1,3-Diaza-1,3-butadienes. Synthesis and Conversion into Pyrimidines by [4π + 2π] Cycloaddition with Electron Deficient Acetylenes. Synthetic Utility of 2-(Trichloromethyl)pyrimidines[1]

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Received November 28, 1995[⊗]

Methods have been devised to generate 1*H*-1,3-diaza-1,3-butadienes bearing a leaving group at position-4 in latent, masked, and unprotected forms. A hallmark of these azadienes is that they undergo thermal [4π + 2π] cycloaddition reactions with electron deficient acetylenes to give adducts which are aromatized to pyrimidine derivatives under the reaction conditions. Thus, 1-(methoxycarbonyl)-3-acylamidines **17** on heating in solution are converted *in situ* into the 1,3-diaza-1,3-dienes **18** and/or **19** which react with dimethyl acetylenedicarboxylate (DMAD) to produce the pyrimidines **20**. The 1-Boc-1,3-diaza-1,3-dienes **24** are masked forms of the 1*H*-dienes inasmuch as they react with DMAD under relatively mild conditions to give the dihydropyrimidine adducts **25**, which are easily detectable by ^{1}H NMR spectroscopy, and which aromatize to pyrimidines **26** at higher temperatures. The 4-methylthio compounds **31** and **33**, and the 2-(trichloromethyl) compounds **37**, are isolable, relatively stable, 1*H*-1,3-diaza-1,3-butadienes. These easily prepared compounds react with electron deficient acetylenes under mild conditions to provide the pyrimidines **20**, **34**, and **38**, respectively, in fair to excellent yields. The 2-(trichloromethyl)pyrimidines **38** are very useful precursors of a wide variety of other 2-substituted pyrimidines **46**-**52**.

Introduction

The first 1,3-diaza-1,3-butadiene **3** was described by Pinner[3,4] in 1889 who synthesized it from benzamidine (**1**) and benzaldehyde (**2**) (Scheme 1). An analogous product is obtained from salicylaldehyde,[5] but non-aromatic aldehydes lead to different products.[4] In 1907, Ley and Müller[6] prepared the triphenyl compound **5** from *N*-phenylbenzimidoyl chloride **4** and benzamidine. In two notable publications[7,8] issued from the Boots Pure Drug Co. (Nottingham, England), the method of Ley and Müller was expanded[7] to include the synthesis of the fully substituted compounds **6**, and then a new process was devised[8] by which a series of 1,3-diaryl compounds **9**, without substituents on the nitrogen termini, were prepared from *N*-thiobenzoylbenzamidines **7** and aryl benzamidines **8**. The conjugated diene forms of **5** and **9**, at least as the hydrochloride salts, were supported by ultraviolet spectroscopic data.[7,8] Tolmacheva et al.[9] have synthesized a series of structural analogs of **9** from perfluorinated aliphatic amidines and perfluorinated aliphatic nitriles. Since 1976, there has been sporadic interest in the synthesis and reactions, especially the cycloaddition reactions,[10,11] of 1,3-diaza-1,3-butadienes. It has been stated[10] that the paucity of studies in this area is a consequence of the inherent instability of the simpler members of this series of compounds. The references cited above, as well as the work described herein, demonstrate that this supposition is invalid. Indeed, quite a variety of 1,3-diaza-1,3-butadienes, with or without a substituent at position-1 can be prepared, and they have acceptable stability provided that the carbon bearing substituents are appropriately chosen.

We became interested in the generation of 1-unsubstituted-1,3-diaza-1,3-butadienes with a leaving group at position-4 since it was expected that such compounds

⊗ Abstract published in *Advance ACS Abstracts,* March 15, 1996.

(1) Contribution No. 934 from the Syntex Institute of Organic Chemistry.

(2) The majority of the research described herein was carried out by M. Romero in partial fulfillment of the requirements for the degree of Doctorado en Química Orgánica in the Facultad de Química, Universidad Nacional Autónoma de México, México, D. F., 1995. Current address: Facultad de Química, Universidad Autónoma del Estado de México, Paseo Colón/Paseo Tollocan, Toluca México 5000.

(3) Pinner, A. *Chem. Ber.* **1889**, *22*, 1600.

(4) Pinner, A. *Chem. Ber.* **1890**, *23*, 2923.

(5) Kunckell, F.; Bauer, R. *Chem. Ber.* **1901**, *34*, 3029.

(6) Ley, H.; Müller, F. *Chem. Ber.* **1907**, *40*, 2950.

(7) Cooper, F. C.; Partridge, M. W.; Short, W. F. *J. Chem. Soc.* **1951**, 391.

(8) Peak, D. A. *J. Chem. Soc.* **1952**, 215.

(9) Tolmacheva, G. M.; Krukovskii, S. P.; Berman, E. L.; Ponamarenko, E. L. *Izv. Akad. Nauk SSSR Ser. Khim.* **1976**, 1963; *Chem. Abstr.* **1977**, *86*, 88663c.

(10) Boger, D. C.; Weinreb, S. M. In *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: San Diego, 1987; pp 272−274.

(11) (a) Crook, S.; Sykes, P. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1791. (b) Mazumdar, S. N.; Ibnasud, I.; Mahajan, M. P. *Tetrahedron Lett.* **1986**, *27*, 5875. (c) Mazumdar, S. N.; Sharma, M.; Mahajan, M. P. *Tetrahedron Lett.* **1987**, *28*, 2641. (d) Luthardt, P.; Würthwein, E.-W. *Tetrahedron Lett.* **1988**, *29*, 921. (e) Barluenga, J.; Tomás, M.; Ballesteros, A.; López, L. A. *Tetrahedron Lett.* **1989**, *30*, 4573. (f) Ibnasud, I.; Malar, E. J. P.; Sundaram, N. *Tetrahedron Lett.* **1990**, *31*, 7357. (g) Mazumdar, S. N.; Mahajan, M. P. *Tetrahedron* **1991**, *47*, 1473. (h) Sain, B.; Singh, S. P.; Sandhu, J. S. *Tetrahedron Lett.* **1991**, *32*, 5151. *Tetrahedron* **1992**, *48*, 4567. (i) Mazumdar, S. N.; Mukherjee, S.; Sharma, A. K.; Sengupta, D.; Mahajan, M. P. *Tetrahedron* **1994**, *50*, 7579.

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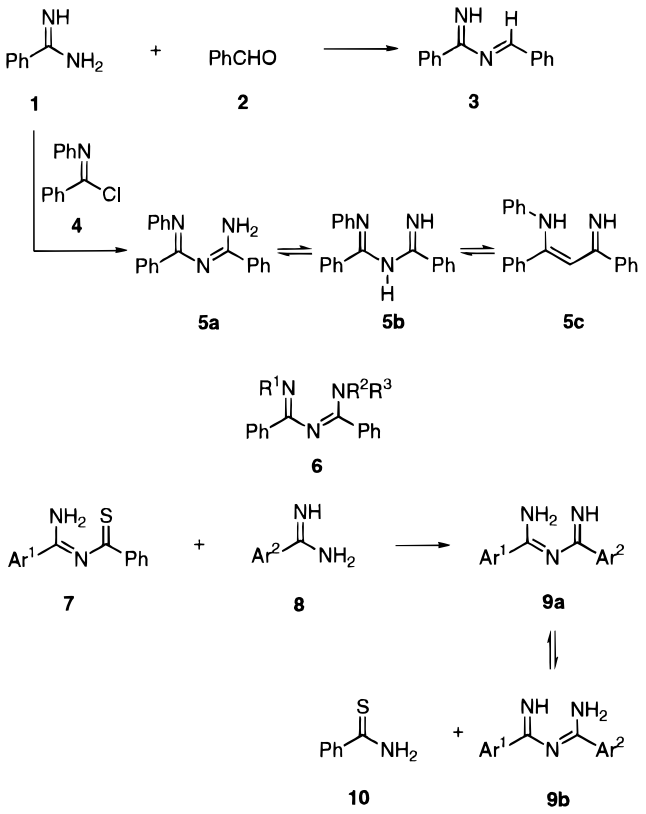
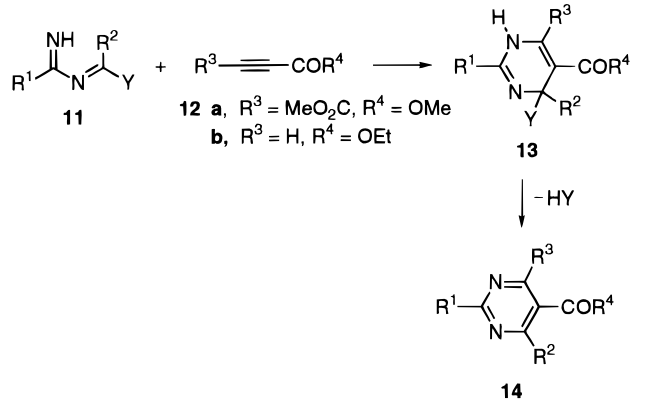
Scheme 1



Scheme 2



would undergo [4π + 2π] cycloaddition reactions with activated acetylenes, such as dimethyl acetylenedicarboxylate (**12a**, DMAD) to produce pyrimidine derivatives (Scheme 2).[12] This article describes the full details of our studies on the synthesis of stable 1-unsubstituted-1,3-diaza-1,3-butadienes, their cycloaddition reactions with activated acetylenes, and some reactions of the pyrimidine derivatives obtained in this way.[13] In addition, we describe several methods of generating latent forms of such 1-unsubstituted 1,3-diaza-1,3-butadienes and trapping studies of these dienes with activated acetylenes. An example of such a strategy was described by Ibnasud et al.[11f] while our work was in progress.

(12) In principle, a 1,3-diaza-1,3-butadiene bearing at least one hydrogen at position-4 and a leaving group at position-1 should also lead to pyrimidines with activated acetylenes. 1,4-Bis(dimethylamino)-2-phenyl-1,3-butadiene was synthesized for this purpose and found to not undergo cycloaddition with DMAD under a wide variety of neutral and acidic (Brϕnsted, Lewis) conditions (R. Greenhouse. Unpublished observations).

(13) For a preliminary communication on these aspects of our studies, see: Guzmán, A.; Romero, M.; Talamás, F. X.; Muchowski, J. M. *Tetrahedron Lett.* **1992**, *33*, 3449.

Results and Discussion

I. Generation of Latent and Masked N-Unsubstituted-1,3-diaza-1,3-butadienes. Our initial studies were based on the erroneous assumption that all N-unsubstituted-1,3-diaza-1,3-butadienes would be too unstable to be readily isolable under ambient conditions. Therefore the synthesis of various protected forms of these entities was undertaken on the expectation that the *in situ* generation of the deprotected forms in the presence of an excess of an activated acetylene would produce pyrimidine derivatives.

a. From N-Acylated Amidines and Methyl Chloroformate. Since amides are O-alkylated by powerful alkylating agents such as dimethyl sulfate,[14] it was thought that *N*-acylamidines might react in an analogous manner. This supposition was incorrect. For example, *N*-benzoylacetamidine (**15e**, Scheme 3) gave a crystalline methosulfate salt of the N-methylated compound **16**. The ^{1}H NMR spectrum of the free base was not consistent with that expected for the O-methylated diene **19e**. In addition, this substance did not react with DMAD.

Imidates are also known to be produced from amides and chloroformates by spontaneous loss of carbon dioxide from the unstable O-acylated primary product.[15] Reaction of equimolar amounts of *N*-(4-methylbenzoyl)benzamidine (**15b**) and methyl chloroformate, in the presence of a base, gave a crystalline product, which initially was taken to be the O-acylated diazadiene **18b**, based on the formation of the diphenylpyrimidine derivative **20b** (43%, Table 1) with excess **12a** at 150 °C in *o*-dichlorobenzene. A single crystal X-ray analysis[16] showed, however, that methoxycarbonylation of **15b** had occurred on the basic nitrogen atom to produce **17b**. This conclusion is obvious from a comparison of the much longer bond of the methoxycarbonyl N1−C8 system (1.395 Å, see Figure 1) vs that of the *p*-toluoyl N2−C8 bond system (1.271 Å). Nevertheless, to account for the formation of the pyrimidine **20b**, it is reasonable to propose that the O-acylated compound **18b** is in equilibrium with **17b** at 150 °C in *o*-dichlorobenzene. Either **18b** itself or **19b** derived there from by loss of CO_2, should undergo [4π + 2π] cycloaddition with **12a**. The diaryl-1,3,5-oxadiazinone (**21b**) is probably not involved in the genesis of **20b**. This was established by the observation that heating a mixture of the known[17] diphenyl-1,3,5-oxadiazinone (**21a)** and DMAD in *o*-dichlorobenzene produced no **20a**. In addition, heating an *o*-dichlorobenzene solution of **17a** did not generate any **21a**. In both cases unidentified mixtures were obtained.

The *N*-(methoxycarbonyl)benzamidines **17a,c,d** also reacted with DMAD to give the expected pyrimidine derivatives **20a,c,d** (Table 1). It is interesting that in the solid state, *N*-(methoxycarbonyl)-*N*′-acetylbenzamidine (**17c**) exists as tautomeric form **22** in which the methoxycarbonyl group is situated on the CN double bond. This is very clear from the X-ray structure (Figure 2)[16] which shows that the bond length (1.393 Å) of the

(14) Pielartzik, H.; Irmisch-Pielartzik, B.; Eicher, T. In *Houben-Weyl, Methoden der Organischen Chimie*; G. Theime: Stuttgart, 1985; Teil I, Vol. E5, pp 813−815.

(15) Snytham, F. H.; Greth, W. E.; Langerman, N. R. *J. Org. Chem.* **1968**, *34*, 292. Mohashi, E.; Gordon, E. M. *Synth. Commun.* **1984**, *14*, 1159.

(16) The authors have deposited atomic coordinates for this structure 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.

(17) Matsuda, I.; Itoh, K.; Ishii, Y. *J. Chem. Soc. (C)* **1971**, 1870.

