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REGIOSELECTIVE ALLYLATION AND PROPARGYLATION OF PYRIMIDINES

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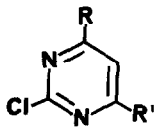
Summary: -Reactions of pyrimidines 1a and 1b with allylic Grignard reagents 3a-f lead to allyldihydropyrimidines 2a-h and 2l-n in very good yields. Dehydrogenation of 2a-d with DDQ furnished excellent yields of allylpyrimidines 1c-f. Propargylation of 1a with 3g and 3h provides propargyl dihydropyrimidines 2g and 2h respectively. 2g can be oxidised with DDQ to 1g. Allylation of 1c and 1i gives 1m and 1n respectively. Reduction of 1f leads to the branched alkyl derivative 1r.

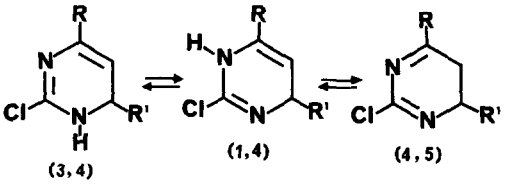
Dihydropyrimidines, easily convertible to pyrimidines exhibit important antioxidant, membranotropic and pharmacological properties.[1] Moreover, a great many dihydropyrimidines have properties potentially useful in stock or crop raising.[2]

The literature contains only a few papers describing the synthesis of dihydropyrimidines, reported often as poorly characterised isomeric mixtures which in some cases are spontaneously oxidised to pyrimidines.[3]

Weis[4] has extensively investigated the 1,4-, 3,4- and 4,5-tautomerism in dihydropyrimidines concluding that they exist in the 1,4-dihydro form in the solid state and as an equilibrium mixture of 3,4- and 1,4-dihydro forms in solution. It was also found that substituents in dihydropyrimidines have influence on their degree of isomerisation.[5]

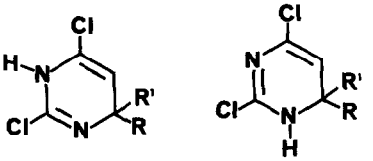
Dihydropyrimidines are normally prepared from α,β-unsaturated carbonyls, β-dicarbonyls or from pyrimidines *via* addition of organometallics, reduction with complex metal hydrides, electrophilic aromatic substitution, desulphurisation of pyrimidine-thiones and electrochemical reduction.[1] In several cases however, yields are very poor and commercial precursors very expensive. Specifically, Grignard reagents have been reported to react with pyrimidines furnishing dihydropyrimidines or cross-coupled pyrimidines;[1,7] however, this applies only to aryl and primary alkyl Grignards. No secondary or tertiary alkyl group could be introduced on the pyrimidine ring by this procedure. Allyl- and propargyl-dihydropyrimidines, very useful because of their potential elaboration to other functionalised pyrimidines, have not been described so far. We report here the synthesis of a series of novel allyl-, and propargyl-dihydropyrimidines based on the regioselective reaction of commercially available and inexpensive pyrimidines with unsaturated Grignard reagents derived from allyl and propargyl halides.



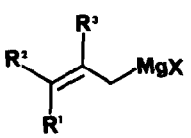


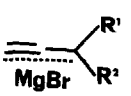
(3,4) (1,4) (4,5)

1a	R = R^1 = H	--
1b	R = Me; R^1 = Cl	--
1c[6]	R = H; R^1 = $-CH_2CH=CH_2$	2a
1d	R = H; R^1 = $-CH(CH_3)CH=CH_2$	2b
1e	R = H; R^1 = $-CH_2C(CH_3)=CH_2$	2c
1f	R = H; R^1 = $-C(CH_3)_2CH=CH_2$	2d
	R = H; R^1 = $-CH(Ph)CH=CH_2$	2e
1g	R = H; R^1 = $-C(CH_3)CH=CH_2$ $(CH_2)_2CH=C(CH_3)_2$	2f
1h	R = H; R^1 = $-CH_2C\equiv CH$	2g
	R = H; R^1 = $-C(CH_3)_2C\equiv CH$	2h
1i[6]	R = H; R^1 = $-CH=CHCH_3$	--
1k	R = H; R^1 = $-CH=C=CH_2$	--
1l	R = R^1 = $-CH_2CH=CH_2$	2i
1m	R = $-CH_2CH=CH_2$ R^1 = $-CH_2C(CH_3)=CH_2$	
1n	R = $-CH=CHCH_3$ R^1 = $-CH_2C(CH_3)=CH_2$	



