Tetrahedron Vol. 48, No. 9, pp. 1643-1656, 1992
Printed in Great Britain

0040-4020/92 $3.00+.00
Pergamon Press plc

SYNTHESIS OF 5-PROPYNYLOXYCYCLOALKANEPYRIMIDINES AND THEIR SELECTIVITY AND REACTIVITY IN INTRAMOLECULAR DIELS-ALDER REACTIONS.

Werner A. W. Stolle, Jacqueline M. Veurink, Antonius T. M. Marcelis and Henk C. van der Plas*.

Laboratory of Organic Chemistry, Agricultural University Wageningen, Dreyenplein 8, 6703 HB Wageningen, The Netherlands.

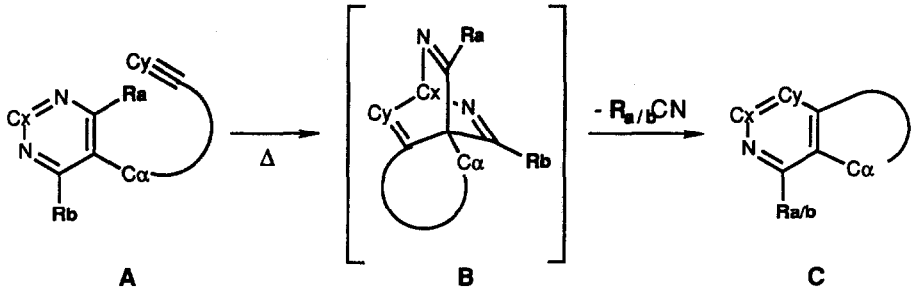
(*Received in UK* 20 *December* 1991)

Key Words: Synthesis; Intramolecular Diels-Alder reactions; Selectivity; Reavtivity

Abstract: The 5-propynyloxycycloalkane pyrimidines **IIIA** (**17** - **20**), **IIIB** (**21** - **24**), and **IIIC** (**25**, **26**) and the 5-(1-propynyloxyethyl)pyrimidines **IIID** (**27**, **28**), easily undergo intramolecular Diels-Alder reactions with inverse electron demand and a subsequent retro Diels-Alder reaction in which R_1CN (R_1 = H, Me) or X-CH_2CN (X = -CH_2, -CH_2CH_2, -H) is expelled. For the compounds **IIIA** and **IIIB** the extrusion of X-CH_2CN is favoured, yielding 3-(3-cyanopropyl)-1,3-dihydro-6-phenyl-R_1-R_2-furo[3,4-c]pyridines (**29** - **36**). The compounds **17** and **21** also yielded 4-phenyl-2*H*-6,7,8,8a-tetrahydro-furo[4,3,2-de]quinoline (**38**), by expulsion of HCN or MeCN respectively, which constitute a new class of heterocyclic compounds. For the compounds **IIIC** and **IIID** the extrusion of HCN is favoured as compared to the extrusion of X-CH_2CN. In case of **IIIC** this also gives a hitherto unknown class of heterocyclic ring systems namely 2*H*-1,6,7,8,9,9a-hexahydro-4-phenyl-9a-R_1-5-aza-1-oxo-benz[c,d]azulenes (**39**, **40**). The reactivity of the compounds **III** towards the cycloaddition appears to be strongly influenced by the nature of the substituent R_2 if R_1 = H. However, if R_1 = Me the effect of R_2 on the reactivity was very small. The ratio of the products **V** and **VI** appears to depend mainly on the nature of -X-.

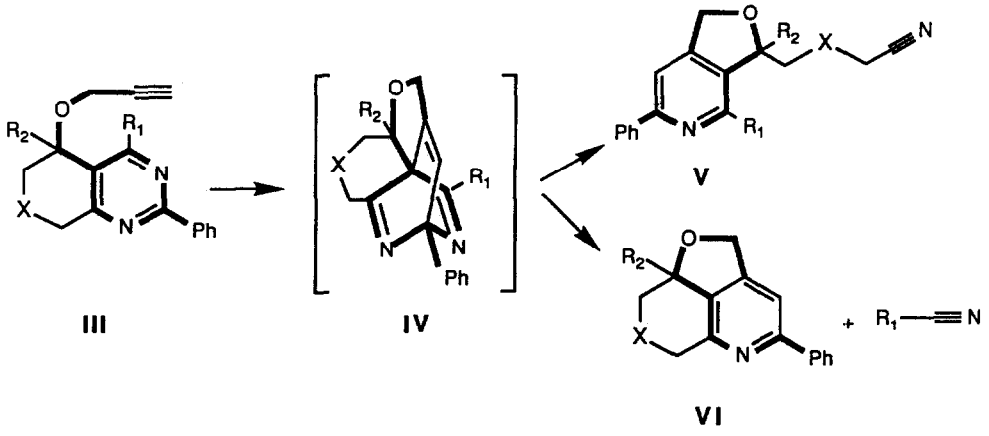
INTRODUCTION

During the last ten years, in our laboratory attention has been focussed on intermolecular cycloaddition reactions of electron-deficient azadienes like tetrazines and pyrimidines with electron-rich dienophiles[1]. Furthermore, we reported on the intramolecular Diels-Alder reactions of pyrazines[2] and pyrimidines[3] with a dienophile containing side chain to prepare bi-



Scheme 1: General reaction sequence for the ringtransformation of a 5-(ω–alkynyl)pyrimidine into an annelated pyridine.

and tricyclic annelated pyridines under relatively mild conditions[4]. In Scheme 1 the general reaction scheme for a ringtransformation of a 5-(ω-alkynyl)pyrimidine into an annelated pyridine derivative is depicted. It is assumed that the initial Diels-Alder reaction is the rate determining step because it was never possible to isolate or detect the intermediate (**B**). The final product (**C**) is formed in a retro Diels-Alder reaction in which expulsion of R_aCN or R_bCN yields an annelated pyridine.



