

# Switching between Reaction Pathways by an Alcohol Cosolvent Effect: Sml<sub>2</sub>–Ethylene Glycol vs Sml<sub>2</sub>–H<sub>2</sub>O Mediated Synthesis of Uracils

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**Supporting Information** 

**ABSTRACT:** A chemoselective switch between reaction pathways by an alcohol cosolvent effect in a general  $SmI_2$ -mediated synthesis of uracil derivatives is described. The method relies on the use of coordinating solvents to increase the redox potential of Sm(II) and results in a chemoselective 1,2-reduction ( $SmI_2-H_2O$ ) or 1,2migration via in situ generated *N*-acyliminium ions ( $SmI_2$ -ethylene glycol, EG). This work exploits the mild conditions of the  $SmI_2$ -



mediated monoreduction of barbituric acids and offers an attractive protocol for the synthesis of uracil derivatives with biological activity from readily accessible building blocks.

Uracil derivatives are ubiquitous pharmacophores in biologically active compounds and pharmaceuticals.<sup>1,2</sup> As direct homologues of primary nucleobases, uracils have appeared as selective modulators of ionotropic glutamate receptors<sup>2a</sup> and exhibit activity against thymidine phosphorylase,<sup>2b</sup> hepatitis C virus,<sup>2c</sup> and HIV-1 integrase<sup>2d</sup> (Figure 1). Thus, it is not



Figure 1. Examples of pharmacologically active uracils.

surprising that the selective synthesis of 5- and 6-substituted uracils has been the subject of numerous investigations.<sup>3,4</sup> While several approaches based on dearomatization, electrophilic substitution, and condensation have been reported, these methods are limited to specific substitution, require preassembly of the uracil framework prior to the formation of desired analogues, or proceed under harsh conditions.<sup>3,4</sup> A powerful approach to increase the diversity of accessible uracil analogues would involve a direct conversion of hemiaminals obtained from modular barbituric acids<sup>5</sup> to divergent products from the same synthetic precursor; however, until recently these hemiaminals remained inaccessible due to the lack of methods for the monoreduction of barbituric acids.<sup>6</sup>

Selective SmI<sub>2</sub>-mediated reductive transformations<sup>7,8</sup> in which selection of a reaction pathway<sup>9</sup> is governed by the choice of alcohol cosolvent have a profound impact on the synthesis of complex molecules and pharmaceutically relevant motifs via

open-shell intermediates.<sup>10</sup> Typically, strongly coordinating alcohols (e.g.,  $H_2O$  and MeOH)<sup>11</sup> are used to increase the redox potential of Sm(II) and accelerate the otherwise slow electron transfer and/or protonation steps.<sup>12</sup> This may result in a fully chemoselective reduction or cyclization depending on the choice of alcohol cosolvent.<sup>11,12</sup> Recently, multicomponent reagents based on dual activation of SmI<sub>2</sub> by alcohols and Lewis bases have also emerged to direct SmI<sub>2</sub>-mediated processes toward the reduction pathway;<sup>13</sup> however, these systems suffer from a prohibitively high redox potential.<sup>14</sup> With few exceptions,<sup>15</sup> the development of *alcohol-controlled selectivity in SmI<sub>2</sub>-mediated reactions* that lead to divergent, synthetically useful products, while controlling the inherent preference of the substrate by a simple change of an additive under mild reaction conditions that tolerate sensitive functional groups,<sup>8</sup> remains an unmet challenge in reductive electron transfer chemistry.

Herein, we report a general SmI<sub>2</sub>-mediated synthesis of 5- and 6-substituted uracils from the same synthetic precursors in which control of the reaction pathway is governed by the alcohol cosolvent (Figure 2A–B).<sup>8,9</sup> To date only a few examples of additive-controlled selectivity in radical electron transfer reactions have been reported.<sup>15</sup> This new process enables an operationally simple and diverse synthesis of functionalized uracils<sup>1-4</sup> from modular barbituric acid building blocks<sup>5</sup> under very mild single electron transfer conditions.<sup>6a</sup> Of general interest is the first application of SmI<sub>2</sub>–ethylene glycol to the synthesis of novel targets.<sup>16</sup> Importantly, our results suggest that the use of ethylene glycol as a coordinating ligand for SmI<sub>2</sub><sup>12c,f</sup> will have broad applications in organic synthesis due to its beneficial selectivity over SmI<sub>2</sub>–H<sub>2</sub>O.<sup>11a</sup> Mechanistic data

