Tetrahedron Vol. 48, No. 27, pp. 5647-5656, 1992
Printed in Great Britain

0040-4020/92 $5.00+.00
Pergamon Press Ltd

Aryl- and Alkynyltri-isopropoxytitanium Reagents in Regioselective Carbon-Carbon Bond Formation in Azines

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(*Received in Germany* 3 *March* 1992)

Abstract: Regioselective arylation in the 4-position in pyridines results from 1:1-adduct formation between an aryltri-isopropoxytitanium reagent and *N*-isobutyloxycarbonyl- or an *N*-silyloxymethyl-3-cyanopyridinium salt after successive DDQ dehydrogenation and cleavage of the 1-substituent. Complete regioselectivity for new *C-C* bond formation in the 4-position results in the adduct formation between aryl- and phenylethynyltri-isopropoxytitanium reagents and pyrimidin-2(1*H*)-ones; with ethynyltri-isopropoxytitanium the new *C-C* bond formation occurs at the 6-position.

Organotitanium compounds show high chemoselectivity and regioselectivity in addition reactions with carbonyl derivatives; the selectivity is consistent with high sensitivity to steric and electronic effects.[1,2] We have studied the use of organotitanates as reagents for regioselective carbon-carbon bond formation in π-electron deficient heterocycles.

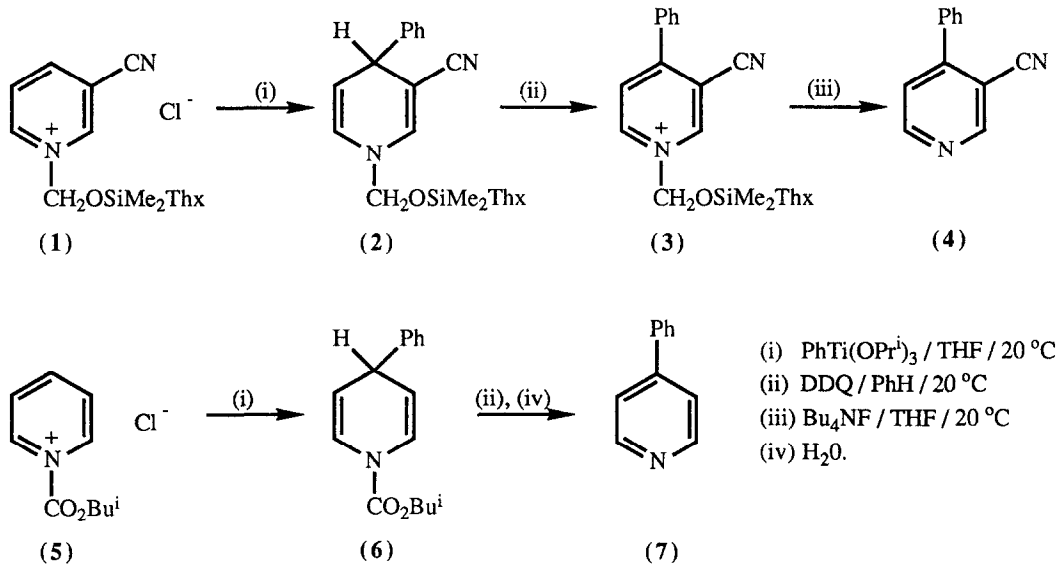
It has become clear that in many of its properties the polarized π-electron deficient azine ring resembles the carbonyl group, e.g. in the 1:1 adduct formation with nucleophiles.[3,4] The azine adducts can be dehydrogenated whereby the original heteroarene with a new carbon substituent is formed.[3,4] Introduction of carbon substituents into heterocyclic systems by this method is complimentary to coupling reactions mainly in benzenoid positions in the azine, although more recently the coupling has been applied in appropriately substituted electrophilic positions.[3,5,6] The regiochemistry in the adduct formation is limited to the electrophilically polarized α - and γ-positions to an annular nitrogen.

The rate of addition of organotitanate in carbonyl reactions is considerably lower than that of the corresponding organolithium or organomagnesium reagent.[7] We have found that pyridine did not react with phenyltri-isopropoxytitanium. Pyridine itself, however, adds organolithium and organomagnesium reagents, preferentially in the 2-position.[4]

To effect reactions between the titanate and pyridines the latter were activated for adduct formation by *N*-alkylation using (dimethylthexylsilyloxy)methyl chloride. We have recently reported on a series of methyl silyl ethers as very useful protecting groups, especially for sterically hindered alcohols;[8] their potential application also extends to organometallic reactions since these silyl ethers survive the normal organolithium conditions. The protecting group is readily removed by fluoride induced cleavage of the silicon-oxygen bond.

The pyridinium salts were prepared by stirring the silyl reagent together with the pyridine. Neither the salt from pyridine nor its 3-chloro derivative did form an adduct with phenyltri-isopropoxytitanium, nor did the methyl nicotinate salt react. The 3-cyano derivative **1**, however, was activated sufficiently for adduct formation with the titanium reagent. The nitrile group was not attacked. With phenylmagnesium bromide a mixture of the 1,4- and 1,6-adducts was formed whereas with the titanate exclusive formation of the 1,4-adduct (**2**) resulted. Nucleophilic displacement of the pyridine ring, as reported in reactions of organosodium and -magnesium reagents with an analogous silyl ether,[9] was not seen in case of the titanate.

The formation of the new carbon bond in the γ-position to a substituted annular nitrogen using titanium reagents (*vide infra*) contrasts with the 1,2-addition reported for organotitanium reactions with α,β-unsaturated carbonyl derivatives,[10] if the comparison of the *N*(1)-*C*(4) part of pyridine as an α,β-unsaturated imine is valid.[3] Since the titanium reagent is sensitive to steric influences, however, the observed regiochemistry may be rationalized on the basis of steric interaction between the *N*-substituent and the bulky titanium reagent.



