Organomanganese(II) Reagents in the Synthesis of 5-Pyrimidinyl Ketones

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Arukwe, J. and Undheim, K., 1986. Organomanganese(II) Reagents in the Synthesis of 5-Pyrimidinyl Ketones. – Acta Chem. Scand. B 40: 764–767.

Substituted alkyl 5-pyrimidinyl ketones were formed from acid chlorides of pyrimidine-5-carboxylic acids and alkylmanganese(II) iodides. The corresponding alcohols were also formed in the case of sterically less requiring organomanganese reagents and the activated pyrimidines.

General methods for the synthesis of 5-acylpyrimidines are of interest in order to make 5-acyl derivatives of the important pyrimidine system available for biological studies. Relatively few 5-acylpyrimidines have been described, but, very recently, we reported a method for the preparation of such derivatives (*2*) from the corresponding lithium 5-lithiopyrimidine-4-carboxylate (*1*) and an acid chloride.[1] The strongly basic conditions of the reaction, however, do not allow the acid chloride reagent to contain α hydrogens. We report an alternative approach, based on organomanganese(II) reagents, for the synthesis of simple aliphatic ketone derivatives. Organomanganese(II) reagents have over the last few years been found useful for the preparation of chemically sensitive ketones from acid halides or anhydrides. The reagent is of low basicity, is highly chemoselective and is obtainable from organolithium or organomagnesium reagents on treatment of ethereal solutions with manganese (II) halides.[2,3]

The carbonyl group in the desired ketone can be contained either in the pyrimidine or alternatively in the aliphatic reagent. The method described here used the former approach. The starting material, the pyrimidine-5-carboxylic acid derivative *3*, and hence *4*, was readily formed in a cyclization reaction between an isothiouronium salt and ethyl 3-*N*,*N*-dimethylamino-2-formylacrylate with subsequent ester hydrolysis. The conditions for the alkaline hydrolysis of *3* could be chosen so as to yield selective ester hydrolysis (*4*) or to allow the reaction to proceed further with replacement of the 2-methylthio group to furnish the 2-oxo acid *8*. With thionyl chloride, the acid *4* was converted to its acid chloride *5*, whereas a mixture of thionyl chloride and phosphorus oxychloride was used to convert *8* into its 2-chloro acid chloride *9*.

For the formation of the ketones *6*, the acid chloride *5* was reacted with organomanganese(II) reagents which were prepared from the corresponding organolithium compounds. The coupling reactions were initially run at −85 to −80 °C and selective attack at the carbonyl chloride function was observed. It was claimed originally that the organomanganese reagents gave exclusively the corresponding ketone with acid chlorides,[2] but, in our reactions, some of the tertiary alcohol was formed, especially with the methylmanganese reagent. The formation of tertiary alcohol is attributed to the electron-withdrawing effect of the pyrimidine ring which activates the carbonyl group for further nucleophilic addition. The second addition appears to be sensitive to the bulkiness of the reagent. The formation of tertiary alcohol agrees well with the recent report that the activated oxo function in α-ketoesters reacts readily with organomanganese reagents.[3]

The 2-chloro derivative *9* was less satisfactory for ketone formation (*10*), presumably because of the ease of substitution of the 2-chloro substituent. With the methyl reagent, formation of the tertiary alcohol *14a* was again an important side reaction. Both the ketones *6* and *10* could be

converted to the same 2(1*H*)-pyrimidinone *11* which, on treatment with benzyl bromide, gave the corresponding *N*-alkylated product *12*. For the preparation of *11*, compound *6* was initially oxidized to the sulfone *7* which was easily hydrolyzed to *11* because of the activation from the keto group. Compound *10* was similarly hydrolyzed to furnish *11*.

