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Introduction of Carbon Substituents into Pyrimidines by Grignard Reagents

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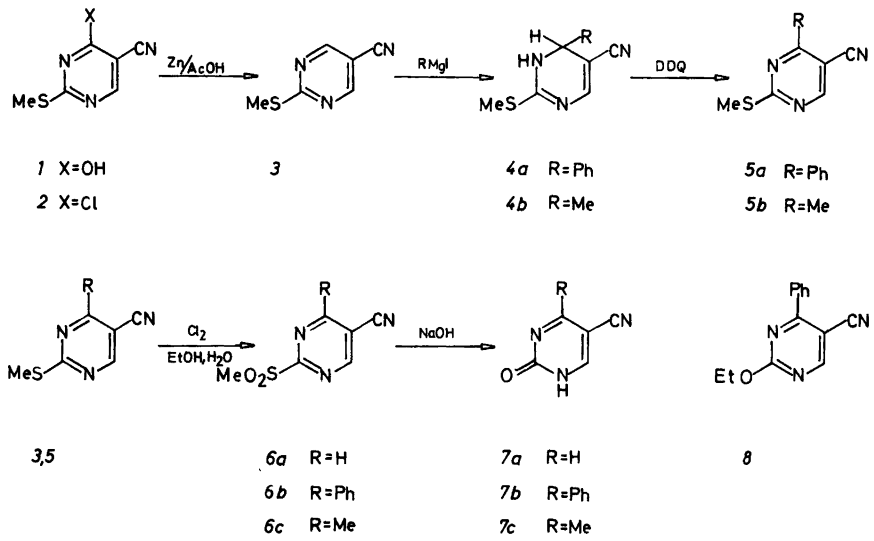
Alkyl- and arylmagnesium halides selectively form 1:1-adducts with the heterocyclic ring in substituted 5-cyanopyrimidines. Dehydrogenation gives the corresponding alkyl or aryl substituted pyrimidine.

Grignard reagents react with halopyrimidines under the influence of nickel-complex catalysis; the nature of the nucleophile is decisive for the preferred reaction path which is either cross-coupling or 1:1 adduct formation.[1] Carbon–carbon bond formation through replacement of thioether groups also seems to require nickel-complex catalysis.[2] We herein report our findings for the reactions of Grignard reagents with 5-cyano-2-methylthiopyrimidine *3* in the absence of a catalytic agent. In the reaction of *3*, addition to the 3,4-azomethine bond of the pyrimidine nucleus [3,4] or the usual addition of Grignard reagents to the nitrile group,[5] can be envisaged. Perhaps surprisingly, in view of the failure of the halopyrimidines to react with Grignard reagents at significant rates in the absence of nickel catalysis, the cyanopyrimidine *3* rapidly formed nuclear adducts as discussed below.

For the synthesis of the 5-cyanide *3*, 5-cyano-2-methylthiopyrimidin-4-one *1* was the starting material; *1* was available by the condensation between *S*-methylisothiouronium iodide and



1 X=OH
2 X=Cl
3
4a R=Ph
4b R=Me
5a R=Ph
5b R=Me
3,5
6a R=H
6b R=Ph
6c R=Me
7a R=H
7b R=Ph
7c R=Me
8

Scheme 1.

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ethyl 2-cyano-3-ethoxyacrylate.[6] *1* was converted to the chloride *2* using phosphorus oxychloride [7] and *2* subjected to hydrogenolysis using zinc in acetic acid; the previously reported synthesis from *2* in auqeous ethanol without acid catalysis, gives much inferior yield of *3*.[8]

In the Grignard reaction, methyl- and phenylmagnesium iodide were used in ether solution. In both cases the adduct *4* was the exclusive product. The reaction is rapid and goes under mild conditions as would be expected for the selectivity observed in the reaction. Dehydrogenation to the aromatic pyrimidine *5* was effected using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

The net result of the above reaction is the introduction of a carbon substituent into the pyrimidine ring. This can be used with advantage in the synthesis of a variety of derivatives, such an example being illustrated by the preparation of the substituted pyrimidinones *7*. The methylthio substituent in the cyanide *3* could be hydrolyzed under alkaline conditions, but it was difficult to effect complete selectivity without attack on the cyano group. Therefore the sulfide substituent in *3* and *5* was oxidized to a sulfonyl group (*6*) using chlorine in aqueous ethanol. The phenyl derivative *5a*, however, furnished the 2-ethoxy derivative *8* under these conditions presumably because the exothermic reaction of *5a* resulted in solvolysis. In aqueous dioxane, however, the sulfone *6b* was smoothly formed from *5b*. Aqueous alkaline hydrolysis of *6* yielded the 5-cyanolactams *7*.

