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SYNTHESIS OF 1,3-DIHYDROFURO[3,4-c]PYRIDINES AND 5,7-DIHYDROFURO[3,4-b]-PYRIDINES BY INTRAMOLECULAR DIELS-ALDER REACTIONS OF PYRIMIDINES. INVESTIGATION OF THE EFFECT OF STERIC INTERACTIONS ON THE REACTION RATE

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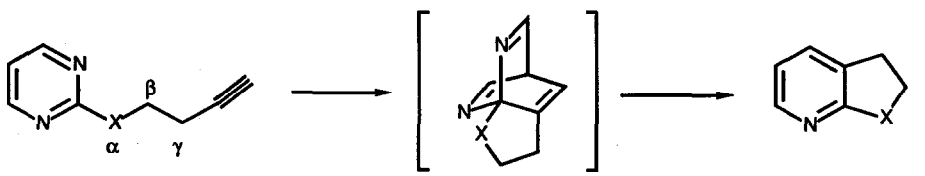
Abstract: Several 2- and 5-propynyloxymethylpyrimidines were synthesized and their intramolecular Diels-Alder reaction was studied. The products of the reaction were 5,7-dihydrofuro[3,4-b]pyridines and 1,3-dihydrofuro[3,4-c]pyridines, respectively. Introduction of one or two alkyl (aryl) groups at the α or γ position of the side-chain of the 5-propynyloxymethylpyrimidines results in an increased reaction rate. This phenomenon is discussed in terms of relative rotamer population. Substitution at the alkyne group or in the pyrimidine ring retards the rate of the cycloaddition reaction.

Recently, there has been a growing interest in inverse electron demand Diels-Alder reactions of six-membered heterocycles like tetrazines and triazines with appropriately substituted alkenes or alkynes[1]. Several less π-electron deficient diazines[1-3] and even pyridines[4,5] have also been shown to undergo this type of reaction, especially when the intramolecular version of this reaction is employed. In previous studies we observed that pyrimidines containing an -X-CH_2-CH_2-C≡CH (X = O, S, NAc, CH_2) group at position 2 (or 5) required reaction temperatures of 180 - 200°C to give these intramolecular Diels-Alder reactions[3]. Surprisingly, when X = $C(CN)_2$ the cycloadditions could be performed at much lower temperatures (about 130°C)[5]. This rate enhan-



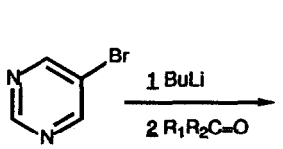
X = O, S, NAc, $C(CN)_2$, CH_2

cement is not uncommon in intramolecular reactions and can be ascribed to two factors[6]. First, the Thorpe-Ingold (scissoring) effect, caused by the two cyano groups, decreases the angle at Cα between diene and dienophile, thus enabling a closer approach between the diene and dienophile and thereby increasing the reaction rate[7]. Secondly, it has been recently recognized

that steric interactions by the cyano groups would relatively enhance the population of the reactive *syn* rotamers around Cα - Cβ, thereby favoring the cycloaddition reaction[8].

To investigate wether the cycloaddition can also occur when the heteroatom is not present in the α–, but in the β–position, we decided to synthesize several 2- and 5-propynyloxymethyl-pyrimidines, **4** and **7** respectively, and to study the course and rate of cycloaddition. To obtain further insight in the relative importance of sterically hindering substituents in the α–position of the side chain in **4** on the intramolecular Diels-Alder reactions of pyrimidines we prepared some 5-propynyloxymethylpyrimidines that contain in the α–position no substituents (**4a**), one methyl group (**4b**), one phenyl group (**4c**), two methyl groups (**4d**) or a cyclopentyl group (**4e**). In addition we studied the influence of two methyl groups in the γ–position of the propynyloxy-methyl side chain (**4f**) and of a *t*-butyl group in position 2 of the pyrimidine ring (**4g**) on the rate of cycloaddition. To gain insight in the influence of sterically hindering substituents at the al-

Scheme 1



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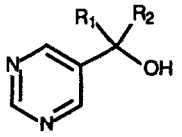
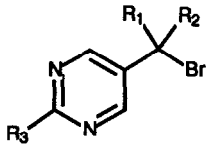
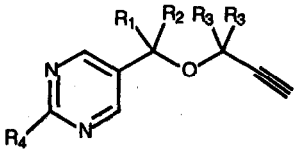


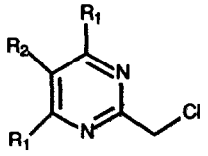
2a; $R_1 = H, R_2 = Ph$
b; $R_1 = R_2 = Me$
c; $R_1,R_2 = -(CH_2)_4-$



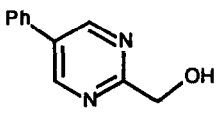
3a; $R_1 = R_2 = R_3 = H$
b; $R_1 = Me, R_2 = R_3 = H$
c; $R_1 = R_2 = H, R_3 = t\text{-Bu}$



4a; $R_1 = R_2 = R_3 = R_4 = H$
b; $R_1 = Me, R_2 = R_3 = R_4 = H$
c; $R_1 = Ph, R_2 = R_3 = R_4 = H$
d; $R_1 = R_2 = Me, R_3 = R_4 = H$
e; $R_1,R_2 = -(CH_2)_4-, R_3 = R_4 = H$
f; $R_1 = R_2 = R_4 = H, R_3 = Me$
g; $R_1 = R_2 = R_3 = H, R_4 = t\text{-Bu}$



