 °C (EtOH); IR (KBr) 2950, 1725, 1684, 1236 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.00 (d, 2H, J = 7.2 Hz), 7.61−7.48 (m, 3H), 6.58−6.55 (m, 1H), 6.13 (app t,1H, J = 3.3 Hz), 6.07 (d, 1H, J = 7.7 Hz), 5.86 (d, 1H, J = 4.1 Hz), 5.83 (d, 1H, J = 8.1 Hz), 5.66 (d, 1H, J = 7.7 Hz), 5.51 (d, 1H, J = 6.1 Hz), 4.06−3.99 (m, 2H), 3.60 (s, 3H), 3.34 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 201.7, 178.6, 174.9, 134.9, 131.7, 128.9, 128.8, 127.4, 118.7, 112.9, 109.4, 104.0, 97.7, 73.5, 68.7, 52.3, 52.2, 51.4, 47.6. Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 66.26; H, 5.42; N, 7.58.

(1*R*,2*R*,3*R*,10a*S*)- and (1*S*,2*S*,3*S*,10a*R*)-3-benzoyl-1,2-dimethoxycarbonyl-1,2,3,10a-tetrahydrodipyrrolo[1,2-*a*;1′,2′-*c*]pyrimidine ((±)−31): IR (KBr) 1718, 1704, 1165 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, 2H, J = 7.8 Hz), 7.63−7.48 (m, 3H), 6.69 (dd, 1H, J = 2.4, 1.3 Hz), 6.23−6.19 (m, 1H), 6.06 (d, 1H, J = 7.5 Hz), 5.97 (d, 1H, J = 3.7 Hz), 5.71 (d, 1H, J = 7.5 Hz), 5.63 (d, 1H, J = 6.6 Hz), 5.46 (d, 1H, J_{3-2} = 3.4 Hz), 4.00−3.93 (m, 2H), 3.81 (s, 3H), 3.73 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.4, 171.2, 170.0, 134.0, 128.9, 128.8, 127.3, 123.0, 116.7, 109.8, 104.0, 98.0, 74.6, 67.7, 53.1, 52.2, 48.3, 45.7. Anal. Calcd for $C_{21}H_{20}N_2O_5$: C, 66.31; H, 5.30; N, 7.36. Found: C, 65.98; H, 5.38; N, 7.51.

Reaction with *N*-Methylmaleimide. (3a*R*,4*R*,11a*S*,11b*S*)- and (3a*S*,4*S*,11a*R*,11b*R*)-4-Benzoyl-2-methyl-1,3-dioxo-3a,4,11a,11b-tetrahydropyrrolo[3′,4′:3,4]pyrrolo-[1,2-*a*]pyrrolo[1,2-*c*]pyrimidine ((±)−32). A mixture of 0.2 g (0.63 mmol) of the salt **20** and 84 mg (0.76 mmol) of *N*-methylmaleimide in 14 mL of CH_2Cl_2 and 7 mL of 50% K_2CO_3 was stirred at room temperature for 4 h. The organic phase was separated, washed with water and a saturated solution of NaCl, dried over Na_2SO_4, and concentrated under reduced pressure to yield an oily residue that was purified by column chromatography using hexane/EtOAc (8:2) as eluent to produce the endo isomer **32**: yield 114 mg (52%); mp 186−188 °C (yellow crystals from EtOH); IR (KBr) 1701, 1675, 1623, 1280 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.10 (d, 2H, J = 7.4 Hz), 7.64−7.49 (m, 3H), 6.77 (dd, 1H, J = 2.9, 1.4 Hz), 6.27 (dd, 1H, J = 3.7, 2.9 Hz), 6.00 (d, 1H, J = 8.0 Hz), 5.97 (d, 1H, J = 3.7, 1.4 Hz), 5.74 (d, 1H, J = 7.3 Hz), 5.57 (d, 1H, J = 8.0 Hz), 5.44 (d, 1H, J = 1.4 Hz), 3.85 (dd, 1H, J_{3a-11b} = 8.0 Hz, J_{3a-4} = 1.4 Hz), 3.61 (dd, 1H, J_{11b-3a} = 8.0 Hz, $J_{11b-11a}$ = 7.3 Hz); 2.85 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 194.1, 181.8, 178.2, 134.7, 133.9, 129.5, 129.3, 127.8, 126.0, 119.2, 110.6, 105.1, 97.5, 74.0, 70.0, 49.2, 47.0, 26.0; MS *m*/*z* (rel int) 347 (M^+, 100), 346 (36), 241 (27). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.15; H, 4.93; N, 12.10. Found: C, 69.40; H, 4.80; N, 12.06.

