Regioselectivity in the Reactions of Aryltri-isopropoxytitanium with Pyrimidinones.

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Complete regioselectivity is observed in the 1 : 1-adduct formation between aryltri-isopropoxytitanium reagents and pyrimidin-2(1*H*)ones; the new carbon–carbon bond is formed at C-4. Dehydrogenation gives the arylated, fully conjugated heterocycle.

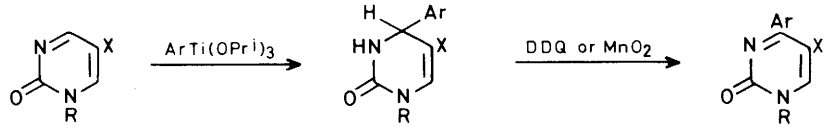
Cross-coupling reactions with organometallic reagents can be used for the introduction of alkyl and aryl substituents into heteroaromatic systems.[1] In π-electron deficient heterocycles there exists an alternative route because such systems form 1 : 1 adducts with the organometallic reagent and the adducts can subsequently be dehydrogenated to the heteroaromatic system.[1a,2] We are investigating the properties of pyrimidin-2(1*H*)ones, some of which are of biological interest because of their ability to arrest the cell cycle during mitosis.[3]

The pyrimidin-2(1*H*)ones are highly polarized and readily form 1 : 1 adducts with organometallic reagents; the new carbon–carbon bond may be formed at either C-4 or C-6. Regioselectivity in such reactions has in some cases been reported for organolithium and organomagnesium reagents.[4,5] We have found, however, that in reactions between 1-benzyl-5-halogeno pyrimidin-2(1*H*)ones and organocopper, organolithium or organomagnesium reagents, coformation of the 3,4- and 3,6-dihydro isomers resulted. In most cases, the major product from the reaction with the Grignard reagent was the 3,6-dihydro isomer, whereas organolithium and organocopper reagents gave mainly the 3,4-dihydro isomer. We now report regioselective 3,4-adduct formation by the use of organotitanium reagents. The application of such reagents to selective reactions in π-electron deficient heterocycles was suggested by the high chemoselectivity and regioselectivity established generally for these reagents consistent with high sensitivity to steric and electronic effects, and in particular to their ability to discriminate between aldehydes and ketones; the latter react much more slowly than the former.[7,8]

The aryltitanium reagents were made available by quenching the corresponding aryl-lithium derivative with chlorotri-isopropoxytitanium.[9]

Only the 3,4-dihydro adduct (**2**) has been isolated from the reaction of the pyrimidinone (**1**) and the aryltitanium reagent. The nature of the 1- and 5-substituents on (**1**) and the substituent on the aryl group of the titanium reagent did not affect the course of the reaction. The regioselectivity observed may, in part, be rationalized by steric repulsion between the 1-substituent and the bulky aryltri-isopropoxytitanium reagent which would be expected to favour bond formation at C-4 in preference to C-6. Alternatively, the formation of the 3,4-adduct can be regarded as a 1,2-addition as found for titanium reagents in reaction with α,β-unsaturated carbonyl compounds.[10,11] In this comparison the N(3)–C(6) part of the pyrimidinone is regarded as possessing electronic properties similar to an α,β-unsaturated carbonyl function. Hence carbon–carbon bond formation at C-6 corresponds to a 1,4-conjugate addition, comparable to the preference for this reaction site shown by Grignard reagents.[6] This preference, however, was not displayed by the corresponding organocopper reagents.[6] The organolithium reagents show a preference for carbon–carbon bond formation at C-4 which corresponds to 1,2-conjugate addition. For a further comparison it has been reported that both organolithium and organomagnesium compounds add to α,β-unsaturated imines, but the organolithium compounds show the greater tendency for 1,2- addition.[12] However, in the pyrimidinone system the regioselectivity in the reactions of these reagents is relatively low, possibly because they are highly reactive towards the pyrimidinone; the reactions between (**1b**–**d**) and the organometallic reagent were run for 10—15 min at room temperature or below,[6] as compared with 24 h for the titanium reagents which gave complete regioselectivity.

To complete the sequence for aromatic substitution at C-4, the dihydro compounds (**2**) were converted to the fully conjugated pyrimidinones (**3**) by means of 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) or activated manganese dioxide.[13] The latter was the more potent reagent and could be used if the yields from the DDQ reactions were unsatisfactory.