Scheme 3

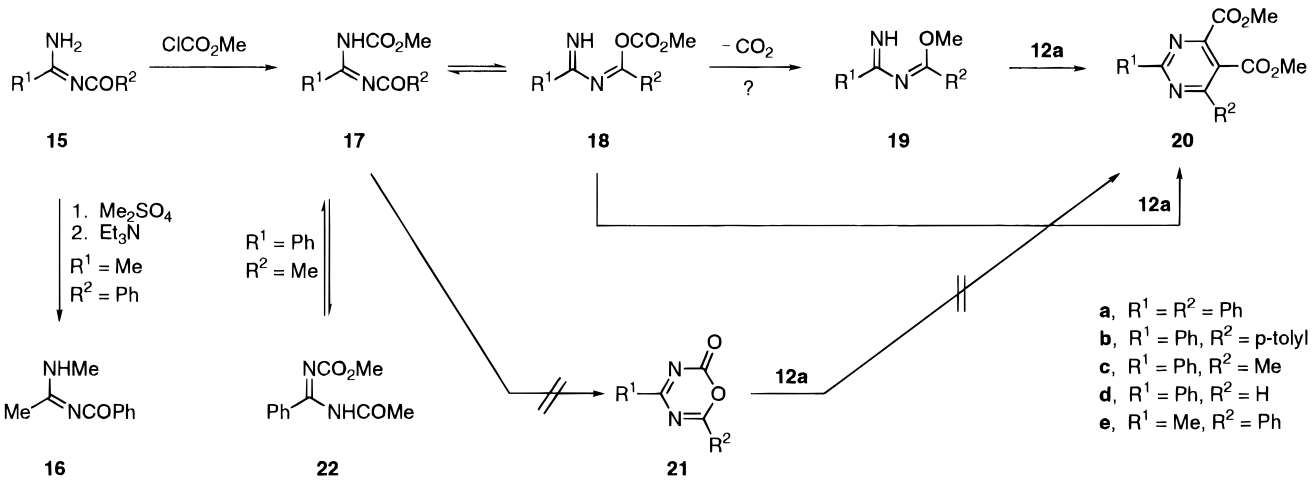


Table 1. Synthesis of Pyrmidine Derivatives 20, 26, and 34 from 17, 24, 31, and 33 and Acetylenic Esters 12a and 12b

diazadiene or precursor	acetylene	product	% yield
17a	**12a**	**20a**	43
17b	**12a**	**20b**	53
17c	**12a**	**20c**	48
17d	**12a**	**20d**	21[a]
24b	**12a**	**20d**	44
24b	**12b**	**26c**	42[b]
24c	**12a**	**26d**	46
24d	**12a**	**26e**	42
27	**12a**	**20c**	45
28	**12a**	**20d**	44[c]
31a	**12a**	**20a**	92
31b	**12a**	**20e**	7−11[d]
33	**12a**	**34a**	65
33	**12b**	**34b**	26

[a] One pot reaction without isolation of **15d** or **17d**. [b] Sealed tube reaction (120 °C). [c] Yield based on **24b**; compound **28** was generated and used without purification. [d] One-pot reaction without isolation of **29**, **30**, or **31**.

methoxycarbonyl N2−C7 system is much greater than that of the acetyl N1−C7 bond system (1.280 Å). This structure difference may be a reflection of a greater degree of conjugation in **17b** vs **17c**, but in solution **22** must tautomerize to **17c** enroute to **20c**.

In startling contrast to **17c** (**22**), *N*-(methoxycarbonyl)-*N′*-benzoylacetamidine (**17e**) does not produce the corresponding pyrimidine (**20e**) on reaction with DMAD. Whereas **17a**−**d** require heating to effect reaction with DMAD, **17e** reacts rapidly with this acetylene even at −10 °C, but a complex mixture containing no **20e** is produced. We are unable to rationalize the greatly differing reactivity and reaction course of **17e** vs **17a**−**d** with DMAD.

b. From 1-(*tert*-Butoxycarbonyl)-4-(dimethylamino)-1,3-diaza-1,3-butadienes. During the course of our studies, Ibnasud et al.[11f] reported that 1-(methoxycarbonyl)-2-(methylthio)-4-(dimethylamino)-1,3-diaza-1,3-butadiene (**24a**, Scheme 4) readily reacted with DMAD in benzene (80 °C) to produce the 2-(methylthio)-pyrimidine derivative **26a** (72%) via the isolable intermediate dihydro compound **25a**. This stratagem circumvented the instability problem thought to be associated with 1-unsubstituted-1,3-diaza-1,3-butadienes. It seemed to us, however, that the aromatization of **25a** had taken place with remarkable ease given the mild reaction conditions. The intramolecular loss of trimethylurethane would require an unfavorable boatlike transition state with the methoxycarbonyl and dimethylamino substituents axially disposed. Furthermore, it was not obvious to us how the constituents of the reaction mixture could effect oxidation of **25a** by an intermolecular process. Our suspicions concerning the facile formation of **25a** were confirmed upon repetition of the cycloaddition process under the reported conditions. Compound **25a** exhibited pronounced and prolonged stability in boiling benzene with less than 10% of **26a** being formed after 24 h. The concept of using stable 1-acyl derivatives as a formal source of 1-unsubstituted-1,3-diazadienes nevertheless has considerable merit. In this context, the known thermal fragmentation of *N*-*tert*-butoxycarbonyl compounds to isobutylene, carbon dioxide, and the NH compound[18] suggested the 1-*tert*-Boc derivatives of **24** as logical equivalents of the N-unsubstituted congeners. Therefore, *tert*-Boc-benzamidine (**23b**) was converted into the corresponding diazadiene **24b** by heating with DMF dimethylacetal in THF at reflux temperature. Heating a toluene solution of this compound with an excess of DMAD or ethyl propiolate (**12b**) in toluene at 100−110 °C, provided the pyrimidines **20d** and **26c**, respectively, in about 40% yields (Table 1). Similarly the 1-*tert*-Boc diazadienes **24c**, **24d**, and **27** led to the dimethyl pyrimidine-4,5-dicarboxylates **26d**, **26e**, and **20c**, respectively.

An experiment which highlights the greatly differing consequences of *N*-*tert*-Boc vs *N*-(methoxycarbonyl) protection of the diazadienes was conducted in an NMR spectrometer probe in deuterated 1,1,2,2-tetrachloroethane. Thus, both **24b** and **24e** were completely converted into the cycloadducts **25b** and **25f** after 1 h at 75 °C (3 equiv of DMAD) as indicated by the disappearance of the singlet absorptions for the NMe_2 and vinyl functions at *ca.* δ 3.8 and 8.5 and the appearance of a new NMe_2 resonance at *ca.* δ 3.2. After 1 h at 100 °C more than 70% of **25b** had been transformed into the pyrimidine **20d** and isobutylene (^{1}H NMR absorptions of δ 1.85 and 5.3.[19,20] In the absence of DMAD, the azadiene **24b** is stable under these conditions). In contrast, the methoxycarbonyl derivatives **25f** was essentially unchanged

(18) Green, T. W.; Wuts, P. G. M. In *Protective Groups in Organic Synthesis*, 2nd ed.; J. Wiley & Sons Inc.: New York, 1991; pp 327−330.

(19) In CCl_4 at 31 °C, isobutylene has absorptions at δ 1.68 and 4.63. Rumens, F. H. A.; Lomas, J. S.; Tiflon, B.; Coupry, C.; Lumbroso-Bader, N. *Org. Magn. Reson.* **1982**, *19*, 35.

(20) It is noteworthy that the Boc-azadiene **24b** is recovered unchanged after heating in xylenes for 6 h in the absence of DMAD.

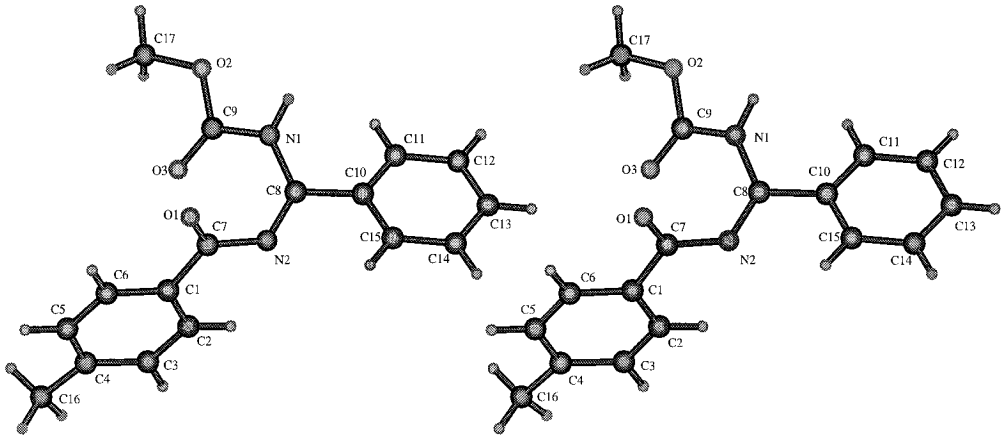


Figure 1. Computer-generated stereoview of *N*-(methoxycarbonyl)-*N*′-(4-methylbenzoyl)benzamidine (**17b**).

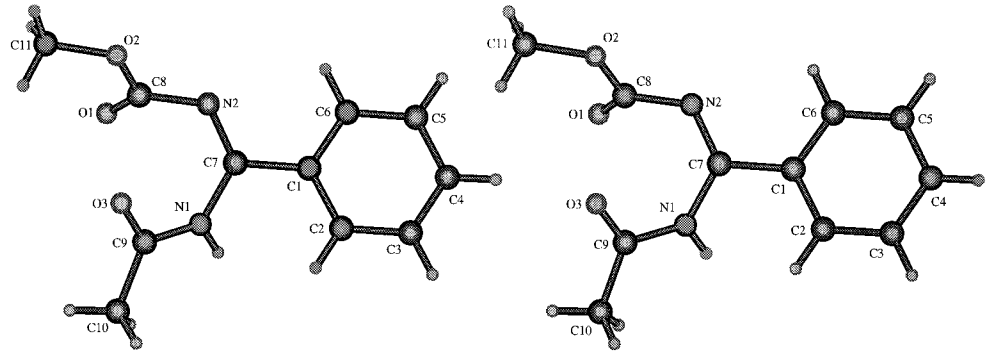
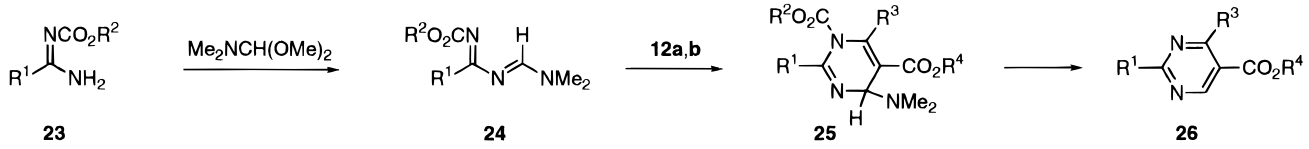


Figure 2. Computer-generated stereoview of *N*-(methoxycarbonyl)-*N*′-acetylbenzamidine [**17c**(**22**)].

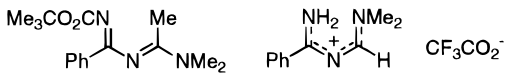
Scheme 4



23 **24** **25** **26**

23, **24** **a**, R^1 = MeS, R^2 = Me
b, R^1 = Ph, R^2 = t-Bu
c, R^1 = EtO_2C, R^2 = t-Bu
d, R^1 = $(EtO)_2CH$, R^2 = t-Bu
e, R^1 = Ph, R^2 = Me

25,**26** **a**, R^1 = MeS, R^2, R^4 = Me, R^3 = CO_2Me
b, R^1 = Ph, R^2 = t-Bu, R^3 = CO_2Me, R^4 = Me
c, R^1 = Ph, R^2 = t-Bu, R^3 = H, R^4 = Et
d, R^1 = EtO_2C, R^2 = t-Bu, R^3 = CO_2Me, R^4 = Me
e, R^1 = $(EtO)_2CH$, R^2 = t-Bu, R^3 = CO_2Me, R^4 = Me
f, R^1 = Ph, R^2, R^4 = Me, R^3 = CO_2Me



27 **28**

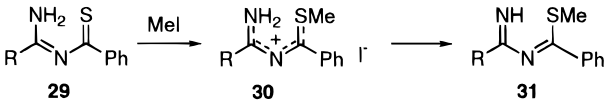
after 2 h at 100 °C. After 24 h at 100 °C, **25f** had completely decomposed, but only a minor amount of **20d** was present in the product mixture.

Another potential advantage of the Boc-substituted diazadienes is that it should be possible to cleave the protecting group under mildly acidic conditions to produce stable salts of the 1*H*-dienes (see above). Indeed, a solution of **24b** in dichloromethane containing excess trifluoroacetic acid was rapidly (<2 h at 15 °C) transformed into a polar material, which was undoubtedly the trifluoroacetic acid salt **28** of the diene. Addition of excess triethylamine to a dichloromethane solution of the crude product (obtained by removal of the solvent and excess acid *in vacuo*) containing excess DMAD at 0 °C resulted in no observable reaction. On warming the solution to room temperature, a mildly exothermic reaction ensued resulting in the formation of the previously described pyrimidine derivative **20d** (Table 1). This process clearly merits further study.

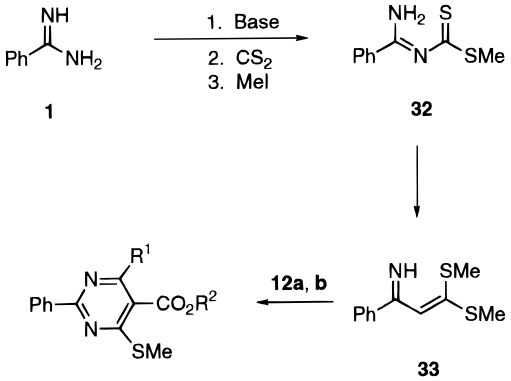
II. Generation of "Stable" N-Unsubstituted-1,3-diaza-1,3-butadienes. (a) From N-Thioacylated Amidines and Methyl Iodide. Thioamides are readily alkylated on sulfur[21] and *N*-thioacylamidines should react analogously. In fact, *N*-thiobenzoylbenzamidine (**29a**, Scheme 5), and methyl iodide gave a crystalline salt **30a**

(21) Smith, P. A. S. In *The Chemistry of Open Chain Nitrogen Compounds*; W. A. Benjamin Inc.: New York, 1965; Vol. 1, p 163.

Scheme 5



Scheme 6

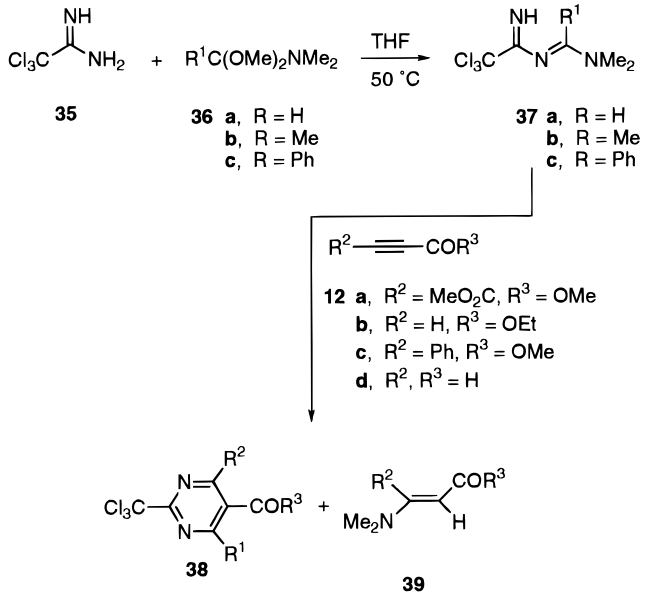


from which the somewhat unstable diene **31a** was liberated with triethylamine. Heating a toluene solution of crude **31a** with excess DMAD gave **20a** in over 90% yield (Table 1). The application of this process to *N*-thiobenzoylacetamidine (**29b**) was much less successful. Liberation of **29b** from its HCl salt with aqueous sodium bicarbonate and reaction of this unstable substance with methyl iodide gave a mixture of **30b** and *S*-methylthiobenziminium iodide. Treatment of this mixture with triethylamine gave a mixture containing the even less stable diene **31b**, which on subsequent reaction with DMAD as for **31a**, produced the pyrimidine derivative **20e** in low yield.

b. By Dimethylation of the Amidine−Carbon Disulfide Adducts. Amidines form zwitterionic adducts with carbon disulfide, and these salts, like those derived from amines,[22] should undergo sequential mono-[23] and di-S-alkylation to generate 4,4-di-*S*-alkyl-1,3-diaza-1,3-butadienes as the ultimate products.[24] Indeed, sequential addition of carbon disulfide and methyl iodide to equimolar amounts of benzamidine and *n*-butyllithium produced the methyl dithio derivatives **32** (Scheme 6) as one of the products. When this process was carried out in a two-phase ether:water system, using sodium hydroxide as the base, **32** was obtained in nearly quantitative yield. Compound **32** could be S-methylated a second time under aqueous or anhydrous conditions to give the 1,3-diaza-1,3-diene **33** as an acid soluble (stable hydrochloride) solid indefinitely stable at −10 °C. The entire reaction sequence could be effected in one pot without isolation of intermediates to produce **33** in 42% (aqueous, phase transfer) −73% (anhydrous) overall yields. Cycloaddition of **33** with DMAD and ethyl propiolate gave the expected pyrimidine derivatives **34a** and **34b**, respectively (Table 1).

