JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Structure–Reactivity Relationships of Zwitterionic 1,3-Diaza-Claisen Rearrangements

Rachel Aranha Potter, Amy M. Bowser, Yanbo Yang, and José S. Madalengoitia*

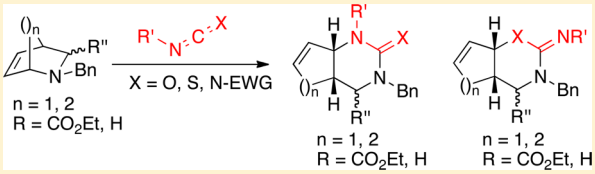
Department of Chemistry, University of Vermont, Burlington, Vermont 05405, United States

Joseph W. Ziller

Department of Chemsitry, University of California, Irvine, California 92697, United States

Supporting Information

ABSTRACT: Bridged bicyclic tertiary allylic amines aza-norbornene **1** and isoquinuclidene **2** add to isocyanates, isothiocyanates, and in situ-generated carbodiimides to form zwitterionic intermediates that undergo 1,3-diaza-Claisen rearrangements to afford highly substituted ureas, thioureas, and guanidines, respectively. Aza-norbornene **1** is significantly more reactive toward 1,3-diaza-Claisen rearrangements than isoquinuclidene **2**. This reactivity difference is most likely due to the inherent ring strain in the aza-bicyclo[2.2.1]heptene ring system of aza-norbornene **1**. The most apparent reactivity trend of the heterocumulenes is that the most electron-deficient heterocumulenes are more reactive toward 1,3-diaza-Claisen rearrangements. The introduction of a new stereocenter α- to the nucleophilic nitrogen in aza-norbornene **1** and isoquinuclidine **2** decreases the reactivity toward 1,3-diaza-Claisen rearrangements, while the exodiastereomers **3b** and **4b** are less reactive than the corresponding endodiastereomers **3a** and **4a**. Isocyanates that bear an electron-withdrawing group react with allylic amines **1**–**3b** to afford mixtures of ureas and isoureas; however, with excess isocyanate and heat, thermodynamic equilibration is possible affording ureas. Inspired by this observation, a one-pot reaction of isocyanates with amines **1**, **2**, and **3b** followed by $BF_3{\cdot}OEt_2$-catalyzed isomerization of the urea/isourea mixture was developed that affords the corresponding ureas in excellent yields.



INTRODUCTION

Because of the importance of guanidine compounds,[1] we have been involved in the development of methods for the synthesis of the guanidine functionality. In particular, we have been interested in developing a rearrangement that affords guanidines since rearrangements often offer an efficient means for the construction of complex molecules from simple starting materials. We have previously disclosed preliminary communications on the reaction of tertiary allylic amines with isocyanates, isothiocyanates, and in situ-generated carbodiimides that afford highly substituted allylic ureas, thioureas, and guanidines respectively via a zwitterionic intermediate that undergoes a 1,3-diaza-Claisen rearrangement.[2−5] Since ureas and thioureas can be easily converted to guanidines,[6] each of these transformations provides access to guanidine products. The present work is an account of the scope and limitations of the zwitterionic 1,3-diaza-Claisen rearrangement.

A mechanistic overview of the reaction of allylic amines with heterocumulenes is shown in Figure 1. Tertiary allylic amines **1** and **2** add to isocyanates, isothiocyanates, and carbodiimides to afford the corresponding zwitterionic intermediates. The zwitterionic intermediates may then rearrange to afford the ureas, thioureas, or guanidines **A**, or alternatively, the isoureas, isothioureas, or regioisomeric guanidines **B**.[7] In the present study, we investigated (1) the electronic factors that influence the reactivity of isocyanates, isothiocyanates, and carbodiimides, (2) ring strain effects on reactivity of rearrangement precursors **1** and **2**, (3) the reactivity effects of steric crowding proximal to the amine functionality on both the aza-norbornene and isoquinuclidine frameworks, and (4) the factors that influence regiochemistry (i.e., **A** vs **B**).

RESULTS AND DISCUSSION

Aza-norbornenes and isoquinuclidenes **1**–**4b** were synthesized as shown in Figure 2 through the hetero-Diels–Alder reaction of in situ-generated iminium ions with either cyclopentadiene or cyclohexadiene as described.[8] All thioureas were synthesized by the reaction of an amine with the corresponding isothiocyanate (not shown),[9] with the exception of *N*-benzyl-*N*′-Tf thiourea **5**, which was synthesized by the reaction of triflamide with NaH and subsequent treatment of the resulting anion with BnNCS, followed by acidic workup in 88% yield (Figure 2).[10] TsNCS and PmcNCS were synthesized as previously reported.[9,11]

I. Reaction of Aza-norbornene 1 and Isoquinuclidene 2 with Isocyanates, Isothiocyanates, and in Situ-Generated Carbodiimides. The reactions of isocyanates

Received: August 16, 2013
Published: October 18, 2013

   dx.doi.org/10.1021/jo401810p | J. Org. Chem. 2013, 78, 11772–11782

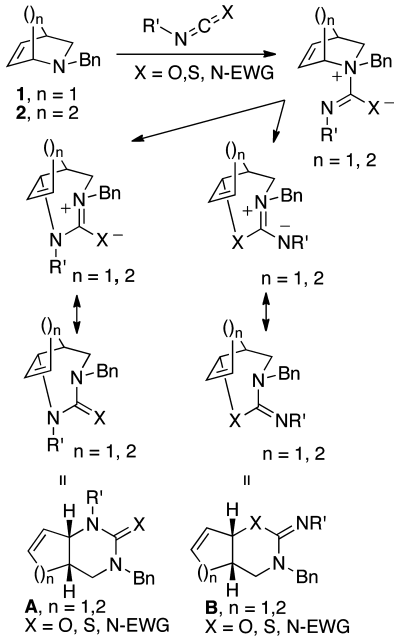


Figure 1. Mechanistic overview of the reaction of allylic amines **1** and **2** with heterocumulenes.

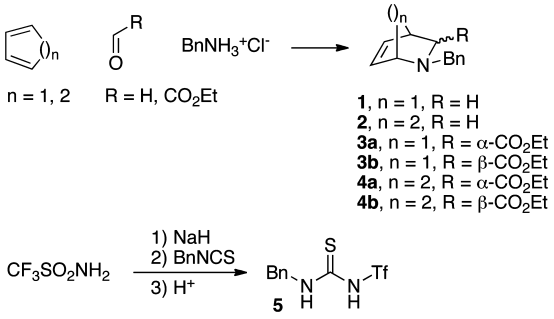
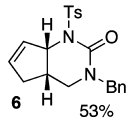
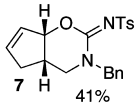
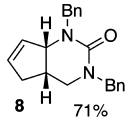
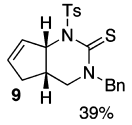
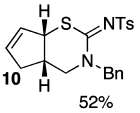
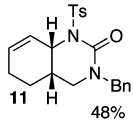
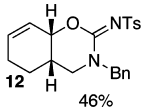
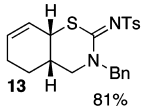


Figure 2. Synthesis of rearrangement precursors.

and isothiocyanates with aza-norbornene **1** and isoquinuclidene **2** are summarized in Table 1. TsNCO reacts with aza-norbornene **1** at room temperature to afford the urea **6** and isourea **7** in isolated yields of 53 and 41%, respectively. These structural assignments are confirmed by IR. The IR spectrum of urea **6** exhibits a C═O stretch 1675 cm^{-1}, while the IR spectrum of isourea **7** exhibits a C═N stretch at 1567 cm^{-1}. BnNCO exhibited diminished reactivity with aza-norbornene **1** requiring heating at reflux in benzene, but afforded only the urea **8** in 71% yield. Interestingly, TsNCS also reacts with aza-norbornene **1** at room temperature in benzene affording thiourea **9** and isothiourea **10** in 39 and 52% yield, respectively. Thus, the more electron-deficient isocyantes TsNCO and BzNCO are more reactive than the less electron-deficient BnNCO. The reaction of TsNCO with the less strained isoquinuclidene **2** required heating in benzene at reflux to afford urea **11** (48%) and isourea **12** (46%). As before, assignments were made on the basis of the C═O IR band at 1669 cm^{-1} and the C═N IR band at 1557 cm^{-1}. Isoquinuclidene **2** failed to afford rearrangement product with the less reactive BnNCO and BzNCO (not shown) even under forcing conditions (neat, 120 °C). The lower reactivity of isoquinuclidene **2** as compared with aza-norbornene **1** may be explained by the lower ring straining in isoquinuclidene **2** and

Table 1. Reaction of Isocyanates and Isothiocyanates with Azanorbornene 1 and Isoquinuclidene 2

allylic amine	R-NCX[a]	conditions	product(s)[b]
 **1**	TsNCO	benzene, rt	 **6** 53%  **7** 41%
1	BnNCO	benzene, reflux	 **8** 71%
1	TsNCS	benzene, rt	 **9** 39%  **10** 52%
 **2**	TsNCO	benzene, reflux	 **11** 48%  **12** 46%
2	BzNCO	neat 120 °C	isocyanate decomposition
2	TsNCS	benzene, rt	 **13** 81%

[a]1.5−2 equiv. [b]Isolated yields.