(**1**) (**2**) (**3**)

a; R = CH_2Ph,	X = H	**a**; R = CH_2Ph,	Ar = Ph,	X = H
b; R = CH_2Ph,	X = Cl	**b**; R = CH_2Ph,	Ar = Ph,	X = Cl
c; R = CH_2Ph,	X = Br	**c**; R = CH_2Ph,	Ar = Ph,	X = Br
d; R = CH_2Ph,	X = I	**d**; R = CH_2Ph,	Ar = Ph,	X = I
e; R = Me,	X = Br	**e**; R = Me,	Ar = *p*-$MeOC_6H_4$,	X = Br
f; R = CH_2OCH_2Ph,	X = Cl	**f**; R = CH_2OCH_2Ph,	Ar = Ph,	X = Cl
g; R = $CH_2SC_6H_4Cl$-*p*,	X = Cl	**g**; R = CH_2OCH_2Ph,	Ar = *p*-ClC_6H_4,	X = Cl
		h; R = CH_2OCH_2Ph,	Ar = *p*-$MeOC_6H_4$,	X = Cl
		i; R = $CH_2SC_6H_4Cl$-*p*,	Ar = Ph,	X = Cl
		j; R = $CH_2SC_6H_4Cl$-*p*,	Ar = *p*-ClC_6H_4,	X = Cl

Scheme

The structure of (**3b**) was verified by *X*-ray analysis and the structures of its analogues were assigned by comparative ^{1}H n.m.r. spectroscopy. We had previously found that in 1-substituted-pyrimidin-2(1*H*)-ones 4-H is more deshielded than 6-H.[6] The chemical shift at 7.6—7.8 p.p.m. for the pyrimidine proton in the present series is in the region for the 6-H resonance.[6]

In the ^{1}H n.m.r. spectra of the dihydro derivatives (**2a—d**) the signals from the diastereotopic methylene protons of the benzyl group appear as a singlet, *cf.* the 3,6-dihydro-6-phenyl isomer of (**3b**) in which the signals for the benzylic protons are split into an AB pattern.[6] Splitting of the signals from the diastereotopic methylene protons in the sulphides (**2i,—j**) may therefore suggest the isomeric 3,6-dihydro structure, but the chemical shifts and couplings in the pyrimidine ring follow the pattern of the series (**2a—h**). The assigned structures are also confirmed by the chemical shift for the pyrimidine proton after dehydrogenation which falls into the pattern of (**3a—3h**).

Experimental.

The ^{1}H n.m.r. spectra were recorded in $CDCl_3$ at 60 MHz. The mass spectra under electron-impact conditions were recorded at 70 eV and for the chemical ionization (c.i.) mass spectra, isobutane was used as the reagent gas.

1-Benzyloxymethyl-5-chloropyrimidin-2(1H)-one (**1f**).—5-Chloropyrimidin-2(1*H*)one hydrochloride (1.67 g, 10 mmol) and triethylamine (2.02 g, 20 mmol) were stirred together in dichloromethane (50 ml) until all the solid had dissolved. A solution of benzyl chloromethyl ether[14] (1.57 g, 10 mmol) in dichloromethane (10 ml) was then added dropwise with stirring during 3 h at room temperature. The solvent was evaporated and the residue shaken with water and ethyl acetate. Evaporation of the dried ($MgSO_4$) ethyl acetate solution left (**1f**) and its *O*-alkylated isomer (2.4 g, 96%), ratio 3:1. The *O*-alkylated isomer was removed by trituration with ether; m.p. 125 °C (acetone) (Found: C, 57.6; H 4.45. $C_{12}H_{11}ClN_2O_2$ requires C 57.5; H 4.45%); δ_H 4.68 (CH_2Ph), 5.32 (CH_2O), 7.30 (Ph), 7.72 (6-H), and 8.48 (4-H, , *J* 4,6 3 Hz); $\nu_{max.}$ (KBr) 1 670 cm^{-1} (CO).