IIIA: **17**: X = -CH_2-, R_1 = H, R_2 = H
18: X = -CH_2-, R_1 = H, R_2 = Me
19: X = -CH_2-, R_1 = H, R_2 = Et
20: X = -CH_2-, R_1 = H, R_2 = Ph
IIIB: **21**: X = -CH_2-, R_1 = Me, R_2 = H
22: X = -CH_2-, R_1 = Me, R_2 = Me
23: X = -CH_2-, R_1 = Me, R_2 = Et
24: X = -CH_2-, R_1 = Me, R_2 = Et
IIIC: **25**: X = -CH_2CH_2-, R_1 = H, R_2 = H
26: X = -CH_2CH_2-, R_1 = H, R_2 = Me
IIID: **27**: X = -H H-, R_1 = H, R_2 = H
28: X = -H H-, R_1 = H, R_2 = Me

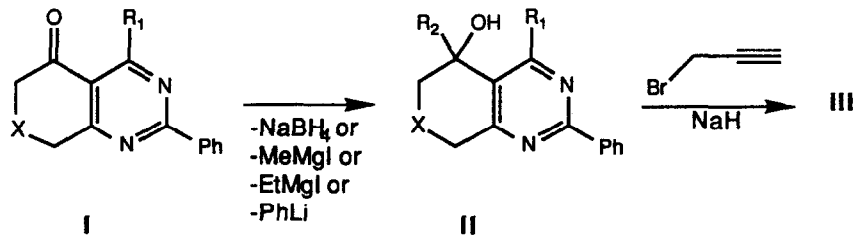
Scheme 2: Reaction scheme for the ringtransformation of the pyrimidines **III**.

In most reports on Diels-Alder reactions of pyrimidines symmetrically substituted pyrimidines are investigated, which contain two equal azadiene parts[5] (C=C($\mathbf{R_a}$)—N=C and C=N—C($\mathbf{R_b}$)=C, $\mathbf{R_a} = \mathbf{R_b}$). These symmetrically substituted pyrimidines ($\mathbf{R_a} = \mathbf{R_b}$) give rise to the formation of only one product by expulsion of $\mathbf{R_{a/b}}$CN. In this paper intramolecular Diels-Alder reactions of pyrimidines are studied, in which two different azadiene systems (C=C($\mathbf{R_a}$)—N=C and C=N—C($\mathbf{R_b}$)=C, $\mathbf{R_a} \neq \mathbf{R_b}$) are present. Therefore, in principle, two different products can be obtained by expulsion of $\mathbf{R_a}$CN or $\mathbf{R_b}$CN, respectively. To investigate the influence of substituents on the ringtransformation reactions of these systems we synthesized the pyrimidines **IIIA, IIIB, IIIC** and **IIID** (Scheme 2). By varying R_1, R_2 and the size of the cycloalkane ring it is rather easy to obtain different aza-diene systems which have in common a 2-phenyl-5-(1-propynyloxyethyl)pyrimidine part (bold formula Scheme 2). Furthermore, the occurence of ringtransformations of the compounds **IIIA-C** would, in principle, give rise to the formation of a new class of heterocyclic compounds (**VI**).

RESULTS AND DISCUSSION

Synthesis of the series IIIA - IIID

The 5-(1-propynyloxyethyl)pyrimidine derivatives **IIIA - D (17 - 28)** were synthesized as depicted in Scheme 3, starting from their keto precursors **I (1 - 4)**. 2-Phenyl-5,6,7,8-tetrahydroquinazolin-5-one (**1**) and 5-acetyl-4-methyl-2-phenyl-pyrimidine (**4**) were prepared from the appropriate 1,3-diones, *N,N*-dimethylformamide dimethyl acetal and benzamidine using the procedure given by Schenone *et al*[6]. Analogously, 2-phenyl-5*H*-6,7,8,9-tetrahydrocyclohepta[b]pyrimidin-5-one (**3**) was synthesized, using 1,3-cycloheptanedione as starting material.



I

II

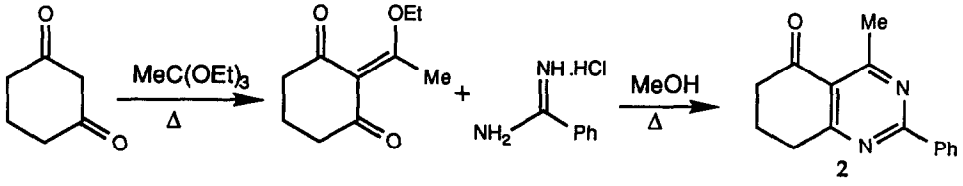
I: **1**: X = -CH_2-, R_1 = H **II:** **5**: X = -CH_2-, R_1 = H, R_2 = H **11**: X = -CH_2-, R_1 = Me, R_2 = Et
2: X = -CH_2-, R_1 = Me **6**: X = -CH_2-, R_1 = H, R_2 = Me **12**: X = -CH_2-, R_1 = Me, R_2 = Ph
3: X = -CH_2CH_2-, R_1 = H **7**: X = -CH_2-, R_1 = H, R_2 = Et **13**: X = -CH_2CH_2-, R_1 = H, R_2 = H
4: X = -H H-, R_1 = H **8**: X = -CH_2-, R_1 = H, R_2 = Ph **14**: X = -CH_2CH_2-, R_1 = H, R_2 = Me
9: X = -CH_2-, R_1 = Me, R_2 = H **15**: X = -H H-, R_1 = H, R_2 = H
10: X = -CH_2-, R_1 = Me, R_2 = Me **16**: X = -H H-, R_1 = H, R_2 = Me

Scheme 3: Reaction scheme for the synthesis of the 5-hydroxy compounds **II (5 - 16)** and the 5-propynyloxy compounds **III (17 - 28)**.

2-Phenyl-4-methyl-5,6,7,8-tetrahydroquinazolin-5-one (**2**) was prepared according to Scheme 4.

The 5-hydroxy compounds **5, 9, 13,** and **15** were obtained from the keto precursors **1, 2, 3** and **4** respectively, by reduction of the carbonyl group with $NaBH_4$. The 5-hydroxy-5-methyl-compounds **6, 10, 14,** and **16** and the 5-hydroxy-5-ethyl-compounds **7** and **11** were prepared from their keto precursors by reaction with an appropriate Grignard reagent (Scheme 3). The 5-phenyl compounds **8** and **12** were conveniently prepared by reaction of the carbonyl compounds **1** and **2** with PhLi.

The four different groups of propargyl ethers **17 - 20** (X = $-CH_2-$, R_1 = H, R = H, Me, Et, Ph; **IIIA**), **21 - 24** (X = $-CH_2-$, R_1 = Me, R_2 = H, Me, Et, Ph; **IIIB**), **25, 26** (X = $-CH_2CH_2-$, R_1 = H, R_2 = H, Me;**IIIC**) and **27, 28** (X = -H H-, R_1 = H, R_2 = H, Me; **IIID**) were easily obtained by treating the corresponding compounds **II** with sodium hydride and 2-3 equivalents of propargyl bromide in refluxing THF (Scheme 3).



Scheme 4: Reaction scheme for the synthesis of 4-methyl-2-phenyl-5,6,7,8-tetrahydro-quinazolin-5-one (**2**).

