



## Optimization of methods for the generation of carbodiimides for zwitterionic 1,3-diaza-Claisen rearrangements



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### ABSTRACT

Strained, tertiary, allylic, amine 2-benzyl-2-azabicyclo[2.2.1]hept-5-ene reacts with in situ generated carbodiimides in a 1,3-diaza-Claisen rearrangement to afford structurally interesting bicyclic guanidines. Use of more electron deficient carbodiimides makes these rearrangements more facile; however, there are not sufficient methods for the synthesis of highly electron deficient carbodiimides. Herein reported is the exploration of the synthesis of such carbodiimides from parent ureas and isothioureas and their use in 1,3-diaza-Claisen rearrangements.

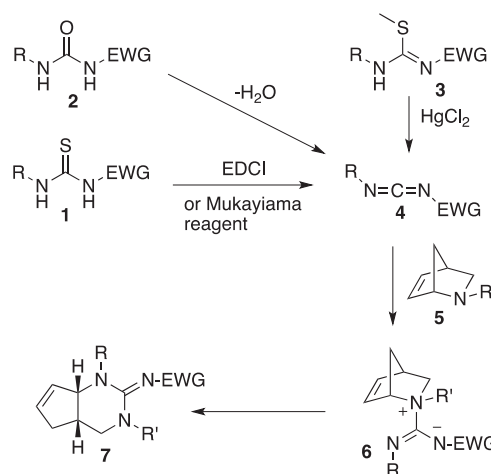
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### Introduction

The reaction of in situ generated carbodiimides **4** (Fig. 1) with aza-norbornenes **5** affords zwitterionic intermediates **6** that undergo a 1,3-diaza-Claisen rearrangement to afford bicyclic guanidines **7**. We have previously reported the in situ generation of carbodiimides through the desulfurization of thioureas **1** with either EDCI or the Mukaiyama salt.<sup>1,2</sup> In this work, we explore and compare alternate methods for the generation of carbodiimides through the dehydration of ureas **2** or desulfurization of isothioureas **3**. The motivation for undertaking this work is to expand the scope of the reaction that is somewhat limited currently by the availability of thioureas. For example, while diacyl thiourea is known,<sup>3</sup> thioureas with more powerful electron withdrawing groups on both nitrogens are unknown.

### Results and discussion

The ureas for this study were easily synthesized as shown in Table 1. Urea **7a** was synthesized through the reaction of Ns-NH<sub>2</sub> with BnNCO under CuCl catalysis in 96% yield in order to avoid potential Smiles rearrangement chemistry.<sup>4</sup> Urea **7b** was synthesized through the reaction of Ts-NH<sub>2</sub> with *i*-PrNCO using NaH as



**Figure 1.** Potential methods for the generation of carbodiimides and subsequent reaction to afford bicyclic guanidines.

a base in 95% yield. Ureas **7c** and **7d** were synthesized through reaction of the corresponding *n*-hexyl and benzyl amines with TsNCO in 91% and 84% yields, respectively. The synthesis of urea **7e** required heating benzamide and TsNCO in toluene with pyridine.<sup>5</sup> Finally, urea **7f** was synthesized through the reaction of TfNH<sub>2</sub> and BnNCO with NaH in 88% yield.

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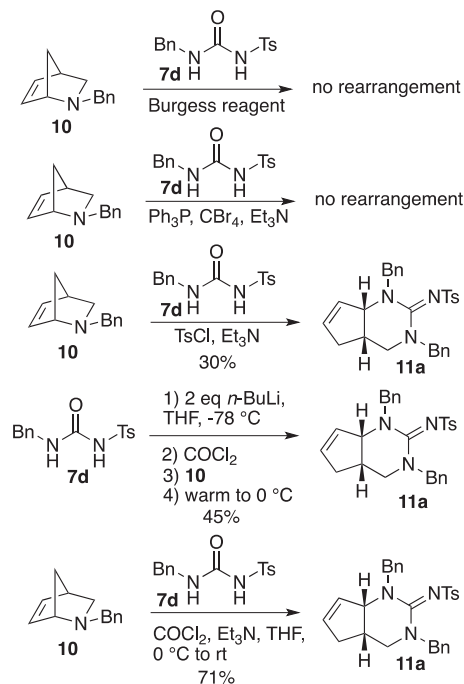
**Table 1**  
Synthesis of ureas
$$R^1-N=C=O + H_2N-R^2 \longrightarrow R^1-NH-C(=O)-NH-R^2$$