1o	R = Me; R^1 = $-CH_2CH=CH_2$	2l
1p	R = Me; R^1 = $-CH(CH_3)CH=CH_2$	2m
1q	R = Me; R^1 = $-CH_2C(CH_3)=CH_2$	2n
1r	R = H; R^1 = $-C(CH_3)_2CH_2CH_3$	





3a: R^1 = R^2 = R^3 = H; X = Br
3b: R^1 = R^3 = H; R^2 = Me; X = Br
3c: R^1 = R^2 = H; R^3 = Me; X = Cl
3d: R^3 = H; R^1 = R^2 = Me; X = Cl
3e: R^1 = R^3 = H; R^2 = Ph; X = Cl
3f: R^1 = R^3 = H; R^2 = $-(CH_2)_2CH=C(CH_3)_2$; X = Cl

3g: R^1 = R^2 = H
3h: R^1 = R^2 = Me

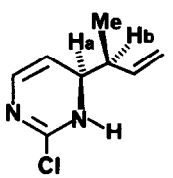
The reaction of 2-chloropyrimidine 1a with allylmagnesium bromide 3a in tetrahydrofuran (or dichloromethane) at 0°C affords almost quantitative

yield of the dihydropyrimidine 2a that, unlike most dihydropyrimidines,[3] is quite stable and can be stored for weeks. It was interesting to note that in contrast with alkyl and aryl Grignards the addition of 3a to 1a does not require Ni(II) or Pd(II) complex as catalyst and the cross-coupling process at the 2 position does not compete at all.[7] Only addition reaction of 3a to 1a took place also in the presence of $NiCl_2(PPh_3)_2$ (3%). Similarly, 1a reacted with Grignard reagents 3b-f leading to dihydropyrimidines 2b-f all quite stable and storable for long. (Table 1).

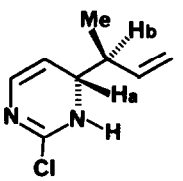
Table 1. Synthesis of dihydropyrimidines 2a-h.

Substrate	Grignard reagent	Solv.	Product Yield (%)
1a	3a	THF	2a (100)
"	3b	"	2b (96)
"	3c	"	2c (83)
"	3d	"	2d (92)
"	3a	CH_2Cl_2	2a (98)
"	3b	"	2b (87)
"	3e	THF	2e (43)
"	3f	"	2f (57)
1b	3a	"	2l (56)
"	3b	"	2m (33)
"	3c	"	2n (60)
1a	3g	"	2g (82)
"	3g	CH_2Cl_2	2g (92)
"	3h	THF	2h (70)

In all cases the addition reaction of Grignards 3 to 1a occurred with complete regioselectivity on the N=C bond: the unsaturated Grignard reagent turns out to be attached through the more substituted carbon atom. Specifically in the reaction of 1a with crotylmagnesium bromide 3b ^{1}H-NMR analysis of the resulting 4-α-methylallyl-2-chloro-1,4(3,4)-dihydropyrimidine 2b clearly indicated that it is actually a mixture of the diastereomeric syn and anti isomers I and II with a certain preference for the anti (higher coupling constant between Ha-Hb protons) isomer II (anti/syn ratio 3/1). Attempts, however, to separate such stereoisomers through column chromatography and HPLC failed.