Received: September 19, 2014 Published: October 24, 2014



**Figure 2.** (a) Previous study: the first selective reduction of barbiturates enabled by Sm(II). (b) This study: chemoselective synthesis of uracils via Sm(II)–solvent effect (SmI<sub>2</sub>-H<sub>2</sub>O vs SmI<sub>2</sub>-EG).

suggest that reaction with SmI<sub>2</sub>–EG proceeds via a ratedetermining conjugate reduction of uracils, which may find applications in the chemoselective  $\alpha,\beta$ -reduction of other substrates.<sup>17</sup> Finally, application to the synthesis of bicyclic uracils<sup>18</sup> is described.

We recently reported the first general reduction of barbituric acids to the corresponding hemiaminals using  $SmI_2-H_2O$  as the key reagent system (Figure 2A).<sup>6a</sup> We have also reported the first generation of N-acyliminium ions<sup>6b</sup> and their vinylogs<sup>6c</sup> derived from barbituric acids (not shown). During the development of this process, we noticed that under certain conditions hemiaminals resulting from the monoreduction of barbituric acids with  $SmI_2-H_2O$  underwent dehydration to give 5-substituted uracils in trace quantities. We recognized that further optimization of the reaction would allow for a streamlined synthesis of 5-substituted uracils.<sup>1–4</sup> Optimization studies were conducted using barbituric acid 1a (Table 1). Pleasingly, the use of SmI<sub>2</sub> at a low concentration of the water additive afforded the desired product, albeit in low yields due to nonselective reduction of barbituric acids, consistent with previous studies on the effect of water concentration on the redox potential of  $Sm(II)^{19}$  (entries 1–2). Oxidation to Sm(III) after completion of the reduction to enhance Lewis acidity<sup>11b</sup> had a minor effect on the reaction efficiency (entry 3). Interestingly, the addition of a protic acid significantly improved the yield (entry 4), with the optimum results obtained when the acid was added after the aqueous workup to remove Sm(III) salts, in a one-pot process (entry 5). Importantly, a variety of other acids gave the desired 5substituted uracil in high yields under mild conditions (entries 6 - 8).

A wide range of barbituric acids was found to afford the products in high yields (Table 2). Alkyl branched (entry 1), linear (entries 2-4), and aromatic substrates (entry 5), including barbituric acids with bulky substitution around the carbonyl (entry 6), yielded the desired products with good efficiency for a two-step process. Electron-donating and -withdrawing groups were compatible with the developed protocol (entries 7-8).



	O H H i-Bu O N O I 1a	SmI <sub>2</sub> -H <sub>2</sub> O		1
entry	conditions	time	$\operatorname{conv}^{b,c}(\%)$	yield <sup><math>b</math></sup> (%)
$1^d$	SmI <sub>2</sub> -H <sub>2</sub> O	60 s	92	34
$2^e$	$SmI_2-H_2O$	60 s	>95	59
3 <sup>f</sup>	[O] to Sm(III)	2 h	39	23
$4^g$	HCl (1.0 N)	2 h	91	72
$5^h$	HCl (1.0 N)	2 h	>95	77
$6^h$	$BF_3 \cdot Et_2O$	2 h	>95	75
$7^h$	$TiCl_4$	2 h	>95	75
8 <sup><i>h</i></sup>	p-TsOH	2 h	>95	77

<sup>*a*</sup>Barbituric acid, SmI<sub>2</sub> (4 equiv), H<sub>2</sub>O (1000 equiv), THF, 23 °C. <sup>*b*</sup>Determined by <sup>1</sup>H NMR. <sup>*c*</sup>Refers to hemiaminal; in all entries >95% conv of **1a**. <sup>*d*</sup>H<sub>2</sub>O (50 equiv). <sup>*c*</sup>H<sub>2</sub>O (100 equiv). <sup>*f*</sup>Oxidized to Sm(III). <sup>*g*</sup>Added in situ. <sup>*h*</sup>Added after aqueous workup.

