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Structural analysis and reactivity of unusual tetrahedral intermediates enabled by SmI_2-mediated reduction of barbituric acids: vinylogous *N*-acyliminium additions to α-hydroxy-*N*-acyl-carbamides†

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Structural characterisation and reactivity of new tetrahedral intermediates based on a highly modular barbituric acid scaffold, formed *via* chemoselective electron transfer using the SmI_2–H_2O reagent, are reported. Lewis acid promoted cleavage of bicyclic α-amino alcohols affords vinylogous *N*-acyliminium ions, which undergo selective (>95 : 5, 1,4 over 1,2) capture with a suite of diverse nucleophiles in a practical sequence to biologically active uracil derivatives.

Tetrahedral intermediates formed in the nucleophilic addition to carboxylic acid derivatives are among the most important intermediates in organic synthesis; however, only a few examples have been isolated to date due to their transient nature.[1] These species have important biological implications as models for *in vivo* acyl-transfer reactions. Moreover, the isolation of tetrahedral intermediates is critical for structural insight into the trajectory of nucleophilic attack onto the carbonyl group and enables the development of novel synthetic equivalents for chemoselective addition reactions with carboxylic acid derivatives.[2]

Bicyclic uracils as direct homologues of primary nucleobases are abundant motifs in medicinal chemistry.[3] Recently, derivatives of this heterocyclic scaffold have been shown to be effective as selective modulators of ionotropic glutamate receptors and exhibit activity against hepatitis C virus and HIV-1 integrase.[4] While several procedures have been developed for the preparation of bicyclic uracils,[5] there is a need for robust methods for the synthesis of structurally diversified analogues (Fig. 1 and 2).

Recently, we reported the preparation of unusual tetrahedral intermediates exploiting the robust nature of the barbituric acid template.[6] The success of our approach relied on a polarity reversal process utilizing SmI_2–H_2O as a mild electron transfer reagent operating under conditions that are fully orthogonal to other single and two-electron reaction pathways.[7,8] In our initial investigation, we found that barbituric acid derived hemiaminals are thermodynamically or kinetically stable, and characterized by the beginning of collapse of the tetrahedral intermediate either by elimination of the hydroxyl group to give acyliminiums or by opening of the C–N(C=O) group to furnish alicyclic ureids. However, these initially structurally-characterised examples were limited to specific cases and did not allow for translation

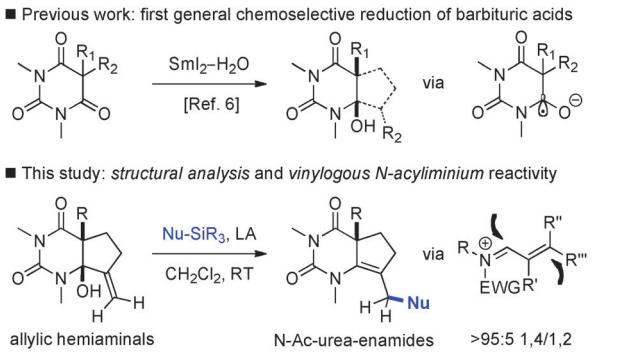

Fig. 1 Previous and current study: synthesis, structural characterisation and reactivity of unusual tetrahedral intermediates enabled by Sm(II).

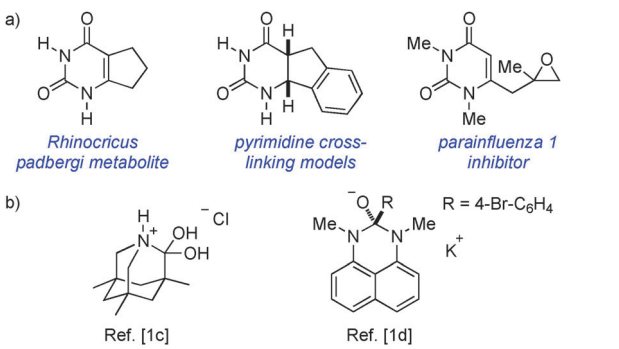

Fig. 2 (a) Biologically-relevant uracil derivatives. (b) Examples of isolated tetrahedral intermediates (cationic and anionic adducts).

