Dipolar Cycloaddition Reactions of Dihydropyrimidine-Fused Mesomeric Betaines. An Approach toward Conformationally Restricted Dihydropyrimidine Derivatives[1]

C. Oliver Kappe*

Institute of Organic Chemistry, Karl-Franzens-University Graz, A-8010 Graz, Austria

Karl Peters and Eva-Maria Peters

Max-Planck-Institut für Festkörperforschung, Heisenbergstrasse 1, D-70506 Stuttgart, Germany

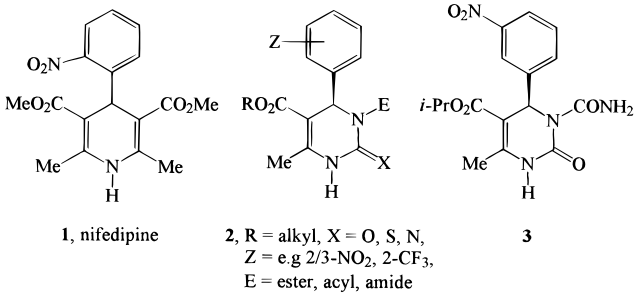
Received January 22, 1997[⊗]

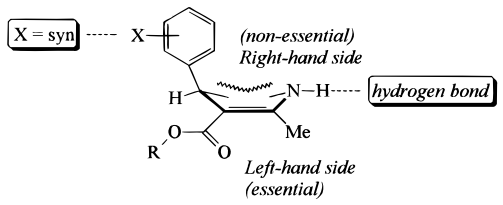
The bimolecular and intramolecular cycloaddition potential of various 4-aryldihydropyrimidine-fused mesomeric betaines was investigated. Dihydropyrimidine-fused isothiomünchnones and isomünchnones were found to undergo 1,3-dipolar cycloaddition reactions with electron-deficient dipolarophiles such as DMAD, methyl propiolate, methyl vinyl ketone, or *N*-methylmaleimide. In contrast, cross-conjugated mesomeric thiazinium betaines underwent 1,4-dipolar cycloaddition reaction with electron-rich dipolarophiles such as ynamines or ketene acetals. In general, these cycloadditions show a high degree of regioselectivity, facial selectivity, and *exo*/*endo* diastereoselectivity. Intramolecular variations of the above processes involving o-alkenylaryl-tethered dihydropyrimidine-fused isomünchnones lead to polycyclic dihydropyrimidine analogs that closely mimic the proposed receptor-bound conformation of dihydropyridine calcium channel modulators. These cycloadducts are the result of an *endo*-addition of the π-bond to the carbonyl ylide dipole embedded in the isomünchnone system. The relative stereochemistry of these cycloadducts was established by single-crystal X-ray analysis.

Introduction

4-Aryl-1,4-dihydropyridines of the nifedipine type (DHPs, e.g., **1**) were first introduced into clinical medicine in 1975 and are still the most potent group of calcium channel modulators available for the treatment of cardiovascular diseases.[2] Dihydropyrimidines of type **2** (DHPMs) show a very similar pharmacological profile, and in recent years, several lead compounds were developed (*e.g.*, **3**) that are equal in potency and duration of antihypertensive activity to classical and second-generation dihydropyridine drugs.[3,4]

Despite many studies on the structure−function relationships of this type of calcium channel modulators, there still remains debate on the exact stereochemical/conformational requirements for activity.[5] In 1995, a detailed structure−activity profile for a series of DHPM derivatives was reported, leading to a general binding-site model for DHP/DHPM calcium channel modulators.[6] The stereochemical relationship between the aryl group and the dihydropyrimidine ring was found to be one of the factors having a pronounced effect on the biological activity.[5,6] It was proposed that in the receptor-bound conformation the substituted aryl ring is positioned axially, perpendicular to, and bisecting the boatlike dihydropyridine/dihydropyrimidine ring, with the 4-aryl substituent X adopting a synperiplanar (relative to C4-H) orientation.[6]





* To whom correspondence should be addressed. Fax: (43)-(316)-3809840. E-mail: kappeco@balu.kfunigraz.ac.at.

⊗ Abstract published in *Advance ACS Abstracts,* April 15, 1997.

(1) Synthesis and Reactions of Biginelli Compounds. 7. Part 6: Kappe, C. O.; Fabian, W. M. F.; Semones, M. A. *Tetrahedron* **1997**, *53*, 2803−2816.

(2) (a) Janis, R. A.; Silver, P. J.; Triggle, D. J. *Adv. Drug. Res.* **1987**, *16*, 309. (b) Bossert, F.; Vater, W. *Med. Res. Rev.* **1989**, *9*, 291−324.

(3) (a) Cho, H.; Ueda, M.; Shima, K.; Mizuno, A.; Hayashimatsu, M.; Ohnaka, Y.; Takeuchi, Y.; Hamaguchi, M.; Aisaka, K.; Hidaka, T.; Kawai, M.; Takeda, M.; Ishihara, T.; Funahashi, K.; Satah, F.; Morita, M.; Noguchi, T. *J. Med. Chem.* **1989**, *32*, 2399−2406. (b) Atwal, K.; Rovnyak, G. C.; Schwartz, J.; Moreland, S.; Hedberg, A.; Gougoutas, J. Z.; Malley, M. F.; Floyd, D. M. *J. Med. Chem.* **1990**, *33*, 1510−1515. (c) Atwal, K. S.; Rovnyak, G. C.; Kimball, S. D.; Floyd, D. M.; Moreland, S.; Swanson, B. N.; Gougoutas, J. Z.; Schwartz, J.; Smillie, K. M.; Malley, M. F. *J. Med. Chem.* **1990**, *33*, 2629−2635. (d) Atwal, K. S.; Swanson, B. N.; Unger, S. E.; Floyd, D. M.; Moreland, S.; Hedberg, A.; O'Reilly, B. C. *J. Med. Chem.* **1991**, *34*, 806−811. (e) Rovnyak, G. C.; Atwal, K. S.; Hedberg, A.; Kimball, S. D.; Moreland, S.; Gougoutas, J. Z.; O'Reilly, B. C.; Schwartz, J.; Malley, M. F. *J. Med. Chem.* **1992**, *35*, 3254−3263. (f) Grover, G. J.; Dzwonczyk, S.; McMullen, D. M.; Normadinam, C. S.; Sleph, P. G.; Moreland, S. J. *J. Cardiovasc. Pharmacol.* **1995**, *26*, 289−294. (g) Negwer, M. *Organic-Chemical Drugs and their Synonyms*; Akademie Verlag: Berlin, 1994; p 2558.

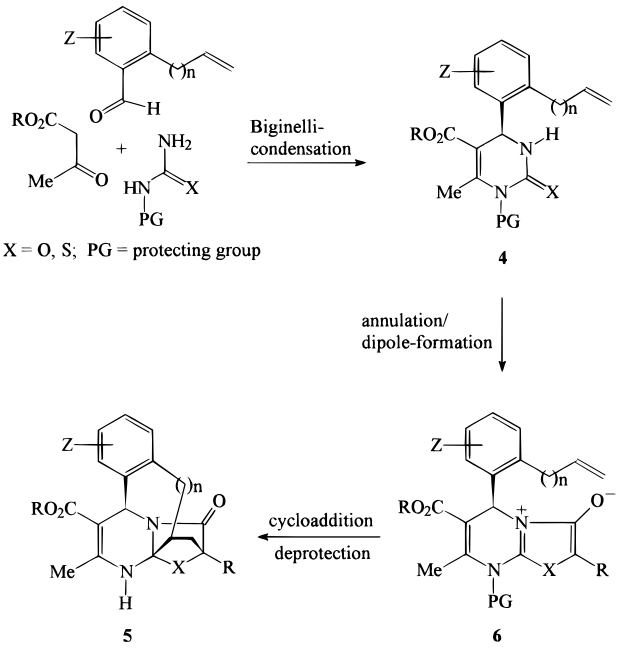
(4) (a) Atwal, K. S.; Moreland, S. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 291−294. (b) Alajarin, R.; Vaquero, J. J.; Alvarez-Builla, J.; Fau de Casa-Juana, M.; Sunkel, C.; Priego, J. G.; Gomez-Sal, P.; Torres, R. *Bioorg. Med. Chem.* **1994**, *2*, 323−329.

(5) For a recent review, see: Goldman, S.; Stoltefuss, J. *Angew. Chem.* **1991**, *103*, 1587−1605; *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1559−1578 and references therein.

(6) For a more detailed discussion, see: Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119−129. For a commentary, see: Triggle, D. J.; Padmanabhan, S. *Chemtracts: Org. Chem.* **1995**, *8*, 191−196.

S0022-3263(97)00121-7 CCC: $14.00

Scheme 1



Herein we describe synthetic methodology leading toward novel types of conformationally restricted dihydropyrimidine derivatives of type **5** that closely mimic the recently proposed receptor-bound conformation of DHP/DHPM calcium channel modulators (see above). Our strategy toward these polycyclic dihydropyrimidines is outlined in Scheme 1 and involves an intramolecular 1,3-dipolar cycloaddition reaction of an *o*-alkenylaryl-tethered dihydropyrimidine-fused mesomeric betaine as the key step (**6** → **5**). In recent years, mesomeric beatines of this general type, *i.e.*, isomünchnones (1,3-oxazolium-4-olates)[7,8] and isothiomünchnones (1,3-thiazolium-4-olates),[7,9] have proven to be very useful intermediates in a variety of synthetic applications.[7−9] The carbonyl ylide or thiocarbonyl ylide dipoles, respectively, incorporated in these mesoionics have been demonstrated to undergo both bimolecular and intramolecular cycloaddition reactions with relative ease.[7−9] There are also a number of examples involving bimolecular and intramolecular 1,4-dipolar cycloaddition reactions of related six-membered analogs, *i.e.*, of cross-conjugated heteroaromatic 1,3-thiazinium betaines.[10,11]

In the present paper, we investigate the dipolar cycloaddition chemistry of dihydropyrimidine-fused five- and six-membered mesomeric betaines. Of particular interest to us are (i) stereochemical aspects in these cycloaddition reactions relating to the presence of a stereocenter in the dipole and (ii) the application of the intramolecular variation of this methodology toward the construction of conformationally restricted dihydropyrimidine derivatives.

