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Novel Ring Contraction of 6-Azauracil Derivatives

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Abstract—Derivatives of 6-azauracil were lithiated at −100°C with and without an electrophilic agent. Reactions of appropriate 6-azauracils with *t*-butyllithium and lithium diisopropylamide gave, as a result of a ring contraction, compounds **5** and **6**. The structure of compound **5** was undeniably established by X-ray analysis. A mechanism of the novel ring transformation of 1,2,4-triazines to imidazoles is discussed.

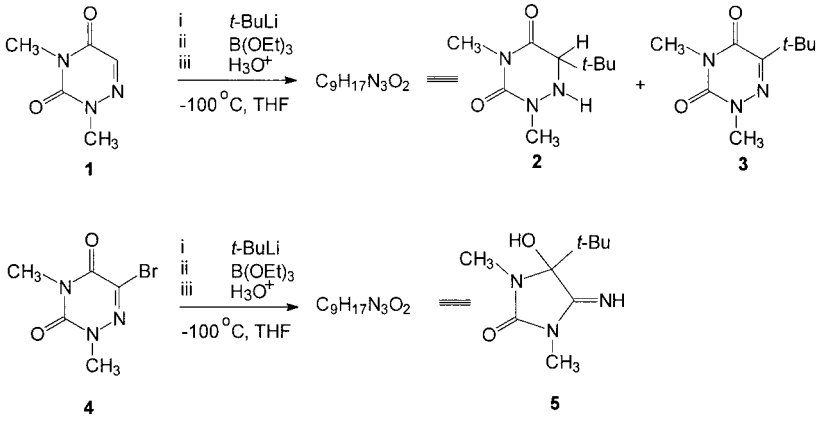
Introduction

The synthesis and reactions of uracil and 6-azauracil derivatives have been the subject of great interest stemming mainly from their biological importance. Numerous examples of reactions in which uracil and 6-azauracil derivatives behave in a similar way have been found.[1,2] Distinct differences in their behaviour appear in the reactions of metallation. The high reactivity of 1,2,4-triazines towards nucleophiles makes the metallation of these compounds more difficult than with the diazines, which are less sensitive to nucleophilic addition. While the lithiation of uracil derivatives at position C(5) can be easily accomplished,[3–6] the lithiation of the derivatives of asymmetric triazine to which 6-azauracil belongs, has been successfully performed recently.[7]

In the present paper we discuss the results of lithiation of some derivatives of 6-azauracil with *t*-butyllithium and the less nucleophilic lithium diisopropylamide (LDA), both in the presence and absence of an electrophilic agent. The reactions were carried out similarly as for our former experiments on uracil derivatives where trialkyl borate acted as an electrophile.[8,9]

Results and Discussion

1,3-Dimethyl-6-azauracil **1**, in reaction with *t*-butyllithium in THF at −100°C, gave typical addition to the double bond. 1,3-Dimethyl-5-bromo-6-azauracil **4** in similar conditions reacted quite differently. The treatment of compound **1** with three equivalents of *t*-butyllithium in THF at −100°C



Scheme 1.

Keywords: metallation; ring contraction; 1,2,4-triazines.

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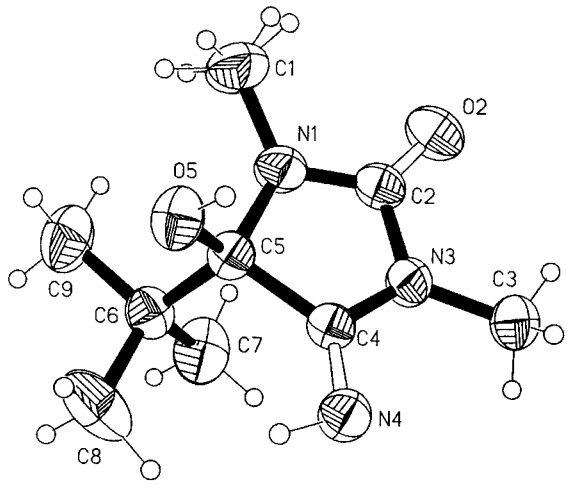


