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Ethynyltriisopropoxytitanium reactions with pyrimidinones

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Abstract

Ethynyltriisopropoxytitanium has been generated in situ from ethynyllithium and chlorotriisopropoxytitanium at −80 °C. It forms 1/1 adducts with pyrimidin-2(1*H*)-ones with exclusive carbon–carbon bond formation at C(6). The products after quenching ethynylmagnesium bromide with chlorotriisopropoxytitanium at −10 °C are 1/1 the mesityl oxide adducts with the pyrimidinones with the new carbon–carbon bond at C(6). Mesityl oxide, as its lithium enolate at −80 °C, forms a mixture of the 3,4- and the 3,6-dihydro-isomeric 1/1 adducts. High resolution NMR was used for the structure assignments.

Introduction

Carbon–carbon bond formation in π-electron deficient heterocycles may be effected by formation of 1/1 adducts with the organometallic reagents and subsequent dehydrogenation to the heteroaromatic species [1]. In studies on the introduction of an alkynyl substituent into 2-pyrimidinones it was found that with phenylethynyl-lithium and -magnesium the 1/1 adducts of the 3,4- and 3,6-dihydro-isomers were formed; with the corresponding triisopropoxytitanium reagent the phenylethynyl group was attached exclusively at the 4-position [2]. With the Grignard derivative of acetylene a mixture of the 3,4- and 3,6-dihydroisomers were formed.

Results and discussion

In a continuation of our development of methods for regioselective introduction of acetylene into the pyrimidine nucleus, we generated the lithium acetylide as a precursor for the desired isopropoxytitanium reagent. The lithium derivative was tried after the magnesium acetylide was found to give another product (see below), and in the light of information that aryltitanium salts generated from the lithium salts are more stable then those made from magnesium precursors [3]. When the lithium acetylide was quenched with chlorotriisopropoxytitanium at −80 °C [4] and

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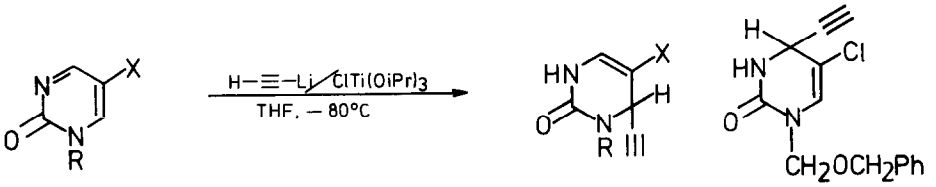


(1a R = CH_2Ph, X=Cl
1b R = CH_2OCH_2Ph, X=Cl
1c R = CH_2Ph, X=F
1d R CH_2Ph, X=Br)

(2) (3b)

Scheme 1

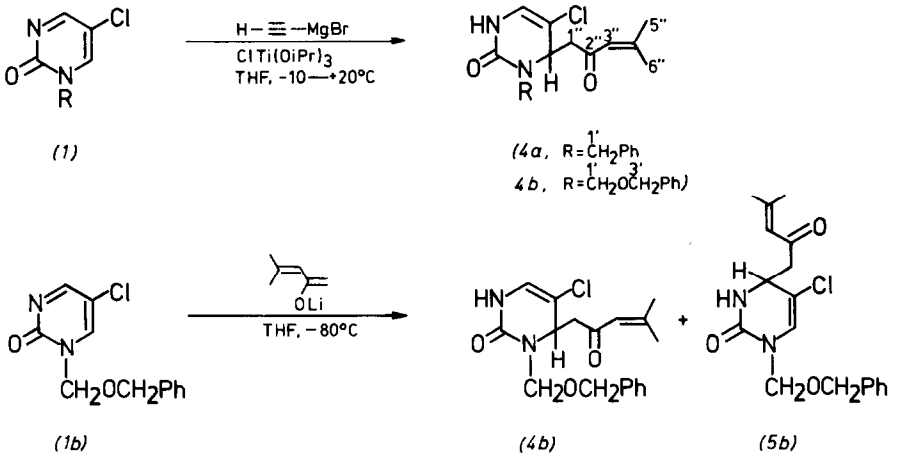
the pyrimidinone added, complete regioselectivity in the adduct formation was observed; the products were the 3,6-adducts **2**. When the reaction was repeated for **1b** with lithium acetylide, without the previous quenching with the triisopropoxytitanium chloride, a mixture of **2b** and the 3,4-dihydro-isomer **3b** were formed in the ratio 4/1. Therefore in the former reaction the lithium acetylide at $-80\,^{\circ}C$ must have reacted with chlorotriisopropoxytitanium prior to the adduct formation.

