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Nickel-catalyzed Addition or Coupling Reactions of Grignard Reagents with Halopyrimidines

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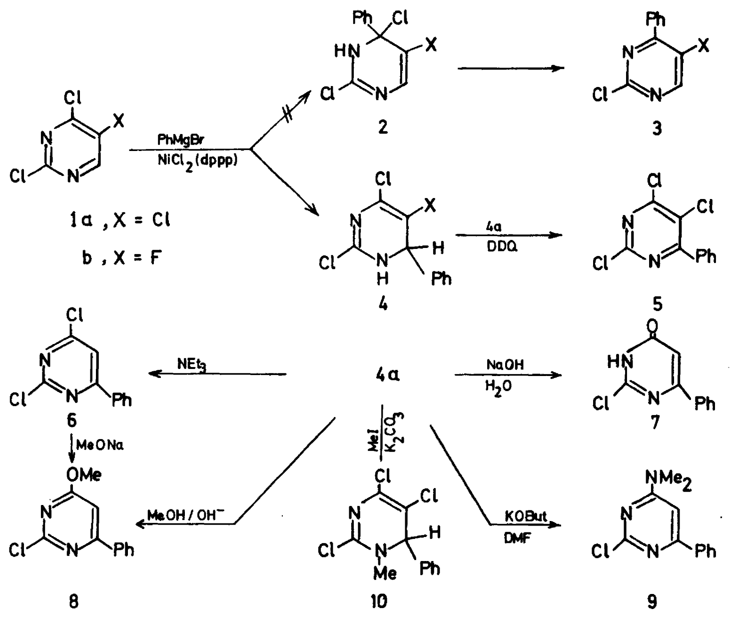
Phenylmagnesium bromide with $NiCl_2$(dppp) catalysis adds selectively to the unsubstituted position in 2,4-dichloro-5-chloro(fluoro)pyrimidine. X-Ray structure analysis of the hydrolyzed adduct shows an infinite chain by $N1-N3'$ hydrogen bonding. The hydrolyzed adduct is aromatized by DDQ. With NEt_3, HCl elimination occurs whereby the 5-halogen atom is replaced by hydrogen; other basic nucleophiles give concurrent replacement of the chlorine in the 4-position. With the phenyl Grignard reagent and $NiCl_2$(dppp) exhaustive coupling results with 2,4-dichloro-6-phenylpyrimidine; with alkyl Grignard reagents and nickel catalysis selective coupling in the 4-position can be effected, but the reaction readily proceeds further to exhaustive coupling.

The coupling reaction between organometallic compounds and organic halides is now well recognized to be one of the most useful methods for the formation of $C-C$ bonds.[1] We are interested in the formation of $C-C$ bonds by coupling reactions to heterocyclic systems of the azine type. Herein we report on the reactivity of halopyrimidines[2,3] towards organonickel reagents as a route for the introduction of carbon substituents into the pyrimidine ring. The organonickel reagent was generated *in situ* as used by the addition of catalytic amounts of either dichlorobis(triphenylphosphine)nickel (II),[4] $NiCl_2(PPh_3)_2$, or dichloro-1,3-bis(diphenylphosphinopropane)nickel (II),[5] $NiCl_2$ (dppp), to a Grig-



Scheme 1.

0302-4369/83 $2.50

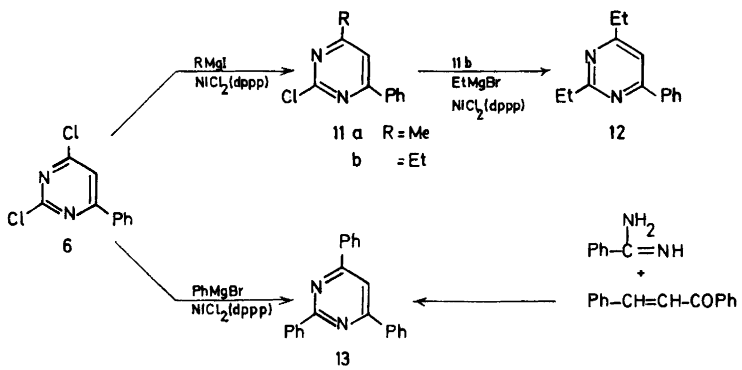
nard reagent. The latter nickel complex seems more efficient in our reactions and was most extensively investigated.

