Nickel-complex Catalysis in the Reaction between Grignard Reagents and Substituted Pyrimidines

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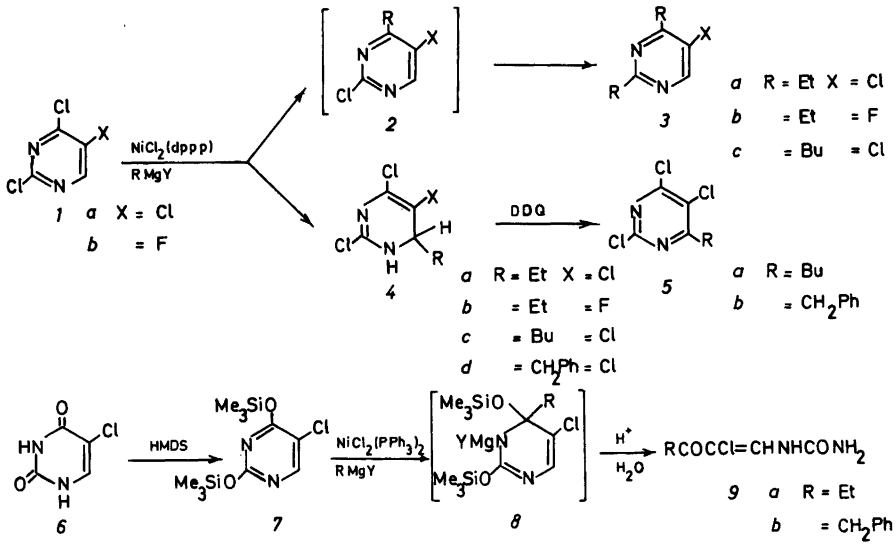
Recently we reported that phenylmagnesium bromide in reactions catalyzed by dichloro-[1,3-bis(diphenylphosphinopropane]nickel(II), $NiCl_2$(dppp), or dichloro-bis(triphenylphosphine)nickel(II), $NiCl_2(PPh_3)_2$, adds the carbon nucleophile selectively to the vacant position in 2,4-dichloro-5-chloro(fluoro)pyrimidine rather than undergoing substitution by cross-coupling.[1] We now report that the main reaction path for alkyl Grignard reagents is different; in this case the expected cross-coupling occurs with substitution of the halogen atoms in the 2- and the 4-position. Thus in the reaction of ethylmagnesium bromide in the presence of $NiCl_2$(dppp) the major new product is the diethylated pyrimidine *3a* even when only one molar equivalent of the Grignard reagent was used; attempts to effect monosubstitution were not successful. In the minor product, the adduct *4a*, the carbon nucleophile has entered the vacant pyrimidine position in *1a*; product ratio *3a*–*4a* is 7:1. The adduct *4a* is not formed in significant amounts if heating of the reaction mixture is avoided. The 5-fluoro analogue *1b* reacted in the same way. Butylmagnesium bromide in its reaction with *1a* gave an analogous product ratio of *3c* and *4c*. The latter, however, was very readily aromatized to *5a* by air oxidation.

As an example from the aralkyl group, the Grignard reagent from benzyl chloride was reacted with *1a*; the product was the adduct *4d*. It is thus notable that the benzyl reagent behaves differently from the alkyl reagents and, in fact, reacts in the same manner as the aryl reagent previously reported upon.[1] The structure *4d* assigned to the product, has been confirmed by a dehydrogenation reaction to furnish *5b* using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ).

The silyl ether *7* was studied as part of a search for pyrimidines with less reactive 2,4-substituents than in *1* in order to attain regioselectivity in substitution reactions. The silyl ether *7* is readily available from 5-chlorouracil *6* by heating with hexamethyldisilazane. The reaction of *7* with both the ethyl and benzyl Grignard reagents using either $NiCl_2(PPh_3)_2$ or $NiCl_2$(dppp) catalysis appears to proceed initially as desired by the addition of the Grignard reagent to the 4-position. During the reaction, or more likely during the aqueous work-up, however, the adduct suffers opening of the ring to furnish the novel *N*-vinylurea derivatives *9*. The reaction sequence *6*→*9* therefore provides a convenient route to this class of compounds.

Experimental. The data from the mass spectra



Scheme 1.