Reaction with Acrylonitrile. (1*R*,3*S*,10a*R*)- and (1*S*,3*R*,10a*S*)-3-Benzoyl-1-cyano-1,2,3,10a-tetrahydrodipyrrolo-[1,2-*a*;1′,2′-*c*]pyrimidine ((±)-33). An aqueous solution of 50% K_2CO_3 (16 mL) and acrylonitrile (0.1 g, 1.8 mmol) was added to a suspension of the salt **20** (0.4 g, 1.26 mmol) in CH_2Cl_2 (28 mL). The mixture was stirred for 4 h at room temperature. The organic phase was separated, washed with water and brine, and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by chromatography. Elution with hexane/EtOAc (8:2) produced the endo isomer **33**: yield 226 mg (62%); mp 167−169 °C (yellow crystals from EtOH); IR (KBr) 2245, 1681, 1614, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 2H, J = 7.3 Hz), 7.67−7.51 (m, 3H), 6.55 (dd, 1H, J = 2.5, 1.5 Hz), 6.30 (dd, 1H, J = 3.4, 2.5 Hz), 6.10 (d, 1H, J = 7.7 Hz), 6.01 (dd, 1H, J = 3.4, 1.5 Hz), 5.65 (d, 1H, J = 7.7 Hz), 5.63 (d, 1H, J = 6.9 Hz), 5.39 (dd, 1H, $J_{3-2'}$ = 8.4 Hz, J_{3-2} = 6.3 Hz), 3.65 (ddd, 1H, J_{1-2} = 7.6 Hz, J_{1-10a} = 6.9 Hz, $J_{1-2'}$ = 2.2 Hz), 2.81 (ddd, 1H, J = 13.9, 8.4, 2.2 Hz), 2.46 (ddd, 1H, H2, J = 13.9, 7.6, 6.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 196.5, 134.4, 129.3, 128.8, 128.3, 126.4, 118.1, 116.1, 113.0, 111.4, 104.3, 95.6, 72.7, 63.2, 35.2, 31.6; MS *m*/*z* (rel int) 289 (M^+, 47), 255 (100), 237 (70). Anal. Calcd for $C_{18}H_{15}N_3O$: C, 74.22; H, 5.23; N, 14.52. Found: C, 74.39; H, 4.98; N, 14.30.

3-Benzoyl-1-cyanodipyrrolo[1,2-*a*;1′,2′-c]pyrimidine (34). A mixture of **33** (50 mg, 0.17 mmol) and DDQ (82 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 2 h. The residue was purified by chromatography (hexane/EtOAc, 6:4) to give the fully aromatized derivative **34** (47 mg, 95%) as a white solid: mp 170−172 °C; IR (KBr) 2221, 1690, 1600, 1228, 1176 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 8.87 (d, 1H, J = 8.0 Hz), 8.20 (d, 1H, J = 2.6 Hz), 7.81 (d, 2H, J = 8.2 Hz), 7.64−7.51 (m, 3H), 7.31 (s, 1H), 7.04 (d, 1H, J = 8.0 Hz), 6.91 (dd, 1H, J = 4.1, 2.6 Hz), 6.64 (d, 1H, J = 4.1 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 193.7, 138.6, 132.4, 130.5, 129.0, 128.6, 126.3, 118.4, 116.0, 115.2, 113.9, 112.9, 107.2, 104.8, 99.3. Anal. Calcd for $C_{18}H_{11}N_3O$: C, 75.78; H, 3.89; N, 14.73. Found: C, 75.91; H, 3.94; N, 14.55.