Aryltri-isopropoxytitanium. The corresponding aryl-lithium compound was quenched by the addition of chlorotri-isopropoxytitanium.[9] The latter was prepared from acetyl chloride and tetraisopropoxytitanium.[15]

General Procedure for the Preparation of 1-Substituted 4-Aryl-3,4-dihydropyrimidin-2(1H)-ones.—A solution of the aryltri-isopropoxytitanium reagent (0.52 mmol) in diethyl ether (50 ml) was added dropwise during 10 min at ambient temperature to a stirred solution of the 1-substituted pyrimidin-2(1*H*)-one (0.17 mmol) in THF (70 ml) under argon. The mixture was stirred at room temperature for 24 h after which it was diluted with water, the pH adjusted to 7 with HCl, diluted further with benzene (100 ml), and the ether solvents then distilled off. The benzene phase of the residue was collected and the aqueous phase extracted with diethyl ether or ethyl acetate. The organic solutions were combined, washed with water and the dried ($MgSO_4$), solution evaporated. The product was purified by recrystallization from ethyl acetate or by chromatography on silica gel or neutral alumina using ethyl acetate or chloroform respectively, as eluant.

1-Benzyl-3,4-dihydro-4-phenylpyrimidin-2(1H)-one[6] (**2a**). This was obtained from (**1a**) and phenyltri-isopropoxytitanium in 87% yield.

1-Benzyl-5-chloro-3,4-dihydro-4-phenylpyrimidin-2(1H)-one[6] (**2b**). This was obtained from (**1b**) and phenyltri-isopropoxytitanium in 50% yield.

1-Benzyl-5-bromo-3,4-dihydro-4-phenylpyrimidin-2(1H)-one[6] (**2c**). This was obtained from (**1c**) and phenyltri-isopropoxytitanium in 70% yield.

1-Benzyl-3,4-dihydro-5-iodo-4-phenylpyrimidin-2(1H)-one (**2d**). This was obtained from (**1d**)[6] and phenyltri-isopropoxytitanium in 79% yield, m.p. 147 °C (EtOAc) (Found: C, 52.65; H, 3.9. $C_{17}H_{15}IN_2O$ requires C, 52.35; H 3.9%); δ_H 4.61 (CH_2Ph), 5.04 (4-H), 5.58 (NH), and 6.38 (6-H); *m/z* 390 (*M*$^+$, 13%), 313 (12), and 91 (100%).

5-Bromo-3,4-dihydro-4-(4-methoxyphenyl)-1-methylpyrimidin-2(1H)-one (**2e**). This was obtained from (**1e**)[6] and *p*-methoxyphenyltri-isopropoxytitanium in 50% yield, m.p. 174 °C (EtOAc) (Found: C, 48.9; H, 4.4. $C_{12}H_{13}BrN_2O_2$ requires C, 48.6; H, 4.4%); δ_H([$^2H_6$]-DMSO). 3.00 (1-Me), 3.77 (OMe), 4.97 (4-H), and 6.75 (6-H); *m/z*(c.i.) 299/297 [(*M* + H)$^+$, 100/100]; *m/z* 298/296 (*M*$^+$, 23/23), 297/295 (14/12), and 217 (100).

1-Benzyloxymethyl-5-chloro-3,4-dihydro-4-phenylpyrimidin-2(1H)-one (**2f**). This was obtained from (**1f**) and phenyltri-isopropoxytitanium in 80% yield, m.p. 106—107 °C (EtOAc) (Found: C, 65.8; H, 5.25. $C_{18}H_{17}ClN_2O_2$ requires C, 65.75; H 5.2%); δ_H 4.53 (CH_2Ph), 4.93 (CH_2O), 4.97 (4-H, d, *J* 1.5 Hz), 5.05 (NH, d), 6.37 (6-H, s), and 6.78 (2 Ph); *m/z* 330/328 (*M*$^+$, 0.6/1.8), 221 (22), and 91 (100).

1-Benzyloxymethyl-5-chloro-4-(4-chlorophenyl)-3,4-dihydropyrimidin-2(1H)-one (**2g**). This was obtained from (**1f**) and *p*-chlorophenyltri-isopropoxytitanium in 63% yield, m.p. 156—157 °C (EtOAc) (Found: C, 59.4; H 4.4. $C_{18}H_{16}Cl_2N_2O_2$ requires C, 59.5; H 4.45%); δ_H 4.57 (CH_2Ph,), 5.00 (CH_2O), 4.92 (4-H,), 6.08 (NH,), and 6.45 (6-H,); $\nu_{max.}$ (KBr) 1 683 cm^{-1} (CO); *m/z*(c.i.) 365 [(*M* + H)$^+$, 4%] and 255 (100); *m/z* 366/364 (*M*$^+$, 0.2/1.6), 362(3), and 91 (100).

