Organic LETTERS

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Stereoselective Capture of *N*-Acyliminium Ions Generated from α-Hydroxy-*N*-acylcarbamides: Direct Synthesis of Uracils from Barbituric Acids Enabled by SmI_2 Reduction

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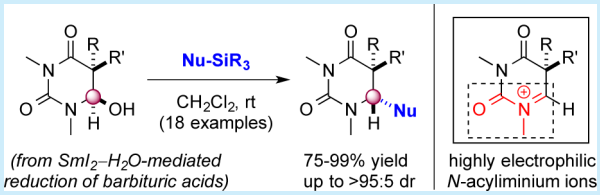
Supporting Information

ABSTRACT: Lewis acid promoted cleavage of α-amino alcohols derived from barbituric acids via chemoselective Sm(II)-mediated electron transfer affords a wide range of C6-substituted 5,6-dihydrouracils. The reaction involves the first generation of *N*-acyliminium ions directly from the versatile barbituric acids and proceeds with excellent stereoselectivity. The products are shown to be active in generic transition metal catalyzed reactions, thus providing a modular and highly practical sequence to the biologically significant uracil derivatives.



As direct homologues of primary nucleobases, C6-substituted uracils are among the most valuable building blocks in medicinal chemistry and play a vital role as pharmacophores in a wide range of bioactive molecules (Figure 1).[1,2] The synthesis of C6-substituted uracils commonly relies on the introduction of carbon and heteroatom substituents by dearomatization, electrophilic substitution, and condensation reactions;[3] however, these methods are limited to specific substitution and do not allow for divergent stereoselective synthesis of uracil analogues. Arguably, the most general approach to C6-substituted uracils would involve a direct conversion of barbituric acids, themselves potent pharmacophores and modular building blocks;[4] however, such a process remains unexplored because of the lack of methods for the selective elaboration of the imide-type (vs urea-like) carbonyls of the barbituric acid template.[4a]

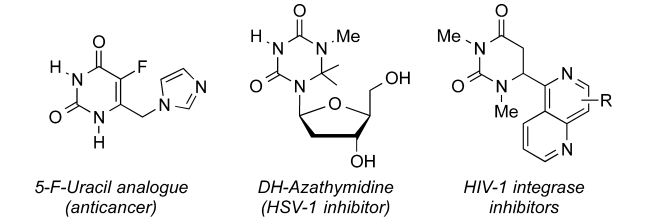


Figure 1. Biologically active uracil derivatives.

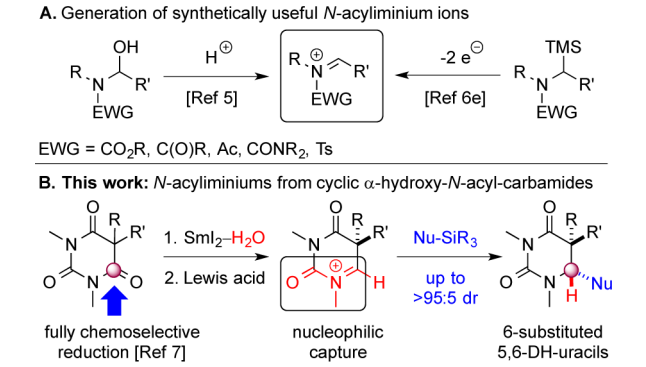
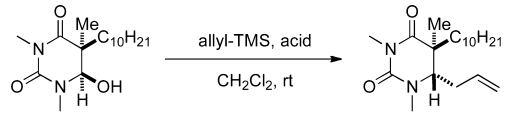


Figure 2. (A) Generation of *N*-acyliminium ions. (B) This study.