5a; $R_1 = R_2 = H$
b; $R_1 = Me, R_2 = H$



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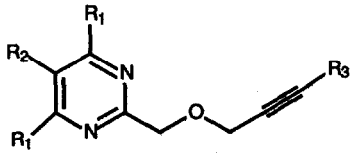


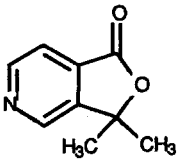
7a; $R_1 = R_2 = R_3 = H$
b; $R_1 = R_3 = H, R_2 = Ph$
c; $R_1 = Me, R_2 = R_3 = H$
d; $R_1 = Me, R_2 = H, R_3 = SiMe_3$

kyne group or in the pyrimidine ring we synthesized some 2-propynyloxymethylpyrimidines which contain no substituents (**7a**), a phenyl group at C-5 of the pyrimidine (**7b**), methyl substituents at C-4 and C-6 of the pyrimidine (**7c**) and a compound with a trimethylsilyl group at the alkyne and methyl groups at C-4 and C-6 of the pyrimidine (**7d**).

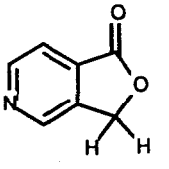
It was found that the 5-propynyloxymethylpyrimidines **4a-g** are easily accessable by the methods outlined in Scheme 1. Treatment of 5-bromopyrimidine **1** at -100°C with n-butyllithium resulting in halogen-lithium exchange[9] and subsequent reaction with benzaldehyde, acetone or cyclopentanone gives the 5-hydroxymethylpyrimidines **2a-c**. These compounds are converted into the propynyloxymethylpyrimidines **4c-e** by reaction with propargyl bromide. The compounds **4a,b,f,g** have been prepared by reaction of the sodium salt of the appropriate propargyl alcohol with 5-bromomethylpyrimidines **3a**[10] and **3b**[11], which have been described in the literature and with 5-bromomethyl-2-*t*-butylpyrimidine **3c**, which was synthesized from 5-bromo-2-*t*-butylpyrimidine[12]. The 2-propynyloxymethylpyrimidines **7a** and **7c** were prepared from the corresponding 2-chloromethylpyrimidines **5a**[13] and **5b**[14] by reaction with the sodium salt of prop-2-yn-1-ol; **7b** was conveniently prepared from 2-hydroxymethyl-5-phenylpyrimidine (**6**) and propargyl bromide. The trimethylsilylated **7d** was obtained in good yield from **7c** by reaction with n-butyllithium in THF at -70 °C followed by treatment with trimethylsilylchloride.

All propynyloxymethylpyrimidines **4** and **7** except **4g** underwent cycloaddition at 140 °C in nitrobenzene into the corresponding 1,3-dihydrofuro[3,4-c]pyridines **8a-f** and 5,7-dihydrofuro-[3,4-b]pyridines **9a-d** in good yields. **4g** reacted very slowly at 140°C and was reacted at 160°C to give **8g** (see Table). The structures of the cycloaddition products were established by their ^{1}H NMR spectra and confirmed by mass spectroscopy and/or elemental analyses. This new method to obtain 1,3-dihydrofuro[3,4-c]pyridines is of interest since they can easily be converted into analogs of pyridoxine (vitamin B_6)[15].

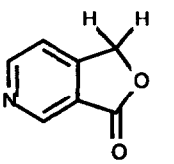
The 1,3-dihydrofuro[3,4-c]pyridines are readily oxidized when kept in contact with air. For example, **8d** appeared to be completely converted into 3,3-dimethylfuro[3,4-c]pyridin-1(3*H*)-one (**10a**) when kept for two months and 1,3-dihydrofuro[3,4-c]pyridine (**8a**) oxidized rapidly to a mixture of the known furo[3,4-c]pyridin-1(3H)-one (**10b**) and furo[3,4-c]pyridin-3(1*H*)-one (**10c**)[16].



10a



10b

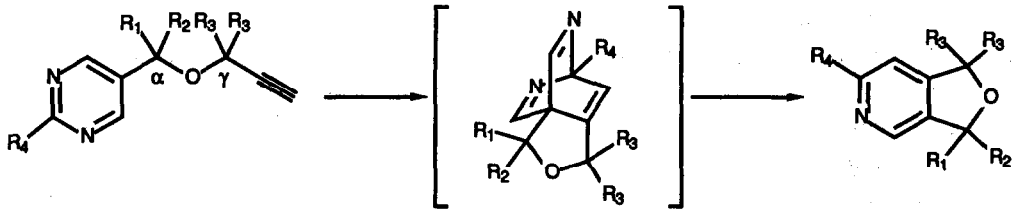


10c

The other compounds **8** also showed a tendency to oxidize rapidly, analogous to the behaviour of 1,3-dihydroisobenzofuran[17]. Therefore, these compounds **8** should be stored under nitrogen.