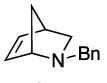
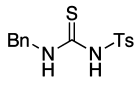
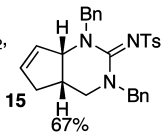
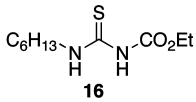
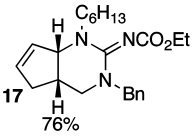
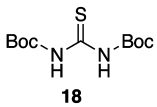
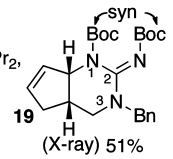
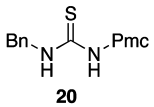
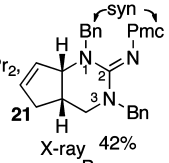
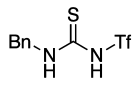
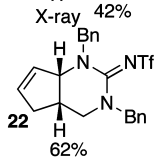
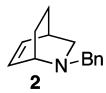
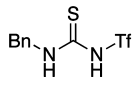
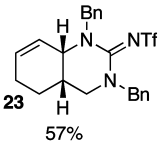
the fact that C−N bond breakage would be coupled to release of ring strain. The highly electron-deficient TsNCS smoothly reacted with isoquinuclidene **2** at room temperature, but afforded exclusively the isothiourea **13** in 81% yield. As in the case of aza-norbornene **1**, isoquinuclidene **2** also exhibited the trend of a more facile rearrangement with the more electron-deficient heterocumulenes; however, the less electron-deficient heterocumulenes BzNCO and BnNCO failed to react with isoquinuclidene **2**.

The reaction of thioureas with a primary or secondary amine in the presence of an activating agent such as EDCI, I_2, *N*-methyl-2-choloropyridinium iodide, Hg(II) salts is one of the most common means by which to synthesize guanidine compounds.[12] The most widely accepted mechanism for this transformation is the conversion of the thiourea (through reaction with an activating agent) to a carbodiimide followed by addition of the amine to the carbodiimide to afford the guanidine. Accordingly, we reasoned that in situ-generated *N*-alkyl-*N*′-EWG-carbodiimides would be sufficiently electrophilic to react with tertiary amines **1** and **2** affording a zwitterionic intermediate that would then undergo a 1,3-diaza-Claisen rearrangement.

The reactions of thioureas and an activating agent with aza-norbornene **1** and isoquinuclodene **2** are summarized in Table 2. Aza-norbornene **1** was smoothly transformed to bicyclic guanidine **15** in 67% yield on treatment with thiourea **14** and EDCI at room temperature. It is worth noting that EDCI itself does not participate in a 1,3-diaza-Claisen rearrangement with aza-norbornene. This is most likely because it is not sufficiently electron-deficient. We have previously reported that *N*-carbamoyl thioureas in the presence of EDCI do not undergo reaction with aza-norbornenes at room temperature, but we are now pleased to report that carbamoyl thiourea **16** on activation

dx.doi.org/10.1021/jo401810p | J. Org. Chem. 2013, 78, 11772−11782

Table 2. Reaction of Thioureas with Aza-norbornene 1 and Isoquinuclidene 2

allylic amine	thiourea[a]	conditions	product[b]
 1	 14	EDCI, EtN*i*-Pr$_2$, CHCl$_3$, rt	 15 67%
1	 16	Mukayiama salt, EtN*i*-Pr$_2$, CHCl$_3$, 60 °C	 17 76%
1	 18	EDCI, EtN*i*-Pr$_2$, CHCl$_3$, rt	 19 (X-ray) 51%
1	 20	EDCI, EtN*i*-Pr$_2$, CHCl$_3$, rt	 21 X-ray 42%
1	 5	Mukayiama salt, EtN*i*-Pr$_2$, CHCl$_3$, rt	 22 62%
 2	 5	Mukayiama salt, EtN*i*-Pr$_2$, CHCl$_3$, 60 °C	 23 57%

[a]1−2 equiv. [b]Isolated yields.

with the Mukayiama salt underwent reaction with aza-norbornene **1** with mild heating at 60 °C affording the bicyclic guanidine **17** in 76% yield. Thus, with mild heating carbamoyl thioureas in the presence of an activating agent also react with aza-norbornene **1**. In contrast, the bis-carbamoyl thiourea **18**, bearing two carbamoyl electron-withdrawing groups underwent rearrangement with aza-norbornene **1** in the presence of EDCI at room temperature affording the bis-Boc-guanidine **19** in 51% yield. Single crystal X-ray analysis of guanidine **19** reveals that the imine Boc-group is syn to N1 and is thus anti to N3. At this juncture it is unclear if the 1,3-diaza-Claisen rearrangement proceeds preferentially by transition state **24** (Figure 3), in which the imine Boc-group is syn to N1 (but not coplanar because of A(1,3) strain) or through transition state **25**, in which the imine Boc-group is syn to N3. Although these transition states would yield alternate isomers **19** and **26**, Kessler and Leibfritz have shown that imine syn/anti isomers of guanidines readily interconvert faster than the NMR time scale, especially when an electron-withdrawing group is on the imine nitrogen.[13] We thus expect that the imine isomers readily interconvert, and isomer **19** is selectively crystallized by crystal packing forces. Reaction of Pmc-thiourea **20** with aza-norbornene **1** in the presence of EDCI afforded guanidine **21** in 42% yield. Again, isomers **21** and **29** should readily interconvert, and **21** selectively crystallizes. The X-ray crystal structure of Pmc-guanidine **21** demonstrates the electron-withdrawing Pmc-group is on the imine nitrogen and not on N1. By analogy, we propose that the guanidines in Table 2 that are derived from unsymmetrical thioureas also possess the electron-withdrawing group (Ts, CO_2Et, etc) on the imine nitrogen and not on N1. Interestingly, under no conditions examined, did thiourea **14** react with isoquinicludene **2** in the presence of an activating agent (data not shown) to afford rearrangement product. For this reason, we were interested in investigating the reactivity of thiourea **5** bearing the highly electron-withdrawing trifluoromethanesulfonyl (Tf) group, as we reasoned that the more electron-deficient *N*-Tf-*N*′-Bn-carbodiimide may react with isoquinuclidene **2** mirroring the reactivity trend of the isocyanates.

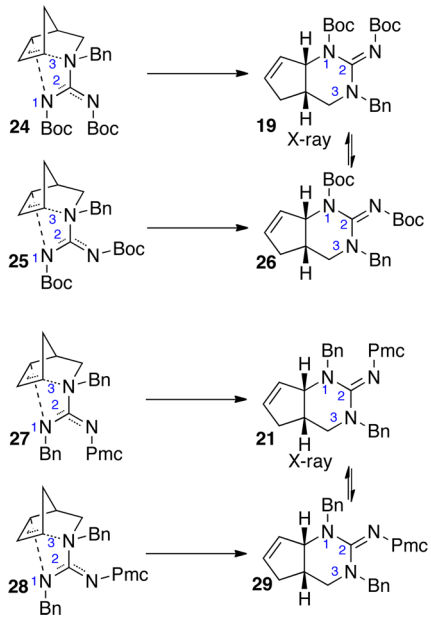


Figure 3. X-ray crystal structures of guanidines **19** and **21** and potential transition states leading to formation of **19** and **21**.

The EDCI-mediated reaction of thiourea **5** with aza-norbornene **1** did not proceed as cleanly as other reactions (data not shown); however, it was discovered that thiourea **5** on activation with the Mukayiama salt afforded *N*-Tf guanidine **22** in 62% yield. Furthermore, when isoquinuclidene **2** was subjected to Tf-thiourea **5** and the Mukayiama salt in $CHCl_3$ at 60 °C, the rearrangement product **23** was obtained in 57% yield.