Scheme 1

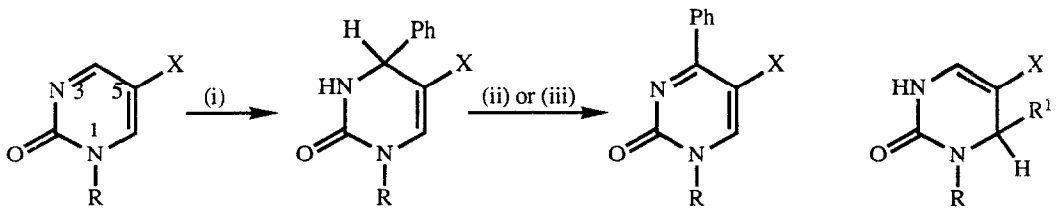
Pyridine was subsequently activated for adduct formation by the preparation of the acylpyridinium salt **5**. The 1,4-dihydro product **6** was isolated from the reaction with phenyltri-isopropoxytitanium. The 1,4-regioselectivity observed is complimentary to the many results reported from reactions between *N*-acylpyridinium salts and organometallics which generally yield mixtures of 1,2- and 1,4-dihydro isomers,[11] but conditions have been reported which result in 1,2 additions between Grignard reagents and both acyl- and acyloxypyridinium salts.[12] Grignard reagents admixed with cuprous iodide, or organocopper reagents may yield 1,4-adducts.[13] The same regiochemistry has been found for reactions with titanium ate complexes.[14]

The 4-phenyl derivative (**4**) of 3-cyanopyridine was generated from the adduct **2** by 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) dehydrogenation and fluoride induced cleavage of the silyl group in the intermediate pyridinium salt **3**. The carbamoyl derivative **6** was also rearomatized by DDQ, and the acylpyridinium intermediate was cleaved by water to the 4-phenyl derivative (**7**).

In the further work on carbon-carbon bond formation in π-electron deficient systems we have concentrated our efforts on pyrimidines, in particular on pyrimidin-2(1*H*)-ones, some of which are of biological interest because of their ability to arrest the cell cycle during mitosis.[15]

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 related reactions has in some cases been reported with organolithium and organomagnesium reagents.[16] We found, however, that in the reactions between 1-benzyl-5-halogenopyrimidin-2(1*H*)-ones and organocopper, organolithium or organomagnesium reagents, coformation of the 3,4- and 3,6-dihydro isomers resulted, e.g. **9** and **11** respectively.[17] In most cases the major product from the reaction with the Grignard reagent was the 3,6-dihydro isomer (**11**), whereas organolithium and and organocopper reagents gave larger amounts of the 3,4-dihydro isomer.

Application of organotitanium reagents, however, has led to regioselective 3,4-adduct formation.[18] Thus the 3,4-dihydro adducts **9** were isolated from the reaction of the pyrimidinones **8** and the phenyltri-isopropoxytitanium. The nature of the 1- and 5-substituents in **8** did not affect the regiochemistry. 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.



(**8a**) R = CH_2Ph X = H (**9a-d**) (**10a-d**) (**11**)
(**8b**) R = CH_2Ph X = Cl
(**8c**) R = CH_2Ph X = Br
(**8d**) R = CH_2OCH_2Ph X = Cl

(i) $PhTi(OPr^i)_3$ / Et_2O / THF / 20 °C
(ii) DDQ / PhH / 20 °C
(iii) MnO_2 / PhH / 20 °C

Scheme 2

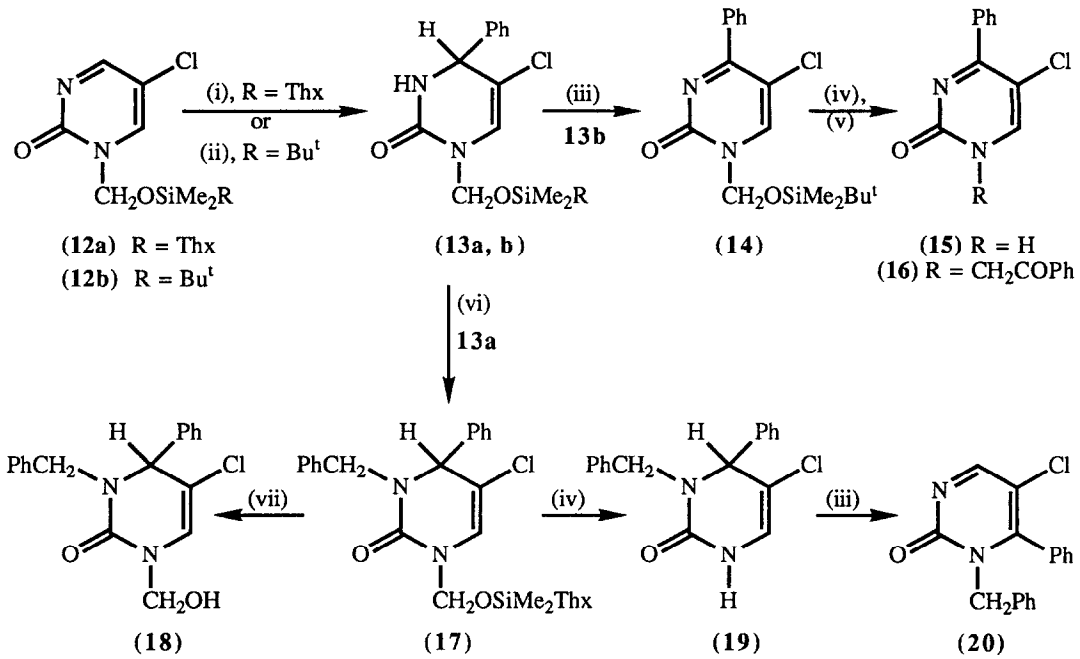
The formation of the 3,4-adduct can be regarded as a 1,2-addition which corresponds to the reactivity pattern of titanates in their reactions with α,β-unsaturated carbonyl compounds. In this comparison the *N*(3)-C(6) part of the pyrimidinone is regarded as possessing electronic properties similar to an α,β-unsaturated carbonyl function, or the closer α,β-unsaturated imine system where both organolithium and organomagnesium compounds add, but the organolithium compounds show the greater tendency for 1,2-addition. The carbon-carbon bond formation at *C*-6 corresponds to 1,4-conjugate addition, comparable to the preference for this reaction shown by Grignard reagents. The organolithium reagents show a preference for carbon-carbon bond formation at *C*-4 which corresponds to 1,2-addition. However, in the pyrimidinone system the regioselectivity of these reagents is relatively low, possibly because of high reactivity towards the pyrimidinone. Thus the reactions with the organolithium and organomagnesium reagents were run for 10 - 15 minutes at ambient temperature or below,[17] as compared with 24 hours for the titanium reagents which gave complete regioselectivity.