I



II

Since the ^{1}H-NMR spectra of allyldihydropyrimidines 2 exhibited the signal of C-4 vinylic proton as a doublet the possibility of the 4,5-dihydro tautomer was ruled out. However, ^{1}H-NMR spectra inspection of 2 did not allow us to establish whether there was just one tautomer (1,4- or 3,4-) or of a rapidly equilibrating mixture of the two. In accordance with what has been reported for other dihydropyrimidines[4] we believe it was an average spectrum. Indeed, the transfer of the proton between the two nitrogens is usually a rapid (in the NMR time scale) process. It could be expected that

on using an aprotic dipolar solvent such as DMSO a decrease in the rate of tautomerism may take place because of strong intermolecular H-bonding with the solvent, thus allowing the observation of the individual tautomers. However, even using DMSO as solvent in our NMR study we observed a spectrum that still was the average one. The IR inspection of the methallyldihydropyrimidine 2c allowed us to conclude that we were dealing with both the 1,4 and 3,4 tautomers. Indeed, the IR spectrum showed three main absorption bands at 1600 (C=C), 1640-1685 (C=N) and 3350-3440 (NH) cm^{-1}. The characteristic absorption bands in the 1640-1685 cm^{-1} region provided a good tool to differentiate the tautomers. As observed for a large number of known dihydropyrimidines[4] the band assigned to the C=C-NH-C=N fragment of the 1,4-tautomer appears at a higher frequency (30-60 cm^{-1}) than the corresponding band for the C=C-N=C-NH fragment belonging to the 3,4-tautomer. The intensity of this peaks correlates well with the ratio of tautomers. Such a ratio depends on the solvent used for the IR spectrum. The 1,4-tautomer largely predominates (85/15) in tetrahydrofuran and acetonitrile, while a 1:1 ratio is observed in dichloromethane, cyclohexane and carbon tetrachloride. A nujol IR spectrum showed a more intense peak for the 3,4-tautomer. The KBr spectrum clearly indicated the peaks of both tautomers (1:1 ratio), notwithstanding that it has been reported that dihydropyrimidines in the solid state exist in the 1,4 structure.

The reaction of 2,6-dichloro-4-methylpyrimidine 1b with allylic Grignard reagents 3a-c furnished good yields of dihydropyrimidines 2n, 2o and 2p respectively together with the cross-coupled products 1o, 1p and 1q. In all cases the addition reaction of 1b which turned out to be much slower than 1a, prevailed over the cross-coupling reaction (see Table 2).

Table 2. Reaction of 2,4-dichloro-6-methylpyrimidine 1b with allylic Grignards 3a-c in THF at RT.

Pyrimidine	Grignard reagent	Addition product Yield (%)	Cross-coupling product Yield (%)
1b	3a	2l (56)	1o (24)
"	3b	2m (33)	1p (15)
"	3c	2n (60)	1q (21)

We have also found that 2-chloropyrimidine 1a undergoes clean addition reaction with Grignard reagents derived from propargyl halides. Indeed, 1a reacts with Grignards 3g and 3h to furnish high yields of 4-propargyl-2-chloro-1,4-(3,4)-dihydropyrimidine 2g and 4-(1,1-dimethylpropargyl)-2-chloro-1,4(3,4)-dihydropyrimidine 2h respectively.

The oxidation of dihydropyrimidines 2a-f and 2g could lead to the useful allyl- and propargyl-pyrimidines 1c-g and 1h. Oxidation with O_2 or SiO_2 gave poor yields, but dehydrogenation of 2a-f with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) provided quite good yields of the allylic pyrimidines 1c-g. Similarly, dehydrogenation of 2g with DDQ led to propargylpyrimidine 1h. Allylpyrimidines and propargylpyrimidines tend to isomerise with time to the corresponding vinylic and allenic derivatives. Indeed we have found that 2a spontaneusly converts to 1i and 1h to 1k. Moreover, we have found that the reduction of the branched allylic pyrimidines

may lead to branched alkyl pyrimidines otherwise difficult to be prepared by using branched alkyl Grignard reagents, even in the presence of Ni(II) or Pd(II) complexes. It is well known the propensity of secondary and tertiary Grignard reagents for undergoing β-elimination[8] or isomerisation[9,10] in the presence of Ni(II) or Pd(II) complexes. Instead, reduction of 1f gives a quantitative yield of the alkyl derivative 1r.