1-Benzyloxymethyl-5-chloro-3,4-dihydro-4-(4-methoxyphenyl)pyrimidin-2(1H)-one (**2h**). This was obtained from (**1f**) and 4-methoxyphenyltri-isopropoxytitanium in 78% yield, m.p. 132 °C (EtOAc) (Found: C, 63.7; H, 5.4. $C_{19}H_{19}ClN_2O_3$ requires C, 63.6; H, 5.35%); δ_H 3.72 (OMe,), 4.52 (CH_2Ph,), 4.92 (OCH_2, 4-H), 6.23 (NH,), and 6.35 (6-H); *m/z*(c.i.) 361/359 [(*M* + H)$^+$, 2.5/9], 360/358 (4/8), and 215 (100); *m/z* 360/358 (*M*$^+$, 1.5/5) and 91 (100).

5-Chloro-1-(4-chlorophenylthiomethyl)-3,4-dihydro-4-phenylpyrimidin-2(1H)-one (**2i**). This was obtained from (**1g**)[16] and phenyltri-isopropoxytitanium in 76% yield, m.p. 114 °C (EtOAc) (Found: C, 55.9; H 4.2. $C_{17}H_{14}Cl_2N_2OS$ requires C, 55.9; H, 3.9%); δ_H 4.56 and 5.09 (NCH_2S, AB, *J* 14 Hz), 4.88 (4-H, d, *J* 2 Hz), and 6.25 (6-H and NH); $\nu_{max.}$ (KBr) 1 685 cm^{-1} (CO); *m/z* 366/364 (*M*$^+$, 1/1.5), 298 (16), 233 (31), and 221 (100).

5-Chloro-4-(4-chlorophenyl)-1-(4-chlorophenylthiomethyl)-3,4-dihydropyrimidin-2(1H)-one (**2j**). This was obtained from (**1g**)[16] and *p*-chlorophenyltri-isopropoxytitanium in 73% yield, m.p. 114 °C (EtOAc) (Found: C, 51.2; H 3.4. $C_{17}H_{13}Cl_3N_2OS$ requires C, 51.1; H 3.3%); δ_H 4.68 and 5.12 (NCH_2S, AB, *J* 14 Hz), 4.95 (4-H, d, *J* 3 Hz), 6.23 (NH, d, *J* 3 Hz), and 6.33 (6-H); *m/z* 402/400 (*M*$^+$, 0.6/2), 257 (59), and 255 (100).

General Procedures for the Preparation of 1-Substituted 4-Arylpyrimidin-2(1H)-ones (**3**).—Method A. The 1-substituted 4-aryl-3,4-dihydropyrimidin-2(1*H*)-one (**2**) (1.50 mmol) and DDQ (1.65 mmol) were dissolved in benzene (100 ml) and the solution stirred at room temperature for 12 h. The precipitated hydroquinone was then filtered off and triturated with benzene. The combined benzene solutions were evaporated and the residue dissolved in a small volume of chloroform and the solution chromatographed on neutral alumina using chloroform.

Method B. A solution of the 1-substituted 4-aryl-3,4-dihydropyrimidin-2(1*H*)-one (**2**) (1 mmol) in benzene (50 ml) was stirred together with activated manganese dioxide[13] (2 g) for 4 days

before the mixture was filtered. The filtrate was evaporated and the product isolated by chromatography as above.

1-Benzyl-4-phenylpyrimidin-2(1H)-one (**3a**). This was obtained from (**2a**) and DDQ (A) in 84% yield, m.p. 224 °C (EtOAc). (Found: C, 77.75; H, 5.5. $C_{17}H_{14}N_2O$ requires C, 77.85; H, 5.4%); δ_H 5.10 (CH_2Ph), 6.65 (5-H, d, $J_{5,6}$ 7 Hz), 7.6 (6-H, d); *m/z*(c.i.) 263 [$(M + H)^+$, 100%] and 91 (4); *m/z* 262 (M^+, 58), 261 (14), and 91 (100).

1-Benzyl-5-chloro-4-phenylpyrimidin-2(1H)-one[6] (**3b**). This was obtained from (**2b**) and MnO_2 (B) in 69% yield.

1-Benzyl-5-bromo-4-phenylpyrimidin-2(1H)-one (**3c**). This was obtained from (**2c**) and MnO_2 (B) in 66% yield, m.p. 144 °C (EtOAc). (Found: C, 59.7; H, 3.9. $C_{17}H_{13}BrN_2O$ requires C, 59.8; H, 3.8%); δ_H 5.13 (CH_2Ph) and 7.90 (6-H); *m/z*(c.i.), 343/341 [$(M + H)^+$, 96/100]; *m/z* 342/340 (M^+, 19/20), 341/339 (13/10), and 91 (100).