Intramolecular Diels-Alder reactions

To perform the intramolecular Diels-Alder reactions the compounds **III** were heated in nitrobenzene at 140 °C. Under these reaction conditions we interestingly observed the formation of the pyridines **V** and/or **VI** by the expulsion of X-CH_2-CN or R_1-CN respectively (Table I). Especially of interest is the formation of **38, 39** and **40,** since the ringsystems present in these compounds have not been described earlier.

To investigate the reactivity of the different types of compounds, the reaction rates were determined by careful integration of the signals in the ^{1}H-NMR spectra between 4.5 and 6.5 ppm, comparing the amounts of the starting compound **III** and the products **V** and **VI**, at appropriate time intervals (Table I).

One of the most remarkable features of the ringtransformations of the compounds **III** is the observed selectivity towards the formation of the products **V** and **VI**. In general the compounds **IIIA** (R_1 = H) and **IIIB** (R_1 = Me) show similar selectivity, although the methyl group at position R_2 causes a slightly electron richer diene system. Therefore, it is assumed that probably sterical or conformational properties of the molecules under study determine the selectivity of the ringtransformation. From Table I it can be seen that replacement of the hydrogen at R_2 in the series **IIIA** and **IIIB** by a larger group (Me, Et, or Ph) prevents the formation of the compounds

VI. However, the replacement of hydrogen at C5 by the larger methyl group in the series IIIC and IIID, has no influence on the formation of VI. The major factor determining the formation of V and VI appears to be the size of the cycloalkane ring present in the compounds III. The presence of a cyclohexane ring (IIIA, IIIB) gives rise to the formation of (mainly) the compounds V, whereas a cycloheptane ring (IIIC) or no ring at all (IIID), changes the reaction completely towards the formation of compounds VI. Combination of these observations leads to the assumption that the geometry of intermediate IV favours the extrusion of -X-CH_2CN when a cyclohexane ring is present or a large substituent R_2. A cycloheptane ring, or no ring at all, gives probably rise to a geometry of the intermediate which favours the extrusion of R_1CN. Furthermore, it appears that the effect of a ring enlargement on the selectivity is larger than that induced by a larger substituent at R_2.

Table I: Yields and reaction rates ($t_{1/2}$) at 140 °C for the ringtransformation of **III** into the annelated pyridines **V** and/or **VI** (for formulas and different substituents R_1, R_2 and X see Scheme 2).

Starting material III		Reaction Rate $t_{1/2}$[a, b]	Products V	yield[c]	VI	yield[c]
A:	17	5.08	29	47	38	33
	18	0.81	30	83		-[d]
	19	1.50	31	78		-[d]
	20	1.23	32	82		-[d]
B:	21	3.22	33	79	38	5
	22	3.08	34	89		-[d]
	23	4.65	35	85		-[d]
	24	1.51	36	93		-[d]
C:	25	7.95		-[d]	39	83
	26	0.71		-[d]	40	92
D:	27	17.45	37	-[d]	41	77[e]
	28	4.50		-[d]	42	81[e]

[a] $t_{1/2}$ in hours, [b] The reactions were assumed completed and worked up after 8 times $t_{1/2}$, [c] % Isolated yields. [d] No product detected. [e] Partially isolated as oxidized material[7].

As can be seen from Table I, the substituents R_1 and R_2 in the compounds III strongly influence the rate of the Diels-Alder reaction. In the series IIIA, IIIC, and IIID the reaction rate increases approximately 4 - 10 times upon replacement of the hydrogen at C5 by a larger group. However, the same replacement hardly influences the reaction rate for the compounds IIIB. Because R_2 is attached to the side-chain of the molecule, it seems very unlikely that the

observed rate enhancements are caused by a change in the energy levels of the diene and dienophile moieties of the molecules. It seems more likely that the enhanced reactivity of the compounds **18 - 20, 26** and **28** as compared to **17, 25** and **27** respectively, can be ascribed to changes in the conformational properties of the molecules. These kind of rate enhancements are commonly asscribed to the Thorpe-Ingold effect[8] (or "*gem*-dialkyl" effect[9]) or to a rotamer effect[10]. In both cases the introduction of a larger R_2 substituent allows the reactive sites of the molecules to be more conveniently positioned for an intramolecular Diels-Alder reaction[11]. The relative insensitivity of the reaction rate of the compounds **IIIB** towards the size of the substituent R_2 has to be ascribed to the presence of the methyl group at the position R_1. Apparently, the geometrical changes in the molecule, which should result in a better orientation of the diene and dienophile moieties to interact, are counteracted by the presence of the methyl group.

Presently, Molecular Mechanics and semi-empirical computations are performed to gain more insight into the observed selectivity and reactivity of the compounds **III**. The results of these investigations will be reported in a forth coming paper.

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H-NMR spectra were recorded on a Bruker AC200 spectrometer. Chemical shifts are determined in ppm downfield from tetramethylsilane. Mass spectral data were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console and a Hewlett Packard 5970B MSD. Column chromatography was performed on Merck silica gel 60 (70-230 mesh ASTM).

The syntheses of 2-phenyl-5,6,7,8-tetrahydroquinazolin-5-one (**1**) and 5-acetyl-4-methyl-2-phenylpyrimidine (**4**) are described by Schenone *et al*[6].

4-Methyl-2-phenyl-5,6,7,8-tetrahydroquinazolin-5-one (**2**).

A solution of 10 mmol of 1,3-cyclohexanedione in 10 ml of triethyl orthoacetate was refluxed for 0.15 h. The excess of the triethyl orthoacetate was evaporated under reduced pressure (1 mm Hg) and the crude oil was dissolved in dry methanol. After addition of 1.6 g of benzamidine.HCl and 1.4 g of K_2CO_3, the mixture was stirred under reflux for 3 h. The solvent was removed under reduced pressure and water was added. The aqueous layer was extracted three times with chloroform. The organic layers were collected, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Column chromatography (eluting with dichloromethane) of the residue afforded **2**. Yield: 34%; mp: 86-87 °C (chloroform/n-hexane 1:10). ^{1}H-NMR ($CDCl_3$) δ: 8.62-8.28 (m, 2H), 7.68-7.25 (3H), 3.18-2.88 (m, 2H), 2.81 (s, 3H), 2.60 (t, 2H), 2.31-1.88 (2H).

Anal. calcd.: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.76; H, 5.97; N, 11.78.