II. Reaction of Aza-norbornenes 3a,b and Isoquinuclidenes 4a,b with Isocyanates. The bridged-bicyclic amines **3a**−**4b** (Figure 4) were synthesized in order to determine what effects steric crowding adjacent to the nucleophilic nitrogen of the tertiary allylic amine would have on reactivity. Our studies began by assessing the reactivity of the diastereomeric aza-norbornenes **3a** (*endo*-ethoxycarbonyl group) and **3b** (*exo*-ethoxycarbonyl group) with TsNCO (highly reactive isocyanate) and BnNCO (less reactive isocyanate). The *endo*-aza-norbornene **3a** reacted smoothly with TsNCO at room temperature to afford the urea **30** in 24% yield and the isourea **31** in 64% yield. The *exo*-aza-norbornene **3b** also smoothly undergoes reaction with TsNCO at room temperature to afford urea **35** in 47% yield, and isourea **36** in 44% yield. Thus, with the highly reactive TsNCO, both diastereomeric aza-norbornenes **3a** and **3b** react at room temperature. In contrast, *endo*-aza-norbornene **3a** did not

dx.doi.org/10.1021/jo401810p | J. Org. Chem. 2013, 78, 11772−11782

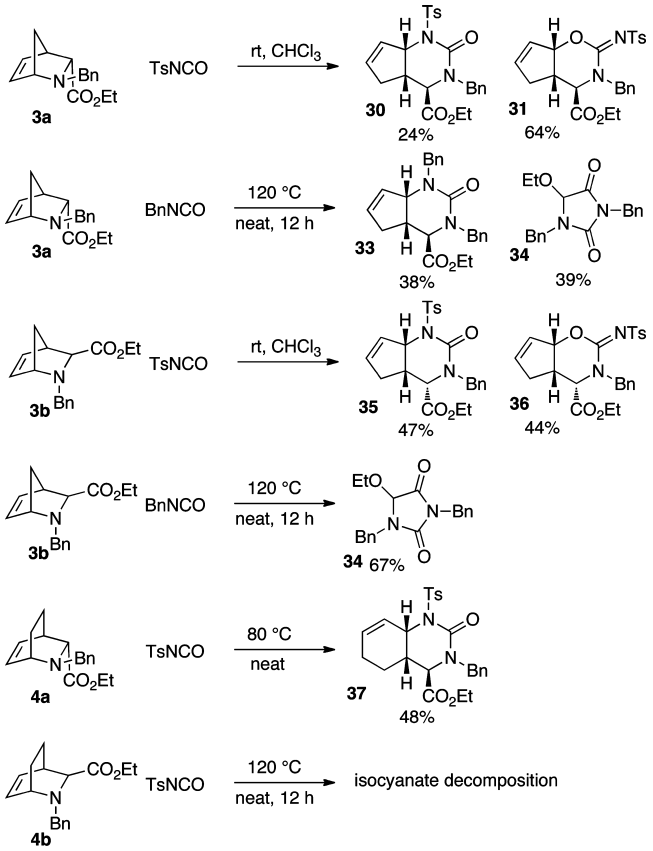


Figure 4. Reaction of Aaza-norbornenes **3a**–**4b** with TsNCO and BnNCO.

undergo reaction with the less reactive BnNCO in benzene at reflux (conditions under which **1** underwent reaction with BnNCO). For BnNCO to react with aza-norbornene **3a**, heating at 120 °C under neat conditions was required to afford the expected urea **33** in 38% yield and the hydantoin **34** in 39% yield. The *exo*-aza-norbornene **3b** proved even less reactive toward rearrangement with BnNCO affording none of the expected urea, but affording as the sole isolable product the hydantoin **34** in 67% yield under forcing conditions (120 °C, neat). Thus, aza-norbornene **3a** exhibits diminished reactivity toward rearrangement with BnNCO as compared with aza-norbornene **1**, and exoisomer **3b** does not afford rearrangement product at all with BnNCO. In the case of the isomeric isoquinuclidenes **4a** and **4b**, the endoisomer **4a** underwent reaction with TsNCO at 80 °C under neat conditions to afford urea **37** in 48% yield, while the exoisomer (**4b**) did not undergo rearrangement with TsNCO under any conditions investigated. Since isoquinuclidene **2** does not undergo rearrangement with BnNCO, we did not attempt the reaction of the less reactive isoquinuclidenes **4a** and **4b** with BnNCO.

In all, the presence of the ethoxycarbonyl-group on the aza-norbornene (i.e., **3a**, **3b**) or isoquinuclidene (i.e., **4a**, **4b**) frameworks regardless of the endo- or exostereochemistry diminishes the reactivity toward rearrangement of these substrates as compared with the unsubstituted aza-norbornene **1** and isoquinuclidene **2**. This may be due to the constrained conformation of these frameworks, which enforce eclipsing interactions either between the CO_2Et and Bn groups or between the CO_2Et and —C(O$^-$)=N-Bn groups depending on the diastereomeric zwitterionic intermediate. These eclipsing interactions will disfavor formation of the zwitterionic intermediates as compared to zwitterionic intermediates arising from the unsubstituted amines **1** and **2**. Lower concentration of zwitterionic intermediates will in turn result in a decrease of the rate of rearrangement.

III. Mechanistic Observations. A key mechanistic insight was made when we initially attempted the reaction of 1 equiv of isoquinuclidene **2** with 1 equi of TsNCO at room temperature. NMR analysis of the crude reaction mixture revealed a deshielding of the resonances α to the amine of the isoquinuclidene **2**, but these changes were not consistent with a skeletal rearrangement. Instead, the shift in the resonances of the isoquinuclidene **2** suggested that the observed shift was due to the formation of the zwitterionic intermediate. The ^{1}H NMR spectrum of 1 equiv of isoquinuclidene **2** with 0.5 equiv of TsNCO at room temperature exhibits a shift in the resonances, but not of the same magnitude as is observed with the 1:1 **2**/TsNCO stoichiometry. Since the ^{1}H NMR spectrum of isoquinuclidene **2** with 0.5 equiv of TsNCO does not exhibit a set of resonances for **2** and another set of resonances for the zwitterionic intermediate, these data are consistent with a fast and reversible addition step on the NMR time scale. Furthermore, as the rearrangement does not take place at room temperature, the rearrangement is obviously the rate-determining step. In this scenario, the rate of formation of product = k_2[zwitterionic intermediate]. In practical terms, this indicates that conditions that increase the concentration of the zwitterionic intermediate will increase the rate of the overall reaction. These observations can in part explain the reactivity trend of the heterocumulenes (i.e., TsNCO > BzNCO > BnNCO), as it would be expected that [zwitterionic intermediate] would increase with the electron deficiency of the heterocumulene.

IV. Proposed Mechanism for the Formation of Hydantoin 34. A proposed scheme for the formation of hydantoin **34** is detailed in Figure 5. Addition of aza-norbornenes **3a** and **3b** to BnNCO will afford the corresponding diastereomeric zwitterionic intermediates **38** and **39**. The retro-Diels–Alder reaction of intermediates **38**

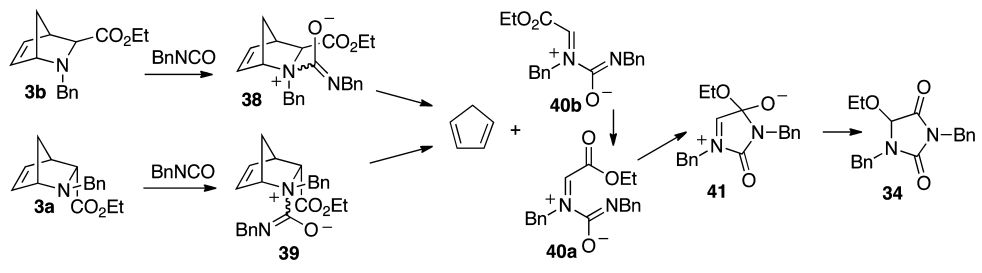


Figure 5. Proposed mechanism for the formation of hydantoin **34**.

dx.doi.org/10.1021/jo401810p | J. Org. Chem. 2013, 78, 11772–11782

and **39** affords cyclopentadiene and the isomeric 1,4-dipoles **40a** and **40b**. The 1,4-dipole **40b** would require isomerization to **40a** for attack of the anionic nitrogen of the 1,4-dipole on the ester carbonyl to give the tetrahedral intermediate **41** that undergoes ethoxide-[1,2]-migration to furnish the hydantoin **34**. The retro-Diels–Alder pathway is reasonable as Grieco has shown that aza-norbornenes can readily undergo retro-Diels–Alder reactions.[14] The most immediate fate of the 1,4-dipoles **40a** and **40b** is likely to be elimination to afford the isomeric imines and benzyl isocyante (Figure 6), but this process should

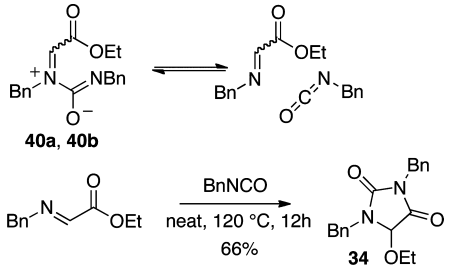


Figure 6. Proposed mechanism for elimination of **40a** and **40b**. Reaction of imine and BnNCO to form hydantoin **34**.

be reversible such that addition of the imine nitrogen to BnNCO would result in formation of the 1,4-dipoles **40a** and **40b**. Indeed, when the glyoxylate imine and BnNCO were subjected to the attempted rearrangement conditions (neat, 120 °C), the hydantoin **34** was formed in 66% yield (Figure 6). Although the formation of the hydantoin **34** from the glyoxylate imine and BnNCO (Figure 6) is consistent with the proposed mechanism for hydantoin formation (Figure 5), it does not unambiguously prove that the reaction proceeds through the proposed mechanism. It is alternatively possible that the zwitterionic intermediates **38** and **39** may undergo attack of the nitrogen on the ester carbonyl prior to retro-Diels–Alder reaction. However, we have good evidence that at high temperatures, the aza-norbonene **1** can undergo a retro-Diels–Alder reaction in the presence of BnNCO.[3] Thus, even in the absence of the α-ester the retro-Diels–Alder is a viable pathway suggesting that zwitterionic intermediates **38** and **39** are also likely to undergo a retro-Diels–Alder reaction at high temperatures.