Figure 1. ORTEP drawing of molecule **5**: the thermal ellipsoids are drawn at 50% probability level, the H atoms are represented as small circles of orbitary radius, and double bonds are shown by double lines. Methyl C(1) is rotationally disordered and six half-occupied H-sites are shown in this drawing.

with or without triethyl borate, results in the formation of compound **2** which is the product of nucleophilic attack at the C(5) position of the 6-azauracil moiety. Traces of compound **3** were also found. The reaction of **4** with three equivalents of *t*-butyllithium in THF at −100°C followed by the addition of triethyl borate yielded compound **5** of the same molecular composition as compound **2** but quite different structure (Scheme 1). Reactions of compound **4** with less than three equivalents of *t*-butyllithium, or without trialkyl borate, led to a complex mixture of several labile compounds as judged from chromatographic studies.

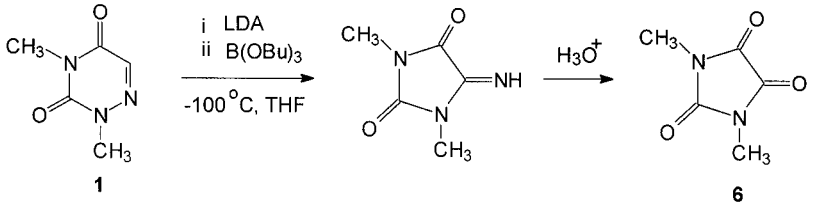
The structure of compound **5** was established by spectroscopy and by X-ray analysis. Fig. 1 shows the structure of molecule **5**, its crystal data, bond lengths, valency angles and selected torsion angles are listed in Table 1.

Transformations of 1,2,4-triazines into triazoles induced by potassium amide are known,[10,11] but no information is given about the reactions of ring contraction of triazines to imidazoles. Some light on the mechanism of this reaction can be shed by the results of the reactions of **4** and **1** with lithium diisopropylamide, which can generate carbanions but does not act as a nucleophilic agent. The reaction of **4** with lithium diisopropylamide gave a complex mixture of several compounds, as indicated by TLC chromatography data, from which no individual compound could be isolated. However, the reaction of compound **1** with lithium diisopropylamide led to ring contraction yielding imidazole derivative, 1,3-dimethylparabanic acid **6**, identified by comparing its spectral data with that of the authentic specimen (Scheme 2).

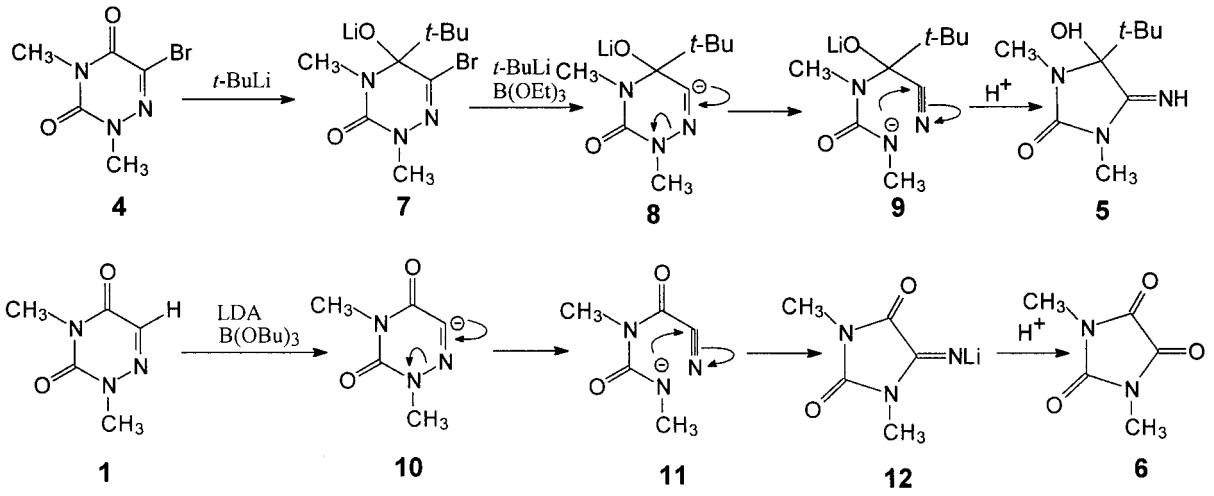
On the basis of these experimental data we propose the following mechanism of ring contraction of 6-azauracil derivatives (Scheme 3): (i) initial addition of the nucleophile at C(4) leading to compound **7**; (ii) generation of unstable carbanion **8** and ring opening between N(1)–N(6); (iii) ring closure of intermediate **9** to the imidazolidinone; and (iv) protonation on acidic work up to give stable compound **5**. Similarly, compound **1** undergoes the generation of carbanion **10**, ring opening to intermediate **11** and subsequent ring closure giving lithium imidazolidinedione **12**. The acidic hydrolysis of **12** gives 1,3-dimethylparabanic acid. An alternative pathway explaining the formation of **5**, involving as the first step the metallation (formation of