To complete the sequence for aromatic substitution at *C*-4, the dihydro compounds **9** were converted to the conjugated pyrimidinones **10** by means of DDQ or activated manganese dioxide. The latter is the more potent reagent and could be used when the yields from the DDQ reactions were unsatisfactory.

An unsubstituted lactam nitrogen must be protected before the organometallic reaction, and the organometallic reaction must precede introduction of the *N*-1 substituent in cases where the the *N*-1 substituent might be incompatible with the organometallic reagent. It is also advantageous that the protecting group can be removed without hydrogenolysis since the pyrimidinone is sensitive to reducing conditions. In Scheme 3 the use of the (*t*-butyldimethylsilyloxy)methyl and the (dimethylthexylsilyloxy)methyl group is shown. Both these groups are resistant to the organometallic reagents employed. The alkylated derivatives **12** were made from the corresponding pyrimidinone by alkylation with the chloromethyl silyl ether with triethylamine as base.[19] Treatment of **12** with the organometallic reagent furnished the adducts. With the phenyltitanium reagent, clean 3,4-adduct (**13**) formation was seen. The regiochemistry, however, was lost using phenylmagnesium bromide since a 1:1 mixture of the 3,4- dihydro derivative **13a** and its 3,6-dihydro isomer resulted.[19]

From the 3,4-adduct **13** either a 1,4-disubstituted pyrimidinone (e.g. **16**) or a 1,6-disubstituted pyrimidinone (e.g. **20**) can be prepared (*vide infra*).

N-3 Alkylation on the adducts **13** resulted from the reaction with benzyl bromide in the presence of a base. The silyl containing protecting group in **17** could be removed in the usual way by the treatment with fluoride ions to give the fully deprotected derivative **19**. The *N*-hydroxymethyl derivative **18** could be isolated when the protecting group was cleaved under acidic conditions. From previous work we know that 3,6-dihydropyrimidine derivatives such as **19** are very slowly oxidized by DDQ, and the rearomatization of **19** to the 6-phenyl derivative **20** is best carried out by activated manganese dioxide.[17]



(i) PhTi(OPr^i)$_3$ / THF / 20 °C; (ii) PhMgBr / THF / 20 °C; (iii) MnO_2 / PhH / 20 °C; (iv) Bu_4NF / THF / 20 °C; (v) $BrCH_2COPh$, Et_3N / CH_2Cl_2 / 20 °C; (vi) $BrCH_2Ph$ / NaH / DMF / 20 °C (vii) AcOH / H_2O / THF / 50 °C

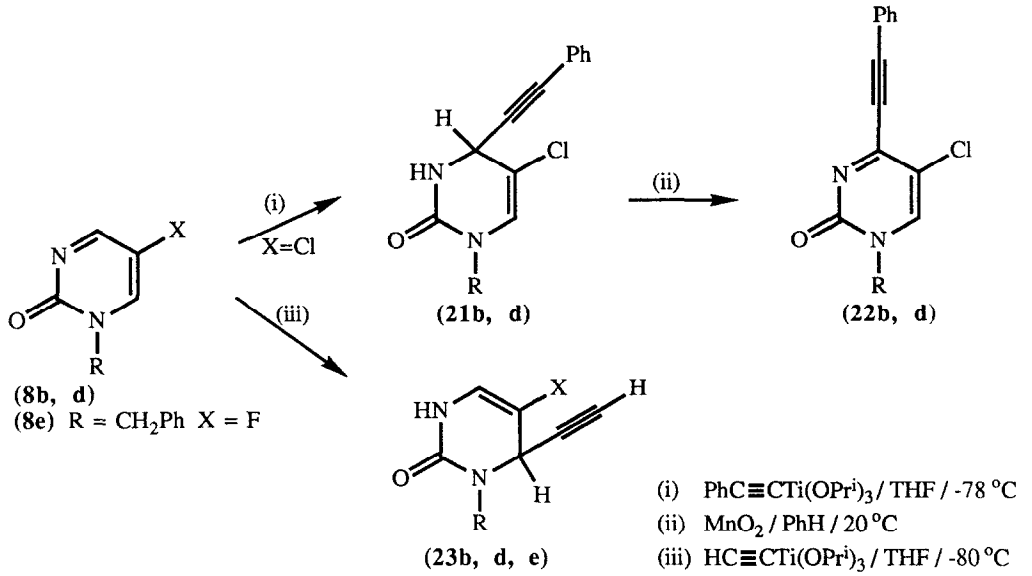
Scheme 3

1,4-Disubstituted isomers are available from the initial adduct **13** by way of manganese dioxide dehydrogenation to give **14** which is subsequently deprotected by the fluoride ion initiated cleavage. *N*-Alkylation of **14** occurs exclusively on the nitrogen in the γ-position to the phenyl substituent; the alkylation with phenacyl bromide gave the 1-phenacyl derivative **16**.[19] The latter contains a carbonyl group which would have been incompatible with the organometallic reactions used in previous steps.