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† Electronic supplementary information (ESI) available. CCDC 972704 and 972705. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc48932a

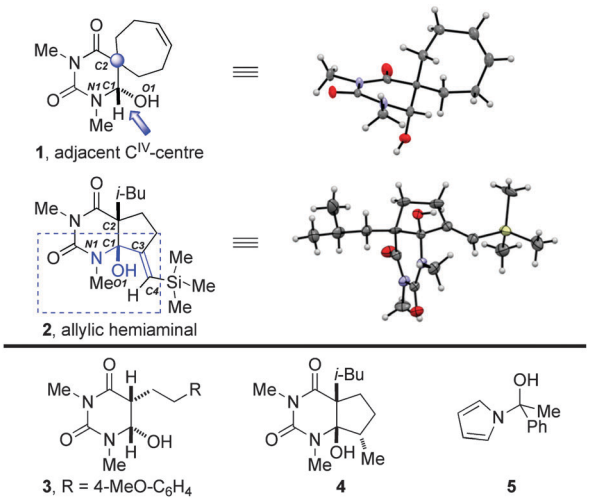


Fig. 3 X-ray structures of **1** and **2**. Structures of related compounds **3–5**.

of structural information into reactivity that would allow the hemiaminals to be used to access valuable uracil analogues.

Herein, we report a study on the structural characterisation of novel tetrahedral intermediates derived from the barbituric acid scaffold that demonstrates the thermodynamic stability of the α-amino alcohol function in both six-membered and heterobicyclic scaffolds. We apply these structural findings to develop a highly divergent process for the synthesis of 6-substituted-uracils *via* nucleophilic capture of *N*-acyliminium ions[9] that proceeds with exclusive (>95 : 5, 1,4 over 1,2) selectivity and demonstrate that the solid state characteristics of these hemiaminals are reflected by their solution properties. Overall, these studies set the stage for the synthesis of a wide range of diverse nitrogen-containing heterocycles and tetrahedral intermediates from cyclic scaffolds (Fig. 3).[10]

The barbiturate template serves as a robust platform for the stabilization of otherwise short-lived, high-energy tetrahedral intermediates due to a combination of the stabilizing $N_{lp} \rightarrow \pi^*_{C=O}$ conjugation and the scaffolding effect of the six-membered ring.[6] Whereas steric effects were previously used to push the N_{lp} and O_{lp} out of conjugation with the corresponding σ^*_{C-O} and σ^*_{C-N} bonds, we considered that a geminal substitution of the adjacent C2–carbon atom would affect the delocalization of N_{lp} and O_{lp} in the α-amino alcohol moiety and provide insight into the extent of stabilization by the scaffold. After extensive investigation, we found that a very sterically-hindered spiro-cyclic hemiaminal **1**, which was readily obtained using our recently reported reduction of barbituric acids by SmI_2–H_2O,[6] can be examined by X-ray crystallography (recryst. from acetone/water, 50 : 1 v/v, mp = 136–138 °C).

Structural parameters of **1** relevant to the geometry at the anomeric centre along with bond lengths and angles of related hemiaminals are presented in Table 1. The X-ray crystal structure of **1** reveals that the C_1–O_1 bond (1.407 Å) is shorter than the average C_{sp3}–O bond (1.432 Å), while the length of the N_1–C_1 bond is 1.463 Å, which corresponds to a typical C_{sp3}–N bond (1.469 Å). The C_1–C_2 bond length of 1.522 Å is slightly shorter than the average C_{sp3}–C_{sp3} bond (1.530 Å). The torsion angle between N_{lp} and C_1–O_1 of 192.2° indicates a reasonably good $N_{lp} \rightarrow \sigma^*_{C-O}$ interaction. In addition,

