A SIMPLE APPROACH TO PYRIMIDINE AND QUINAZOLINE DERIVATIVES BY [4+2] CYCLOADDITION OF 1,3-DIAZADIENES AND ENAMINES

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Abstract- The reaction of 2-trimethylsilyloxy- (**1**) and 2-trimethylsilylthio-1,3-diazabutadienes (**2**) with enamines derived from aliphatic aldehydes leads regio- and stereoselectively to substituted tetrahydropyrimidin-2(1*H*)-ones (**3**) and thiones (**4**) in high yields. Extension of this cycloaddition to cyclic enamines, *e.g.* derived from cyclohexanone, leading to quinazoline derivatives (**9**-**10**) is also described. These heterocycles undergo hydrolysis and dehydration to 3,4-dihydropyrimidine (**7**-**8**) and 3,4,5,6,7,8-hexahydroquinazoline (**11**-**12**) derivatives.

In the last years azadienes have become valuable materials for the synthesis of heterocycles;[1] in particular, the [4+2] cycloaddition reaction has been demonstrated by several groups to be a powerful and versatile tool for constructing interesting pyridine and related structures.[2] Moreover, the preparation of complex polycyclic molecules has been nicely achieved by means of the intramolecular Diels-Alder reaction of 1- and 2-azadienes.[3] Heterodienes containing two heteroatoms have also been studied, though to a much lesser extent; among them, significant examples are 1,2-diaza-,[4] 1-oxa-2-aza-,[5] 1-oxa-3-aza-,[6] and 1-thia-3-azadienes.[7] On the other hand, we turned some attention to the synthetic utility of 1,3-diazadienes[8] and we learned from the literature that most reports on [4+2] cycloadditions of these systems dealt with reactive dienophiles, like heterocumulenes (ketenes,[9] isocyanates,[8,10] and sulfene[11]) and dimethyl acetylenedicarboxylate (DMAD)[9c,10b,12] (Figure 1).

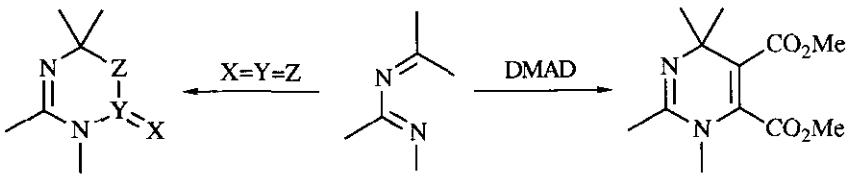


Figure 1

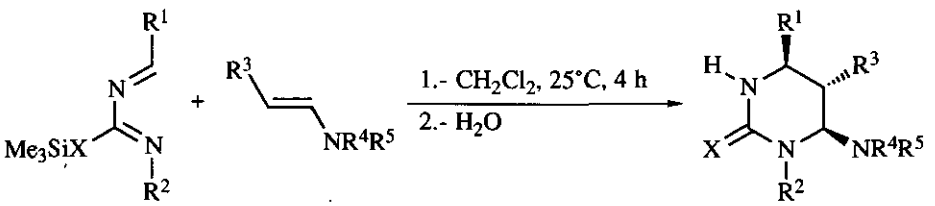
On the contrary, cycloaddition reactions of 1,3-diazadienes with electron-rich olefines have not been reported, as far as we are aware.[13] However, the potential of this reaction has been advanced by Boger and co-workers, who synthesized desacetamido P-3A, a peptide-derived natural product, by the [4+2] cycloaddition of a cyclic 1,3-diazadiene, 2,4,6-tris(ethoxycarbonyl)-1,3,5-triazine, with diaminoethene.[14] In this paper we detail the inverse electron demand [4+2] cycloaddition of 2-trimethylsilyloxy- and 2-trimethylsilylthio-1,3-diazadienes with enamines derived from both aldehydes and cyclohexanone leading to pyrimidine and quinazoline derivatives.[15]

RESULTS AND DISCUSSION

The preparation of 1,3-diazadienes (**1**) and (**2**) is readily carried out at 25-60°C, in quantitative yield, by treatment of *N*-trimethylsilylimines[16] with one equivalent of the corresponding isocyanate or isothiocyanate, respectively, as reported previously.[8] However, throughout this work, compounds (**1-2**) were not isolated, but formed *in situ* and then reacted with the appropriate enamine.

Synthesis of Pyrimidine Derivatives.

