Umpolung of Reactivity of Lithium Trimethylsilyldiazomethane at the C-5 Position of 6-Substituted Uracil Derivatives

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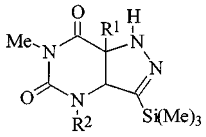
The nucleophilic addition of TMSC(Li)N_2 at the low reactive C-5 position of the uracil ring of C-6 substituted uracil derivatives is reported. The ratio of C-5 *versus* C-6 nucleophilic addition of TMSC(Li)N_2 dramatically depends on the stereoelectronic properties of the C-6 substituent. In particular, substituents characterized both by sterically bulky and/or electron-withdrawing (EWG) effects appear to direct the nucleophile mainly (methyl, chloromethyl or halogen) or completely (isopropyl) toward the C-5 position. The fine-tuned substituent selectivity found in the nucleophilic addition of TMSC(Li)N_2 to C-6 substituted uracils plays a leading role in the synthesis of new trimethylsilyl-1*H*-[4,3-*d*]pyrimidin-5,7-dione derivatives, which can in turn be easily modified through known silicon chemistry.

Introduction

Lithium trimethylsilyldiazomethane, [TMSC(Li)N_2], easily prepared from trimethylsilyldiazomethane and *n*-butyllithium,[1] is a very useful [C−N−N] synthon for the preparation of azoles.[2] The reaction of TMSC(Li)N_2 with β-substituted α,β-unsaturated nitriles,[3] sulfones[4] or ketones[5] usually proceeds by nucleophilic attack on the β-carbon followed by cyclization and elimination processes. Recently, as part of a project based on the study of the reactivity of organolithium-containing silicon reagents with uracil derivatives and pyrimidine nucleosides,[6] we reported the first example of reactivity of TMSC(Li)N_2 toward the 5,6-double bond of several 5-substituted uracil and uridine derivatives.[7] This transformation, which provides a general method for the synthesis of annulated and fused 1*H*-pyrazolo[4,3-*d*]pyrimidindiones **I** (Figure 1), proceeds through a selective addition of TMSC(Li)N_2 at the C-6 position of the uracil ring. Nucleophiles invariably react at the C-6 position of uracil and C-5 substituted uracil derivatives giving rise to a 5,6-dihydrouracil intermediate from which the respective product is formed. Reactions of nucleophiles at the C-6 position of uracil derivatives are of biological significance since they represent significant steps in the biosynthesis of DNA in both bacteria and animals. In particular, the thymidylate synthase-catalysed conversion of 2′-deoxyuridine monophosphate (dUMP) to 2′-deoxythymidine monophosphate (dTMP), which requires the nucleophilic attack of a cysteine thiolate anion at the C-6 position of dUMP, is the sole de novo pathway for dTMP synthesis.[8] The blocking of this activity has a dramatic effect on the proliferating cells, and 5-substituted uracil and dUMP analogues bearing electron-withdrawing groups (EWG) as substituents at the C-5 position have shown potent antitumor effects.



I

R^1= H, F, NO_2, R^2= methyl or ribose

Figure 1. Structure of 1*H*-pyrazolo[4,3-*d*]pyrimidindiones **I**

In contrast to the extensive studies on 5-substituted uracil and uridine derivatives, less attention has been devoted to the 6-substituted isomers, probably because of their complicated synthesis and their supposed biological inactivity.[9] Thus, with the exception of the conversion of 6-cyano-1,3-dimethyluracil to its 5-cyano derivatives by treatment with CN^-, reported by Senda,[10] and the addition of thiolate ions at the C-5 position in 6-cyano-1,3-dimethyluracil, described by Kumar,[11] there are no reports in the literature dealing with the addition of nucleophiles to C-6 substituted uracil derivatives. On the other hand, during the last few years, C-6 substituted uracil and pyrimidinone derivatives have emerged in the field of chemotherapy. Among the important 6-substituted uracils, 1-[(2-hydroxyethoxy)methyl]-6-phenylthiothymine (HEPT),[12] and 3,4-dihydro-2-alkoxy-6-benzyl-4-oxopyrimidines (DABOs),[13] have shown important anti-HIV-1 activity as non-nucleoside reverse transcriptase inhibitors (NNRTI). Moreover, the 6-oxiranyl- and 6-methyloxiranyluracil derivatives showed a potent and selective inhibition against african swine fever virus (ASFV),[14] vesicular stomatitis virus (VSV)[15] and parainfluenza 1 (Sendai) virus,[16] and (*E*)-6-(acylvinyl)uracils ex-