Results and Discussion

Whereas dihydropyridines of the nifedipine type (DHPs) are generally prepared by the well-known Hantzsch synthesis,[12] the aza-analogs **2** (DHPMs) are readily available through the Biginelli dihydropyrimidine synthesis (Scheme 1)[13] or other related methods.[13,14] These dihydropyrimidine derivatives are inherently asymmetric and have the advantage that the (thio)amide moiety embedded in the dihydropyrimidine ring allows a selective functionalization of the biologically less important "right-hand side" of the molecule (see above),[13] a process that is more troublesome in the dihydropyridine series.[15]

We began by first exploring the intermolecular cycloaddition properties of a series of dihydropyrimidine-fused betaines in order to establish the general viability of dipolar cycloaddition reactions in this series of fused mesoionics. Our studies commenced with the synthesis of dihydropyrimidine-fused isothiomünchnone **8** (Scheme 2). The required dihydropyrimidine-2-thione **7** was readily available by condensation of benzaldehyde, ethyl acetoacetate, and *N*-methylthiourea under standard Biginelli conditions.[16] Thioisomünchnone **8** was obtained as a stable, orange-red solid by sequential addition of α-bromophenylacetyl chloride and triethylamine to a solution of **7** in chloroform, following a protocol developed by Potts et al.[17,18] Thioisomünchnone **8** reacted smoothly with dimethyl acetylenedicarboxylate (DMAD) and methyl propiolate at *ca.* 100 °C in toluene to produce pyridopyrimidines **10a**,**b** in high yields. The intermediate primary cycloadducts **9a**,**b** could not be isolated and underwent clean extrusion of sulfur (**9** → **10**). In the reaction with methyl propiolate complete regioselectivity was observed, no trace of the other isomer being observed. The position of the methyl ester group in **10b** was established unequivocally by determination of long-range ^{1}H-^{13}C connectivities through an HMBC NMR experiment,[19] which confirms the expected and well-precedented regiochemistry of this bimolecular 1,3-dipolar cycloaddition.[20,21] Recent semiempirical calculations on the FMO interactions in the cycloaddition of related

(7) For reviews of the cycloaddition chemistry of isomünchnones and isothiomünchnones, see: (a) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123−141. (b) Newton, C. G.; Ramsden, C. A. *Tetrahedron* **1982**, *38*, 2965−3011. (c) Ollis, W. D.; Ramsden, C. A. *Adv. Heterocycl. Chem.* **1976**, *19*, 1−122.

(8) (a) Padwa, A.; Austin, D. J.; Price, A. T.; Weingarten, M. D. *Tetrahedron* **1996**, *52*, 3247−3260. (b) Padwa, A.; Hertzog, D. L.; Nadler, W. R.; Osterhout, M. H.; Price, A. T. *J. Org. Chem.* **1994**, *59*, 1418−1427 and references cited therein.

(9) (a) Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Higes, F. J.; Jimenez, J. L.; Palacios, J. C. *J. Org. Chem.* **1996**, *61*, 3738−3748. (b) Padwa, A.; Kinder, F. R.; Nadler, W. R.; Zhi, L. *Heterocycles* **1993**, *35*, 367−383 and references cited therein.

(10) For reviews and classifications of this type of heteroaromatic betaines, see: (a) Ollis, W. D.; Stanforth, S. P.; Ramsden, C. A. *Tetrahedron* **1985**, *41*, 2239−2329. (b) Friedrichsen, W.; Böttcher, A.; Kappe, T. *Heterocycles* **1982**, *19*, 1082−1148.

(11) For more recent examples, see: Padwa, A.; Coats, S. J.; Semones, M. *Tetrahedron* **1995**, *51*, 6651−6668 and references therein.

(12) For reviews of the Hantzsch synthesis and related reactions, see: (a) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269−289. (b) Stout, D. M.; Meyers, A. J. *Chem. Rev.* **1982**, *82*, 223−243. (c) Eisner, U.; Kuthan, J. *Chem. Rev.* **1972**, *72*, 1−42.

(13) For a review of the Biginelli-condensation, see: Kappe, C. O. *Tetrahedron* **1993**, *49*, 6937−6963.

(14) (a) O'Reilly, B. C.; Atwal, K. S. *Heterocycles* **1987**, *26*, 1185−1188. (b) Atwal, K. S.; O'Reilley, B. C.; Gougoutas, J. Z.; Malley, M. F. *Heterocycles* **1987**, *26*, 1189−1192. (c) Atwal, K. S.; Rovnyak, G. C.; O'Reilly, B. C.; Schwartz, J. *J. Org. Chem.* **1989**, *54*, 5898−5907.

(15) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 291−314.

(16) Kappe, C. O.; Roschger, P. *J. Heterocycl. Chem.* **1989**, *26*, 55−64.

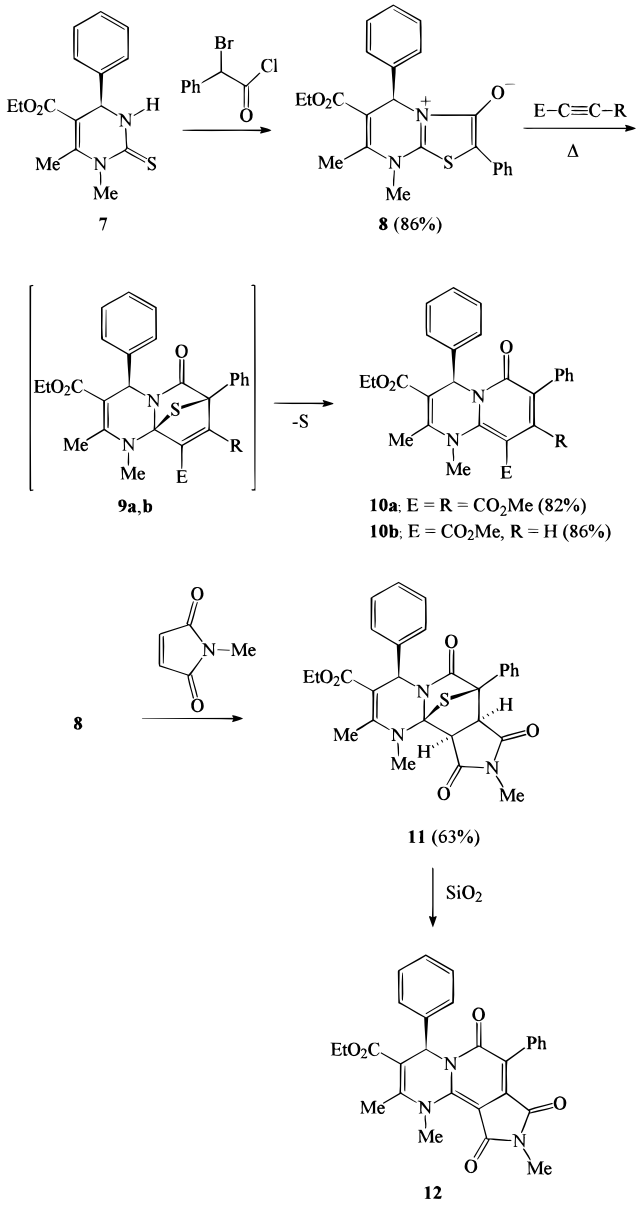
(17) Potts, K. T.; Chen, S. J.; Kane, J.; Marshall, J. L. *J. Org. Chem.* **1977**, *42*, 1633−1638.

(18) Potts, K. T.; Houghton, E.; Singh, U. P. *J. Org. Chem.* **1974**, *39*, 3627−3631.

(19) Heteronuclear multiple-bond correlation (HMBC), see: Bax, A.; Summers, M. F. *J. Am. Chem. Soc.* **1986**, *108*, 2093−2094. 2-D NMR spectra of **10b** and **17** are presented in the Supporting Information.

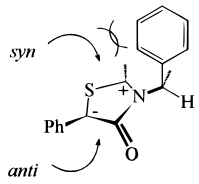
(20) (a) Fischer, U.; Möhler, H.; Schneider, F.; Widmer, U. *Helv. Chim. Acta* **1990**, *73*, 763−781. (b) Potts, K. T.; Bordeaux, K. G.; Kuehnling, W. R.; Salsbury, R. L. *J. Org. Chem.* **1985**, *50*, 1666−1676.

Scheme 2



2-amino-substituted isothiomünchnones with electron-deficient alkenes[9a] further support the here observed regiochemistry and allow the classification of this type of cycloaddition as $HOMO_{dipol}$ − $LUMO_{dipolarophile}$-controlled (Sustmann type I)[21] addition.

The reaction of thioisomünchnone **8** with olefinic dipolarophiles such as *N*-methylmaleimide is more complex. Treatment of dipole **8** with *N*-methylmaleimide in toluene at 110 °C for 20 min resulted in the formation of cycloadduct **11** in 63% isolated yield. Investigation of the crude reaction mixture by ^{1}H-NMR revealed the presence of a number of minor byproducts that could, however, not be separated or identified (with the exception of **12**, see below). Variations in the reaction conditions, *i.e.*, performing the reaction at room temperature over a longer period of time or changing the solvent, did not raise the yield of **11** or reduce the number of byproducts. Due to the presence of the stereocenter at C-5 of the dipole, four diastereoisomeric cycloadducts can *a priori* be expected if facial and *exo*/*endo* diastereoselectivities are considered. According to recent computational studies on the conformation of 4-aryldihydropyrimidines of type **2**,[1] the dihydropyrimidine ring is not planar but adopts a boatlike conformation, with the 4-aryl substituent in axial position. This geometric arrangement has also been found to exist in the solid state for bicyclic derivatives related to **8**.[16] Due to the steric effect of the comparatively bulky axial phenyl group, attack of the dipolarophile *anti* to the phenyl substituent (*i.e.*, from the less hindered "bottom-face" of the molecule) should be strongly favoured.



The relative stereochemistry of **11** was established by an X-ray analysis[22] confirming that the isolated cycloadduct is the result of an "*anti*/*exo*-addition" of the dipolarophile to the isothiomünchnone. Due to the complexity of the crude ^{1}H-NMR spectrum, the presence of minor amounts of other diastereoisomers (<5%) cannot be excluded with certainty. Cycloadduct **11** is relatively stable; however, on prolonged standing of a chloroform solution at room temperature or in the presence of silica gel, slow conversion into **12** takes place.[7,23]

In order to compare the cycloaddition behavior of the "masked" 1,3-dipole **8** with a related 1,4-dipolar system, we have prepared the fused 1,3-thiazinium betaines **13a**,**b**. These cross-conjugated heteroaromatic betaines[10] were readily prepared by cyclocondensation of thioamide **7** with (chlorocarbonyl)phenylketene[24] or methylmalonyl dichloride,[25] respectively (Scheme 3). Both betaines are bright yellow, thermally stable solids that can be stored for long periods of time at room temperature. Whereas mono- and bicyclic thiazinium betaines in general are known to participate readily in 1,4-dipolar cycloaddition reactions,[10,11] betaines **13a**,**b** proved to be inert against electron-deficient dipolarophiles such as *N*-methylmaleimide or DMAD even under forcing conditions. The supression of 1,4-dipolar character in 2-amino-substituted mesomeric 1,3-thiazinium betaines has been noted previously[24,26] and may be due to unfavorable FMO interactions.[11a]

On the other hand, **13a**,**b** did undergo 1,4-dipolar cycloaddition with electron-rich dipolarophiles such as 1-(diethylamino)-1-propyne (8 h, rt) and 1,1-diethoxyethene (2 h, 110 °C), although the yields of isolated cycloadducts **15a**,**b** and **17** were moderate. In both cases, the primary cycloadducts (**14**, **16**) were not isolable and did undergo spontaneous extrusion of carbonyl sulfide[10,11] to furnish pyridopyrimidines **15** and **17** as the final products. According to recent semiempirical calcula-

(21) (a) Sustmann, R. *Tetrahedron Lett.* **1971**, *2717*−2720. (b) Sustmann, R.; Trill, H. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 838−840.