Preliminary experiments with alkylamidines, such as *n*-nonanamidine or phenylacetamidine, indicate that the mono-*S*-methyldithiocarbonyl analogs of **32** are readily

Scheme 7



formed, albeit in much lower yields, but that the diazadienes derived therefrom are much less stable than **33** and decompose as they are generated.[24] The generation of alkyl analogs of **33** at low temperatures under more carefully controlled conditions nevertheless merits further study.

c. From Trichloroacetamidine and Amide Acetals. The facile generation of 2-phenyl-1,3-diaza-1*H*-1,3-butadiene as its stable trifluoroacetic acid salt (**28**) suggested that it might be possible to prepare congeners of **28** directly from amidines or their salts and amide acetals. We have not yet found conditions to effect this condensation reaction in a general way, using either the amidines or various salts thereof. The very readily available trichloroacetamidine (**35**)[26] is, however, an exception. Heating a THF solution of this amidine with a slight excess of the amide acetals **36a-c** produced the 1,3-diaza-1*H*-1,3-butadienes **37a-c** (Scheme 7) as oils (90−100% yields) which have prolonged stability at −10 °C. These dienes react rapidly at room temperature with DMAD to give the 2-(trichloromethyl)pyrimidines **38a,e,g** in high yields (see Table 2) accompanied by the dimethylamine−acetylene adduct[27] **39a**. Analogous reactions occurred with propiolic aldehyde (**12d**) at room temperature and with ethyl propiolate and methyl phenylpropynoate (**12c**) under more vigorous conditions (see Table 2).

Only one cycloaddition reaction with an activated olefin has so far been examined. An attempt to generate 2-(trichloromethyl)pyrimidine (**41**, Scheme 8) from **37a**

(22) Chabrier, P.; Nachmias, G. *Bull. Soc. Chim. Fr.* **1950**, D43−D65.

(23) Eul, W.; Gattow, G. *Z. Anorg. Allg. Chem.* **1987**, *545*, 125.

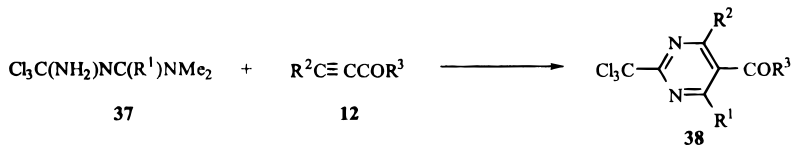
(24) Eul and Gattow[23] reported that the carbon disulfide:acetamidine adduct reacted with methyl iodide to produce, among other products, $MeC(NH_2)NCS_2Me$, $MeSCSNH_2$, and 2-(methylthio)-4,6-dimethyl-1,3,5-triazine. The last two products are consistent with the formation of the 1,3-diaza-1,3-butadiene $MeC(NH)NC(SMe)_2$ as an intermediate. On the basis of the results described herein, this diene is expected to fragment to $MeSCSNH_2$ and acetonitrile, and the latter on $[4\pi + 2\pi]$ cycloaddition with the diazadiene would give rise to the observed triazine. This type of cycloaddition has been observed at least in one instance.[25]

(25) Burger, K.; Penninger, S. *Synthesis* **1978**, 524.

(26) Dachlauer, K. Ger. Patent 671,785, 1939; *Chem. Abst.* **1939**, *33*, 6345.[1] Albert, A.; Paal, B. *Chem. Ind. (London)* **1974**, 874. Trichloroacetamidine is a much weaker base ($pK_a = 6.5$) than acetamidine ($pK_a = 12.4$; Albert, A.; Paal, B. *Ibid.*).

(27) Such addition products were also obtained in the cycloaddition reactions of the diazadienes **23**, **31**, and **33**.

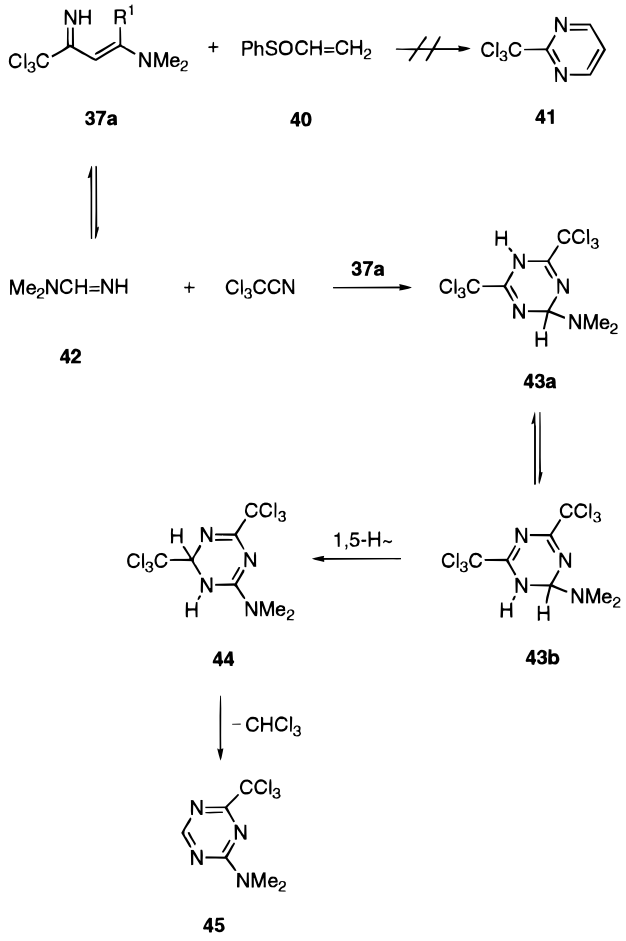
Table 2. Reaction of 2-Trichloromethyl-4-dimethylamino-1,3-diaza-1,3-butadienes 37 with Electron Deficient Acetylenes 12[a,b]



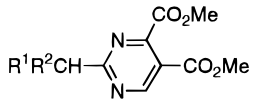
R^1	R^2	R^3	moles of **12** per mole of **37**	temp (°C)	time (h)	CC sol system hex:EtOAc	prod	% yield	mp (°C)[c]
H	MeOOC	OMe	4	rt	0.5	4:1	**38a**	98	65−66
H	H	OEt	4	70	24	4:1	**38b**	75	58−60
H	Ph	OMe	2	101	30	9:1	**38c**	51	68−69
H	H	H	1	rt	0.5	85:15	**38d**	66	75−76
Me	MeOOC	OMe	4	rt	0.5	9:1	**38e**	76	68−69
Me	H	OEt	4	80[d]	1	9:1	**38f**	65	83−84
Ph	MeOOC	OMe	4	rt	0.5	85:15	**38g**	73	111−112
Ph	H	OEt	4	80	3	9:1	**38h**	56	49−50
Ph	Ph	OMe	2.7	101	4	9:1	**38i**	40	165−166
Ph	H	H	1.3	rt	1	9:1	**38j**	43	99−100[e]

[a] In toluene solution except where indicated otherwise. [b] The dimethylamine−acetylene adduct **39** was also isolated in all cases. [c] Crystallized from hexane−dichloromethane mixtures unless stated otherwise. [d] Benzene as solvent. [e] Crystallized from hexane−ethyl acetate.

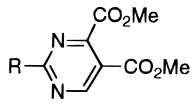
Scheme 8



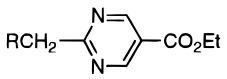
Scheme 9



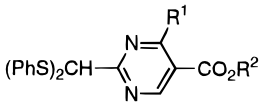
46 a, R^1,R^2 = Cl
b, R^1 = Cl, R^2 = H
c, R^1, R^2 = H
d, R^1, = n-Pr, R^2 = H
e, R^1 = EtO_2CCH_2, R^2 = H
f, R^1, R^2 = Me
g, R^1 = PhSO, R^2 = n-Pr



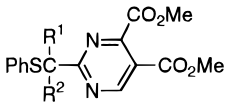
47 a, R = MeO
b, R = $PhSCH_2$
c, R = $EtSCH_2$
d, R = $PhSOCH_2$
e, R = $PhSO_2CH_2$
f, R = CHO
g, R = CHNOH
h, R = CN
i, R = t-EtCH=CH



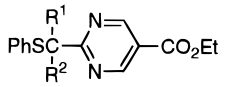
48 a, R = PhS
b, R,= PhSO



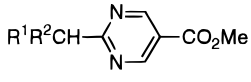
49 a, R^1 = CO_2Me, R^2 = Me
b, R^1 = H, R^2 = Et



50 a, R^1 = n-Pr, R^2 = H
b, R^1 = CH_2CO_2Et, R^2 = H
c, R^1, R^2 = Me
d, R^1 = $(CH_2)_2CO_2Me$, R^2 = H
e, R^1, R^2 = $(CH_2)_2CO_2Me$
f, R^1 = $MeCO_2$, R^2 = H



51 a, R^1 = n-Pr, R^2 = H
b, R^1, R^2 = Me
c, R^1 = $MeCO_2$, R^2 = H



52 a, R^1 = Pr, R^2 = H
b, R^1, R^2 = Me

and phenyl vinyl sulfoxide (**40**) (toluene/101 °C) failed and produced 2-(trichloromethyl)-4-(dimethylamino)-1,3,5-triazine (**45**) as the only isolable product (20%). This compound is suggested to arise as a consequence of a partial fragmentation of **37a** to *N*,*N*-dimethylformamidine (**42**) and trichloroacetonitrile. Cycloaddition of trichloroacetonitrile with the diazadiene **37a** would produce the dihydrotriazine **43a**, which upon tautomerization to **43b**, and sequential 1,5-hydrogen shift and loss of chloroform would produce **45**. Consistent with this mechanistic proposal is that the 1,3-diaza-1,3-diene **37a** is formed (ca. 50% yield) from a mixture of trichloroacetonitrile and *N*,*N*-dimethylformamidine, and the triazine **45** is obtained from a mixture of the diazadiene **37a** and trichloroacetonitrile (83% yield).

Table 3. 2-(Trichloromethyl)pyrimidine 38a and 38b as a Source of Other Pyrimidine Derivatives[a]

stg mat.	product(s)	CC sol system hex:EtOAc	% yield	stg mat.	product(s)	CC sol system hex:EtOAc	% yield
38a	**46a, 46b**	4:1	71,[b] 24	**48a**	**51b**	4:1	82
38a	**46b, 46c**	4:1	62, 14	**47b**	**50d**	4:1	71
38a	**46c**	4:1	72	**47b**	**50e**	4:1	71
38a	**47a**	4:1	66	**47c**	**46c**	4:1	82
38a	**47b**	4:1	97[c]	**50a**	**46d**	4:1	62
38b	**48a**	9:1	100[d]	**50b**	**46e**	4:1	72
38a	**47c**	4:1	90	**50c**	**46f**	9:1	85
38a	**47b, 49a**	4:1	5, 64	**51a**	**52a**	9:1	87
38b	**48a, 49b**	9:1	23, 70	**51b**	**52b**	9:1	80
47b	**47d**	1:1	76	**47c**	**50f**	7:3	93
47b	**47e**	1:1	92[e]	**48b**	**51c**	4:1	92
48a	**48b**	1:1	95	**50f**	**47g**	1:1	59[f]
47b	**50a**	4:1	72	**47g**	**47h**	4:1	87
47b	**50b**	85:15	85	**50a**	**47i**	9:1	86
47b	**50c**	85:15	71				
48a	**51a**	9:1	68				

[a] All compounds, except those indicated, were oils. Solid compounds were crystallized from CH_2Cl_2−hexane mixtures. [b] Mp 83−84 °C. [c] Mp 65−66 °C. [d] Mp 58−59 °C. [e] Mp 103−104 °C. [f] Mp 143−144 °C.

It is noteworthy that the fragmentation of **37a** to *N*,*N*-dimethylformamidine and trichloroacetonitrile is not an unique process. This type of cleavage reaction occurs to a greater or lessor extent with all of the 1*H*-1,3-diaza-1,3-butadienes described in this study.

III. 2-(Trichloromethyl)pyrimidines as Precursors of Other 2-Substituted Pyrimidines. The trichloromethyl group in **38** is quite reactive and these compounds serve as a source of a wide variety of other 2-substituted pyrimidines. Thus, catalytic hydrogenolysis of **38a** at atmospheric pressure ($Pd-CaCO_3/Et_3N$) is easily controlled to produce the 2-(dichloromethyl) and the 2-(chloromethyl) compounds **46a** and **46b** selectively, or the 2-methyl derivatives **46c** exclusively (Scheme 9, Table 3). Reaction of **38a** with an equimolar amount of methanolic sodium methoxide also took place at room temperature to give the 2-methoxy compound **47a**, possibly by the loss of trichloromethide ion. In sharp contrast, excess sodium thiophenolate or sodium ethanethiolate (3 equiv) reacted rapidly to give the sulfides **47b** and **47c** exclusively in near quantitative yields. Ethyl 2-(trichloromethyl)pyrimidine-5-carboxylate (**38b**) was converted into the corresponding (phenylthio)methyl compound **48a** in the same manner. The efficient formation of the sulfides **47b** and **48a** at least requires the presence of free thiophenol, since under otherwise identical conditions, the bis(phenylthio) compounds **49a** and **49b** are the major products. These compounds presumably are derived from the corresponding anions by protonolysis on workup. The bis(phenylthio) compound **49a** was instantly converted into the sulfide **47b** by an equimolar amount of the 1:1 thiophenol−sodium thiophenolate mixture in THF at room temperature, and it was demonstrated to be the penultimate intermediate in the formation of the sulfide. When the reaction was effected at −78 °C, both **49a** and **47b** were present in significant amounts (TLC) by 5 min, but **49a** was by far the major species. By 10 min the **49a:47b** ratio had decreased to unity, and then it remained approximately constant, at least up to 30 min. When this mixture was left to warm to room temperature, **49a** disappeared completely in favor of **47b**. We no longer believe that the formation of the sulfides occurs by a radical process.[13] The reaction shows no induction period; even at −78 °C, it proceeds at the same rate in the dark or under laboratory light and is not affected in any way by the presence of *p*-dinitrobenzene.[28] It is probable that the process involves the formation and protonation of a series of anions generated by the attack of thiophenolate on chlorine resulting in the rapid production of **49a** as the immediate precursor of **47b**. It is possible that carbenes might be intermediates in the formation of **49a**, but no evidence for or against such species was sought.