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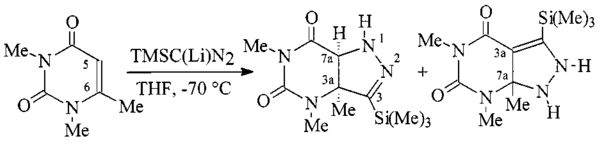
hibited excellent antitumor activities.[17] In this context, model reactions of the addition of nucleophiles to C-6 substituted uracil derivatives play an important role in order to understand the reactivity and, at least in some cases, to rationalize the biological activity of newly synthesized 6-substituted uracil derivatives. We report here that TMSC(Li)N_2 adds to 6-substituted uracil derivatives both at the C-5 and the C-6 positions, the ratio of addition products depending on the nature of the substituent present at the C-6 position. In particular, substituents characterized by a steric encumbering and/or an EWG effect considerably enhance the yield of the unexpected C-5 addition product. This procedure is a new example of the scarcely reported C-5 addition of nucleophiles to the uracil ring, and a new and efficient entry to 3a,7a-dihydro-7a-substituted 5,7-dimethyl-3-trimethylsilyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4,6-diones.

Results and Discussion

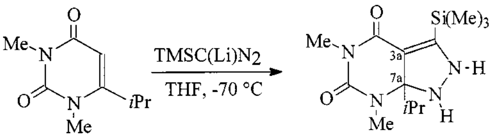
Unprotected uracil derivatives do not usually react with nucleophiles because of anion formation in basic media which makes attack by nucleophiles more difficult. For this reason, 1,3-dialkylated uracils, such as 1,3-dimethyluracil derivatives, are more susceptible to nucleophilic attack and are extensively used as model substrates. In the present study, all the reactions were performed with 1 mmol of 6-substituted 1,3-dimethyluracil derivatives using a small excess (1.3 equiv./mol) of a freshly prepared TMSC(Li)N_2 (2 N hexane solution) in dry THF at −70°C. The reaction of 1,3,6-trimethyluracil (**1**) with TMSC(Li)N_2 gave 3a,7a-dihydro-3a,4,6-trimethyl-3-trimethylsilyl-1*H*-pyrazolo[4,3-*d*]-pyrimidin-5,7-dione (**2**), and the pyrazolidine derivative **3** in 49% and 26% yields (ratio **2**:**3** ca. 2:1), respectively (SCHEME 1). The stereochemistry of the 3a and 7a positions in compounds **2** and **3** was determined by NMR spectroscopy. The conformational analysis of the 5,6-dihydrouracil derivatives showed that these compounds present a half-chair conformation, the [N−CO−N−CO] moiety being approximately coplanar.[18] Irradiation of the 7a-H proton signal at δ = 3.60 in the ^{1}H NMR spectrum of **2** gave a ca. 6.5% enhancement of the 3a-Me proton signal in NOE experiments, thus showing a *cis* stereochemistry. Furthermore, the irradiation of the N(4)−Me proton signal at δ = 3.15 gave a ca. 7% enhancement of the 3a-Me proton signal and a 5.9% enhancement of the 3-SiMe proton signal in NOE experiments. On the basis of these data compound **2** appears to be formed by addition of TMSC(Li)N_2 at the C-6 position of **1**. On the other hand, the absence of any detectable NOE effect between the 7a-Me signal proton and the SiMe moiety, besides the absence of the resonance of the 3a-H proton, led us to consider that **3** is formed by addition of TMSC(Li)N_2 at the C-5 position of the uracil ring, followed by previously observed[6] removal of the 3a-H during the workup of the reaction (Scheme 1).



1 **2** **3**

Scheme 1. Reaction of 1,3,6-trimethyluracil (**1**) with TMSC(Li)N_2

To evaluate the effect of the C-6 substituent on the reaction pathway (usual C-6 versus unusual C-5 nucleophilic addition), we studied the reaction of a number of 6-substituted uracil derivatives: 6-isopropyl-1,3-dimethyluracil (**4**), 1,3-dimethyl-6-chloromethyluracil (**6**), 1,3-dimethyl-6-chlorouracil (**9**), 6-iodo-1,3-dimethyluracil (**11**), and 6-cyano-1,3-dimethyluracil (**13**), with TMSC(Li)N_2 under the previously reported experimental conditions. The reaction of 6-isopropyl-1,3-dimethyluracil (**4**) with TMSC(Li)N_2 gave 2,7a-dihydro-7a-isopropyl-5,7-dimethyl-3-trimethylsilyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4,6-dione (**5**) (73% yield), as the only recovered product (Scheme 2). In this case, products of C-6 addition were not observed even in the presence of an excess of TMSC(Li)N_2 and with a longer reaction time.