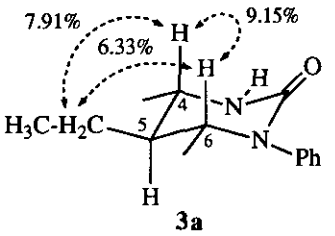
The resulting solutions of 1,3-diazadienes (**1-2**) in methylene chloride were stirred at room temperature with enamines derived from aliphatic aldehydes and pyrrolidine or piperidine; further aqueous work-up led, in high yields (80-93%), to solid pyrimidines (**3-4**), which were washed with ether and recrystallized from hexane-chloroform (Scheme 1, Table I). The reaction proved to be regio- and stereoselective, a sole isomer being detected in the crude reaction mixture (^{1}H nmr, 300 MHz). The regiochemistry was assigned on the basis of the ^{13}C nmr data, which show the C_6 aminal carbon at 79.5-86.5 ppm; moreover, hydrolysis and dehydration leading to their 3,4-dihydro derivatives confirmed this assesment (*vide infra*). The proposed stereochemistry, formally arising from an *endo*-transition state, is evidenced from the large coupling constants (^3J > 9 Hz) found in most instances for H_4-H_5 and for H_5-H_6 as well as from nuclear Overhauser enhancement experiments (Figure 2). Selected NOE data for compound (**3a**): irradiation at axial hydrogen H_4 (δ = 4.35) caused positive enhancement of H_6 (9.15%) and the methylene protons at C_5 (7.91%); in turn, irradiation at H_6 (δ = 4.55) resulted in positive enhancement of H_4 (8.89%) and the methylene protons at C_5 (6.33%).



1 (X = O)
2 (X = S)

3 (X = O)
4 (X = S)

Scheme 1



3a

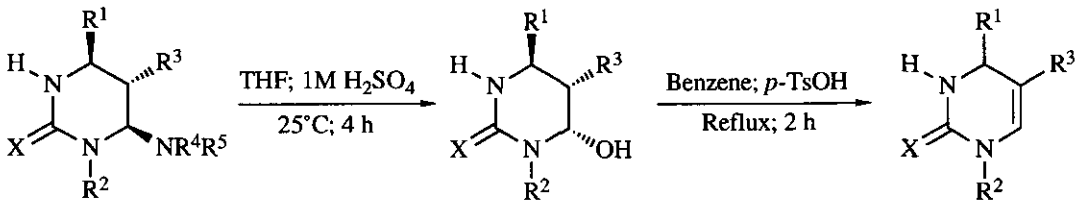
Figure 2

Table I. Pyrimidin-2(1*H*)-ones (**3**) and -thiones (**4**)

Compound	R^1	R^2	R^3	R^4-R^5	Yield (%)	mp (°C)[a]
3a	Ph	Ph	Et	$-(CH_2)_4-$	80	138-139
3b	Ph	4-MeC_6H_4	Me	$-(CH_2)_5-$	89	169-170
3c	2-Thienyl	4-MeC_6H_4	Me	$-(CH_2)_5-$	87	161-162
3d	2-Thienyl	Ph	Me	$-(CH_2)_5-$	93	173-174
4a	Ph	Ph	Me	$-(CH_2)_5-$	91	177-178
4b	2-Thienyl	Ph	Me	$-(CH_2)_5-$	82	159-160

[a] Recrystallized from hexane-chloroform.

Then heterocycles (**3-4**) were dissolved in THF and converted stereoselectively into their hydroxy derivatives (**5-6**) by stirring with 1M H_2SO_4 at room temperature (Scheme 2, Table II).The stereochemistry of the isomer formed, in which the hydroxy group is axially oriented in the corresponding chair-like conformation, was based on the ^1H nmr data [J (H_4-H_5) = 11.1-11.3 Hz, J (H_5-H_6) = 2.3-2.5 Hz] and reflects the contribution of the anomeric effect.[17]



3 (X = O)
4 (X = S)

5 (X = O)
6 (X = S)

7 (X = O)
8 (X = S)

Scheme 2

Tetrahydropyrimidinones (**5**) and -thiones (**6**) were then dehydrated in nearly quantitative yield to the dihydro derivatives (**7-8**) by refluxing in benzene in the presence of *p*-toluenesulfonic acid (Scheme 2, Table II). The structure shown is in agreement with the ^1H and ^{13}C nmr data and confirmed the regiochemistry given for their precursors (**3-6**); thus, H_4 and H_6 appears around 5.1 and 6.1 ppm, respectively, as singlets and the β-enamine carbon C_5 is observed at 110-116 ppm as a quaternary carbon (DEPT experiments).

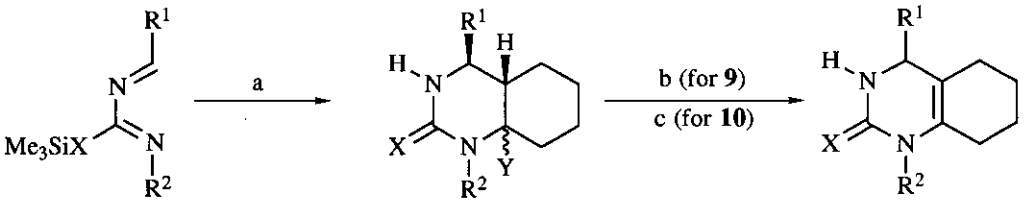
Table II: Pyrimidin-2(1*H*)-ones (**5**, **7**) and -thiones (**6**, **8**)

Compound	R^1	R^2	R^3	Yield (%)	mp (°C)[a]
5a	Ph	Ph	Et	84	133-135
7a				98	112-114
5b	2-Thienyl	Ph	Me	91	146-148
7b				97	123-125
5c	Ph	4-MeC_6H_4	Me	87	138-139
7c				87	107-109
6	Ph	Ph	Me	90	142-143
8				91	130-132

[a] Recrystallized from hexane-tetrahydrofuran (**5** and **6**) and from hexane-chloroform (**7** and **8**).