The rate of the cycloaddition reaction was monitored by ^{1}H NMR spectroscopy. A solution of 20 - 50 mg of the pyrimidine was dissolved in 0.5 ml of nitrobenzene, flushed with nitrogen, stoppered and heated at 140°C in an oil bath. The temperature was kept constant within 1°C and

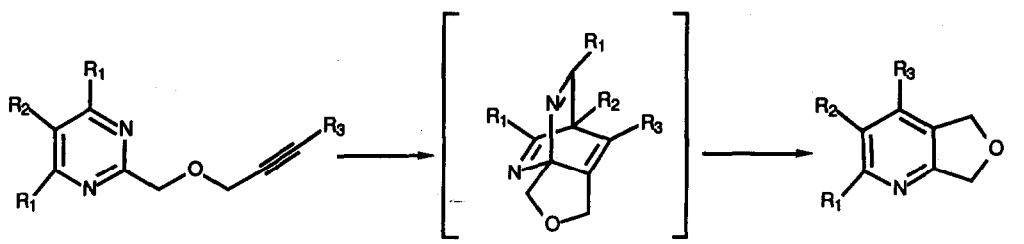
TABLE **Reaction rates, products and yields of the intramolecular Diels-Alder reaction of 4a-g and 7a-d in nitrobenzene at 140 ± 1°C.**



4 8

	R_1	R_2	R_3	R_4	rate constant x 10^3 (s^{-1})	$t_{1/2}$ (h)	product	yield (%)
4a	H	H	H	H	0.069	2.80	**8a**	90
4b	Me	H	H	H	0.128	1.50	**8b**	84
4c	Ph	H	H	H	0.108	1.75	**8c**	81
4d	Me	Me	H	H	0.667	0.28	**8d**	68
4e	-$(CH_2)_4$-		H	H	1.194	0.16	**8e**	81
4f	H	H	Me	H	0.231	0.83	**8f**	70
4g	H	H	H	*t*-Bu	a)	a)	**8g**	59

a) This compound was reacted at 160°C. Rate constant = 0.055 x 10^{-3} s^{-1}; $t_{1/2}$ = 3.4 h.



7 9

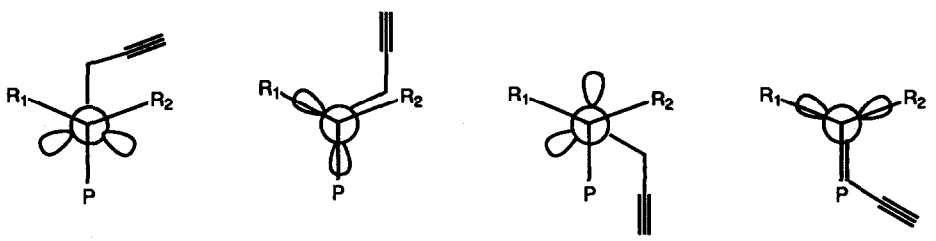
	R_1	R_2	R_3	rate constant x 10^3 (s^{-1})	$t_{1/2}$ (h)	product	yield (%)
7a	H	H	H	0.169	1.13	**9a**	63
7b	H	Ph	H	0.128	1.50	**9b**	87
7c	Me	H	H	0.139	1.39	**9c**	92
7d	Me	H	$SiMe_3$	0.081	2.40	**9d**	53

after several time intervals a spectrum was measured and the high-field signals were integrated. A plot of -ln C_t/C_0 against t revealed that the reaction obeys simple first order kinetics and thus

the reaction constant k and the half-life time ($t_{1/2}$) could be calculated. Addition of *p*-nitrotoluene as internal reference revealed that after heating the mixture for at least six half-life times ($t_{1/2}$) the signals of the product accounted for at least 90% of the starting material. Therefore, decomposition hardly occurs. In the spectra of the reaction mixture formed after partial reaction of the starting material an extra signal at $\delta = \pm 5$ ppm was observed, which disappeared after prolonged heating. In the reaction mixture obtained from the compounds **7c** and **7d** a larger signal appeared at ± 2 ppm accounting for about 3H as compared to product formed. These signals are ascribed to hydrogen cyanide or acetonitrile, respectively. No trace of a tricyclic intermediate is observed in the ^1H NMR spectra, indicating that the cycloreversion reaction to the pyridine compounds is fast and the rate determining step is the addition of the acetylene group to C-2 and C-5 of the pyrimidine.

From the rate of cycloaddition of compounds **4a-e** (see Table) it is clearly seen that the reaction rate increases when substituents are introduced at the α-position. The presence of one methyl or phenyl group only has a small enhancing effect on the reaction rate (± 1.8), but two geminal substituents increase the reaction rate significantly (± 10). This increase of reaction rate is satisfactorally explained by a relative increase of the population of the reactive *syn*-rotamers about the Cα - O bond (Scheme 2). In compound **4e** (R_1,R_2 = -$(CH_2)_4$-) the cyclopentyl group sterically hinders the unreactive *anti*-rotamers and consequently the highest reaction rate is found for this compound.

Scheme 2



anti-periplanar *anti*-clinal *syn*-clinal *syn*-periplanar

P = pyrimidine

For compound **4f**, which contains two methyl groups at the γ-position there is also a significant rate enhancement. Again, this can be explained by a more easily attainable reactive *syn*-rotamer about the O - Cγ bond, although the rate enhancing effect is smaller then for substituents on Cα. For compound **4g** a strong decrease of reaction rate as compared to **4a** is observed. Due to steric hindrance by the *t*-butyl group approach of the alkyne group to the pyrimidine ring will be hindered. This same effect is also found for the 2-propargyloxymethylpyrimidines **7b-d**, which all react slower than the unsubstituted **7a**. Introduction of substituents on the diene or on the dienophilic acetylene causes a decrease of the cycloaddition rate. Substituents on the ace-

tylene or on C-5 of the pyrimidine give more rate decrease than substituents on C-4 (C-6) which are not attached to reacting atoms.