Phenylmagnesium bromide in the presence of either nickel complex, formed a 1:1 adduct (MS) with the trihalopyrimidines *1* rather than the expected 4-substitution product *3* as observed for alkyl Grignard reagents,[6] and also observed for the further Grignard reaction discussed below. The structures *2* and *4* must be considered for the adduct after hydrolysis. The latter (*4*) results from preferential addition of the organometallic reactants to unsubstituted carbon in electron deficient azine systems, a type of reaction presently being investigated.[7] The ^{1}H NMR signals from the heterocyclic ring in the adduct appear as a singlet at δ 5.2 (H-6) and as a broad singlet at 4.7 which rapidly fades out in deuterium oxide (*NH*). The ^{13}C NMR signals from the same moiety are found at 146.3 (C-2), 142.1 (C-4), 111.1 (C-5) and at 63.3 ppm (C-6), the latter having the line separation 144 Hz. Interpretation of these data is in accordance with an X-ray analysis (see below) which shows that the adduct has structure *4*. Chemically, the structure assignment has also been verified by dehydrogenation of the adduct from *1a* by means of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) which gave the phenylated trichloropyrimidine *5*; the latter has previously been described.[8]

When the adduct *4a* was heated with triethylamine in toluene, HCl elimination occurred. The product, which was isolated in 84 % yield, has been identified as compound *6*, which corresponds to chlorine-hydrogen exchange at C-5. Presumably the reaction is initiated by proton abstraction from the *NH* function in *4a*. The further reaction can be rationalized as reprotonation to the 5,6-dihydro-isomer which is the species undergoing HCl elimination to form *6*. The fluoride *4b* also gave *6* but only in 20 % yield presumably because HF elimination is more difficult. The structure *6* was assigned to the product by spectroscopy; ^{1}H NMR has H-5 at *ca.* δ 7.3 and ^{13}C NMR has the signals from the heterocyclic ring at 167.7, 162.9, 161.3 (C-2, C-4, C-6) and at 114.8 ppm (C-5), the latter having a line separation of 172 Hz which is consistent with a pyrimidine 5-position.[9] Chemically the assigned structure *6* has been verified by a further reaction with phenyl magnesium bromide with $NiCl_2$ (dppp) catalysis which gave 2,4,6-triphenylpyrimidine *13* (Scheme 2); for comparative purposes the latter was independently synthesized from benzylideneacetophenone and benzamidine.[10]

HCl elimination from *4a* also occurs in the presence of other bases. With aqueous sodium hydroxide or with alkaline methanol concurrent 4-substitution occurs with formation of the lactam *7* and the methoxy derivative *8*, respectively. Potassium *tert*-butoxide in DMF leads to the 4-dimethylamino derivative *9*. A further evidence for the structures assigned is available from the reaction of *6* with methanolic sodium methoxide; the chlorine in the more reactive 4-position is replaced with the formation of *8*. With methyl iodide and sodium carbonate in acetone the adduct *4a* is *N*-methylated without any elimination reaction occurring, the product being assigned structure *10*.

2,4-Dichloro-6-phenylpyrimidine (*6*) undergoes selective cross-coupling with primary alkyl Grignard reagents using $NiCl_2$ (dppp) catalysis to form the 4-alkyl derivatives *11*. This finding contrasts the behaviour of 2,4-dichloro-6-methylpyrimidine towards alkyl magnesium halide and catalysis in which case no selective cross-coupling could be



Scheme 2.

Table 1. Final fractional coordinates with estimated standard deviations. Hn are bonded to Cn. HNn are bonded to Nn.