Synthesis of Quinazoline Derivatives.

Next we used enamines derived from cyclohexanone in order to apply the reaction to the synthesis of the fused pyrimidine skeleton (Scheme 3, Table III). Therefore, heterodienes (**1**) were treated with 1-morpholinocyclohexene at room temperature giving rise, after aqueous work-up, to quinazoline-2-ones (**9**); in the same way, compounds (**2**) reacted with 1-morpholinocyclohexene to furnish quinazoline-2-thiones (**10**). In the former case, the initially generated morpholino substituted quinazolines underwent hydrolysis in water to the hydroxy derivatives (**9**). Both quinazolines (**9**) and (**10**) were formed in a stereoselective fashion based on the ^1H nmr of the crude reaction mixture; the relative stereochemistry of the C_{8a} center was not determined because of signal overlaping in the ^1H nmr spectra, while the *trans*-diaxial relationship between H_4 and H_{4a} becomes clear from the large coupling constants [J (H_4-H_{4a}) = 10-12 Hz] found. Compounds (**9**) were subjected to dehydration in the presence of *p*-toluenesulfonic acid yielding hexahydropyrimidin-2-ones (**11**); similarly, quinazolines (**10**) could be converted into (**12**) by successive hydrolysis with diluted sulfuric acid and dehydration with *p*-toluenesulfonic acid in refluxing benzene.



1 (X = O)
2 (X = S)

9 (X = O, Y = OH)
10 (X = S, Y = Morpholino)

11 (X = O)
12 (X = S)

Reagents: a. i) 1-Morpholinocyclohexene, CH_2Cl_2, 25°C, 4 h; ii) H_2O
b. *p*-TsOH, C_6H_6, reflux, 2 h
c. i) 1M H_2SO_4, THF, 25°C, 4 h; ii) *p*-TsOH, C_6H_6, reflux, 2 h

Scheme 3

Table III: Quinazolin-2(1*H*)-ones (**9**, **11**) and -thiones (**10**, **12**)

Compound	R^1	R^2	Yield (%)	mp (°C)[a]
9a	Ph	Ph	88	138-140
11a			95	129-131
9b	Ph	4-MeC_6H_4	87	174-176
10a	2-Thienyl	Ph	82	138-140
12a			84	108-110
10b	Ph	Ph	84	136-138
12b			86	117-119
10c	4-$MeOC_6H_4$	Ph	88	129-130

[a] Recrystallized from hexane-chloroform.

Conclusions.

The present work describes for the first time the ability of 1,3-diazadienes to undergo a [4+2] cycloaddition to electron-rich olefines, like enamines. The process takes place at room temperature leading regio- and stereoselectively to pyrimidine and quinazoline derivatives; this approach to the pyrimidine ring combines four- and two-atom fragments and involves formation of N_1-C_6 and C_4-C_5 bonds. It should be pointed that high yields are obtained in all instances and that the process requires starting materials as simple and available as trimetylsilylimines, iso(thio)cyanates and enamines.

ACKNOWLEDGEMENT

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EXPERIMENTAL

Ir spectra were recorded on a Pye-Unicam SP-1000 or a Perkin-Elmer 298 and nmr spectra were performed on a Varian FT-80A and a Brüker AC-300 spectrometers using $CDCl_3$ as a solvent and tetramethylsilane as an internal reference, except the ^{13}C nmr spectra of compounds (**5**) and (**6**) which were recorded in DMSO-d_6. Mass spectra were obtained by EI (70 eV) from a Hewlett Packard 5987 apparatus. Melting points were measured in open capillary tubes using a Buchi-Tottoli apparatus, and are uncorrected. All solvents used were distilled prior to use. The reagents were of the best commercial grade available. Diazabutadienes were prepared *in situ* according to a previous report.[8]

General Procedure for the Preparation of Cycloadducts (3) and (4).

To a solution of 1,3-diazabutadiene (**1-2**) (5.4 mmol) in methylene chloride (20 ml) was added a solution of enamine (6.5 mmol) in methylene chloride (10 ml) at room temperature and the mixture was stirred for 4 h. The resulting mixture was diluted with ice-water, extracted with methylene chloride and the organic layer was dried over sodium sulfate. Evaporation of the solvent *in vacuo* gave yellow solids, which were washed with ether to give pure compounds (**3-4**); for analytical purposes, these compounds were recrystallized from hexane-chloroform. Reaction yields and mp are given in Table I.