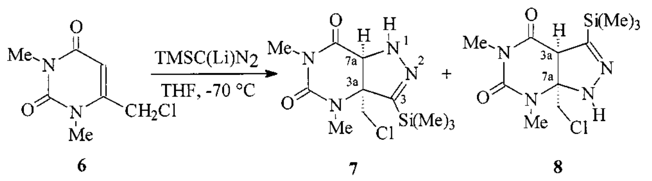


4 **5**

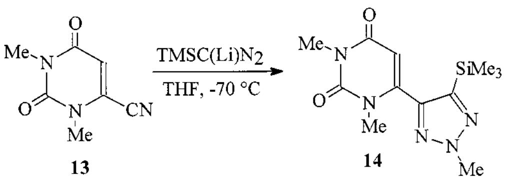
Scheme 2. Reaction of 6-isopropyl-1,3-dimethyluracil (**4**) with TMSC(Li)N_2

The reaction of 6-chloromethyl-1,3-dimethyluracil (**6**) with TMSC(Li)N_2 gave 3a-chloromethyl-3a,7a-dihydro-4,6-dimethyl-3-trimethylsilyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5,7-dione (**7**), and 7a-chloromethyl-3a,7a-dihydro-5,7-dimethyl-3-trimethylsilyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4,6-dione (**8**) in 45 and 35% yield (ratio **7**:**8** = 1.3:1), respectively. In this case, the migration of the 3a proton in compound **8** did not occur during the workup of the reaction. The regio- and stereochemistry of compounds **7** and **8** was determined by NMR spectroscopy. Irradiation of the 7a-H proton signal at δ = 4.15 in the ^{1}H NMR spectrum of **7** gave a ca. 5.7% NOE effect of the 3a-chloromethyl moiety, thus showing a *cis* stereochemistry. Furthermore, irradiation of the N(4)−Me proton signal at δ = 3.22 gave a significant enhancement of both the proton signal of chloromethyl moiety and the SiMe proton signal. In the case of **8**, a *cis* stereochemistry was again observed, and the lack of any detectable NOE effect between the N(7)−Me proton signal and the SiMe group further confirmed the proposed structure (Scheme 3). It is interesting to note that the possible dehydrogenation of the primary dihydro cycloadducts during the workup or purification procedures did not occur under our experimental conditions.

Unexpectedly, the reaction of 6-chloro-1,3-dimethyluracil (**9**) with TMSC(Li)N_2 gave the diuracilmethane derivative **10** in 47% yield as the only recovered product (Scheme 4). Compound **10** was characterized by the presence of all the expected signals in the ^{1}H and ^{13}C NMR spectra. In particular, the presence of a CH singlet signal at δ = 6.37 (typi-



Scheme 3. Reaction of 6-chloromethyl-1,3-dimethyluracil (**6**) with TMSC(Li)N_2



Scheme 5. Reaction of 6-cyano-1,3-dimethyluracil (**13**) with TMSC(Li)N_2

cal of the C(6)−H uracil proton) and the presence of a CH singlet signal at δ = 5.61 (typical of the C(5)−H uracil proton) in the ^{1}H NMR spectrum suggested a C(5)/C(6) bond link between the two uracil moieties. Compound **10** was succesively obtained in 70% yield by the reaction of 1,3-dimethyl-6-iodouracil **(11)** with TMSC(Li)N_2 under similar experimental conditions (Scheme 4).

We have not investigated in detail the reaction pathway which yielded compound **10**, but it is reasonable to suggest that the reaction proceeds through the initial addition of TMSC(Li)N_2 at the C-5 position of one molecule of the substrate followed by elimination of HX to give the intermediate **12** (not isolated by chromatographic separation probably due to its instability). The elimination of the nitrogen leaving group present in this intermediate by a 6-lithium uracil[19] of a second molecule of substrate, followed by spontaneous protodesilylation could afford compound **10**. This hypothesis is in agreement with the GC-MS characterization of traces of the intermediate **12** in the reaction mixture.[20] The synthesis of the bis(uracil)methane derivate **10** is a new and efficent entry to biologically important bipyrimidinylmethane derivatives,[21] and a further example of umpolung of reactivity of nucleophiles at C-5 position of the uracil ring.