During introduction of alkynyl groups it was found that phenylethynylmagnesium iodide in reactions with the pyrimidinones **8b,d** gave a mixture of the isomeric 3,4- and 3,6- dihydro isomers in almost equimolar amounts. The isomers can be separated by chromatography on alumina.[20] These results contrast the recent report that 1-methylpyrimidin-2(1*H*)-one reacts with phenylmagnesium bromide to form the new carbon bond at *C*-6.[16b] In our case, however, complete regiocontrol and formation of the 4-isomer resulted by the use of phenylethynyltri-isopropoxytitanium. The latter was prepared *in situ* by quenching the corresponding lithium derivative with tri-isopropoxytitanium chloride. The adduct formation was slow, and an excess of the titanium reagent had to be used to compensate for its partial decomposition. Manganese dioxide was used for dehydrogenation of the adducts **21** to form the 4-alkynylpyrimidinones **22**.[20]

Unsubstituted acetylene can also be introduced into the pyrimidine nucleus with regiochemical control using the corresponding titanium reagent.[21] The latter was generated from lithium acetylide by titanating with tri-isopropoxytitanium chloride at -80 °C. Initially the titanation was attempted on ethynylmagnesium bromide at -10 °C. The organometallic species from this preparation showed low reactivity towards the pyrimidinones, but the reaction eventually gave a product in which a mesityl oxide unit had been added to the pyrimidinone.[21] Since aryltitanium reagents generated from the lithium precursors are more stable than those from magnesium

precursors,[22] it was felt that this may well be true for other organotitanium species as well, and ethynyllithium was used for the successful titanation.



Scheme 4

With the ethynyltitanium reagent at -80 °C, the 3,6-dihydro isomers **23** were formed almost exclusively. The reasons for the reversal of the regiochemistry (*vide supra*) remains unclear; the reactions with both ethynyltitanium reagents were run at low temperature. When the reaction was repeated for **8d** with lithium acetylide, a mixture of the 3,6-dihydro isomer **23d** and its 3,4-dihydro isomer was formed in the ratio 4:1.[20] With ethynylmagnesium bromide and **8d** an almost equimolar amount of the isomers were formed;[21] the isomers can be separated by chromatography. The ethynyl derivatives are unstable on storage when there is no substitution on the terminal acetylenic carbon. Aromatization of the dihydro derivatives is difficult to achieve because the dehydrogenated products are also unstable.[23]

The nature of the 5-halogen substituent in **8** may affect the reactivity, because of steric and inductive effects. Thus the chloro **8b,d** and the fluoro **8e** derivatives readily formed adducts, whereas the homologue 1-benzyl-3-bromo-2(1*H*)-pyrimidinone, failed to react under the standard reaction conditions used.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded at 200 MHz and the ^{13}C NMR spectra at 50 MHz unless otherwise specified. The MS spectra were recorded at 70 eV and are presented as *m/z* (% rel. int.). Methane was used for chemical ionization unless otherwise specified.

THF was dried by reflux and distillation over metallic sodium and benzophenone. Dichloromethane was distilled from calcium hydride and DMF from barium oxide.

3-Cyano-1-(dimethylthexylsilyloxy)methylpyridinium chloride (1). (Dimethylthexylsilyloxy)methyl chloride[8] (836 mg, 4.0 mmol) was added to a solution of 3-cyanopyridine (416 mg, 4.0 mmol) in dry dichloromethane (7 ml), and the mixture was stirred at ambient temperature under N_2 for 16 h. Diethyl ether (10 ml) was added, the solid was filtered off and washed with diethyl ether (4x10 ml); yield 1.05 g (84 %) of a white solid. ^{1}H NMR (DMSO-d_6): δ 0.27 ($SiMe_2$), 0.86 (Me in thexyl, d, *J* 6.9 Hz), 0.89 (Me in thexyl), 1.63 (CH in thexyl, m, *J* 6.9 Hz), 6.21 (CH_2), 8.47 (H-5, m), 9.22 (H-4, d, *J* 8.1 Hz), 9.49 (H-6, d, *J* 5.9

Hz), 10.03 (H-2). ^{13}C NMR (DMSO-d_6): δ -3.0 ($SiMe_2$), 18.7 and 20.2 (Me in thexyl), 25.0 (C in thexyl), 33.8 (CH in thexyl), 83.1 (CH_2), 112.8 and 114.2 (C-3, CN) 128.7 (C-5), 140.5 (C-4), 147.1 (C-6), 150.3 (C-2). MS(CI): 277 (1, *M*-Cl), 213 (1), 197 (5), 193 (18), 123 (12), 105 (100), 93 (15), 89 (78).

3-Cyano-1,4-dihydro-1-(dimethylthexylsilyloxy)methyl-4-phenylpyridine (2). A 0.5 M solution of phenyltri-isopropoxytitanium in THF (6 ml, 3 mmol), generated *in situ* from phenylmagnesium bromide and tri-isopropoxytitanium chloride,[24] was added dropwise to a stirring mixture of 3-cyano-1-(dimethylthexylsilyloxy)methylpyridinium chloride (625 mg, 2 mmol) in dry THF (10 ml). After stirring at ambient temperature under N_2 for 2 h, water (20 ml) was added, the phases separated and the aqueous phase extracted with diethyl ether (3x30 ml). The combined organic solution was washed with brine (1x20 ml) and dried ($MgSO_4$). The crude product was purified by flash chromatography on silica gel using EtOAc:hexane 1:15; yield 586 mg (87 %) of a pale yellow oil. (Found: C, 71.36; H, 8.67. Calc. for $C_{21}H_{30}N_2OSi$: C, 71.14; H, 8.53 %). ^{1}H NMR ($CDCl_3$): δ 0.10 ($SiMe_2$), 0.89 (Me in thexyl), 0.92 (Me in thexyl, d, *J* 6.8 Hz), 1.66 (CH in thexyl, m, *J* 6.8 Hz), 4.32 (H-4, d, *J* 4.0 Hz), 4.67 (CH_2), 4.7-4.8 (H-5, m), 6.04 (H-6, dd, *J* 8.1 and 1.3 Hz), 6.70 (H-2), 7.3-7.4 (Ph, m). ^{13}C NMR ($CDCl_3$): δ -2.4 ($SiMe_2$), 19.1 and 20.7 (Me in thexyl), 25.6 (C in thexyl), 34.7 (CH in thexyl), 40.3 (C-4), 77.9 (CH_2), 85.5 (C-3) 106.8 (C-5), 121.0 (CN) 126.8 (C-6), 127.7, 128.4 and 129.2 (CH in Ph), 129.5 (C in Ph), 141.1 (C-2). MS(CI): 355 (3, *M*+1), 354 (2, *M*), 269 (3), 255 (18), 195 (10), 181 (100), 145 (7), 143 (7).