Table 1. Crystal data and structure refinement for **5** and **16**

	5	**16**
Empirical formula	$C_9H_{17}N_3O_2$	$C_7H_{13}N_3O_2$
Formula weight	199.26	171.20
Temperature	293(2) K	293(2) K
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/n$
Unit cell dimensions	a=9.814(2) Å	a=7.1700(10) Å
	b=7.4460(10) Å	b=11.962(2) Å
	c=15.027(3) Å	c=10.926(2) Å
	β=100.35(3) deg.	β= 94.32(3) Å
Volume	1080.2(3) Å^3	934.4(3) Å^3
Z	4	4
Absorption coefficient	0.088 mm^{-1}	0.091 mm^{-1}
Reflections collected	5264	2130
Independent reflections	2662 [R_{int}=0.0209]	1391 [R_{int}=0.0348]
Goodness-of-fit on F^2	1.115	1.136
Final R indices [I>2σ(I)]	$R1$=0.0513, $wR2$=0.1513	$R1$=0.0653, $wR2$=0.1708



Scheme 2.



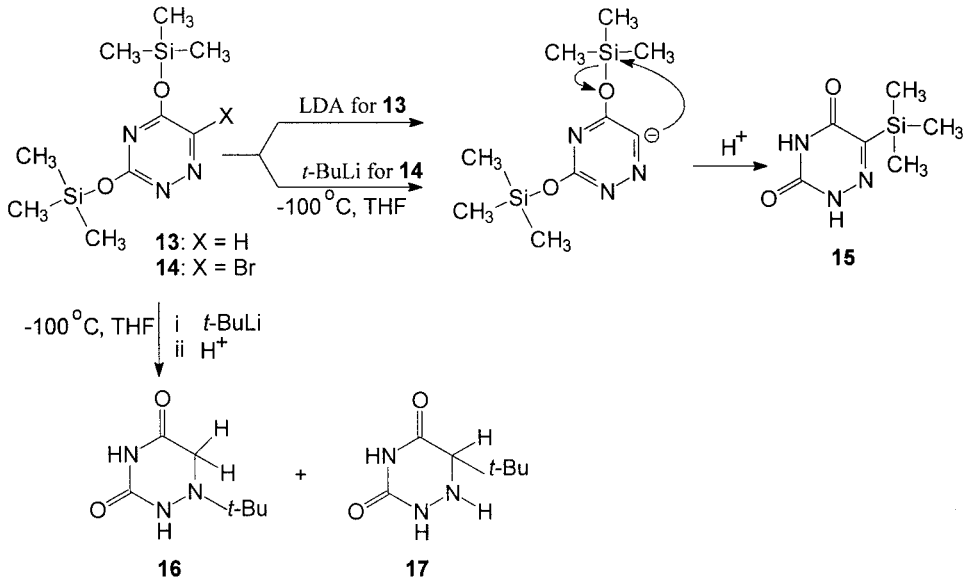
Scheme 3.

carbanion), ring opening, contraction and then the irreversible addition of nucleophile at C(4) was also considered, but finally was excluded as the reaction of **4** with one and two equivalents of *t*-butyllithium in the presence of triethyl borate, followed by protonation, gave no traces of compound **6**. In the case of reaction of *t*-butyllithium with compound **1**, the addition is preferred and **1** undergoes very easily nucleophilic attack followed by covalent hydration.