The reaction of 1,3-dimethyl-6-cyanouracil **(13)** with TMSC(Li)N_2 (two equivalents) gave 1,3-dimethyl-6-[(2′-methyl-5′-trimethylsilyl)-1′,2′,3′-triazol-4′-yl]uracil **(14)** in 82% yield (Scheme 5).[2b]

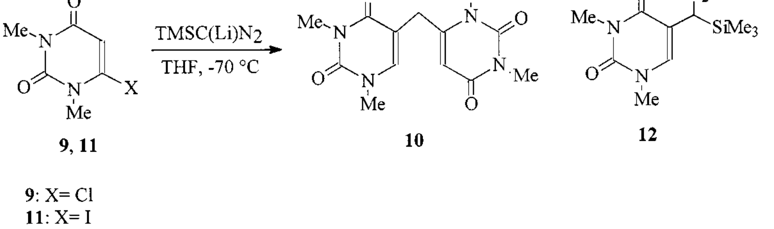
The structure of **14** was confirmed by the presence in the ^{1}H NMR spectrum of the characteristic C-5 uracil signal proton at δ = 5.85 and by the absence of any detectable NOE effect. In the latter case, the addition of the TMSC(Li)N_2 at the 6-carbonitrile moiety, followed by methylation of one azole nitrogen atom, was the only observed transformation. The high reactivity of the exocyclic carbonitrile substituent is in agreement with previously reported data on the reaction of TMSC(Li)N_2 with 5-formyl-1,3-dimethyluracil and 5-formyluridine derivatives, in which addition products at the C-5,6 double bond were not observed.[2b,7]

Conclusions

On the basis of these data, the nucleophilic addition of TMSC(Li)N_2 at the low reactive C-5 position of the uracil ring is operative when a substituent is also present on the C-6 position. The ratio of C-5 versus C-6 nucleophilic addition of TMSC(Li)N_2 dramatically depends on the stereoelectronic properties of the C-6 substituent. In particular, substituents characterized both by sterically bulky and/or electronwithdrawing (EWG) effects appear to direct the nucleophile mainly (methyl, chloromethyl, and halogen) or completely (isopropyl) toward the C-5 position. On the other hand, substituents with a reactive electrophilic site, such as the carbonitrile group, react efficiently with TMSC(Li)N_2 to give exocyclic azole derivatives. The fine-tuned substituent selectivity found in the nucleophilic addition of TMSC(Li)N_2 to C-6 substituted uracils plays a leading role in the synthesis of new trimethylsilyl-1*H*-[4,3-*d*]pyrimidin-5,7-dione derivatives, which can in turn be easily modified through known silicon chemistry. Furthermore, a nucleophilic addition at the C-5 position of the uracil ring, which in principle may be possible for activated nucleophilic groups present in biologically important enzymes, is in our opinion a useful clue to design models for the interpretation of the unexpected antiviral and anticancer activities recently shown by several 6-substituted uracil derivatives. Further studies are now underway to confirm its generality

Experimental Section

General: All solvents were ACS reagent grade and when necessary where redistilled and dried according to standard procedures. − NMR spectra were recorded on a Bruker (200) MHz spectrometer



Scheme 4. Reactions of 6-chloro-1,3-dimethyluracil (**9**) and 6-iodo-1,3-dimethyluracil (**11**) with TMSC(Li)N_2

and are reported in δ values relative to tetramethylsilane. − Infrared spectra were recorded on a Perkin−Elmer 298 spectrophotometer using NaCl plates. − Microanalyses were performed with a C. Erba 1106 analyser. − Mass spectra were recorded on VG 70/250S spectrometer with an electron beam of 70 eV. − Melting points were obtained on Mettler apparatus and are uncorrected. − Chromatographic purifications were performed on columns packed with Merck silica gel, 230−400 mesh for flash technique. − Thin-layer chromatography was carried out using Merck platten Kieselgel 60 F254.