5-Ethyl-1,4-diphenyl-6-pyrrolidino-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (3a).

Ir (KBr) 3310, 1690 cm^{-1}. ^1H Nmr δ 0.85 (t, 3H, J = 7.5 Hz), 1.3-1.5 (m, 6H), 2.20 (m, 1H), 2.35 (m, 4H), 4.35 (d, 1H, J = 7.1 Hz), 4.55 (d, 1H, J = 6.5 Hz), 4.90 (s, 1H, NH), 7.1-7.4 (m, 10H). ^{13}C Nmr δ 156.5 (s), 142.3 (s), 141.5 (s), 128.5 (d), 128.3 (d), 128.2 (d), 127.6 (d), 127.0 (d), 126.2 (d), 79.5 (d), 57.5 (d), 48.2 (t), 44.8 (d), 24.0 (t), 22.9 (t), 10.9 (q) ppm. Ms *m/z* 349 (M^+). Anal. Calcd for $C_{22}H_{27}N_3O$: C, 75.61; H, 7.79; N, 12.02. Found: C, 75.42; H, 7.81; N, 12.18.

5-Methyl-1-(4-methylphenyl)-4-phenyl-6-piperidino-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (3b).

Ir (KBr) 3290, 1700 cm^{-1}. ^1H Nmr δ 0.80 (d, 3H, J = 6.6 Hz), 1.1-1.3 (m, 6H), 2.25 (m, 1H), 2.30 (s, 3H), 2.4-2.6 (m, 4H), 4.10 (d, 1H, J = 10.5 Hz), 4.35 (d, 1H, J = 8.9 Hz), 4.80 (s, 1H, NH), 7.1-7.4 (m, 9H). ^{13}C Nmr δ 157.4 (s), 140.1 (s), 139.0 (s), 135.8 (s), 128.9 (d), 128.6 (d), 128.2 (d), 127.2 (d), 84.7 (d), 60.0 (d), 49.0 (t), 39.8 (d), 26.4 (t), 24.6 (t), 21.0 (q), 15.1 (q) ppm. Ms *m/z* 363 (M^+). Anal. Calcd for $C_{23}H_{29}N_3O$: C, 76.00; H, 8.04; N, 11.56. Found: C, 75.87; H, 8.13; N, 11.72.

5-Methyl-1-(4-methylphenyl)-6-piperidino-4-(2-thienyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (3c).

Ir (KBr) 3300, 1690 cm^{-1}. ^1H Nmr δ 0.90 (d, 3H, J = 6.5 Hz), 1.1-1.3 (m, 6H), 2.20 (m, 1H), 2.30 (s, 3H),

2.4-2.6 (m, 4H), 4.35 (d, 1H, J = 8.9 Hz), 4.50 (d, 1H, J = 10.5 Hz), 4.90 (s, 1H, NH), 6.9-7.3 (m, 7H). ^{13}C Nmr δ 156.7 (s), 143.3 (s), 138.7 (s), 135.7 (s), 128.8 (d), 128.0 (d), 126.3 (d), 125.7 (d), 125.0 (d), 84.5 (d), 55.5 (d), 48.8 (t), 40.8 (d), 26.2 (t), 24.5 (t), 20.9 (q), 15.1 (q) ppm. Ms *m/z* 369 (M^+). Anal. Calcd for $C_{21}H_{27}N_3OS$: C, 68.26; H, 7.36; N, 11.37. Found: C, 68.23; H, 7.38; N, 11.25.

5-Methyl-1-phenyl-6-piperidino-4-(2-thienyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (3d).
Ir (KBr) 3290, 1700 cm^{-1}. ^{1}H Nmr δ 0.90 (d, 3H, J = 6.6 Hz), 1.1-1.3 (m, 6H), 2.30 (m, 1H), 2.4-2.6 (m, 4H), 4.40 (d, 1H, J = 8.9 Hz), 4.50 (d, 1H, J = 10.5 Hz), 4.90 (s, 1H, NH), 6.9-7.4 (m, 8H). ^{13}C Nmr δ 156.5 (s), 142.7 (s), 138.8 (s), 128.6(d), 128.4 (d), 128.0 (d), 127.1 (d), 125.7 (d), 125.1 (d), 84.3 (d), 58.6 (d), 48.7 (t), 40.1 (d), 26.3 (t), 24.6 (t), 15.2 (q) ppm. Ms *m/z* 355 (M^+). Anal. Calcd for $C_{20}H_{25}N_3OS$: C, 67.57; H, 7.09; N, 11.82. Found: C, 67.49; H, 7.18; N, 11.92.