3-Cyano-4-phenylpyridine (4). DDQ (272 mg, 1.2 mmol) was added to a solution of 3-cyano-1,4-dihydro-1-(dimethylthexylsilyloxy)methyl-4-phenylpyridine (354 mg, 1.0 mmol) in benzene (40 ml). After stirring at ambient temperature under N_2 for 1 h, the mixture was concentrated to ca. 10 ml, a 0.5 M solution of tetrabutylammonium fluoride in THF (4 ml) was added and the resulting mixture was stirred at ambient temperature under N_2 for 14 h. The reaction mixture was evaporated and the product isolated by flash chromatography on silica gel using EtOAc:hexane 1:2; yield 156 mg (87 %) of a white solid, m.p. 71-72 °C.[25] ^{1}H NMR ($CDCl_3$): δ 7.5-7.6 (Ph and H-5, m), 8.81 (H-6, d, *J* 4.7 Hz), 8.95 (H-2). ^{13}C NMR ($CDCl_3$): δ 116.0 , 117.2 (C-3, CN), 124.4 (C-5), 128.9, 129.7 and 130.8 (CH in Ph), 135.0 (C in Ph), 152.0 ((C-4), 153.3 (C-6), 154.5 (C-2). MS: 180 (100, *M*), 154 (16), 153 (23), 152 (11), 127 (11), 126 (12), 77 (12), 76 (17).

***1-iso*Butyloxycarbonyl-1,4-dihydro-4-phenylpyridine (6)** *iso*Butyl chloroformate (0.52 ml, 4.0 mmol) was added to a stirred solution of pyridine (0.32 ml, 4.0 mmol) in dry THF (5 ml) at 0 °C under N_2. After 15 min, a 0.5 M solution of phenyltri-isopropoxytitanium in dry THF (12 ml) was added dropwise, and the mixture stirred for 3 h at ambient temperature. Water (20 ml) was added, the phases separated and the aqueous phase extracted with diethyl ether (3x30 ml). The combined organic solution was washed with brine (1x20 ml) and dried ($MgSO_4$). The crude product was purified by flash chromatography on silica gel using EtOAc:hexane 1:30; yield 395 mg (40 %) of a pale yellow oil which decomposed on storage. ^{1}H NMR ($CDCl_3$): δ 0.98 (Me, d, *J* 6.8 Hz), 1.9-2.1 (CH in *i*-Bu, m), 4.03 (CH_2, d, *J* 7.0 Hz), 4.19 (H-4, m), 4.9-5.0 (H-3 and H-5, m), 6.8-7.0 (H-2 and H-6, m), 7.2-7.5 (Ph, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 19.1 (Me), 28.0 (CH in *i*-Bu), 39.2 (C-4), 72.6 (CH_2), 121.1 (C-3 and C-5), 127.9, 128.7 and 129.1 (CH in Ph), 129.5 (C in Ph), 145.9 (CO), 150.3 (C-2 and C-6). MS: 257 (13, *M*), 256 (51), 206 (12), 200 (16), 187 (13), 171 (23), 156 (42), 144 (23), 115 (21), 58 (100).

4-Phenylpyridine (7). DDQ (272 mg, 1.2 mmol) was added to a solution of 1-*iso*butyloxycarbonyl-1,4-dihydro-4-phenylpyridine (245 mg, 1.0 mmol) in benzene (40 ml). After stirring at ambient temperature under N_2 for 1 h, the mixture was shaken with water (30 ml). The phases were separated and the aqueous phase extracted with benzene (2x30 ml). The combined benzene solution was dried ($MgSO_4$) and evaporated, and the crude product purified by flash chromatography on silica gel using EtOAc; yield 132 mg (85 %) of a white solid, m.p. 69-71.[26] ^{1}H NMR ($CDCl_3$): δ 7.4-7.7 (Ph, H-3 and H-5, m) 8.67 (H-2 and H-6, m). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 126.9 (C-3 and C-5), 128.8, 129.1 and 129.2 (CH in Ph), 138.1 (C in Ph), 148.4 (C-4), 149.9 (C-2 and C-6). MS: 155 (100, *M*), 140 (16), 128 (48), 127 (45), 115 (39), 102 (42), 77 (34).

Preparation of 1-Substituted 3,4-Dihydro-4-phenylpyrimidin-2(1H)-ones (9). A solution of phenyltri-isopropoxytitanium (40 mmol) in diethyl ether (80 ml) was added dropwise during 10 min at ambient temperature to a stirred solution of the 1-substituted pyrimidin-2(1*H*)-one (13 mmol) in THF (80 ml) under argon. The mixture was stirred at ambient temperature for 24 h, diluted with water, the pH adjusted to 7 with HCl before addition of benzene (100 ml) and the ether solvents were 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 crystallization 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 (9a)[18] was obtained from **8a** in 87 % yield.

1-Benzyl-5-chloro-3,4-dihydro-4-phenylpyrimidin-2(1H)-one (9b)[18] was obtained from **8b** in 50 % yield.

1-Benzyl-5-bromo-3,4-dihydro-4-phenylpyrimidin-2(1H)-one (9c)[18] was obtained from **9c** in 70 % yield.

1-Benzyloxymethyl-5-chloro-3,4-dihydro-4-phenylpyrimidin-2(1H)-one (9d)[18] was obtained from **8d** in 80 % yield.

Preparation of 1-Substituted 4-Phenylpyrimidin-2(1H)-ones (10). -- Method A. The 1-substituted 3,4-dihydro-4-phenylpyrimidin-2(1*H*)-one (1.50 mmol) and DDQ (1.65 mmol) were dissolved in benzene (100 ml), and the solution stirred at ambient 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 for chromatography on neutral alumina using chloroform.

Method B: A solution of the 1-substituted 3,4-dihydro-4-phenylpyrimidin-2(1*H*)-one (1 mmol) in benzene (50 ml) was stirred together with activated manganese dioxide (2 g) for 4 d at ambient temperature before the mixture was filtered. The filtrate was evaporated and the product isolated by chromatography (*vide supra*).