We also looked at the possibility that the pyrimidine moiety may undergo di- and tri-allylation. Indeed, monoallylpyrimidine 1c led to a good yield of diallylpyrimidine 1l upon treatment with allylmagnesium bromide and subsequent dehydrogenation with DDQ of the related dihydropyrimidine intermediate 2i. Moreover, the reaction of the chloromethallylpyrimidine 1e with allylmagnesium bromide 3a and subsequent oxidation of the related dihydropyrimidine with DDQ furnished a very good yield of the allylmethallylpyrimidine 1m. Similarly the vinylpyrimidine 1h was transformed into the propenylmethallylpyrimidine 1n. Attempts to carry out triallylation of the pyrimidine nucleus failed. Indeed, the reaction of the allylmethallylpyrimidine 1m with dimethylallylmagnesium chloride in the presence of catalytic amount of $NiCl_2$(dppe) [dppe = $Ph_2PCH_2CH_2PPh_2$] in order to achieve cross-coupling led to a mixture of many products that could not be separated and characterised. Work is in progress to make triallylation of pyrimidine possible since triallylpyrimidine appears to be an interesting substrate.

EXPERIMENTAL

^{1}H-NMR spectra were recorded on a Varian EM 360A or a Varian XL 200 spectrometers; chemical shifts are reported in parts per million (δ) from internal Me_4Si. Melting points were determined on a Electrothermal apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 598 spectrophotometer. Thin layer chromatography (TLC) was performed on a silica gel sheet with fluorescent (DC-Alufolien Kiesegel 60 F_{254}, Merck). Flash chromatography were done with Merck 230-400 mesh silica gel. All new compounds gave satisfactory microanalytical data.

Materials: -Tetrahydrofuran (THF) and diethyl ether of commercial grade (RS Carlo Erba) were purified by distillation (twice) from sodium wire in a N_2 atmosphere. Petroleum ether (RS C.E.) refers to the 40-60°C boiling fraction. Dichloromethane (RS C.E.) was purified by distillation. 2-Chloropyrimidine, 2,6-dichloro-4-methylpyrimidine and all other chemicals were commercial grade and were used without further purification. The Grignard reagents 3a-f[11] and 3g-h[12] were prepared as reported.

Reaction of 2-chloropyrimidine 1a with allylic 3a-f and propargylic 3g-h Grignard reagents.

The reaction of allylmagnesium bromide 3a with 2-chloropyrimidine is described as an example. To a THF or CH_2Cl_2 (30 ml) solution of 1a (13.09 mmol) a solution of 3a (22.45 ml, 15.71 mmol) was added dropwise with stirring at room temperature under nitrogen. After 15 min. the solution was quenched with aqueous NH_4Cl. Extraction with Et_2O or CH_2Cl_2 (3 x 25 ml), drying over $MgSO_4$ and solvent removal under reduced pressure yielded the dihydropyrimidine 2a. Yields for dihydropyrimidines 2a-h are reported in Table 1. Spectral data are given below.

4-allyl-2-chloro-1,4(3,4)-dihydropyrimidine 2a: - oil; ν_{max} (film) 3100-3220 (NH), 1680, 1640 (C=N), 1590 cm^{-1} (C=C); δ_H (CCl_4) 2.2 (m, 2H), 4.2 (m, 1H), 4.5 (m, 1H), 4.6-5.2 (m, 2H), 5.2-5.7 (m, 1H), 5.9 (d, 1H, J=8Hz), 8.0 (s, 1H exch. with D_2O).