ATOM	X	Y	Z
CL1	.32948(8)	-.15226(5)	.01931(2)
CL2	.26895(10)	-.34741(5)	.16026(3)
CL3	.06510(10)	-.21629(5)	.20078(3)
CL4	-.09066(8)	.03483(5)	.06193(2)
CL5	.43693(9)	.06440(5)	.04816(3)
CL6	.41605(8)	.26130(5)	.05694(2)
N1	.29265(26)	-.24011(15)	.09261(9)
N2	.17818(27)	-.11129(17)	.08462(9)
N3	.16996(27)	.06077(16)	.05555(9)
N4	.03083(28)	.17798(16)	.06547(9)
C1	.26049(32)	-.17100(19)	.07164(10)
C2	.23147(34)	-.25182(19)	.13419(10)
C3	.15028(33)	-.19717(19)	.15210(10)
C4	.12362(34)	-.11198(20)	.13098(10)
C5	.18823(33)	-.04312(20)	.16278(10)
C6	.10885(38)	.00024(22)	.19198(11)
C7	.16923(39)	.06218(22)	.22139(12)
C8	.30705(38)	.08214(22)	.22134(12)
C9	.38765(38)	.03843(23)	.19208(12)
C10	.32845(36)	-.02397(22)	.16355(12)
C11	.05464(31)	.09729(19)	.06072(10)
C12	.28312(33)	.11437(20)	.05536(10)
C13	.27557(32)	.19681(20)	.05983(10)
C14	.14146(34)	.24065(20)	.06661(11)
C15	.15232(32)	.29069(19)	.11236(11)
C16	.14504(40)	.25212(25)	.15527(12)
C17	.15855(44)	.29810(27)	.19664(14)
C18	.17976(42)	.38228(28)	.19565(16)
C19	.18795(42)	.42083(26)	.15315(17)
C20	.17251(38)	.37590(23)	.11128(14)
HN2	.1762(33)	-.0628(22)	.0685(11)
HN4	-.0573(39)	.1962(21)	.0719(12)
H4	.0254(32)	-.1043(18)	.1245(9)
H6	.0156(37)	-.0120(21)	.1919(11)
H7	.1138(34)	.0917(21)	.2400(11)
H8	.3447(36)	.1249(23)	.2411(12)
H9	.4914(37)	.0520(20)	.1909(11)
H10	.3839(35)	-.0545(21)	.1455(11)
H14	.1185(30)	.2756(19)	.0395(10)
H16	.1268(42)	.1934(27)	.1568(14)
H17	.1553(42)	.2699(26)	.2269(15)
H18	.1915(46)	.4160(28)	.2238(16)
H19	.1994(40)	.4773(26)	.1506(13)
H20	.1744(31)	.4025(20)	.0838(11)

achieved.[11] With two molar equivalents of the ethyl Grignard reagent, *6* gave the 2,4-dialkylated product *12* in 76 % yield. Using phenylmagnesium bromide and $NiCl_2$ (dppp) controlled stepwise substitution could not be effected; in the presence of less than two molar equivalents of the Grignard reagent, unreacted dichloride *6* and the triphenylpyrimidine *13* were the products.

X-Ray crystallographic analysis of 4. The crystals are monoclinic with cell dimensions $a=9.677(4)$ Å, $b=16.138(7)$ Å, $c=28.54(1)$ Å, $\beta=96.47(3)°$, space group $C2/c$, and $Z=16$ ($D_m=1.55$ gcm^{-3}, $D_X=$ 1.56 gcm^{-3}. The structure was solved by direct methods[12] and refined by full-matrix least squares technique[13,*] to an R-value of 3.7 % ($R_W=4.2$ %) for 3038 reflections measured on an automatic four-circle diffractometer at −150 °C. Final fractional coordinates and bond distances and angles with estimated standard deviations may be found in Table 1 and Table 2, respectively. Fig. 1 is a schematic drawing which shows the numbering of atoms and the hydrogen bonding system. The hydrogen bonds N2···N3 [2.900(3) Å] and N4···N1′ [2.844(3) Å] form infinite chains. The bond distances of Table 2 have normal values within estimated limits of errors. Bond angles are also normal except for those at C1 (128.3°) and C11 (128.5°), which are somewhat larger than expected.

Lists of thermal parameters and observed and calculated structure factors are available from P. Groth.

EXPERIMENTAL

^1H NMR data were recorded on a Varian A-60 spectrometer and the ^{13}C data on an FX-60 Fourier transform NMR spectrometer. The mass spectra were recorded on an MM70-70F VG Micromass spectrometer at 70 eV; the data are reported as MS [70 eV; m/z (% rel. int.)].