EXPERIMENTAL

The MS data are given as MS 70 eV; *m/z* (% rel.int.).

5-Cyano-2-methylthiopyrimidine [8] 3. 4-Chloro-5-cyano-2-methylthiopyrimidine [7] (7.3 g, 39 mmol) was dissolved in ethanol (65 ml) and water (12 ml) and zinc dust (12.4 g) added. Acetic acid (0.5 ml×5, 44 mmol) was added at intervals (0, 30, 60, 90 and 120 min) to the vigorously stirred mixture and the stirring continued at room temperature for 2.5 h when TLC (silica gel and chloroform) showed the reaction to be complete. The reaction mixture was then filtered, the solid washed with warm ethanol and the combined washings and filtrate evaporated to dryness at reduced pressure. The residue was extracted with chloroform and the chloroform solution filtered through an alumina column (neutral). Evaporation of the chloroform eluate left the title compound which was recrystallized from ethanol, yield 4.0 g (67 %), m.p. 79–80 °C. [5] ^{1}H NMR ($CDCl_3$): δ 2.62 (SMe), 8.76 (H-4, H-6).

5-Cyano-2-methylthio-4-phenyl-3,4-dihydropyrimidine 4a. A solution of 5-cyano-2-methylthiopyrimidine (2.3 g, 15.2 mmol) in dry ether (50 ml) was added dropwise with stirring at 0 °C to an ethereal solution of phenylmagnesium iodide, which had been prepared from iodobenzene (6.21 g, 31 mmol) and Mg (0.75 g, 31 mmol) in dry ether (100 ml). After the addition had been completed the mixture was stirred for 10 min at room temperature, the mixture poured into 20 % aqueous NH_4Cl, the ether layer separated, the aqueous layer extracted with ether, the combined ether solutions washed with water, the dried ($MgSO_4$) solution evaporated and the residue chromatographed on neutral alumina (Woelm-activity II) using $CHCl_3$: hexane 7:3 for elution; yield 2.1 g (60 %) of an oily material which was analyzed as such. Anal. $C_{12}H_{11}N_3S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.36 (S–Me), 4.87 (H-4), 6.20 (NH), 6.98 (H-6), 7.23 (Ph). MS: 229 (M, 31), 228 (19), 214 (23), 152 (100).

5-Cyano-4-methyl-2-methylthio-3,4-dihydropyrimidine 4b was prepared as above using methylmagnesium iodide. The product was purified by chromatography on basic alumina (activity II) using $CHCl_3$–EtOAc 7:3 after initial elution with $CHCl_3$–hexane 7:3 to remove some starting material; yield 1.8 g (54 %) of an oily material. ^{1}H NMR ($CDCl_3$) δ 1.38 (4-Me, *J* 6.5 Hz), 2.40 (SMe), 4.30 (H-4, *J* 6.5 Hz), 6.90 (H-6), 6.5–7 (NH).

5-Cyano-2-methylthio-4-phenylpyrimidine 5a. 5-Cyano-2-methylthio-4-phenyl-3,4-dihydropyrimidine (2.5 g, 10.9 mmol) and DDQ (2.7 g, 12.0 mmol) were stirred together in benzene (50 ml) for 10 min. The solution was then concentrated to one third of its volume, the precipitate removed and extracted with boiling benzene, the benzene solutions combined, most of the solvent distilled off and the concentrated solution passed through a short (4 cm) alumina column. The title compound was eluted with chloroform; yield 1.65 g (67 %), m.p. 141–143 °C (EtOH). Anal. $C_{12}H_9N_3S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.58 (S–Me), 7.3–7.6 and 7.8–8.2 (Ph), 8.65 (H-6). IR (KBr): 2200 cm^{-1} (CN). MS: 227 (M, 100), 226 (31), 181 (28), 180 (54), 154 (11), 127 (13), 77 (11).