Urea	Conditions	Yield (%)
<b>7a</b> : R <sup>1</sup> = Bn, R <sup>2</sup> = Ns	10 mol % CuCl, DMF, rt, 20 h	96
<b>7b</b> : R <sup>1</sup> = <i>i</i> -Pr, R <sup>2</sup> = Ts	NaH, THF, 0 °C	95
<b>7c</b> : R <sup>1</sup> = Ts, R <sup>2</sup> = <i>n</i> -hexyl	CH <sub>2</sub> Cl <sub>2</sub> , 0 °C	91
<b>7d</b> : R <sup>1</sup> = Ts, R <sup>2</sup> = Bn	CH <sub>2</sub> Cl <sub>2</sub> , 0 °C	84
<b>7e</b> : R <sup>1</sup> = Bz, R <sup>2</sup> = Ts	Toluene, reflux 4 h, pyridine	79
<b>7f</b> : R <sup>1</sup> = Bn, R <sup>2</sup> = Tf	NaH, THF, 0 °C to rt	88

The isothioureas were synthesized from known *N*-sulphonyl *S,S*-dimethylcarbodiimides **8a** and **8b**.<sup>6,7</sup> Reaction of **8a** with benzyl amine in methanol under reflux for 3 h afforded the isothiourea **9a** in 97% yield (Table 2). Isothioureas **9b** and **9c** were similarly synthesized in 70% and 89% yields, respectively. In contrast, *N*-Ts, *N'*-Bz isothiourea **9d** was synthesized through deprotonation of benzamide with NaH in THF, followed by reaction of the subsequent anion with **8a**. We found the *N*-Tf *S,S*-dimethylcarbodiimide **8b** to be highly reactive such that the addition of benzyl amine could take place at 0 °C in 30 min to afford the isothiourea **9e** in 75% yield.

With the synthesis of the urea and isothiourea carbodiimide precursors in hand, we next turned our attention to exploring methods for the dehydration of ureas. Several methods for the dehydration of ureas have been reported in the literature.<sup>8–10</sup> For example, ureas have been dehydrated with the Burgess reagent, CBr<sub>4</sub>/Ph<sub>3</sub>P, and TsCl, R<sub>3</sub>N.<sup>8–10</sup> To the best of our knowledge, these reagents have not been utilized to dehydrate ureas that possess an electron withdrawing-group, let alone a powerful electron-withdrawing group such as tosyl. To evaluate the dehydration chemistry, rather than attempting to isolate a highly reactive *N*-Ts, *N'*-alkyl carbodiimide, the dehydrations were carried out in the presence of aza-norbornene **10** as a 'trap' for carbodiimide generated in the dehydration reaction.

The attempted dehydration of *N*-Ts, *N'*-Bn-urea **7d** followed by subsequent reaction of the generated carbodiimide with aza-norbornene **10** is detailed in Figure 2. Neither the Burgess reagent, nor CBr<sub>4</sub>/Ph<sub>3</sub>P afforded any rearrangement product when urea **7d** was subjected to these reagents in the presence of aza-norbornene **10**. TsCl/Et<sub>3</sub>N did dehydrate urea **7d** to some extent as the rearrangement product **11a** was isolated in 30% yield. However, these results signified that an alternative dehydrating method was needed. We next attempted a one pot di-deprotonation of urea **7d** with 2 equiv *n*-Buli at –78 °C followed by reaction with

**Figure 2.** Optimization of urea dehydration conditions.

phosgene. After addition of aza-norbornene **10**, the reaction mixture was allowed to warm to 0 °C. While the crude reaction mixture looked clean by <sup>1</sup>H NMR spectroscopy, the yield of guanidine **11a** after flash chromatography was only 45% and we could not account for the mass balance despite various attempts to modify the procedure. Finally, we attempted the dehydration of urea **7d** with phosgene and Et<sub>3</sub>N as the base in THF at 0 °C followed by addition of aza-norbornene **10**. This method at last afforded the rearrangement product **11a** in 71% yield after purification. These conditions were subsequently applied to the dehydration of all ureas synthesized for this study (shown below).