1-Benzyl-4-phenylpyrimidin-2(1H)-one (10a)[18] was obtained in 84 % yield using DDQ (Method A).

1-Benzyl-5-chloro-4-phenylpyrimidin-2(1H)-one (10b)[18] was obtained in 69 % yield using manganese dioxide (Method B).

1-Benzyl-5-bromo-4-phenylpyrimidin-2(1H)-one (10c)[18] was obtained in 66 % yield using manganese dioxide (Method B).

1-Benzyloxymethyl-5-chloro-4-phenylpyrimidin-2(1H)-one (10d)[18] was obtained in 61 % yield using DDQ (Method A).

5-Chloro-1-(dimethylthexylsilyloxy)methylpyrimidin-2(1H)-one (12a). Triethylamine (1.00 ml, 7.2 mmol) was added to a suspension of 5-chloropyrimidin-2(1*H*)-one (783 mg, 6.0 mmol) in dry dichloromethane (12 ml). After stirring for 15 min at ambient temperature under N_2, the solution was cooled to -78 °C and (dimethylthexylsilyloxy)methyl chloride[8] (1.76 g, 8.4 mmol) in dichloromethane (8 ml) was added dropwise during 30 min. The resulting mixture was stirred for 14 h while reaching ambient temperature, diluted with dichloromethane (50 ml), washed with brine (2x20 ml), dried ($MgSO_4$) and evaporated. The crude product was purified by flash chromatography on silica gel using EtOAc:hexane 1:1; yield 1.29 g (71 %) of a white solid. (Found: C, 51.38; H, 7.77. Calc. for $C_{13}H_{23}ClN_2O_2Si$: C, 51.55; H, 7.65 %). ^1H NMR ($CDCl_3$): δ 0.18 ($SiMe_2$), 0.88 (Me in thexyl), 0.89 (Me in thexyl, d, *J* 6.9 Hz), 1.64 (CH in thexyl, m, *J* 6.9 Hz), 5.38 (CH_2), 7.94 (H-6, d, *J* 3.2 Hz), 8.55 (H-4, br s). ^{13}C NMR (DMSO-d_6, 75 MHz): δ -3.4 ($SiMe_2$), 18.3 and 19.9 (Me in thexyl), 24.6 (C in thexyl), 33.6 (CH in thexyl), 73.7 (CH_2), 109.5 (C-5), 145.7 (C-6), 153.2 (C-2), 165.7 (C-4). MS: 274 (1), 259 (2), 217 (31), 189 (43), 187 (100), 93 (8), 75 (9), 73 (15).

5-Chloro-1,4-dihydro-1-(dimethylthexylsilyloxy)methyl-4-phenyl-2(1H)pyrimidinone (13a). A 0.5 M solution of phenyltri-isopropoxytitanium in THF (24.0 ml, 12.0 mmol) was added dropwise to a stirred mixture of 5-chloro-1-(dimethylthexylsilyloxy)methylpyrimidin-2(1*H*)-one (1.21 g, 4.0 mmol) in dry THF (15 ml). The resulting mixture was stirred for 24 h under N_2 at ambient temperature before water (20 ml) was added and the pH was adjusted to ca. 6 with conc. HCl. The phases were separated and the aqueous phase extracted with diethyl ether (3x50 ml). The combined organic solution was washed with brine (1x20 ml) and

dried ($MgSO_4$). The crude product was purified by flash chromatography on silica gel using EtOAc:hexane 1:5; yield 883 mg (58 %) of a white solid. (Found: C, 60.02; H, 7.43. Calc. for $C_{19}H_{29}ClN_2O_2Si$: C, 59.90; H, 7.67 %). ^1H NMR ($CDCl_3$): δ 0.20 ($SiMe_2$), 0.88 (Me in thexyl), 0.92 (Me in thexyl, d, *J* 6.9 Hz), 1.66 (CH in thexyl, m, *J* 6.9 Hz), 4.95 (CH_2, H_A, d, *J* 9.5 Hz), 5.00 (H-4, d, *J* 1.9 Hz), 5.07 (CH_2, H_B, d, *J* 9.5 Hz), 5.89 (NH, br s), 6.40 (H-6), 7.2-7.5 (Ph, m). ^{13}C NMR ($CDCl_3$): δ -2.2 ($SiMe_2$), 19.4 and 21.1 (Me in thexyl), 25.5 (C in thexyl), 35.0 (CH in thexyl), 62.0 (C-4), 70.8 (CH_2), 109.5 (C-5), 125.4 (C-6), 127.6, 129.1 and 129.2 (CH in Ph), 141.1 (C in Ph), 151.7 (C-2). MS (CI): 383/381 (2/8, *M*+1), 365 (39), 351 (11), 297 (85), 295 (100), 221 (57), 167 (22), 120 (6), 89 (20), 73 (11).

5-Chloro-1,4-dihydro-1-(tert-butyldimethylsilyloxy)methyl-4-phenyl-2(1H)pyrimidinone (13b) was prepared from **12b** as previously described.[19]