In the reaction of BnNCO with the aza-norbornenes **3a** and **3b**, the factors that influence the ratio of the hydantoin **34** arising from the proposed retro-Diels–Alder pathway versus product arising from the rearrangement pathway are complex. A schematic that explains these factors is shown in Figure 7 for the reaction of aza-norbornene **3b** with BnNCO. Aza-norbornene **3b** has two possible conformers **42** and **45** arising from nitrogen lone-pair inversion. Conformer **45** can react with BnNCO to give the zwitterionic intermediate **46** whose geometry does not allow a concerted 1,3-diaza-Claisen rearrangement. Thus, zwitterionic intermediate **46** can only undergo a retro-Diels–Alder reaction with rate constant k_2 to give cyclopentadiene and the 1,4-dipole **40** that in turn leads to hydantoin **34**. In contrast, conformer **42** can react with BnNCO to give the diastereomeric zwitterionic intermediate **43**. Zwitterionic intermediate **43** could undergo rearrangement with rate constant k_1 to give urea **44** or undergo retro-Diels–Alder reaction with rate constant k_3. The Curtin–Hammett principle dictates that if the energies of activation for the conversion of intermediate **43** to intermediate **40b** and product **44** and for the conversion of intermediate **46** to intermediate **40a** are greater than the energy of activation for the interconversion of conformers **42** and **45** (as should be the case), then the energy difference between conformers **42** and **45** should not influence the ratio of ureas **34**/**44**, instead, the ratio **34**/**44** = $(k_2[\mathbf{46}] + k_3[\mathbf{43}])/k_1[\mathbf{43}]$.[15] As the reaction of aza-norbornene **3b** with BnNCO does not afford isolable quantities of the urea **44**, this indicates that $k_1[\mathbf{43}]$ is small relative to the term $(k_2[\mathbf{46}] + k_3[\mathbf{43}])$. Although we have not included a discussion of the product distribution in the reaction of aza-norbornene **3a** with BnNCO, similar arguments may be made for the factors that influence product distribution in that reaction.

V. Variables Influencing Urea/Isourea Distribution. In the reaction of TsNCO and BzNCO with aza-norbornenes and isoquinuclidenes, we had been observing some variation in the ratio of urea/isourea products. This prompted a thorough investigation of the reaction conditions in order to resolve what led to the variability in these ratios. Figure 8 details the examination of reaction conditions for the reaction of TsNCO with aza-norbornene **1**. When aza-norbornene **1** is allowed to react with 0.75 equiv of TsNCO (less than 1 equiv) in benzene at room temperature a 1:1 ratio is obtained of urea **6** to isourea **7** in 15 min as determined by ^{1}H NMR analysis. As this reaction is complete in 15 min, the 0.75 equiv of TsNCO are consumed within 15 min. If the same reaction is carried out identically, but after 15 min, the reaction is brought to reflux for 12 h, a 1:1 mixture of products **6**/**7** is also obtained. When aza-norbornene **1** is allowed to react with 1.5 equiv of TsNCO in benzene at room temperature again a 1:1 ratio is obtained of urea **6** to isourea **7** within 15 min. However, in this case when after 15 min the reaction mixture is heated at reflux for 12 h, a 2:1 ratio of products **6**/**7** is obtained, and if the mixture is

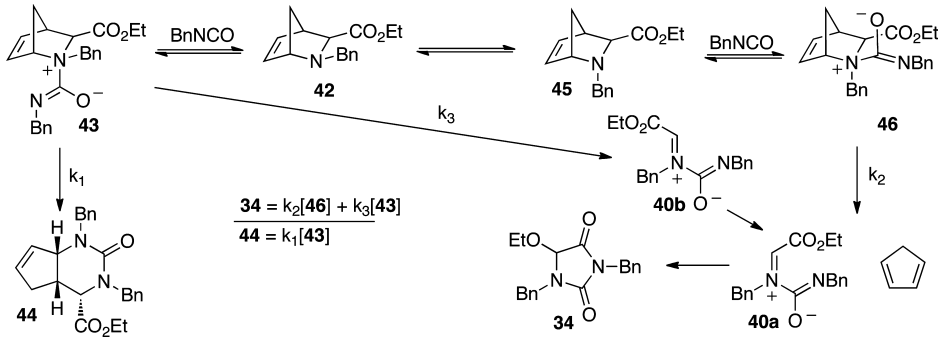


Figure 7. Factors influencing the ratio of hydantoin **34** and urea **44**.

dx.doi.org/10.1021/jo401810p | J. Org. Chem. 2013, 78, 11772–11782

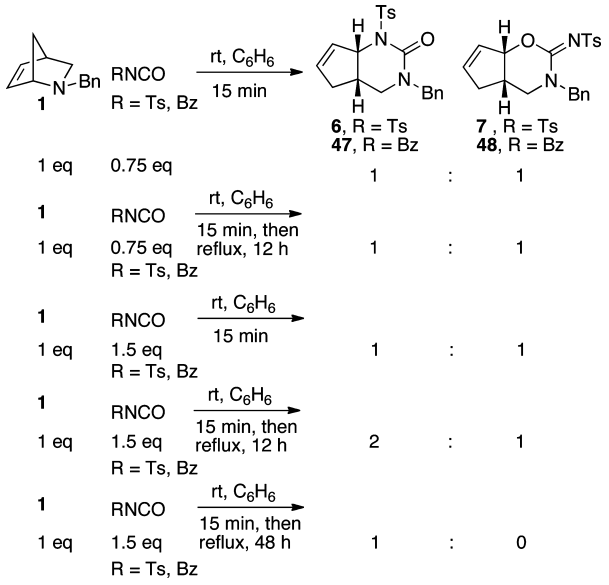


Figure 8. Variables influencing urea/isourea ratios.

heated at reflux for 48 h, only the urea **6** is obtained as determined by ^{1}H NMR analysis. This indicates that with excess TsNCO and heat, the mixture of urea/isourea can be isomerized to afford only urea **6**. Similarly, results were obtained with aza-norbornene **1** and BzNCO (not shown). These data indicate that thermodynamic control can be achieved in these rearrangements by using excess isocyanate and heat. Figure 9 details the proposed mechanism for the

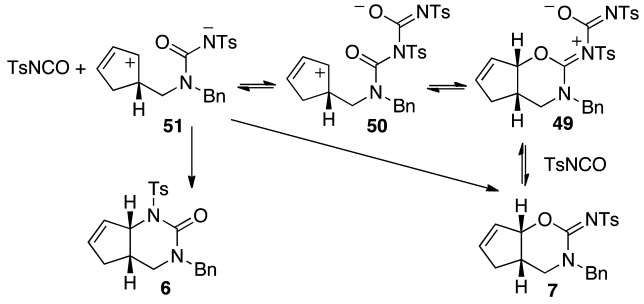


Figure 9. Proposed mechanism for isocyanate-mediated isomerization of isourea to urea.

TsNCO-catalyzed isomerization of isourea **7** to urea **6**. The imine nitrogen of isourea **7** adds to TsNCO affording the zwitterion **49**. Rupture of the allylic C−O bond affords the allylic cation **50**. Elimination to re-form TsNCO gives intermediate **51** that may cyclize to give either the urea **6** or the isourea **7**. This proposed scheme would allow for isomerization of isourea **7** to the thermodynamically more stable urea **6**. We propose that thermodynamic equilibration by this mechanism is the reason why, in the reaction of amine **4a** with TsNCO (Figure 4), the urea **37** is isolated without any of the corresponding isourea.

The isocyanate-catalyzed isomerization of isourea **7** to urea **6** appeared reminiscent of a Lewis acid-catalyzed process and thus prompted the hypothesis that a Lewis acid could coordinate the imine nitrogen of the isourea and promote an analogous allylic C−O bond rupture, and recyclization to afford the urea. Figure 10 shows the yields of urea obtained for rearrangement reactions followed by the addition of catalytic

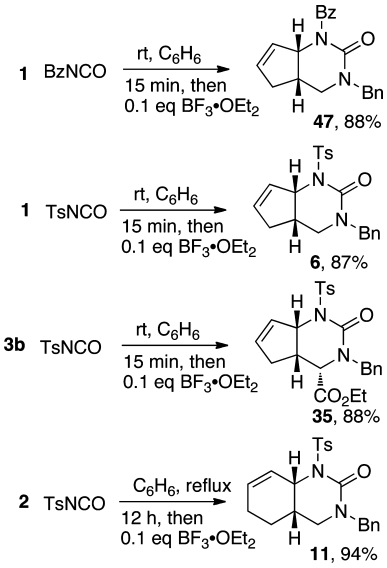


Figure 10. One pot reaction of isocyanates with allylic amines **1**, **2**, and **3b**, followed by thermodynamic equilibration with catalytic BF_3·OEt_2.