The results that allow a comparison of the three different methods for carbodiimide generation (from thioureas, ureas and isothioureas) are summarized in Table 3. The data for carbodiimide generation from thioureas with EDCI or the Mukaiyama reagent have been previously reported,<sup>1,2</sup> but is shown for comparison. Overall, yields of bicyclic guanidine **11a** were quite comparable regardless of whether the carbodiimide was generated from the thiourea with EDCI, the urea with phosgene, or the isothiourea with HgCl<sub>2</sub>. As for guanidines **11b** and **11c**, the yields are also comparable for all three methods, but the yields are slightly better when the carbodiimide was generated from the thiourea with EDCI.

In stark contrast to the reactions noted above in which all methods for carbodiimide generation afforded rearrangement product, the next set of reactions exhibited varied results. For example, while the reaction of *N*-Tf, *N'*-Bn thiourea **12d** afforded the guanidine **11d** in 62% yield, the dehydration of urea **7f** with phosgene and the desulfurization of the isothiourea **9e** with HgCl<sub>2</sub> afforded complex mixtures. We have found that the choice of solvent can have a profound effect on the outcome of these reactions, but a range of different solvents did not improve the reactions originating from urea **7f** and isothiourea **9e**. The next series incorporating the *Ns*-group features only the dehydration of *N*-*Ns*, *N'*-Bn urea **7a**. The reactions originating from the corresponding thiourea and isothiourea were not investigated since a search of the literature did not reveal any *N*-*Ns*, *N'*-alkyl thioureas or isothioureas. We suspect this is due to Smiles chemistry that is possible when using the

**Table 2**  
Synthesis of isothioureas
$$R^2-NH_2 + \begin{matrix} \text{MeS} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{MeS} \end{matrix} \begin{matrix} \text{O} \\ \diagup \\ \text{S} \\ \diagdown \\ \text{O} \end{matrix} \begin{matrix} \text{O} \\ \diagup \\ \text{S} \\ \diagdown \\ \text{O} \end{matrix} \begin{matrix} \text{R}^1 \\ \diagdown \\ \text{N} \\ \diagup \\ \text{R}^1 \end{matrix} \longrightarrow \begin{matrix} \text{MeS} \\ \diagup \\ \text{C} \\ \diagdown \\ \text{MeS} \end{matrix} \begin{matrix} \text{O} \\ \diagup \\ \text{S} \\ \diagdown \\ \text{O} \end{matrix} \begin{matrix} \text{O} \\ \diagup \\ \text{S} \\ \diagdown \\ \text{O} \end{matrix} \begin{matrix} \text{R}^1 \\ \diagdown \\ \text{N} \\ \diagup \\ \text{R}^1 \end{matrix}$$

**8a**: R = Ts  
**8b**: R = Tf

Isothiourea	Conditions	Yield (%)
<b>9a</b> : R <sup>1</sup> = Ts, R <sup>2</sup> = Bn	MeOH, reflux, 3 h	97
<b>9b</b> : R <sup>1</sup> = Ts, R <sup>2</sup> = <i>i</i> -Pr	MeOH, Et <sub>3</sub> N, reflux, 3 h <sup>a</sup>	70
<b>9c</b> : R <sup>1</sup> = Ts, R <sup>2</sup> = <i>n</i> -hexyl	MeOH, reflux, 3 h	89
<b>9d</b> : R <sup>1</sup> = Ts, R <sup>2</sup> = Bz	NaH, THF, rt	51
<b>9e</b> : R <sup>1</sup> = Tf, R <sup>2</sup> = Bn	MeOH, 0 °C, 30 min	75

<sup>a</sup> Isopropyl amine hydrochloride was used instead of the free base.

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