Because of the availability of the sulfides **47b** and **48a**, the oxidation thereof to the sulfoxides **47d** and **48b** and the sulfone **47e** was effected using *m*-chloroperbenzoic acid. These compounds, and the sulfides from which they were derived, were sufficiently acidic to the deprotonated by sodium hydride in DMF at room temperature. Although the alkylation of all of these anions was readily accomplished, only that of the sulfide-derived anions was studied preparatively. Thus, monoalkylation with *n*-propyl iodide or ethyl bromoacetate to **50a**, **50b**, and **51a**, as well as dimethylation with methyl iodide to **50c** and **51c**, were effected efficiently. Furthermore, the mono- and dialkylation of the sulfide **47b** in the Michael sense with methyl acrylate catalyzed by Triton B produced compounds **50d** and **50e** uneventfully.

Several of the above sulfides, including **47c**, were reductively desulfurized with Raney nickel to the 2-alkylpyrimidines **46c-f** and **52a,b** (Note transesterification in these two cases).

The sulfoxides **47d** and **48b** were converted into the Pummerer products **50f** and **51c** by hot acetic anhydride. We were unable to generate the aldehyde **47f** from **50f** under a variety of conditions, but the oxime **47g** could be obtained under acidic conditions, and this compound was dehydrated to the nitrile **47h** with polyphosphate ester.

The sulfide **50a** was selectively oxidized to the sulfoxide **46g**. Thermolysis of **46g** in toluene at reflux temperature gave the *trans* disubstituted olefin **47i**.

Summary

Methodology has been developed to prepare 1*H*-1,3-diaza-1,3-butadienes in latent (**17**), masked (**24**), and unprotected (**31**, **33**, and **37**) forms. For example, the 1-(methoxycarbonyl)-3-acylamidines **17** undergo thermal

(28) Kornblum, N.; Michel, R. E.; Kerber, R. C. *J. Am. Chem. Soc.* **1966**, *88*, 5660. Kornblum, N.; Davies, T. M.; Earl, G. W.; Holy, K. L.; Kerber, R. C.; Musser, M. T.; Snow, D. H. *J. Am. Chem. Soc.* **1967**, *89*, 725.

conversion into the 1,3-diaza-1,3-dienes **18** and/or **19** which can be trapped with DMAD to produce the pyrimidines **20**. The 1-Boc-1,3-diaza-1,3-dienes **24** are masked forms of the corresponding 1*H*-dienes. They react with DMAD under mild conditions to give the adducts **25**, which under more vigorous conditions are aromatized to the pyrimidines **26** by loss of Me_2NH, CO_2, and isobutylene. The readily preparable 1*H*-1,3-diaza-1,3-dienes **31**, **33**, and **37** all react with electron deficient acetylenes under mild conditions to produce the pyrimidines **20**, **34**, and **38**, respectively. The (trichloromethyl)pyrimidines **38** are versatile precursors of numerous other 2-substituted pyrimidines **46**−**52**.

Finally, the facile generation of the relatively stable 1*H*-1,3-diaza-1,3-butadienes **31**, **33**, and **37** now makes it possible to undertake a detailed study of other reactions and properties of these compounds.

Experimental Section

The ^{1}H NMR were measured on 90 or 200 MHz instruments in $CDCl_3$ solution (except where stated otherwise) and are reported in δ (ppm) from internal tetramethylsilane. ^{13}C NMR spectra were also recorded in $CDCl_3$ solution. High resolution mass spectra were obtained on samples which were judged to be at least of 90% purity by TLC and ^{1}H NMR spectroscopy. The IR spectra were measured in $CHCl_3$ solution unless specified otherwise. The melting points are not corrected.

The following compounds were prepared by the literature methods cited: *N*-benzoylbenzamidine (**15a**),[3] *N*-acetylbenzamidine (**15c**),[29] *N*-benzoylacetamidine (**15e**),[30] 1-(ethoxycarbonyl)formamidine hydrobromide,[31] 1,1-bis(ethoxycarbonyl)-formamidine hydrochloride,[31] *N*-thiobenzoylbenzamidine (**29a**),[8] hydrochloride salt of *N*-thiobenzoylacetamidine (**29b**),[32] hydrochloride salt of *N*,*N*-dimethylformamidine (**42**).[33]

The spectroscopic data not found in the Experimental Section is located in Table 4 of the supporting information.

***N*-(4-Methylbenzoyl)benzamidine (15b).** This compound was prepared from benzamidine hydrochloride and 4-methylbenzoyl chloride using the method described by Chua et al.[30] for the preparation of *N*-benzoylacetamidine (**15e**). After crystallization of the crude product from hexane−ethyl acetate pure **15b** was obtained in 78% yield as a solid: mp 101−102 °C; IR 3460, 3215, 1590, 1562, 1553 cm^{-1}; ^{1}H NMR δ 2.42 (s, 3H), 7.26 (d, 2H, J = 8.0 Hz), 7.47−7.65 (m, 3H), 8.05−8.14 (m, 2H), 8.29 (d, 2H, J = 8.0 Hz); mass spectrum m/z 238 (30, M$^+$), 119 (100), 91 (40). Anal. Calcd for $C_{15}H_{14}N_2O$: 0.125 H_2O: C, 74.89; H, 5.97; N, 11.65. Found: C, 74.76; H, 5.83; N, 11.64.

1-Methyl-3-benzoylacetamidine (16). A solution of *N*-benzoylacetamidine (**15e**, 1.0 g, 6.2 mmol) in dimethyl sulfate (3 mL) was stirred at room temperature for 15 h. The reaction mixture was washed with hexane to remove the excess dimethyl sulfate, and the solid residue was washed with ether. Crystallization of this solid from methanol gave the methosulfate salt of **16** as a solid (1.5 g, 89% yield) with mp 174−175 °C; IR (KBr) 3260, 3142, 1693, 1662, 1550, 1544 cm^{-1}; ^{1}H NMR (DMSO d_6) δ 2.57 (s, 3H), 3.24 (s, 3H), 3.43 (s, 3H), 7.54−7.83 (m, 3H), 7.98−8.13 (m, 2H); mass spectrum m/z 176 (35; M$^+$, free base), 175 (100), 105 (78), 99 (50). Anal. Calcd for $C_{10}H_{12}N_2O\cdot HSO_4Me$: C, 45.82; H, 5.59; N, 9.71. Found: C, 45.80; H, 5.59; N, 9.72.

A suspension of the above salt (0.580 g, 2.0 mmol) in anhydrous THF (10 mL) containing anhydrous triethylamine (0.55 mL, 0.4 g, 4.0 mmol) was stirred at room temperature for 0.5 h. The solid was removed by filtration and washed with ethyl acetate, and the filtrate was washed with water, dried over sodium sulfate, and evaporated *in vacuo*. After drying in high vacuum compound **16** was obtained as a clear oil in quantitative yield: IR 3472, 1595, 1580 cm^{-1}; ^{1}H NMR δ 2.21 (s, 3H), 3.03 (s, 3H), 7.31−7.55 (m, 3H), 8.12−8.35 (m, 2H); ^{13}C NMR δ 21.76, 30.64, 128.50, 128.51, 129.69, 138.38, 172.75, 180.37. Anal. Calcd for $C_{10}H_{11}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.49; H, 6.83; N, 15.74.

Synthesis of the *N*-(Methoxycarbonyl)-*N*′-acylamidines 17. Methyl chloroformate (10.2 mmol) was added slowly at room temperature to a stirred solution of the *N*-acylamidine (**15**, 10 mmol) in anhydrous dichloromethane (10 mL) containing anhydrous pyridine (10.2 mmol) maintained in a nitrogen atmosphere. The reaction mixture was stirred for an additional 1−2 h, it was then diluted with dichloromethane (50 mL), and the mixture was washed with water. The organic phase was combined with a dichloromethane extract of the aqueous phase, dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was then subjected to column chromatographic purification on silica gel using a hexane−ethyl acetate mixture to elute the product.

***N*-(Methoxycarbonyl)-*N*′-benzoylbenzamidine (17a).** Hexane−ethyl acetate (4:1) eluted the product as a solid in 72% yield. After crystallization from hexane−dichloromethane it had mp 79−80 °C; IR (KBr) 3120, 1753, 1634 cm^{-1}; ^{1}H NMR δ 3.78 (s, 3H), 7.41−7.66 (m, 6H), 7.71−7.82 (m, 2H), 8.08−8.26 (m, 2H); mass spectrum m/z 282 (32, M$^+$), 223 (15), 205 (13), 105 (100), 77 (39). Anal. Calcd for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 67.92; H, 4.95; N, 9.76.

***N*-(Methoxycarbonyl)-*N*′-(4-methylbenzoyl)benzamidine (17b).** Hexane−ethyl acetate (85:15) eluted the product as a solid (80% yield) which after crystallization from hexane−dichloromethane had mp 120−122 °C; IR (KBr) 3202, 1762, 1624 cm^{-1}; ^{1}H NMR δ 2.43 (s, 3H), 3.77 (s, 3H), 7.29 (d, 2H, J = 8.0 Hz), 7.41−7.61 (m, 2H), 7.77 (d, 2H, J = 8.0 Hz), 7.89−8.18 (m, 2H); mass spectrum m/z 296 (16, M$^+$), 119 (100), 91 (32). Anal. Calcd for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.45. Found: C, 68.05; H, 5.48; N, 9.41.

***N*-(Methoxycarbonyl)-*N*′-acetylbenzamidine (17c).** Eluted from the column with hexane−ethyl acetate (4:1) as a solid in 86% yield. After crystallization from hexane−dichloromethane it had mp 118−119 °C; IR (KBr) 3251, 1720, 1676 cm^{-1}; ^{1}H NMR δ 2.29 (s, 3H), 3.77 (s, 3H), 7.38−7.62 (m, 5H), 9.11−9.72 (bs, 1H); mass spectrum m/z 219 (98, M$^+$ − 1), 205 (100), 147 (65), 104 (56). Anal. Calcd for C_{11} $H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 59.87; H, 5.36; N, 12.67.

***N*-(Methoxycarbonyl)-*N*′-benzoylacetamidine (17e).** Prepared in the general manner except that triethylamine was used instead of pyridine. Chromatographic purification of this material was not necessary. The pure material, obtained in 75% yield after crystallization from hexane−dichloromethane, had mp 50−52 °C; IR (KBr) 3371, 3182, 1761, 1657 cm^{-1}; ^{1}H NMR δ 2.63 (s, 3H), 3.80 (s, 3H), 7.32−7.62 (m, 3H), 7.90−8.25 (m, 2H); mass spectrum m/z 220 (20, M$^+$), 219 (35), 105 (100). Anal. Calcd for $C_{11}H_{12}N_2O_3$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.00; H, 5.64; N, 12.82.

Synthesis of Dimethyl 2-Phenylpyrimidine-4,5-dicarboxylates (20a-c) by Thermolysis of *N*-(Methoxycarbonyl)-*N*′-acylbenzamidines (17a−c) in the Presence of Dimethyl Acetylenedicarboxylate. A solution of **17** (1 equiv) and DMAD (2 equiv) in anhydrous *o*-dichlorobenzene (5−10 mL/mmol **17**) was heated at 150 °C (N_2 atmosphere) for 24−28 h. The solution was absorbed onto a column of silica gel, and the solvent was eluted with hexane. The product was then eluted from the column with the appropriate hexane−ethyl acetate mixture. See Table 1 for product yields.

Dimethyl 2,6-Diphenylpyrimidine-4,5-dicarboxylate (20a). Eluted from the column with hexane−ethyl acetate (9:1) to give the product as a solid, which, after crystallization from hexane−dichloromethane, had mp 144−145 °C; IR 1728 cm^{-1}; ^{13}C NMR δ 53.00, 53.48, 123.02, 128.64, 128.91, 130.66, 131.75, 136.12, 136.99, 154.94, 164.62, 164.94, 165.40, 167.37; mass spectrum m/z 348 (70, M$^+$), 333 (100), 273 (34), 232 (95).

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(30) Chua, S.-W.; Cook, M. J.; Katritzky, A. R. *J. Chem. Soc., Perkin Trans. 2* **1974**, 546.
(31) Schaefer, F. C. *J. Org. Chem.* **1962**, *27*, 3608.
(32) Goerdeler, J.; Porrmann, H. *Chem. Ber.* **1961**, *94*, 2856.
(33) Matterstock, K.; Jensen, H. Ger. Patent 1,168,896, 1964; *Chem. Abstr.* **1964**, *61*, 6991f. Jentzsch, W.; Seefedler, M. *Chem. Ber.* **1965**, *98*, 1342.

Anal. Calcd for $C_{20}H_{16}N_2O$: C 68.95; H, 4.63; N, 8.04. Found: C, 68.87; N, 4.58; N, 8.02.

Dimethyl 2-Phenyl-6-(4-methylphenyl)pyrimidine-4,5-dicarboxylate (20b). Eluted from the column with hexane−ethyl acetate (95:5) to give a solid, which after crystalliztion from hexane−dichloromethane, had mp 134−135 °C. Anal. Calcd for $C_{21}H_{18}N_2O_4$: C, 69.60; H, 5.00; N, 7.73. Found: C, 69.57; H, 5.01; N, 7.64.

Dimethyl 2-Phenyl-6-methylpyrimidine-4,5-dicarboxylate (20c). Eluted from the column with hexane−ethyl acetate (9:1) as a solid, which after crystallization from hexane−dichloromethane, had mp 88−89 °C; ^{13}C NMR δ 23.78, 53.51, 53.85, 123.31, 129.14, 129.37, 132.18, 136.56, 155.39, 165.12, 165.76 (2), 167.12, 167.96; mass spectrum *m*/*z* 286 (50, M^+), 256 (20), 227 (15), 198 (30), 170 (100). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.92; N, 9.78. Found: C, 62.85; H, 4.95; N, 9.73.

Dimethyl 2-Phenylpyrimidine-4,5-dicarboxylate (20d) without Isolation of (17d). Because of the pronounced tendency of *N*-formylbenzamidine (**15d**) to be converted into 2,4-diphenyl-*s*-triazine under formylation conditions,[34] this substance was generated and used directly for the synthesis of **20d** without isolation of either **15d** or **17d**. Thus, 50 wt % aqueous sodium hydroxide (1.6 mL) was added dropwise at 0 °C to a stirred suspension of benzamidine hydrochloride (1.56 g, 10 mmol) in acetone (50 mL), and after 5 min freshly prepared formic acid anhydride (10 mmol) was added. The reaction mixture was stirred for an additional 2 h at 0 °C. The presence of diphenyl-*s*-triazine at this stage was confirmed by TLC (silica gel). An additional quantity of 50% sodium hydroxide (0.8 mL) was added followed by dropwise addition of methyl chloroformate (0.8 mL, 0.98 g, 10 mmol). After a further 2 h at 0 °C, ethyl acetate (50 mL) was added to the reaction mixture, and the organic phase was separated, washed with saturated NaCl solution, and dried (Na_2SO_4). Evaporation of the solvent *in vacuo* gave a residue which was dissolved in *o*-dichlorobenzene (10 mL), DMAD (1.2 mL, 1.39 g, 9.8 mmol) was added, and the solution was then heated at 100 °C in a nitrogen atmosphere for 15 h. The solution was then worked up as described above for **20a**−**c**. Compound **20d** was eluted from the column as a solid, which after crystallization from hexane−dichloromethane, had mp 115−116 °C; IR (KBr) 1733, 1569, 1540 cm^{-1}; ^{1}H NMR δ 3.96 (s, 3H), 4.04 (s, 3H), 7.46−7.55 (m, 3H), 8.50−8.54 (m, 2H), 9.32 (s, 1H); ^{13}C NMR δ 53.47; 53.77, 118.93, 129.55, 129.74, 132.82, 136.20, 159.98, 160.11, 164.08, 166.22, 167.35; mass spectrum *m*/*z* 272 (55, M^+), 241 (15), 213 (30), 184 (45), 156 (100). Anal. Calcd for $C_{14}H_{12}N_2O_4$: C, 61.76; H, 4.44; N, 10.29. Found: C, 61.57; H, 4.33; N, 10.19.

