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REGIOSELECTIVITY IN REACTIONS OF ALKYNYLMETAL COMPLEXES WITH PYRIMIDINONES

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Summary

Regioselectivity is observed in 1/1-adduct formation between phenylethynyltriisopropoxytitanium and 2(1*H*)-pyrimidinones; the new carbon–carbon bond is formed at C(4). In contrast the 3,4- and 3,6-dihydro products are formed together from the corresponding magnesium and lithium reagents, but from the magnesium compound the major product is the 3,6-dihydro isomer. Ethynylmagnesium bromide gives equimolar amounts of the 3,4- and 3,6-dihydro isomers. Dehydrogenation of the products gives the alkynylated aromatic heterocycles.

Introduction

Cross-coupling reactions using catalytic or stoichiometric amounts of organometallic reagents derived from copper [1], nickel [2], or most frequently palladium [3] can be used for the introduction of an alkynyl group into heteroaromatic systems. This approach requires the presence of a readily displaceable substituent such as a halogen atom or a thio group in the heterocycle. In π-electron deficient heterocycles carbon–carbon bond formation should also be possible in an unsubstituted position because such heterocycles form 1/1-adducts with organometallic reagents [4]. The adducts on dehydrogenation furnish the heteroaromatic system.

We are investigating carbon–carbon bond forming reactions particularly of 2(1*H*)-pyrimidinones, since certain of its derivatives have been found to be of biological interest because of their ability to arrest the cell cyclus during mitosis [5].

The main objective of our work was to develop a method for the introduction of an alkynyl substituent into the 4-position of 1-substituted 2(1*H*)-pyrimidinones. The latter compounds are highly polarized and readily form 1/1 complexes with organometallic reagents; simultaneous formation of both the 3,4- and the 3,6-dihydro isomers is often formed [6].

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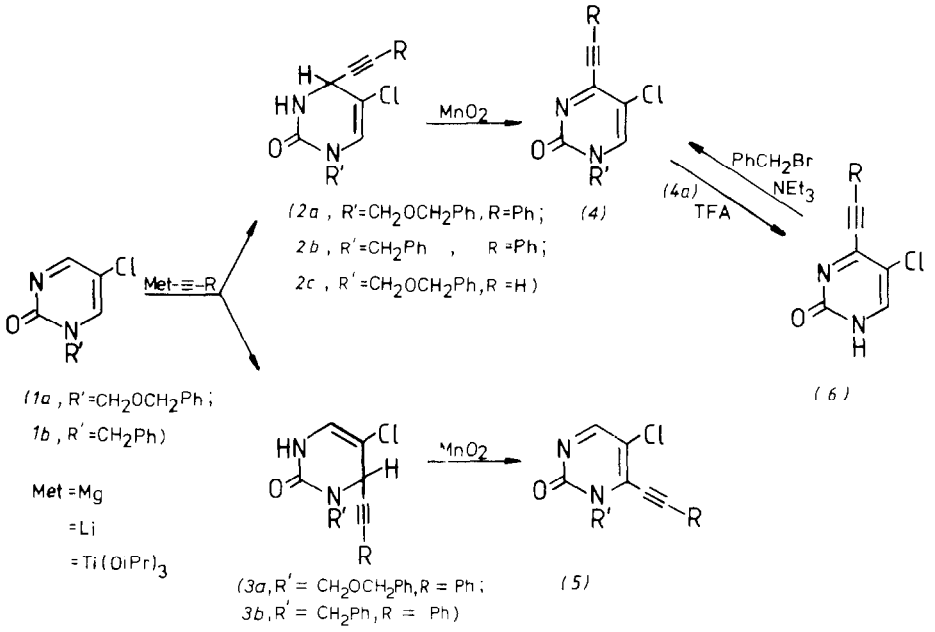

SCHEME 1

Results and discussion

Phenylethynylmagnesium iodide was found to react with the pyrimidinone (**1a**) to furnish a 1/1 mixture of the isomeric 3,4- and 3,6-dihydro species (**2a** and **3a**) in almost equimolar amounts. The 1-benzyl analogue (**1b**) reacted similarly. The isomers can be separated by chromatography on alumina. These results contrast with the recent report that 1-methyl-2(1*H*)-pyrimidinone reacts with phenylethynylmagnesium bromide to form the new carbon–carbon bond at C(6) [7].