Table 2. Scope of the Synthesis of 5-Alkyl Uracils<sup>a</sup>



<sup>a</sup>Barbituric acid, SmI<sub>2</sub> (4 equiv), H<sub>2</sub>O (1000 equiv), THF, 60 s, 23 °C. Then, Conditions A: HCl (1.0 N), 2 h. Conditions B: BF<sub>3</sub>·Et<sub>2</sub>O (3 equiv), 2 h. Conditions C: *p*-TsOH (3 equiv), 2 h. Conditions D: D<sub>2</sub>O instead of H<sub>2</sub>O, *p*-TsOH, 2 h. <sup>*b*</sup>>98% D<sub>1</sub>.

Furthermore, substrates bearing halide functional handles gave the uracil product with no reduction in yield (entry 9). Importantly, several of these functional groups are not compatible with other SET conditions.<sup>7,8</sup> Finally, by exploiting the affinity of water for Sm(II),<sup>12c-f</sup> we demonstrated that the protocol can be readily extended to the chemoselective synthesis of 6- $D_1$ -uracils with >98% deuterium incorporation (entries 10– 11).<sup>20</sup> The synthesis of these biologically important analogues would be very difficult using current methods.

Remarkably, during optimization of the reaction conditions (Table 1), we established that the use of bidentate alcohols as ligands for  $SmI_2$  resulted in the formation of 6-substituted-5,6-

dihydrouracils via a net reduction/iminium formation/1,2migration/conjugate reduction process (Table 3).<sup>16</sup> This trans-



<sup>*a*</sup>Barbituric acid, SmI<sub>2</sub> (6 equiv), THF, 23 °C. Quenched with air after the indicated time. <sup>*b*</sup>Determined by <sup>1</sup>H NMR. <sup>*c*</sup>Refers to barbituric acid; in all entries, <5% of hemiaminal. <sup>*d*</sup>Selectivity refers to the ratio of rearrangement (3) vs dehydration (2) product. <sup>*e*</sup>SmI<sub>2</sub> (4 equiv). <sup>*f*</sup>SmI<sub>2</sub> (2 equiv).

formation was further evaluated using barbituric acid 1d. Essentially, no reaction occurred in the absence of alcohol (entry 1). The use of water at low concentration led to decomposition and inconsistent results (entry 2). Notably, when ethylene glycol<sup>16a</sup> was employed as the alcohol cosolvent, the desired product was formed in high yield and with excellent selectivity for 1,2-migration (cf. 1,2-reduction) (entry 3). A reagent stoichiometry study revealed optimal conditions in terms of yield and selectivity (entries 4-7): (i) at a high concentration of EG oxidation to Sm(III) was observed, consistent with previous studies (entry 5);<sup>14</sup> (ii) at a lower SmI<sub>2</sub> loading incomplete conversion was observed (entries 6-7), consistent with the presence of a reaction intermediate. Interestingly, other chelating additives, including diethylene glycol (DEG), ethylenediamine (ED), and trans-N,N'-dimethyl-1,2-cyclohexyldiamine (DCH), were less effective in promoting the reaction (entries 8-10), which contrasts with studies on 5-exo-trig cyclizations and suggests a unique role for ethylene glycol in this process.<sup>16a</sup>

The synthesis of 6-substituted uracils from barbituric acids using SmI<sub>2</sub>–EG is broad in scope and can accommodate an array of substrates (Table 4). Thus, hindered (entries 1–4), electronrich (entry 5), electron-poor (entry 6), halide-containing (entry 7), and aryl substrates (entry 8) furnish the reductive 1,2migration products in good yields. Mono- and disubstitution are tolerated (entries 1–8); however, at present,  $\alpha,\alpha$ -dialkyl substituted barbituric acids are not viable substrates due to steric hindrance around the carbonyl group (see Supporting Information).<sup>19</sup> Notably, the reaction selectivity is uniformly high for all examples, favoring alkyl and aryl migration over hydride and alkyl migration, respectively.<sup>21</sup> Overall, the reaction provides general access to 6-substituted uracils starting from the same synthetic precursor as for the synthesis of 5-substituted uracils by a simple change of the reaction conditions.