***N*-(*tert*-Butoxycarbonyl)benzamidine (23b).** A solution of sodium hydroxide (1.0 g, 25 mmol) in water (20 mL) was added dropwise at 0 °C to a stirred suspension of benzamidine hydrochloride (1.56 g, 10 mmol) in THF (20 mL), and di-*tert*-butyl dicarbonate (2.2 g, 10 mmol) was added immediately thereafter. After 1 h at 0 °C, ethyl acetate was added, and the organic phase was separated, washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo*. Crystallization of the solid residue from hexane−dichloromethane gave pure **23b** (2.0 g, 91% yield) mp 102−103 °C; IR 3497, 3310, 1611, 1578 cm^{-1}; ^{13}C NMR δ 28.07, 79.51, 127.11, 128.39, 131.69, 134.84, 163.86, 167.31; mass spectrum *m*/*z* 220 (5, M^+), 165 (100), 147 (45), 104 (45). Anal. Calcd for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.45; H, 7.40; N, 12.77.

***N*-(*tert*-Butoxycarbonyl)-1-(ethoxycarbonyl)formamidine (23c).** Triethylamine (0.72 mL, 0.52 g, 5.2 mmol) was added dropwise to stirred suspension of 1-(ethoxycarbonyl)-formamidine hydrobromide (0.985 g, 5.0 mmol) in anhydrous THF (15 mL) containing 4-(dimethylamino)pyridine (0.06 g, 0.5 mmol) and di-*tert*-butyl dicarbonate (1.10 g, 5.0 mmol) at room temperature (N_2 atmosphere). After 2 h the reaction mixture was worked up as described for **23b** above giving the product as a somewhat unstable oil in quantitative yield: IR 3471, 3407, 1724, 1667, 1632 cm^{-1}; ^{1}H NMR δ 1.27 (t, 3H), 1.40 (2, 9H), 4.20 (q, 2H), 8.16−8.82 (bs, 2H); mass spectrum *m*/*z* 217 (100, M^+), 135 (25). Anal. Calcd for $C_9H_{16}N_2O_4$: C, 49.98; H, 7.45; N, 12.95. Found: C, 50.08; H, 7.33; N, 12.94.

***N*-(*tert*-Butoxycarbonyl)-2-(diethoxymethyl)formamidine (23d).** 2-(Diethoxymethyl)formamidine hydrochloride was converted into the corresponding *N*-(*tert*-butoxycarbonyl) compound **23d** in the same manner as described for the synthesis of **23c**. After crystallization from hexane−dichloromethane pure **23d** was obtained in 97% yield and had mp 75−77 °C; IR 3476, 3329, 1737, 1663, 1625 cm^{-1}; ^{13}C NMR δ 14.92, 27.98, 63.10, 100.12, 163.84, 167.85; mass spectrum *m*/*z* 247 (22, MH^+), 191 (100), 147 (50), 103 (62). Anal. Calcd for $C_{11}H_{22}N_2O_4$: C, 53.63; H, 9.00; N, 11.37. Found: C, 53.41; H, 9.08; N, 11.42.

***N*-(Methoxycarbonyl)benzamidine (23e).** This compound was prepared in the same manner as described for compound **23b** except that methyl chloroformate was used as the acylating agent. After crystallization of the crude product from hexane−dichloromethane pure **23e** was obtained in 85% yield and had mp 95−98 °C; IR 3498, 3311, 1659, 1613, 1579 cm^{-1}; mass spectrum *m*/*z* 178 (50, M^+), 163 (18), 147 (100), 120 (45), 104 (60), 77 (40). Anal. Calcd for $C_9H_{10}N_2O_2$: C, 60.65; H, 5.65; N, 15.72. Found: C, 60.59; H, 5.70; N, 15.76.

Synthesis of the 1-(Alkoxycarbonyl)-4-(dimethylamino)-1,3-diaza-1,3-butadienes (24). A solution of the *N*-(alkoxylcarbonyl)amidine **23** (1 equiv) in anhydrous THF (1−7 mL/mmol **23**) containing dimethylformamide dimethyl acetal (1.1−1.5 equiv) was heated at reflux temperature for 2−5 h. The solution was then diluted with ethyl acetate, and it was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo*.

1-(*tert*-Butoxycarbonyl)-2-phenyl-4-(dimethylamino)-1,3-diaza-1,3-butadiene (24b). Obtained in quantitative yield as an oil: IR 1695, 1636, 1590, 1572 cm^{-1}; ^{1}H NMR δ 1.43 (s, 9H), 3.01 (s, 3H), 3.05 (s, 3H), 7.32−7.36 (m, 3H), 7.77−7.82 (m, 2H), 7.92 (s, 1H); ^{13}C NMR δ 28.52, 35.12, 41.15, 80.75, 128.42, 129.15, 131.07, 137.00, 156.13, 162.69; 166.24; mass spectrum *m*/*z* 275 (10, M^+), 202 (13), 176 (60), 57 (100). Anal. Calcd for C_{15} $H_{21}N_3O_2$: C, 65.43; H, 7.69; N, 15.26. Found: C, 65.56; H, 7.74; N, 15.59.

1-(*tert*-Butoxycarbonyl)-2-(ethoxycarbonyl)-4-(dimethylamino)-1,3-diaza-1,3-butadiene (24c). Obtained in quantitative yield as an oil: IR 1736, 1668, 1154, 1531 cm^{-1}; ^{1}H NMR δ 1.33 (t, 3H), 1.51 (s, 9H), 3.06 (s, 3H), 3.10 (s, 3H), 4.26 (q, 2H), 8.35 (s, 1H); ^{13}C NMR δ 13.83, 28.01, 41.21, 62.09, 80.71, 158.01, 163.41, 166.10, 168.29; FAB HRMS calcd for $C_{22}H_{22}N_3O_4$ 272.1610, found 272.1618 (MH^+).

1-(*tert*-Butoxycarbonyl)-2-(diethoxymethyl)-4-(dimethylamino)-1,3-diaza-1,3-butadiene (24d). Obtained in quantitative yield as an oil: IR 1704, 1583 cm^{-1}; ^{1}H NMR δ 1.24 (t, 6H), 1.52 (s, 9H), 3.02 (s, 3H), 3.06 (s, 3H), 3.58−3.78 (m, 4H), 4.98 (s, 1H), 8.41 (s, 1H); ^{13}C NMR δ 15.08, 28.04, 40.74, 63.24, 80.18, 102.65, 157.48, 161.90, 162.35. Anal. Calcd for $C_{14}H_{27}N_3O_4$: C, 55.79; H, 9.03, N, 13.94. Found: C, 55.70; H, 9.34; N, 13.88.

1-(Methoxycarbonyl)-2-phenyl-4-(dimethylamino)-1,3-diaza-1,3-butadiene (24e). Obtained in quantitative yield as an oil: IR 1702, 1633, 1589, 1570 cm^{-1}; ^{1}H NMR δ 3.06 (s, 3H), 3.10 (s, 3H), 3.77 (s, 3H), 7.32−7.48 (m, 3H), 7.75−7.91 (m, 2H), 7.96 (s, 1H); ^{13}C NMR δ 34.78, 40.76, 52.83, 128.05, 128.62, 130.79, 136.28, 156.14, 163.63, 166.97; mass spectrum *m*/*z* 233 (18, M^+), 201 (100), 118 (30), 104 (35); FAB HRMS calcd for $C_{12}H_{16}N_3O_2$ 234.1243, found 234.1231 (MH^+).

1-(*tert*-Butoxycarbonyl)-2-phenyl-4-(dimethylamino)-1,3-diaza-1,3-pentadiene (27). A solution of the N-acylated amidine **23b** (0.440 g, 2 mmol) in dry THF (10 mL) containing *N*,*N*-dimethylacetamide dimethyl acetal (0.6 mL, 0.55 g, 4 mmol) was heated at reflux temperature for 5 h. The crude product was obtained in quantitative yield as a solid, which on crystallization from hexane−ethyl acetate had mp 99−100 °C; IR 1702, 1620, 1576 cm^{-1}; ^{1}H NMR δ 1.52 (s, 9H), 1.96 (s, 3H), 3.07 (s, 6H), 7.31−7.42 (m, 3H), 7.82−8.01 (m, 2H); ^{13}C NMR δ 18.18, 28.05, 38.06, 79.71, 127.91, 128.51, 130.95, 136.05, 157.62, 162.58, 164.53; mass spectrum *m*/*z* 289 (3,

(34) Bredereck, H.; Effenberger, F.; Hofmann, A. *Chem. Ber.* **1963**, *96*, 3265.

M^+), 216 (21), 57 (100). Anal. Calcd for $C_{16}H_{23}N_3O_2$: 0.2 H_2O: C, 65.59; H, 8.05; N, 14.34. Found: C, 65.85; H, 8.09; N, 14.18.

Synthesis of Pyrimidine Derivatives from 1-(*tert*-Butoxycarbonyl)-1,3-diaza-1,3-dienes 24 and 27 and Acetylenic Esters. A solution of the diazadiene (1 equiv) in toluene (1−5 mL/mmol diene) containing the acetylenic ester (4 mol/mol diene) was heated at reflux temperature in a nitrogen atmosphere for 24−48 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel using a hexane−ethyl acetate or hexane−acetone mixtures to elute the product (Table 1 for yields).

Ethyl 2-Phenylpyrimidine-5-carboxylate (26c). This reaction was carried out in a sealed tube at 120 °C for 24 h. The product was eluted from the column with hexane−ethyl acetate (9:1) as a solid, which after crystallization from hexane−dichloromethane, had mp 95−97 °C; IR 1723, 1589 cm^{-1}; ^1H NMR δ 1.42 (t, 3H), 4.44 (q, 2H), 7.49−7.53 (m, 3H), 8.49−8.53 (m, 2H), 9.30 (s, 2H); ^{13}C NMR δ 61.61, 121.00, 128.67, 128.91, 131.74, 136.59, 158.35 (2), 163.94, 167.00; mass spectrum *m*/*z* 228 (95, M^+), 200 (35), 183 (98), 103 (100). Anal. Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.18; H, 5.28, N, 12.04.

Dimethyl 2-(Ethoxycarbonyl)pyrimidine-4,5-dicarboxylate (26d). Eluted from the column with hexane−ethyl acetate (7:3) as a solid which, after crystallization from hexane−ethyl acetate, had mp 112−114 °C; mass spectrum *m*/*z* 237 (25, M^+ − OMe), 196 (100), 164 (60), 152 (40), 59 (65). Anal. Calcd for $C_{11}H_{12}N_2O_6$: C, 49.25; H, 4.51; N, 10.45. Found: C, 49.43; H, 4.60; N, 10.38.

Dimethyl 2-(Diethoxymethyl)pyrimidine-4,5-dicarboxylate (26e). Eluted from the column with hexane−acetone (9:1) as an oil; ^1H NMR δ 1.27 (t, 6H), 3.66−3.82 (m, 4H), 3.94 (s, 3H), 4.02 (s, 3H), 5.63 (s, 1H), 9.34 (s, 1H); mass spectrum *m*/*z* 267 (10, M^+ − OMe), 254 (15), 225 (70), 193 (90), 193 (90), 137 (40), 103 (100). Anal. Calcd for $C_{13}H_{18}N_2O_6$: C, 52.34; H, 6.08; N, 9.39. Found: C, 52.21; H, 6.47; N, 9.53.

Synthesis of Dimethyl 2-Phenylpyrimidine-4,5-dicarboxylate (20d) from 2-Phenyl-4-(dimethylamino)-1,3-diaza-1,3-butadienium Trifluoroacetate (28). Trifluoroacetic acid (10 mL) was added to a stirred solution of the Boc diene **24b** (1.00 g, 3.6 mmol) in dichloromethane (20 mL) at 0 °C. Stirring at 0−15 °C was continued for 2 h, and then the solvent was removed *in vacuo* at room temperature. The residue **28** was dissolved in dichloromethane (30 mL) and cooled to 0 °C (N_2 atmosphere). DMAD (4 mL) was added to the stirred solution, and then a solution of triethylamine (1.1 mL, 0.8 g, 8 mmol) in dichloromethane (30 mL) was added dropwise. The solution was allowed to reach room temperature, and a further quantity of triethylamine (1.0 mL, 0.73 g, 7.3 mmol) was added. The solution turned yellow in color and an exothermic reaction commenced. The reaction mixture was placed in an ice-water bath until the reaction subsided, and then it was left at room temperature for 1 h. The solvent was removed *in vacuo*, and the residue was subjected to column chromatographic purification on silica gel using hexane−ethyl acetate (88:12) to elute the solid product (0.438 g, 44% yield) which was identical in all respects to compound **20d** prepared by the methods described above.

Synthesis of 2,4-Diphenyl-4-(methylthio)-1,3-diaza-1,3-butadienium Iodide (30a) and 2,4-Diphenyl-4-(methylthio)-1,3-diaza-1,3-butadiene (31a). A solution of *N*-thiobenzoylbenzamidine (**29a**, 0.480 g, 2.0 mmol) in anhydrous acetone (5 mL) containing methyl iodide (0.13 mL, 0.3 g, 2 mmol) was stirred at room temperature in a nitrogen atmosphere for 15 h. The solvent was removed *in vacuo*, and the crystalline residue was washed with ether and dried *in vacuo*. Crystalline **30a** (0.520 g, 91% yield) thus obtained, on recrystallization from dichloromethane−ether, had mp 155−156 °C dec; ^1H NMR (DMSO-d_6) δ 2.73 (s, 3H), 7.52−7.66 (m, 8H), 8.02−8.06 (d, 2H, J = 7.7 Hz); ^{13}C NMR (DMSO-d_6) δ 16.05, 127.32, 127.55, 129.37, 129.60, 129.88, 133.32, 133.72, 135.84, 172.17, 179.16; mass spectrum *m*/*z* 254 (8, M^+, free base), 253 (40), 239 (58), 104 (100), 77 (37). Anal. Calcd for $C_{15}H_{14}N_2S$: HI: C, 47.13; H, 3.95; N, 7.32. Found: C, 47.00; H, 4.03; N, 7.32.

Triethylamine (0.5 mL, 0.36 g, 3.6 mmol) was added to a suspension of **30a** (0.690 g, 1.81 mmol) in ethyl acetate (20 mL) with stirring. The solution was then washed with saturated NaCl solution, dried over sodium sulfate, and evaporated *in vacuo* giving **31a** as a somewhat unstable solid in quantitative yield: ^1H NMR δ 2.66 (s, 3H), 7.57 (m, 6H), 8.06 (m, 2H), 8.40 (m, 2H), 8.81 (m, 4H). This material was used without purification for the synthesis of **20a**.