It is interesting to note that 2-propynyloxymethylpyrimidine (**7a**) reacts much faster than 2-(pent-4-yn-1-yl)pyrimidine[5]. It is possible that repulsion between the lone pairs on the β-oxygen and on the pyrimidine nitrogen atoms favors a perpendicular conformation between the Cα - O group and the aromatic ring[18] in which the repulsion is minimized. The molecule must adopt such a conformation before cycloaddition can occur. This phenomenon also explains the higher reactivity of **7a** as compared to **4a**. It is possible that other factors that influence the rotational barrier about the aromatic-alkyl (C-2/5 - Cα) bond also have an effect on the observed reaction rates[19].

EXPERIMENTAL SECTION

Melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian EM 390 spectrometer. Chemical shifts are determined in ppm downfield from Me_4Si. Mass spectral data were obtained on a AEI MS 902 spectrometer equipped with a VG ZAB console. Column chromatography was performed with Merck silica gel 60 (70 - 230 mesh ASTM).

Synthesis of 5-hydroxymethylpyrimidines **2a-c**.
A solution of 5-bromopyrimidine **1** (4.0 g; 25 mmol) in a 1:1 mixture of dry THF and diethyl ether (60 ml) was cooled under a nitrogen atmosphere to -100 to -110°C. Under vigorous stirring a solution of n-butyllithium in hexane (16 ml; 1.6 M) was introduced while keeping the temperature below -100°C. After 0.25 h a solution of the appropriate carbonyl compound (35 mmol) in THF (10 ml) was added. The mixture was allowed to warm to room temperature. Then water (40 ml) was added and the mixture was extracted with ether (3 x 75 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated by evaporation of the solvent. The residue was purified by column chromatography using ether / ethyl acetate as eluent.
Phenyl(pyrimidin-5-yl)methanol (**2a**). Yield 80%; oil; ^{1}H NMR ($CDCl_3$) δ 8.88 (s, 1H, H-2), 8.62 (s, 2H, H-4 and H-6), 7.30 (s, 5H), 5.80 (s, 1H), 4.8 (br, 1H). HRMS Calcd. for $C_{11}H_{10}N_2O$ (M^+): 186.0793. Found: 186.0796.
Dimethyl(pyrimidin-5-yl)methanol (**2b**). Yield 55%; oil; ^{1}H NMR ($CDCl_3$) δ 9.06 (s, 1H, H-2), 8.85 (s, 2H, H-4 and H-6), 3.9 (br, 1H), 1.63 (s, 6H). HRMS Calcd. for $C_7H_{10}N_2O$ (M^+): 138.0793. Found: 138.0785.
1-Hydroxy-1-(pyrimidin-5-yl)cyclopentane (**2c**). Yield 33%; mp 77-78°C (hexane/toluene); ^{1}H NMR ($CDCl_3$) δ 9.00 (s, 1H, H-2), 8.82 (s, 2H, H-4 and H-6), 3.64 (s, 1H), 2.0 (br, 8H). HRMS Calcd. for $C_9H_{12}N_2O$ (M^+): 164.0950. Found: 164.0950.
Anal. Calcd. for $C_9H_{12}N_2O$ (M = 164.20): C, 65.82; H, 7.36; N, 17.06. Found: C, 65.91, H, 7.42; N, 17.14.

5-Bromomethyl-2-*t*-butylpyrimidine (**3c**).
2-*t*-Butyl-5-cyanopyrimidine. A mixture of 5-bromo-2-*t*-butylpyrimidine[12] (10.75 g; 50 mmol) and CuCN (5.4 g) in freshly distilled dry quinoline (35 ml) was refluxed for 2 h. After cooling the reaction mixture was distilled under vacuo. A solution of the destillate in ether was washed with a 1 N HCl solution. The organic layer was dried ($MgSO_4$) and concentrated by evaporation of the solvent and the residue was recrystallized from hexane to give 2-*t*-butyl-5-cyanopyrimidine. Yield: 75%; mp 82-84°C (hexanes); ^{1}H NMR ($CDCl_3$) δ 8.91 (s, 2H, H-4 and H-6), 1.39 (s, 9H); IR (KBr) 2225 cm^{-1} (C≡N stretch). HRMS Calcd. for $C_9H_{11}N_3$ (M^+): 161.0953. Found: 161.0952.
Anal. Calcd. for $C_9H_{11}N_3$ (M = 161.20): C, 67.05; H, 6.88; N, 26.07. Found: C, 67.01; H, 7.09; N, 26.46.
2-*t*-Butylpyrimidine-5-carboxylic acid. A solution of 2-*t*-butyl-5-cyanopyrimidine (5.5 g; 34 mmol) in a mixture of water (50 ml), sulfuric acid (50 ml) and acetic acid (50 ml) was refluxed for 1 h. After removal of the acetic acid by repeated coevaporation with water the mixture was diluted with water and continuously extracted with ether to give 2-*t*-butylpyrimidine-5-