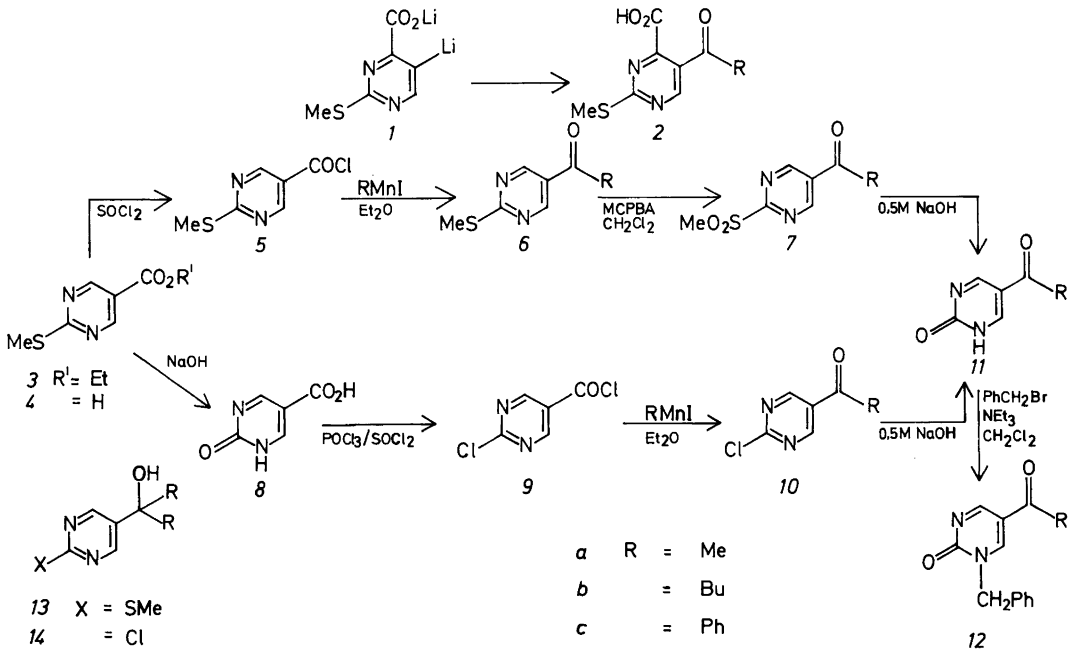
Experimental

The ^{1}H NMR spectra were recorded at 60 MHz unless otherwise specified. The mass spectra were recorded at 70 eV ionizing voltage. The organometallic reactions were carried out under N_2; the ether solvents were distilled over lithium aluminum hydride.

Ethyl 2-methylthiopyrimidine-5-carboxylate 3. Ethyl 3-*N*,*N*-dimethylamino-2-formylacrylate[4] (20.0 g, 120 mmol) and *S*-methylisothiouronium sulfate (48.6 g, 260 mmol) were added to sodium ethoxide (260 mmol) in anhydrous ethanol (300 ml) and the mixture heated under reflux for 6 h. The cold reaction mixture was filtered, the filtrate neutralized by HCl, evaporated to about 1/3 the volume, water (200 ml) added, the mixture extracted with diethyl ether (5×100 ml) and the washed and dried ($MgSO_4$) solution evaporated. The residual oil was chromatographed on silica gel using 1:1 light petroleum/diethyl ether. Yield 11.2 g (48%), b.p. 104°C/0.001 mmHg. Anal. $C_8H_{10}N_2O_2S$: C,H. ^{1}H NMR ($CDCl_3$): δ 1.50 and 4.40 (OEt), 2.65 (SMe), 9.00 (2H, H-4,6). IR(film): 1721 cm^{-1} (CO). M: 198 (100, M), 172 (3), 171 (6), 170 (75), 169 (16), 153 (38).

2-Methylthiopyrimidine-5-carboxylic acid 4. Ethyl 2-methylthiopyrimidine-4-carboxylate (11.7 g, 58 mmol) was added to ethanolic KOH (5.6 g, 100 mmol; 80 ml), the solution stirred at ambient temperature for 15 min before most of the solvent was distilled off at reduced pressure and water (30 ml) added. The mixture was extracted with diethyl ether and the product precipitated by addition of HCl to the aqueous solutions. Yield 9.70 g (98%), m.p. 267°C (MeOH). Anal. $C_6H_6N_2O_2S$: C,H. ^{1}H NMR (DMSO-d_6): δ 2.65 (SMe), 9.00 (2H, H-4,6). MS: 170 (100, M), 169 (20), 124 (4), 125 (13), 124 (42), 97 (12).