5-Methyl-1,4-diphenyl-6-piperidino-3,4,5,6-tetrahydropyrimidin-2(1*H*)-thione (4a).
Ir (KBr) 3280 cm^{-1}. ^{1}H Nmr δ 0.80 (t, 3H, J = 6.5 Hz), 1.0-1.2 (m, 6H), 2.3-2.4 (m, 3H), 2.5-2.6 (m, 2H), 4.20 (d, 1H, J = 10.6 Hz), 4.40 (d, 1H, J = 9.6 Hz), 6.50 (s , 1H, NH), 7.3-7.4 (m, 10H). ^{13}C Nmr δ 181.4(s), 144.2 (s), 138.3 (s), 128.9 (d), 128.7 (d), 128.6 (d), 128.0 (d), 127.3 (d), 126.9 (d), 86.4 (d), 61.7 (d), 48.6 (t), 37.9 (d), 25.9 (t), 24.2 (t), 14.57 (q) ppm. Ms *m/z* 365 (M^+). Anal. Calcd for $C_{22}H_{27}N_3S$: C, 72.29; H, 7.44; N, 11.49. Found: C, 72.23; H, 7.52; N, 11.47.

5-Methyl-1-phenyl-6-piperidino-4-(2-thienyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-thione (4b).
Ir (KBr) 3310 cm^{-1}. ^{1}H Nmr δ 0.90 (t, 3H, J = 6.5 Hz), 1.1-1.3 (m, 6H), 2.3-2.4(m, 3H), 2.5-2.6 (m, 2H), 4.40 (d, 1H, J = 9.6 Hz), 4.60 (d, 1H, J = 10.8 Hz), 6.60 (s, 1H, NH), 6.9-7.4 (m, 8H). ^{13}C Nmr δ 181.0 (s), 144.1 (s), 141.2 (s), 128.9 (d), 128.1 (d), 127.0 (d), 126.7 (d), 126.6 (d), 125.7 (d), 86.5 (d), 57.0 (d), 48.7 (t), 39.0 (d), 26.0 (t), 24.2 (t), 14.9 (q) ppm. Ms *m/z* 371 (M^+). Anal. Calcd for $C_{20}H_{25}N_3S_2$: C, 64.65; H, 6.78; N, 11.31. Found: C, 64.54; H, 6.89; N, 11.41.

General Procedure for the Hydrolysis of Compounds (3) and (4) to (5) and (6).
A mixture of aminopyrimidine (3-4) (2 mmol) and sulfuric acid (1 M, 5 ml) in tetrahydrofuran (20 ml) was stirred at room temperature for 4 h. The resulting mixture was diluted with water, extracted with methylene chloride, and was dried over sodium sulfate. Evaporation of the solvent *in vacuo* gave white solids, which were washed with ether to give pure compounds (5-6); for analytical purposes, these compounds were recrystallized from hexane-tetrahydrofuran. Reaction yields and mp are given in Table II.

5-Ethyl-6-hydroxy-1,4-diphenyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (5a).
Ir (KBr) 3400, 3280, 1670 cm^{-1}. ^{1}H Nmr δ 0.85 (t, 3H, J = 7.5 Hz), 1.10 (m, 1H), 1.35 (m, 1H), 1.95 (m, 1H), 4.40 (d, 1H, J = 11.3 Hz), 4.95 (s, 1H, NH), 5.10 (d, 1H, J = 2.5 Hz), 7.15-7.5 (m, 11H). ^{13}C Nmr δ 153.1 (s), 141.8 (s), 141.4 (s), 128.4 (d), 128.3 (d), 128.1 (d), 127.7 (d), 127.1 (d), 126.3 (d), 82.6 (d), 56.9 (d), 42.5 (d), 23.0 (t), 11.8 (q) ppm. Ms *m/z* 296 (M^+). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.85; H, 6.81; N, 9.50.

6-Hydroxy-5-methyl-1-phenyl-4-(2-thienyl)-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (5b).
Ir (KBr) 3450, 3280, 1690 cm^{-1}. ^1H Nmr δ 0.80 (d, 3H, J = 6.9 Hz), 2.20 (m, 1H), 4.60 (d, 1H, J = 11.2 Hz), 4.90 (d, 1H, J= 2.3 Hz), 4.95 (s, 1H, NH), 6.8-7.4 (m, 9H). ^{13}C Nmr δ 153.3 (s), 145.7 (s), 143.1 (s), 128.4 (d), 127.1 (d), 126.6 (d), 126.2 (d), 125.6 (d), 125.4 (d), 83.0 (d), 52.7 (d), 41.5 (d), 13.7 (q) ppm. Anal. Calcd for $C_{15}H_{16}N_2O_2S$: C, 62.48; H, 5.59; N, 9.71. Found: C, 62.38; H, 5.67; N, 9.69.