The boron reagent presumably acts as a typical Lewis acid, because the ring contraction does not take place without trialkylborate. Its electrophilicity is not strong enough to react with the generated carbanion and form a boron–carbon bond, but most likely it can stabilise the carbanion just enough to change the reaction course.

4-Imino-2-imidazolidinone **5** shows a surprising stability in acidic conditions. While the standard acid hydrolysis of **12** produces imidazolidinetrione **6**, heating of **5** for 15 min at 80°C and pH 2 gave no detectable amount of the desired 2,4-imidazolidinedione. Compound **5** hydrolysed at 95°C and pH 2, after 12 h. The formation of 2,4-imidazolidinedione was confirmed by ^{1}H NMR spectroscopy and mass spectrometry.

It is evident from our observations that the bromo substitution of the C(5) position of 6-azauracil derivatives has the dramatic effect on the reaction with organolithium reagents. Reaction of 5-bromo derivatives should proceed via a generation of carbanion for both of the lithiating agents. Reactions of 6-azauracil derivatives with unsubstituted C(5) should proceed with lithium diisopropylamide analogously, while the reactions with *t*-butyllithium, acting in this case as a nucleophile rather than a lithiating agent, should give products of addition to C(5)–N(6) bond. We therefore attempted the lithiation of trimethylsilyl derivatives **13** and **14**. Unfortunately, in reactions of **14** with lithium diisopropylamide, we obtained a complex mixture of products under all condition we tried. Indeed reaction of **13** with lithium diisopropylamide or **14** with *t*-butyllithium



Scheme 4.

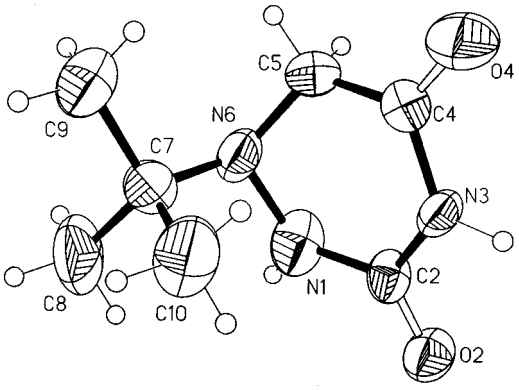


Figure 2. ORTEP drawing of molecule **16** with 50%-level thermal ellipsoids.

results in metallation at C(5); however, it does not lead to ring contraction, but to the migration of a trimethylsilyl group to a vicinal anionic carbon. Treatment of **13** with *t*-butyllithium results in the formation of compound **16** (the main product) and **17**, respectively (Scheme 4).

Organolithium induced rearrangement of the trimethylsilyl group is observed in reactions of trimethylsilyl derivatives of uracils as a competitive reaction to that with electrophiles.[12,13] However, the formation of two isomeric adducts **16** and **17** with overwhelming predominance of compound **16** was unexpected, that its structure was additionally confirmed by X-ray analysis. The formation of **16** theoretically should not take place because it is the position C(5), not N(6), that has the lowest electron density and shows a high susceptibility for nucleophilic addition. On the other hand compound **13** has two unsubstituted nitrogen atoms N(1), N(6) able to bind Li^+. The third nitrogen atom N(3) may be neglected because of very strong hindering effect of the bulky trimethylsilyl groups. Moreover, the neighbouring nitrogens enable formation of a bridged complex with enhanced stability where the Li^+ bridges the two N(1)–N(6) positions.[14] Such an intermediate could undergo easily nucleophilic attack at C(5) giving isomer **17**, or at N(6) position giving isomer **16**. Fig. 2 shows the structure of compound **16**, while the crystal data bond lengths, valency angles and selected torsion angles are presented in Table 1.