carboxylic acid. Yield: 75%; mp 170-171°C (hexanes); ^{1}H NMR ($CDCl_3$) δ 9.30 (s, 2H, H-4 and H-6), 1.41 (s, 9H). HRMS Calcd. for $C_9H_{12}N_2O_2$ (M^+): 180.0899. Found: 180.0898.
Anal. Calcd. for $C_9H_{12}N_2O_2$ (M = 180.20): C, 59.98; H, 6.71; N, 15.55. Found: C, 60.09; H, 6.64; N, 15.49.
2-*t*-Butyl-5-hydroxymethylpyrimidine. A mixture of 2-*t*-butyl-5-pyrimidinecarboxylic acid (1.44 g; 8 mmol) and $LiAlH_4$ (570 mg) in dry THF (50 ml) was stirred for 6 h at room temperature under a nitrogen atmosphere. After hydrolysis with a few drops of ethyl acetate followed by a few drops of a 0.01 N H_2SO_4 solution, the mixture was filtered and the filtrate was concentrated. Water (20 ml) was added to the residue and the aqueous layer was extracted with chloroform (3 x 20 ml). After drying ($MgSO_4$) and concentration of the organic layer the residue was subjected to column chromatography using chloroform/methanol 19:1 as eluent. After a first fraction, which was identified as 2-*t*-butyl-5-pyrimidine carboxaldehyde a second fraction containing 2-*t*-butyl-5-hydroxymethyl-pyrimidine was isolated as a colourless oil. Yield 11%; ^{1}H NMR ($CDCl_3$) δ 8.62 (s, 2H, H-4 and H-6), 4.63 (s, 2H), 1.32 (s, 9H). HRMS Calcd. for $C_9H_{14}N_2O$ (M^+): 166.1106. Found: 166.1107.
A mixture of 2-*t*-butyl-5-hydroxymethylpyrimidine (150 mg; 0.9 mmol) and $POBr_3$ (1 ml) was heated at 120°C for 4h. After cooling the mixture was poured on ice and neutralized with K_2CO_3. Extraction with chloroform, drying ($MgSO_4$) of the organic layer and concentration gave 5-bromomethyl-2-*t*-butylpyrimidine (**3c**). Yield 95%; mp 31-32°C; ^{1}H NMR ($CDCl_3$) δ 8.75 (s, 2H, H-4 and H-6), 4.40 (s, 2H), 1.40 (s, 9H). HRMS Calcd. for $C_9H_{13}BrN_2$ (M^+): 228.0263. Found: 228.0271.

Synthesis of the 5-(2-propynyloxymethyl)pyrimidines **4a,b,f,g** from 5-bromomethylpyrimidines **3a-c**.
The bromide (1 mmol) was added to a solution of sodium propynolate (prepared by the addition of 1.5 mmol of 80% sodium hydride to 2 mmol of propynol in dry THF (15 ml)). The mixture was refluxed for 3 h. Water (30 ml) was added and the aqueous layer was extracted with ether (3 x 50 ml). The organic layers were combined, dried ($MgSO_4$) and concentrated by evaporation of the solvent. The residue was purified by column chromatography with ether as eluent.
5-(2-Propynyloxymethyl)pyrimidine (**4a**). This compound was prepared from the hydrobromide salt of **3a**[10] and sodium propynolate. Yield 34% (based on the pyrimidine hydrobromide salt, which was neutralized with one extra eq of sodium propynolate); mp 30-31°C (hexane at -20°C); ^{1}H NMR ($CDCl_3$) δ 9.20 (s, 1H, H-2), 8,78 (s, 2H, H-4 and H-6), 4.66 (s, 2H), 4.28 (d, J = 2.4 Hz, 2H), 2.61 (t, J = 2.4 Hz, 1H).
Anal. Calcd. for $C_8H_8N_2O$ (M = 148.16): C, 64.84; H, 5.44; N, 18.90. Found: C, 64.56; H, 5.47; N, 19.22.
5-(1-(2-Propynyloxy)ethyl)pyrimidine (**4b**). This compound was prepared from **3b** (synthesized from 5-ethylpyrimidine and N-bromosuccinimide without isolation of **3b**[11]) and sodium propynolate. Yield 44% (based on 5-ethylpyrimidine); mp 70-71°C (hexane); ^{1}H NMR ($CDCl_3$) δ 9.21 (s, 1H, H-2), 8.78 (s, 2H, H-4 and H-6), 4.80 (q, J = 7 Hz, 1H), 4.13 (m, 2H), 2.50 (t, J = 2.4 Hz, 1H), 1.55 (d, J = 7 Hz, 3H).
Anal. Calcd. for $C_9H_{10}N_2O$ (M = 162.19): C, 66.64; H, 6.21; N, 17.27. Found: C, 66.52; H, 6.29; N, 17.39.
5-(2-Methyl-3-butyn-2-yloxymethyl)pyrimidine (**4f**). This compound was prepared from the hydrobromide salt of **3a**[10] and the sodium salt of 1,1-dimethylpropynol. Yield 4% (based on the pyrimidine hydrobromide salt, which was neutralized with one extra equivalent of sodium 1,1-dimethylpropynolate); oil; ^{1}H NMR ($CDCl_3$) δ 9.16 (s, 1H, H-2), 8.72 (s, 2H, H-4 and H-6), 4.66 (s, 2H), 2.52 (s, 1H), 1.56 (s, 6H). HRMS Calcd. for $C_{10}H_{12}N_2O$ (M^+): 176.0950. Found: 176.0949.
2-*t*-Butyl-5-(2-propynyloxymethyl)pyrimidine (**4g**). This compound was prepared from **3c** and sodium propynolate. Yield 89%; oil; ^{1}H NMR ($CDCl_3$) δ 8.67 (s, H-4 and H-6, 2H), 4.57 (s, 2H), 4.22 (d, J = 2.7 Hz, 2H), 2.47 (t, J = 2.7 Hz, 1H), 1.39 (s, 9H). HRMS Calcd. for $C_{12}H_{16}N_2O$ (M^+): 204.1263. Found: 204.1260.