2-Methylthiopyrimidine-5-carbonyl chloride 5. 2-Methylthiopyrimidine-5-carboxylic acid (9.70 g, 57 mmol) and thionyl chloride (200 ml) were heated together for 2 h, excess thionyl chloride distilled off and the solid residue crystallized



from dry diethyl ether. Yield 8.20 g (76 %), m.p. 170 °C. ^{1}H NMR ($CDCl_3$): δ 2.65 (SMe), 9.10 (2H, H-4,6). IR (KBr): 1735 cm^{-1} (CO).

Preparation of 5-acyl-2-methylthiopyrimidines 6. Methyllithium in hexane, or butyl or phenyllithium in diethyl ether (15 mmol; 10 ml) was added dropwise from a syringe to a stirred suspension of manganese(II) iodide (15 mmol) in dry diethyl ether (40 ml) at −10 °C, the mixture stirred for 15 min before the temperature was allowed to reach 10 °C during 30 min. The mixture was then cooled to −85 °C before dropwise addition (syringe) during 20 min of a solution of 2-methylthiopyrimidine-5-carbonyl chloride (13 mmol) in dry THF (30 ml), stirred at −80 °C for 4 h and allowed to reach 0 °C during 1 h. The resultant deep red solution was poured into 1 M HCl (30 ml), the organic phase collected and the aqueous phase extracted with chloroform (3×40 ml). The combined organic solution was shaken with aqueous sodium bisulfite (30 ml) which removed the colour, with aqueous sodium carbonate (30 ml) and the washed and dried ($MgSO_4$) solution evaporated. (The ketone product may contain some of the corresponding tertiary alcohol. These are separated by chromatography on silica gel, being the ketone first eluted by chloroform).

5-Acetyl-2-methylthiopyrimidine 6a. The yield of *6a* was 73 %, m.p. 128 °C (MeOH). The product was identical to that obtained from a cyclization reaction.[5] The second product, eluted by chloroform, was *2-(2-methylthiopyrimidin-5-yl)propan-2-ol* 13a. Yield 25 %. Anal. $C_8H_{12}N_2OS$: C,H. ^{1}H NMR ($CDCl_3$): δ 1.60 (C-Me_2), 2.65 (SMe), 2.90 (OH), 8.60 (2H, H-4,6). IR (film: 3300 cm^{-1} (OH).

2-Methylthio-5-pentanoylpyrimidine 6b. The yield of *6b* was 70 %, m.p. 62 °C (EtOH). Anal. $C_{10}H_{14}N_2OS$: C,H. ^{1}H NMR ($CDCl_3$): δ 0.9–1.9 and 3.00 (Bu), 2.65 (S-Me), 9.00 (2H, H-4,6). IR (KBr): 1675 cm^{-1} (CO). MS: 210 (14, M), 170 (5), 169 (8), 168 (68), 155 (5), 154 (8), 153 (100). The second product, eluted by chloroform, was *5-(2-methylthiopyrimidin-5-yl)nonan-5-ol* 13b. The product was further purified by chromatography on neutral alumina using 1:1 light petroleum/diethyl ether. Yield 7 %. Anal. $C_{14}H_{24}N_2OS$: C,H. ^{1}H NMR ($CDCl_3$): δ 0.9–2.0 (2 Bu), 2.65 (SMe), 8.55 (2 H, H-4,6), IR (film): 3300 cm^{-1} (OH). MS: 268 (3, M), 212 (13), 211 (100), 169 (4), 168 (3), 155 (7).