Starting Materials: 1,3,6-trimethyluracil (**1**) was synthesised according to the procedure reported by Allen;[22] 6-isopropyl-1,3-dimethyluracil **(4)** was prepared according to the procedure reported by Botta,[23] 6-chloromethyl-1,3-dimethyluracil **(6)** was prepared from commercially available 6-chloromethyluracil (Aldrich) by treatment with an ethereal solution diazomethane in MeOH at 25°C; 1,3-dimethyl-6-chlorouracil **(9)** was prepared starting from commercially available 2,4,6-trichloropyrimidine (Aldrich) according to the procedure reported by Creswell;[24] 6-iodo-1,3-dimethyluracil **(11)** was synthesised according to the procedure reported by Tanaka.[19]

Reaction of Compounds 1, 4, 6, 9, 11 or 13 with Lithium Trimethylsilyldiazomethane [TMSC(Li)N$_2$]. − General Procedure: The reactions were performed by adding TMSC(Li)N$_2$ (1.3 equiv./mol.) via a cannula to the appropriate substrate in dry THF (5 mL) and stirring at −78°C for 6 h. The mixture was quenched by addition of NH$_4$Cl (saturated solution). The organic layer was diluted with EtOAc, separated, washed with NaHCO$_3$ and brine, dried with anhydrous Na$_2$SO$_4$, and evaporated under reduced pressure. Chromatographic separation using CH$_2$Cl$_2$/EtOAc (4:1) as eluent gave products **2**, **3**, **5**, **7**, **8**, **10** and **14** in acceptable to good yields.

3a,7a-Dihydro-3a,4,6-trimethyl-3-trimethylsilyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5,7-dione (2): 132 mg (49%), oil. − ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.20 [s, 9 H, Si(*CH$_3$*)$_3$], 1.47 (s, 3 H, CH$_3$), 3.13 (s, 3 H, N*CH$_3$*), 3.15 (s, 3 H, N*CH$_3$*), 3.60 (s, 1 H, CH), 6.71 (br. s., 1 H, N*H*). − ^{13}C NMR (CDCl$_3$): δ = −1.80 (CH$_3$), 9.42 (CH$_3$), 26.88 (CH$_3$), 34.51 (CH$_3$), 124.28 (CH), 140.69 (C), 146.22 (C), 156.41 (C), 169.6 (C). − MS (70 eV); *m*/*z* (%): 268.4 (8) [M$^+$]; 253.4 (9.5) [M$^+$ − CH$_3$]. − C$_{11}$H$_{20}$N$_4$O$_2$Si (268.3925): calcd. C 49.18, H 7.45, N 20.86; found C 49.20, H 7.43, N 20.96.

Pyrazolidine Derivative (3): 70 mg (49%), oil. − ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.22 [s, 9 H, Si(*CH$_3$*)$_3$], 2.20 (s, 3 H, CH$_3$), 2.95 (s, 3 H, N*CH$_3$*), 3.31 (s, 3 H, N*CH$_3$*), 9.11 (br. s., 1 H, N*H*), 10.70 (br. s., 1 H, N*H*). − ^{13}C NMR (CDCl$_3$): δ = −1.85 (CH$_3$), 10.0 (CH$_3$), 27.15 (CH$_3$), 35.31 (CH$_3$), 142.10 (C), 147.0 (C), 156.42 (C), 161.10 (C), 169.1 (C). − MS (70 eV); *m*/*z* (%): 268.4 (11) [M$^+$]; 253.4 [M$^+$ − CH$_3$]. − C$_{11}$H$_{20}$N$_4$O$_2$Si (268.3925): calcd. C 49.18, H 7.45, N 20.86; found C 49.21, H 7.44, N 20.92.

2,7a-Dihydro-7a-isopropyl-5,7-dimethyl-3-trimethylsilyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4,6-dione (5): 216 mg (73%), oil. − ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.20 [s, 9 H, Si(*CH$_3$*)$_3$], 1.25 [d, *J* = 8.0 Hz, 6 H, CH(*CH$_3$*)$_2$], 3.20 [m, 1 H, *CH*(CH$_3$)$_2$], 3.28 (s, 3 H, N*CH$_3$*), 3.30 (s, 3 H, N*CH$_3$*), 8.90 (br. s., 1 H, N*H*), 10.10 (br. s., 1 H, N*H*). − MS (70 eV); *m*/*z* (%): 296.4 (21) [M$^+$]; 281.4 (8.5) [M$^+$ − CH$_3$]. − C$_{13}$H$_{24}$N$_4$O$_2$Si (296.4466): calcd. C 52.70, H 8.20, N 18.90; found C 52.19, H 8.22, N 18.92.