BF_3·OEt_2. When aza-norbornene **1** is allowed to react with BzNCO followed by addition of 0.1 equiv of BF_3·OEt_2, the urea **47** is obtained in 88% yield. Similarly, when aza-norbornene **1** is allowed to react with TsNCO followed by the addition of catalytic BF_3·OEt_2, the urea **6** is obtained in 87% yield. In addition, when the reaction of aza-norbornene **3b** with TsNCO is followed by rearrangement with catalytic BF_3·OEt_2, the urea **35** is obtained in 88% yield. The reaction of isoquinuclidene **2** with TsNCO, followed by BF_3·OEt_2-catalyzed isomerization affords the urea **11** in 94% yield. It is of note that all the examples above afford urea/isourea mixtures if the BF_3·OEt_2-catalyzed isomerization is not applied.

VI. Cyclic Nonbridged Tertiary Allylic Amines. We have additionally investigated the rearrangement of cyclic nonbridged tertiary allylic amines *N*-benzyl pyrroline **51** and *N*-benzyl tetrahydropyridine **52**[16,17] (Figure 11). However, under

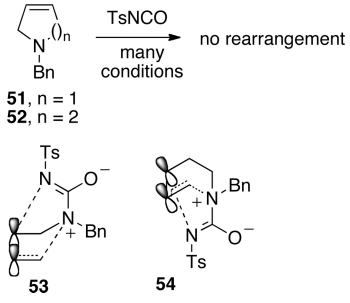


Figure 11. Failed rearrangement of pyrroline **51** and tetrahydropyridine **52**. Transition states **53** and **54** that would be required for proper alignment of the breaking bond with the alkene π-bond.

all conditions investigated, neither underwent rearrangement with the highly reactive TsNCO. We propose that the unreactivity of the amines **51** and **52** may be explained by a stereoelectronic effect. The concerted reaction would require an approximate coplanar alignment of the breaking bond with the π-bond of the alkene in the transition state. To accommodate this geometry the transition state arising from the pyrroline **51** would require severely puckering the pyrroline

dx.doi.org/10.1021/jo401810p | J. Org. Chem. 2013, 78, 11772−11782

nitrogen out of the plane of the other four carbons as in transition state **53** (Figure 11). In addition, for proper orbital alignment, the transition state arising from the tetrahydropyridine **52** would require a boat geometry such as **54**. We thus believe that these are higher energy transition states that make the rearrangement less favorable than those arising from the aza-norbornene **1** and isoquinuclidene **2**, which would proceed through a better orbital alignment.

CONCLUSIONS

We have explored the scope and limitations of the reaction between isocyanates, isothiocyanates, and in situ-generated carbodiimides with bridged, bicyclic tertiary allylic amines. The most apparent trend that arises from these studies regarding the reactivity of the heterocumulene component is that adding an electron-withdrawing substituent to a heterocumulene or increasing the strength of the electron-withdrawing substituent increases the rate of the overall reaction. A potential reason for this effect is that in the reaction of a tertiary allylic amine with a heterocumulene to form a zwitterionic intermediate, the more electron-deficient heterocumulene would favor a larger K_{eq} for formation of the zwitterionic intermediate; hence, the greater the concentration of zwitterionic intermediate, the greater the rate of the overall reaction. At this junction, it is unknown what effect if any an electron-withdrawing substituent has on the rate-determining rearrangement step. The use of more electron-deficient heterocumulenes may represent an overall strategy by which to accomplish 1,3-diaza-Claisen rearrangements with less reactive tertiary allylic amines. In comparing the reactivity of aza-norbornene **1** with isoquinuclidene **2**, it is apparent that aza-norbornene **1** is more reactive toward 1,3-diaza-Claisen rearrangements, and this reactivity is most likely due to the inherent ring strain in aza-norbornene **1**. Interestingly, in the reactions of in situ generated carbodiimides with aza-norbornene **1**, the substituent on the imino-nitrogen of the resulting guanidine crytallizes syn to N1 as determined by the X-ray crystal structures of guanidines **19** and **21**, but this is attributed to crystal packing forces.

The rearrangement precursors **3a**,**b** and **4a**,**b** that possess an additional stereocenter α- to nitrogen exhibit diminished reactivity toward 1,3-diaza-Claisen rearrangements when compared with the rearrangement precursors **1** and **2**. In comparing the reactivity of these species, the exoisomers **3b** and **4b** were clearly less reactive toward 1,3-diaza-Claisen rearrangement than the corresponding endoisomers **3a** and **4a**. The reasons for the reactivity profiles of these compounds are complex, but ultimately, the Curtin–Hammett principle dictates that the product distribution is determined by the concentration of each possible diastereomeric zwitterionic intermediate times the rate constant for that reaction.

We have additionally established that with excess isocyanate and heat, it is possible to achieve thermodynamic control over rearrangements and thus equilibrate urea/isourea mixtures to obtain exclusively the urea product (within our detection limits). Inspired by this observation, we developed a one-pot process that involves first the reaction of an isocyanate with a rearrangement precursor to afford a mixture of ureas/isoureas followed by $BF_3{\cdot}OEt_2$ catalyzed isomerization of that mixture to afford the ureas in excellent yields.

EXPERIMENTAL SECTION

All reactions were carried out under an atmosphere of nitrogen using flame-dried glassware. All reagents and solvents were purchased and used as received. Column chromatography was carried out using standard grade silica gel P60 (40–63 μm particle size), which was purchased and used as received. ^{1}H and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer in $CDCl_3$ at ambient temperature unless otherwise noted. Splitting patterns were designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Coupling constants were reported in Hz. Chemical shits were referenced to residual ^{1}H and ^{13}C signals at 7.27 and 77.0 ppm for deuterated chloroform.

2-Benzyl-2-aza-bicyclo[2.2.1]hept-5-ene (1). Following the procedure by Grieco,[8a,b] a mixture of benzylamine hydrochloride (2.14 g, 14.9 mmol), 37% w/w aqueous formaldehyde (1.7 g, 21 mmol), freshly distilled cyclopentadiene (2.0 g, 30 mmol), and water (10 mL) was stirred vigorously for 16 h at room temperature. The resulting mixture was diluted with water (20 mL) and washed with a 1:1 Et_2O–hexanes mixture (2 × 10 mL). The aqueous layer was made basic by the addition of 4 g of KOH pellets, and the mixture was extracted with Et_2O (3 × 15 mL). The Et_2O extracts were combined, dried (Na_2SO_4), and concentrated. Purification of the residue on silica gel afforded 2.78 g (100%) of **1** as a colorless oil. ^{1}H and ^{13}C NMR spectra were consistent with those reported in the literature.[8a,b]

3-Benzyl-1-(toluene-4-sulfonyl)-1,3,4,4a,5,7a-hexahydro-cyclopentapyrimidin-2-one (6). Toluenesulfonyl isocyanate (0.10 g, 0.5 mmol) was added at room temperature to a stirred solution of aza-norbornene **1** (0.10 g, 0.5 mmol) in $CHCl_3$ (3 mL) under N_2. After stirring for 1 h, the reaction mixture was concentrated in vacuo and dissolved in EtOAc (10 mL). The organic layer was washed with water (2 × 10 mL) and brine (10 mL). The organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product over silica gel, eluting with 3:2 (hexanes–EtOAc), gave 0.10 g (53%) of urea **6** as a colorless foam and 0.08 g (41%) of the isourea **7** as yellow oil. **6**: mp 171–173 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 7.8 Hz, 2H), 7.27–7.26 (m, 3H), 7.15 (d, J = 5.8 Hz, 2H), 5.77–5.76 (m, 1H), 5.63–5.62 (m, 1H), 5.42 (d, J = 8.7 Hz, 1H), 4.50 (d, J = 14.6 Hz, 1H), 4.41 (d, J = 14.6 Hz, 1H), 3.30–3.27 (m, 1H), 2.93–2.86 (m, 2H), 2.43 (s, 3H), 2.41–2.40 (m, 1H), 1.83 (d, J = 14.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 153.9, 143.8, 137.3, 136.3, 134.3, 129.9, 129.2, 128.4, 128.2, 127.5, 126.4, 65.1, 50.8, 47.5, 36.6, 36.1, 21.9 ppm; IR (ATR) υ_{max} 2920, 1675, 1342, 1163 cm^{-1}; MS (ESI-TOF) calcd for $C_{21}H_{22}N_2O_3S$ $[M + Na]^+$ 405.1249, found 405.1252.

***N*-(3-Benzyl-4,4a,5,7a-tetrahydro-3*H*-cyclopenta[*e*][1,3]-oxazin-2-ylidene)-4-methyl-benzenesulfonamide (7).** Yield 41%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.3 Hz, 2H), 7.31–7.26 (m, 5H), 7.21 (d, J = 8.3 Hz, 2H), 5.89–5.85 (m, 1H), 5.60–5.57 (m, 1H), 4.74 (d, J = 15.1 Hz, 2H), 4.59 (d, J = 15.1 Hz, 1H), 3.32 (dd, J = 5.8 Hz, 1H), 2.99 (dd, J = 4.8 Hz, 1H), 2.38 (s, 3H), 1.98–1.84 (m, 1H), 1.43 1.36 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.4, 141.7, 141.0, 137.3, 135.1, 128.8, 128.7, 128.5, 128.3, 128.1, 127.0, 87.8, 53.5, 46.2, 36.6, 35.8, 21.4 ppm; IR (ATR) υ_{max} 2919, 1567, 1471, 1086, 886 cm^{-1}; MS (ESI-TOF) calcd for $C_{21}H_{22}N_2O_3S$ $[M + Na]^+$ 405.1249, found 405.1245.