(22) The authors have deposited atomic coordinates for structures **11**, **21**, **23**, and **27a**,**b** 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.

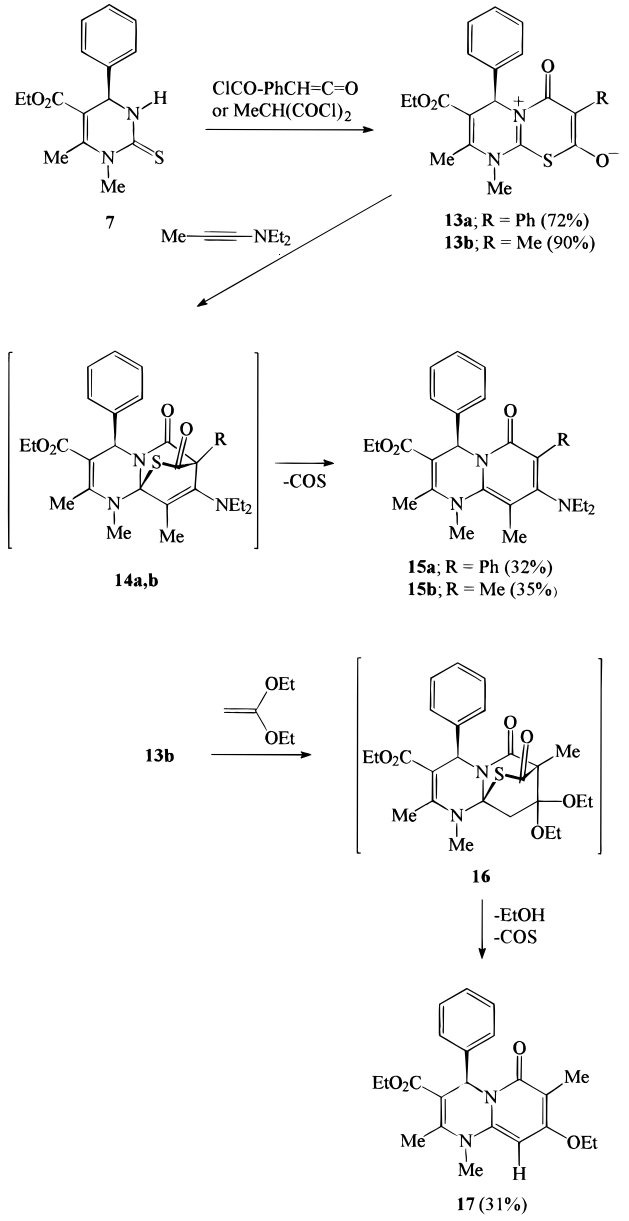
(23) Potts, K. T.; Choudhury, D. R. *J. Org. Chem.* **1978**, *43*, 2697−2700.

(24) Potts, K. T.; Ehlinger, R.; Nichols, W. M. *J. Org. Chem.* **1975**, *40*, 2596−2600.

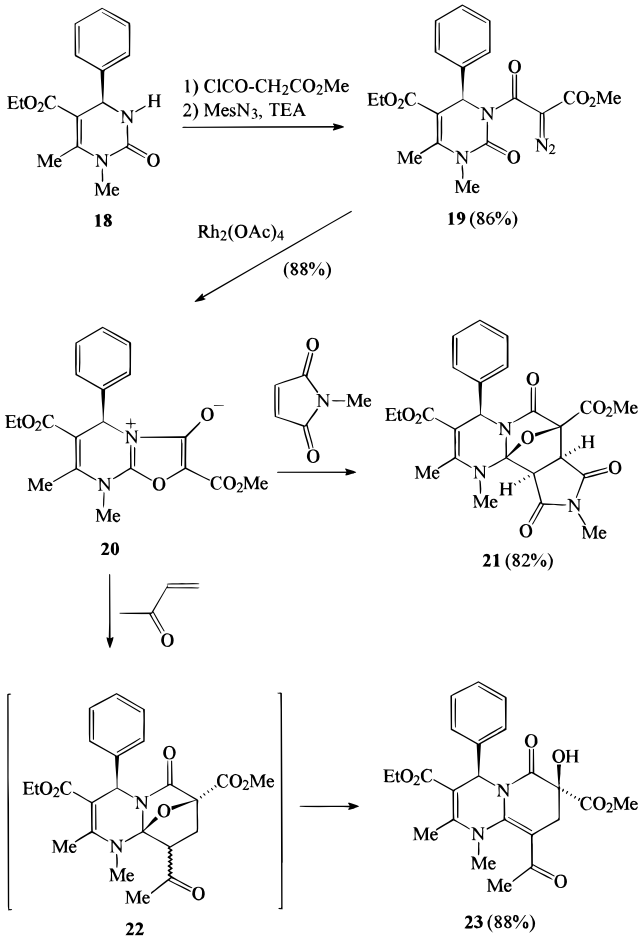
(25) Kappe, T.; Golser, W. *Synthesis* **1972**, 312−314.

(26) Potts, K. T.; Ehlinger, R.; Kanemasa, S. *J. Org. Chem.* **1980**, *45*, 2474−2479.

Scheme 3



Scheme 4



tions,[11a] cycloadditions of thiazinium betaines with electron-rich π-systems are $LUMO_{dipol} - HOMO_{dipolarophile}$ (Sustmann type III)[21] controlled. The observed regiochemistry here is in full accord with FMO theory[27] and related cycloadditions.[11a] In addition, the structure of cycloadduct **17** was confirmed by determination of long-range $^1H-^{13}C$ connectivities through an HMBC NMR experiment.[19]

It should be noted that the reaction of isothiomünchnone **8** with 1-(diethylamino)-1-propyne (*i.e.*, with an electron-rich dipolarophile) did not produce any isolable cycloaddition products. Therefore, the cycloaddition reactions of isothiomünchnone **8** and thiazinium betaines **13** nicely supplement each other, the former undergoing cycloaddition with electron-deficient π-systems and the latter undergoing cycloaddition with electron-rich π-systems.

We next turned our attention to dihydropyrimidine-fused isomünchnone dipoles of type **20** (Scheme 4). Isomünchnones contain a masked carbonyl ylide dipole and have been shown to be considerably more reactive than their sulfur analogs.[7,8] In general, these mesoionic systems are prepared *in situ* by cyclization of suitable diazo imides *via* metallo carbenoid intermediates.[7,8] In the dihydropyrimidine series, the required diazo imide precursor **19** was readily prepared in high overall yield by *N*-malonylacylation[8] of **8** with methyl malonyl chloride, followed by standard diazo-transfer reaction with mesyl azide.[28] Decomposition of diazo imide **19** with a catalytic amount of $Rh_2(OAc)_4$ in refluxing benzene in the presence of a slight excess of *N*-methylmaleimide gave cycloadduct **21** in 80% isolated yield. The relative stereochemistry of **21** was proven by an X-ray analysis[22] and is analogous to the stereochemistry observed for **11** (Scheme 2). Surprisingly, when the rhodium-catalyzed decomposition of **19** was carried out in the absence of a dipolarophile, isomünchnone **20** precipitated from the hot benzene solution as a colorless solid in 88% yield and analytical purity! This carbonyl ylide dipole proved to be remarkably stable and could even by recrystallized from methanol. Although isomünchnones bearing aryl substituents at the C-2 and C-5 positions have been isolated and reported as being stable in the open air for weeks,[29] the comparable stability of "aminoisomünchnone" **20** is notable.[30] The stability of isomünchnone **20** allowed us to investigate the cycloaddition step **20** → **21** in more detail. ^1H-NMR monitoring of this reactin in $CDCl_3$ at 25 °C demonstrated the ease of the 1,3-dipolar

(27) Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976.

(28) Taber, D. F.; Ruckle, R. E., Jr.; Hennesy, M. *J. Org. Chem.* **1986**, *51*, 4077−4078.

(29) Hamaguchi, M.; Ibata, T. *Tetrahedron Lett.* **1974**, 4475−4478.

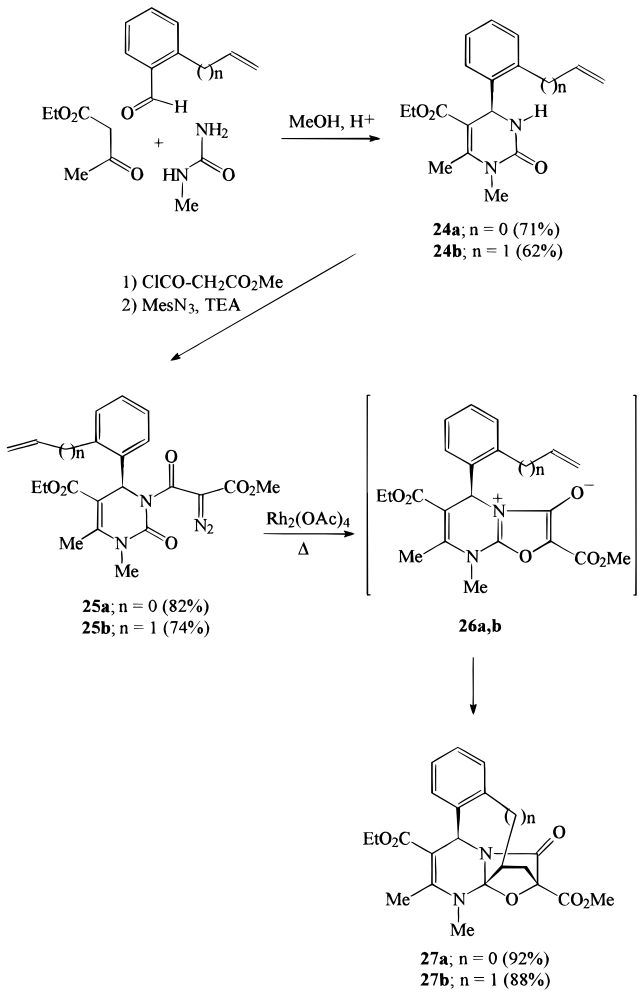
cycloaddition (complete consumption of dipol **20** within 20 min) and the essentially clean formation of diastereoisomer **21** as the only cycloaddition product (82% isolated yield).

