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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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1. Introduction

The reaction of *in-situ* generated carbodiimides **4** (Figure 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 Mukayama salt.^{1,2} 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,³ thioureas with more powerful electron withdrawing groups on both nitrogens are unknown.

2. 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-NH₂ with BnNCO under CuCl catalysis in 96% yield in order to avoid potential Smiles rearrangement chemistry.⁴ Urea **7b** was synthesized through the reaction of Ts-NH₂ with *i*-PrNCO using NaH as 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.⁵ Finally, urea **7f** was synthesized through the reaction of TNH₂ and BnNCO with NaH in 88% yield.

The isothioureas were synthesized from known N-sulphonyl S,S-dimethylcarbodithioimidates **8a** and **8b**.^{6,7} 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-dimethylcarbodithioimide **8b** to be highly reactive such that the addition of benzyl amine could take place at 0 °C in 30 minutes to afford the isothiourea **9e** in 75% yield.

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

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With the synthesis of the urea and isothioureia 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.⁸⁻¹⁰ For example, ureas have been dehydrated with the Burgess reagent, CBr₄/Ph₃P, and TsCl, R₃N.⁸⁻¹⁰ 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.

$$R^1-N=C=O + H_2N-R^2 \longrightarrow R^1-N=C=N-R^2$$

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

Table 1. Synthesis of ureas.

$$R^2-NH_2 + MeS-C(=S)-N(R^1)-S(=O)_2-Me \longrightarrow R^2-NH-C(=S)-N(R^1)-S(=O)_2-Me$$

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

Table 2. Synthesis of isothioureas. ^aIsopropyl amine hydrochloride was used instead of the free base.

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 CBr₄/Ph₃P afforded any rearrangement product when urea **7d** was subjected to these reagents in the presence of aza-norbornene **10**. TsCl/Et₃N 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 eq. *n*-Buli at -78 °C followed by reaction with 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 ¹H 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 Et₃N 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)

Figure 2. Optimization of urea dehydration conditions.

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 Mukayama reagent has been previously reported,^{1,2} 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 isothioureia with HgCl₂. 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 the isothioureia **9e** with HgCl₂ 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 isothioureia **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 isothioureia were not

investigated since a search of the literature did not reveal any N-Ns, N'-alkyl thioureas or isothiureas. We suspect this is due to Smiles chemistry that is possible when using the usual methods for the synthesis of thioureas and isothiureas.^{6,11} Dehydration of the N-Ns, N'-Bn urea **7a** followed by reaction of the subsequent carbodiimide with aza-norbornene **10** afforded the guanidine **11e** in 78% yield. The reaction of nosyl-urea **7a**, thus exemplifies how alternate methods for the generation of carbodiimides can expand the scope of the reaction if the corresponding thiourea or isothiurea are not easily accessible.

The final entries on Table 3 correspond to the Ts-Bz-thiourea/urea/isothiureas. It should be noted that the corresponding N-Ts, N'-Bz thiourea is unknown, most likely due to its instability,¹² however, the corresponding N-Ts, N'-Bz urea **7e** is known. Unfortunately, the attempted dehydration of this urea with phosgene in the presence of aza-norbornene **10** afforded a complex mixture. Out of this complex mixture we were able to isolate the bicyclic ureas **16** and **17** (Figure 3). In addition, a mass spectrum of the crude reaction mixture revealed products of mass to charge ratio = 422 (corresponding to guanidine **14**, Figure 3) and mass to charge ratio = 472 (corresponding to guanidine **15**). From these data, we propose a plausible mechanism for the formation of these products (Figure 3). Dehydration of urea **7e** affords the highly reactive N-Ts, N'-Bz carbodiimide as expected. However, deprotonation of either nitrogen of urea **7e** by Et₃N followed by addition of the subsequent anions to N-Ts, N'-Bz carbodiimide would afford the isomeric urea-guanidines **12** and **13**. We propose that urea-guanidine **12** eliminates TsNCO to afford guanidine **14** (detected by MS). TsNCO, in turn, reacts with aza-norbornene **10** through a 1,3-diaza-Claisen rearrangement to afford the isolated urea **16**. We additionally propose that urea-guanidine **13** also eliminates to afford BzNCO and guanidine **15** (detected by MS). BzNCO then reacts with aza-norbornene **10** through a 1,3-diaza-Claisen rearrangement to afford the urea **17**. It is worth noting that the reaction of BzNCO and TsNCO with aza-norbornene **10** affords urea/isourea mixtures and that while we did not isolate the corresponding isoureas they should have contributed to the complexity of the reaction mixture. Overall, the factors that contribute to this alternate undesired reaction pathway are the

highly electrophilic nature of the N-Ts, N'-Bz carbodiimide as well as the acidity of the nitrogen protons of urea **7e**.