3a-Chloromethyl-3a,7a-dihydro-4,6-dimethyl-3-trimethylsilyl-1*H*-pyrazolo[4,3-*d*]pyrimidin-5,7-dione (7): 136 mg (45%), oil. − ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.22 [s, 9 H, Si(*CH$_3$*)$_3$], 3.20 (s, 3 H, N*CH$_3$*), 3.22 (s, 3 H, N*CH$_3$*), 3.65 (m, 2 H, *CH$_2$*Cl), 4.15 (s, 1 H, CH), 6.89 (br. s., 1 H, N*H*); − ^{13}C NMR (CDCl$_3$): δ = −1.30 (CH$_3$), 28.32 (CH$_3$), 31.54 (CH$_3$), 42.49 (CH$_2$), 61.42 (CH), 100.01 (C), 151.22 (C), 157.64 (C), 167.98 (C). − MS (70 eV); *m*/*z* (%): 302 (13) [M$^+$]; 287 (7.8) [M$^+$ − CH$_3$]. − C$_{11}$H$_{19}$ClN$_4$O$_2$Si (302.0966): calcd. C 43.59, H 6.27, N 18.5; found C 43.61, H 6.25, N. 18.50.

7a-Chloromethyl-3a,7a-dihydro-5,7-dimethyl-3-trimethylsilyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-4,6-dione (8): 106 mg (35%), oil. − ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.20 [s, 9 H, Si(*CH$_3$*)$_3$], 3.16 (s, 1 H, CH), 3.37 (s, 3 H, N*CH$_3$*), 3.41 (s, 3 H, N*CH$_3$*), 3.55 (m, 2 H, *CH$_2$*Cl) 8.01 (br. s., 1 H, NH). − ^{13}C NMR (CDCl$_3$): δ = −2.63 (CH$_3$), 27.92 (CH$_3$), 31.60 (CH$_3$), 34.07 (CH), 45.71 (CH$_2$), 109.48 (C), 136.63 (C), 152.11 (C), 159.91 (C). − MS (70 eV); *m*/*z* (%): 302 (21) [M$^+$]; 287 (23) [M$^+$ − CH$_3$]. − C$_{11}$H$_{19}$ClN$_4$O$_2$Si (302.0966): calcd. C 43.59, H 6.27, N 18.5; found C 43.60, H. 6.24, N 18.51.

Bis(uracil)methane Derivate (10): 102 mg (70%), oil. − ^{1}H NMR (200 MHz, CDCl$_3$): δ = 3.33 (s, 3 H, N*CH$_3$*), 3.39 (s, 3 H, N*CH$_3$*), 3.49 (s, 3 H, N*CH$_3$*), 3.60 (s, 3 H, N*CH$_3$*), 5.61 (s, 1 H, CH$_2$), 5.72 (s, 1 H, CH), 6.37 (s, 1 H, CH). − ^{13}C NMR (CDCl$_3$): δ = 28.31 (CH$_3$), 29.63 (CH$_3$), 31.78 (CH$_3$), 34.42 (CH$_3$), 53.27 (CH$_2$), 103.92 (CH), 105.07 (CH), 140.04 (C), 144.78 (C), 151.83 (C), 152.12 (C), 161.44 (C), 161.66 (C). − MS (70 eV); *m*/*z* (%): 292 (21) [M$^+$]. − C$_{13}$H$_{16}$N$_4$O$_4$ (292.2964): calcd. C 53.38, H 5.47, N 19.16; found C 53.34, H 5.49, N 19.19.

1,3-Dimethyl-6[(2′-methyl-5′-trimethylsilyl)-1′,2′,3′-triazolyl-4′]-uracil (14): 240 mg (83%), oil. − ^{1}H NMR (200 MHz, CDCl$_3$): δ = 0.27 [s, 9 H, Si(*CH$_3$*)$_3$], 3.17 (s, 3 H, N*CH$_3$*), 3.41 (s, 3 H, N*CH$_3$*), 4.27 (s, 3 H, N*CH$_3$*), 5.74 (s, 1 H, CH). − ^{13}C NMR (CDCl$_3$): δ = −0.91 (CH$_3$), 28.19 (CH$_3$), 33.83 (CH$_3$), 41.84 (CH$_3$), 104.62 (CH), 145.54 (C), 161.90 (C), 163.50 (C), 165.31 (C). − MS (70 eV); *m*/*z* (%): 293 (11) [M$^+$]; 278 (9) [M$^+$ − CH$_3$]. − C$_{12}$H$_{19}$N$_5$O$_2$Si (293.4025): calcd. C 49.08, H 6.47, N 23.87; found C 49.10, H 6.48, N 23.92.

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