Furthermore, we have extended the reaction scope to include bicyclic uracils prepared via reductive cyclization<sup>6a</sup> (Figure 2B and Table 1-SI). The obtained products feature an endocyclic



	О R2 R1 Sml	₂−EG F, rt	$ \begin{array}{c}                                     $	
3	$R_1$	$R_2$	yield of <b>3</b> (%)	selectivity <sup>b</sup>
3a	<i>i</i> -Bu	Н	76	89:11
3b	$(CH_2)_2Ph$	Н	85	97:3
3c	CH <sub>2</sub> CH(Me)Ph	Н	83	91:9
3d	CH <sub>2</sub> Cy	Н	85	90:10
3e	$(CH_2)_2$ -p-MeO-C <sub>6</sub> H <sub>4</sub>	Н	84	93:7
3f	$(CH_2)_2 - p - CF_3 - C_6H_4$	Н	89	93:7
3g	$(CH_2)_2$ -p-Br-C <sub>6</sub> H <sub>4</sub>	Н	78	93:7
3h	Ph	Et	77	>95:5 <sup>e</sup>
	3 3a 3b 3c 3d 3e 3f 3g 3h	$\begin{array}{c c} & & & & \\ & & & \\ & & & \\ & & & \\ \hline & & & \\ \hline & & & \\ \hline \\ \hline$	$\begin{array}{c c} & & & & \\ & & & \\ & & & \\ & & & \\ & & & \\ \hline \\ & & & \\ & &$	$\begin{array}{c ccccccccccccccccccccccccccccccccccc$

<sup>*a*</sup>Barbituric acid, SmI<sub>2</sub> (6 equiv), EG (36 equiv), THF, 3 h, 23 °C. <sup>*b*</sup>Selectivity refers to the ratio of rearrangement (3) vs dehydration (2) product. <sup>*c*</sup>S5:45 dr. <sup>*d*</sup>62:38 dr. <sup>*e*</sup>Ph/Et migration selectivity.

olefin poised for further functionalization and are analogous to xantine alkaloids,<sup>18a</sup> millipede metabolites,<sup>18b</sup> and pyrimidine cross-linking models<sup>18c</sup> with important biological applications.

Several studies were conducted to gain insight into the mechanism of the  $SmI_2$ -EG promoted process (Scheme 1): (i)

Scheme 1. Studies Designed To Probe the Mechanism of Rearrangement of Barbituric Acids Using SmI $_2$ -EG



Deuterium incorporation studies demonstrate that anions are generated and protonated in a series of electron transfer steps.<sup>16</sup> Exchange of acidic protons with SmI<sub>2</sub>–ROH systems is a common process.<sup>19b</sup> (ii) Determination of the kinetic isotope effect suggests that the olefin reduction may be involved in the rate-determining step;<sup>22</sup> the KIE value is in an excellent agreement with studies on the conjugate reduction of activated acyclic olefins.<sup>12f</sup> (iii) Studies with a limiting amount of the reagent led to the formation of a 6-hydrated intermediate. (iv) Control experiments with  $\alpha_{j}\beta$ -unsaturated uracils using SmI<sub>2</sub>–H<sub>2</sub>O and SmI<sub>2</sub>–EG demonstrate that the major reaction pathway does not involve unsaturated 5-substituted uracils. These results indicate the high levels of chemoselectivity possible with the SmI<sub>2</sub>–EG system (cf. SmI<sub>2</sub>–H<sub>2</sub>O)<sup>11a</sup> for all stages of the process. A mechanism that is consistent with the reactivity and mechanistic studies outlined above is shown in Scheme 2.<sup>23</sup>

## Scheme 2. Proposed Mechanism



In conclusion, we have described a mild and general,  $SmI_2$ mediated method for the divergent synthesis of uracil derivatives. This study provides one of the very few examples of alcohol additive-controlled selectivity in  $SmI_2$ -mediated reductive processes that lead to synthetically useful products. Furthermore, this study features the development of the  $SmI_2$ -ethylene glycol system as a mild and chemoselective reagent with redox properties tailored to the desired transformation. We anticipate that our findings will contribute to the development of new cosolvent-controlled chemoselective  $SmI_2$  reactions. Studies in this direction are underway in our laboratory.

# ASSOCIATED CONTENT

## **Supporting Information**

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

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Notes

The authors declare no competing financial interest.

#### ACKNOWLEDGMENTS

We thank the EPSRC and Leverhulme Trust for support. M.S. thanks Rutgers University for support during the preparation of this manuscript.

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