6-Hydroxy-5-methyl-1-(4-methylphenyl)-4-phenyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-one (5c).
Ir (KBr) 3400, 3280, 1690 cm^{-1}. ^1H Nmr δ 0.80 (d, 3H, J = 6.8 Hz), 2.20 (m, 1H), 2.30 (s, 3H), 4.40 (d, 1H, J = 11.2 Hz), 4.90 (s, 1H, NH), 4.95 (d, 1H, J = 2.5 Hz), 7.0-7.4 (m, 10H). ^{13}C Nmr δ 153.9 (s), 141.8 (s), 140.7 (s), 134.4 (s), 128.8 (d), 128.5 (d), 127.8 (d), 127.0 (d), 83.3 (d), 56.8 (d), 40.4 (d), 20.8 (q), 13.7 (q) ppm. Ms *m/z* 296 (M^+). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.85; H, 6.81; N, 9.50.

6-Hydroxy-5-methyl-1,4-diphenyl-3,4,5,6-tetrahydropyrimidin-2(1*H*)-thione (6).
Ir (KBr) 3400, 3300 cm^{-1}. ^1H Nmr δ 0.80 (d, 3H, J = 7.6 Hz), 2.10 (m, 1H), 4.40 (d, 1H, J = 11.1 Hz), 5.00 (d, 1H, J = 2.5 Hz), 6.10 (s, 1H, NH), 7.1-7.5 (m, 11H). ^{13}C Nmr δ 180.7 (s), 145.1 (s), 137.7 (s), 129.0 (d), 128.5 (d), 128.3 (d), 128.0 (d), 127.3 (d), 126.9 (d), 83.2 (d), 61.5 (d), 38.5 (d), 13.1 (q) ppm. Ms *m/z* 298 (M^+). Anal. Calcd for $C_{17}H_{18}N_2OS$: C, 68.43; H, 6.08; N, 9.39. Found: C, 68.40; H, 6.12; N, 9.27.

General Procedure for the Dehydration of Compounds (5) and (6) to (7) and (8).
In a flask equiped with a Dean-Stark trap, hydroxypyrimidines (**5-6**) (1.5 mmol) were dissolved in benzene (20 ml) containing a catalytic amount of *p*-toluenesulfonic acid. The mixture was heated to reflux for 2 h and allowed to cool to room temperature. The resulting mixture was washed with a saturated solution of sodium bicarbonate, extracted with methylene chloride and was dried over sodium sulfate. Evaporation of the solvent *in vacuo* gave compounds (**7-8**) as solid materials, which were recrystallized from hexane-chloroform. Reaction yields and mp are given in Table II.

5-Ethyl-1,4-diphenyl-3,4-dihydropyrimidin-2(1*H*)-one (7a).
Ir (KBr) 3280, 1670 cm^{-1}. ^1H Nmr δ 1.00 (t, 3H, J= 7.4 Hz), 1.80 (q, 2H, J= 7.4 Hz), 5.00 (s, 1H), 5.30 (s, 1H, NH), 6.10 (s, 1H), 7.3-7.5 (m, 10H). ^{13}C Nmr δ 152.1 (s), 142.4 (s), 140.9 (s), 128.9 (d), 128.8 (d), 128.2 (d), 127.0 (d), 126.4 (d), 126.1 (d), 123.3 (d), 116.5 (s), 60.0 (d), 23.1 (t), 11.4 (q) ppm. Ms *m/z* 278 (M^+). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.58; H, 6.52; N, 10.12.

5-Methyl-1-phenyl-4-(2-thienyl)-3,4-dihydropyrimidin-2(1*H*)-one (7b).
Ir (KBr) 3300, 1670 cm^{-1}. ^1H Nmr δ 1.50 (s, 3H), 5.20 (s, 1H), 5.40 (s, 1H, NH), 6.10 (s, 1H), 6.9-7.4 (m, 8H). ^{13}C Nmr δ 151.7 (s), 146.2 (s), 140.1 (s), 128.2 (d), 126.1 (d), 125.7 (d), 125.6 (d), 124.8 (d), 123.9 (d), 110.4 (s), 54.7 (d), 16.0 (q) ppm. Ms *m/z* 270 (M^+). Anal. Calcd for $C_{15}H_{14}N_2OS$: C, 66.64; H, 5.22; N, 10.36. Found: C, 66.59; H, 5.32; N, 10.41.

5-Methyl-1-(4-methylphenyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (7c).
Ir (KBr) 3300, 1700 cm^{-1}. ^1H Nmr δ 1.50 (s, 3H), 2.30 (s, 3H), 5.00 (s, 1H), 5.20 (s, 1H, NH), 6.10 (s, 1H), 7.1-7.4 (m, 9H). ^{13}C Nmr δ 152.1 (s), 146.3 (s), 139.7 (s), 135.3 (s), 128.1 (d), 127.7 (d), 127.6 (d), 127.3 (d), 127.0 (d), 126.8 (d), 110.4 (s), 56.3 (d), 20.9 (q), 16.0 (q) ppm. Ms *m/z* 278 (M^+). Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.54; H, 6.58; N, 10.01.