General procedure for the Grignard coupling reactions. The Grignard reagent (12 mmol) in ether (12 ml) was added with stirring over 5 min at 0 °C to a solution of $NiCl_2$ (dppp)[5] or$NiCl_2$ (PPh_3)[4] (0.2 mmol) and the halopyrimidine[2,3] *1* (10 mmol) in dry ether (100 ml) in an N_2-atmosphere. The nickel complex reacted at once with the Grignard reagent. When the addition was complete, the reaction mixture was removed from the cooling bath; after a few minutes an exothermic reaction ensued which turned the mixture dark yellow. The mixture was allowed to stand at room temperature overnight, it was then heated under reflux for 10 h, the cooled mixture cautiously hydrolyzed with 2 M HCl, the organic layer separated, the aqueous layer extracted with ether (3 x 25 ml), the combined ether solutions washed successively with water, saturated aqueous $NaHCO_3$ and water and the dried ($MgSO_4$) solution evaporated. The remaining product was further purified by recrystallization or chromatography.

6-Phenyl-2,4,5-trichloro-1,6-dihydropyrimidine 4a. *Method A*. From Mg (0.28 g, 0.012 gram atom) bromobenzene (1.8 g, 0.012 mol), $NiCl_2$(dppp) (108 mg, 0.02 mmol), and 2,4,5-trichloropyrimidine

* All programs used in the X-ray work (except those for phase determination) are included in this reference.

Table 2. Bond distances and angles with estimated standard deviations.

DISTANCE	(Å)	DISTANCE	(Å)
CL1 - C1	1.731(3)	CL2 - C2	1.735(3)
CL3 - C3	1.723(3)	CL4 - C11	1.737(3)
CL5 - C12	1.729(3)	CL6 - C13	1.724(3)
N1 - C1	1.289(4)	N1 - C2	1.399(4)
N2 - C1	1.331(4)	N2 - C4	1.480(4)
N3 - C11	1.287(4)	N3 - C12	1.398(4)
N4 - C11	1.334(4)	N4 - C14	1.473(4)
C2 - C3	1.324(4)	C3 - C4	1.514(4)
C4 - C5	1.525(4)	C5 - C6	1.387(5)
C5 - C10	1.392(5)	C6 - C7	1.392(5)
C7 - C8	1.375(5)	C8 - C9	1.398(5)
C9 - C10	1.380(5)	C12 - C13	1.341(5)
C13 - C14	1.512(4)	C14 - C15	1.530(4)
C15 - C16	1.384(5)	C15 - C20	1.392(5)
C16 - C17	1.389(5)	C17 - C18	1.376(6)
C18 - C19	1.375(6)	C19 - C20	1.392(6)

ANGLE	(°)	ANGLE	(°)
C1 - N1 - C2	114.1(3)	C1 - N2 - C4	122.0(3)
C11 - N3 - C12	114.1(3)	C11 - N4 - C14	122.7(3)
CL1 - C1 - N1	117.1(2)	CL1 - C1 - N2	114.6(2)
N1 - C1 - N2	128.3(3)	CL2 - C2 - N1	113.3(2)
CL2 - C2 - C3	122.2(2)	N1 - C2 - C3	124.4(3)
CL3 - C3 - C2	123.5(3)	CL3 - C3 - C4	114.1(2)
C2 - C3 - C4	122.3(3)	N2 - C4 - C3	107.5(3)
N2 - C4 - C5	111.3(3)	C3 - C4 - C5	112.7(3)
C4 - C5 - C6	120.5(3)	C4 - C5 - C10	120.4(3)
C6 - C5 - C10	119.0(3)	C5 - C6 - C7	120.1(3)
C6 - C7 - C8	120.7(3)	C7 - C8 - C9	119.4(3)
C8 - C9 - C10	119.9(3)	C5 - C10 - C9	120.8(3)
CL4 - C11 - N3	116.9(2)	CL4 - C11 - N4	114.6(2)
N3 - C11 - N4	128.5(3)	CL5 - C12 - N3	113.5(2)
CL5 - C12 - C13	122.2(3)	N3 - C12 - C13	124.3(3)
CL6 - C13 - C12	122.9(3)	CL6 - C13 - C14	114.7(2)
C12 - C13 - C14	122.3(3)	N4 - C14 - C13	108.0(3)
N4 - C14 - C15	111.2(3)	C13 - C14 - C15	112.3(3)
C14 - C15 - C16	120.8(3)	C14 - C15 - C20	120.0(3)
C16 - C15 - C20	119.1(3)	C15 - C16 - C17	120.2(4)
C16 - C17 - C18	120.7(4)	C17 - C18 - C19	119.3(4)
C18 - C19 - C20	120.7(4)	C15 - C20 - C19	119.9(4)