3-Benzyl-1-(toluene-4-sulfonyl)-1,3,4,4a,5,7a-hexahydro-cyclopentapyrimidine-2-thione (9). *p*-Toluenesulfonyl isothiocyanate (0.11 g, 0.5 mmol) was added to a solution of aza-norbornene **1** (0.09 g, 0.5 mmol) in $CHCl_3$ (3 mL) under N_2 with stirring at room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo and dissolved in EtOAc (10 mL). The organic layer was washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue over silica gel, eluting with 60:40 (hexanes–EtOAc) afforded the thiourea **9** (0.08 g, 39%) and isothiourea **10** (0.11 g, 52%) as a colorless solid. **9**: mp 56–58 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.31–7.26 (m, 5H), 5.75–5.73 (m, 1H), 5.70–5.69 (m, 1H), 5.32–5.29 (m, 1H), 5.23 (d, J = 14.6 Hz, 1H), 4.98 (d, J = 14.6 Hz, 1H), 3.60–3.56 (m, 1H), 3.26 (m, 1H), 3.13 (d, J = 12.6 Hz, 1H), 2.44 (s, 3H), 2.42–2.40 (m, 1H), 1.63–1.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 182.4, 143.9, 136.8, 135.8, 135.3, 129.1, 129.0, 128.6, 128.5, 128.1, 127.5, 66.3, 56.6, 51.7, 39.7, 37.1, 21.6 ppm; IR (ATR) υ_{max} 2920, 1599, 1484, 1159,

1096 cm^{-1}; MS (ESI-TOF) calcd for $C_{21}H_{22}N_2O_2S_2$ $[M + Na]^+$ 421.1021, found 421.1015.

***N*-(3-Benzyl-4,4a,5,7a-tetrahydro-3*H*-cyclopenta[*e*][1,3]-thiazin-2-ylidene)-4-methyl-benzenesulfonamide (10).** Yield 52%: mp 157−160 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.32−7.23 (m, 7H), 5.65−5.63 (m, 1H), 5.22−5.19 (m, 1H), 4.90 (d, J = 14.1 Hz, 1H), 4.74 (d, J = 14.1 Hz, 1H), 4.29 (d, J = 9.27 Hz, 1H), 3.44−3.41 (m, 1H), 3.22−3.18 (m, 1H), 2.91−2.85 (m, 1H), 2.57−2.48 (m, 1H), 2.40 (s, 3H), 1.91 (d, J = 17.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 166.4, 141.9, 139.9, 135.5, 132.6, 129.8, 128.7, 128.6, 128.4, 128.0, 127.1, 55.0, 53.4, 52.6, 39.0, 36.9, 21.4 ppm; IR (ATR) υ_{max} 2917, 1522, 1441, 1144, 907 cm^{-1}; MS (ESI-TOF) calcd for $C_{21}H_{22}N_2O_2S_2$ $[M + Na]^+$ 421.1021, found 421.1011.

2-Benzyl-2-aza-bicyclo[2.2.2]oct-5-ene (2). The same procedure was used as in the synthesis of **1** except that 1,3-cyclohexadiene (2.38 g, 29.8 mmol) was used instead of cyclopentadiene. Purification of the residue over silica gel, eluting with 70:30 (hexanes−EtOAc), gave 1.69 g (57%) of **2** as a colorless oil. ^{1}H and ^{13}C NMR spectra were consistent with those reported in the literature.[8a,b]

3-Benzyl-1-(toluene-4-sulfonyl)-3,4,4a,5,6,8a-hexahydro-1*H*-quinazolin-2-one (11). Toluenesulfonyl isocyanate (0.09 g, 0.5 mmol) was added to a solution of azabicyclo[2.2.2]octene **2** (0.1 g, 0.5 mmol) in C_6H_6 (1.5 mL) at room temperature. The mixture was then heated at reflux for 12 h. The resulting reaction mixture was concentrated in vacuo and dissolved in EtOAc (15 mL). The organic layer was washed with water (2 × 15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue over silica gel, eluting with 7:3 (hexanes−EtOAc), gave (0.091 g, 48%) of urea **11** as a pale yellow solid and (0.095 g, 46%) of the isourea **12** as a yellow oil. **11**: yield 48%; mp 141−144 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 7.9 Hz, 2H), 7.27−7.23 (m, 3H), 7.13 (d, J = 6.2 Hz, 2H), 5.81(d, J = 10.1 Hz, 1H), 5.73 (d, J = 10.1 Hz, 1H), 5.20−5.15 (m, 1H), 4.65 (d, J = 15.0 Hz, 1H), 4.27 (d, J = 15.2 Hz, 1H), 3.25 (t, J = 11.8 Hz,1H), 2.94−2.87 (m, 1H), 2.42 (s, 3H), 2.40−2.37 (m, 1H), 2.07−1.98 (m, 1H), 1.97−1.88 (m, 2H), 1.76−1.65 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 151.2, 143.7, 138.0, 136.4, 129.1, 128.5, 128.2, 127.7, 127.4, 127.3, 54.8, 50.8, 44.5, 29.5, 23.4, 21.5, 20.3 ppm; IR (ATR) υ_{max} 2921, 1669, 1491, 1163 cm^{-1}; MS (ESI-TOF) calcd for $C_{22}H_{24}N_2O_3S$ $[M + Na]^+$ 419.1405, found 419.1404.

***N*-(3-Benzyl-3,4,4a,5,6,8a-hexahydro-benzo[*e*][1,3]oxazin-2-ylidene)-4-methyl-benzenesulfonamide (12).** Yield 46%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.32 Hz, 2H), 7.33−7.23 (m, 5H), 7.21 (d, J = 8.3 Hz, 2H), 5.89−5.84 (m, 1H), 5.60−5.56 (m, 1H), 4.74−4.70 (m, 2H), 4.59 (d, J = 14.6 Hz, 1H), 3.34−3.27 (m, 1H), 3.01−2.94 (m, 1H), 2.38 (s, 3H), 2.16−2.07 (m, 1H), 1.98−1.95 (m, 2H), 1.44−1.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 154.6, 141.3, 141.0, 135.2, 133.3, 128.7, 128.5, 128.2, 128.0, 127.1, 122.9, 73.9, 53.5, 46.6, 29.3, 23.3, 21.4, 21.1; IR (ATR) υ_{max} 2923, 1570, 1473, 1288, 1135 cm^{-1}; MS (ESI-TOF) calcd for $C_{22}H_{24}N_2O_3S$ $[M + Na]^+$ 419.1405, found 419.1404.

***N*-(3-Benzyl-3,4,4a,5,6,8a-hexahydro-benzo[*e*][1,3]thiazin-2-ylidene)-4-methyl-benzenesulfonamide (13).** *p*-Toluenesulfonyl isothiocyanate (0.053 g, 0.25 mmol) was added to a solution of azabicyclooctene **2** (0.049 g, 0.25 mmol) in benzene (2 mL) at room temperature. The reaction was maintained at room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo and dissolved in EtOAc (5 mL). The organic layer was washed with water (2 × 5 mL) and brine (5 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified over silica gel, eluting with 7:3 (hexanes−EtOAc) and then 10:90 (CH_2Cl_2−acetone) to afford isothiourea **13** (0.083 g, 81%) as a yellow oil. **13**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.8 (d, J = 8.1 Hz, 2H), 7.31−7.25 (m, 3H), 7.23−7.19 (m, 4H), 5.90−5.85 (m, 1H), 5.62−5.56 (m, 1H), 4.78 (s, 2H), 3.91−3.85 (m, 1H), 3.46 (dd, J = 4.7 Hz, 1H), 3.21 (dd, J = 6.8 Hz, 1H), 2.39 (s, 3H), 2.26−2.18 (m, 1H), 2.08−1.96 (m, 2H), 1.66−1.59 (m, 1H), 1.44−1.36 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 164.8, 141.9, 140.0, 135.6, 131.3, 128.8, 128.6, 128.2, 127.9, 126.8, 123.8, 55.0, 52.5, 42.4, 33.0, 23.4, 22.0, 21.3 ppm; IR (ATR) υ_{max} 2922, 1523, 1403, 1143, 912 cm^{-1}; MS (ESI-TOF) calcd for $C_{22}H_{24}N_2O_2S_2$ $[M + Na]^+$ 435.1177, found 435.1173.