5-Methyl-1,4-diphenyl-3,4-dihydropyrimidin-2(1*H*)-thione (8).
Ir (KBr) 3300 cm^{-1}. ^1H Nmr δ 1.50 (s, 3H), 5.30 (s, 1H), 6.20 (s, 1H), 6.70 (s, 1H, NH), 7.1-7.5 (m, 10H). ^{13}C Nmr δ 179.2 (s), 142.3 (s), 137.8 (s), 128.8 (d), 128.7 (d), 128.4 (d), 127.4 (d), 126.5 (d), 126.3 (d), 124.0 (d), 114.3 (s), 61.1 (d), 15.8 (q) ppm. Ms *m/z* 280 (M^+). Anal. Calcd for $C_{17}H_{16}N_2S$: C, 72.82; H, 5.75; N, 9.99. Found: C, 72.75; H, 5.67; N, 10.11.

General Procedure for the Preparation of Cycloadducts (9) and (10).
The procedure described for compounds (**3-4**) was applied for cycloadducts (**9-10**). The reaction yields and mp are given in Table III.

8a-Hydroxy-1,4-diphenyl-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2(1*H*)-one (9a).
Ir (KBr) 3500, 3300, 1670 cm^{-1}. ^1H Nmr δ 1.1-2.0 (m, 9H), 3.10 (s, 1H, OH), 4.30 (d, 1H, J = 11Hz), 5.10 (s, 1H, NH), 7.1-7.8 (m, 10H). ^{13}C Nmr δ 155.7 (s), 140.6 (s), 138.7 (s), 129.3 (d), 129.1 (d), 128.8 (d), 128.1 (d), 128.0 (d), 84.2 (s), 57.4 (d), 48.3 (d), 38.1 (t), 24.9 (t), 24.7 (t), 22.3 (t) ppm. Ms *m/z* 322 (M^+). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.88; N, 8.69. Found: C, 74.49; H, 6.79; N, 8.81.

8a-Hydroxy-1-(4-methylphenyl)-4-phenyl-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2(1*H*)-one (9b).
Ir (KBr) 3450, 3280, 1680 cm^{-1}. ^1H Nmr δ 1.1-1.8 (m, 9H), 2.20 (s, 3H), 3.00 (s, 1H, OH), 4.70 (d, 1H, J = 10.8 Hz), 5.10 (s, 1H, NH), 7.0-7.6 (m, 9H). ^{13}C Nmr δ 156.9 (s), 140.9 (s), 137.0 (s), 136.7 (s), 128.9 (d), 128.2 (d), 127.7 (d), 126.8 (d), 78.3 (s), 54.0 (d), 43.2 (d), 32.8 (t), 24.8 (t), 22.6 (t), 20.6 (q), 19.0 (t) ppm. *Ms m/z 336 (M^+). Anal. Calcd for $C_{21}H_{24}N_2O_2$:* C, 74.97; H, 7.19; N, 8.33. Found: C, 74.93; H, 7.29; N, 8.40.

8a-Morpholino-1-phenyl-4-(2-thienyl)-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2(1*H*)-thione (10a).
Ir (KBr) 3310 cm^{-1}. ^1H Nmr δ 1.3-1.9 (m, 8H), 2.10 (m, 1H), 2.6-2.8 (m, 4H), 3.3-3.6 (m, 4H), 5.25 (d, 1H, J = 11.9 Hz), 6.65 (s, 1H, HN), 7.0-7.6 (m, 8H) ^{13}C Nmr δ 180.1 (s), 143.0 (s), 142.2 (s), 131.9 (d), 129.6 (d), 128.7 (d), 128.6 (d), 128.2 (d), 126.8 (d), 126.5 (d), 125.8 (d), 81.7 (s), 67.7 (t), 52.4 (d), 42.5 (broad), 41.7 (d), 31.3 (t), 23.0 (t), 22.0 (t), 19.2 (t) ppm. Ms *m/z* 413 (M^+). Anal. Calcd for $C_{22}H_{27}N_3OS_2$: C, 63.89; H, 6.58; N, 10.16. Found: C, 63.81; H, 6.59; N, 10.08.

8a-Morpholino-1,4-diphenyl-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2(1*H*)-thione (10b).
Ir (KBr) 3300 cm^{-1}. ^1H Nmr δ 1.0-1.8 (m, 8H), 2.10 (m, 1H), 2.4-2.6 (m, 4H), 3.1-3.4 (m, 4H), 4.80 (d, 1H,J = 10.8 Hz), 6.60 (s, 1H, NH), 7.0-7.4 (m, 10H). ^{13}C Nmr δ 180.0 (s), 142.8 (s), 139.3 (s), 131.5 (d), 129.4 (d), 128.6 (d), 128.4 (d), 128.8 (d), 128.3 (d), 127.8 (d), 126.9 (d), 81.2 (s), 67.4 (t), 56.4 (d), 44.2 (broad), 40.5 (d), 30.7 (t), 22.4 (t), 21.8 (t), 18.9 (t) ppm. Ms *m/z* 407 (M^+). Anal. Calcd for $C_{24}H_{29}N_3OS$: C, 70.73; H, 7.17; N, 10.31. Found: C, 70.65; H, 7.18; N, 10.22.