The reason for the complete selectivity for the 6-position remains unclear, especially since corresponding aryl- and heteroaryl-triisopropoxy reagents attack exclusively in the 4-position [1b]. It is also noteworthy that both the 1-benzyl- and the 1-benzyloxymethyl-pyrimidinone (**1a** and **1b**) react in the same regioselective manner, and hence a determining complexation with the oxygen in the side-chain can be excluded.

The nature of the 5-halogen substituent in **1** may affect the reactivity in that the chloro **1a** and the fluoro **1c** derivatives readily form adducts, whereas the bromo **1d** derivative fails to react. The latter failure to react we attribute mainly to the size of the bromine atom, but also in part to the lower electronegativity of the bromine which results in a lowering of the activation of the pyrimidine ring towards nucleophilic addition.

In our initial attempt to prepare the triisopropoxytitanium derivative of acetylene, ethynylmagnesium bromide was quenched by the addition of chlorotriisopropoxytitanium at $-10\,^{\circ}C$, which corresponded to the conditions used for making titanium reagents in our previous work [2]. The reaction between this mixture and the pyrimidinones **1a** and **1b** was slow, requiring several weeks at ambient temperature. The product obtained was identified by spectroscopy as a 1/1 adduct between the heterocycle and mesityl oxide. The NMR spectra were consistent with the 3,6-dihydro-isomer **4** (Scheme 2).

The possibility that the mesityl oxide would come from the acetone present in the acetylene used for the preparation of ethynylmagnesium bromide, was excluded by passing the gas through concentrated sulfuric acid and then over aluminum oxide [5,6]. Furthermore, small amounts of acetone would have been expected to be trapped as the carbinolate $HC{\equiv}CCMe_2OMgBr$ by reaction with ethynylmagnesium bromide. The formation of product **4** in this reaction was not further investigated. It



Scheme 2

was noticed, however, that on mixing chlorotriisopropoxytitanium with ethynylmagnesium bromide the mixture turned dark, presumably because of formation of titanium(II) species [3], which could be caused by proton abstraction from an isopropoxy group by the magnesium acetylide. The acetone liberated could in part form mesityl oxide, which would eventually be responsible for the 23% yield of the adduct **4**.

For confirmation of the assigned structure both the isomeric products from **1b**, viz. the 3,6-dihydro-isomer **4b** and the 3,4-dihydro-isomer **5b** were prepared from mesityl oxide. The reaction was best carried out by generation of the lithium enolate of mesityl oxide by means of lithium diisopropylamide (LDA) in THF at $-80\,^{\circ}C$ before the pyrimidinone was added. The products **4b** and **5b** were formed in the ratio 1/1, and were isolated in 75% yield. Attempts to use the potassium enolate of mesityl oxide at higher temperatures were less satisfactory.

The ^{1}H and ^{13}C NMR data are recorded in the experimental section. The structure and resonance assignments for **4a, 4b** and **5b** are based on DEPT, heterocorrelated 2D [7] (optimized for J 140 Hz and for J -8 Hz) selective proton decoupling, and NOE difference spectroscopy. The 2-methylpropenyl fragment in **4a** and **4b** can be identified by the multiplet pattern caused by long-range coupling between the methyl and olefinic protons and by the homonuclear decoupling of these resonances. Connection of this fragment to the 2″-carbonyl, hence to the 1″-methylene and finally to the ring, is confirmed by the observation of coupling between H(3″) and C(2″) in a hetero-correlated 2D experiment optimised for J(CH) 8 Hz, and by the observation of a proton NOE at H(6) and H(3″) upon selective irradiation of the H(1″) protons. Assignment of the H(6) resonance was based on the absence of coupling to the N-H proton at position 3, whilst a 5 Hz coupling was observed between H(3) and the resonance assigned to H(4). Assignment of the proton resonances to *cis* and *trans* methyl groups, respectively, was made on the basis of a NOE observed on the resonance at δ 5.99 ppm in **4a** when the selective irradiation was at δ 1.88 ppm but not when it was at at δ 2.15 ppm. The resonance at δ 153.9 ppm in the ^{13}C spectrum of **4a** deserves special mention, as

it was so broad as to be almost unobservable at +25 °C but became sharp at −10 °C. The broadening is presumably due to incompletely averaged scalar coupling between C(2) and ^{14}N at 25 °C, which becomes completely averaged at −10 °C owing to enhanced relaxation of the nitrogen atom(s). The corresponding resonance (153.68) in the ^{13}C spectrum of **4b** was also visibly broadened at +25 °C but to a much smaller extent.