5-Benzoyl-2-methylthiopyrimidine 6c. The yield of *6c* was 40 %, m.p. 100 °C (EtOH). The physical data of the product were the same as previously described.[1]

Preparation of 5-acyl-2-methylsulfonylpyrimidines 7. A solution of 5-acyl-2-methylthiopyrimidine (3 mmol) and *m*-chloroperbenzoic acid (9 mmol) in dichloromethane (80 ml) was stirred at ambient temperature until monitoring by TLC showed that the reaction was complete (~2.5 h). The mixture was shaken with aqueous sodium bisulfite (2×30 ml), with aqueous sodium bicarbonate, the washed and dried ($MgSO_4$) solution evaporated and the residue purified by recrystallization.

5-Acetyl-2-methylsulfonylpyrimidine 7a. The yield of *7a* was 95 %, m.p. 132 °C (EtOH). The physical data for the product were as previously reported.[6]

2-Methylsulfonyl-5-pentanoylpyrimidine 7b. The yield of *7b* was 67 %, m.p. 90 °C (2-PrOH). Anal. $C_{10}H_{12}N_2O_3S$: C,H. ^{1}H NMR ($CDCl_3$): δ 3.50 ($MeSO_2$), 0.9–1.9 and 3.00 (Bu), 9.40 (2H, H-4,6). MS: 242 (2, M), 203 (3), 202 (8), 201 (50), 200 (78), 185 (7), 163 (19), 137 (100).

2-Oxo-1,2-dihydropyrimidine-5-carboxylic acid 8. A solution of KOH (5.0 g, 89 mmol) and ethyl 2-methylthiopyrimidine-5-carboxylate (5.00 g, 25 mmol) in ethanol (50 ml) was heated under reflux for 1 h, evaporated, the residue dissolved in water, and the product precipitated on acidification with HCl. Yield 2.53 g (72 %), m.p. 290 °C (dec.; H_2O). Anal. $C_5H_4N_2O_3$: C,H. ^{1}H NMR (DMSO-d_6): δ 8.70 (2H, H-4,6). MS: 140 (100 M), 123 (8), 122 (6), 112 (8), 96 (20), 95 (16).

2-Chloropyrimidine-5-carbonyl chloride 9. A mixture of 2-oxo-1,2-dihydropyrimidine-5-carboxylic acid (2.45 g, 17.5 mmol) phosphorus oxychloride (30 ml) and thionyl chloride (30 ml) was heated under reflux for 2 h, the solution evaporated and the solid residue sublimed: white crystalline material in 56 % yield (1.72 g), m.p. 52 °C. ^{1}H NMR ($CDCl_3$): δ 9.30 (2H, H-4,6). IR (KBr): 1747 cm^{-1} (CO). MS: 180/178/176 (1/6/9, M), 143 (32), 141 (100), 113 (13).

Preparation of 5-acyl-2-chloropyrimidine 10. The conditions for the reaction of 2-chloropyrimidine-

5-carbonyl chloride with methyl, butyl or phenylmanganese iodide were the same as described for the reaction with 2-methylthiopyrimidine-5-carbonyl chloride in the syntheses of *6*. The products were chromatographed on silica gel using chloroform.

5-Acetyl-2-chloropyrimidine 10. The yield of *10a* was 30 %, m.p. 90 °C (subl. at 70 °C/1.0 mmHg). Anal. $C_6H_5ClN_2O$: C,H. ^{1}H NMR ($CDCl_3$): δ 2.08 (Me), 9.10 (2H, H-4,6). IR (KBr): 1684 cm^{-1} (CO). MS: 158/156 (9/26, M), 143/141 (32/100), 113 (23), 86 (18). The second product, eluted by chloroform, was *2-(2-chloro-pyrimidin-5-yl)-propan-2-ol* 14. Yield 15 %. Anal. $C_7H_9ClN_2O$: C,H. ^{1}H NMR ($CDCl_3$): δ 170 (2 Me), 3.05 (OH), 8.80 (2H, H-4,6). MS: 174/172 (1/3, M), 159/157 (34/100), 141 (2), 129 (1).