When methyl vinyl ketone was employed as dipolarophile, similar results were obtained leading to high yields of pyridopyrimidine **23** from isomünchnone **20** (88%) or directly from diazo compound **19** *via in situ* generated **20** (71%). The primary cycloadduct **22** was not isolated and underwent facile rearrangement to alcohol **23**, presumably through nitrogen lone-pair-assisted opening of the oxygen bridge followed by proton loss from the resulting acyl iminium intermediate.[31] Here, eight possible diastereoisomeric primary cycloadducts are possible if one considers regioselectivity, facial selectivity (*syn*/*anti*), and *exo*/*endo* diastereoselectivity, although the information about *exo*/*endo* selectivity is "lost" during the rearrangement of **22** to **23**. The relative stereochemistry of alcohol **23** was established unequivocally by an X-ray crystal analysis[22] and is consistent with the mechanistic concept discussed above. Attack of the dipolarophile occurs *anti* to the phenyl group, which places the oxygen bridge *syn* to the phenyl ring in cycloadduct **22**. This stereochemical arrangement is then conserved during the ring-opening step **22** → **23**. The regiochemical outcome of the 1,3-dipolar cycloaddition again is consistent with FMO theory[27] and not without precedent in isomünchnone chemistry.[31] According to semiempirical calculations,[31] such cycloadditions are $HOMO_{dipol}$ − $LUMO_{dipolarophile}$ (Sustmann type I)[21] controlled.

A critical comparison of the results obtained in the bimolecular cycloaddition reactions of the various dihydropyrimidine-fused mesomeric betaines described above (Schemes 2−4) led us to select the isomünchnone dipole as a model system for the planned intramolecular cycloaddition reactions (Scheme 1). The relative ease of dipole generation, the high reactivity of the dipole itself, and the high yields and selectivities observed in the cycloaddition reactions make this mesoionic system an obvious choice.

In order to construct the desired conformationally restricted polycyclic DHPM systems, an intramolecular variation of the bimolecular cycloaddition protocol described above was developed (Scheme 5). This was readily achieved by incorporating an alkenyl tether into the *ortho*-position of the aryl moiety in the DHPM framework. The required starting materials **24a**,**b** were obtained by classical Biginelli condensation of ethyl acetoacetate, with *N*-methylurea, and 2-vinylbenzaldehyde (or 2-allylbenzaldehyde, respectively). *N*-Malonylacylation,[8] followed by standard diazo-transfer,[28] produced the corresponding diazo precursors **25a**,**b** in high yield. Treatment of diazo imides **25a**,**b** with a catalytic amount of $Rh_2(OAc)_4$ in refluxing benzene produced directly the desired pentacyclic dihydropyrimidine derivatives **27a**,**b** in high yields. In this *tandem-cyclization*−*cycloaddition* sequence[8] the initially generated transient isomünchnone dipole **26** adds spontaneously across the unactivated π-bond of the olefinic tether in a regio- and stereospecific manner. Analysis of the crude reaction mixtures for both homologs ($n = 0$, $n = 1$) by ^{1}H-NMR (200 MHz) confirmed that **27a** and **27b**, respectively, were the only isomers formed (within the detection limit of ^{1}H-NMR spectroscopy). The stereospecificity and relative ease of these intramolecular cycloadditions are readily explained by considering molecular models (Dreiding) of the transition states involved.[32] The pseudoaxial orientation of the aryl substituent allows for an extremely favorable alignment of the double bond relative to the dipole, placing the π-bond in close proximity above the dipole.[33] For $n = 0$, only an *endo* approach of the π-bond with the terminal end of the olefin directed toward the negative center of the dipole is possible (*endo* **A**). Transition states according to types **B**−**D** leading to *exo* isomers and/or different regioisomers cannot be modeled at all or place a too high steric demand on the transition state. For $n = 1$, the *endo* **A** approach again is the most favorable, although an *endo* **B** and even an *exo* **C** approach cannot be totally excluded. The structures of both cycloadducts were unequivocally established by an X-ray crystallographic analysis (Figure 1; additional

Scheme 5



(30) To the best of our knowledge, **20** is the first non-aryl-substituted stable isomünchnone reported. A crystalline sample of **20** could be kept in the open air for 2 months without any sign of decomposition (^{1}H-NMR). For previous examples of the generation of aminoisomünchnones as transient intermediates, see: Doyle, M. P.; Pieters, R. J.; Taunton, J.; Pho, H. Q.; Padwa, A.; Hertzog, D. L.; Precedo, L. *J. Org. Chem.* **1991**, *56*, 820−829. Kappe, C. O. *Tetrahedron Lett.* **1997**, *38*, in press.

(31) Padwa, A.; Hertzog, D. L. *Tetrahedron* **1993**, *49*, 2589−2560.

(32) Potts, K. T.; Dery, M. O.; Juzukonis, W. H. *J. Org. Chem.* **1989**, *54*, 1077−1088.

(33) The conformation necessary for an intramolecular cycloaddition requires the tether on the aryl substituent close to antiperiplanar arrangement with C4-H (*i.e.*, above the dihydropyrimidine ring). According to recent ab initio and semiempirical calculations,[1] this type of DHPM conformation is only slightly higher in energy than the lowest energy conformation with synperiplanar orientation of an *o*-aryl substituent (*i.e.*, away from the dihydropyrimidine ring).

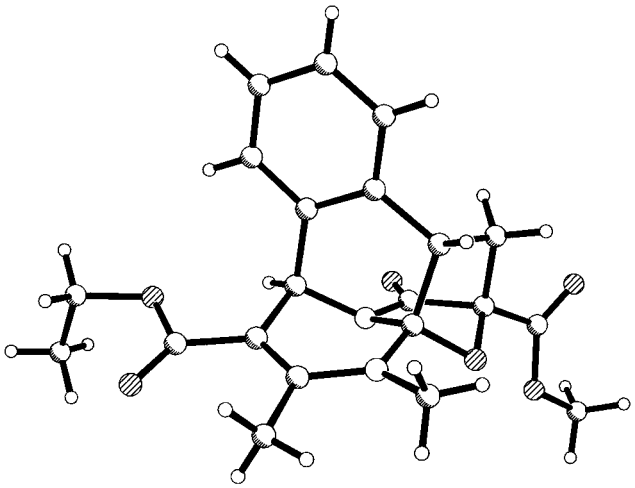
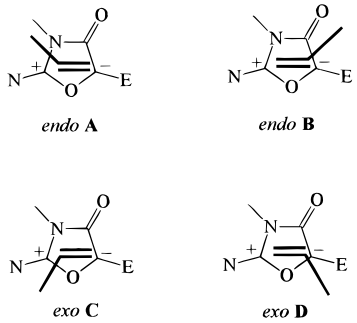


Figure 1. Solid-state structure of **27a**.

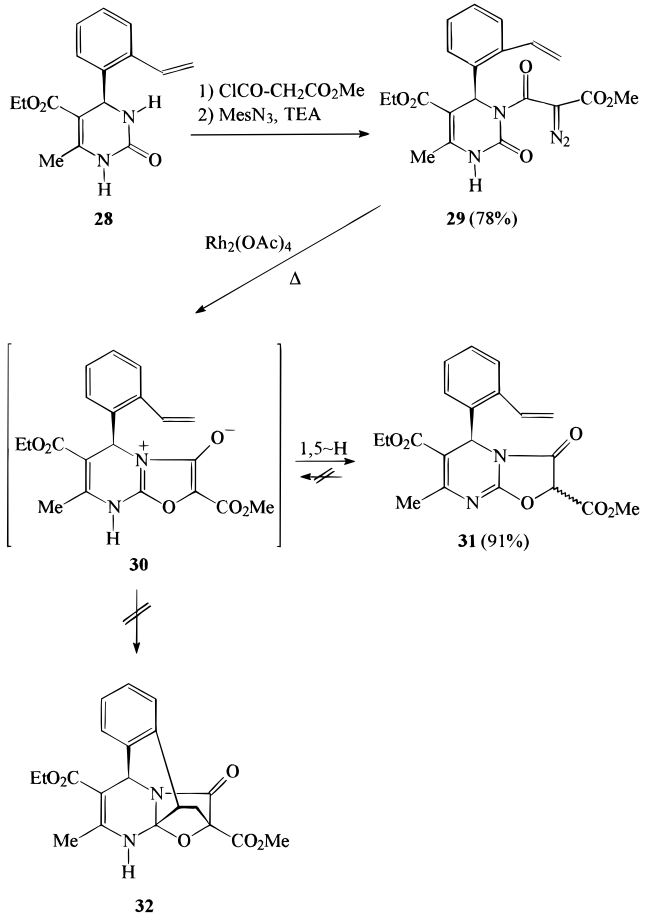
X-ray plots of **27a** and **27b** are presented in the Supporting Information),[22] confirming that both cycloadducts result from an *endo* **A** type transition state.



The solid-state structure of **27a** demonstrates that the geometry of this conformationally restricted DHPM derivative is very similar to the receptor-bound conformation proposed in the recent binding-site model for DHP/DHPM calcium channel modulators (see above).[5,6] The aryl group is "tied" into the axial position and is perpendicular to and (nearly) bisecting the boatlike dihydropyrimidine ring. Any additional substituent on the aromatic ring (*i.e.*, Z in **6**) would be forced into the synperiplanar orientation relative to C4-H. Importantly, by using this cycloaddition protocol all manipulations on the DHPM system are occuring on the nonessential "right-hand" side of the molecule, thereby not interfering with the receptor-sensitive groups on the "left-hand" side (see above).

Polycycles **27** above differ significantly from the proposed calcium channel modulator targets of type **5** regarding the absence of the enamidic NH on the dihydropyrimidine. Thus, we have investigated the potential cycloaddition reactivity of fused isomünchnone **30** with an N−H functionality next to the dipole. Biginelli condensation of ethyl acetoacetate with urea and 2-vinylbenzaldehyde provided dihydropyrimidine **28** (74% yield), which was converted smoothly into diazo imide **29** by sequential *N*-malonylacylation and diazo transfer (Scheme 6). Decomposition of **29** in benzene in the presence of a catalytic amount of $Rh_2(OAc)_4$, *i.e.*, under identical conditions as described above for the N-protected analog **25a**, did not provide any product derived from an intramolecular cycloaddition reaction. Instead, oxazolopyrimidine **31** was obtained in 91% yield as an

Scheme 6



equilibrium mixture (1:1) of C-2 epimers (see the Experimental Section). Apparently, a facile and thermally allowed 1,5-sigmatropic hydrogen shift in oxazolopyrimidiniumolate **30** leads to a collapse of the dipole before cycloaddition (**30** → **32**) can take place. Since it has been suggested that 4(5*H*)-oxazolones can undergo 1,3-dipolar cycloaddition reaction *via* tautomerization to an isomünchnone dipole,[34] we have tried to effect the desired cycloaddition reaction by subjecting **31** to a number of different experimental conditions (polar solvents, heat, acid catalysis). However, no evidence for an intramolecular cycloaddition from **31** could be obtained. Therefore, a protecting group strategy as outlined in Scheme 1 for the preparation of biologically active DHPM derivatives of type **6** (Scheme 1) is essential.