Comparison of the ^{1}H NMR spectra of the isomers **4b** and **5b** shows that the 3,4-dihydro-isomer **5b** has a more shielded N-H proton and that the NH–H(4) coupling is more than halved because of the different hybridization of the C(4) carbon. In the **5b** isomer allylic coupling is seen between H(4) and H(6). The corresponding coupling in **4b** was not seen.

Experimental

The mass spectra under electron impact conditions were recorded at 70 eV. Isobutane was used for chemical ionization (CI) mass spectra.

The ^{1}H NMR spectra were normally recorded at 60 MHz. Special NMR spectra were acquired in the FT mode using a Varian XL-300 spectrometer equipped with a 5 mm ^{1}H/broadband switchable probe. The samples were dissolved in $CDCl_3$ containing TMS as reference. Parameters for strongly coupled nuclei in the spectra of **4a, 4b** and **5b** were derived by iterative spin simulation using the LAME programme as implemented on the Varian XL-300 Spectrometer. Nuclear Overhauser effect (NOE) experiments were performed as follows. The relevant resonance was irradiated at low power for 4 seconds, the decoupler was then gated off, and the FID was acquired; this process was repeated with the decoupler set at a frequency remote from resonances, and this FID was then subtracted from the first. In the case of multiplets, low power irradiation was applied at several points in the multiplet rather than using higher power, the resulting FID's were added, and an appropriately weighted reference FID subtracted.

The solvent, tetrahydrofuran (THF), was distilled over Na/benzophenone. The acetylene gas was purified by bubbling through concentated sulfuric acid and passed through aluminium oxide [3]. All reactions were carried out under nitrogen.

The 1-substituted 5-halo-2(1*H*)-pyrimidinones are described in the literature: **1a** [8], **1b** [1b], **1c** [9], **1d** [1a].

General procedure for the preparation of 1-substituted 5-halo-3,6-dihydro-6-ethynyl-2(1H)-pyrimidinones (2). Acetylene was slowly bubbled through THF (25 ml), pre-saturated with acetylene, kept at −80 °C and at the same time a solution of n-butyllithium in hexane (1.53 *M*, 6.52 ml) was added dropwise with stirring [4]. The solution was stirred at this temperature for 2 h before a precooled solution (−80 °C) of chlorotriisopropoxytitanium (2.68 g, 9.97 mol) in THF (10 ml) was added via a cannula during 15 min. The solution was stirred at −80 °C for 2 h and the pyrimidinone (1.99 mmol) then added at intervals during 30 min. The mixture was stirred at −80 °C for 48 h, then water (20 ml) was added and the pH was adjusted to ca. 7 with dilute HCl. Toluene (30 ml) was added and most of the THF removed by distillation at reduced pressure. The two phases were separated and the aqueous phase was extracted with chloroform (4 × 50 ml). The combined organic phases were shaken with dilute HCl (15 ml), saturated aqueous $NaHCO_3$ (15 ml), and saturated aqueous NaCl (15 ml), then dried ($MgSO_4$) and evaporated. The

residue was purified by chromatography on neutral aluminum oxide (activity 3 or 4, Fluka) with chloroform or dichloromethane as eluant.

The compounds were isolated as slightly yellow oils which darkened and decomposed fairly quickly. Owing to the instability of the compounds [2], only ^{1}H NMR spectra were recorded for spectroscopic characterization.

*1-Benzyl-5-chloro-3,6-dihydro-6-ethynyl-2(1H)-pyrimidinone (**2a**).* This compound was obtained in 46% yield. 40% of the substrate **1a** was recovered after chromatography. ^{1}H NMR ($CDCl_3$) (ppm): H(3) δ 8.75 (d, J 5.5 Hz, 1H); H(4) 6.33 (d, J 5.5 Hz, 1H); H(6), 4.62 (d, J 2 Hz), ≡C–H, 2.55 (d, J 2 Hz), CH_2-Ph, 4.10 and 5.42 (AB, J, 10.5 Hz), Ph, 7.43 (s, 5H).

*1-Benzyloxymethyl-5-chloro-3,6-dihydro-6-ethynyl-2(1H)pyrimidinone (**2b**) [2].* This compound was obtained in 87% yield from substrate **1b**. ^{1}H NMR ($CDCl_3$) (ppm): H(3) δ 8.62 (d, J 5 Hz, 1H); H(4), 6.13 (d, J 5 Hz, 1H); H(6), 4.95 (d, J 2 Hz, 1H); ≡C-H, 2.53 (d, J 2 Hz, 1H); CH_2O, 4.54 and 5.68 (AB, J 11 Hz; CH_2Ph, 4.58 (s, 2H); Ph, 7.37 (s, 5H).