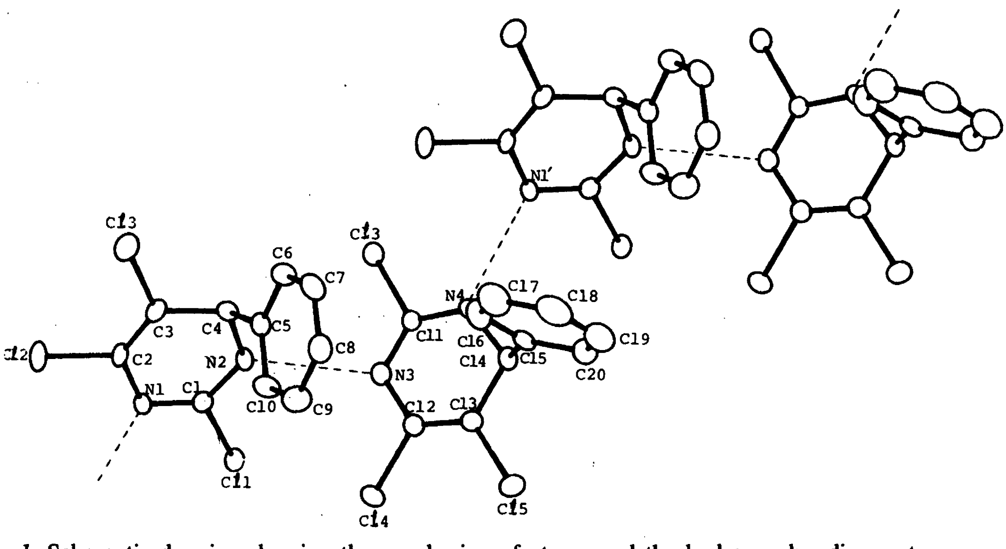


Fig. 1. Schematic drawing showing the numbering of atoms and the hydrogen bonding system.

(1.8 g, 0.01 mol). Colourless crystalline material; yield 82 %, m.p. 146 °C (MeOH). Anal. $C_{10}H_7Cl_3N_2$: C, H. ^{1}H NMR ($CDCl_3$): δ 4.7 (NH, exchanged in D_2O), 5.2 (H-6) and 7.3 (Ph). ^{13}C NMR (Me_2CO-d_6): δ146.3 (C-2), 142.1 (C-4); 135.3, 133.5, 130.1, 128.3 (Ph), 111.1 (C-5), 63.3 (C-6, $J_{C,H}$ 144 Hz). IR (KBr): 3100 cm^{-1} (NH).

Method B. The experimental conditions were the same as in method A except that the catalyst was changed; here was used $NiCl_2$ (PPh_3) (130 mg, 0.2 mol; yield of *4a* was 72 %.

2,4-Dichloro-5-fluoro-6-phenyl-1,6-dihydropyrimidine 4b. From Mg (0.28 g, 0.012 gram atom), bromobenzene (1.8 g, 0.012 mol), $NiCl_2(PPh_3)$ (130 mg, 0.2 mmol) and 2,4-dichloro-5-fluoropyrimidine (1.66 g, 0.01 mol). Colourless crystalline material; yield 66 %, m.p. 148 °C (CH_2Cl_2). Anal. $C_{10}H_7Cl_2FN_2$: C, H. ^{1}H NMR (DMSO-d_6): δ 3.4 (NH, exchanged in D_2O), 5.65 (H-6, $J_{H,F}$ 4.5 Hz) and 7.35 (Ph). IR (KBr): 3160 cm^{-1} (NH). MS: 246/244 (18/30, M), 245/243 (17/21), 211/209 (9/30), 169/167 (64/100) 133/131 (12/33), 78 (66), 77(18).