Synthesis of the 5-(2-propynyloxymethyl)pyrimidines **4c-e** from the 5-hydroxymethyl-pyrimidines **2a-c**.
The appropriate alcohol (1 mmol) was added to a suspension of 1.1 mmol of sodium hydride in THF (25 ml). The mixture was stirred until the evolution of hydrogen had ceased. Then propargyl bromide (2 mmol) was added and the mixture was refluxed for 3 h. Water (50 ml) was added and the mixture was extracted with ether (3 x 50 ml). The organic layers were dried ($MgSO_4$) and concentrated by evaporation of the solvent and the residue was purified by column chromatography using ether as eluent.

5-(Phenyl-2-propynyloxymethyl)pyrimidine (4c). This compound was prepared from 2a. Yield 60%; oil; ^{1}H NMR ($CDCl_3$) δ 9.13 (s, 1H, H-2), 8.71 (s, 2H, H-4 and H-6), 7.37 (s, 5H), 5.73 (s, 1H), 4.18 (m, 2H), 2.53 (t, J = 2.4 Hz, 1H). HRMS Calcd. for $C_{14}H_{12}N_2O$ (M^+): 224.0950. Found: 224.0940.
5-(1-Methyl-1-(2-propynyloxy)ethyl)pyrimidine (4d). This compound was prepared from 2b. Yield 45%; mp 48-49°C (hexane); ^{1}H NMR ($CDCl_3$) δ 9.12 (s, 1H, H-2), 8.80 (s, 2H, H-4 and H-6), 4.00 (d, J = 2.4 Hz, 2H), 2.48 (t, J = 2.4 Hz, 1H), 1.63 (s, 6H). HRMS Calcd. for $C_{10}H_{12}N_2O$ (M^+): 176.0950. Found: 176.0945.
Anal. Calcd. for $C_{10}H_{12}N_2O$ (M = 176.21): C, 68.15; H, 6.86; N, 15.89. Found: C, 68.27; H, 6.99; N, 15.99.
1-(2-Propynyloxy)-1-(pyrimidin-5-yl)cyclopentane (4e). This compound was prepared from 2c. Yield 32 %; oil; ^{1}H NMR ($CDCl_3$) δ 9.12 (s, 1H, H-2), 8.78 (s, 2H, H-4 and H-6), 3.82 (d, J = 2.4 Hz, 2H), 2.34 (t, J = 2.4 Hz, 1H), 2.5-1.7 (br, 8H). HRMS Calcd. for $C_{12}H_{14}N_2O$ (M^+): 202.1106. Found: 202.1108.

2-Hydroxymethyl-5-phenylpyrimidine (6). A 2 M methanolic solution of sodium methoxide (5.3 ml) was added dropwise at room temperature to a stirred mixture of hydroxyacetamidine hydrochloride[20] (500 mg) and 1-dimethylamino-3-dimethylimonio-2-phenyl-prop-1-ene tetrafluoroborate[21] (908 mg) in methanol (10 ml). The mixture was refluxed for 2 h, neutralized with acetic acid and concentrated. Water (25 ml) was added to the residue and the aqueous layer was extracted with ether (2 x 50 ml). After drying ($MgSO_4$) and concentration by evaporation of the solvent 2-hydroxymethyl-5-phenylpyrimidine (6) was obtained as pale yellow crystals. Yield 80%; mp 109 -111°C (hexanes/toluene); ^{1}H NMR ($CDCl_3$) δ 8.90 (s, H-4 and H-6, 2H), 7.50 (br, 5H), 4.92 (s, 2H).
Anal. Calcd. for $C_{11}H_{10}N_2O$ (M = 186.21): C, 70.95; H, 5.41; N, 15.05. Found: C, 70.87; H, 5.38; N, 15.09.

2-(2-Propynyloxymethyl)pyrimidine (7a). A solution of 2-chloromethylpyrimidine (5a)[13] (1 mmol) in THF (5 ml) was added to a solution of sodium propynolate (1.5 mmol) in THF (10 ml). The mixture was refluxed for 3h. After cooling, water (30 ml) was added and the mixture was extracted with ether (3 x 50 ml). The ethereal extracts were dried ($MgSO_4$) and concentrated by evaporation of the solvent. Column chromatography of the residue with ether as eluent gave 7a. Yield 51%; oil; ^{1}H NMR ($CDCl_3$) δ 8.75 (d, J = 5.0 Hz, 2H, H-4 and H-6), 7.22 (t, J = 5.0 Hz, 1H, H-5), 4.90 (s, 2H), 4.42 (d, J = 2.4 Hz, 2H), 2.46 (t, J = 2.4 Hz, 1H). HRMS Calcd. for $C_8H_7N_2O$ (M^+-1): 147.0556. Found: 147.0558.