The final entry, features the reaction of isothiurea **9d** with HgCl₂ in the presence of aza-norbornene **10** which afforded the isomeric guanidines **11f** and **11g** in 54% and 36% yields respectively (90% combined yield). This was another case in which the choice of solvent was critical, with CH₂Cl₂ being the optimal solvent. The regiochemical assignment was accomplished through n.O.e. experiments (Figure 4). The hydrogens ortho to the sulfonyl group in isomer **11f** exhibited an n.O.e. enhancement with the ring junction and alkene hydrogens, while in **11g**, they exhibited an n.O.e. enhancement with the benzylic hydrogens. It is worth noting that it is somewhat unusual that the major product has the sulfonyl group on the endocyclic nitrogen in contrast to the imine nitrogen. For example, for guanidines **11a-11c**, the only product we can detect has the sulfonyl group on the imine nitrogen. In light of the complex mixture obtained from the dehydration of urea **7e**, it is interesting that while this transformation proceeds through the same highly electrophilic N-Ts, N'-Bz carbodiimide the products are obtained in high overall yield. We hypothesize that this reaction is so much cleaner because addition of the anion **18** (Figure 5) to give the intermediate **19** is reversible (while **19** can not undergo an elimination like urea-guanidines **12** and **13**). Thus, N-Ts, N'-Bz carbodiimide can be regenerated from intermediate **19** for reaction with aza-norbornene **10**.

3. Conclusions

In this work, we have examined the generation of carbodiimides for 1,3-diaza-Claisen rearrangements through desulfurization of thioureas with EDCI, dehydration of ureas, and desulfurization of isothiureas with HgCl₂. Through the course of this work, we found that ureas could be dehydrated with phosgene with Et₃N as a base. Generation of carbodiimides from N-Ts, N'-alkyl thioureas, ureas and isothiureas, and subsequent reaction with aza-norbornene **10** afforded the corresponding bicyclic guanidines in comparable yields. However, in the N-Tf, N'-Bn series, carbodiimide generation from the urea and isothiurea only resulted in a complex mixture. Only carbodiimide generation from the thiourea afforded bicyclic

thiourea	conditions	yield	urea	conditions	yield	isothiurea	conditions	yield
12a: R ¹ = Ts, R ² = Bn	EDCI, EtN <i>i</i> -Pr ₂ , CHCl ₃ , rt	67% (11a)	7d: R ¹ = Ts, R ² = Bn	COCl ₂ , THF, 0 °C to rt, 6 h	71% (11a)	9a: R ¹ = Ts, R ² = Bn	HgCl ₂ , Et ₃ N, THF, rt	69% (11a)
12b: R ¹ = Ts, R ² = <i>i</i> -Pr	EDCI, EtN <i>i</i> -Pr ₂ , CHCl ₃ , rt	72% (11b)	7b: R ¹ = Ts, R ² = <i>i</i> -Pr	COCl ₂ , THF, 0 °C to rt, 6 h	61% (11b)	9b: R ¹ = Ts, R ² = <i>i</i> -Pr	HgCl ₂ , Et ₃ N, THF, rt	56% (11b)
12c: R ¹ = Ts, R ² = <i>n</i> -hexyl	EDCI, EtN <i>i</i> -Pr ₂ , CHCl ₃ , rt	77% (11c)	7c: R ¹ = Ts, R ² = <i>n</i> -hexyl	COCl ₂ , THF, 0 °C to rt, 6 h	67% (11c)	9c: R ¹ = Ts, R ² = <i>n</i> -hexyl	HgCl ₂ , Et ₃ N, DMF, rt	67% (11c)
12d: R ¹ = Tf, R ² = Bn	Mukaiyama salt, EtN <i>i</i> -Pr ₂ , CHCl ₃ , rt	62% (11d)	7f: R ¹ = Tf, R ² = Bn	COCl ₂ , THF, 0 °C to rt, 6 h	complex mixture	9e: R ¹ = Tf, R ² = Bn	HgCl ₂ , Et ₃ N, DMF, rt	complex mixture
—	—	—	7a: R ¹ = Ns, R ² = Bn	COCl ₂ , CH ₂ Cl ₂ , 0 °C to rt, 6 h	78% (11e)	—	—	—
—	—	—	7e: R ¹ = Ts, R ² = Bz	COCl ₂ , THF, 0 °C to rt, 6 h	complex mixture	9d: R ¹ = Ts, R ² = Bz	HgCl ₂ , Et ₃ N, CH ₂ Cl ₂ , rt	54% (11f) 36% (11g)

Table 3. Comparison of methods for carbodiimide generation for subsequent 1,3-diaza-Claisen generation.

Figure 3. Proposed mechanism for the formation of compounds **14**, **15**, **16** and **17**.

guanidine **11d**. In addition, dehydration of N-Ts, N'-Bn followed by reaction with aza-norbornene **10** afforded the bicyclic guanidine **11e** in 78% yield. The corresponding urea and thiourea in the nosyl series are unknown. Lastly, in the N-Ts, N'-Bz series, only desulfurization of the isothiurea **9d** followed by reaction with aza-norbornene **10** was the only method that afforded the corresponding regioisomeric guanidines **11f** and **11g** in 90% combined yield. The conclusion that can be drawn from these results is that no one method for carbodiimide generation works effectively for all carbodiimides.

Figure 4. Observed n.O.e. enhancements for guanidines **11f** and **11g**.

Figure 5. Addition of the anion **18** to the highly electrophilic N-Ts, N'-Bz carbodiimide would afford **19**. This addition is most likely reversible allowing for reaction of N-Ts, N'-Bz carbodiimide with aza-norbornene **10**.

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