2-Chloro-5-pentanoylpyrimidine 10b. The yield of *10b* was 43 %, m.p. 49 °C (subl. at 60 °C/0.10 mmHg). Anal. $C_9H_{11}ClN_2O$: C,H. ^{1}H NMR ($CDCl_3$): δ 0.9–1.9 and 3.00 (Bu), 9.20 (2H, H-4,6). IR (KBr): 1692 cm^{-1} (CO). MS (CI): 201/199 (33/100, M+H), 183 (2), 181 (5), 158 (12), 157 (12), 156 (38).

5-Benzoyl-2-chloropyrimidine 10c. The yield of *10c* was 29 %, m.p. 74 °C (subl. at 90 °C/0.10 mmHg). Anal. $C_{11}H_7ClN_2O$: C,H. ^{1}H NMR ($CDCl_3$): δ 7.3–7.8 (Ph), 8.98 (2H, H-4,5). IR (KBr): 1662 cm^{-1} (CO). MS: 220/218 (27/81, M), 219 (18), 217 (23), 183 (7), 156 (20), 141 (31), 105 (100).

Preparation of 5-acryl-2(1H)-pyrimidinones 11. The 5-acyl-2-methylsulfonylpyrimidine *7* or the 5-acyl-2-chloropyrimidine *10* (3.5 mol) was added to 0.5 M 1:1 aqueous dioxane (15 ml), the mixture stirred at ambient temperature until a clear solution resulted (~15 min), the acidified (HCl) mixture evaporated, the residue extracted with methanol and the residue after evaporation of the methanol solution crystallized from water.

5-Acetyl-2(1H)-pyrimidinone 11a. The yield of *11a* from *7a* was 33 %, from *10a* 25 %, m.p. 170 °C. The physical properties were as previously described.[6]

5-Pentanoyl-2(1H)-pyrimidinone 11b. The yield of *11b* from *7b* was 49 %, from *10b* 23 %, m.p. 138 °C. Anal. $C_9H_{12}N_2O$: C,H. ^{1}H NMR (DMSO-d_6): δ 1.9–2.9 and 2.90 (Bu), 8.90 (2H, H-4,6). MS: 180 (4, M), 176 (6), 163 (3), 151 (6), 138 (70), 137 (44), 123 (88), 122 (100).

5-Benzoyl-2(1H)-pyrimidinone 11c. The yield of *11c* from *7c* was 33 %, m.p. 244 °C. The physical data were as previously described.[1]

Preparation of 5-acyl-1-benzyl-2(1H)-pyrimidinones 12. Benzyl bromide (4 mmol) was added to a solution of the 5-acyl-2(1*H*)-pyrimidinone (1.2 mmol) and triethylamine (1.3 mmol) in dichloromethane (25 ml), the mixture stirred at ambient temperature overnight, washed with water (2×15 ml) and the dried ($MgSO_4$) organic solution evaporated to yield the product.

5-Acetyl-1-benzyl-2(1H)-pyrimidinone 12a. The yield of *12a* was 61 %, m.p. 160 °C (H_2O). Anal. $C_{13}H_{12}N_2O$: C,N. ^{1}H NMR ($CDCl_3$): δ 2.37 (Me), 5.08 (CH_2Ph), 7.32 (Ph), 8.32 (1H, H-6, d, *J* 3 Hz), 9.00 (1H, H-4, d, *J* 3 Hz). MS: 228 (49, M), 185 (4), 137 (13), 123 (5), 95 (8), 92 (15), 91 (100).

1-Benzyl-5-pentanoyl-2(1H)-pyrimidinone 12b. The yield of *12b* was 64 %, m.p. 90 °C (H_2O). Anal. $C_{16}H_{18}N_2O$: C,H. ^{1}H NMR ($CDCl_3$); δ 0.9–1.7 and 2.65 (Bu), 5.12 (CH_2 Ph), 7.41 (Ph), 8.45 (1H, H-6, d, *J* 3.5 Hz), 9.07 (1H, H-4, d, *J* 3.5 Hz). MS: 270 (4, M), 228 (3), 213 (2), 170 (2), 92 (8), 91 (100).

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Received May 12, 1986.