5-Phenyl-2-(2-propynyloxymethyl)pyrimidine (7b). A solution of 2-hydroxymethyl-5-phenylpyrimidine (6) (150 mg) in THF (5 ml) was added to a stirred suspension of sodium hydride (27 mg; 80% suspension in oil) in dry THF (10 ml). After the initial effervescence had subsided propargyl bromide (1 ml) was added and the reaction mixture was refluxed for 3 h. After addition of water (25 ml) the aqueous layer was extracted with ether (2 x 50 ml). The ethereal extracts were dried ($MgSO_4$) and concentrated by evaporation of the solvent. Column chromatography of the residue with ether as eluent gave 7b. Yield 40%; oil; ^{1}H NMR ($CDCl_3$) δ 8.93 (s, 2H, H-4 and H-6), 7.49 (m, 5H), 4.90 (s, 2H), 4.41 (d, J = 2.4 Hz, 2H), 2.47 (t, J = 2.4 Hz, 1H). HRMS Calcd. for $C_{14}H_{12}N_2O$ (M^+): 224.0941. Found: 224.0950.

4,6-Dimethyl-2-(2-propynyloxymethyl)pyrimidine (7c). A solution of 2-chloromethyl-4,6-dimethylpyrimidine (5b)[14] (4.70 g; 30 mmol) in dry THF (15 ml) was added to a solution of sodium propynolate (50 mmol) in THF (50 ml). The mixture was refluxed for 3 h. After cooling water (40 ml) was added and the mixture was extracted with ether (3 x 75 ml). The organic layers were dried ($MgSO_4$) and concentrated by evaporation of the solvent. The residue was purified by column chromatography using ether as eluent. Yield 4.35 g (82%); oil; ^{1}H NMR ($CDCl_3$) δ 6.94 (s, 1H, H-5), 4.74 (s, 2H), 4.35 (d, J = 2.4 Hz, 2H), 2.45 (7H, 2 CH_3 and C≡CH). HRMS Calcd. for $C_{10}H_{11}N_2O$ (M^+-1): 175.0872. Found: 175.0872. Picrate; mp 100-102°C.
Anal. Calcd. for $C_{16}H_{15}N_5O_8$ (picrate; M = 405.32): C, 47.41; H, 3.73; N, 17.28. Found: C, 47.17; H, 3.61; N, 17.34.

4,6-Dimethyl-2-(3-trimethylsilyl-2-propynyloxymethyl)pyrimidine (7d). A solution of n-butyllithium in hexane (1.3 ml; 1.6 M) was added to a solution of 7c (352 mg; 2 mmol) in dry THF (15 ml) at -70°C under a nitrogen atmosphere. Then a solution of trimethylsilyl chloride (250 mg) in dry THF (10 ml) was added. After stirring for 1 h at -15°C a 1 M HCl solution (30 ml) was added and the mixture was extracted with ether (3 x 75 ml). After drying ($MgSO_4$) of the organic

layers and concentration compound **7d** was obtained. Yield 350 mg (71%); oil; ^{1}H NMR ($CDCl_3$) δ 6.98 (s, 1H, H-5), 4.80 (s, 2H), 4.41 (s, 2H), 2.50 (s, 6H, 2 CH_3), 0.17 (s, 9H). HRMS Calcd. for $C_{13}H_{20}N_2OSi$ (M^+): 247.1267. Found: 247.1280.

Cycloaddition reaction of the 5-(2-propynyloxymethyl)pyrimidines **4a-g** to the corresponding 1,3-dihydrofuro[3,4-c]pyridines **8a-g** and of the 2-(2-propynyloxymethyl)pyrimidines **7a-d** to the corresponding 5,7-dihydrofuro[3,4-b]pyridines **9a-d**.

A solution of the appropriate 5-(2-propynyloxymethyl)pyrimidine **4a-g** or 2-(2-propynyloxymethyl)pyrimidine **7a-d** (1 mmol) in nitrobenzene (2 ml) was heated at 140 ± 1°C under a nitrogen atmosphere. After heating the mixture for 6 times $t_{1/2}$ the product was isolated by column chromatography using ether/ethyl acetate 1:1 as eluent.

1,3-Dihydrofuro[3,4-c]pyridine (**8a**). Yield 90%; oil; ^{1}H NMR ($CDCl_3$) δ 8.53 (s, 1H, H-4), 8.50 (d, J = 5.1 Hz, 1H, H-6), 7.20 (d, J = 5.1 Hz, 1H, H-7), 5.09 (br, 4H). HRMS Calcd. for C_7H_7NO (M^+): 121.0528. Found: 121.0531.

1,3-Dihydro-3-methylfuro[3,4-c]pyridine (**8b**). Yield 84%; oil; ^{1}H NMR ($CDCl_3$) δ 8.51 (d, J = 5.1 Hz, 1H, H-6), 8.47 (s, 1H, H-4), 7.2 (d, 1H, J = 5.1 Hz, H-7), 5.38 (m, 1H, H-3), 5.05 (m, 2H), 1.53 (d, J = 7 Hz, 3H). HRMS Calcd. for C_8H_9NO (M^+): 135.0684. Found: 135.0685.

1,3-Dihydro-3-phenylfuro[3,4-c]pyridine (**8c**). Yield 81%; mp 60-61°C (hexane); ^{1}H NMR ($CDCl_3$) δ 8.48 (d, J = 5.0 Hz, 1H, H-6), 8.33 (s, 1H, H-4), 7.30 (s, 5H), 7.17 (d, 1H, J = 5.0 Hz, H-7), 6.18 (br, 1H, H-3), 5.17 (m, 2H). HRMS Calcd. for $C_{13}H_{11}NO$ (M^+): 197.0841. Found: 197.0834;

Anal. Calcd. for $C_{13}H_{11}NO$ (M = 197.23): C, 79.16; H, 5.62; N, 7.10. Found: C, 78.84; H, 5.62; N, 7.03.