***N*-(1,3-Dibenzyl-1,3,4,4a,5,7a-hexahydro-cyclopentapyrimidin-2-ylidene)-4- methylbenzenesulfonamide (15).** Aza-norbornene **1** (0.10 g, 0.54 mmol) and EtN*i*-Pr_2 (0.09 mL, 0.54 mmol) were added to a solution of EDCI (0.10 g, 0.54 mmol), thiourea **14** (0.17 g, 0.54 mmol) in $CHCl_3$ (5 mL) under N_2 at room temperature. After stirring overnight at room temperature, the reaction mixture was poured into a mixture of EtOAc (10 mL) and 0.25 M aqueous citric acid (10 mL). The layers were separated; the organic layer was washed with 0.25 M aqueous citric acid (5 mL), water (2 × 5 mL), brine (5 mL), dried (Na_2SO_4), and concentrated. Purification of the crude product over silica gel, eluting with 2:3 (hexanes−EtOAc), gave 0.170 g (67%) of **15** as a colorless oil. **15**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, J = 8.1 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.31- 7.05 (m, 10H), 5.76 (s, 2H), 5.22 (d, J = 15.2 Hz, 1H), 4.79 (d, J = 14.6 Hz, 1H), 4.62 (d, J = 14.5 Hz, 1H), 4.39 (d, J = 15.2 Hz, 2H), 4.26 (d, J = 9.0 Hz, 1H), 3.20 (m, 1H), 2.98 (m, 1H), 2.54 (m, 1H), 2.30 (s, 3H), 1.72 (d, J = 17.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 157.9, 143.5, 140.5, 137.2, 136.4, 133.5, 128.9, 128.8, 128.7, 128.6, 128.4, 127.9, 127.8, 127.5, 125.3, 64.0, 54.7, 53.6, 47.4, 37.2, 36.3, 20.9 ppm; FTIR (film) 1527 cm^{-1}; MS (FAB-magnetic sector) m/z 478.2128 (MLi, 478.2141 calcd for $C_{28}H_{29}N_3O_2SLi$).

(3-Benzyl-1-hexyl-1,3,4,4a,5,7a-hexahydro-cyclopentapyrimidin-2-ylidene)-carbamic acid ethyl ester (17). Aza-norbornene **1** (0.26 g, 1.4 mmol) and EtN*i*-Pr_2 (0.37 g, 2.8 mmol) were added to a solution of 2-chloro-1-methyl pyridinium iodide (0.37 g, 1.4 mmol) and thiourea **16**[17] (0.34 g, 1.4 mmol), in $CHCl_3$ (10 mL) under N_2 at room temperature. The mixture was then allowed to heat at 80 °C for 5 h with constant stirring. The reaction mixture was then cooled to room temperature and concentrated in vacuo to remove chloroform, and the residue was poured into EtOAc (10 mL) and washed with water (3 × 10 mL) and brine (10 mL). The layers were separated; the organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification over silica gel, eluting with 3:7 (hexanes−EtOAc), gave 0.43 g (76%) of **17** as a brown oil. **17**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31−7.29 (m, 5H), 5.82 (s, 2H), 4.57 (dd, J = 14.6 Hz, J = 37.1 Hz 2H), 4.45 (d, J = 9.7 Hz, 1H), 4.07 (q, J = 6.8 Hz, 2H), 3.56−3.50 (m, 1H), 3.39−3.34 (m, 1H), 3.11−3.07 (m, 1H), 2.94−2.90 (m, 1H), 2.66−2.60 (m, 1H), 2.45−2.40 (m, 1H), 1.83 (d, J = 15.6 Hz, 1H), 1.70−1.62 (m, 2H), 1.31 (s, 6H), 1.24 (t, J = 6.8 Hz, 3H), 0.89 (t, J = 6.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 161.5, 158.7, 136.5, 132.6, 129.4, 128.5, 128.4, 127.5, 65.0, 60.3, 53.3, 49.4, 46.8, 36.4, 36.3, 31.3, 27.9, 26.4, 22.4, 14.8, 13.8 ppm; IR (ATR) υ_{max} 2928, 2233, 1632, 1515, 1064 cm^{-1}; MS (ESI-TOF) calcd for $C_{23}H_{33}N_3O_2$ $[M + H]^+$ 384.2651, found 384.2645.

3-Benzyl-2-*tert*-butoxycarbonylimino-2,3,4,4a,5,7a-hexahydro-cyclopentapyrimidine-1-carboxylic acid *tert*-butyl ester (19). The same procedure was used as in the synthesis of guanidine **15** except that thiourea **18**[18] (0.24 g, 0.86 mmol) was used instead of **14**. Purification of the residue over silica gel eluting with 1:1 (hexanes−EtOAc) afforded the guanidine **19** (0.19 g, 51%) as a colorless solid: mp 113−115 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30−7.26 (m, 5H), 5.79 (d, J = 23.9 Hz, 2H), 5.50 (d, J = 9.2 Hz, 1H), 4.85 (d, J = 14.6, 1H), 4.58 (d, J = 14.64 Hz, 1H), 3.35 (dd, J = 4.3 Hz, 1H), 2.95−2.90 (m, 1H), 2.88 (d, J = 13.1 Hz, 1H), 2.42 −2.36 (m, 1H), 1.66 (d, J = 16.1 Hz, 1H), 1.51 (d, J = 5.3 Hz, 18 H); ^{13}C NMR (125 MHz, $CDCl_3$) 159.7, 154.0, 151.5, 136.6, 134.4, 129.8, 128.8, 128.4 127.7, 82.1, 78.3, 63.2, 52.7, 48.9, 38.0, 37.1, 28.5, 28.2 ppm; IR (ATR) υ_{max} 2975, 2852, 1714, 1674, 1579, 1366, 1131 cm-1; MS (ESI-TOF) calcd for $C_{24}H_{33}N_3O_4$ $[M + H]^+$ 428.2549, found 428.2545.

2,2,5,7,8-Pentamethyl-chroman-6-sulfonic acid (1,3-dibenzyl- 1,3,4,4a,5,7a-hexahydro-cyclopentapyrimidin-2-ylidene)-amide (21). The same procedure was used as in the synthesis of guanidine **15** except that thiourea **20**[9] (0.519 g, 1.20 mmol) was used instead of **14**. Purification of the residue over silica gel eluting with 2:3 (hexanes−EtOAc) gave 0.596 g (85%) of **21** as a colorless solid. **21**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32−7.20 (m, 10H), 5.83−5.80 (m, 1H), 5.78−5.75 (m, 1H), 5.28 (d, J = 15.4 Hz, 1H), 4.82 (d, J = 14.7

dx.doi.org/10.1021/jo401810p | J. Org. Chem. 2013, 78, 11772−11782

Hz, 1H), 4.53 (d, J = 14.7 Hz, 1H), 4.43 (d, J = 15.4 Hz, 1H), 4.28–4.25 (m, 1H), 3.25–3.21 (m, 1H), 3.00–2.96 (m, 1H), 2.57 (s, 4H), 2.54 (s, 3H), 2.38–2.31 (m, 1H), 2.07 (s, 3H), 1.76 (t, J = 6.7 Hz, 3H), 1.26–1.25 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) 157.7, 152.2, 137.5, 136.5, 136.4, 134.3, 133.5, 133.1, 129.1, 128.6, 128.3, 128.1, 127.8, 127.6, 127.3, 123.0, 117.2, 73.3, 64.3, 55.1, 54.2, 48.0, 37.9, 37.0, 33.3, 26.7, 21.4, 18.8, 17.5, 12.0 ppm.

_N_-(1,3-Dibenzyl-1,3,4,4a,5,7a-hexahydro-cyclopentapyrimidin-2-ylidene)-_C,C,C_-trifluoro-methanesulfonamide (22). Aza-norbornene **1** (0.098g, 0.53 mmol) and EtNi-Pr$_2$ (0.14 g, 1.07 mmol) were added to a solution of 2-chloro-1-methyl pyridinium iodide (0.13 g, 0.53 mmol) and thiourea **5** (0.15 g, 0.53 mmol) in $CHCl_3$ (10 mL) under N_2 at room temperature. After stirring overnight at room temperature, the reaction mixture was concentrated in vacuo to remove chloroform, and the residue was poured into EtOAc (10 mL) and washed with water (2 × 15 mL) and brine (10 mL). The layers were separated; the organic layer was dried over Na_2SO_4 and concentrated in vacuo. Purification of the crude product over silica gel, eluting with 60:40 (hexanes–EtOAc), gave 0.14 g (62%) of **22** as a colorless oil. **22**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.29 (m, 10H), 5.83 (d, J = 12.2 Hz, 2H), 5.41 (d, J = 15.1 Hz, 1H), 4.98 (d, J = 15.1 Hz, 1H), 4.66 (d, J = 14.6 Hz, 1H), 4.44 (d, J = 15.1 Hz, 1H), 4.29 (d, J = 8.7 Hz, 1H), 3.20 (dd, J = 4.8 Hz, J = 13.1 Hz, 1H), 3.04 (dd, J = 5.8 Hz, J = 12.7 Hz, 1H), 2.57–2.53 (m, 1H), 2.40–2.35 (m, 1H), 1.83 (d, J = 15.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 158.3, 136.0, 135.2, 134.0, 128.9, 128.8, 128.3, 128.2, 121.3 (q), 64.1, 55.3, 53.8, 47.6, 36.9, 36.4 ppm; IR (ATR) υ_{max} 2929, 1541, 1507, 1320, 737 cm^{-1} MS (ESI-TOF) calcd for $C_{22}H_{22}F_3N_3O_2S$ [M + Na]$^+$ 472.1283, found 472.1282.