Reaction with Phenylisothiocyanate. 3-Benzoyl-1-phenylimidazo[1,2-*a*]pyrrolo[1,2-*c*]pyrazin-4-ium-2-thiolate (35). A mixture of **20** (0.1 g; 0.31 mmol), phenylisothiocyanate (51 mg; 0.37 mmol), and anhydrous K_2CO_3 (174 mg; 1.23 mmol) in 8 mL of dry acetonitrile was stirred at room temperature for 40 h. The K_2CO_3 was filtered off, and the organic phase was washed with water and brine and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the crude extract was chromatographed using hexane/EtOAc (7:3) as eluent to yield **35** (14 mg, 12%): mp 185−187 °C (brown powder, EtOH); IR (KBr) 1674, 1598, 1238; ^1H NMR (300 MHz, $CDCl_3$) 8.64 (d, 1H, J = 6.4 Hz), 8.00 (d, 2H, J = 7.1 Hz),7.68 (d, 1H, J = 6.4 Hz), 7.62−7.55 (m, 3H), 7.48−7.40 (m, 6H), 6.84−6.79 (m, 1H), 6.19 (d, 1H, J = 4.2 Hz). Anal. Calcd for $C_{22}H_{15}N_3OS$: C, 71.52; H, 4.09; N, 11.37. Found: C, 71.34; H, 4.13; N, 11.30.

Dipolar Cycloaddition Reactions of 21. Reaction with DMAD. A mixture of **21** (0.2 g, 0.7 mmol), DMAD (0.25 g; 1.75 mmol), and anhydrous K_2CO_3 (0.38 g; 2.8 mmol) in 10 mL of dry CH_3CN was stirred at room temperature for 30 h. The K_2CO_3 was filtered off, and the organic extracts were washed with water and a saturated solution of NaCl. The organic phase was dried over Na_2SO_4 and the solvent removed under reduced pressure, to yield an oily residue that was purified by silica gel chromatography. Elution with hexane/EtOAc (8:2) gave an inseparable mixture of the dihydro derivative and the fully aromatized compound. This mixture was treated with DDQ (0.07 mmol) to exclusively produce **37** as an oil (25 mg, 10%). Alternatively, using hexane/EtOAc (8.5:1.5) as eluent, the hydroxy derivative **38** was isolated as an oil (78 mg, 50%).

3-Ethoxycarbonyl-1,2-dimethoxycarbonyldipyrrolo-[1,2-*a*; 1′,2′-*c*]pyrimidine (37): IR (film) 1741, 1682, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.78 (d, 1H, J = 2.4 Hz), 8.41 (d, 1H, J = 7.4 Hz), 7.00 (d, 1H, J = 7.4 Hz), 6.78 (dd, 1H, J = 4.0, 2.4 Hz), 6.54 (dd, 1H, H7, J = 4.0, 1.5 Hz), 4.28 (q, 2H, J = 7.2 Hz), 3.90 (s, 3H), 3.78 (s, 3H), 1.26 (t, 3H, J = 7.2 Hz). Anal. Calcd for $C_{17}H_{16}N_2O_6$: C, 59.30; H, 4.68; N, 8.14. Found: C, 59.18; H, 4.89; N, 8.23.