Table 1 Selected bond lengths [Å] and angles [deg] of hemiaminals **1–5**

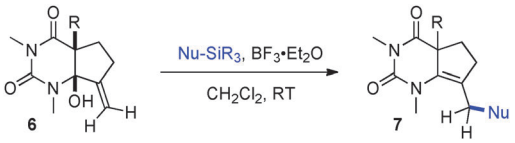
Entry	Aminal	C1–O1	N1–C1	C1–C2	$N_{lp} \rightarrow \sigma^*_{C1-O1}$	$O_{lp1} \rightarrow \sigma^*_{C1-N1}$	$O_{lp2} \rightarrow \sigma^*_{C1-H/C3}$
1	**1**	1.407	1.463	1.522	12.2	163.5	197.4
2	**2**	1.422	1.470	1.530	62.7	165.1	171.0
3	**3**	1.413	1.461	1.518	7.4	131.5	131.7
4	**4**	1.407	1.466	1.549	57.4	171.0	55.1
5	**5**	1.412	1.478	1.528	46.7	182.0	179.1

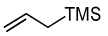
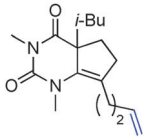
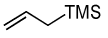
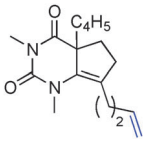
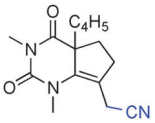
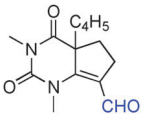
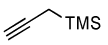
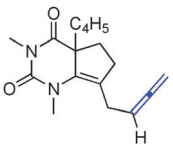
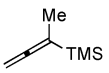
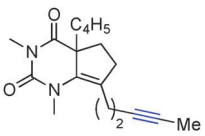
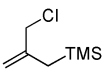
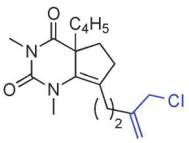
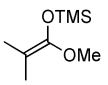
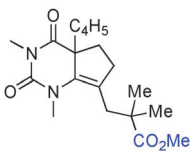
there is a good overlap between the O_{1lp1} and the N_1–C_1 bond (~164°) and between the O_{1lp2} and the C_1–H bond (~197°). These structural features indicate that the stability of the α-amino alcohol function in geminally substituted hemiaminals is thermodynamic in origin (*i.e.* it involves equilibrium between cyclic and alicyclic ureides as well as between hemiaminal and the corresponding iminium), thus suggesting that these systems could be applied towards generation of synthetically useful iminium ions.[9]

To gain insight into the extent of electronic stabilization on the N_{lp} and O_{lp} donation, we considered a barbituric acid hemiaminal **2** featuring an unusual allylic α-amino alcohol moiety. The X-ray structure of **2** (recryst. from acetone/water, 50 : 1 v/v, mp = 156–158 °C) is consistent with the thermodynamic stability. The torsion angle between N_{lp} and C_1–O_1 of 62.7° is in agreement with the absence of $N_{lp} \rightarrow \sigma^*_{C-O}$ interactions. However, there is a good overlap between the O_{1lp1} and the N_1–C_1 bond (~165°) and between the O_{1lp2} and the C_1–C_3 bonds (~171°). The N1–C1–C3–C4 torsion angle of ~20° and O1–C1–C3–C4 of ~100° reveal co-planarity of the *exo*-cyclic double bond with the hemiaminal nitrogen. These structural features indicate electronic stabilization at the anomeric carbon and suggest the propensity of these hemiaminals to form extended *N*-acyliminium ions *via* hydroxyl elimination. The structural differences between **1** and **2** are further indicated by the bond lengths of the alpha hydroxyl urea moiety (**1**, N–C(O) bond length of 1.413 Å, C=O of 1.224 Å; **2**, N–C(O) = 1.386 Å, C=O = 1.231 Å), consistent with an enhanced $N_{lp} \rightarrow \sigma^*_{C-O}$ donation in **1**.