1,3-Dihydro-3,3-dimethylfuro[3,4-c]pyridine (**8d**). Yield 68%; oil; ^{1}H NMR ($CDCl_3$) δ 8.52 (d, J = 5.1 Hz, 1H, H-6), 8.47 (s, 1H, H-4), 7.19 (d, 1H, J = 5.1 Hz, H-7), 5.05 (s, 2H), 1.52 (s, 6H). HRMS Calcd. for $C_9H_{10}NO$ (M^+-1); 148.0762. Found: 148.0762.

1,3-Dihydro-3-spirocyclopentylfuro[3,4-c]pyridine (**8e**). Yield 81%; mp 59-61°C (hexane -20°C); ^{1}H NMR ($CDCl_3$) δ 8.48 (d, J = 5.1 Hz, 1H, H-6), 8.43 (s, 1H, H-4), 7.16 (d, J = 5.1 Hz, 1H, H-7), 5.00 (s, 2H), 2.2-1.8 (br, 8H).

Anal. Calcd. for $C_{11}H_{13}NO$ (M = 175.22): C, 75.39; H, 7.47; N, 7.99. Found: C, 75.42; H, 7.62; N, 7.88.

1,3-Dihydro-1,1-dimethylfuro[3,4-c]pyridine (**8f**). Yield 70%; oil; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, J = 5.1 Hz, 1H, H-6), 8.49 (s, 1H, H-4), 7.08 (d, J = 5.1 Hz, 1H, H-7), 5.10 (s, 2H), 1.47 (s, 6H). HRMS Calcd. for $C_9H_{11}NO$ (M^+): 149.0841.Found: 149.0840.

6-*t*-Butyl-1,3-dihydrofuro[3,4-c]pyridine (**8g**). This compound was obtained upon heating of a solution of **4g** in nitrobenzene at 160°C for 24 h. Yield 59%; oil; ^{1}H NMR ($CDCl_3$) δ 8.48 (s, 1H, H-4), 7.26 (s, 1H, H-7), 5.09 (s, 4H), 1.37 (s, 9H). HRMS Calcd. for $C_{11}H_{15}NO$ (M^+): 177.1154. Found: 177.1149.

5,7-Dihydrofuro[3,4-b]pyridine (**9a**). Yield 63%; oil; ^{1}H NMR ($CDCl_3$) δ 8.48 (d, J = 4.8 Hz, 1H, H-2), 7.54 (d, J = 7.5 Hz, 1H, H-4), 7.15 (dd, J_1 = 4.9 Hz, J_2 = 7.6 Hz, 1H, H-3), 5.15 (br s, 2H), 5.07 (br s, 2H). HRMS Calcd. for C_7H_7NO (M^+): 121.0528. Found: 121.0526.

5,7-Dihydro-3-phenylfuro[3,4-b]pyridine (**9b**). Yield 87%; mp 126-128°C; ^{1}H NMR ($CDCl_3$) δ 8.70 (s, 1H, H-2), 7.70 (s, 1H, H-4), 7.50 (mc, 5H), 5.21 (br s, 2H), 5.12 (t, J = 1.8 Hz, 2H).

Anal. Calcd. for $C_{13}H_{11}NO$ (M = 197.23): C, 79.16; H, 5.62; N, 7.10. Found: C, 79.04; H, 5.56; N, 6.80.

5,7-Dihydro-2-methylfuro[3,4-b]pyridine (**9c**). Yield 92%; mp 92-93°C (hexane); ^{1}H NMR ($CDCl_3$) δ 7.47 (d, J = 7.5 Hz, 1H, H-4), 7.06 (d, J = 7.5 Hz, 1H, H-3), 5.13 (br, 2H), 5.04 (br, 2H), 2.57 (s, 3H).

Anal. Calcd. for C_8H_9NO (M = 135.16): C, 71.09; H, 6.71; N, 10.36. Found: C, 71.25; H, 6.87; N, 10.36.

5,7-Dihydro-2-methyl-4-trimethylsilylfuro[3,4-b]pyridine (**9d**). Yield 53%; oil; ^{1}H NMR ($CDCl_3$) δ 7.16 (s, 1H, H-3), 5.22 (br, 2H), 5.07 (br, 2H), 2.60 (s, 3H), 0.30 (s, 9H). HRMS Calcd. for $C_{11}H_{17}NOSi$ (M^+): 207.1079. Found: 207.1073.

3,3-Dimethylfuro[3,4-c]pyridin-1(3*H*)-one (**10a**). This compound was obtained in good yield by air oxidation of compound **8a**. Mp 97-98°C (hexanes/toluene); ^{1}H NMR ($CDCl_3$) δ 8.83 (s, 1H, H-4), 8.79 (d, J = 5.0 Hz, 1H, H-6), 7.70 (d, J = 5.0 Hz, 1H, H-7), 1.74 (s, 6H). HRMS Calcd. for $C_9H_9NO_2$ (M^+): 163.0633. Found: 163.0632.

Anal. Calcd. for $C_9H_9NO_2$ (M = 163.17): C, 66.24; H, 5.56; N, 8.58. Found: C, 66.54; H, 5.76; N, 8.64.

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