Synthesis of Dimethyl 2,6-Diphenylpyrimidine-4,5-dicarboxylate (20a) from 31a and DMAD. A solution of the diazadiene **31a** (0.460 g, 1.81 mmol) in toluene (20 mL) containing DMAD (0.5 mL, 0.58 g, 4.1 mmol) was heated at reflux temperature (N_2 atmosphere) for 4 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatophraphy on silica gel using hexane−ethyl acetate to elute solid **20a** (0.580 g, 92%) identical in all respects to that obtained by the methods described above.

Synthesis of Dimethyl 2-Methyl-6-phenylpyrimidine-4,5-dicarboxylate (20e) without Isolation of Intermediates 29b, 30b, and 31b. *N*-Thiobenzoylacetamidine hydrochloride (5.7 g, 26.5 mmol) was stirred with a mixture of saturated $NaHCO_3$ solution (50 mL) and ethyl acetate (50 mL). After 5 min, the organic phase was separated, dried (Na_2SO_4), and evaporated *in vacuo* to give crude **29b**. A solution of crude **29b** (0.400 g, 2.24 mmol) in anhydrous acetone (5 mL) containing methyl iodide (0.15 mL, 0.36 g, 2.5 mmol) was stirred at room temperature (N_2 atmosphere) for 15 h. The solvent was removed *in vacuo*, and the solid residue was washed with ether and dried *in vacuo* giving a mixture of **30b** and *S*-methylthiobenzimidate hydriodide (0.32 g). This mixture was suspended in ethyl acetate (10 mL) containing triethylamine (0.55 mL, 0.4 g, 4 mmol) and stirred at room temperature for 10 min. The mixture was washed with saturated NaCl solution, and the organic phase was dried (Na_2SO_4) and evaporated *in vacuo* giving an oily mixture of **31b** and *S*-methylthiobenzimidate. The crude mixture of methyl thiobenzimidate and the diazadiene **31b** in anhydrous toluene (5 mL/mmol mixture) containing DMAD (4 mmol/mmol crude **31b**) was heated at reflux temperature (N_2 atmosphere) for 18 h. The solvent was removed *in vacuo*, and the residue was subjected to column chromatograhy on silica gel using hexane−ethyl acetate (85:15) to elute **20e** as a solid (7−11%) which, after crystallization from hexane−dichloromethane, had mp 75−77 °C; IR (KBr) 1739, 1717, 1554 cm^{-1}; ^1H NMR δ 2.90 (s, 3H), 3.80 (s, 3H), 4.03 (s, 3H), 7.47−7.52 (m, 3H), 7.66−7.71 (m, 2H); mass spectrum *m*/*z* 286 (44, M^+), 271 (100), 255 (24), 170 (78). Anal. Calcd for $C_{15}H_{14}N_2O_4$: C, 62.93; H, 4.92; N, 9.78. Found: C, 62.85; H, 4.95; N, 9.73.

***N*-[(Methylthio)thiocarbonyl]benzamidine (32). (a) *n*-Butyllithium as Base.** *n*-Butyllithium (38 mL of a 2.5 M solution in THF, 95.0 mmol) was added dropwise to a solution of benzamidine (13.1 g, 109.2 mmol) in anhydrous THF (375 mL, freshly distilled from sodium benzophenone ketyl) at −20 °C (N_2 atmosphere) over a 5 min period. After a further 5 min, carbon disulfide (5.2 mL, 6.4 g, 84.1 mmol) was added and the temperature was allowed to reach 0 °C. Methyl iodide (5.65 mL, 13.1 g, 92.3 mmol) was added all at once to the clear yellow solution, and the reaction temperature was allowed to rise to ambient temperature. After 0.5 h, the reaction was quenched with saturated NH_4Cl solution, ether was added, and the organic phase was separated and combined with an ether extract of the aqueous phase. The combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatrography on silica gel, and the product was eluted with hexane−ethyl acetate (9:1 → 4:1) to give **32** as a yellow solid (5.45 g, 31% yield based on CS_2) which, after crystallization from hexane−ether, had mp 97−98 °C; IR (KBr) 3420, 1597, 1578 cm^{-1}; ^1H NMR (300) δ 2.60 (s, 3H), 7.43−7.48 (m, 2H), 7.52−7.58 (m, 1H), 7.89−7.93 (m, 2H); ^{13}C NMR δ 19.03, 127.56 (2), 128.90 (2), 132.60, 134.35, 161.60, 218.79; mass spectrum *m*/*z* 210 (15, M^+), 163 (100), 104 (43). Anal. Calcd for $C_9H_{10}N_2S_2$: C, 51.39; H, 4.79; N, 13.32. Found: C, 51.30; H, 4.75; N, 13.35.

(b) Sodium Hydroxide as Base in a Two-Phase Ether−Water Solvent System. Benzamidine hydrochloride hydrate (15.0 g, 85.9 mmol) was suspended in ether (500 mL) and

saturated aqueous bicarbonate solution (100 mL) was added all at once. The amidine hydrochloride dissolved. To the stirred two-phase mixture were added carbon disulfide (20 mL, 24.6 g, 323 mmol), methyl iodide (20 mL, 45.6 g, 321 mmol), and sodium hydroxide (15 g, 375 mmol) sequentially. After 4.5 h the bright yellow ether phase was separated from the colorless aqueous layer. It was dried ($MgSO_4$) and evaporated *in vacuo* to give **32** as a solid (17.7 g, 98% yield) identical in all respects to that prepared by method a.

2-Phenyl-4,4-bis(methylthio)-1,3-diaza-1,3-butadiene (33). (a) From Compound 32. *n*-Butyllithium [2.0 mL of a 2.5 M solution in THF (5.0 mmol)] was added to a stirred solution of compound **32** (1.00 g, 4.75 mmol) in anhydrous THF (20 mL, distilled from sodium benzophenone ketyl) at −20 °C (N_2 atmosphere). After 5 min, methyl iodide (0.4 mL, 0.91 g, 6.4 mmol) was added and the solution was stirred for 20 min. The reaction mixture was quenched with saturated NH_4Cl solution, ether was added, and the organic phase was separated, dried (Na_2SO_4), and evaporated *in vacuo* to give an oil, in quantitative yield, which was a solid in the refrigerator: ^{1}H NMR (300) δ 2.50 (s, 6H), 7.38−7.45 (m, 3H), 7.83−7.85 (m, 2H); ^{13}C NMR δ 15.11, 127.55, 128.34, 130.98, 134.25, 165.33, 169.14; HRMS calcd for $C_{10}H_{11}N_2S_2$ 223.0364, found 223.0361 $(M - H)^+$, HRMS calcd for $C_9H_9N_2S_2$ 209.0207, found 209.0204 $(M - Me)^+$.

The hydrochloride salt was obtained by adding a slight excess of ethereal 1 N hydrogen chloride to an ether solution of **33**. The mixture was evaporated to dryness, and the residue was crystallized from ethyl acetate−methanol to give material with mp 162−165 °C dec; ^{13}C NMR δ 17.01 (2), 126.76, 129.47 (2), 130.07 (2), 135.38, 171.25, 179.92. Anal. Calcd for $C_{10}H_{12}N_2S_2$·HCl: C, 46.05; H, 5.02; N, 10.74. Found: C, 45.97; H, 5.05; N, 10.68.

(b) From Benzamidine in a One-Pot Reaction. *n*-Butyllithium [(56.7 mL of a 1.49 M solution in THF (84.5 mmol)] was added at 0 °C to a stirred solution of benzamidine (10.2 g, 84.7 mmol) in freshly distilled anhydrous THF (250 mL, N_2 atmosphere). Precipitation of a white solid occurred. Carbon disulfide (5.1 mL, 6.27 g, 82.4 mm) was added with stirring, giving a red-brown solution, and then methyl iodide (5.3 mL, 12.0 g, 84.6 mmol) was added. After 10 min, a further quantity of *n*-butyllithium solution (56.7 mL) was added followed by more methyl iodide (10.0 mL, 22.8 g, 161 mmol), and the reaction mixture was stirred for 0.5 h. The reaction mixture was worked up as described in a to give a solid (13.5 g, 73% based on CS_2) identical in all respects to compound **33** obtained as described above.

Dimethyl 2-Phenyl-6-(methylthio)pyrimidine-4,5-dicarboxylate (34a). A solution of the diazadiene **33** (0.67 g, 2.99 mmol) in neat DMAD (2.5 mL) was heated at 55 °C for 1 h. The mixture thus produced was subjected to column chromatography on silica gel using hexane−dichloromethane to elute the product (0.62 g, 65% yield) which on crystallization from hexane had mp 140−141 °C; IR (KBr) 1757, 1725, 1528 cm^{-1}; ^{13}C NMR δ 13.75, 52.83, 53.14, 128.57 (2), 129.07 (2), 131.98, 156.40, 163.67, 164.77, 165.66, 172.45. Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.80. Found: C, 56.31; H, 4.48; N, 8.54.

Ethyl 2-Phenyl-4-(methylthio)pyrimidine-5-carboxylate (34b). A solution of the diene **33** (freshly prepared from the hydrochloride salt (1.00 g, 3.83 mmol) by partitioning it between ether and saturated $NaHCO_3$ solution, followed by drying ($MgSO_4$) and evaporation of the ether *in vacuo*) in toluene (10 mL) was added dropwise to a solution of ethyl propiolate (2.0 mL, 1.94 g, 20 mmol) in toluene (20 mL) at reflux temperature (N_2 atmosphere). The solution was heated at reflux temperature for 1.5 h after the addition was completed. At this time an additional 10 mmol of ethyl propiolate was added and 1 h thereafter the cooled solution was evaporated *in vacuo*. The residue was purified by flash column chromatography on silica gel using hexane−dichloromethante (4:1 to 2:1 to 1:1) to elute the solid ester **34b** (0.33 g, 31% yield) which on crystallization from hexane gave pure **34b** (0.27 g, 26% yield): mp 79−80 °C; IR (KBr) 1709, 1557, 1512 cm^{-1}; ^{1}H NMR (300) δ 1.43 (t, 3H), 2.68 (s, 3H), 4.43 (q, 2H), 7.48−7.55 (m, 3H), 8.50−8.55 (m, 2H), 9.08 (s, 1H); ^{13}C NMR δ 13.53, 14.21, 61.46, 118.68, 128.55 (2), 131.65, 136.76, 158.01, 164.33, 172.70. Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21. Found: C, 61.36; H, 5.15; N, 10.28.

Synthesis of the 2-(Trichloromethyl)-4-(dimethylamino)-1,3-diaza-1,3-dienes (37). A solution of trichloroacetamidine (1 equiv) in anhydrous THF (2.5 mL/mmol **35**) containing the appropriate amide acetal (1 equiv) was heated at 40−50 °C (N_2 atmosphere) for 2−3 h. Excess ethyl acetate was added, and the solution was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo*.

2-(Trichloromethyl)-4-(dimethylamino)-1,3-diaza-1,3-butadiene (37a). Obtained in quantitative yield as an oil which, though unstable at room temperature, can be stored at −10 °C for prolonged periods with only minor decomposition; IR 3316, 1634, 1587 cm^{-1}; ^{1}H NMR δ 3.06 (s, 3H), 3.08 (s, 3H), 8.20 (bs, 1H), 8.30 (s, 1H); ^{13}C NMR δ 35.42, 41.35, 97.61, 157.93, 168.74. A satisfactory elemental analysis could not be obtained due to contamination with varying amounts of the amidine **42** and the triazine **45**. Anal. Calcd for $C_5H_8Cl_3N_3$: C, 27.74; H, 3.72; N, 19.41. Found: C, 27.27; H, 3.22; N, 20.01.

2-(Trichloromethyl)-4-(dimethylamino)-1,3-diaza-1,3-pentadiene (37b). Obtained in 91% yield as an oil: ^{13}C NMR δ 15.71, 38.28, 38.75, 98.14, 160.78, 167.24. Anal. Calcd for $C_6H_{10}Cl_3N_3$: C, 31.26; H, 4.37; N, 18.23. Found: C, 31.22; H, 4.57; N, 18.52.

2-(Trichloromethyl)-4-(dimethylamino)-4-phenyl-1,3-diaza-1,3-butadiene (37c). Obtained in 96% yield as an oil: ^{1}H NMR δ 3.11 (s, 3H), 3.22 (s, 3H), 2.72−7.35 (m, 3H), 7.96−8.10 (m, 2H). It was not possible to obtain an analytically pure sample of this compound because it was always contaminated with *N*,*N*-dimethylbenzamide (ca 5%) derived from hydrolysis of the amide acetal **36c**. It was therefore used without further purification.

Synthesis of 2-(Trichloromethyl)-4-(dimethylamino)-1,3-diaza-1,3-butadiene (37a) from Trichloroacetonitrile and *N*,*N*-Dimethylformamidine (42). 1,3-Diazabicyclo-[5.4.0]undec-7-ene (0.75 mL, 0.76 g, 5.0 mmol) was added to a stirred suspension of *N*,*N*-dimethylformamidine hydrochloride (0.553 g, 5.1 mmol) in anhydrous THF (10 mL) containing trichloroacetonitrile (0.5 mL, 0.72 g, 5.0 mmol) at room temperature (N_2 atmosphere). After stirring for 2 h, the reaction mixture was diluted with ethyl acetate, water was added, and the organic phase was separated. The organic phase was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo* to give **37a** as an oil (0.563 g, 52% yield) identical in all respects to material obtained as described above.

Synthesis of 2-(Trichloromethyl)pyrimidines 38 by Cycloaddition of Diazadienes 37 and Electron Acetylenes 12. A solution of the diazadiene **37** in anhydrous toluene or benzene (3−8 mL/mmol **37**) containing the activated acetylene **12** (1−4 molar equiv/mol of **37**; see Table 2), in a nitrogen atmosphere, was maintained at the temperature and for the time indicated in Table 2. The solvent was removed *in vacuo* and the pure pyrimidine was obtained by column chromatography on silica using a hexane−ethyl acetate mixture (see Table 2) as the eluant. Crystalline pyrimidines were recrystallized from the solvent mixtures indicated in Table 2.

Dimethyl 2-(Trichloromethyl)pyrimidine-4,5-dicarboxylate (38a): IR 1742, 1572 cm^{-1}; ^{1}H NMR δ 4.01 (s, 3H), 4.06 (s, 3H), 9.41 (s, 1H); ^{13}C NMR δ 54.28, 54.42, 95.89, 122.00, 160.27, 160.79; 163.13, 164.19. Anal. Calcd for $C_9H_7Cl_3N_2O_4$: C, 34.47; H, 2.25; Cl, 33.92; N, 8.93. Found: C, 34.58; H, 2.23; Cl, 33.99; H, 8.86.

Ethyl 2-(Trichloromethyl)pyrimidine-5-carboxylate (38b): IR 1733, 1588 cm^{-1}; ^{1}H NMR δ 1.43 (t, 3H), 4.48 (q, 2H), 9.40 (s, 2H); ^{13}C NMR δ 14.60, 62.81, 96.44, 124.47, 159.38 (2), 162.94, 168.39. Anal. Calcd for $C_8H_7Cl_3N_2O_2$: C, 35.65; H, 2.61; Cl, 39.46; N, 10.39. Found: C, 35.44; H, 2.71; Cl, 39.62; N, 10.44.

Methyl 2-(Trichloromethyl)-4-phenylpyrimidine-5-carboxylate (38c): IR 1736, 1600, 1567 cm^{-1}; ^{13}C NMR δ 53.15, 96.12, 123.97, 128.73, 129.37, 131.41, 136.09, 159.43, 166.07, 166.16, 166.21; HRMS calcd for $C_{13}H_9{}^{35}Cl_3N_2O_2$ 329.9730, found 329.9738.