2-chloro-4-(1-methyl-2-propenyl)-1,4(3,4)-dihydropyrimidine 2b: - oil. This compound is a mixture of syn-anti diastereoisomers; ν_{max} (CCl_4) 3470 (NH), 1680, 1640 (C=N), 1600 cm^{-1} (C=C); δ_H ($CDCl_3$-D_2O) [1.04 (d, J=7Hz), 1.05 (d, J=7Hz), 3H], 2.25-2.37 (m, 1H), 4.14-4.25 (m, 1H), 4.67-4.72 (m, 1H), 5.02-5.13 (m, 2H), 5.63-5.9 (m, 1H), 6.1 (d, 1H, J=7.4Hz).

2-chloro-4-(2-methyl-2-propenyl)-1,4(3,4)-dihydropyrimidine 2c: - m.p. 55-56°C (ether-petroleum ether); ν_{max} (CCl_4) 3470 (NH), 1675, 1635 (C=N), 1600 cm^{-1} (C=C); δ_H ($CDCl_3$) 1.65 (s, 3H), 2.2 (m, 2H), 4.2 (m, 1H), 4.6 (m, 3H), 5.4 (s, 1H, exch. with D_2O), 5.85 (d, 1H, J=8Hz).

2-chloro-4-(1,1-dimethyl-2-propenyl)-1,4(3,4)-dihydropyrimidine 2d: - m.p. 93-94°C (benzene-petroleum ether); ν_{max} (CH_2Cl_2) 3450 (NH), 1695, 1635 (C=N), 1585 cm^{-1} (C=C); δ_H ($CDCl_3$-D_2O) 0.95 (s, 3H), 1.0 (s, 3H), 3.75 (d, 1H, J=3.2Hz), 4.3-4.95 (m, 3H), 5.25-5.55 (m, 1H), 5.95 (d, 1H, J=8Hz).

2-chloro-4-(1-phenyl-2-propenyl)-1,4(3,4)-dihydropyrimidine 2e: - oil; δ_H (CCl_4) 3.12-3.52 (m, 1H), 4.5-4.52 (m, 2H), 4.6-5.2 (m, 2H), 5.6-6.0 (m, 2H), 6.8-7.3 (m, 5H), 6.6 (s, 1H, exch. with D_2O).

2-chloro-4-(1-vinyl-1,5-dimethyl-4-hexenyl)-1,4(3,4)-dihydropyrimidine 2f: - oil; ν_{max} (film) 3150 (NH), 1680, 1640 (C=N), 1585 cm^{-1} (C=C); δ_H ($CDCl_3$-D_2O) 1.0 (s, 3H), 1.5 (s, 3H), 1.6 (s, 3H), 1.0-2.2 (m, 4H), 3.9 (d, 1H, J=4Hz), 4.55-5.55 (m, 5H), 6.0 (d, 1H, J=7Hz).

2-chloro-4-(2-propynyl)-1,4(3,4)-dihydropyrimidine 2g: - m.p. 89-90°C (ether petroleum ether); ν_{max} (CH_2Cl_2) 3450 (NH), 2120 (C=C) 1675, 1640 cm^{-1} (C=N); δ_H ($CDCl_3$) 2.0 (m, 1H), 2.4 (dd, 2H, J=2Hz, J=6Hz) 4.4 (m, 1H), 4.7 (m, 1H), 6.1 (d, 1H, J=8Hz), 6.4 (s, 1H, exch. with D_2O).

2-chloro-4-(1,1-dimethyl-2-propynyl)-1,4(3,4)-dihydropyrimidine 2h: - m.p. 94-95°C (CCl_4); ν_{max} (CH_2Cl_2) 3450 (NH), 2120 (C=C), 1680, 1640 cm^{-1} (C=N); δ_H ($CDCl_3$) 1.1 (s, 3H), 1.2 (s, 3H), 2.1 (s, 1H), 4.1 (d, 1H, J=4Hz), 4.7 (dd, 1H, J=3Hz, J=8Hz), 6.2 (d, 1H, J=8Hz).

Oxidation of allylic 2a-d, 2f and propargylic 2g dihydropyrimidines with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ).