N-Acyliminium ions are important intermediates in synthesis,[5] which have been utilized for the stereoselective construction of

Table 1. Optimization of Allylsilane Addition to α-Hydroxy-*N*-acyl-carbamides Derived from Cyclic 1,3-Diimides



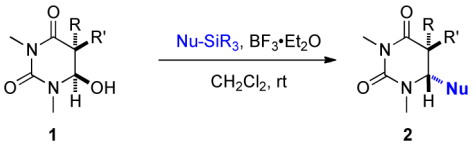
entry	acid	conv (%)[a]	yield (%)[a]	dr[a]
1	$TiCl_4$	>95	86	89:11
2	$SnCl_4$	>95	81	90:10
3	$AlCl_3$	>95	68	>95:5
4	Me_3Al	<5	<5	–
5	Me_2AlCl	<5	<5	–
6	TMSOTf	>95	87	>95:5
7	TFA	>95	31	>95:5
8	$BF_3{\cdot}Et_2O$	>95	91	>95:5
9[b]	$BF_3{\cdot}Et_2O$	>95	88	>95:5
10[c]	$BF_3{\cdot}Et_2O$	>95	<5	–

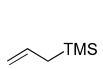
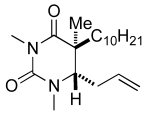
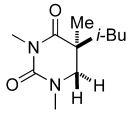
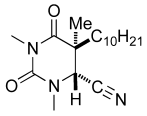
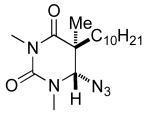
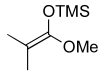
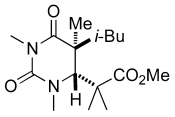
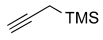
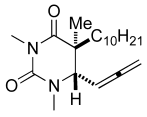
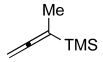
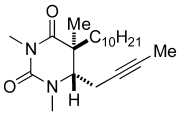
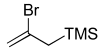
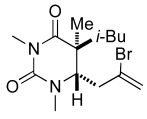
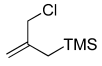
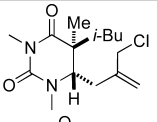
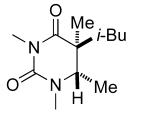
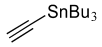
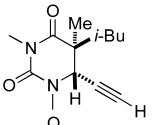
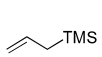
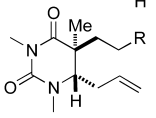
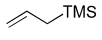
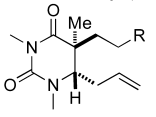
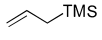
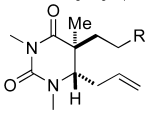
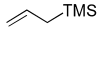
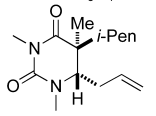
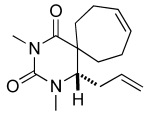
[a]Determined by ^1H NMR. [b]The reaction was carried out at −78 °C. [c]Allylmagnesium bromide was used. TFA = trifluoroacetic acid. TMS = trimethylsilyl.

Received: November 19, 2013
Published: December 20, 2013

dx.doi.org/10.1021/ol403340j | *Org. Lett.* 2014, 16, 452–455

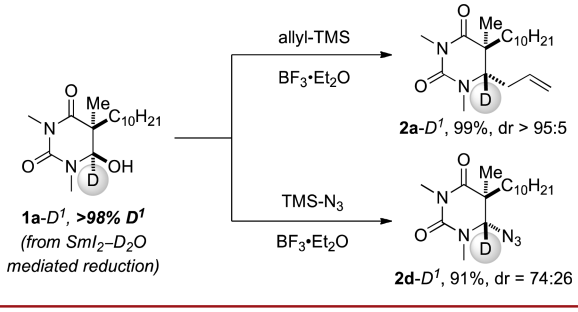
Table 2. Effect of Structure on the Nucleophilic Addition to *N*-Acyliminiums Generated from α-Hydroxy-*N*-acyl-carbamides