Having identified structural features contributing to the stability of these tetrahedral intermediates, we next investigated their synthetic utility. In particular, we recognized that intermediates analogous to **2** could function as vinylogous *N*-acyliminium equivalents whose electrophilic character is revealed under suitably acidic conditions. We were delighted to find that upon exposure of **6a** to mildly Lewis acidic conditions in the presence of allyltrimethylsilane highly regioselective formation of *N*-Ac-urea-enamide **7a** occurred in excellent yield (Table 2, entry 1). Under these reaction conditions the 1,2-addition product was not observed.[11] A broad range of nucleophiles is suitable for this 1,4-addition. The addition of small nucleophiles such as nitrile and azide occurred with excellent regiocontrol (entries 3 and 4). In the latter case loss of N_2 occurred, furnishing an α,β-unsaturated aldehyde bearing a vinylogous enamide. Propargyl and allenylsilane nucleophiles gave products with π systems ready for elaboration (entries 5 and 6). An electron deficient allylsilane afforded the product containing a halide functional handle (entry 7). Most remarkably, the addition of a very sterically-hindered ketene acetal $Me_2C{=}C(OMe)(OSiMe_3)$ delivered a methyl ester bearing an adjacent quaternary centre

Table 2 Selective 1,4-addition to bicyclic α-alkoxy-*N*-Ac-carbamides[a]



Entry	Nu-SiR$_3$	Product	7	Yield (%)
1			**7a**	89
2			**7b**	82
3	TMSCN		**7c**	74
4	$TMSN_3$		**7d**	51
5			**7e**	77
6			**7f**	64
7			**7g**	76
8			**7h**	81

[a] Substrate **6a**, R = i-butyl; substrate **6b**, R = but-3-ynyl. Prepared by SmI_2–H_2O-mediated radical cyclization (see ref. 6).

with full control of regioselectivity (entry 8). Overall, these studies demonstrate that barbituric acid derived tetrahedral intermediates afford diverse bicyclic uracils that would be very difficult to prepare using other currently available methods.

Spectroscopic studies lend additional support to the reactive properties of the α-amino alcohol moiety (Table 3 and ESI†). The solution of **1** in acetone shows a ^{13}C NMR peak at 84.6 ppm,

Table 3 Spectroscopic properties of hemiaminals **1–4**[a]

Entry	Aminal	δ^{13}C–OH	δ^{13}C=O1	δ^{13}C=O2	$\Delta\delta^{13}$C–OH	νC=O1	νC=O2
1	**1**	84.6	153.7	175.0	4.0	1658	1709
2	**2**	93.2	153.6	174.2	12.6	1645	1709
3	**3**	80.6	154.1	171.5	—	1657	1711
4	**4**	95.4	153.1	173.9	14.8	1644	1704

[a] δ^{13}C–OH and δ^{13}C=O [ppm], measured at 100 MHz in $CD_3C(O)CD_3$. $\Delta\delta^{13}$C–OH = [δ^{13}C–OH − 80.6]. νC=O [cm^{-1}].

which moves downfield by *ca.* 10 ppm in bicyclic hemiaminals such as **2**, consistent with deshielding of the anomeric carbon and decomposition *via* C–N cleavage as the predominant pathway. IR ν(C=O) frequencies indicate that the *N*-Ac carbonyl absorbs in the region corresponding to saturated uracil derivatives (*ca.* 1710 cm^{-1}), while the carbonyl group attached to the α-amino alcohol exhibits the reactive properties of an urea (bicyclic aminals, *ca.* 1645 cm^{-1}) or an imide (monocyclic six-membered aminals, *ca.* 1658 cm^{-1}). Thus, the spectroscopic properties correlate well with the structural stability, which decreases in the order six-membered > bicyclic hemiaminals.

In summary, tetrahedral intermediates derived from barbituric acids *via* electron transfer using SmI_2–H_2O indicate the tendency to eliminate hydroxyl and/or N–(C=O) groups to furnish *N*-acyliminium ions or alicyclic ureids, which is consistent with the thermodynamic stability of α-amino alcohols embedded in six-membered uracil frameworks. Studies on the synthesis of a wide range of N-containing heterocycles and tetrahedral intermediates are ongoing and will be reported shortly.[12]

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