The oxidation of 2a is here described. To a solution of 2a (11.0 mmol) in 20 ml of dioxane was added dropwise at room temperature a solution of DDQ (11.0 mmol) in 20 ml of dioxane. After 5 min., the solvent was removed and the residue was flash-chromatographied to give 1c. Data for pyrimidines 1c-h are reported below.

4-allyl-2-chloropyrimidine 1c: 58% yield, oil; δ_H (CCl_4) 3.3 (d, 2H, J=6 Hz), 4.7- 5.2 (m, 2H), 5.3-6.1 (m, 1H), 6.8 (d, 1H, J=5Hz), 8.2 (d, 1H, J=5Hz)

2-chloro-4-(1-methyl-2-propenyl)-pyrimidine 1d: 82% yield, oil; δ_H ($CDCl_3$ 1.3 (d, 3H, J= 8Hz), 3.25-3.85 (m, 1H), 4.95-5.4 (m, 2H), 5.75-6.4 (m, 1H) 7.22 (d, 1H, J= 5Hz), 8.6 (d, 1H, J= 5Hz).

2-chloro-4-(2-methyl-2-propenyl)-pyrimidine 1e: 78% yield, oil; δ_H (CCl_4) 1.8 (s, 3H), 3.4 (s, 2H), 4.8 (m, 2H), 7.0 (d, 1H, J=5Hz), 8.3 (d, 1H, J=5Hz).

2-chloro-4-(1,1-dimethyl-2-propenyl)-pyrimidine 1f: 60% yield, oil; δ_H ($CDCl_3$) 1.4 (s, 6H), 4.7-5.1 (m, 2H), 5.5-6.1 (m, 1H), 7.0 (d, 1H, J=5Hz), 8.1 (d, 1H, J=5Hz).

2-chloro-4-(1-vinyl-1,5-dimethyl-4-hexenyl)-pyrimidine 1g: 80% yield, oil; δ_H (CCl_4) 1.4 (s, 3H), 1.5 (s, 3H), 1.6 (s, 3H), 1.7-2.1 (m, 4H), 4.8-5.2 (m, 3H), 5.7-6.2 (m, 1H), 6.95 (d, 1H, J=5Hz), 8.2 (d, 1H, J=5Hz).

2-chloro-4-(2-propynyl)-pyrimidine 1h: 28% yield, oil; δ_H ($CDCl_3$) 2.4 (t, 1H, J=2Hz), 3.86 (d, 2H, J=2Hz), 7.46 (d, 1H, J=5Hz), 8.8 (d, 1H, J=5Hz).

Reaction of allylmagnesium halides 3a-c with 2,6-dichloro-4-methylpyrimidine 1b.

The reaction of 3a with 1b is here described. To a THF or CH_2Cl_2 (30 ml) solution of 1b (13.09 mmol) a solution of 3a (15.71 mmol) was added dropwise with stirring at room temperature under nitrogen. After 15 min the solution was quenched with sat. aqueous NH_4Cl. Extraction with CH_2Cl_2 (3 x 25 ml), drying over $MgSO_4$ and solvent removal under reduced pressure gave a mixture of 2,6-dichloro-4-allyl-4-methyl-1,4(3,4)-dihydro-pyrimidine 2l (56%) together with the cross-coupling product 6-allyl-2-chloro-4-methyl-pyrimidine 1o. Yields are reported in Table 2. Spectral data are given below.

2,6-dichloro-4-methyl-4-(2-propenyl)-1,4(3,4)-dihydropyrimidine 2l: - m.p. 119-120°C (CCl_4); ν_{max} (CH_2Cl_2) 3409 cm^{-1} (NH); δ_H ($CDCl_3$-D_2O) 1.35 (s, 3H), 2.3 (d, 2H, J=7Hz), 4.85 (s, 1H), 4.9-5.3 (m, 2H), 5.4-6.1 (m, 1H).

2-chloro-4-methyl-6-(2-propenyl)-pyrimidine 1o: oil; δ_H ($CDCl_3$) 1.9 (m, 2H), 2.5 (s, 3H), 6.2-6.7 (m, 2H), 6.9 (s, 1H), 6.9-7.5 (m, 1H).