0302-4369/83 $2.50

are reported as MS[70 eV; *m/z*(% rel. int.)].

General procedure for the Grignard coupling reactions. The Grignard reagent (12 mmol) in ether (25 ml) was added under nitrogen over 10 min at 0 °C to a stirred suspension from the halopyrimidine *1* (10 mmol) and $NiCl_2(dppp)$[2] or $NiCl_2(PPh_3)$[3] (0.2 mmol) in dry ether (100 ml). There was an immediate change of colour through yellow to brown. The mixture was allowed to reach room temperature, left stirring overnight and finally heated under reflux for 10 h. The cold mixture was hydrolyzed with 2 M HCl, the organic layer separated, the aqueous layer extracted with ether (3×25 ml), the combined ether solutions washed with water, with saturated sodium carbonate solution and water again, and the dried ($MgSO_4$) ether solution evaporated. The product was further purified by recrystallization or chromatography as described.

2,4-Diethyl-5-chloropyrimidine 3a *and 2,4,5-trichloro-6-ethyl-1,6-dihydropyrimidine* 4a were obtained from ethylmagnesium bromide and 2,4,5-trichloropyrimidine[4] using $NiCl_2(dppp)$ admixed with some starting material. The products were separated by preparative TLC (ether–light petroleum; 1:1).

3a. Colourless oil, yield 47 %. Anal. $C_8H_{11}ClN_2$: C,H. ^1H NMR (CCl_4): δ 1.30 and 2.83 (Et), 8.25 (H-6). MS: 172/170 (19/61, M), 171 (40), 169 (100), 157 (8), 155 (24), 149 (24), 147 (40), 120 (10).

4a. Colourless crystals, m.p. 105 °C (heptane), yield 7 %. Anal. $C_6H_7Cl_3N_2$: C, H, N. ^1H NMR (CCl_4): δ 0.9–2.0 (CH_3 and CH_2), 4.6 (t, H-6), 10.2 (NH; H–D exchange in D_2O). IR (KBr): 3120 cm^{-1} (NH). MS: 214 (8), 212 (13, M), 195 (97), 193 (100), 76 (6), 149 (27), 147 (45).

When the reaction was run at 0 °C and room temperature the product was a mixture of *3a* and *1a*.

When the reaction was run with 2 molar equivalents of ethylmagnesium bromide the yield of *3a* was 70 % and of *4a* 9 %.

2,4-Diethyl-5-fluoropyrimidine 3b was obtained from ethylmagnesium bromide, 2,4-dichloro-5-fluoropyrimidine[5] and $NiCl_2(dppp)$. Small amounts of the adduct *4b* was also formed but were not isolated. *3b* was isolated from the reaction mixture by preparative TLC (ether–pentane; 1:4); yield 53 % of colourless oil. Anal. $C_8H_{11}FN_2$: C, H. ^1H NMR (CCl_4): δ 1.3 and 2.8 (Et), 8.1 (H-6). MS: 154 (67, M), 153 (100), 126 (17), 100 (3), 98 (8).

2,4-Dibutyl-5-chloropyrimidine 3c *and 2,4,5-trichloro-6-butylpyrimidine* 5a were obtained from butylmagnesium bromide and 2,4,5-trichloropyrimidine using $NiCl_2(dppp)$. The products were separated by preparative TLC (ether–pentane; 1:5). During the isolation work the part of the product which was the adduct *4c* was oxidized by air to furnish *5a* which was the product isolated.

3c. Colourless oil, yield 40 %. Anal. $C_{12}H_{19}ClN_2$: C, H. ^1H NMR (CCl_4): δ 0.9, 1.5, 2.8 (Bu), 8.22 (H-6). MS: 228/226 (1/3, M), 213 (3), 210 (6), 197 (6), 149 (53), 113 (13), 57 (100).

5a. Colourless oil, yield 8 %. Anal. $C_8H_9Cl_3N_2$: ^1H NMR (CCl_4): δ 0.95, 1.65, 2.90 (Bu). MS: 238 (4, M), 202 (4), 200 (30), 198 (90), 164 (3), 162 (9).

When the reaction was run in the presence of 2.2 mol equivalents of the Grignard reagents, the yields of *3c* and *5a* were increased to 65 and 15 %, respectively.