1-Benzyl-5-iodo-4-phenylpyrimidin-2(1H)-one (**3d**). This was obtained from (**2d**) and MnO_2 (B) in 86% yield, m.p. 134 °C (EtOAc) (Found: C, 52.8; H, 3.4. $C_{17}H_{13}IN_2O$ requires C, 52.6; H, 3.4%); δ_H 5.08 (CH_2Ph) and 8.22 (6-H); *m/z* 3.88 (M^+, 36%), 387 (20), and 91 (100).

5-Bromo-4-(4-methoxyphenyl)-1-methylpyrimidin-2(1H)-one (**3e**). This was obtained from (**2e**) and DDQ (A) in 69% yield, m.p. 227 °C (EtOAc) (Found: C, 49.0; H, 3.8. $C_{12}H_{11}BrN_2O_2$ requires C, 48.85; H 3.7%); δ_H 3.61 (Me), 3.85 (OMe), and 7.93 (6-H); *m/z*(c.i.) 297/295 [$(M + H)^+$, 87/100]; *m/z* 296/294 (M^+, 26/26) and 295/293 (98/100).

1-Benzyloxymethyl-5-chloro-4-phenylpyrimidin-2(1H)-one (**3f**). This was obtained from (**2f**) and DDQ (A) in 61% yield, m.p. 152 °C (EtOAc) (Found: C, 66.15; H, 4.7. $C_{18}H_{15}ClN_2O$ requires C, 66.15; H, 4.6%); δ_H 4.68 (CH_2Ph), 5.38 (CH_2O), and 7.75 (6-H); *m/z*(c.i.) 329/327 [$(M + H)^+$, 33/100], 299 (23), and 297 (71).

1-Benzyloxymethyl-5-chloro-4-(4-chlorophenyl)pyrimidin-2(1H)-one (**3g**). This was obtained from (**2g**) and DDQ (A) in 87% yield, m.p. 86 °C (EtOAc) (Found: C, 60.0; H, 3.9. $C_{18}H_{14}Cl_2N_2O_2$ requires C, 59.85; H, 3.9%); δ_H 4.73 (CH_2Ph), 5.45 (OCH_2), and 7.77 (6-H); $\nu_{max.}$ (KBr) 1 645 cm^{-1} (CO); *m/z*(c.i.) 365/363/361 [$(M + H)^+$, 11/64/100].

1-Benzyloxymethyl-5-chloro-4-(4-methoxyphenyl)pyrimidin-2(1H)-one (**3h**). This was obtained from (**2h**) and DDQ (A) in 87% yield; non-crystalline material (Found: C, 63.85; H, 4.75. $C_{19}H_{17}ClN_2O_3$ requires C, 63.95; H, 4.8%); δ_H 3.87 (OMe), 4.70 (CH_2Ph), 5.40 (CH_2O), and 7.87 (6-H); *m/z*(c.i.) 359/357 [$(M + H)^+$, 34/100], 327 (22), and 252 (51).

5-Chloro-1-(4-chlorophenylthiomethyl)-4-phenylpyrimidin-2(1H)-one (**3i**). This was obtained from (**2i**) and DDQ (A) in 59% yield, m.p. 122 °C (EtOAc) (Found: C, 56.0; H, 3.5. $C_{17}H_{12}Cl_2N_2OS$ requires C, 56.2; H, 3.35%); δ_H 5.30 (CH_2S) and 7.73 (6-H); $\nu_{max.}$ (film) 1 662 cm^{-1} (CO); *m/z* 364/362 (M^+, 0.6/0.8%), 230 (12), and 154 (100).

5-Chloro-4-(4-chlorophenyl)-1-(4-chlorophenylthiomethyl)-pyrimidin-2(1H)-one (**3j**). This was obtained from (**2j**) and DDQ (A) in 89% yield, m.p. 131 °C (EtOAc) (Found: C, 51.2; H. 2.85. $C_{17}H_{11}Cl_3N_2OS$ requires C, 51.35; H, 2.8%); δ_H 5.28 (CH_2S) and 7.73 (6-H); $\nu_{max.}$ (KBr) 1 651 cm^{-1} (CO); *m/z* 400/398/396 (M^+, 3/9/9%), 255 (60), 253 (87), and 224 (100).

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