2,6-dichloro-4-methyl-4-(1-methyl-2-propenyl)-1,4(3,4)-dihydropyrimidine 2m: -m.p. 86-88°C (ether-petroleum ether); ν_{max} (CH_2Cl_2) 3409 cm^{-1} (NH); δ_H ($CDCl_3$) 1.1 (d, 3H, J= 7Hz), 1.3 (s, 3H), 2.1-2.6 (m, 1H), 4.8 (s, 1H), 4.85-5.25 (m, 2H), 5.3-6.0 (m, 1H), 6.4 (s, 1H, exch. with D_2O).

2-chloro-4-methyl-6-(1-methyl-2-propenyl)-pyrimidine 1p: oil; - δ_H ($CDCl_3$) 1.3 (m, 3Hz), 3.5 (s, 3H), 3.3-3.9 (m, 2H), 4.7-5.3 (m, 2H), 5.5-6.5 (m, 1H), 6.9 (d, 1H, J= 12Hz).

2.6-dichloro-4-methyl-4-(2-methyl-2-propenyl)-1,4(3,4)-dihydropyrimidine 2n: -m.p. 93-95°C (ether-petroleum ether); ν_{max} (CH_2Cl_2) 3420 cm^{-1} (NH); δ_H (CCl_4) 1.3 (s, 3H), 1.7 (s, 3H), 2.2 (m, 1H), 4.6 (s, 1H), 4.4-5.8 (m, 2H), 6.3 (s, 1H, exch. with D_2O).

2-chloro-4-methyl-6-(2-methyl-2-propenyl)-pyrimidine 1q: oil; - δ_H (CCl_4) 1.7 (s, 3H), 2.4 (s, 3H), 3.4 (s, 2H), 4.7 (s, 2H), 6.7 (s, 1H).

Reaction of 4-allyl-2-chloropyrimidine 1c with allylmagnesium bromide 3a.

To a solution of 1c (1.94 mmol) in THF (30 ml) was added dropwise with stirring at -70°C under nitrogen a solution of allylmagnesium bromide 3a (2.33 mmol). After 15 min. the reaction mixture was allowed to warm to room temperature and then quenched with sat. aqueous NH_4Cl. Extraction with Et_2O (3 x 25 ml), drying over $MgSO_4$ and solvent removal under reduced pressure yielded:

2-chloro-4,6-diallyl-1,4(3,4)-dihydropyrimidine 2i: - oil; 100% yield; δ_H ($CDCl_3$-D_2O) 2.1-2.4 (m, 2H), 2.7 (d, 2H, J=6Hz), 4.0-4.4 (m, 1H), 4.7-5.2 (m, 4H), 5.2-5.9 (m, 3H).

Reaction of 2-chloro-4,6-diallyl-1,4(3,4)-dihydropyrimidine 2i with DDQ:

This reaction was carried out as previously described for 2a-c and 2f oxidation. The reaction product was:

2-chloro-4,6-diallylpyrimidine 1l: oil; 100% yield; δ_H (CCl_4) 3.3 (d, 4H, J=5Hz), 4.8-5.2 (m, 4H), 5.5-6.2 (m, 2H), 6.7 (s, 1H).

Reactions of 2-chloro-4-(2-methyl-2-propenyl)-pyrimidine 1e and 2-chloro-4-(1-propenyl)-pyrimidine 1i with allyl- and methallyl-magnesium bromide 3a and 3c respectively.

Reaction were carried out as the reaction of 4-allyl-2-chloropyrimidine 1c with allyl-magnesium bromide 3a. The intermediate dihydropyrimidines were not isolated but immediately oxidised with DDQ in dioxane. The obtained diallylpyrimidines were purified by flash chromatography.

2-chloro-4-(2-propenyl)-6-(2-methyl-2-propenyl)-pyrimidine 1m: - oil; 100% yield; δ_H (CCl_4) 1.78 (s, 3H), 3.2-3.5 (m, 4H), 4.6-5.2 (m, 4H), 5.5-6.1 (m, 1H), 6.7 (s, 1H).