In conclusion, we have demonstrated that dihydropyrimidine-fused mesomeric betaines (*i.e.*, **8**, **13**, **20**) serve as useful intermediates for the preparation of bicyclic dihydropyrimidine derivatives. In effect, these cycloadditions constitute a two-step annulation sequence of dihydropyrimidines providing a novel entry into bicyclic DHPM analogs. In the model studies described herein, a high degree of regioselectivity, facial selectivity, and *exo*/*endo* diastereoselectivity was observed. In its intramolecular variation, the described isomünchnone cycloaddition sequence leads to a rigid, polycyclic DHPM skeleton, which closely resembles the recently proposed receptor-bound conformation of dihydropyridine calcium channel modulators. The ease of generation of the key dipolar intermediates makes this an attractive method for the preparation of pharmacologially interesting DHPM

(34) Potts, K. T.; Marshall, J. L. *J. Org. Chem.* **1979**, *44*, 626−628.

derivatives. The application and further development of this methodology for the preparation of properly functionalized DHPM calcium channel modulators is under investigation.

Experimental Section

Melting points are uncorrected. ^{1}H- and ^{13}C-NMR spectra were obtained from 200 or 360 MHz instruments. HMBC-NMR measurements were performed on a 360 MHz spectrometer. IR spectra were recorded on dispersive or FT instruments. Flash chromatography was performed with silica gel 60, 40−63 μm, using mixtures of hexane and ethyl acetate as eluent. For further details, see ref 1.

Methylene chloride, benzene, and toluene were distilled and dried over 4 Å molecular sieves. Triethylamine (TEA) was distilled from solid KOH before use. All reactions were carried out in a dry N_2 atmosphere to minimize contact with moisture.

6-[(Ethyloxy)carbonyl]-7,8-dimethyl-2,5-diphenyl−5*H*,8*H*-[1,3]thiazolo[3,2-*a*]pyrimidin-4-ium-3-olate (8). A solution of 701 mg (3.00 mmol) of α-bromophenylacetyl chloride[35] in 10 mL of alcohol-free $CHCl_3$ was added dropwise to a solution of 870 mg (3.00 mmol) of pyrimidine **7**[16] in 10 mL of $CHCl_3$. After the solution was stirred at rt for 5 min, a solution of 606 mg (6.00 mmol) of TEA in 5 mL of $CHCl_3$ was added dropwise, and the resulting red solution was stirred for an additional 5 min before the mixture was washed twice with ice−water. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give 1.05 g (86%) of pure **8** as an orange-red solid: mp 230−232 °C (acetone); IR (KBr) 1706, 1653, 1588, 1533 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 7.5 Hz), 2.62 (s, 3H), 3.27 (s, 3H), 4.14 (q, 2H, J = 7.5 Hz), 6.58 (s, 1H), 6.96−7.70 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 14.0, 15.0, 34.5, 53.9, 60.8, 85.1, 105.0, 122.2, 122.9, 127.3, 128.3, 128.5, 128.6, 134.3, 139.8, 145.5, 151.0, 153.9, 164.8; MS *m/e* 407, 406 (M$^+$, base). Anal. Calcd for $C_{23}H_{22}N_2O_3S$: C, 67.96; H, 5.46; N, 6.89. Found: C, 67.63; H, 5.47; N, 6.66.

3-Ethyl 8,9-Dimethyl 1,2-Dimethyl-6-oxo-4,7-diphenyl-1,6-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3,8,9-tricarboxylate (10a). A mixture of 406 mg (1.00 mmol) of isothiomünchnone **8**, 185 mg (1.30 mmol) of distilled dimethyl acetylenedicarboxylate (DMAD), and 10 mL of toluene was heated under reflux for 20 min. After the solvent was removed under reduced pressure, the crude product was purified by flash chromatography to yield 423 mg (82%) of cycloadduct **10a** as a colorless solid: mp 170−172 °C (cyclohexane); IR (KBr) 1752, 1721, 1702, 1655, 1520 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.5 Hz), 2.56 (s, 3H), 3.12 (s, 3H), 3.55 (s, 3H), 3.81 (s, 3H), 4.24 (q, 2H, J = 7.5 Hz), 7.17−7.35 (m, 11H); ^{13}C-NMR ($CDCl_3$) δ 14.2, 15.9, 38.6, 51.6, 52.2, 52.5, 60.8, 93.9, 110.4, 122.5, 126.1, 127.9, 128.0, 128.6, 129.7, 133.9, 138.8, 143.1, 147.4, 152.1, 159.8, 164.6, 164.7, 166.9; MS *m/e* 516 (M$^+$, base). Anal. Calcd for $C_{29}H_{28}N_2O_7$: C, 67.37; H, 5.46; N, 5.42. Found: C, 67.66; H, 5.43; N, 5.34.

3-Ethyl 9-Methyl 1,2-Dimethyl-6-oxo-4,7-diphenyl-1,6-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3,9-dicarboxylate (10b). A mixture of 406 mg (1.00 mmol) of isothiomünchnone **8**, 228 mg (3.00 mmol) of distilled methyl propiolate, and 10 mL of toluene was heated at 90−100 °C for 30 min. After the solvent was removed under reduced pressure, the crude product was purified by flash chromatography to yield 394 mg (86%) of cycloadduct **10b** as a colorless solid: mp 212−215 °C (1-propanol); IR (KBr) 1711sh, 1704, 1650, 1519 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.34 (t, 3H, J = 7.5 Hz), 2.57 (s, 3H), 3.15 (s, 3H), 3.86 (s, 3H), 4.28 (q, 2H, J = 7.5 Hz), 7.18−7.42 (m, 9H), 7.72 (m, 2H), 8.07 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.3, 16.2, 39.6, 51.2, 52.0, 60.8, 95.9, 110.5, 122.9, 126.1, 127.4, 127.7, 128.1, 128.3, 128.5, 136.1, 139.5, 139.8, 148.3, 152.4, 159.9, 164.6, 164.9. Anal. Calcd for $C_{27}H_{26}N_2O_5$: C, 70.72; H, 5.72; N, 6.11. Found: C, 70.61; H, 5.70; N, 6.06.

Ethyl 2,3,11-Trimethyl-7,10,12-trioxo-5,8-diphenyl-14-thia-2,6,11-triazatetracyclo[6.5.1.0^{1,6}.0^{9,13}]tetradec-3-ene-4-carboxylate (11). A mixture of 102 mg (0.25 mmol) of isothiomünchnone **8**, 35 mg (0.32 mmol) of *N*-methylmaleimide, and 5 mL of toluene was heated under reflux for 20 min. After the solvent was removed under reduced pressure, the remaining oil was crystallized by addition of a small amount of cold ethanol to give 81 mg (63%) of cycloadduct **11** as a colorless solid: mp 215 °C (1-propanol); IR (KBr) 1776, 1704, 1690, 1593 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.25 (t, 3H, J = 7.5 Hz), 2.70 (s, 3H), 2.97 (s, 3H), 3.26 (s, 3H), 3.77 and 4.00 (2 d, 2H, J = 7.0 Hz each), 4.12 (q, 2H, J = 7.5 Hz), 5.68 (s, 1H), 7.17−7.40 (m, 10H); ^{13}C-NMR ($CDCl_3$) δ 14.2, 17.1, 25.2, 36.6, 51.0, 54.1, 54.7, 60.1, 70.9, 90.4, 105.7, 127.2, 127.3, 128.1 (2 carbons), 128.5, 129.0, 129.9, 141.7, 155.2, 165.9, 169.8, 172.0, 172.4. Anal. Calcd for $C_{28}H_{27}N_3O_5S$: C, 64.97; H, 5.26; N, 8.12. Found: C, 64.69; H, 5.33; N, 8.01.

Ethyl 1,2,9-Trimethyl-6,8,10-trioxo-4,7-diphenyl-1,4,6,-8,9,10-hexahydropyrrolo[3′4′:3,4]pyrido[1,2-*a*]-pyrimidine-3-carboxylate (12). A mixture of 52 mg (0.10 mmol) of cycloadduct **11**, 1.0 g of silica gel 60, and 5 mL of CH_2Cl_2 was stirred at rt for 1−2 weeks. After all starting material was consumed (TLC), the mixture was filtered and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give 48 mg (ca. 100%) of tricyclus **12** as a greenish solid: mp 228−231 °C; IR (KBr) 1753, 1701, 1660, 1561 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.5 Hz), 3.06 (s, 3H), 3.61 (s, 3H), 4.25 (q, 2H, J = 7.5 Hz), 7.24−7.44 (m, 11H); ^{13}C-NMR ($CDCl_3$) δ 14.2, 16.2, 24.2, 40.5, 52.0, 61.0, 91.6, 104.9, 110.6, 124.4, 126.4, 127.6, 128.3, 128.7, 128.8, 130.4, 120.9, 136.8, 138.8, 144.4, 151.1, 161.8, 164.6, 165.4. Anal. Calcd for $C_{28}H_{25}N_3O_5$: C, 69.55; H, 5.27; N, 8.69. Found: C, 69.27; H, 5.23; N, 8.55.

7-(Ethoxycarbonyl)-8,9-dimethyl-4-oxo-3,6-diphenyl-4*H*,6*H*,9*H*-pyrimido[2,1-*b*][1,3]thiazin-5-ium-2-olate (13a). To a solution of 1.16 g (4.00 mmol) of pyrimidine **7** in 10 mL of alcohol-free $CHCl_3$ was added 812 mg (4.50 mmol) of distilled phenyl(chlorocarbonyl)ketene.[36] After the solution was stirred for 1 h at rt, the solvent was removed under reduced pressure to give 1.25 g (72%) of betaine **13a** as a yellow solid: mp 202−203 °C (MeCN); IR (KBr) 1711, 1685, 1652, 1611, 1500 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.5 Hz), 2.61 (s, 3H), 3.33 (s, 3H), 4.24 (q, 2H, J = 7.5 Hz), 7.19−7.51 (m, 10H), 7.61 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.0, 15.4, 35.2, 51.7, 61.7, 99.5, 111.0, 126.3, 127.8, 128.9, 129.0, 130.9, 134.3, 137.1, 145.9, 159.6, 163.9, 164.2, 165.3; MS *m/e* 435 (M + 1), 406 (base). Anal. Calcd for $C_{24}H_{22}N_2O_4S$: C, 66.34; H, 5.10; N, 6.45. Found: C, 66.35; H, 5.09; N, 6.36.