Conclusion

Results reported in this paper provide conclusive evidence that organolithium reagents react with 6-azauracil derivatives to generate a carbanion which cannot be trapped with triethyl borate, but which is stable enough to undergo further reactions. In some conditions the 6-azauracil underwent a novel type of ring contraction to imidazolidinedione and imino-imidazolidinone derivatives.

Experimental

Methods

Melting points were determined on a Boetius apparatus and are reported uncorrected. The ^1H NMR and ^{13}C NMR spectra were recorded on Varian Gemini 300 MHz spectrometer in $CDCl_3$ and DMSO-d_6. The mass spectra were recorded on a AMD 402 spectrometer, ionization was achieved through electron impact (EI) and fast atom bombarding (FAB). High-resolution data were obtained on the same instrument using a peak matching technique. Elemental composition of the discussed ion was determined with an error of less than 10 ppm in relation to perfluorokerosene at resolving power of 10000. IR spectra were recorded on Nicolet Magna-IR 760 spectrometer. The elemental analyses were made on Perkin–Elmer apparatus. TLC was carried out on commercially available plates coated with silica gel 60 F_{254} (Merck). X-Ray data were collected on a KM4-CCD diffractometer equipped with a graphite monochromator and a sealed tube; the structures were solved by SHELXS-86[15] and refined by full matrix least-squares using SHELXL-93[16]. In **5** all H-atoms were located from difference Fourier maps and refined with isotopic thermal parameters, except for the H-atoms at methyl C(1), which were constrained in the idealised geometry disordered in two orientations (see Fig. 1)—thermal vibrations of these half occupied H-sites refined to reasonable values. In **16** the methylene and methyl hydrogens were located in idealised positions after each cycle of refinement and their U_{iso} assumed as 1.3 or 1.5 of U_{eq} of their carriers respectively. Two other H atoms were found in difference Fourier maps and refined with U_{iso}. The experimental details of the crystals determinations are listed in Table 1 and available from the Cambridge Crystallographic Data Centre.[†]

Materials

Reaction of (1) with *t*-butyllithium. 1,3-Dimethyl-6-azauracil (1.5 g, 10.6 mmol) was dissolved in dry, freshly distilled THF (80 mL) and cooled to −100°C under an argon atmosphere, using a N_2/hexane bath. A 1.6 M solution of *t*-butyllithium in pentane (20 mL, 32 mmol) was injected through a septum at such a rate that the internal temperature did not exceed −80°C. The temperature was decreased to −100°C, the yellow solution was stirred for additional 5 min and triethylborate (5.5 mL, 32 mmol) was added. The reaction mixture was kept at the same temperature for 30 min and then was allowed to warm to room temperature over a period of 1 h. The solution was evaporated to dryness under reduced pressure and then water was added (40 mL). The aqueous solution was acidified with 1 M HCl to pH 2–3 The solution was extracted with $CHCl_3$ (3×25 mL) and the combined chloroform extracts were dried over $MgSO_4$. The solvent was removed and the residue was separated by column chromatography on silica gel (Aldrich silica gel, 70–230 mesh) with hexane/CH_2Cl_2 (using a gradient from 1:1 v/v to 1:9 v/v) to yield compound **2** (1092 mg, 52%) as white crystals and compound **3** (150 mg, 7%) obtained as an oil. The product **2** was recrystallised from hexane.

2. Mp 91–93°C; MS (EI) *m/z* 199 (29) $[M]^+$, 143 (89), 142 (80), 85 (66), 58 (100), 57 (49); MS (FAB) *m/z* 200 $[M+1]^+$; Anal. Calcd for $C_9H_{17}N_3O_2$: C 54.25%; H 8.53 %; N 21.07%. Found: C 54.28%; H 8.28%; N: 20.90%; ν_{max} (KBr) 3254, 1702 and 1652 cm^{-1}; δ_H (DMSO-d_6)

[†] CCDC reference numbers CCDC 143140 and 143141. See http://www.rsc.org/suppdata for crystallographic files in CIF format.