2-chloro-4-(1-propenyl)-6-(2-methyl-2-propenyl)-pyrimidine 1n: - oil; 100% yield; δ_H (CCl_4) 1.7 (s, 3H), 1.96 (dd, 3H, J=2Hz, J=6.5Hz), 3.2 (s, 2H), 4.5-4.8 (m, 2H), 5.7-6.1 (m, 1H), 6.4-7.1 (m, 2H).

Isomerisation of 2-chloro-4-propynylpyrimidine 1h to a 2-chloro-4-allenyl-pyrimidine 1k.

The isomerisation was spontaneous and complete after 25 day at room temperature.

2-chloro-4-allenylpyrimidine 1k: - oil; >95% yield; δ_H ($CDCl_3$) 5.5 (d, 2H, J=7Hz), 6.4 (t, 1H, J=7Hz), 7.75 (d, 1H, J=5Hz), 8.66 (d, 1H, J=5Hz).

Reduction of 2-chloro-4-(1,1-dimethyl-2-propenyl)-1,4(3,4)-dihydropyrimidine 1f.
0.2 g (1.1 mmol) of 1f in 5 ml of CH_2Cl_2 and 0.1 g of 10% Pd/C were treated with H_2 (1 atm, 1.1 mmol) for 20 min. The catalyst was then removed by filtration and CH_2Cl_2 evaporated to give 0.2 g (100%) of 2-chloro-4-(2-methyl-2-butyl)-pyrimidine 1r: oil; δ_H ($CDCl_3$) 0.7 (t, 3H, J=7Hz), 1.3 (s, 6H), 1.6 (q, 2H, J=7Hz), 6.9 (d, 1H, J=5Hz), 8.1 (d, 1H, J=5Hz).

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References

1) A.L. Weis, Adv. Heterocyclic Chem., 38, 1 (1985).

2) For a review see: D.J. Brown in "Comprehensive Heterocyclic Chemistry" Vol. 3, pg. 57, Ed by A.J. Boulton and A. McKillop, Pergamon Press, Oxford, 1984.

3) W. Wendelin, K. Schermanz, J. Heterocyclic Chem., 21, 65, (1984); A.L. Weis, F. Frolow, D. Zamir, M. Bernstein, Heterocycles, 22, 657 (1984).

4) A.L. Weis, Tetrahedron Lett., 23, 449 (1982).

5) C. Kashima, M. Shimizu, Y. Omote, Tetrahedron Lett., 26, 5057 (1985).

6) E.Epifani, S. Florio, G. Ingrosso, Tetrahedron, 44, 5869 (1988).

7) M.R.H. Elmoghayar, P. Groth, K. Undheim, Acta Chem. Scan., B, 37, 109 (1983); M.R.H. Elmoghayar, K. Undheim, ibid., 37, 160 (1983).

8) E.D. Thorsett, F.R. Stermitz, J. Heterocyclic Chem., 10, 243 (1973); L.N. Pridgen, ibid., 12, 443 (1975).

9) Y. Kiso, K. Tamao, and M. Kumada, J. Organomet. Chem., 50, C12-C14 (1973); T. Hayashi, M. Konishi, and M. Kumada, Tetrahedron Lett., 21, 1871 (1979).

10) M. Kumada has recently reported that in some cases the isomerisation could be suppressed by using particular Pd complexes. T. Hayashi, K. Konishi, Y. Kobori, M. Kumada, T. Higuchi, and K. Hirotsu, J. Am. Chem. Soc., 106, 158 (1984).

11) F. Babudri, S. Florio, L. Ronzini, Tetrahedron, 42, 3905 (1986) and Refs. therein.

12) M. Gaudemar, Ann. Chim., 1, 161 (1956); Y. Pasternak, J.C. Traynard, Bull. Soc. Chim. Fr., 356 (1966).