3-Benzyl-5-chloro-1,4-dihydro-1-(dimethylthexylsilyloxy)methyl-4-phenylpyrimidin-2(1H)-one (17). 5-Chloro-1,4-dihydro-1-(dimethylthexylsilyloxy)methyl-4-phenylpyrimidin-2(1*H*)-one (761 mg, 2.0 mmol) was dissolved in dry DMF (15 ml). A ca. 50 % oily suspension of sodium hydride (125 mg, ca. 2.6 mmol) and benzyl bromide (0.36 ml, 3.0 mmol) were added and the resulting mixture was stirred at ambient temperature under N_2 for 30 h. Water (30 ml) was added and the aqueous solution was extracted with hexane (4x50 ml). The hexane phase was washed with 1 M NaOH (1x50 ml) and brine (6x50 ml), dried ($MgSO_4$), and the crude product was purified by flash chromatography on silica gel using EtOAc:hexane 1:30; yield 705 mg (75 %) of a colourless oil. (Found: C, 66.32; H, 7.61. Calc. for $C_{26}H_{35}ClN_2O_2Si$: C, 66.29; H, 7.49 %). ^1H NMR ($CDCl_3$): δ 0.26 ($SiMe_2$), 0.93 (Me in thexyl), 0.95 (Me in thexyl, d, *J* 6.9 Hz), 1.71 (CH in thexyl, m, *J* 6.9 Hz), 3.51 (CH_2Ph, H_A, d, *J* 15.3 Hz), 4.74 (H-4), 5.12 (CH_2O, H_A, d, *J* 9.3 Hz), 5.24 (CH_2O, H_B, d, *J* 9.3 Hz), 5.41 (CH_2Ph H_B, d, *J* 15.3 Hz), 6.42 (H-6), 7.2-7.4 (Ph, m). ^{13}C NMR ($CDCl_3$): δ −2.2 ($SiMe_2$), 19.4 and 21.1 (Me in thexyl), 25.8 (C in thexyl), 35.0 (CH in thexyl), 48.8 (CH_2Ph), 64.9 (C-4), 71.9 (CH_2O), 109.1 (C-5) 125.2 (C-6), 128.1, 128.6, 129.1 and 129.3 (CH in Ph), 136.7 and 139.2 (C in Ph), 152.1 (C-2). MS (CI): 473/471 (2/6, *M*+1), 455 (22), 387 (76), 385 (100), 311 (55), 295 (7), 222 (6), 207 (6), 178 (24), 91 (31).

3-Benzyl-5-chloro-1,4-dihydro-1-hydroxymethyl-4-phenyl-2(1H)pyrimidinone (18). 3-Benzyl-5-chloro-1,4-dihydro-1-(dimethylthexylsilyloxy)methyl-4-phenylpyrimidin-2(1*H*)-one (235 mg, 0.5 mmol) was dissolved in THF (1 ml) and 2 ml of a 60 % aqueous solution of acetic acid was added. The resulting mixture was stirred at 50 °C for 8 h. The pH was adjusted to ca. 6 with 1 M NaOH and the aqueous solution extracted with dichloromethane (4x20 ml). The organic solution was washed with brine (2x10 ml), dried ($MgSO_4$) and the crude product purified by flash chromatography on silica gel using EtOAc; yield 117 mg (71 %) of a colourless oil. (Found: C, 65.42; H, 5.58. Calc. for $C_{18}H_{17}ClN_2O_2$: C, 65.75; H, 5.21 %). ^1H NMR ($CDCl_3$): δ 3.53 (CH_2Ph, H_A, d, *J* 15.3 Hz), 4.74 (H-4), 4.87 (CH_2O, H_A, d, *J* 10.7 Hz), 5.18 (CH_2O, H_B, d, *J* 10.7 Hz), 5.33 (CH_2Ph, H_B, d, *J* 15.3 Hz), 6.44 (H-6), 7.3-7.5 (Ph, m). ^{13}C NMR ($CDCl_3$): δ 48.1 (CH_2Ph), 64.4 (C-4), 72.6 (CH_2O), 108.5 (C-5), 125.0 (C-6), 127.4, 127.6, 127.9, 128.1, 128.6 and 128.8 (CH in Ph), 135.7 and 138.2 (C in Ph), 152.4 (C-2). MS (CI-isobutane): 331/329 (1/3, *M*+1), 311 (10), 301 (33), 299 (100), 221 (7), 207 (12), 133 (7), 91 (44), 85 (11), 69 (19).

1-Benzyl-5-chloro-3,6-dihydro-6-phenylpyrimidin-2(1H)-one (19).[17] 3-Benzyl-5-chloro-1,4-dihydro-1-(dimethylthexylsilyloxy)methyl-4-phenylpyrimidin-2(1*H*)one (235 mg, 0.5 mmol) was dissolved in THF (2 ml) and 2.0 ml of a 0.5 M solution of tetrabutylammonium fluoride in THF was added. The resulting mixture was stirred at ambient temperature under N_2 for 1.5 h, water (10 ml) was added and the mixture extracted with dichloromethane (4x20 ml). The organic solution was washed with brine (1x 20 ml), dried ($MgSO_4$) and the product isolated by flash chromatography on silica gel using EtOAc:hexane 1:1; yield 112 mg (75 %) of a white solid. ^1H NMR ($CDCl_3$): δ 3.51 (CH_2Ph, H_A, d, *J* 15.3 Hz), 4.76 (H-6), 5.36 (CH_2Ph, H_B, d, *J* 15.3 Hz), 6.31 (H-4, d, *J* 4.8 Hz), 7.2-7.6 (Ph, m), 8.54 (NH, d).

Preparation of 1-Substituted 3,4-Dihydro-4-phenylethynylpyrimidin-2(1H)-ones (21). Butyllithium (1.6 M in n-hexane, 40 mmol) was added gradually to a solution of phenylacetylene (40 mmol) in dry diethyl ether (100 ml) under argon at -78 °C with stirring. To this solution at -78 °C was added dropwise

with stirring a solution of tri-isopropoxytitanium chloride (40 mmol) in dry diethyl ether (100 ml). The cold, resultant solution was added dropwise with stirring to a fine suspension of the 1-substituted 5-chloropyrimidin-2(1*H*)-one (8 mmol) in dry THF (100 ml) at -78 °C. The stirring was continued at this temperature for 1h before the reaction mixture was allowed to warm up to ambient temperature. The reaction mixture was dark in colour due to partial polymerization of the titanium reagent. The mixture was worked up by slow addition of 1M HCl to pH ca. 6, addition of benzene (75 ml) followed by evaporation of the ether solvents. The benzene solution was separated from the aqueous phase, the aqueous phase extracted with diethyl ether and the combined organic solution washed and dried ($MgSO_4$). The dried solution was concentrated to a small volume and chromatographed on neutral alumina (activity II) using chloroform for elution. The 3,4-dihydro isomer comes off the column before any 3,6-isomer which might be present.