2-(Trichloromethyl)pyrimidine-5-carboxaldehyde (38d): IR 1726, 1567, 1534 cm^{-1}; ^1H NMR δ 9.35 (s, 2H), 10.21 (s, 1H); ^{13}C NMR δ 96.02, 128.21, 159.49, 168.90, 188.05. Anal. Calcd for $C_6H_3Cl_3N_2O$:0.33 CH_2Cl_2: C, 29.88; H, 1.46; Cl, 47.17. Found: C, 30.09; H, 1.30; Cl, 47.43.

Dimethyl 2-(Trichloromethyl)-6-methylpyrimidine-4,5-dicarboxylate (38e). Anal. Calcd for $C_{10}H_9Cl_3N_2O_4$: C, 36.66; H, 2.76; Cl, 32.42; N, 8.55. Found: C, 36.92; H, 2.72; Cl, 32.30; N, 8.58.

Ethyl 2-(Trichloromethyl)-4-methylpyrimidine-5-carboxylate (38f): ^1H NMR δ 1.42 (t, 3H), 2.92 (s, 3H), 4.44 (q, 2H), 9.25 (s, 1H); ^{13}C NMR δ 14.68, 25.01, 62.63, 96.58, 123.82, 160.00, 164.29, 166.66, 170.80. Anal. Calcd for $C_9H_9Cl_3N_2O_2$: C, 38.12; H, 3.19; Cl, 37.51; N, 9.88. Found: C, 38.42; H, 3.27; Cl, 37.28; N, 9.68.

Dimethyl 2-(Trichloromethyl)-6-phenylpyrimidine-4,5-dicarboxylate (38g). Anal. Calcd for $C_{15}H_{11}Cl_3N_2O_4$: C, 46.23; H, 2.84; Cl, 27.30; N, 7.19. Found: C, 46.30; H, 2.87; Cl, 27.01; N, 7.14.

Ethyl 2-(Trichloromethyl)-4-phenylpyrimidine-5-carboxylate (38h): ^{13}C NMR δ 14.21, 62.91, 96.22, 129.04, 129.79, 131.66, 136.62, 159.75, 166.12, 166.37, 166.59; HRMS calcd for $C_{14}H_{11}{}^{35}Cl_3N_2O_2$ 343.9886, found 343.9886.

Methyl 2-(Trichloromethyl)-4,6-diphenylpyrimidine-5-carboxylate (38i). Anal. Calcd for $C_{19}H_{13}Cl_3N_2O_2$: C, 55.97; H, 3.21; Cl, 26.08; N, 6.87. Found: C, 55.90; H, 3.09; Cl, 26.27; N, 6.92.

2-(Trichloromethyl)-4-phenylpyrimidine-5-carboxaldehyde (38j): ^{13}C NMR δ 96.03, 125.55, 129.28, 130.79, 132.03, 133.89, 159.24, 166.99, 168.45, 188.97; FAB HRMS calcd for $C_{12}H_9{}^{35}Cl_3N_2O$ 300.9702, found 300.9707 (MH^+).

Synthesis of 2-(*N,N*-Dimethylamino)-4-(trichloromethyl)-1,3,5-triazine (45) from Trichloroacetonitrile and Diazadiene (37a). A solution of the diazadiene **37a** (0.2165 g, 1.0 mmol) in toluene (2 mL) containing trichloroacetonitrile (0.22 ml, 0.289 g, 2.0 mmol) was left at room temperature for 4 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel using hexane−ethyl acetate (9:1) to elute the product (0.195 g, 83% yield) as a solid. Crystallization of this material from hexane−dichloromethane gave pure **45** with mp 71−73 °C; ^1H NMR δ 3.28 (s, 3H), 3.30 (s, 3H), 8.70 (s, 1H); ^{13}C NMR δ 36.97, 37.12, 96.60, 164.89, 167.22, 172.72. Anal. Calcd for $C_6H_7Cl_3N_4$: C, 29.84; H, 2.92; Cl, 44.03. Found: C, 29.90; H, 2.86; Cl, 43.81.

Dimethyl 2-(Dichloromethyl)pyrimidine-4,5-dicarboxylate (46a). A solution of the (trichloromethyl)pyrimidine **38a** (0.470 g, 1.5 mmol) in ethyl acetate (10 mL) containing triethylamine (0.66 mL, 0.455 g, 4.5 mmol) and suspended 5% $Pd/CaCO_3$ (0.250 g) was hydrogenated at atmospheric pressure at room temperature until 1 mmol of hydrogen had been absorbed. The mixture was filtered through Celite, the filter cake was washed with ethyl acetate, and the filtrate was washed with water, dried (Na_2SO_4), and evaporated *in vacuo*. The residue was separated by column chromatography on silica gel using hexane−ethyl acetate to give the dichloro compound **46a** (0.300 g) and the monochloro compound **46b** (0.090 g). See Table 3 for column chromatographic solvent systems, product yields, mps, etc. Pure **46a** was a solid: ^{13}C NMR δ 53.95, 54.12, 70.18, 121.95, 159.93, 160.90, 163.13, 164.85, 167.92. Anal. Calcd for $C_9H_8Cl_2N_2O_4$: C, 38.73; H, 2.88; Cl, 25.40; N, 10.03. Found: C, 38.73; H, 2.83; Cl, 25.14; N, 9.99.

For data for **46b** see below.

Dimethyl 2-(Chloromethyl)pyrimidine-4,5-dicarboxylate (46b). This compound was prepared in the same manner as described for **46a** except that the hydrogenolysis was conducted until 2 molar equiv of hydrogen had been absorbed. Chromatographic separation gave **46c** (see below) as the minor product and **46b** as the major product: ^{13}C NMR δ 46.50, 53.80, 54.02, 120.86, 159.75, 160.28, 163.57, 165.28, 168.93. Anal. Calcd for $C_9H_9ClN_2O_4$: C, 44.18; H, 3.70; Cl, 14.49; N, 11.45. Found: C, 44.25; H, 3.70; Cl, 14.17; N, 11.15.

Dimethyl 2-Methylpyrimidine-4,5-dicarboxylate (46c). A solution of **38a** (0.630 g, 2 mmol) in methanol (50 mL) containing triethylamine (2.0 mL, 1.82 g, 18 mmol) and suspended 5% $Pd/CaCO_3$ (0.315 g) was hydrogenated at room temperature and atmospheric pressure for 3 h. The reaction mixture was then worked up as described above for **46a** giving dimethyl 2-methylpyrimidine-4,5-dicarboxylate as an oil: IR 1738, 1574, 1534 cm^{-1}; ^1H NMR δ 2.80 (s, 3H), 3.91 (s, 3H), 3.97 (s, 3H), 9.14 (s, 1H); ^{13}C NMR δ 26.69, 53.48, 53.82, 119.10, 159.51, 160.26, 164.06, 165.85, 172.09. Anal. Calcd for $C_9H_{10}N_2O_4$: C, 51.43; H, 4.80; N, 13.33. Found: C, 51.43; H, 4.84; N, 13.16.

Dimethyl 2-Methoxypyrimidine-4,5-dicarboxylate (47a). A solution of **38a** (0.313 g, 1.0 mmol) in anhydrous methanol (5 mL) containing sodium methoxide [prepared from sodium (0.023 g, 1.0 mmol)] was stirred at room temperature (N_2) for 5 h. Sufficient acetic acid was then added to give a neutral solution, and the solvent was removed *in vacuo*. After purification of the crude product by column chromatography, pure **47a** was obtained as an oil: ^{13}C NMR δ 53.25, 53.74, 56.60, 115.00, 162.78, 163.03, 163.71, 165.88, 167.22. Anal. Calcd for $C_9H_{10}N_2O_5$: C, 47.78; H, 4.45; N, 12.38. Found: C, 47.72; H, 4.42; N, 12.28.

Synthesis of 2-[(Phenylthio)methyl]pyrimidines from 2-(Trichloromethyl)pyrimidines. Thiophenol (6.6 equiv) was added to a suspension of sodium hydride (3.3 equiv, prepared from a 50% suspension of NaH in mineral oil; washed free of mineral oil with dry hexane) in anhydrous THF (1−3 mL/mmol pyrimidine derivative) in a nitrogen atmosphere. After ca. 10 min the (trichloromethyl)pyrimidine **38a** or **38b** (1 equiv) was added, and the reaction mixture was stirred at room temperature for 15 min. Sufficient acetic acid was then added to give a neutral solution and then a large volume of ehtyl acetate was added. The solution was washed successively with water and saturated NaCl solution, and it was dried (Na_2SO_4) and evaporated *in vacuo*. The product was then obtained from the residue by column chromatography on silica gel.

Dimethyl 2-[(Phenylthio)methyl]pyrimidine-4,5-dicarboxylate (47b): ^{13}C NMR δ 41.46, 53.14, 53.40, 119.35, 126.91, 128.96, 130.32, 134.64, 159.10, 159.42, 163.33, 165.04, 170.85; mass spectrum *m/z* 318 (100, M^+), 303 (20), 386 (15), 226 (15), 200 (40). Anal. Calcd for $C_{15}H_{14}N_2O_4S$: C, 56.59; H, 4.43; N, 8.79; S, 10.07. Found: C, 56.51; H, 4.39; N, 8.69; S, 10.09.

Ethyl 2-[(Phenylthio)methyl]pyrimidine-5-carboxylate (48a): ^{13}C NMR δ 14.14, 41.41, 61.77, 122.02, 128.56, 128.83, 129.57, 134.97, 163.48, 171.00; mass spectrum *m/z* 274 (100, M^+), 259 (25), 241 (22), 213 (45). Anal. Calcd for $C_{14}H_{14}N_2O_2S$: C, 61.29; H, 5.14; N, 10.21; S, 11.68. Found: C, 61.20; H, 5.12; N, 10.13; S, 11.96.

Dimethyl 2-[(Ethylthio)methyl]pyrimidine-4,5-dicarboxylate (47c). A suspension of sodium hydride in mineral oil (50%, 0.173 g, 3.6 mmol) was washed free of the carrier with dry hexane (N_2) and layered with anhydrous THF (15 mL), and ethanethiol (0.25 mL, 0.205 g, 3.3 mmol) dissolved in anhydrous THF (2 mL) was added. The reaction mixture was stirred at room temperature for 1 h and then worked up as described for **47b** and **48a** above: ^{13}C NMR δ 14.47, 26.48, 38.70, 53.57, 53.84, 119.64, 159.65, 159.93, 163.85, 165.64, 172.39; mass spectrum *m/z* 270 (12, M^+), 239 (10), 210 (100), 178 (45), 150 (90). Anal. Calcd for $C_{11}H_{14}N_2O_4S$: C, 48.87; H, 5.22; N, 10.36; S, 11.86. Found: C, 48.90; H, 5.26; N, 9.99; S, 11.62.

Synthesis of the [Bis(phenylthio)methyl]pyrimidines from the (Trichloromethyl)pyrimidines. The appropriate (trichloromethyl)pyrimidine (1 equiv) was added to a solution of sodium thiophenolate (3.3 equiv, prepared as described above from equimolar quantitites of sodium hydride and thiophenol) in anhydrous THF (5.25 mL/mmol (trichloromethyl)pyrimidine). The reaction mixture was stirred at room temperature (N_2 atmosphere) for 15 min and then worked up as described above to give a mixture of the bis(phenylthio) (major) and mono(phenylthio) (minor) compounds which was separated by column chromatography on silica gel.

Dimethyl 2-[Bis(phenylthio)methyl]pyrimidine-4,5-dicarboxylate (49a): ^{13}C NMR δ 53.33, 53.51, 62.91, 119.60, 128.64, 129.17, 133.01, 133.47, 159.27, 159.70, 163.27, 164.92, 171.09; mass spectrum *m/z* 426 (15, M^+), 317 (100), 284 (55).

Anal. Calcd for $C_{21}H_{18}N_2O_4S_2$: C, 59.13; H, 4.25; N, 6.56; S, 15.03. Found: C, 59.03; H, 4.29; N, 6.48; S, 14.75.

Ethyl 2-[Bis(phenylthio)methyl]pyrimidine-5-carboxylate (49b): ^{13}C NMR δ 14.02, 61.75, 62.52, 122.13, 128.10, 128.10, 128.79, 132.31, 132.66, 132.78, 133.06, 157.26 (2), 163.13, 171.15; mass spectrum *m*/*z* 382 (10, M^+), 273 (100), 240 (70), 212 (42). Anal. Calcd for $C_{20}H_{18}N_2O_2S_2$: C, 62.80; H, 4.74; N, 7.32; S, 16.26. Found: C, 62.57; H, 4.53; N, 7.16; S, 16.20.

Oxidation of the [(Phenylthio)methyl]pyrimidine to the Corresponding Sulfoxides or Sulfones. *m*-Chloroperbenzoic acid (80%, 1 or 2 equiv) was added to a stirred solution of the sulfide (1 molar equiv) in anhydrous dichloromethane (3−5 mL/mmol sulfide) at 0 °C (N_2 atmosphere), and agitation was continued for 0.5 h. The solution was diluted with dichloromethane, extracted with saturated aqueous $NaHCO_3$ solution, and dried (Na_2SO_4). The solvent was removed *in vacuo*, and the residue was subjected to column chromatographic separation on silica gel to give the product.

Dimethyl 2-[(Phenylsulfinyl)methyl]pyrimidine-4,5-dicarboxylate (47d): ^{13}C NMR δ 53.08, 53.21, 66.07, 119.78, 123.96, 129.14, 131.47, 142.77, 158.96, 159.20, 162.98, 164.45 (2); mass spectrum *m*/*z* 334 (70, M^+), 303 (20), 286 (100), 125 (55). Anal. Calcd for $C_{15}H_{14}N_2O_5S$: C, 53.88; H, 4.22; N, 8.38; S, 9.59. Found: C, 53.98; H, 4.28; N, 8.26; S, 9.38.

Dimethyl 2-[(Phenylsulfonyl)methyl]pyrimidine-4,5-dicarboxylate (47e): ^{13}C NMR δ 53.47, 53.51, 65.51, 120.51, 128.68, 129.30, 134.26, 138.51, 159.23, 159.63, 162.51, 163.14, 164.54; mass spectrum *m*/*z* 319 (15, M^+ − MeO), 285 (100), 168 (15). Anal. Calcd for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.02; N, 7.99; S, 9.14. Found: C, 51.21; H, 4.00; N, 8.00; S, 9.13.

Ethyl 2-[(Phenylsulfinyl)methyl]pyrimidine-5-carboxylate (48b): ^{1}H NMR δ 1.43 (t, 3H), 4.33−4.57 (m, 4H), 9.22 (s, 2H); mass spectrum *m*/*z* 290 (38, M^+), 242 (100), 213 (22), 125 (95). Anal. Calcd for $C_{14}H_{14}N_2O_3S$: C, 57.91; H, 4.85; N, 9.65; S, 11.04. Found: C, 57.61; H, 4.90; N, 9.47; S, 10.92.