7-(Ethoxycarbonyl)-4-oxo-6-phenyl-3,8,9-trimethyl-4*H*,6*H*,9*H*-pyrimido[2,1-*b*][1,3]thiazin-5-ium-2-olate (13b). To a mixture of 290 mg (1 mmol) of pyrimidine **7** in 5 mL of CH_2Cl_2 was added dropwise at 0 °C 232 mg (1.5 mmol) of methyl malonyl dichloride. The resulting yellow solution was stirred for 12 h at rt. The reaction mixture was diluted with 30 mL of CH_2Cl_2 and washed with saturated $NaHCO_3$ and brine. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude product was purified by flash chromatography to give 335 mg (90%) of betaine **13b** as a yellow solid: mp 157−162 °C; IR (KBr) 1702, 1654, 1605, 1504 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.5 Hz), 2.02 (s, 3H), 2.65 (s, 3H), 3.38 (s, 3H), 4.28 (q, 2H, J = 7.5 Hz), 7.14−7.32 (m, 5H), 7.62 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 11.0, 14.0, 15.4, 35.2, 51.6, 61.6, 93.6, 110.8, 126.2, 128.7, 129.0, 137.2, 145.0, 159.8, 163.7, 163.9, 165.1. Anal. Calcd for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52. Found: C, 61.19; H, 5.47; N, 7.43.

Ethyl 8-(Diethylamino)-1,2,9-trimethyl-6-oxo-4,7-diphenyl-1,6-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (15a). A mixture of 217 mg (0.50 mmol) of betaine **13a**, 167 mg (1.50 mmol) of 1-(diethylamino)-1-propyne,[37] and 5 mL of CH_2Cl_2 was kept at rt for 8 h. The solvent and excess reagent were removed under reduced pressure, and the remaining residue was purified by flash chromatography to

(35) Harpp, D. N.; Bao, L. Q.; Black, C. J.; Gleason, J. G.; Smith, R. A. *J. Org. Chem.* **1975**, *23*, 3420−3426.

(36) Nakanishi, S.; Butler, K. *Org. Prep. Proced. Int.* **1975**, *7*, 155−158.

(37) Brandsma, L. *Preperative Acetylene Chemistry*; Elsevier: Amsterdam, 1971; p 146.

give 78 mg (32%) of cycloadduct **15a** as a colorless solid: mp 144−146 °C; IR (KBr) 1675, 1630, 1565, 1510 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 0.96 (t, 6H, J = 7.5 Hz), 1.30 (t, 3H, J = 7.5 Hz), 2.04 (s, 3H), 2.56 (s, 3H), 2.68−2.88 (m, 4H), 3.22 (s, 3H), 4.12 (m, 2H), 7.12−7.39 (m, 6H). Anal. Calcd for $C_{30}H_{35}N_3O_3$: C, 74.20; H, 7.26; N, 8.65. Found: C, 73.97; H, 7.39; N, 8.51.

Ethyl 8-(Diethylamino)-1,2,7,9-tetramethyl-6-oxo-4-phenyl-1,6-dihydro-4*H*-pyrido−[1,2-*a*]pyrimidine-3-carboxylate (15b). This cycloadduct was prepared in analogy to **15a** described above using betaine **13b**: yield 74 mg (35%) of **15b** as a colorless solid; mp 137−139 °C; IR (KBr) 1670, 1630, 1570, 1510 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (t, 6H, J = 7.5 Hz), 1.32 (t, 3H, J = 7.5 Hz), 2.01 (s, 3H), 2.08 (s, 3H), 2.49 (s, 3H), 3.11 (s, 3H), 3.00−3.32 (m, 4H), 4.22 (q, 2H, J = 7.5 Hz), 7.15−7.28; ^{13}C-NMR ($CDCl_3$) δ 14.1, 14.3, 14.4, 15.9, 16.8, 39.6, 45.9, 50.9, 60.3, 100.2, 110.0, 114.8, 126.2, 127.2, 129.4, 141.6, 142.7, 154.7, 159.3, 161.5, 165.9. Anal. Calcd for $C_{25}H_{33}N_3O_3$: C, 70.89; H, 7.85; N, 9.92. Found: C, 70.91; H, 7.99; N, 9.78.

Ethyl 8-Ethoxy-1,2,7-trimethyl-6-oxo-4-phenyl- 1,6-dihydro-4*H*-pyrido[1,2-*a*]pyrimidine-3-carboxylate (17). A mixture of 186 mg (0.50 mmol) of betaine **13b**, 290 mg (2.50 mmol) of 1,1-diethoxyethene, and 5 mL of toluene was heated under reflux for 2 h. After removal of the solvent under reduced pressure, the crude oil was purified by flash chromatography to provide 60 mg (31%) of cycloadduct **17** as a colorless solid: mp 190−192 °C (ethyl acetate); IR (KBr) 1700, 1638, 1530, 1258 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.31 (t, 3H, J = 7.5 Hz) 1.43 (t, 3H, J = 7.5 Hz), 2.00 (s, 3H), 2.58 (s, 3H), 3.24 (s, 3H), 4.08 (q, 2H, J = 7.5 Hz), 4.22 (m, 2H), 5.46 (s, 1H), 7.19 (s, 5H), 7.29 (s, 1H); ^{13}C-NMR ($CDCl_3$) δ 8.9, 14.3, 14.8, 15.9, 34.2, 49.9, 60.3, 64.0, 78.1, 103.5, 105.5, 126.3, 127.3, 128.3, 140.6, 144.1, 150.2, 161.5, 163.8, 165.6. Anal. Calcd for $C_{22}H_{26}N_2O_4$: C, 69.09; H, 6.85; N, 7.32. Found: C, 69.02; H, 6.80; N, 7.28.

Ethyl 3-[2-Diazo-2-[(methyloxy)carbonyl]acetyl]-1,6-dimethyl-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (19). A mixture of 822 mg (3.00 mmol) of pyrimidine **18**, 680 mg (5.00 mmol) of distilled methyl malonyl chloride, and 30 mL of benzene was heated at reflux for 30 min. After all starting material had been consumed (TLC), the solution was cooled to ambient temperature and washed twice with saturated $NaHCO_3$ and brine. The solvent was removed under reduced pressure and the crude product titurated with ether to give 1.07 g (95%) of ethyl 1,6-dimethyl-3-[2-[(methyloxy)carbonyl]acetyl]-2-oxo-4-phenyl-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate as a colorless solid: mp 143−145 °C (ethanol); IR (KBr) 1743, 1704, 1693, 1631, 1379 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.26 (t, 3H, J = 7.5 Hz), 2.55 (s, 3H), 3.15 (s, 3H), 3.73 (s, 3H), 3.92 (s, 2H), 4.21 (q, 2H, J = 7.5 Hz), 6.77 (s, 1H), 7.23−7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 14.1, 16.0, 31.2, 44.9, 51.1, 52.2, 60.6, 108.9, 126.1, 127.8, 128.5, 138.5, 148.6, 152.2, 165.0, 166.8, 167.6. Anal. Calcd for $C_{19}H_{22}N_2O_6$: C, 60.95; H, 5.92; H, 7.48. Found: C, 60.84; H, 5.99; N, 7.54.

A mixture of 748 mg (2.00 mmol) of the above 1,3-dicarbonyl compound, 290 mg (2.40 mmol) of $MesN_3$, 485 mg (4.80 mmol) of TEA, and 20 mL of dry CH_2Cl_2 was stirred at rt for 24−48 h. After all starting material had been consumed (^{1}H-NMR), the reaction mixture was washed with ice-cold 5% KOH and brine. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude diazo compound was purified by flash chromatography to give 720 mg (90%) of **19** (86% based on **18**) as a pale yellow oil that slowly crystallized on prolonged standing: mp 115 °C dec; IR (KBr) 2145, 1707, 1686, 1643, 1338 cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 1.27 (t, 3H, J = 7.5 Hz), 2.60 (s, 3H), 3.17 (s, 3H), 3.77 (s, 3H), 4.21 (q, 2H, J = 7.5 Hz), 6.23 (s, 1H), 7.27−7.30 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 14.2, 16.2, 30.9, 52.3, 54.0, 60.7, 73.4, 109.7, 126.3, 127.8, 128.5, 138.8, 149.1, 152.0, 161.3, 162.8, 165.1. Anal. Calcd for $C_{19}H_{20}N_4O_6$: C, 57.00; H, 5.04; N, 13.99. Found: C, 56.93; H, 5.10; N, 13.90.

6-[(Ethyloxy)carbonyl]-7,8-dimethyl-2-[(methyloxy)-carbonyl]-5-phenyl-5*H*,8*H*-[1,3]oxazolo[3,2-*a*]pyrimidin-4-ium-3-olate (20). A solution of 800 mg (2.00 mmol) of diazo compound **19** in 40 mL of benzene containing a catalytic amount of $Rh_2(OAc)_4$ (ca. 5 mg) was heated under reflux for 30−60 min. After all starting material had been consumed (TLC), the solution was cooled and kept at rt for 1 h. The precipitated solid was filtered to give 655 mg (88%) of analytically pure isomünchnone **20**: mp 235 °C dec; IR (KBr) 1719, 1682, 1669, 1584, 1544 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.13 (t, 3H, J = 7.5 Hz), 2.66 (s, 3H), 3.52 (s, 3H), 3.78 (s, 3H), 4.10 (q, 2H, J = 7.5 Hz), 6.35 (s, 1H), 7.30−7.43 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 13.9, 14.9, 31.0, 50.8, 53.1, 61.3, 106.5, 116.7, 127.6, 128.9, 129.2, 137.9, 144.3, 147.2, 150.8, 159.8, 164.0. Anal. Calcd for $C_{19}H_{20}N_2O_6$: C, 61.28; H, 5.41; N, 7.52. Found: C, 61.09; H, 5.42; N, 7.41.

4-Ethyl 8-Methyl 2,3,11-trimethyl-7,10,12-trioxo-5-phenyl-14-oxa-2,6,11-triazatetracyclo[6.5.1.0^{1,6}.0^{9,13}]tetradec-3-ene-4,8-dicarboxylate (21). (a) From Diazo Compound 19. A solution of 300 mg (0.75 mmol) of diazo compound **19** and 89 mg (0.80 mmol) of *N*-methylmaleimide in 10 mL of benzene containing a catalytic amount of $Rh_2(OAc)_4$ was heated at reflux for 1 h (TLC). After the solvent was removed under reduced pressure, the crude product was purified by flash chromatography to give 290 mg (80%) of cycloadduct **21** as a colorless solid, mp 190 °C.

(b) From Isomünchnone 20. A solution of 186 mg (0.50 mmol) of isomünchnone **20** and 67 mg (0.60 mmol) of *N*-methylmaleimide in 4 mL of CH_2Cl_2 was stirred at rt for 20 min. After the solvent was removed under reduced pressure, the crude product was titurated with a small amount of cold ethanol to give 198 mg (82%) of cycloadduct **21** as a colorless solid: mp 190 °C (ethanol), identical in all respects with the product prepared above; IR (KBr) 1770, 1750, 1705, 1590 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.18 (t, 3H, J = 7.5 Hz), 2.66 (s, 3H), 3.03 (s, 3H), 3.09 (s, 3H), 3.67 (m, 2H), 3.94 (s, 3H), 4.05 (q, 2H, J = 7.5 Hz), 5.58 (s, 1H), 7.19−7.36 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 14.0, 16.4, 25.5, 30.5, 48.6, 49.7, 53.3, 54.2, 60.0, 84.9, 99.6, 103.1, 127.6, 127.7, 128.1, 140.3, 153.3, 161.9, 164.2, 165.7, 171.5, 171.9. Anal. Calcd for $C_{24}H_{25}N_3O_8$: C, 59.62; H, 5.21; N, 8.69. Found: C, 59.57; H, 5.22; N, 8.56.