6.04 (1H, d, J=5.8 Hz, N(6)H), 3.15 (1H, d, J=5.8 Hz, C(5)H), 3.00 and 3.01 (6H, s, CH_3), 0.97 (9H, s, C–CH_3); δ_C ($CDCl_3$) 170.4, 153.3, 66.6, 37.0, 27.0, 34.1 and 27.6.

3. MS (EI) m/z 197 (27) $[M]^+$, 182 (49), 142 (68), 97 (59), 57 (100); HRMS: calculated for $C_9H_{15}N_3O_2$ 197.1164, Found 197.1160; ν_{max} (film) 1717 and 1669 cm^{-1}; δ_H ($CDCl_3$) 3.63 and 3.33 (6H, s, CH_3), 1.33 (9H, s, C–CH_3); δ_C ($CDCl_3$) 155.1, 149.5, 128.2, 39.4, 37.0, 27.7 and 27.0.

Reaction of (4) with *t*-butyllithium. White crystalline compound **5** was prepared from 5-bromo-1,3-dimethyl-6-azauracil in 32% yield using the procedure described for **2**. More polar crude compound **5** was extracted from the acidified aqueous solution with $CHCl_3$:CH_3OH in ratio 5:1 to give a white solid which was recrystallised from a C_2H_5OH/ethyl acetate mixture in ratio 1:1.

5. Mp 189–190°C; MS (EI) m/z 200 (3) $[M+1]^+$, 142 (100), 57 (30); MS (FAB) m/z 200 $[M+1]^+$; Anal. Calcd for $C_9H_{17}N_3O_2$: C 54.25%; H 8.53 %; N 21.07%. Found: C 54.25%; H 8.74%; N: 21.05%; ν_{max} (KBr) 3320, 2757, 1737 and 1643 cm^{-1}; δ_H (DMSO-d_6) 7.66 (1H, s, N–H), 6.58 (1H, s, OH), 2.86 and 2.76 (6H, s, CH_3), 0.92 (9H, s, C–CH_3); δ_C ($CDCl_3$) 168.6, 157.0, 90.5, 39.5, 25.1, 27.8 and 24.8.

Reaction of (1) with lithium diisopropylamide. A 1.5 M solution of lithium diisopropylamide in cyclohexane (11.8 mL, 17.7 mmol) was added to freshly distilled THF (50 mL) at −10°C under argon atmosphere and the reaction mixture was cooled to −100°C using a N_2/hexane bath. The solution of 1,3-dimethyl uracil (1 g, 7.1 mmol) in 5 mL of THF was injected through a septum at such a rate that the internal temperature did not exceed −96°C. The yellow solution was stirred for 30 min at −100°C and then tributylborate (4.5 mL, 18 mmol) was added. The reaction mixture was kept at the same temperature for 30 min and then was allowed to warm to room temperature over a period of 2 h. The solution was evaporated to dryness under reduced pressure and water was added (40 mL). The aqueous solution was acidified with 1 M HCl to pH 2–3. The solution was extracted with CH_2Cl_2 (2×30 mL) and the combined extracts were dried over $MgSO_4$. The solvent was evaporated and the residue was purified by column chromatography on silica gel with hexane/CH_2Cl_2 1:4 v/v to yield compound **6** (362 mg, 36%) obtained as white crystals.

6. Mp 146–151°C (literature mp 148–151°C[17]); MS (EI) m/z 142 (100) $[M]^+$, 114 (22), 70 (14), 58 (75); Anal. Calcd for $C_5H_6N_2O_3$: C 42.26%; H 4.22 %; N 19.71%. Found: C 42.43%; H 4.12%; N: 19.60%; ν_{max} (KBr) 1760, 1730 and 11 708 cm^{-1}; δ_H ($CDCl_3$) 3.19 (s); δ_C ($CDCl_3$) 156.8, 153.9 and 24.6.