5*H*-2-phenyl-6,7,8,9-tetrahydrocyclohepta[b]pyrimidin-5-one (3)

This compound was synthesized according to the general procedure of Schenone *et al*[6], using 1,3-cycloheptanedione as a starting material. Yield: 78%; mp: 64-65 °C (n-hexane). ^{1}H-NMR ($CDCl_3$) δ: 9.00 (s, 1H), 8.62-8.30 (m, 2H), 7.60-7.28 (3H), 3.31-3.00 (m, 2H), 2.95-2.59 (m, 2H), 2.18-1.69 (4H).

Anal. calcd.: C, 75.60; H, 5.92; N, 11.75. Found: C, 75.65; H, 5.91; N, 11.74.

General procedure for the synthesis of the compounds 5, 9, 13 and 15.

To a stirred solution of 10 mmol of the appropriate keto compound I in 10 ml of absolute ethanol at room temperature, were added 50 mmol of $NaBH_4$. After 0.5 h the solvent was evaporated under reduced pressure and the residue was treated with 30 ml of wet diethyl ether, followed by 30 ml of water. The aqueous layer was extracted three times with diethyl ether. The organic layers were collected, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Column chromatography (eluting with diethyl ether) of the residue afforded the desired products.

5-Hydroxy-2-phenyl-5,6,7,8-tetrahydroquinazoline (5).

From **1**, according to the general procedure described above. Yield: 95%; mp: 89-90 °C (n-hexane). ^{1}H-NMR ($CDCl_3$) δ: 8.64 (s, 1H), 8.45-8.16 (m, 2H), 7.58-7.24 (3H), 4.88-4.58 (m, 1H), 3.85 (bd, OH), 3.00-2.62 (2H), 2.20-1.50 (4H). HRMS calcd for: $C_{14}H_{14}N_2O$: 226.1106. Found: 226.1106.

Anal. calcd.: C, 74.30; H, 6.23; N, 12.38. Found: C, 74.18; H, 6.29; N, 12.39.

5-Hydroxy-4-methyl-2-phenyl-5,6,7,8-tetrahydroquinazoline (9).

From **2**, according to the general procedure described above. Yield: 98%; colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 8.50-8.21 (m, 2H), 7.58-7.27 (3H), 5.02-4.80 (m, 1H), 3.00- 2.78 (2H), 2.60 (s, 3H), 2.08-1.79 (5H). HRMS calcd for: $C_{15}H_{16}N_2O$: 240.1263. Found: 240.1265.

5*H*-5-Hydroxy-2-phenyl-6,7,8,9-tetrahydrocyclohepta[b]pyrimidine (13).

From **3**, according to the general procedure described above. Yield: 99%; mp: 166-167 °C (dichloromethane). ^{1}H-NMR ($CDCl_3$) δ: 8.72 (s, 1H), 8.51-8.22 (m, 2H), 7.60-7.26 (3H), 5.0-4.75 (m, 1H), 3.66-2.58 (4H), 2.25-1.48 (4H). HRMS calcd for: $C_{15}H_{16}N_2O$: 240.1257. Found: 240.1257.

Anal. calcd.: C, 74.97; H, 6.71; N, 11.65. Found: C, 74.97; H, 6.68; N, 11.65.

6-Methyl-2-phenyl-5-(1-hydroxyethyl)pyrimidine (15).

From **4**, according to the general procedure described above. Yield: 99%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.69 (s, 1H), 8.36-8.29 (m, 2H), 7.47-7.40 (3H), 5.0 (q, J = 6.2 Hz, 1H), 2.65 (bs, OH), 2.48 (s, 3H), 1.46 (d, J = 6.2 Hz, 3H). HRMS calcd for: $C_{14}H_{16}N_2O$: 214.1104. Found: 214.1104.

General procedure for the synthesis of the compounds 6, 7, 10, 11, 14, and 16.

To a stirred suspension of 11 mmol of the appropriate Grignard reagent (MeMgI or EtMgI) in dry THF, was added dropwise a solution of 10 mmol of the 5-keto compound 1, 2 or 3, in 10 ml of dry THF. The reaction mixture was refluxed for 2 h. Water was added and the aqueous layer was extracted three times with 25 ml of diethyl ether. The organic layers were collected, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Column chromatography (eluting with n-hexane/ether 2:1) of the residue afforded the desired products.

5-Hydroxy-5-methyl-2-phenyl-5,6,7,8-tetrahydroquinazoline (6).

From 1 according to the general procedure described above. Yield: 86%; colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 8.80 (s, 1H), 8.48-8.21 (m, 2H), 7.58-7.30 (3H), 3.14 (bs, OH), 2.95-2.62 (2H), 2.09-1.52 (4H), 1.51 (s, 3H). HRMS calcd for: $C_{15}H_{16}N_2O$: 240.1260. Found: 240.1263.

4,5 Dimethyl-5-hydroxy-2-phenyl-5,6,7,8-tetrahydroquinazoline (10).

From 2 according to the general procedure described above. Yield: 69 %; colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 8.50-8.21 (m, 2H), 7.52-7.28 (3H), 3.05-2.68 (2H), 2.79 (s, 3H), 2.31-1.60 (5H), 1.53 (s, 3H). HRMS calcd for: $C_{14}H_{14}N_2O$: 226.1106. Found: 226.1106.

5-*H*-5-Hydroxy-5-methyl-2-phenyl-6,7,8,9-tetrahydrocyclohepta[b]pyrimidine (14).

From 3 according to the general procedure described above. Yield: 79%; mp: 152-153 °C (n-hexane/ether 2:1). ^{1}H-NMR ($CDCl_3$) δ: 8.94 (s, 1H), 8.43-8.38 (m, 2H), 7.48-7.41 (3H), 3.29-3.24 (2H), 3.12-3.05 (2H), 1.98-1.81 (4H), 1.62 (s, 3H). HRMS calcd for: $C_{16}H_{18}N_2O$: 254.1418. Found: 254.1418.

Anal. calcd. (+ 1 mol H_2O): C, 70.56; H, 7.40; H, 10.29. Found: C, 70.41; H, 7.39; H, 10.17.

6-Methyl-2-phenyl-5-(1-hydroxy-1-methylethyl)pyrimidine (16).

From 4, according to the general procedure described above. Yield: 99%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.64 (s, 1H), 8.36-8.30 (m, 2H), 7.43-7.39 (m, 3H), 2.75 (s, 3H), 2.56 (bs, OH), 1.60 (s, 6H). HRMS calcd for: $C_{14}H_{16}N_2O$: 228.1266. Found: 228.1262.