3-Ethyl 7-Methyl 9-Acetyl-7-hydroxy-1,2-dimethyl-6-oxo-4-phenyl-1,6,7,8-tetrahydro-4*H*-pyrido[1,2-*a*]pyrimidine-3,7-dicarboxylate (23). (a) From Diazo Compound 19. A solution of 300 mg (0.75 mmol) of diazo compound **19** and 105 mg (1.5 mmol) of distilled methyl vinyl ketone in 10 mL of benzene containing a catalytic amount of $Rh_2(OAc)_4$ was heated at reflux for 6 h (TLC). After the solvent and excess reagent were removed under reduced pressure, the crude product was purified by flash chromatography to give 235 mg (71%) of cycloadduct **23** as pale yellow solid, mp 125−127 °C.

(b) From Isomünchnone 20. A mixture of 189 mg (0.50 mmol) of isomünchnone **20**, 105 mg (1.50 mmol) of distilled methyl vinyl ketone, and 2 mL of benzene was heated at reflux for 40 min. The solvent and excess reagent were removed under reduced pressure, and the crude product was purified by flash chromatography to give 195 mg (88%) of cycloadduct **23**, identical in all respects with the product prepared above: mp 125−127 °C; IR (KBr) 3400, 1740, 1716, 1709, 1637, 1540 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.30 (t, 3H, J = 7.5 Hz), 2.24 (s, 3H), 2.50 (s, 3H), 2.83 and 3.31 (2 d, 2H, J = 14.5 Hz), 2.88 (s, 3H), 3.71 (s, 3H), 4.22−4.28 (m, 2H), 4.38 (br s, 1H), 6.83 (s, 1H), 7.16−7.33 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 14.0, 17.0, 28.9, 32.0, 40.1, 50.2, 52.9, 60.7, 75.8, 90.1, 112.6, 125.8, 127.8, 128.6, 138.5, 146.4, 151.7, 164.7, 168.8, 169.4, 192.9. Anal. Calcd for $C_{23}H_{26}N_2O_7$: C, 62.43; H, 5.92; N, 6.33. Found: C, 62.39; H, 5.92; N, 6.27.

Ethyl 1,6-Dimethyl-2-oxo-4-(2′-vinylphenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (24a). A mixture of 660 mg (5.00 mmol) of 2-vinylbenzaldehyde,[38] 975 mg (7.50 mmol) of ethyl acetoacetate, 480 mg (6.50 mmol) of *N*-methylurea, 5 mL of MeOH, and two drops of concd HCl was stirred at 50−55 °C for 10 h. One drop of concd HCl was added every 2 h. After the mixture was allowed to stand at 0 °C overnight, the precipitate was filtered to give 1.13 g (71%) of pyrimidine **24a**: mp 153−155 °C (ethanol); IR (KBr) 3220, 3090, 1710, 1685, 1638, 1418 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.03 (t, 3H, J = 7.5

(38) Dale, W. J.; Starr, L.; Strobel, C. W. *J. Org. Chem.* **1961**, *26*, 2225−2227.

Hz), 2.59 (s, 3H), 3.23 (s, 3H), 3.99 (q, 2H, J = 7.5 Hz), 5.40 (dd, 1H, J = 11.0, 1.5 Hz), 5.43 (br s, 1H), 5.63 (dd, 1H, J = 16.0, 1.5 Hz), 5.69 (d, 1H, J = 2.0 Hz), 7.04−7.42 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 14.1, 16.6, 30.2, 50.3, 60.1, 102.9, 118.2, 126.3, 127.1, 128.1, 128.5, 134.0, 136.2, 139.8, 150.1, 153.2, 165.0. Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.08; H, 6.66; N, 9.24.

Ethyl 4-(2′-Allylphenyl)-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (24b). This pyrimidine was prepared in analogy to **24a** (see above), employing 2-allylbenzaldehyde[39] as the aldehyde component: yield 62%; mp 146−147 °C (methanol); IR (KBr) 3220, 3090, 1710, 1680, 1635, 1480 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.05 (t, 3H, J = 7.5 Hz), 2.58 (s, 3H), 3.25 (s, 3H), 3.28−3.43 and 3.55−3.78 (2 m, 2H), 3.98 (q, 2H, J = 7.5 Hz), 4.92−5.19 (m, 2H), 5.40 (br s, 1H), 5.60 (d, 1H, J = 2.0 Hz), 5.96−6.16 (m, 1H), 7.10−7.24 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 13.9, 16.5, 30.1, 37.2, 50.1, 60.0, 103.5, 116.2, 127.1, 127.5, 127.9, 130.3, 136.1, 138.6, 141.2, 149.7, 152.8, 165.8. Anal. Calcd for $C_{18}H_{22}N_2O_3$: C, 68.77; H, 7.05; N, 8.91. Found: C, 68.71; H, 7.27; N, 8.78.

Ethyl 3-[2-Diazo-2-[(methyloxy)carbonyl]acetyl]-1,6-dimethyl-2-oxo-4-(2′-vinylphenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (25a). A mixture of 900 mg (3.00 mmol) of pyrimidine **24a**, 680 mg (5.00 mmol) of distilled methyl malonyl chloride, and 30 mL of benzene was heated at reflux for 30 min. After all starting material had been consumed (TLC), the solution was cooled to ambient temperature and washed twice with saturated $NaHCO_3$ and brine. The solvent was removed under reduced pressure and the crude product titurated with ether to give 1.03 g (86%) of ethyl 1,6-dimethyl-3-[2-[(methyloxy)carbonyl]acetyl]-2-oxo-4-(2′-vinylphenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate as a colorless solid: mp 111−113 °C (methanol); IR (KBr) 1737, 1694sh, 1690, 1631, 1331 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.21 (t, 3H, J = 7.5 Hz), 2.54 (s, 3H), 3.29 (s, 3H), 3.66 (s, 3H), 3.77 and 4.00 (2 d, 2H, J = 16.5 Hz), 4.04−4.19 (m, 2H), 5.36 (dd, 1H, J = 12.0, 1.5 Hz), 5.62 (dd, 1H, J = 17.0, 1,5 Hz), 6.88 (s, 1H), 7.06−7.60 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 14.1, 16.3, 31.2, 45.0, 49.3, 52.2, 60.7, 110.2, 116.0, 126.3, 126.8, 128.1, 128.5, 135.3, 136.3, 137.1, 147.0, 152.2, 164.8, 166.7, 167.7. Anal. Calcd for $C_{21}H_{24}N_2O_6$: C, 62.99; H, 6.04; H, 7.00. Found: C, 62.92; H, 6.06; N, 7.00.

A mixture of 800 mg (2.00 mmol) of the above 1,3-dicarbonyl compound, 290 mg (2.40 mmol) of $MesN_3$, 485 mg (4.80 mmol) of TEA, and 20 mL of CH_2Cl_2 was stirred at rt for 24−48 h. After all starting material had been consumed (^{1}H-NMR), the diazo-transfer reaction mixture was washed with ice-cold 5% aqueous KOH and brine. The organic layer was dried over Na_2SO_4 and the solvent removed under reduced pressure. The crude diazo compound was purified by flash chromatography to give 809 mg (95%) of **25a** (82% based on **24a**) as a pale yellow foam: IR (neat) 2134, 1715, 1696, 1651, 1331 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.21 (t, 3H, J = 7.5 Hz), 2.56 (s, 3H), 3.34 (s, 3H), 3.76 (s, 3H), 4.02−4.21 (m, 2H), 5.38 (dd, 1H, J = 12.0, 1.5 Hz), 5.66 (dd, 1H, J = 17.0, 1.5 Hz), 6.35 (s, 1H), 7.09−7.67 (m, 5H); ^{13}C-NMR ($CDCl_3$) δ 14.1, 16.4, 30.9, 51.8, 52.2, 60.5, 71.8, 110.5, 115.8, 126.0, 126.6, 128.3, 128.4, 135.0, 136.4, 137.2, 147.1, 151.6, 161.4, 163.1, 164.8. Anal. Calcd for $C_{21}H_{22}N_4O_6$: C, 59.15; H, 5.26; N, 13.14. Found: C, 59.08; H, 5.21; N, 13.00.

Ethyl 4-(2′-Allylphenyl)-3-[2-diazo-2-[(methyloxy)carbonyl]acetyl]-1,6-dimethyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (25b). A 942 mg (3.00 mmol) portion of pyrimidine **24b** was *N*-malonylacetylated in a similar manner as described above for **24a** to give 1.00 g (81%) of ethyl 4-(2′-allylphenyl)-1,6-dimethyl-3-[2-[(methyloxy)carbonyl]acetyl]-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate as a colorless solid: mp 106−108 °C (methanol); IR (KBr) 1745, 1710, 1690, 1640, 1335 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.22 (t, 3H, J = 7.5 Hz), 2.57 (s, 3H), 3.28 (s, 3H), 3.67 (s, 3H), 3.68−3.75 (m, 2H), 3.74 and 3.99 (2 d, 2H, J = 16.5 Hz), 4.01−4.24 (m, 2H), 5.00−5.14 (m, 2H), 5.89−6.10 (m, 1H), 6.89 (s, 1H), 7.05−7.22 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 14.1, 16.3, 31.2, 36.1, 44.7, 48.8, 52.2, 60.7, 110.6, 116.0, 126.4, 126.5, 128.4, 130.3, 135.9, 137.4, 138.9, 147.5, 152.3, 164.9, 166.2, 167.7. Anal. Calcd for $C_{22}H_{26}N_2O_6$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.86; H, 6.45; N, 6.78.

A sample of 828 mg (2.00 mmol) of the above 1,3-dicarbonyl compound was transformed into the diazo derivative as described above for **25a** to yield 800 mg (91%) of **25b** (74% based on **24b**) as a pale yellow oil: IR (neat) 2140, 1720, 1700, 1650, 1340 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.24 (t, 3H, J = 7.5 Hz), 2.57 (s, 3H), 3.34 (s, 3H), 3.76 (s, 3H), 3.79−3.96 (m, 2H), 4.08−4.22 (m, 2H), 5.12−5.24 (m, 2H), 5.93−6.15 (m, 1H), 7.09−7.20 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 14.2, 16.6, 31.0, 35.7, 51.7, 52.3, 60.7, 71.4, 110.9, 116.4, 126.2, 126.8, 128.3, 129.6, 137.4, 138.4, 147.3, 151.8, 161.5, 162.8, 165.0. Anal. Calcd for $C_{22}H_{24}N_4O_6$: C, 59.99; H, 5.49; N, 12.72. Found: C, 60.12; H, 5.48; N, 12.53.