Inspection of the pyrimidinone ring reveals that the N(3)–C(6) framework corresponds to an α,β-ethenylimine system. It has been reported that both organomagnesium and organolithium compounds will add to α,β-ethenylimines, but the organolithium compounds show a greater tendency towards 1,2-conjugated addition [8]. In reaction of **1a** with phenylethynyllithium the product ratio **2a**/**3a** was 7/1.

Complete regiocontrol for the formation of the 4-isomer was finally achieved by the use of a titanium complex. The use of the latter was suggested by the high chemoselectivity and regioselectivity reported for such reagents, which are also much less reactive and more sensitive to steric factors than the corresponding magnesium and lithium reagents [9].

The reagent, phenylethynyltriisopropoxytitanium, was prepared in situ by quenching the corresponding lithium derivative with chlorotriisopropoxytitanium. The reaction is slow and an excess of the titanium reagent must be used to compensate for its partial decomposition.

This organotitanium reagent also reacted with the 1-benzylpyrimidinone **1b** to give the 3,4-dihydro isomer **2b**. In this case, however, a trace of the 3,6-dihydro isomer (**3b**) was also detected (< 1%).

Ethynylmagnesium bromide [10] was used to prepare the 4- and 6-ethynyl derivatives **2c** and **3c**, which were formed in almost equimolar amounts. These products, are chemically very sensitive, however, and our attempts to effect dehydrogenation to the fully conjugated heterocycles **4c** and **5c** were unsuccessful. However, the dehydrogenation of the other derivatives **2** and **3** is brought about by activated manganese dioxide. The dehydrogenation of the 3,4-dihydro isomer **2** is much faster, requiring 6 h compared with several days for **3**.

The isomers **4a** and **5a** have an acid labile *N*-side-chain which can be cleaved off. Product **6**, however, readily decomposes. Trifluoroacetic acid in chloroform was used for the cleavage, and the product was purified by reverse phase chromatography. The product **6** thus obtained can be realkylated; thus treatment with benzyl bromide gave **4b** in a regioselective reaction. The *N*-alkylation of **6**, however, proceeds less readily than the corresponding reaction of **1** (R = H) because of the effect of the electron-withdrawing ethynyl substituent. Since the ethynyl derivative **6** is chemically labile, it appears that 4-ethynyl-*N*-alkylated-2(1*H*)-pyrimidinones are best prepared by the route **1** → **2** → **4**.

The structures of the products were assigned on the basis of the ^{1}H NMR spectra. We have previously observed that in 1-substituted-2(1*H*)-pyrimidinones H(4) is more deshielded than H(6); thus the chemical shift values for H(6) in **4a** and for H(4) in **5a** were 7.70 and 8.50 ppm respectively [6]. In the adducts **2a** and **3a** a chiral center has been formed at C(4) and C(6), respectively. The proximity of the chiral center in the latter leads to a splitting of the proton signals from the *N*-methylene group, as observed in related adducts for which the structure has been correlated with X-ray analyses [6].

Experimental

The ^{1}H NMR spectra were recorded at 60 MHz. The mass spectra under electron impact conditions were recorded at 70 eV ionizing voltage. Isobutane was used for the chemical ionization (CI) mass spectra.

*1-Benzyloxymethyl-5-chloro-3,4-dihydro-4-phenylethynyl-2(1H)-pyrimidinone (**2a**) and 1-benzyloxymethyl-3,6-dihydro-6-phenylethynyl-2(1H)-pyrimidinone (**3a**)*

Method A. Use of the Grignard reagent. Phenylethynylmagnesium iodide [11] (39.9 mmol) in dry THF (100 ml) was added dropwise with stirring to a solution of 1-benzyloxymethyl-5-chloro-2(1*H*)-pyrimidinone [12] (2.00 g, 7.98 mmol) in dry THF (200 ml) at room temperature. The mixture was stirred for 4 h at room temperature then dilute hydrochloric was added to pH ca. 6. Benzene (75 ml) was added to the mixture and the ether solvents evaporated. The benzene solution was separated from the aqueous phase, the aqueous phase extracted with ether, and the combined organic solution washed and dried ($MgSO_4$). The solution was concentrated to small volume and chromatographed on neutral alumina (activity II) using chloroform for elution. The 3,4-dihydro isomer **2a** was eluted first. Physical data for the 3,4-dihydro isomer **2a**: yield 1.21 g (43%), m.p. 121°C (EtOAC). (Found: C, 68.02; H, 4.91. $C_{20}H_{17}ClN_2O_2$ calcd.: C, 68.09; H, 4.86%). ^{1}H NMR ($CDCl_3$): δ 4.56 (CH_2Ph), 4.97 (CH_2O), 5.03 (H(4), $J_{3,4}$ 2 Hz), 6.35 (H(6)), 6.76 (NH), 7.33 (2 Ph). MS/CI: 355/353 ([M + H]$^+$, 2/6%), 247 (35), 245 (100), 91 (36). Physical data for the 3,6-dihydro isomer **3a**: Yield 1.32 g (46%), m.p. 117°C