5-Cyano-4-methyl-2-methylthiopyrimidine 5b was prepared as above from 5-cyano-4-methyl-2-methylthio-3,4-dihydropyrimidine. The reaction mixture was left at room temperature overnight

before isolation *via* chromatography; yield 83 %, m.p. 52–53 °C (EtOH). Anal. $C_7H_7N_3S$: C, H. ^{1}H NMR ($CDCl_3$): δ 2.58 (Me), 2.66 (Me), 8.61 (H-6).

5-Cyano-2-methylsulfonylpyrimidine 6a was prepared from *3* by chlorine oxidation in aqueous ethanol as described for *6c*.

5-Cyano-2-methylsulfonyl-4-phenylpyrimidine 6b. Chlorine was bubbled through a stirred solution of 5-cyano-2-methylthio-4-phenylpyrimidine (0.70 g, 3.0 mmol) in dioxane (55 ml) and water (15 ml) at 0 °C for 15 min. On concentrating the solution at reduced pressure the product crystallized; yield 0.65 g (81 %), m.p. 155–157 °C. Anal. $C_{12}H_9N_3O_2S$: C, H. ^{1}H NMR ($CDCl_3$): δ 3.40 (Me), 7.4–7.7 and 8.0–8.3 (Ph), 9.10 (H-6). IR (KBr): 2200 cm^{-1} (CN). MS: 260 (14), 259 (M, 72), 196 (31), 181 (34), 180 (60), 128 (100), 77 (40).

5-Cyano-4-methyl-2-methylsulfonylpyrimidine 6c. Chlorine gas was bubbled through a stirred solution of 5-cyano-4-methyl-2-methylthiopyrimidine (0.72 g, 4.3 mmol) in ethanol (25 ml) and water (10 ml) at 10 °C for 10 min and left at this temperature for 4 h before the precipitate was collected and recrystallized from ethanol; yield 0.45 g (52 %), m.p. 115 °C. Anal. $C_7H_7N_3O_2S$: C, H. ^{1}H NMR (DMSO-d_6): δ 2.80 (4-Me), 3.43 ($MeSO_2$), 9.45 (H-6).

5-Cyanopyrimidin-2-one [9] 7a was prepared from 5-cyano-2-methylthiopyrimidine as described for *7b* below allowing the hydrolysis to proceed overnight; m.p. 260–262 °C after sublimation (190 °C/0.5 mmHg). ^{1}H NMR (TFA): δ 9.02 (H-4, H-6).

5-Cyano-4-phenylpyrimidin-2-one 7b. 2 M NaOH was added dropwise with stirring to a solution of 5-cyano-2-methylsulfonyl-4-phenylpyrimidine (0.20 g, 0.77 mmol) in dioxane (2 ml) and water (2 ml) at room temperature. The mixture was stirred for 15 min after the addition was completed and then acidified with HCl when the product crystallized; yield 0.11 g (72 %), m.p. 214 °C. Anal. $C_{11}H_7N_3O$: C, H. ^{1}H NMR (DMSO-d_6): δ 7.3–7.8 (Ph), 8.78 (H-6). IR (KBr): 2210 cm^{-1} (CN). MS: 197 (M, 87), 196 (100), 171 (10), 170 (5), 169 (14), 155 (6), 142 (7), 77 (19).

5-Cyano-4-methylpyrimidin-2-one 7c was prepared from 5-cyano-4-methyl-2-methylsulfonylpyrimidine as *7b* above by allowing the hydrolysis to proceed for 1 h. After acidification the product was obtained in 56 % yield, m.p. 258–260 °C (sublimed). Anal. $C_6H_5N_3O$: C, H. ^{1}H NMR (TFA): δ 3.01 (Me), 9.15 (H-6).

5-Cyano-2-ethyloxy-4-phenylpyrimidine 8 was obtained in a mixture with the lactam *7b* when chlorine gas was bubbled into a solution of 5-cyano-2-methylthio-4-phenylpyrimidine (1.0 g, 4.4 mmol) in a solution of ethanol (35 ml) and water (10 ml) at −10 °C for 10 min. Fractional sublimation from the precipitate gave the title compound in 60 % yield (0.60 g), m.p. 76–77 °C. Anal. $C_{13}H_{11}N_3O$: C, H. ^{1}H NMR ($CDCl_3$): δ 1.45 and 4.54 (Et), 7.3–7.6 and 7.8–8.1 (Ph), 8.70 (H-6). MS: 225 (M, 42), 224 (31), 197 (33), 196 (66), 181 (100), 180 (16), 104 (18).

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