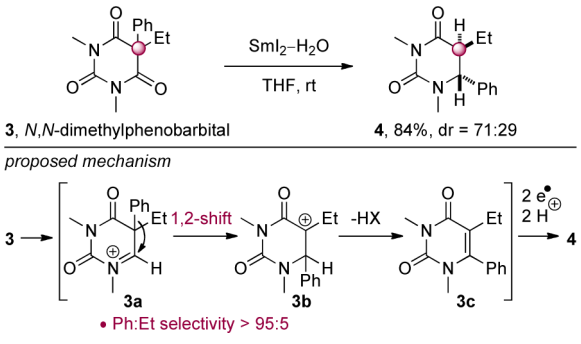
entry	2	Nu-SiR$_3$	product	dr	yield (%)
1	**2a**			>95:5	86
2	**2b**	Et_3SiH		-	79
3	**2c**	TMSCN		83:17	99
4	**2d**	$TMSN_3$		76:24	99
5	**2e**			>95:5	96
6	**2f**			89:11	77
7	**2g**			90:10	96
8	**2h**			>95:5	86
9	**2i**			>95:5	85
10[a]	**2j**	$AlMe_3$		>95:5	88
11[b]	**2k**			88:12	99
12	**2l**		 R = 4-MeO-C_6H_4	>95:5	75
13	**2m**		 R = 4-CF_3-C_6H_4	>95:5	92
14	**2n**		 R = 4-Br-C_6H_4	>95:5	77
15	**2o**			92:8	76
16	**2p**			-	83

[a]Aluminum-based nucleophile. [b]Tin-based nucleophile.

Scheme 1. Synthesis of 6-D^1-Deuterated Uracils



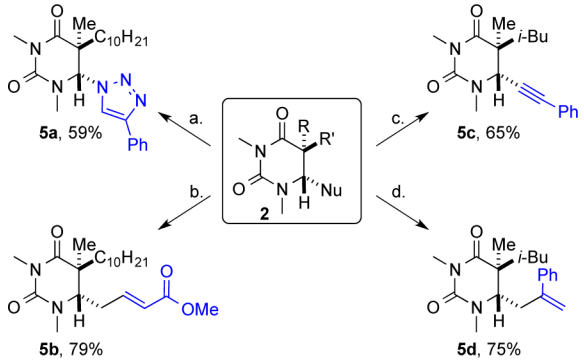
Scheme 2. Rearrangement of *N*,*N*-Dimethylphenobarbital via *N*-Acyliminium/1,2-Aryl Shift/Conjugate Reduction Using SmI_2–H_2O



C–C bonds adjacent to nitrogen atoms (Figure 2A).[6] In theory, hemiaminals derived from the monoreduction of imide carbonyls of barbituric acids would be ideal precursors to *N*-acyliminium ions, highly electrophilic intermediates for the formation of C–C bonds at the C6 position. However, until recently the general monoreduction of barbituric acids was unknown, thereby prohibiting the development of a stereoselective method for the modular synthesis of uracil derivatives via *N*-acyliminium ions.

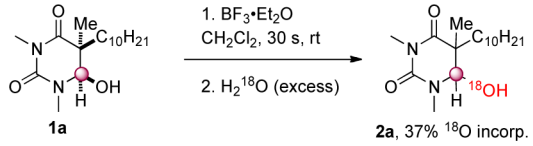
dx.doi.org/10.1021/ol403340j | *Org. Lett.* 2014, 16, 452–455

Scheme 3. Toward Library Development: Synthesis of Substituted Uracils Using Generic Metal-Catalyzed Reactions[a]



[a](a) **2d**, PhCCH, $CuSO_4$; (b) **2a**, CH_2=$CHCO_2Me$, Hoveyda–Grubbs II; (c) **2k**, PhI, $Pd(PPh_3)_4$, CuI; (d) **2h**, $PhBF_3K$, $Pd(PPh_3)_4$, K_2CO_3.

Scheme 4. Investigating the Mechanism: $H_2{}^{18}O$ Incorporation



Herein, we report the first general method for the synthesis of 6C-uracil derivatives via the corresponding *N*-acyliminium ions, which relies on our recently reported chemoselective mono-reduction of barbituric acids[7] using SmI_2–H_2O complex[8,9] (Figure 2B). We demonstrate that, in the presence of nucleophiles, Lewis acid promoted cleavage of α-hydroxy-*N*-acylcarbamides derived directly from the barbiturate scaffold affords a wide range of C6-substituted 5,6-dihydrouracils. The reaction features a very broad substrate scope and proceeds with excellent stereoselectivity (dr up to >95:5). Moreover, the products are shown to be active in Sonogashira and Suzuki cross-coupling reactions, click [3 + 2] cycloadditions, and cross-metathesis, providing a generic and highly practical sequence to biologically significant uracil derivatives.