4-Ethyl 14-Methyl 2,3-Dimethyl-15-oxo-17-oxa-2,16-diazapentacyclo[12.2.1.0^{1,12}.0^{5,16}.0^{6,11}]heptadeca-3,6(11),7,9-tetraene-4,14-dicarboxylate (27a). A solution of 213 mg (0.50 mmol) of diazo compound **24a** in 5 mL of benzene containing a catalytic amount (ca. 5 mg) of $Rh_2(OAc)_4$ was heated under reflux for 30 min. After all starting material was consumed (TLC), the solvent was removed under reduced pressure and the crude product purified by flash chromatography to yield 183 mg (92%) of **27a** as a colorless solid: mp 170−171 °C; IR (KBr) 1759, 1736, 1680, 1569, 1444 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.40 (t, 3H, J = 7.5 Hz), 1.95 (dd, 1H, J = 12.5, 3.0 Hz), 2.43 (s, 3H), 2.80 (dd, 1H, J = 12.5, 10.5 Hz), 3.08 (s, 3H), 3.76 (dd, 1H, J = 10.5, 3.0 Hz), 4.20−4.33 (m, 2H), 6.05 (s, 1H), 7.10−7.22 (m, 3H), 7.46−7.49 (m, 1H); ^{13}C-NMR ($CDCl_3$) δ 14.5, 15.7, 29.9, 39.5, 44.9, 50.1, 53.0, 59.6, 86.2, 97.8, 99.7, 126.5, 127.5, 127.8, 130.0, 132.2, 136.6, 152.9, 164.4, 165.8, 167.3. Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03. Found: C, 63.29; H, 5.58; N, 6.92.

4-Ethyl 15-Methyl 2,3-Dimethyl-16-oxo-18-oxa-2,17-diazapentacyclo[13.2.1.0^{1,13}.0^{5,17}.0^{6,11}]octadeca-3,6(11),7,9-tetraene-4,15-dicarboxylate (27b). This polycycle was prepared in a similar manner as described above for **27a** from diazo compound **24b**: yield 88% of **27b** as a colorless solid; mp 222−224 °C; IR (KBr) 1765, 1730, 1690, 1570, 1450 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.23 (t, 3H, J = 7.5 Hz), 1.49 (dd, 1H, J = 13.0, 5.0 Hz), 2.38 (dd, 1H, J = 13.0, 9.5 Hz), 2.57 (s, 3H), 2.71−2.82 (m, 2H), 3.14 (3H), 3.15−3.28 (m, 1H), 3.82 (s, 3H), 3.92−4.17 (m, 2H), 5.73 (s, 1H), 6.97−7.51 (m, 4H); ^{13}C-NMR ($CDCl_3$) δ 14.2, 16.2, 29.7, 31.1, 32.0, 38.9, 53.0, 54.3, 59.7, 85.6, 95.7, 98.8, 126.4, 127.7, 132.1, 132.4, 133.3, 138.7, 152.5, 165.1, 166.5, 166.6. Anal. Calcd for $C_{22}H_{24}N_2O_6$: C, 64.07; H, 5.87; N, 6.79. Found: C, 64.22; H, 5.96; N, 6.77.

Ethyl 6-Methyl-2-oxo-4-(2′-vinylphenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (28). A mixture of 660 mg (5.00 mmol) of 2-vinylbenzaldehyde,[38] 975 mg (7.50 mmol) of ethyl acetoacetate, 390 mg (6.50 mmol) of urea, 5 mL of MeOH, and two drops of concd HCl was stirred at 50−55 °C for 10 h. One drop of concd HCl was added every 2 h. After the mixture was allowed to stand at rt overnight, the precipitate was filtered to give 1.06 g (74%) of pyrimidine **28** as a colorless solid: mp 211−213 °C (ethanol); IR (KBr) 3350, 3220, 3100, 1690, 1640, 1455 cm^{-1}; ^{1}H-NMR (DMSO-d_6) δ 0.97 (t, 3H, J = 7.5 Hz), 2.30 (s, 3H), 3.86 (q, 2H, J = 7.5 Hz), 5.36 (dd, 1H, J = 11.0, 1.5 Hz), 5.53 (d, 1H, J = 2.5 Hz), 5.67 (dd, 1H, J = 17.0, 1.5 Hz), 7.21−7.51 (m, 5H), 7.65 (br s, 1H), 9.21 (br s, 1H); ^{13}C-NMR ($CDCl_3$) δ 13.9, 17.7, 50.3, 59.1, 99.3, 116.6, 125.9, 127.1, 127.6, 128.4, 134.5, 135.3, 142.2, 148.5, 151.5, 165.2. Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 66.93; H, 6.30; N, 9.79.

Ethyl 3-[2-Diazo-2-[(methyloxy)carbonyl]acetyl]-6-methyl-2-oxo-4-(2′-vinylphenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (29). This 1,3-dicarbonyl compound was prepared from pyrimidine **28** and methyl malonyl chloride in an analogous manner as described above for **25a**: yield 89% of ethyl 6-methyl-3-[2-[(methyloxy)carbonyl]acetyl]-2-oxo-4-(2′-vinylphenyl)-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate as a colorless solid; mp 160−162 °C (ethanol); IR (KBr) 3230, 3140, 1755, 1720, 1710sh, 1695, 1640 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.20 (t, 3H, J = 7.5 Hz), 2.38 (s, 3H), 3.63 (s, 3H), 3.82 and 4.04 (2 d, 2H, J = 16.0 Hz), 4.08 (m, 2H), 5.39 (dd, 1H, J = 11.0, 1.5

(39) Hartman, G. D.; Halczenko, W.; Phillips, B. T. *J. Org. Chem.* **1985**, *50*, 2427−2431.

Hz), 5.67 (dd, 1H, J = 17.0, 1.5 Hz), 6.79 (s, 1H), 7.19−7.74 (m, 5H), 8.54 (br s); ^{13}C-NMR ($CDCl_3$) δ 14.2, 17.6, 46.1, 51.8, 52.2, 60.5, 106.5, 115.6, 126.2, 126.9, 128.3, 128.4, 135.2, 136.5, 138.3, 143.4, 152.2, 164.5, 166.8, 167.5. Anal. Calcd for $C_{20}H_{22}N_2O_6$: C, 62.17; H, 5.74; N, 7.25. Found: C, 62.05; H, 5.71; N, 7.09.

A sample of the above 1,3-dicarbonyl compound was transformed into diazo compound **29** employing the standard procedure given above for **25a**. The crude diazo compound was purified by flash chromatography to give 88% of **29** (78% based on **28**) as a pale yellow oil that crystallized on standing: mp 134 °C dec; IR (KBr) 3230, 3130, 2140, 1740sh, 1720sh, 1705, 1660, 1645sh cm^{-1}, ^{1}H-NMR ($CDCl_3$) δ 1.19 (t, 3H, J = 7.5 Hz), 2.39 (s, 3H), 3.78 (s, 3H), 4.09 (m, 2H), 5.39 (dd, 1H, J = 11.0, 1.5 Hz), 5.69 (dd, 1H, J = 17.0, 1.5 Hz), 6.36 (s, 1H), 7.21−7.66 (m, 5H), 7.78 (br s, 1H); ^{13}C-NMR ($CDCl_3$), δ 14.2, 17.8, 52.4, 53.8, 60.4, 72.7, 106.6, 115.8, 126.2, 126.7, 128.4, 128.5, 134.9, 136.2, 138.7, 144.0, 151.7, 161.4, 163.2, 164.6. Anal. Calcd for $C_{20}H_{20}N_4O_6$: C, 58.25; H, 4.89; N, 13.59. Found: C, 58.44; H, 4.86; N, 13.40.

6-Ethyl 2-Methyl 7-Methyl-3-oxo-5-(2′vinylphenyl)-2,3-dihydro-5*H*-[1,3]oxazolo[3,2-*a*]pyrimidine-2,6-dicarboxylate (31). A solution of 824 mg (2.00 mmol) of diazo compound **29** in 40 mL of dry benzene containing a catalytic amount of $Rh_2(OAc)_4$ (ca. 5 mg) was heated under reflux for 2 h. After all starting material had been consumed (TLC), the solution was cooled and the solvent removed under reduced pressure. The crude product was titurated with ether to yield 699 mg (91%) of oxazolopyrimidine **31** as a colorless solid: mp 178−180 °C (ethanol); IR (KBr) 1785, 1760, 1695, 1655, 1570 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 1.08 and 1.09 (2 t, 3H, J = 7.5 Hz), 2.47 and 2.49 (2 s, 3H), 3.68 and 3.87 (2 s, 3H), 4.02 (q, 2H, J = 7.5 Hz), 5.10 and 5.14 (2 s, 1H), 5.42 (dd, 1H, J = 11.0, 1.5 Hz), 5.66 (dd, 1H, J = 17.0, 1.5 Hz), 6.35 (s, 1H), and 7.22−7.51 (m, 5H); 1:1 mixture of epimers, the signals at 5.10 and 5.14 disappeared on addition of D_2O; ^{13}C-NMR ($CDCl_3$) δ 13.8, 22.8, 51.8/52.2, 53.3/53.5, 59.7/59.9, 76.2/76.3, 107.1/107.2, 116.7/117.1, 125.6/125.8, 128.0/128.3, 128.4/128.5, 128.6/128.7, 133.8/134.2, 136.3/136.6, 137.0/137.1, 152.8/152.9, 155.1, 162.5/162.8, 163.7/164.1, 164.3/164.4; 1:1 mixture of epimers. Anal. Calcd for $C_{20}H_{20}N_2O_6$: C, 62.49; H, 5.24; N, 7.29. Found: C, 62.55; H, 5.12; N, 7.20.

Addition of an excess of triethylamine to a solution of **31** in CH_2Cl_2 and rapid workup of the resulting yellow solution with excess aqueous NH_4Cl produced a single epimer of **31** (>90% purity): ^{1}H-NMR ($CDCl_3$) δ 1.09 (t, 3H, J = 7.5 Hz), 2.47 (s, 3H), 3.68 (s, 3H), 4.02 (q, 2H, J = 7.5 Hz), 5.14 (s, 1H), 5.42 (dd, 1H, J = 11.0, 1.5 Hz), 5.66 (dd, 1H, J = 17.0, 1.5 Hz), 6.35 (s, 1H), and 7.22−7.51 (m, 5H); complete equilibration of epimers took place within 30 min in $CDCl_3$ at rt.

Acknowledgment. This work was supported by the Austrian Academy of Sciences (Austrian Programme for Advanced Research and Technology, APART 319) and the Austrian Science Foundation (FWF, Project P-11994-CHE).

Supporting Information Available: 2D-HMBC spectra of compounds **10b** and **17** and ORTEP representations of X-ray structures for compounds **11**, **21**, **23**, and **27a**,**b** (8 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.

JO970121Q