1-Benzyl-5-chloro-3,4-dihydro-4-phenylethynylpyrimidin-2(1H)-one(21b) was obtained from **8b** in 69 % yield, m.p. 119 °C (EtOAc). ^{1}NMR ($CDCl_3$, 60 MHz): δ 4.57 (CH_2Ph), 4.96 (H-4, *J* 4 2 Hz), 6.07 (H-6), 6.73 (NH), 7.33 (2 Ph). MS: (4/11, M^+), 245 (4), 102 (12), 91 (100).

Continued elution of the chromatoghraphic column after the title compound had been eluted, gave ca. 1% yield of the regioisomer, viz. 1-benzyl-5-chloro-3,6-dihydro-4-phenylethynylpyrimidin-2(1*H*)-one.[20]

1-Benzyloxymethyl-5-chloro-3,4-dihydro-4-phenylethynylpyrimidin-2(1H)-one (21d) was obtained in 58 % yield from **8d**, m.p. 121 °C (EtOAc). ^{1}H NMR ($CDCl_3$, 60 MHz): δ 4.56 (CH_2Ph), 4.97 (CH_2O), 5.03 (H-4, *J* 4 2 Hz), 6.35 (H-6), 6.76 (NH), 7.33 (2 Ph). MS(CI-isobutane) : 355/353 (2/6, *M*+1), 247 (35), 245 (100), 91 (36).[20]

Preparation of 1-Substituted 4-Phenylethynylpyrimidin-2(1H)-ones (22). A solution of the 1-substituted 3,4-dihydro-4-phenylethynylpyrimidin-2(1*H*)-one (1 mmol) in benzene (50 ml) was stirred together with activated manganese dioxide (3 g) for 6 - 24 h at ambient temperature before the mixture was filtered. The solid was repeatedly extracted with benzene (6x100 ml), extracts and filtrate combined and the solvent distilled off. The residue was crystallized fom ethyl acetate.

1-Benzyl-5-chloro-4-phenylethynylpyrimidin-2(1H)-one (22b) was obtained in 64 % , m.p. 224 °C (EtOAc). ^{1}H NMR ($CDCl_3$, 60 Mz): δ 5.05 (CH_2Ph), 7.33 (2 Ph), 7.61 (H-6). MS: 322/320 (23/53, *M*+), 321 (20), 319 (23), 243 (25), 91 (100).[20]

1-Benzyloxymethyl-5-chloro-4-phenylethynylpyrimidin-2(1H)-one (22d) was obtained in 84 % yield, m.p. 134 °C (EtOAc). ^{1}H NMR ($CDCl_3$, 60 MHz): δ 4.62 (CH_2Ph), 5.38 (CH_2O), 7.70 (H-6). MS(CI-isobutane): 353/351 (23/65, *M*+1), 323 (40), 321 (100), 244 (45), 91 (71).[20]

Preparation of 1-Substituted 3,6-Dihydro-6-ethynylpyrimidin-2(1H)-ones (23). Acetylene was bubbled slowly through dry THF (25 ml) at -80 °C. When the solution had been saturated with acetylene, *n*-butyllithium in hexane(1.53 M, 6.52 ml) was added dropwise to the stirred solution while maintaining a slow stream of acetylene. The solution was stirred at -80 °C for 2 h before a solution of tri-isopropoxytitanium chloride (10 mmol) in THF (10 ml) at -80 °C was added via a cannula during 15 min. After stirring the solution at -80 °C for 2 h the 1-substituted 5-halogenopyrimidin-2(1*H*)-one (2 mmol) was added at intervals during 30 min. The mixture was stirred at this temperature for 48 h before the reaction was quenched by the addition of water (20 ml) and the pH adjusted to ca. 7 with dilute HCl. Toluene (30 ml) was then added, most of the THF in the mixture removed by distillation at reduced pressure, the toluene and aqueous phases separated, the aqueous phase extracted with chloroform (4x5 ml) and the organic solutions combined. The combined organic solution was shaken with 1 M HCl (15 ml), saturated aqueous $NaHCO_3$ (15 ml), saturated aqueous NaCl (15 ml) and the dried ($MgSO_4$) solution evaporated.The residue was purified by chromatography on neutral aluminum oxide (activity III) with chloroform or dichloromethane as eluant.

The products were yellow oils which slowly decomposed and were characterized by their NMR spectra.

1-Benzyl-5-chloro-3,6-dihydro-6-ethynylpyrimidin-2(1H)-one (23b) was obtained in 46 % yield from **8b**. The reaction was incomplete; 40 % of **8b** was recovered from the reaction after chromatographic separation of the products. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 2.55 (acetylene-H, d, *J* 2Hz), 4.10 and 5.42 (CH_2Ph, AB, *J* 10.5 Hz), 4.62 (H-6, d, *J* 2 Hz), 6.33 (H-4, d, *J* 5.5 Hz), 7.43 (Ph, s), 8.75 (H-3, d, *J* 5.5 Hz).[21]

1-Benzyloxymethyl-5-chloro-3,6-dihydro-6-ethynylpyrimidin-2(1H)-one (23d) was obtained in 87 % yield from **8d**. ^{1}H NMR ($CDCl_3$, 60 MHz): δ 2.53 (acetylene-H, d, *J* 2 Hz), 4.54 and 5.68 (CH_2O, AB, *J* 11 Hz), 4.58 (CH_2Ph, s), 4.95 (H-6, d, *J* 2 Hz), 6.13 (H-4, d, *J* 5 Hz), 7.43 (Ph, s), 8.62 (H-3, d, *J* 5 Hz).[21]
1-Benzyl-3,6-dihydro-6-ethynyl-5-fluoropyrimidin-2(1H)-one (23e) was obtained in 88 % yield from **8e**. The reaction was incomplete in that 9 % of **8e** was recovered from the reaction after chromatographic separation of the products. ^{1}H NMR ($CDCl_3$60 MHz): δ 2.45 (acetylene-H, d, *J* 2 Hz), 4.06 and 5.43 (CH_2Ph, AB, *J* 15 Hz), 4.70 (H-6, d, *J* 2 Hz), 6.17 (H-4, d, *J* 4.5 Hz), 7.40 (Ph, s), 8.40 (H-3, d, *J* 4.5 Hz).[21]

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