5-Ethyl-5-hydroxy-2-phenyl-5,6,7,8-tetrahydroquinazoline (7).

From 1 according to the general procedure described above. Yield: 50%; mp: 107-108°C (dichloromethane). ^{1}H-NMR ($CDCl_3$) δ: 8.80 (s, 1H), 8.58-8.21 (m, 2H), 7.60-7.24 (3H), 3.08-2.65 (2H), 2.38 (bs, OH), 2.20-1.51 (6H), 0.90 (t, J = 7.4 Hz, 3H). HRMS calcd for: $C_{16}H_{18}N_2O$: 254.1422. Found: 254.1419.

Anal. calcd.: C, 75.55; H, 7.13; N, 11.01. Found: C, 75.59; H, 7.34, N, 10.74.

5-Ethyl-5-hydroxy-4-methyl-2-phenyl-5,6,7,8-tetrahydroquinazoline (11).
From 2 according to the general procedure described above. Yield: 69%; colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 8.60-8.21 (m, 2H), 7.61-7.28 (3H), 3.06-2.68 (2H), 2.78 (s, 3H), 2.33-1.50 (7H), 0.86 (t, J = 7.5 Hz, 3H). HRMS calcd for: $C_{17}H_{20}N_2O$: 268.1575. Found: 268.1575.

General procedure for the synthesis of the compounds 8 and 12.
To a stirred solution of 10 mmol of the appropriate 5-keto compound I in 15 ml of dry THF at -10 °C, was added dropwise 2.2 ml of a 2M solution of PhLi in hexane/ether. The reaction mixture was allowed to warm up to room temperature in about 0.5 h and additionally refluxed for 1 hour. Water was added carefully and the aqueous layer was extracted three times with 25 ml of diethyl ether. The organic layers were collected, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Column chromatography (eluting with chloroform/ether 10:1) of the residue afforded the desired products.

2,5-Diphenyl-5-hydroxy-5,6,7,8-tetrahydroquinazoline (8).
From 1 according to the general procedure described above. Yield: 80%; mp: 155-156 °C (chloroform/n-hexane). ^{1}H-NMR ($CDCl_3$) δ: 8.60-8.13 (3H), 7.68-7.30 (3H), 7.29 (s, 5H), 3.12-2.82 (2H), 2.25-1.71 (5H), 1.40-1.04 (2H).
Anal. calcd.: C, 77.14; H, 6.00, N, 9.26. Found: C, 76.86; H, 5.86; N, 8.99.

2,5-Diphenyl-5-hydroxy-4-methyl-5,6,7,8-tetrahydroquinazoline (12).
From 2 according to the general procedure described above. Yield: 93%; colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 8.58-8.20 (m, 2H), 7.60-7.31 (3H), 7.30 (s, 5H), 3.18-2.90 (2H), 2.54 (bs, OH), 2.32-1.72 (4H), 2.21 (s, 3H). HRMS calcd for: $C_{21}H_{20}N_2O$: 316.1575. Found: 316.1575.

General procedure for the synthesis of the compounds IIIA, IIIB, IIIC and IIID.
To a stirred suspension of sodium hydride (11 mmol, 80% oil dispersion) in dry THF (10 ml) at room temperature was added 10 mmol of the appropriate 5-hydroxy compound II. After the initial effervescence had subsided, 2-3 equivalents of propargyl bromide were added in one portion. Subsequently, the reaction mixture was refluxed for 24 h. The solvent was evaporated under reduced pressure and the residue was treated with 30 ml of wet diethyl ether, followed by 30 ml of water. The aqueous layer was extracted three times with 25 ml of diethyl ether. The organic layers were collected, dried ($MgSO_4$) and the solvent was evaporated under reduced pressure. Column chromatography (eluting with diethyl ether) of the residue afforded the desired products.

2-Phenyl-5-propynyloxy-5,6,7,8-tetrahydroquinazoline (17).
From 5, according to the general procedure described above. Yield: 77%; colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 8.74 (s, 1H), 8.55-8.29 (m, 2H), 7.54-7.32 (3H), 4.82-4.45 (m, 1H), 4.25 (d, J = 2.5 Hz, 2H),

3.06-2.71 (2H), 2.50 (t, J = 2.4, 1H), 2.22-1.62 (5H). HRMS calcd for: $C_{17}H_{16}N_2O$: 264.1263. Found: 264.1265.

4-Methyl-2-phenyl-5-propynyloxy-5,6,7,8-tetrahydroquinazoline (21).
From **9**, according to the general procedure described above. Yield: 89%; mp: 59-60 °C. ^{1}H-NMR ($CDCl_3$) δ: 8.50-8.32 (m, 2H), 7.56-7.21 (3H), 5.84-5.68 (m, 1H), 1.24 (d, J = 3.0 Hz, 2H), 3.15-2.78 (2H), 2.60 (s, 3H), 2.44 (t, J = 2.4 Hz, 1H), 2.28-1.62 (4H).
Anal. calcd.: C, 77.66; H, 6.51; N, 10.06. Found: C, 77.42; H, 6.51; N, 9.95.

5-*H*-2-Phenyl-5-propynyloxy-6,7,8,9-tetrahydrocyclohepta[b]pyrimidine (25).
From **13**, according to the general procedure described above. Yield: 53%; mp: 80-81 °C (dichloromethane). ^{1}H-NMR ($CDCl_3$) δ: 8.58 (s, 1H), 8.49-8.39 (m, 2H), 7.50-7.38 (3H), 4.71 (d, J = 4.5 Hz, 1H), 4.21 (dd, J_1 = 16.0 Hz, J_2 = 2.4 Hz, 1H), 3.99 (dd, J_1 = 16.0 Hz, J_2 = 2.4 Hz, 1H), 3.14-2.88 (2H), 2.42 (t, J = 2.4 Hz), 2.19-1.48 (6H). HRMS calcd for: $C_{18}H_{18}N_2O$: (M-HCN) 251.1310. Found: 251.1310.
Anal. calcd.: C, 77.66; N, 10.06; H, 6.51. Found: C, 77.07; N, 9.58; H, 6.78.