6-Phenyl-2,4,5-trichloropyrimidine 5. A solution of 6-phenyl-2,4,5-trichloro-1,6-dihydropyrimidine (1.3 g, 5 mmol) and DDQ (1.13 g) in dioxane (40 ml) was stirred at room temperature for 48 h. The hydroquinone was then filtered off, the filtrate evaporated at reduced pressure and the residual product purified by recrystallization; yield 45 %, m.p. 90 °C (MeOH).[8] ^{1}H NMR (DMSO-d_6): δ 7.6 (m, Ph).

2,4-Dichloro-6-phenylpyrimidine 6. A solution of 6-phenyl-2,4,5-trichloro-1,6-dihydropyrimidine (2.6 g, 10 mmol) and triethylamine (1.2 g, 12 mmol) in toluene (100 ml) was heated under reflux for 5 h. The cold reaction mixture was filtered, the filtrate evaporated at reduced pressure and the remaining product purified by preparative TLC (ether – light petroleum, 1:4); yield 84 %, m.p. 83 °C (heptane). Anal. $C_{10}H_6Cl_2N_2$: C, H. ^{1}H NMR (CCl_4): δ 7.3 (m, 4H; H-5 and *m,p*-Ph), 7.9 (m, 2H; *o*-Ph). ^{13}C NMR (CCl_4): δ 167.7 (C-2), 162.9 and 161.3 (C-4, C-6), 134.3, 132.2, 129.0, 127.5 (Ph), 114.8 (C-5, $J_{C,H}$ 172 Hz). MS: 226/224 (6/100, M), 191/189 (22/67), 164/162 (6/12), 154 (2), 128 (66), 127 (13), 77 (36). Compound *6* was also obtained in 20 % yield when the 5-fluoro analogue *4b* was used instead of *4a* in the above reaction.

2-Chloro-6-phenylpyrimidin-4-one 7. 1 M sodium hydroxide (10 ml) was added to a solution of 6-phenyl-2,4,5-trichloro-1,6-dihydropyrimidine (1,3 g, 5 mmol) in acetonitrile (30 ml) and the mixture heated at 80 °C for 2 h. The volume was then concentrated to *ca.* one fourth, the solution acidified (HCl) and the pricipitate purified by recrystallization; yellow crystalline material in 58 % yield, m.p. 185 °C (MeOH). Anal. $C_{10}H_7ClN_2O$: C, H. ^{1}H NMR (DMSO-d_6): δ 4.0 (NH, exchanged by D_2O), 7.03 (H-5), 7.4 and 7.9 (m, Ph) IR (KBr): 1648 cm^{-1} (CO). MS: 208/206 (31/100, M), 180/178 (5/15), 171 (34), 116 (16), 103 (36), 77 (18).

2-Chloro-4-methoxy-6-phenylpyrimidine 8. *Method A.* 1M sodium hydroxide (10 ml) was added to a solution of 6-phenyl-2,4,5-trichloro-1,6-dihydropyrimidine (1,3 g, 5 mmol) in methanol (20 ml) and the mixture heated under reflux for 3 h. The mixture was then concentrated to half its original volume and the precipitated product collected and recrystallized from methanol; colourless material in 86 % yield, m.p. 105 °C. Anal. $C_{11}H_9ClN_2O$: C, H. ^{1}H NMR ($CDCl_4$): δ 3.97 (OMe), 6.80 (H-5), 7.2 and 7.9 (m, Ph). MS: 222/220 (30/100, M), 221/219 (37/71), 191/189 (20/89), 155 (51), 128 (39), 102 (30), 77 (29).

Method B. A solution of 2,4-dichloro-6-phenylpyrimidine (1.13 g, 5 mmol) in methanol (15 ml) was added to a solution of sodium methoxide (from 0.13 g Na in 25 ml of MeOH). The mixture was heated to 40 °C and stirred at this temperature for 1 d. The mixture was then filtered, the filtrate evaporated, a little water added, the mixture extracted with ether, the solution evaporated and the product crystallized as above; yield 62 %.