We hypothesized that hemiaminals obtained in the mono-reduction of barbiturates with Sm(II)[7] could provide a direct entry to uracil derivatives. Our study started by screening a range of Lewis acids for the nucleophilic addition of allyltrimethylsilane to hemiaminal **1a** (Table 1).[7b]

We were delighted to discover that under mildly acidic conditions stereoselective formation of 6-allyluracil **2a** occurred in excellent yield (entry 1). Importantly, the *N*-acyliminium intermediate was formed directly from the α-amino alcohol. Optimization of the reaction conditions revealed that a range of Lewis acids promotes the desired reaction in generally high yields and excellent stereoselectivity; however, less reactive Lewis acids (entries 4–5) resulted in an unproductive process. This is consistent with activation of the α-amino alcohol moiety as the rate determining step.[5] We determined that $BF_3{\cdot}Et_2O$ is an optimal Lewis acid in terms of yield and stereoselectivity of the nucleophilic addition (entry 8). The reaction could be performed at cryogenic temperatures (entry 9), which demonstrates that generation of the *N*-acyliminium ion is rapid. The use of less selective reagents resulted in extensive decomposition (entry 10), which is in agreement with the previous studies on the nucleophilic addition to related derivatives.[4]

Having identified optimal conditions, the scope of the nucleophilic addition was next evaluated (Table 2). Products containing a cyano, azide, and methyl ester bearing an adjacent quaternary center were formed in high yields and uniformly excellent levels of stereocontrol (entries 3–5). The use of propargyl and allenyl nucleophiles resulted in the introduction of π-systems ready for further elaboration (entries 6–7). Electron deficient allylsilanes afforded vinyl and allyl halide functional handles (entries 8–9). The reaction conditions could be extended to aluminum (entry 10) and tin-based nucleophiles (entry 11). Substrates bearing electronically diverse substituents underwent allylation in high yields and excellent diastereoselectivity (entries 12–13). Importantly, an aryl bromide is well tolerated by both steps of the procedure (entry 14). Notably, allylation of the hemiaminal derived from amobarbital (entry 15) proceeded in high yield, demonstrating the potential of this method for the synthesis of drug analogues.[4b] Finally, we were pleased to find that a sterically hindered spirocyclic hemiaminal could be allylated in an excellent yield (entry 16).

It is particularly noteworthy that our method can be applied to the stereocontrolled synthesis of 6-D^1-uracil derivatives (Scheme 1).[10] Reduction of barbituric acids with SmI_2–D_2O affords deuterated hemiaminals with >98% D^1 incorporation. *N*-Acyliminum ion generation and nucleophilic capture gave 6-D^1-uracils with excellent stereoselectivity.

We have also demonstrated that the hemiaminal derived directly from *N*,*N*-dimethylphenobarbital[4b] undergoes an unprecedented 1,2-shift via the corresponding *N*-acyliminium ion under Sm(II)/(III) conditions (Scheme 2).[11]

In an extension of the nucleophilic addition, we have demonstrated that the products are readily elaborated in several generic transition metal catalyzed reactions (Scheme 3). Sonogashira and Suzuki cross-coupling, click [3 + 2] cycloaddition, and cross-metathesis proceeded in good yields, highlighting the ability of the developed method to provide a modular and highly practical sequence to biologically significant uracil derivatives.[12]

To gain preliminary insights into the mechanism, we conducted $H_2{}^{18}O$ quenching and stability experiments (Scheme 4 and Supporting Information). These results are consistent with facile generation of *N*-acyliminium ions and show that the formation of open-chain ureides (as suggested by X-ray analysis)[7] is not a predominant pathway.[13]

In summary, we have demonstrated a new approach to the generation and nucleophilic capture of *N*-acyliminium ions directly from barbituric acids. The reaction features a very broad substrate scope and proceeds with excellent stereoselectivity. The products have been shown to be active in generic transition metal catalyzed reactions, greatly expanding the utility of the approach. Application of this method to the synthesis of multicomponent libraries of stereodifferentiated analogues is underway, and these results will be reported shortly.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

dx.doi.org/10.1021/ol403340j | *Org. Lett.* 2014, 16, 452–455

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank the EPRSC for support.

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