6-Methyl-2-phenyl-5-(1-propynyloxyethyl)pyrimidine (27).
From **15**, according to the general procedure described above. Yield: 87%; oil. ^{1}H-NMR ($CDCl_3$) δ:8.69 (s, 1H), 8.45-8.39 (m, 2H), 7.46-7.40 (3H), 4.93 (q, J = 3.0 Hz, 1H), 4.18 (dd, J_1 = 18.0 Hz, J_2 = 3.2 Hz), 3.95 (dd, J_1 = 18.0 Hz, J_2 = 3.2 Hz), 2.59 (s, 3H), 2.42 (t, J = 2.4 Hz), 1.50 (d, J = 3.0 Hz). HRMS calcd for:

5-Methyl-2-phenyl-5-propynyloxy-5,6,7,8-tetrahydroquinazoline (18).
From **6**, according to the general procedure described above. Yield: 69%; colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 8.84 (s, 1H), 8.52-8.30 (m, 2H), 8.60-8.29 (3H), 3.95 (d, J = 2.4 Hz, 2H), 2.91 (m, 2H), 2.38 (t, J = 2.4 Hz), 2.36-1.67 (4H), 1.56 (s, 3H). HRMS calcd for: $C_{18}H_{18}N_2O$: 278.1419. Found: 278.1418.

4,5-Dimethyl-2-phenyl-5-propynyloxy-5,6,7,8-tetrahydroquinazoline (22).
From **10**, according to the general procedure described above. Yield: 82%; mp: 85-86 °C (n-hexane). ^{1}H-NMR ($CDCl_3$) δ: 8.58-8.24 (m, 2H), 7.58-7.32 (3H), 4.08 (dd, J_1 = 15.0 Hz, J_2 = 3.0 Hz, 1H), 3.86 (dd, J_1 = 15.0 Hz, J_2 = 3.0 Hz, 1H), 3.08-2.71 (2H), 2.79 (s, 3H), 2.40 (t, J = 2.4 Hz, 1H), 2.28-1.72 (4H), 1.64 (s, 3H). HRMS calcd for: $C_{16}H_{15}N_2O$: 254.1416. Found: 254.1419.

5-*H*-5-Methyl-2-phenyl-5-propynyloxy-6,7,8,9-tetrahydrocyclohepta[b]pyrimidine (26).
From **14**, according to the general procedure described above. Yield: 21 %; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.62 (s, 1H), 8.50-8.31 (m, 2H), 7.53-7.38 (3H), 3.98 (dd, J_1 = 15.2 Hz, J_2 = 2.4 Hz, 1H), 3.79 (dd, J_1 = 15.2 Hz, J_2 = 2.4 Hz, 1H), 3.42 (m, 2H), 3.08-2.90 (2H), 2.34 (t, J = 2.4 Hz, 1H), 2.80-1.42 (4H), 1.84 (s, 3H). HRMS calcd for: $C_{19}H_{20}N_2O$: (M - HCN) 265.1472. Found: 265.1472.

6-Methyl-2-phenyl-5-(1-methyl-1-propynyloxyethyl)pyrimidine (28).
From **16**, according to the general procedure described above. Yield: 40%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.58 (s, 1H), 8.44-8.38 (m, 2H), 7.49-7.40 (3H), 3.84 (d, J = 2.4 Hz, 2H), 2.84 (s, 3H), 2.37 (t, J = 2.4 Hz, 1H), 1.66 (s, 6H). HRMS calcd for: $C_{17}H_{18}N_2O$: 266.1415. Found: 266.1419.

5-Ethyl-2-phenyl-5-propynyloxy-5,6,7,8-tetrahydroquinazoline (19).
From **7**, according to the general procedure described above. Yield: 68%; colorless oil. ^{1}H-NMR ($CDCl_3$) δ: 8.80 (s, 1H), 8.58-8.22 (m, 2H), 7.64-7.26 (3H), 3.95 (d, J = 4.0 Hz, 2H), 3.14-2.70 (2H), 2.40 (t, J = 3.0 Hz, 1H), 2.25-1.64 (6H), 0.95 (t, J = 6.0 Hz, 3H). HRMS calcd for: $C_{19}H_{20}N_2O$: 292.1576. Found: 292.1571.

5-Ethyl-4-methyl-2-phenyl-5-propynyloxy-5,6,7,8-tetrahydroquinazoline (23).
From **11**, according to the general procedure described above. Yield: 81%; mp: 86-87 °C (n-hexane/chloroform). ^{1}H-NMR ($CDCl_3$) δ: 8.60-8.29 (m, 2H), 7.61-7.30 (3H), 4.08 (dd, J_1 = 15.2 Hz, J_2 = 3.0 Hz, 1H), 3.79 (dd, J_1 = 15.2 Hz, J_2 = 3.0 Hz, 1H), 3.08-2.78 (2H), 2.80 (s, 3H), 2.35 (t, 2.4 Hz, 1H), 2.28-1.78 (6H), 0.91 (t, J = 9.0 Hz, 3H).
Anal. calcd.: C, 78.39; N, 9.14; H, 7.23. Found: C, 78.53; N, 9.02;, H, 7.47.

2,5-Diphenyl-5-propynyloxy-5,6,7,8-tetrahydroquinazoline (20).
From **8**, according to the general procedure described above. Yield: 88%; colorless oil.
^{1}H-NMR ($CDCl_3$) δ: 8.58 (s, 1H), 8.49-839 (m, 2H), 7.50-7.38 (3H), 4.71 (d, J = 4.5 Hz, 1H), 4.14 (dd, J_1 = 15.0 Hz, J_2 = 2.4 Hz, 1H), 4.14 (dd, J_1 = 15.0 Hz, J_2 = 2.4 Hz, 1H), 3.41-2.88 (2H), 2.42 (t, J = 2.4 Hz, 1H), 2.39-1.48 (6H). HRMS calcd for: $C_{23}H_{20}N_2O$: 340.1566. Found: 340.1566.

2,5-Diphenyl-4-methyl-5-propynyloxy-5,6,7,8-tetrahydroquinazoline (24).
From **12**, according to the general procedure described above. Yield: 72%; mp: 160-161 °C (dichloromethane). ^{1}H-NMR ($CDCl_3$) δ: 8.78-8.33 (m, 2H), 7.60- 7.29 (3H), 7.28 (s, 5H), 4.17 (dd, J_1 = 15.0 Hz, J_2 = 2.4 Hz, 1H), 3.85 (dd, J_1 = 15.0 Hz, J_2 = 2.4 Hz, 1H), 3.19-2.83 (2H), 2.36 (t, J = 2.4 Hz, 1H), 2.28 (s, 3H), 2.18-1.30 (4H).
Anal. calcd.: C, 79.70; H, 6.36; N, 7.75. Found: C, 79.87; H, 6.19; N, 7.49.