2-[(Ethoxycarbonyl)methyl]-1-hydroxy-1,2-dihydropyrrolo[1,2-*c*]pyrimidine (38): IR (KBr) 3324, 1732, 1680, 1216 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 10.52 (bs, 1H), 8.17 (s, 1H), 6.83 (dd, 1H, J = 4.0, 2.5 Hz), 6.24 (d, 1H, J = 8.4 Hz), 6.23−6.21 (m, 1H), 6.15 (d, 1H, J = 2.5 Hz), 5.62 (d, 1H, J = 8.4 Hz), 4.27 (q, 2H, J = 7.0 H), 4.16 (s, 2H), 1.31 (t, 3H, J = 7.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 170.7, 163.6, 125.5, 121.1, 120.0, 118.5, 113.0, 109.0, 62.5, 46.6, 14.3; MS *m*/*z* (rel int) 222 (M^+, 46), 194 (55), 121 (100). Anal. Calcd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.35; N, 12.60. Found: C, 59.32; H, 6.48; N, 12.51.

Reaction with Methyl Propiolate. Anhydrous K_2CO_3 (0.38 g, 2.8 mmol) and methyl propiolate (0.17 g, 1.75 mmol) were added to a suspension of **21** (0.2 g, 0.7 mmol) in 10 mL of dry CH_3CN. The reaction mixture was stirred at room temperature for 30 h. Then, the K_2CO_3 was filtered off, and the organic extracts were washed with water and brine, dried over Na_2SO_4, and concentrated under vacuum. The crude extract was chromatographed to produce 24 mg (12%) of **39** using hexane/EtOAc (8:2) as eluent and 57 mg (37%) of **38**.

3-Ethoxycarbonyl-1-methoxycarbonyldipyrrolo[1,2-*a*;1′,2′-*c*]pyrimidine (39): IR (film) 1702, 1240 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.04 (d, 1H, J = 2.6 Hz), 8.76 (d, 1H, J = 7.8 Hz), 7.64 (s, 1H), 6.88 (d, 1H, J = 7.8 Hz), 6.84 (dd, 1H, J = 4.2, 2.6 Hz), 6.70 (dd, 1H, J = 4.2, 1.3 Hz), 4.30 (q, 2H, J = 7.1 Hz), 3.90 (s, 3H), 1.36 (t, 3H, J = 7.1 Hz). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.93; N, 9.78. Found: C, 62.75; H, 4.98; N, 10.03.

Dipolar Cycloaddition Reactions of 22. Reaction with Methyl Propiolate. 1-Methoxycarbonyldipyrrolo[1,2-*a*;1′,2′-*c*]pyrimidine (41). CsF (56 mg, 0.37 mmol) and methyl propiolate (37 mg, 0.44 mmol) were added to a solution of of **22** (0.13 g, 0.37 mmol) in 8 mL of dry DME, under argon atmosphere. The mixture was refluxed for 18 h, poured into an ice−water bath, and extracted with CH_2Cl_2. The combined organic phase was dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was chromatographed with a silica gel column, using hexane/EtOAc 7:3 as eluent, to produce 12 mg (15%) of the title compound as a yellow solid: mp 145−146 °C (EtOH); IR (KBr)1731, 1639, 1252 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (d, 1H, J = 1.8 Hz), 7.32−7.29 (m, 1H), 7.18 (d, 1H, J = 7.7 Hz), 6.66 (d, 1H, J = 7.7 Hz), 6.61 (d, 1H, J = 3.3 Hz), 6.54−6.52 (m, 1H), 6.41 (d, 1H, J = 2.5 Hz), 3.87 (s, 3H). Anal. Calcd for $C_{12}H_{10}N_2O_2$: C, 67.28; H, 4.71; N, 13.08. Found: C, 66.87; H, 4.78; N, 13.38.

Acknowledgment. The authors acknowledge support of this work from the Comisión Interministerial de Ciencia y Técnología (CICYT) through the projects PM97-0074 and SAF98-0093 and a grant from the Ministerio de Educación y Ciencia (J.M.M.). We thank the Servicios Informáticos Universidad de Alcalá and the Centro de Computación de Galicia (CESGA) for use of their computer facilities.

JO9907080