4-(4-Methoxyphenyl)-8a-morpholino-1-phenyl-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2(1*H*)-thione (10c).
Ir (KBr) 3300 cm^{-1}. ^1H Nmr δ 1.1-1.8 (m, 8H), 2.20 (m, 1H), 2.6-2.8 (m, 4H), 3.3-3.5 (m, 4H), 3.90 (s, 3H), 4.80 (d, 1H, J = 11.0 Hz), 6.60 (s, 1H, NH), 6.9-7.5 (m, 9H). ^{13}C Nmr δ 180.1 (s), 159.6 (s), 143.0 (s), 131.7 (d), 131.1 (s), 129.5 (d), 128.5 (d), 128.2 (d), 128.0 (d), 114.1 (d), 81.5 (s), 67.6 (t), 56.0 (d), 55.1 (q), 44.3 (broad), 40.7 (d), 31.0 (t), 22.5 (t), 21.9 (t), 19.1 (t) ppm. Ms *m/z* 437 (M^+). Anal. Calcd for $C_{25}H_{31}N_3O_2S$: C, 68.62; H, 7.14; N, 9.60. Found: C, 68.59; H, 7.12; N, 9.73.

Preparation of 1,4-diphenyl-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (11a).
The compound (**11a**) was prepared by dehydration of its hydroxy precursor (**9a**) following the method given for the preparation of (**7-8**). Yield and mp is given in Table III.
Ir (KBr) 3200, 1670 cm^{-1}. ^1H Nmr δ 1.2-2.0 (m, 8H), 4.80 (s, 1H), 5.50 (s, 1H, NH), 7.2-7.5 (m, 10H). ^{13}C Nmr δ 153.5 (s), 143.0 (s), 137.9 (s), 130.5 (s), 129.8 (d), 128.7 (d), 128.6 (d), 127.9 (d), 127.6 (d), 126.8 (d), 108.7 (s), 60.1 (d), 26.7 (t), 25.9 (t), 22.4 (t), 21.7 (t) ppm. Ms *m/z* 304 (M^+). Anal. Calcd for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.89; H, 6.68; N, 9.32.

General Procedure for the Preparation of Compounds (12).
A mixture of aminoquinazoline (**10**) (2 mmol) and sulfuric acid (1 M, 5 ml) in tetrahydrofuran (25 ml) was stirred at room temperature for 4 h. The resulting mixture was diluted with water, extracted with methylene chloride and the organic layer dried over sodium sulfate. Evaporation of the solvent *in vacuo* gave a solid residue, which was dissolved in benzene (30 ml) containing a catalytic amount of *p*-toluenesulfonic acid. A Dean-Stark trap was attached to the flask and the mixture heated to reflux for 2h and then allowed to cool to room temperature. The resulting mixture was washed with a saturated solution of sodium bicarbonate, extracted with methylene chloride and dried over sodium sulfate. Evaporation of the solvent *in vacuo* gave compounds (**12**) as pure solid materials, which were recrystallized from hexane-chloroform. Reaction yields and mp are given in Table III.

1-Phenyl-4-(2-thienyl)-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-thione (12a).
Ir (KBr) 3280 cm^{-1}. ^1H Nmr δ 1.4-2.0 (m, 8H), 5.00 (s, 1H), 6.9-7.4 (m, 8H), 7.60 (s, 1H, NH). ^{13}C Nmr δ 176.4 (s), 145.9 (s), 140.6 (s), 130.7 (s), 128.1 (d), 128.0 (d), 126.8 (d), 125.6(d), 125.1 (d), 112.3 (s), 53.9 (d), 26.8 (t), 26.0 (t), 22.4 (t), 21.2 (t) ppm. Ms *m/z* 326 (M^+). Anal. Calcd for $C_{18}H_{18}N_2S_2$: C, 66.22; H, 5.56; N, 8.58. Found: C, 66.20; H, 5.48; N, 8.63.

1,4-Diphenyl-3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-thione (12b).
Ir (KBr) 3310 cm^{-1}. ^1H Nmr δ 1.4-1.9 (m, 8H), 4.90 (s, 1H), 6.90 (s, 1H, NH), 7.2-7.6 (m, 10H). ^{13}C Nmr δ 176.5 (s), 141.7 (s), 140.8 (s), 129.9 (s), 128.9 (d), 128.8 (d), 128.6 (d), 128.2 (d), 128.0 (d), 126.9 (d), 111.8 (s), 59.6 (d), 27.0 (t), 26.1 (t), 22.5 (t), 21.2 (t) ppm. Anal. Calcd for $C_{20}H_{20}N_2S$: C, 74.96; H, 6.29; N, 8.74. Found: C, 74.78; H, 6.40; N, 8.61.

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