*1-Benzyl-3,6-dihydro-6-ethynyl-5-fluoro-1(1H)-pyrimidinone (**2c**).* This compound was obtained in 88% yield. 9% of the substrate **1c** was recovered after chromatography. ^{1}H NMR ($CDCl_3$): H(3) δ 8.40 (d, J 4.5 Hz, 1H); H(4), 6.17 (d, J 4.5 Hz, 1H); H(6), 4.70 (d, J 2 Hz, 1H); ≡C-H, 2.45 (d, J 2 Hz, 1H); CH_2Ph, 4.06 and 5.43 (AB, J 15 Hz, 2H); Ph, 7.40 (s, 5H).

*1-Benzyl-5-chloro-3,6-dihydro-6-(4-methyl-2-oxo-4-penten-1-yl)-2(1H)-pyrimidinone (**4a**).* Ethylmagnesium bromide was prepared from ethyl bromide (22.7 mmol), magnesium (22.7 g-atom), and acetylene gas in THF (100 ml) [5]. This solution was cooled to −10 °C and added to a solution of chlorotriisopropoxytitanium (5.91 g, 22.7 mmol) in THF (100 ml) at −10 °C. The mixture was stirred at −10 °C for 3 h and 1-benzyl-5-chloro-2-(1*H*)-pyrimidinone (4.53 mmol) was then added gradually. The mixture was stirred at room temperature for 2 months, then water (200 ml) was added. The mixture was neutralized with aqueous HCl, benzene (100 ml) was added, and the THF distilled off, the benzene layer was separated and the aqueous phase extracted with ether (5 × 50 ml). The combined organic solutions were washed with water (3 × 75 ml) then dried ($MgSO_4$) and evaporated. The residue was redissolved in chloroform and chromatographed on neutral alumina. The product was eluted with chloroform; yield 23%, m.p. 100–112 °C (EtOAc). Found: C, 63.97; H, 5.31. $C_{17}H_{19}ClN_2O_2$ calcd.: C, 64.25; H, 5.71%). MS: 318 (0.2, M^+), 229 (3), 227 (10), 221 (7), 220 (7), 91 (100).

^{1}H NMR (300 MHz) (ppm): H(3), δ 8.10 (d, J 5.1 Hz, 1H); H(4), 6.20 (d, J 5.1 Hz, 1H); H(6), 4.41 (AB*X*, J 4.9 and 5.4 Hz, 1H); H(1″), 2.76 (*A*BX, J 16.0 and 4.9 Hz, 1H) and 2.82 (A*B*X, J 16.0 Hz and 5.4 Hz, 1H); H(3″), 5.99 (heptet, J 1.2 Hz, 1H); H(5″), 1.88 (d, J 1.2 Hz, 3H); H(6″), 2.15 (d, J 1.2 Hz, 3H); H(1′), 4.08 (d, J 15.6, 1H) and 5.08 (d, J 15.6, 1H); phenyl 7.37–7.24 (m, 5H).

^{13}C NMR (75 MHz) (ppm): C(2) δ 153.9; C(4), 122.9; C(5) 106.8; C(6), 56.9; C(1′), 48.7; C(4′), 136.8; C(5′), 128.6; C(6′), 127.8; C(7′), 127.5; C(1″), 46.8; C(2″), 197.0; C(3″), 123.7; C(4″), 157.1; C(5″), 27.7; C(6″), 21.0.

*1-Benzyloxymethyl-5-chloro-3,6-dihydro-6-(4-methyl-2-oxo-4-penten-1-yl)-2(1H)-pyrimidinone (**4b**).* This compound was obtained as described above in 56% yield from 1-benzyloxymethyl-5-chloro-2(1*H*)-pyrimidinone, m.p. 127–128 °C (EtOAc). (Found: C, 62.04; H, 6.07. $C_{18}H_{21}ClN_2O_3$ calc.: C, 61.97; H, 6.07%). MS: 348 (0, M^+), 251 (0.3), 240 (2), 221 (5), 91 (100). MS/CI: 315 (2), 313 (4), 283 (5), 251 (9),