(EtOAC). (Found: C, 68.19; H, 4.87. $C_{20}H_{17}ClN_2O$ calcd.: C, 68.09; H, 4.86%). ^1H NMR ($CDCl_3$): δ 4.60 (CH_2Ph), 4.73 and 5.42 (CH_2O), AB, J 10 Hz), 5.16 (H(6)), 6.17 (H(4), $J_{3,4}$ 5 Hz), 7.33 (2 Ph), 8.08 (NH). MS/CI: 355/353 ($[M + H]^+$, 1/3%), 247 (29), 245 (100), 91 (29).

Method B. Use of the organolithium reagent. The lithium salt of phenylacetylene in dry diethyl ether (60 ml) was prepared from phenylacetylene (7.30 g, 71.4 mmol) and butyllithium (1.6 M in n-hexane, 34 ml) at −78°C. This solution was added dropwise to a rapidly stirred suspension of 1-benzyloxymethyl-5-chloro-2(1H)-pyrimidinone [12], (10.00 g, 39.9 mmol) in dry THF (250 ml) at −78°C. After stirring for 1 h at this temperature the mixture was allowed to reach room temperature, and worked up as above. The yield was 63% of **2a** and 9% of **3a**.

Method C. Use of the organotitanium reagent. The (phenylethynyl)triisopropoxytitanium reagent was made by the addition of a solution of chlorotriisopropoxytitanium [13] (10.40 g, 39.90 mmol) in diethyl ether (100 ml) to a solution of phenylethynyllithium (39.9 mmol) in diethyl ether (100 ml) which had been prepared as above at −78°C. This solution was added dropwise with stirring to a fine suspension of 1-benzyloxymethyl-5-chloro-2(1H)-pyrimidinone [12] (2.00 g, 7.99 mmol) in dry THF (200 ml) at −78°C. The stirring was continued for 1 h at this temperature before the mixture was allowed to reach room temperature. The reaction mixture was black because of polymerization of the titanium reagent. The mixture was worked up as above. The product was the 3,4-dihydro isomer **2a**, yield 1.63 g (58%).

*1-Benzyl-5-chloro-3,4-dihydro-4-phenylethynyl-2(1H)-pyrimidinone (**2b**) and 1-benzyl-3,6-dihydro-6-phenylethynyl-2(1H)-pyrimidinone (**3b**).*

Method A. Use of the Grignard reagent. Phenylethynylmagnesium iodide [11] (45.3 mmol) in dry THF (100 ml) was added to a solution of 1-benzyl-5-chloro-2(1H)-pyrimidinone [14] (2.00 g, 9.06 mmol) in dry THF (200 ml) at room temperature. The mixture was stirred at room temperature for 4 h and then worked up as described above (**2a**/**3a**). Physical data for the 3,4-dihydro isomer (**2b**): Yield 0.85 g (29%), m.p. 119°C (EtOAC). (Found: C, 70.50; H, 4.69. $C_{19}H_{15}ClN_2O$ calcd.: C, 70.70; H, 4.68%). ^1H NMR ($CDCl_3$): δ 4.57 (CH_2Ph), 4.96 (H(4), $J_{3,4}$ 2 Hz), 6.07 (H(6)), 6.73 (NH), 7.33 (2 Ph). MS: 324/322 (M^+, 4/11%), 245 (4), 102 (12), 91 (100).

Physical data for the 3,6-dihydro isomer **3b**. Yield 1.79 g (61%), m.p. 132°C (EtOAC). (Found: C, 70.51; H, 4.88. $C_{19}H_{15}ClN_2O$ calcd.: C, 70.70; H, 4.68%). ^1H NMR ($CDCl_3$): δ 4.21 and 5.36 (CH_2Ph, AB, J 16 Hz), 4.80 (H(6)), 6.20 (H(4), $J_{3,4}$ 5 Hz), 6.97 (2 Ph), 9.00 (NH). MS: 324/322 (M^+, 1/5%), 245 (6), 233 (14), 231 (40), 91 (100).