General procedure for the conversion of the compounds III into V and/or VI.
1.0 mMol of the appropriate compound **III** was dissolved in 1.0 ml of nitrobenzene. The reaction mixture was heated at 140 °C. ^{1}H-NMR spectra were taken every hour to monitor the proceeding of the conversion of **III** into **V** and/or **VI**. After disappearence of the signal of compound **III**, the reaction mixture was allowed to cool to room temperature. Column chromatography, first eluting with dichloromethane, followed by diethyl ether afforded the reaction product(s).

3-(3-Cyanopropyl)-1,3-dihydro-6-phenylfuro[3,4-c]pyridine (29).
From **17**, according to the general procedure described above. Yield: 47%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.50 (s, 1H), 8.18-7.81 (m, 2H), 7.58-7.24 (4H), 5.50-5.16 (m, 1H), 5.10 (bs, 2H), 2.63-2.28 (2H), 2.15-1.61 (4H). HRMS calcd for: $C_{17}H_{16}N_2O$: 264.1263. Found: 264.1263

3-(3-Cyanopropyl)-1,3-dihydro-3-methyl-6-phenylfuro[3,4-c]pyridine (30).
From **18**, according to the general procedure described above. Yield: 83%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.42 (s, 1H), 8.14-7.80 (m, 2H), 7.67-7.24 (4H), 5.08 (bs, 2H), 2.45-1.09 (6H), 1.50 (s, 3H). HRMS calcd for: $C_{18}H_{18}N_2O$: 278.1419. Found: 278.1414.

3-(3-Cyanopropyl)-1,3-dihydro-3-ethyl-6-phenylfuro[3,4-c]pyridine (31).
From **19**, according to the general procedure described above. Yield: 78%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.42 (s, 1H), 8.16-7.90 (m, 2H), 7.58 (s, 1H), 7.52-7.38 (3H), 5.11 (bs, 2H), 2.32 (t, J = 4.0 Hz, 2H), 2.15-1.34 (6H), 0.81 (t, J = 4.0 Hz, 3H). HRMS calcd for: $C_{19}H_{20}N_2O$: 292.1576. Found: 292.1576.

3-(3-Cyanopropyl)-1,3-dihydro-3,6-diphenylfuro[3,4-c]pyridine (32).
From **20**, according to the general procedure described above. Yield: 82%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.71 (s, 1H), 8.10-7.83 (m, 2H), 7.58-7.17 (9H), 5.18 (bs, 2H), 2.52-2.11 (4H), 1.84-1.40 (2H). HRMS calcd for: $C_{23}H_{20}N_2O$: (M - C_4H_6N) 272.1075. Found: 272.1080.

3-(3-Cyanopropyl)-1,3-dihydro-4-methyl-6-phenylfuro[3,4-c]pyridine (33).
From **21**, according to the general procedure described above. Yield: 55%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.10-7.79 (m, 2H), 7.58-7.26 (4H), 5.42-5.18 (m, 1H), 5.05 (bs, 2H), 2.50 (s, 3H), 2.48-2.21 (2H), 2.14-1.51 (4H). HRMS calcd for: $C_{18}H_{18}N_2O$: 278.1419. Found: 278.1415.

3-(3-Cyanopropyl)-1,3-dihydro-3,4-dimethyl-6-phenylfuro[3,4-c]pyridine (34).
From **22**, according to the general procedure described above. Yield: 89%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.21-7.87 (m, 2H), 7.68-7.24 (4H), 5.10 (bs, 2H), 1.62 (s, 3H), 2.50-1.14 (6H), 1.59 (s, 3H). HRMS calcd for: $C_{19}H_{20}N_2O$: 292.1576. Found: 292.1578.

3-(3-Cyanopropyl)-1,3-dihydro-3-ethyl-4-methyl-6-phenylfuro[3,4-c]pyridine (35).
From **23**, according to the general procedure described above. Yield: 85%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.38-8.12 (m, 2H), 7.93-7.58 (4H), 5.31 (bs, 2H), 2.82 (s, 3H), 2.70-1.39 (8H), 1.00 (t, J = 9.0 Hz, 3H). HRMS calcd for: $C_{20}H_{22}N_2O$: (M - C_2H_5) 277.1341. Found: 277.1336.

3-(3-Cyanopropyl)-1,3-dihydro-3,6 diphenyl-4-methylfuro[3,4-c]pyridine (36).
From **23**, according to the general procedure described above. Yield: 93%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.14-7.88 (m, 2H), 7.60-7.17 (9H), 5.11 (bs, 2H), 2.67-2.21 (2H), 2.45 (s, 3H), 2.08-1.21 (4H). HRMS calcd for: $C_{24}H_{22}N_2O$: (M - C_6H_5) 277.1341. Found: 277.1339.

2-*H*-4-Phenyl-6,7,8,8a-tetrahydrofuro[4,3,2-de]quinoline (38).
From **17** and **21** , according to the general procedure described above. Yield: 33% (from **17**), 5% (from **21**); mp: 93-94 °C (dichloromethane). ^{1}H-NMR ($CDCl_3$) δ: 8.18-7.79 (m, 2H), 7.64-7.30 (3H), 7.38 (s, 1H), 5.18- 4.74 (3H), 3.30-1.05 (6H). HRMS calcd for: $C_{16}H_{15}NO$: 271.1151. Found: 271.1154. Anal. calcd.: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.68; H, 6.36; N, 5.74.

2-*H*-1,6,7,8,9,9a-hexahydro-4-phenyl-1-oxo-5-azabenz[c,d]azulene (39).
From **25** , according to the general procedure described above. Yield: 83%; mp: 92-93 °C (dichloromethane). ^{1}H-NMR ($CDCl_3$) δ: 7.97-7.92 (m, 2H), 7.48-7.32 (4H), 5.31- 4.99 (3H), 3.29-2.81 (2H), 2.33-1.39 (6H). HRMS calcd for: $C_{17}H_{17}NO$: 251.1304. Found: 251.1304.
Anal. calcd.: C, 81.24; H, 6.81; N, 5.57. Found: C, 81.03; H, 6.95; N, 5.47.

2-*H*-1,6,7,8,9,9a-hexahydro-9a-methyl-1-oxo-4-phenyl-5-azabenz[c,d]azulene (40).
From **26** , according to the general procedure described above. Yield: 92%; oil. ^{1}H-NMR ($CDCl_3$) δ: 8.02-9.92 (m, 2H), 7.55-7.31 (4H), 5.00 (bs, 2H), 3.29-1.95 (2H), 2.18-1.64 (6H), 1.48 (s, 3H). HRMS calcd for: $C_{18}H_{19}NO$: 265.1467. Found: 265.1471.