6-Benzyl-2,4,5-trichloro-1,6-dihydropyrimidine 4d was formed almost exclusively from benzylmagnesium chloride and 2,4,5-trichloropyrimidine using $NiCl_2(dppp)$ as above; colourless crystalline material in 86 % yield, m.p. 168 °C ($CHCl_3$). Anal. $C_{11}H_9Cl_3N_2$: C, H. ^1H NMR (DMSO-d_6): δ 2.85 (CH_2), 4.7 (H-6), 4.95 (NH; H–D exchange in D_2O), 7.2 (Ph). IR (KBr): 3125 cm^{-1} (NH). MS: 239 (3, M–Cl), 187 (30), 185 (90), 183 (100), 149 (21), 147 (30), 91 (36).

When $NiCl_2(PPh_3)$ was used as the catalyst, the yield of *4d* dropped to 78 %.

6-Benzyl-2,4,5-trichloropyrimidine 4d. A solution of 6-benzyl-2,4,5-trichloro-1,6-dihydropyrimidine (0.55 g, 2 mmol) and DDQ (0.45 g) in dioxan (25 ml) was stirred at room temperature for 48 h. The precipitated material was then filtered off, the filtrate evaporated under reduced pressure and the product isolated from the residual material by preparative TLC (ether–pentane; 1:3); yield 39 %, m.p. 85 °C (hexane). Anal. $C_{11}H_7Cl_3N_2$: C, H. ^1H NMR ($CDCl_3$): δ 4.25 (CH_2), 7.2 (Ph). MS: 274/272 (66/100, M), 239 (35), 237 (56), 204 (4), 202 (15), 91 (67).

2,4-Bis(trimethylsilyloxy)-5-chloropyrimidine 7. A mixture of 5-chlorouracil[6] (14.5 g, 0.1 mol), hexamethyldisilazane (50 ml) and ammonium sulfate (0.08 g) was heated under reflux and stirring under anhydrous conditions for 5 h. Fractional distillation yielded the title compound in 95 % yield, b.p. 92 °C/1 mmHg. ^1H NMR ($CDCl_3$): δ 0.35 (SiMe), 8.10 (H-6).

2-Chloro-1-ureido-1-penten-3-one 9a. Ethylmagnesium bromide, prepared from Mg (0.28 g, 0.012 g.atom) and ethyl bromide (1.3 g, 0.012 mol) in anhydrous ether (25 ml), was added gradually to a solution of 2,4-bis(trimethylsilyloxy)-5-chloropyrimidine (2.9 g, 0.01 mol) and $NiCl_2(PPh_3)$ (130 mg, 0.2 mmol) in anhydrous ether (100 ml) at 0 °C. The mixture was stirred overnight, heated under reflux for 24 h, the cooled mixture hydrolyzed with 2 M HCl, the

organic layer separated, the aqueous layer extracted with ethyl acetate (4×25 ml), the combined organic solutions washed with water, with saturated aqueous sodium carbonate and again with water, and the dried ($MgSO_4$) solution evaporated; yield 56 %, m.p. 218 °C (EtOAc). Anal. $C_6H_9ClN_2O_2$: C, H. ^1H NMR (DMSO-d_6): 0.9, 1.5 (Et), 4.6 (=CH), 3.8, 7.75, 10.4 (NH, H–D exchange in D_2O). IR (KBr): 3320, 3180, 3050 (NH, NH_2), 1700 cm^{-1} (CO). MS: 178/176 (8/24, M), 149 (13), 147 (40), 106 (14), 104 (42), 93 (27), 58 (100).

2-Chloro-4-phenyl-1-ureido-1-buten-3-one 9b was prepared from benzylmagnesium chloride as above; yield 52 %, m.p. 207 °C (EtOAc; decomp.). Anal. $C_{11}H_{11}ClN_2O_2$: C, H. ^1H NMR (DMSO-d_6): 2.95 (CH_2), 4.15 (=CH), 7.3 (Ph), 3.5, 7.8, 11.1 (NH and NH_2, H–D exchange in D_2O). IR (KBr): 3900, 3200, 3100 (NH, NH_2), 1720 cm^{-1} (CO). MS: 203 (3, M–Cl), 149 (2), 147 (6), 91 (100).

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