Method C. Use of the organotitanium reagent. A solution of (phenylethynyl)triisopropoxytitanium (20.62 mmol) in dry diethyl ether (100 ml) was prepared as above at −78°C and added dropwise with stirring to a fine suspension of 1-benzyl-5-chloro-2(1H)-pyrimidinone (0.91 g, 41.42 mmol) in dry THF (100 ml) at −78°C. The stirring was continued for 1 h at this temperature and the mixture was then allowed to reach room temperature and stirred for 2 d. The mixture was then worked up as above. The yield of the 3,4-dihydro isomer **2b** was 0.92 g (69%) and of the 3,6-dihydro isomer **3b** 0.012 g (0.9%).

*1-Benzyloxymethyl-5-chloro-3,4-dihydro-4-ethynyl-2(1H)-pyrimidinone (**2c**) and 1-benzyloxymethyl-5-chloro-3,6-dihydro-6-ethynyl-2(1H)-pyrimidinone (**3c**)*

Ethynylmagnesium bromide [10] (88 mmol) in dry THF (85 ml) was added dropwise with stirring to a solution of 1-benzyloxymethyl-5-chloro-2(1*H*)-pyrimidinone [12] (5.00 g, 20 mmol) in dry THF (250 ml) at room temperature. The mixture was stirred for 4 h then dilute hydrochloric acid was added to pH ca. 6. Benzene (100 ml) was then added, the THF evaporated, and the benzene solution separated from the aqueous phase then dried ($MgSO_4$) and concentrated before chromatography on neutral alumina (activity II). Chloroform was used for elution, and the 3,4-dihydro isomer **2c** was eluated before **3c**. Physical data for 3,4-dihydro isomer **2c**: yield 0.65 g (13%), m.p. 90°C (EtOAC; gradual decomposition). (Found: C, 60.48; H, 4.83. $C_{14}H_{13}ClN_2O_2$ calcd.: C, 60.74; H, 4.73%). ^{1}H NMR ($CDCl_3$): δ 2.50 (≡–H, d, J 2 Hz), 4.55 (CH_2Ph), 4.83 (H(4)), 4.93 (CH_2O), 6.37 (H(6)), 6.67 (NH), 7.33 (Ph). MS/CI: 279/277 ([M + H]$^+$, 5/14%), 171 (34), 169 (100), 91 (35). Physical data for the 3,6-dihydro isomer (**3c**): Yield 0.79 g (15%); non-crystalline material, which gradually decomposed; elemental analysis was therefore not carried out. ^{1}H NMR ($CDCl_3$): δ 3.45 (≡–H, d, J 2 Hz), 4.58 (CH_2Ph), 4.54 and 5.68 (CH_2O, AB, J 11 Hz), 4.95 (H(6), d, J 2Hz), 6.13 (H(4), $J_{3,4}$ 5 Hz), 7.37 (Ph), 8.62 (NH).

*1-Benzyloxymethyl-5-chloro-4-phenylethynyl-2(1H)-pyrimidinone (**4a**)*

*From **2a**:* Activated manganese dioxide [15] (3.0 g) was added to a solution of 1-benzyloxymethyl-5-chloro-3,4-dihydro-4-phenylethynyl-2(1*H*)-pyrimidinone (0.30 g, 0.85 mmol) in benzene (50 ml) and the mixture was stirred at room temperature for 6 h then filtered. The solid was repeatedly extracted with benzene (6 × 100 ml) and the filtrate and the extracts were combined. The benzene was distilled off and the residual material crystallized from ethyl acetate; yield 0.25 g (84%), m.p. 134°C. (Found: C, 68.42; H, 4.45. $C_{17}H_{18}ClN_2O$ calcd.: C, 68.48; H, 4.31%). ^{1}H NMR ($CDCl_3$): δ 4.62 (CH_2Ph), 5.30 (CH_2O), 7.70 (H(6)). MS/CI: 353/351 ([M + H]$^+$, 23/65%), 323 (40), 321 (100), 244 (45), 91 (71).