2-Chloro-4-dimethylamino-6-phenylpyrimidine 9. A mixture prepared from potassium *tert*-butoxide (0.26 g, 2.2 mmol) and 6-phenyl-2,4,5-trichloro-1,6-dihydropyrimidine (0.5 g, 2 mmol) in DMF (30 ml) was heated at 140 °C for 3 h. The solvent was then distilled off at reduced pressure, the residue extracted with ether, the ether extracts washed with water, the dried ($MgSO_4$) ethereal solution evaporated and the residual material purified by TLC (Et_2O: pentane, 1:4); yellow crystalline material in 38 % yield, m.p. 122 °C (pentane). ^{1}H NMR (CCl_4): δ 3.30 (NMe_2), 6.8 (H-5), 7.4 and 7.9 (m, Ph). MS: 235/233 (26/72, M), 220/218 (25/75), 206/204 (30/89), 191/189 (4/6), 155 (30), 128 (89), 77 (31).

1-Methyl-6-phenyl-2,4,5-trichloro-1,6-dihydropyrimidine 10. A mixture of methyl iodide (1.0 g, 7 mmol), 6-phenyl-2,4,5-trichloro-1,6-dihydropyrimidine (1.3 g, 5 mmol) and potassium carbonate (0.69 g) in anhydrous acetone (100 ml) was heated under reflux for 24 h. The solvent was then distilled off, the residue triturated with water, and then recrystallized from methanol; colourless crystalline material in 64 % yield, m.p. 170 °C (dec.). Anal. $C_{11}H_9Cl_3N_2$: C, H. ^{1}H NMR (CCl_4): δ 2.93 (Me), 4.90 (H-6), 7.20 (Ph). MS: 276/274 (12/13, M), 241/239 (25/36), 203/201 (14/30), 199/197 (92/100), 128 (13), 77 (12).

2-Chloro-4-methyl-6-phenylpyrimidine 11a. Methylmagnesium iodide (6 mmol) in anhydrous ether (25 ml) was added at 0 °C to an ethereal suspension of 2,4-dichloro-6-phenylpyrimidine (1.1 g, 5 mmol) and $NiCl_2$(dppp) (54 mg, 0.1 mmol). The reaction mixture was treated in the same way as described above for Grignard reactions; yield 49 %, m.p. 53 °C. ^{1}H NMR (CCl_4): δ 2.55 (Me), 7.4 (m, 4 H; H-5 and 3H, m, *p*-Ph), 7.9 (m, 2H, *o*-Ph). MS 206/204 (29/100, M), 191/189 (4/12), 169 (24), 141 (23), 129/127 (9/4), 77 (15).

2-Chloro-4-ethyl-6-phenylpyrimidine 11b was prepared as *11a* above using ethylmagnesium bromide. The product was purified by preparative TLC on silica (Et_2O–pentane, 1:4), yield 55 % of a colourless liquid. ^{1}H NMR (CCl_4): δ 1.33 and 2.77 (Et), 7.13 (H-5), 7.3 (m, 3H; m, *p*-Ph).

2,4-Diethyl-6-phenylpyrimidine 12 was prepared as above using 2 molar equivalents of ethylmagnesium bromide. The product was isolated after preparative TLC on silica (Et_2O – pentane); yield 76 % of a colourless liquid. ^{1}H NMR (CCl_4): δ 1.20 and 3.62 (Et), 6.70 (H-5), 7.2 and 7.8 (m, Ph).

2,4,6-Triphenylpyrimidine 13. Phenylmagnesium bromide, prepared from Mg (0.28 g, 0.012 gram atom) and bromobenzene (1.8 g, 0.012 mol), in anhydrous ether (25 ml) was gradually added to a solution of 2,4-dichloro-6-phenylpyrimidine (1.1 g, 5 mmol) and $NiCl_2$ (dppp) (54 mg, 0.1 mmol) in anhydrous ether (50 ml) at 0 °C. The reaction was worked up in the usual way and the product crystallized as white needles from heptane; yield 95 %, m.p. 190 °C.[10] Anal. $C_{22}H_{16}N_2$: C, H. ^{1}H NMR (CCl_4): δ 7.8 (H-5), 7.4, 8.2, 8.6 (3 × Ph). MS: 308 (100, M), 205 (55), 102 (65), 77 (14).

When one equivalent of the Grignard reagent was used the triphenylpyrimidine *13* and the dichloride starting material *6* were isolated from the reaction in 55 and 40 % yields, respectively.

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