243 (28), 241 (84), 91 (100). ^{1}H NMR (300 MHz) (ppm): H(3), δ 8.00 (d, J 5.2 Hz, 1H); H(4) δ 6.17 (d, J 5.2, 1H); H(6) δ 4.66 (ABX, J 4.1 and 6.1 Hz, 1H); H(1″) δ 2.79 (ABX, J 16.5 and 4.1, 1H) and δ 2.94 (ABX, J 16.5 and 6.1 Hz, 1H); H(3″), 5.97 (heptet, J 1.2 Hz, 1H); H(5″), 1.80 (d, J 1.2 Hz, 3H); H(6″), 2.10 (d, J 1.2 Hz, 3H); H(1′), 4.86 (d, J 10.4 Hz, 1H) and 4.97 (d, J 10.4 Hz, 1H); H(3′), 4.53 (d, J 12.0 Hz, 1H) and 4.50 (d, J 12.0 Hz, 1H); phenyl 7.37–7.24 (m, 5H).

^{13}C NMR (75 MHz) (ppm): C(2), 153.6; C(4), 122.5; C(5), 107.6; C(6), 56.9; C(1′), 76.6; C(3′), 70.6; C(4′), 137.9; C(5′), 127.8, C(6′), 128.3; C(7), 127.6; C(1″), 47.2; C(2″), 196.5; C(3″), 123.9; C(4″), 156.6, C(5″), 27.6; C(6″), 21.0.

*1-Benzyloxymethyl-5-chloro-3,6-dihydro-6-(4-methyl-2-oxo-4-penten-1-yl)-2(1H)-pyrimidinone (**4b**) and 1-benzyloxomethyl-5-chloro-3,4-dihydro-4-(4-methyl-2-oxo-4-penten-1-yl)-2(1H)-pyrimidinone (**5b**).* Lithium diisopropylamide was made from diisopropylamine (0.594 ml, 4.19 mmol) and n-butyllithium (1.53 M in hexane, 2.61 ml) in THF (25 ml), and mesityl oxide (392 mg, 3.99 mmol) was added to this solution at $-80\,^\circ$C [4]. The mixture was stirred at $-80\,^\circ$C for 2 h then 1-benzyloxymethyl-5-chloro-2(1H)-pyrimidinone was gradually added. The mixture was stirred at $-80\,^\circ$C for 4 d then water (20 ml) was added at $-80\,^\circ$C. The pH was adjusted to 7 with dilute hydrochloric acid and toluene (30 ml) was added. The THF was evaporated off at reduced pressure, and layers were separated. The aqueous phase was extracted with chloroform (4 × 50 ml). The chloroform and toluene solutions were washed separately with dilute hydrochloric acid (15 ml), saturated aqueous sodium bicarbonate (15 ml), and saturated aqueous sodium chloride (15 ml). The combined organic solutions were dried ($MgSO_4$) and evaporated. The isomers were separated and purified by chromatography on neutral alumina with chloroform as eluent; the 3,4-dihydro-isomer **5b** was eluted before the 3,6-dihydro-isomer **4b**.

*The 3,6-dihydro-isomer **4b**.* Yield 38%. The physical data were as described above.

*The 3,4-dihydro-isomer **5b**.* Yield 37%, slightly yellow oil. MS/CI: 351 (6, $M+1^+$), 349 (120, $M+1^+$), 253 (7), 251 (17), 243 (34), 241 (100), 223 (7), 221 (18), 99 (15), 91 (68). ^{1}H NMR (300 MHz) (ppm): H(3), 5.80 (d, J 2.3 hz, 1H); H(4), 4.47 (d, J 10.2 Hz, t, J 2.2 Hz, d, J 0.6 Hz, 1H); H(6), 6.31 (d, J 0.6 Hz, 1H); H(1″), 2.63 (d, J 18.0 Hz, d, J 10.2 Hz, 1H) and 2.98 (d, J 18.0 Hz, d, J 2.2 Hz, 1H); H(3″), 6.00 (heptet, J 1.3 Hz, 1H); H(5″), 1.88 (d, J 1.3 Hz, 3H); H(6″), 2.12 (d, J 1.3 Hz, 3H); H(1′), 4.89 (J 10.7 Hz, 1H) and 4.91 (d, J 10.7 Hz, 1H), H(3′), 5.45 (s, 2H); phenyl, 7.35–7.22 (m, 5H). ^{13}C NMR (75 MHz) (ppm): C(2), 151.4, C(4), 52.8; C(5), 107.8, C(6), 122.3; C(1′), 75.4; C(3′), 70.3; C(4′), 137.5, C(5′), 127.4; C(6′), 128.1; C(7′); 127.4; C(1″), 48.5; C(2″), 197.2; C(3″), 122.8; C(4″), 157.4; C(5″), 27.7; C(6″), 21.0.

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