*1-Benzyl-5-chloro-4-phenylethynyl-2(1H)-pyrimidinone (**4b**)*

4b was prepared from **2b** (0.30 g, 0.93 mmol) and manganese dioxide [15] (3.0 g) as above, except that the reaction mixture was stirred for 24 h; yield 0.19 g (64%), m.p. 224°C (EtOAC). (Found: C, 71.03; H, 4.15. $C_{19}H_{13}ClN_2O$ calcd.: C, 71.14; H, 4.08%). ^{1}H NMR ($CDCl_3$): δ 5.05 (CH_2Ph), 7.33 (2 Ph), 7.61 (H(6)). MS: 322/320 (M^+, 23/53%), 321 (20), 319 (23), 243 (25), 91 (100).

*1-Benzyl-5-chloro-4-phenylethynyl-2(1H)-pyrimidinone (**4b**) by benzylation of **6***

Benzyl bromide (0.22 g, 2.20 mmol) was added to a solution from 5-chloro-4-phenylethynyl-2(1*H*)-pyrimidinone (0.50 g, 2.20 mmol) and triethylamine (0.37 g, 2.20 mmol) in dichloromethane (50 ml) and the mixture was stirred at room temperature for 6 h. Dichloromethane (200 ml) was then added and the mixture extracted with water. The dried ($MgSO_4$) organic solution was evaporated, and the residue recrystallized from ethyl acetate and ethanol; yield 0.45 g (65%).

*1-Benzyloxymethyl-5-chloro-6-phenylethynyl-2(1H)-pyrimidinone (**5a**)*

5a was prepared as above from 1-benzyloxymethyl-5-chloro-3,6-dihydro-6-phenylethynyl-2(1*H*)-pyrimidinone (7.1 mmol) and manganese dioxide [15]. The mixture

was stirred at room temperature under nitrogen for 2 d before being worked up as above. After chromatography 44% of the starting material was recovered. The yield of **5** was 22%, m.p. 130°C (EtOAC). (Found: C, 68.42; H, 4.45. $C_{20}H_{17}ClN_2O_2$ calcd.: C, 68.48; H, 4.31%). ^{1}H NMR ($CDCl_3$): δ 4.78 (CH_2Ph), 5.72 (CH_2O), 8.50 (H(4)). MS/CI: 353/351 ([M + H]$^+$, 16/45%), 323 (23), 321 (68), 244 (43), 91 (100).

*1-Benzyl-5-chloro-6-phenylethynyl-2(1H)-pyrimidinone (**5b**)*

5b was prepared from **3b** (0.25 g, 0.77 mmol) and manganese dioxide [15] (2.5 g) as above except that the reaction mixture was stirred at room temperature for 4 d. On chromatography on silica gel with ethyl acetate as solvent 0.09 g (36%) of **3b** was eluted followed by the product **5b**; yield 0.14 g (56%), m.p. 166°C (EtOAC). (Found: C, 70.95; H, 4.10. $C_{19}H_{13}ClN_2O$ calcd.: C, 71.14; H, 4.08%). ^{1}H NMR ($CDCl_3$): δ 5.54 (CH_2Ph), 7.67 (2 Ph), 8.63 (H(4)). MS: 322/320 (M^+, 24/45%), 321 (21), 319 (22), 243 (35), 91 (100).

*5-Chloro-4-phenylethynyl-2-(1H)-pyrimidinone (**6**)*

Trifluoroacetic acid (1.0 ml) was added to a solution of 1-benzyloxymethyl-5-chloro-4-phenylethynyl-2(1*H*)-pyrimidinone (0.20 g, 0.80 mmol) in chloroform (15 ml) free from ethanol, and the solution was left at room temperature for 24 h. The solvents were removed with a stream of nitrogen and finally in vacuum. The residue was triturated with ether and the remaining material subjected to reverse phase chromatography on C_1-silanished Merck silica gel 60 using methanol: 4‰ TFA in water in the ratio 1/1. The product **6** is readily decomposed. It was best isolated by concentrating the fractions eluted from the column at reduced pressure and then filtering off the precipitated product. In this manner **6** was isolated in 14% yield (0.014 g), m.p. 180°C (decomp.). ^{1}H NMR (DMSO-d_6): δ 5.4 (NH), 7.60 (Ph), 8.35 (H(6)). MS: 232/230 (M^+, 33/100), 202 (42), 140 (21), 128 (37).

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