1,3-dihydro-3,4-dimethyl-6-phenylfuro[3,4-c]pyridine (41).
From **27**, according to the general procedure described above. Yield: 65%; oil. ^{1}H-NMR ($CDCl_3$) δ: 7.96-7.90 (m, 2H), 7.47-7.36 (4H), 5.50-5.38 (m, 1H), 5.16-4.96) (m, 2H), 2.54 (s, 3H), 1.52 (d, J = 12 Hz, 3H). HRMS calcd for: $C_{15}H_{15}NO$: 225.1152. Found: 225.1153.

1,3-dihydro-3,3,4-trimethyl-6-phenylfuro[3,4-c]pyridine (42).
From **28**, according to the general procedure described above. Yield: 78%; oil. ^{1}H-NMR ($CDCl_3$) δ: 7.96-7.90 (m, 2H), 7.45-7.36 (4H), 5.04 (s, 2H), 2.62 (s, 3H), 1.59 (s, 6H). HRMS calcd for: $C_{16}H_{17}NO$: 239.1311. Found: 239.1310.

ACKNOWLEDGEMENTS

The present investigations have been carried out under the auspices of the Netherlands Foundation for Chemical Research (SON), with financial aid from the Netherlands Organization for Scientific Research (NWO). Furthermore, we are indebted to Mr. C. Teunis for recording the mass spectra, Mr. A. van Veldhuizen for recording the NMR spectra and Mr. M. van Dijk for the analytical data.

REFERENCES AND NOTES

1 a. V.N. Charushin and H.C. van der Plas, *Tetrahedron Lett.*, **1982**, *23*, 3965. b. A.T.M. Marcelis and H.C. van der Plas, *Heterocycles*, **1985**, *23*, 683. c. A.T.M. Marcelis and H.C. van

der Plas, *J. Org. Chem.*, **1986**, *51*, 67. d. A.T.M. Marcelis and H.C. van der Plas, *J. Heterocyclic Chem.*, **1987**, *24*, 545. e. A.T.M. Marcelis and H.C. van der Plas, *Tetrahedron*, **1989**, *45*, 2693.

2 a. D.A. de Bie, G. Geurtsen and H.C. van der Plas, *J. Org. Chem.*, **1986**, *51*, 67. b. D.A. de Bie, A. Ostrowicz, G. Geurtsen and H.C. van der Plas, *Tetrahedron*, **1988**, *44*, 2977. c. B. Geurtsen, D.A. de Bie and H.C. van der Plas, *Tetrahedron*, **1989**, *45*, 6519. d. N. Haider and H.C. van der Plas, *Tetrahedron*, **1990**, *46*, 3641.

3 a. A.E. Frissen, A.T.M. Marcelis and H.C. van der Plas, *Tetrahedron*, **1989**, *45*, 803. b. A.E. Frissen, A.T.M. Marcelis, D.G. Buurman, C.A.M. Pollmann and H.C. van der Plas, *Tetrahedron*, **1989**, *45*, 5611. c. W.A.W. Stolle, A. Koetsier, A.T.M. Marcelis and H.C. van der Plas. *Tetrahedron*, **1989**, *45*, 6511. d. A.E. Frissen, A.T.M. Marcelis, W.C. Melger and H.C. van der Plas, *Tetrahedron*, **1989**, *45*, 6891. e. A.E. Frissen, G. Geurtsen, A.T.M. Marcelis and H.C. van der Plas, *Tetrahedron*, **1990**, *46*, 595. f. A.E. Frissen, A.T.M. Marcelis, G. Geurtsen, D.A. de Bie and H.C. van der Plas, *Tetrahedron*, **1989**, *45*, 5151.

4 Other recent publications describing intramolecular Diels-Alder reactions with inverse electron demand.
a. D.L. Boger, *Chem. Rev.*, **1986**, *86*, 781. b. D.L. Boger and R.S. Coleman, *J. Org. Chem.*, **1986**, *51*, 3250. c. D.L. Boger and R.S. Coleman, *J. Am. Chem. Soc.*, **1987**, *109*, 2717. d. L.S. Trifonov and A.S. Orahovats, *Helv. Chim. Acta*, **1987**, *70*, 1732. e. E.C. Taylor and J.E. Macor, *J. Org. Chem.*, **1987**, *52*, 4280. f. E.C. Taylor and J.L. Pont, *J. Org. Chem.*, **1987**, *52*, 4287. g. E.C. Taylor and J.E. Macor, *J. Org. Chem.*, **1989**, *54*, 4984. h. E.C. Taylor, J.E. Macor and L.G. French, *J. Org. Chem.*, **1991**, *56* 1807. i. A.T.M. Marcelis and H.C. van der Plas, *Trends in Heterocyclic Chem.*, **1991**, *1*, 111.

5 Intramolecular Diels-Alder reaction with assymmetrically substituted pyrimidines have been reported in the references 3b and 3f

6 a. P. Schenone, L. Mosti and G. Menozzi, *J. Heterocyclic Chem.*, **1982**, *19*, 1355. b. L. Mosti, G. Menozzi and P. Schenone, *J. Heterocyclic Chem.*, **1983**, *20*, 649.

7 The compounds **41** and **42** appeared to oxidize rapidly during their isolation yielding 1,3-dihydro-6-phenylfuro[3,4-c]pyridine-1(3*H*)-ones. Similar observations were reported in reference 3b.

8 a. Beesley, R.M.; Ingold, C.K.; Thorpe, J.F. *J. Chem. Soc.*, **1915**, *31*, 1080. b. Ingold, C.K. *J. Chem. Soc.*, **1921**, *37*, 841.

9 a. Allinger, N.L.; Zalkow, V. *J. Org. Chem.*, **1960**, *25*, 701. b. von R. Schleyer, P. *J. Am. Chem. Soc.*, **1961**, *83*, 1368.

10 a. M. Harfenist and E. Thom, *J. Org. Chem.*, **1972**, *17*, 841. b. D.D. Sternbach, D.M. Rosanna and K.B. Onan, *Tetrahedron Lett.*, **1985**, *26*, 593. c. R.K. Boeckman Jr. and S.S. Ko, *J. Am. Chem. Soc.*, **1982**, *104*, 1033.

11 a. W. A. W. Stolle, A. T. M. Marcelis and H. C. van der Plas, *Tetrahedron*, **1991**, *47*, 1753. b. W. A. W. Stolle, A. E. Frissen, A. T. M. Marcelis , H. C. van der Plas, Y. Wang, L. Häming and C. H. Stam, *J. Org. Chem.*, **1991**, *56*, 2411.