Reaction of (14) with *t*-butyllithium. A trimethylsilyl derivative of 5-bromo-6-azauracil **14**[18] (2.3 g, 6.9 mmol) was dissolved in dry, freshly distilled THF (80 mL) and cooled to −100°C under argon atmosphere. A 1.6 M solution of *t*-butyllithium in pentane (5.2 mL, 8.3 mmol) was injected through a septum at a rate such that the internal temperature did not exceed −95°C. The temperature was decreased to −100°C, the dark blue solution was stirred for 30 min at a higher temperature and then was allowed to warm to room temperature over a period of 2 h. The solution was evaporated to dryness under reduced pressure and water was added (40 mL). The aqueous solution was acidified with 1 M HCl to pH 2–3, extracted with $CHCl_3$ (3×30 mL), the combined extracts were dried over $MgSO_4$ and filtrated over silica gel. The solvent was evaporated and the residue was crystallised from C_2H_5OH/ethyl acetate mixture in ratio 1:1 to yield compound **15** (760 mg, 60%) as white crystals. In the repeated reaction with the presence of electrophile, the trialkylborate has no influence on the reaction course.

15. Mp 220–222°C (dec.); MS (EI) m/z 185 (1) $[M]^+$, 170 (100), 100 (7), 84 (44), 73 (9), 43 (4); HRMS: Calcd for $C_6H_{11}N_3O_2Si$ 185.0621, Found 185.0618; Anal. Calcd for $C_6H_{11}N_3O_2Si$: C 38.90%; H 5.98 %; N 22.68%. Found: C 38.78%; H 5.70%; N: 22.47%; ν_{max} (KBr) 3263, 3199, 3032, 1735, 1666 and 1250 cm^{-1}; δ_H (DMSO-d_6); 12.48 and 11.74 (2H, s, NH), 0.22 (9H, s, Si–CH_3); δ_C (DMSO-d_6) 159.7, 151.0, 149.1 and −2.2.

Reaction of (13) with lithium diisopropylamide. The compound **15** was prepared from trimethylsilyl derivative of 6-azauracil **13**[19] in 66% yield using the procedure described for **6**.

Reaction of (13) with *t*-butyllithium. Two white crystalline compounds **16** and **17** were prepared from trimethylsilyl derivative of 6-azauracil **13** (2.3 g, 8.9 mmol) using the procedure described for **2**. The crude solid mixture of two isomeric adducts was separated by column chromatography on silica gel with CH_2Cl_2 and then with CH_2Cl_2/CH_3OH 25:1 v/v to yield compound **16** (556 mg, 36%) and compound **17** (124 mg, 8%), both as white crystals. Compound **16** for X-ray studies was recrystallised from a C_2H_5OH/water mixture.

16. Mp 210–212°C; MS (EI) m/z 171 (12) $[M]^+$, 115 (23), 57 (100); MS (FAB) m/z 172 $[M+1]^+$; HRMS: Calcd for $C_7H_{13}N_3O_2$ 171.1008, Found 171.1012; ν_{max} (KBr) 3257, 3183, 3052, 1725 and 1695 cm^{-1}; δ_H (DMSO-d_6) 10.35 and 9.06 (2H, s, NH), 3.60 (2H, s, C(5)H_2), 1.03 (9H, s, C–CH_3); δ_C (DMSO-d_6) 171.0, 153.1, 59.1, 48.4 and 26.0.

17. Mp 222–225°C; MS (EI) m/z 171 (7) $[M]^+$, 115 (100), 57 (56); HRMS: Calcd for $C_7H_{13}N_3O_2$ 171.1008, Found 171.1004; ν_{max} (KBr) 3205, 3083, 1735 and 1694 $cm^{-1;}$ δ_H (DMSO-d_6) 10.14 and 8.67 (2H, s, NH), 5.55 (1H, d, J=6.0 Hz, N(6)H), 2.88 (1H, d, J=6.0 Hz, C(5)H), 1.00 (9H, s, C–CH_3); δ_C (DMSO-d_6) 171.7, 154.0, 64.3, 33.5 and 27.5.

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