Alkylation of the [(Phenylthio)methyl]pyrimidines with Alkyl Halides. To a stirred suspension of sodium hydride (1 or 3 equiv, from 50% suspension in mineral oil which had been washed with dry hexane) in anhydrous DMF (5−7.5 mL/mmol sulfides) was added the sulfide (1 equiv) at room temperature (N_2 atmosphere). After stirring for about 10 min, the alkyl halide (see below for molar equivalents used) was added and stirring was continued for 4−15 h. The reaction was quenched by the addition of saturated aqueous NH_4Cl, and the product was extracted into ethyl acetate. The extract was washed with water and dried (Na_2SO_4), the solvent was removed *in vacuo*, and the product was separated from the residual mixture by column chromatography on silica gel.

Dimethyl 2-[1-(Phenylthio)butyl]pyrimidine-4,5-dicarboxylate (50a). From *n*-propyl iodide (1 equiv): ^{1}H NMR δ 0.92 (t, 3H), 1.21−1.62 (m, 2H), 1.83−2.29 (m, 2H), 3.94 (s, 3H), 3.99 (s, 3H), 4.50 (t, 1H), 7.20−7.33 (m, 5H), 9.18 (s, 1H); ^{13}C NMR δ 13.89, 20.86, 35.93, 53.22, 53.44, 55.06, 119.15, 127.77, 129.00, 132.72, 133.83, 159.24, 159.44, 163.59, 165.38, 174.29; mass spectrum *m*/*z* 360 (74, M^+), 327 (100), 251 (32), 191 (33). Anal. Calcd for $C_{18}H_{20}N_2O_4S$: C, 59.98; H, 5.59; N, 7.77. Found: C, 59.46; H, 5.64; N, 7.39.

Dimethyl 2-[1-(Phenylthio)-2-(ethoxycarbonyl)ethyl]-pyrimidine-4,5-dicarboxylate (50b). From ethyl bromoacetate (1 equiv): IR 1734, 1571, 1549 cm^{-1}; ^{1}H NMR δ 1.16 (t, 3H), 3.05 (dd, J = 6.0, 16.0 Hz, 1H), 3.34 (dd, J = 10.0, 16.0 Hz, 1H), 3.94 (s, 3H), 3.98 (s, 3H), 4.06 (q, 2H), 4.88 (dd, J = 6.0, 10.0 Hz, 1H), 7.23−7.36 (m, 5H), 9.16 (s, 1H); mass spectrum *m*/*z* 404 (100, M^+), 331 (30), 249 (18). Anal. Calcd for $C_{19}H_{20}N_2O_6S$: C, 56.42; H, 4.98; N, 6.92; S, 7.92. Found: C, 56.25; H. 5.01; N, 6.83; S, 7.70.

Dimethyl 2-[1-(Phenylthio)-1-methylethyl]pyrimidine-4,5-dicarboxylate (50c). From methyl iodide (8 equiv): ^{13}C NMR δ 27.45 (2), 52.98, 53.11, 53.89, 118.06, 128.48, 129.14, 131.35, 136.94, 158.64, 158.80, 163.48, 165.41, 176.19; mass spectrum *m*/*z* 346 (40, M^+), 237 (100), 205 (45), 177 (60). Anal. Calcd for $C_{17}H_{18}N_2O_4S$: C, 58.19; H, 5.31; N, 7.98. Found: C, 58.37; H, 5.22; N, 7.90.

Ethyl 2-[1-(Phenylthio)butyl]pyrimidine-5-carboxylate (51a). From *n*-propyl iodide (1 equiv): ^{13}C NMR δ 13.67, 14.91, 20.67, 36.11, 54.91, 61.73, 121.93, 127.20, 128.76, 131.92, 134.25, 158.20 (2), 163.65, 174.41; mass spectrum *m*/*e* 316 (55, M^+), 283 (100), 274 (60), 207 (42), 179 (65). Anal. Calcd for $C_{17}H_{20}N_2O_2S$: C, 64.52; H, 6.37; N, 8.85; S, 10.11. Found: C, 64.50; H, 6.34; N, 8.83; S, 10.14.

Ethyl 2-[1-(Phenylthio)-1-methylethyl]pyrimidine-5-carboxylate (51b). From methyl iodide (4 equiv): ^{13}C NMR δ 14.46, 28.05, 54.35, 61.94, 121.67, 128.67, 129.26, 132.15, 137.02, 157.89 (2), 164.08, 176.85; mass spectrum *m*/*z* 302 (25, M^+), 257 (5), 193 (100), 165 (58). Anal. Calcd for $C_{16}H_{18}N_2O_2S$: C, 63.54; H, 5.99; N, 9.26; S, 10.60. Found: C, 63.49; H, 6.10; N, 9.19; S, 10.68.

Michael Addition of Sulfide 47b to Methyl Acrylate. A solution of **47b** (1 equiv) in anhydrous acetonitrile (2.5 mL/mmol **47b**) containing ethyl acrylate (1 or 2 equiv) and Triton B (100 μL/mmol **47b**) was stirred at room temperature (N_2 atmosphere) for 3 h. The reaction was quenched with acetic acid and diluted with ethyl acetate, and then saturated NaCl solution was added. The organic phase was separated, dried (Na_2SO_4), and evaporated *in vacuo*, and the product was recovered from the residue by column chromatography on silica gel.

Dimethyl 2-[1-(Phenylthio)-3-(methoxycarbonyl)propyl]pyrimidine-4,5-dicarboxylate (50d): ^{13}C NMR δ 28.52, 31.65, 51.85, 53.22, 53.41, 54.51, 119.27, 128.07, 129.05, 133.19, 132.97, 159.29, 159.45, 163.43, 165.22, 173.05, 173.21; mass spectrum *m*/*z* 404 (100, M^+), 373 (38), 331 (43). Anal. Calcd for $C_{19}H_{20}N_2O_6S$: C, 56.42; H, 4.98; N, 6.92; S, 7.92. Found: C, 56.52; H, 4.97; N, 6.84; S, 7.78.

Dimethyl 4-(Phenylthio)-4-[3,4-(bismethoxycarbonyl)-pyrimidin-2-yl]heptane-1,7-dioate (50e): ^{1}H NMR δ 2.44 (m, 8H), 3.66 (s, 6H), 3.96 (s, 3H), 3.97 (s, 3H), 7.06−7.39 (m, 5H), 9.17 (s, 1H); mass spectrum *m*/*z* 490 (18, M^+), 459 (20), 381 (100), 349 (85), 275 (50). Anal. Calcd for $C_{23}H_{26}N_2O_8S$: C, 56.31; H, 5.34; N, 5.71; S, 6.53. Found: C, 56.20; H, 5.25; N, 5.88; S, 6.32.

Reductive Desulfurization of Pyrimidines with Raney Nickel. Raney nickel (1−1.5 g/mmol pyrimidine) was added portionwise to a solution of the pyrimidine derivative in methanol (10 mL/mmol pyrimidine) at reflux temperature. The mixture was then stirred at reflux temperature for 0.5 −1 h, the mixture was filtered through Celite, the filter cake was washed with methanol, and the filtrate was evaporated *in vacuo*. The product was isolated from the residue by column chromatography on silica gel.

Dimethyl 2-*n*-Butylpyrimidine-4,5-dicarboxylate (46d): ^{13}C NMR δ 13.77, 22.42, 30.48, 39.29, 52.92, 53.26, 118.57, 158.95, 163.64, 165.51, 175.02; HRMS calcd for $C_{12}H_{16}N_2O_4$ 252.1110, found 252.1114.

Dimethyl 2-[2-(Ethoxycarbonyl)ethyl]pyrimidine-4,5-dicarboxylate (46e): ^{13}C NMR δ 14.08, 31.25, 33.78, 52.94, 53.21, 60.49, 118.84, 158.84, 158.94, 163.48, 165.31, 172.36, 172.73; mass spectrum *m*/*z* 296 (38, M^+), 265 (35), 251 (78), 223 (100), 191 (62). Anal. Calcd for $C_{13}H_{16}N_2O_6$: C, 52.96; H, 5.44; N, 9.45. Found: C, 52.73; H, 5.42; N, 9.28.

Dimethyl 2-Isopropylpyrimidine-4,5-dicarboxylate (46f): IR 1737, 1574 cm^{-1}; ^{1}H NMR δ 1.38 (d, 6H), 3.33 (sept, 1H), 3.96 (s, 3H), 4.03 (s, 3H), 9.22 (s, 1H); ^{13}C NMR δ 21.41 (2), 37.88, 52.95, 53.28, 118.50, 159.03 (2), 163.66, 165.70, 178.91; mass spectrum *m*/*z* 238 (38, M^+), 223 (100), 206 (90), 120 (70). Anal. Calcd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.92; N, 11.75. Found: C, 55.79; H, 5.45; N, 11.35.

Methyl 2-*n*-Butylpyrimidine-5-carboxylate (52a). Ester interchange took place in this desulfurization: ^{1}H NMR δ 0.95 (t, 3H), 1.41 (m, 2H), 1.82 (m, 2H), 3.03 (t, 2H), 3.97 (s, 3H), 9.19 (s, 1H); mass spectrum *m*/*z* 194 (10, M^+), 165 (25), 152 (100), 121 (18). Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.26; N, 14.42. Found: C, 61.89; H, 7.26; N, 13.97.

Methyl 2-Isopropylpyrimidine-5-carboxylate (52b). Ester interchange occurred in this desulfurization reaction: ^{1}H NMR δ 1.38 (d, 6H), 3.31 (sept, 1H), 3.98 (s, 3H), 9.21 (s, 2H); ^{13}C NMR δ 21.49 (2), 37.92, 52.48, 121.26, 158.09 (2), 164.45, 179.14; mass spectrum *m*/*z* 180 (22, M^+), 165 (100), 152 (22). Anal. Calcd for $C_9H_{12}N_2O_2$: C, 59.98; H, 6.71; N, 15.54. Found: C, 60.11; H, 6.83; N, 15.27.

Pummerer Reaction with Sulfoxides 47d and 48b. A solution of the sulfoxide in acetic anhydride (5 mL/mmol sulfoxide) was heated at 100 °C (N_2 atmosphere) for 1−2 h. The solvent was removed *in vacuo*, and the product was obtained from the residue by column chromatography on silica gel.

Dimethyl 2-[1-Acetoxy-1-(phenylthio)methyl]pyrimidine-4,5-dicarboxylate (50f): IR 1740, 1572 cm^{-1}; ^1H NMR δ 2.21 (s, 3H), 3.97 (s, 3H), 4.02 (s, 3H), 7.10 (s, 1H), 7.30−7.52 (m, 5H), 9.18 (s, 1H); ^{13}C NMR δ 21.14, 53.42, 53.57, 81.93, 120.25, 129.26, 129.34, 130.44, 134.62, 159.51, 163.21, 164.93, 167.92, 169.92; mass spectrum *m/z* 376 (10, M^+), 267 (10), 225 (100), 193 (50). Anal. Calcd for $C_{17}H_{16}N_2O_6S$: C, 54.25; H, 4.28; N, 7.44; S, 8.51. Found: C, 54.16; H, 4.32; N, 7.35; S, 8.58.

Ethyl 2-[1-Acetoxy-2-(phenylthio)methyl]pyrimidine-5-carboxylate (51c): IR 1731, 1587 cm^{-1}; ^1H NMR δ 1.41 (t, 3H), 2.20 (s, 3H), 4.43 (q, 2H), 7.10 (s, 1H), 7.30−7.49 (m, 5H), 9.20 (s, 2H); ^{13}C NMR δ 14.40, 21.20, 62.21, 82.21, 123.03, 129.24, 130.70, 134.45, 158.62, 163.41, 168.22, 170.09; mass spectrum *m/z* 332 (15, M^+), 181 (100), 153 (15), 110 (22). Anal. Calcd for $C_{16}H_{16}N_2O_4S$: C, 57.81; H, 4.85; N, 8.43; S, 9.64. Found: C, 57.76; H, 4.86; N, 8.19; S, 9.70.

Oxime of Dimethyl 2-Formylpyrimidine-4,5-dicarboxylate (47g). A solution of compound **50f** (0.376 g, 1.0 mmol) in formic acid (5 mL containing hydroxylamine hydrochloride (0.140 g, 2.0 mmol) was heated at reflux temperature (N_2 atmosphere) for 5 h. The solvent was removed *in vacuo*, and the product was obtained from the residue by column chromatography on silica gel: ^{13}C NMR δ 52.75, 52.90, 128.09, 147.03, 158.90, 159.10, 162.76, 162.83, 164.57; mass spectrum *m/z* 239 (30, M^+), 209 (99), 207 (100), 179 (70). Anal. Calcd for $C_9H_9N_3O_5$: C, 45.19; H, 3.79; N, 17.56. Found: C, 44.96; H, 3.76; N, 17.31.

Dimethyl 2-Cyanopyrimidine-4,5-dicarboxylate (47h). The above oxime (0.100 g, 0.41 mmol) was dissolved in a chloroform solution of polyphosphate ester (10 mL)[35] and the solution was heated at reflux temperature (N_2 atmosphere) for 18 h. The chloroform was removed *in vacuo*, the residue was partitioned between ethyl acetate and water, and the organic phase was washed with saturated NaCl solution, dried (Na_2SO_4), and evaporated *in vacuo*. The product was obtained from the residue by column chromatography on silica gel: IR 2252, 1744, 1564, 1547 cm^{-1}; ^{13}C NMR δ 53.85, 53.90, 114.48, 123.62, 146.18, 159.34, 159.98, 162.05, 163.33; mass spectrum *m/z* 221 (15, M^+), 191 (100), 163 (20). Anal. Calcd for $C_9H_7N_3O_4$: C, 48.82; H, 3.19; N, 18.99. Found: C, 48.71; H, 3.21; N, 19.01.

Dimethyl 2-(*trans*-buten-1-yl)pyrimidine-4,5-dicarboxylate (47i). A solution of compound **50a** (0.300 g, 0.83 mmol) in anhydrous dichloromethane (5 mL) was cooled to 0 °C (N_2 atmosphere) and 80% *m*-chloroperbenzoic acid (0.180 g, 0.83 mmol) was added with stirring. After 15 min the reaction mixture was worked up as described above for the synthesis of **47d,e,** etc. The crude sulfoxide **46g** was dissolved in dry toluene and heated at 100 °C for 1 h. The solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel: ^1H NMR δ 1.55 (t, 3H), 2.38 (q, 2H), 3.94 (s, 3H), 4.02 (s, 3H), 6.63 (dt, 1H, J = 15.5 Hz, 2.0 Hz), 7.48 (dt, 1H, J = 15.5 Hz, 6.5 Hz), 9.18 (s, 1H); ^{13}C NMR δ 12.51, 26.03, 52.94, 53.31, 117.84, 127.60, 148.88, 159.24, 159.37, 163.67, 165.71, 167.15; mass spectrum *m/z* 250 (60, M^+), 235 (28), 190 (35), 160 (38), 132 (100). Anal. Calcd for $C_{12}H_{14}N_2O_4$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.02; H, 5.68; N, 10.75.

Acknowledgment. The authors are very grateful to Drs. Aaron B. Miller and Daniel L. Severance for generating the stereoscopic views of compounds **17b** and **17c** (**22c**).

Supporting Information Available: Miscellaneous spectroscopic data for **20a-c**, **23b,d,e**, **26d,e**, **30**, **33**, **34a,b**, **37b**, **38c,e-g,i,j**, **46a,b,d,e**, **47a-e,g,i**, **48a,b**, **49a,b**, **50a,c-e**, **51a,b**, and **52a** (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO952106W

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