_N_-(1,3-Dibenzyl-3,4,4a,5,6,8a-hexahydro-1_H_-quinazolin-2-ylidene)-_C,C,C_-trifluoromethanesulfonamide (23). Aza-bicyclo-[2.2.2]octene **2** (0.19 g, 1 mmol) and EtNi-Pr$_2$ (0.51 g, 4 mmol) were added to a solution of 2-chloro-1-methyl pyridinium iodide (0.51 g, 2 mmol) and thiourea **5** (0.59 g, 2 mmol) in $CHCl_3$ (8 mL) at room temperature under N_2 with stirring. The resulting mixture was heated at 80 °C for 10 h after which time it was concentrated. The resulting crude was dissolved in EtOAc (15 mL) and washed with water (2 × 20 mL) and brine (15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. Purification of the crude product over silica gel eluting with 60:40 (hexanes–EtOAc) afforded 0.26 g (57%) of the guanidine **23** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.29 (m, 10 H), 5.79–5.75 (m, 1H), 5.64–5.62 (m, 1H), 5.53 (d, J = 15.1 Hz, 1H), 5.09 (d, J = 14.6 Hz, 1H), 4.69 (d, J = 14.6 Hz, 1H), 4.44 (d, J = 15.1 Hz, 1H), 3.81–3.79 (m, 1H), 3.14–31.0 (m, 2H), 2.12–2.02 (m, 1H), 1.96–1.88 (m, 1H), 1.61–1.56 (m, 2H), 1.25–1.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 155.0, 135.4, 135.1, 130.3, 128.9, 128.7, 128.3, 128.1, 128.2, 123.7, 121.4 (q), 55.9, 53.7, 52.8, 46.0, 28.8, 21.9, 21.4, 21.0 ppm; IR (ATR) υ_{max} 2929, 1553, 1497, 1314, 1206, 911 cm^{-1}; MS (ESI-TOF) calcd for $C_{23}H_{24}F_3N_3O_2S$ [M + H]$^+$ 464.1620, found 464.1617.

2-Benzyl-2-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid ethyl ester (3a, 3b). Benzylamine hydrochloride (29 g, 0.21 mol) was dissolved in water (25 mL), to which a 50% solution of ethyl glyoxylate in toluene (25 g, 0.24 mol) and cyclopentadiene (26 g, 0.40 mol) were added. The mixture was stirred at room temperature until TLC indicated no further accumulation of adduct (35 h). The resulting aqueous mixture was washed with ether (2 × 30 mL), the pH adjusted to 9–10 with $NaHCO_3$, and the layer extracted with EtOAc (30 mL). The organic layer was separated, washed with brine (30 mL), dried over $MgSO_4$, and concentrated in vacuo. Purification of the crude on silica gel, eluting with 70:30 (hexanes–EtOAc), gave (30.3 g, 53%) of the exoisomer and (14.0 g, 27%) of the endoisomer. The spectral data was consistent with published data.[8c]

3-Benzyl-2-oxo-1-(toluene-4-sulfonyl)-2,3,4,4a,5,7a-hexahydro-1_H_-cyclopentapyrimidine-4-carboxylic acid ethyl ester (30). _p_-Toluenesulfonyl isocyanate (0.11 mL, 0.77 mmol) was added to a solution of the _endo_-ethoxycarbonyl aza-norbornene derivative **3a** (0.20 g, 0.77 mmol) in $CHCl_3$ (5 mL) under N_2 with stirring at room temperature. After stirring for 2 h, the reaction mixture was concentrated in vacuo and dissolved in EtOAc (10 mL). The organic layer was washed with water (2 × 10 mL) and brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the residue over silica gel, eluting with 70:30 (hexanes–EtOAc), gave (0.08 g, 24%) of the urea **30** and (0.22 g, 64%) of isourea **31** as colorless oil. **30**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, J = 8.3 Hz, 2H), 7.33 (d, J = 8.3 Hz, 2H), 7.29–7.27 (m, 3H), 7.19–7.16 (m, 2H), 5.74–5.71 (m, 1H), 5.53–5.49 (m, 1H), 5.42 (d, J = 9.7 Hz, 1H), 5.17 (d, J = 14.6 Hz, 1H), 4.26–4.16 (m, 2H), 3.90 (d, J = 14.6 Hz, 1H), 3.58 (s, 1H), 3.54–3.48 (m, 1H), 2.43 (s, 3H), 2.39–2.32 (m, 1H), 1.63–1.56 (m, 1H), 1.29 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.4, 157.3, 141.7, 140.6, 135.1, 134.3, 128.8, 128.7, 128.67, 128.6, 128.2, 126.9, 85.5, 61.7, 56.7, 52.6, 38.7, 33.4, 21.3, 13.4 ppm; IR (ATR) υ_{max} 2924, 1735, 1696, 1422, 1164 cm^{-1}; MS (ESI-TOF) calcd for $C_{24}H_{26}N_2O_5S$ [M + Na]$^+$ 477.1460, found 477.1445.

3-Benzyl-2-(toluene-4-sulfonylimino)-2,3,4,4a,5,7a-hexahydro-cyclopenta[_e_][1,3]oxazine-4-carboxylic acid ethyl ester (31). Yield 64%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 8.3 Hz, 2H), 7.35–7.30 (m, 3H), 7.27–7.23 (m, 4H), 5.86–5.82 (m, 1H), 5.36–5.31 (m, 3H), 4.20–4.07 (m, 2H), 4.05 (d, J = 14.6 Hz, 1H), 3.69 (s, 1H), 3.34–3.29 (m, 1H), 2.39 (s, 3H), 2.36–2.35 (m, 1H), 1.60 (d, J = 17.5 Hz, 1H), 1.15 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 168.9, 157.5, 141.7, 140.7, 138.3, 134.2, 129.3, 128.6, 128.4, 127.9, 126.8, 86.3, 62.2, 58.5, 52.8, 37.9, 36.5, 21.1, 13.7 ppm; IR (ATR) υ_{max} 2249, 1738, 1563, 1465, 1151 cm^{-1}; MS (ESI-TOF) calcd for $C_{24}H_{26}N_2O_5S$ [M + Na]$^+$ 477.1460, found 477.1452.

1,3-Dibenzyl-2-oxo-2,3,4,4a,5,7a-hexahydro-1_H_-cyclopentapyrimidine-4-carboxylic acid ethyl ester (33). Benzyl isocyanate (0.51 g, 3.8 mmol) was added to the _endo_-ethoxycarbonyl aza-norbornene derivative **3a** (0.49 g, 1.9 mmol) under N_2, and the mixture was allowed to heat at 120 °C for 12 h under solvent free conditions. Purification of the resulting deep brown crude over silica gel, eluting with 65:35 (hexanes–EtOAc), gave (0.23 g, 38%) of the urea **33** as a colorless oil. **33**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.20 (m, 10H), 5.84–5.80 (m, 1H), 5.77–5.73 (m, 1H), 5.38 (d, J = 14.6 Hz, 1H), 5.24 (d, J = 15.1 Hz, 1H) 4.20–4.07 (m, 3H), 3.92–3.84 (m, 2H), 3.61 (s, 1H), 3.24–3.15 (m, 1H), 2.38–2.29 (m, 1H), 2.10–1.95 (m, 1H), 1.21 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 171.6, 158.5, 138.2, 137.6, 134.4, 129.1, 128.8, 128.4, 128.3, 128.1, 127.5, 127.1, 61.5, 61.3, 59.2, 50.8, 48.8, 38.7, 36.7, 14.2 ppm; IR (ATR) υ_{max} 1730, 1645, 1227 cm^{-1}; MS (ESI-TOF) calcd for $C_{24}H_{26}N_2O_3$ [M + Na]$^+$ 413.1841, found 413.1837.

1,3-Dibenzyl-5-ethoxyimidazolidine-2,4-dione (34). Yield 39%: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.28 (m, 10H), 4.92–4.88 (d, J = 14.65 Hz, 1H), 4.86 (s, 1H), 4.75- 4.63 (q, J = 14.40 Hz, 2H), 4.24 - 4.20 (d, J = 14.91 Hz, 1H), 3.61- 3.54 (m, 1H), 3.42- 3.35 (m, 1H), 1.19- 1.15 (t, J = 7.07 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.1, 155.2, 135.2, 135.7, 135.3, 128.8, 128.7, 128.6, 128.1, 127.9, 82.6, 62.2, 44.0, 42.3, 14.8 ppm; IR (ATR) υ_{max} 3078, 2922, 177, 1683, 1557, 1202, 695 cm^{-1}; MS (ESI-TOF) calcd for $C_{19}H_{20}N_2O_3$ [M + Na]$^+$ 347.1372, found. 347.1374.

3-Benzyl-2-oxo-1-(toluene-4-sulfonyl)-2,3,4,4a,5,7a-hexahydro-1_H_-cyclopentapyrimidine-4-carboxylic acid ethyl ester (35). _p_-Toluenesulfonyl isocyanate (0.207 g, 1.05 mmol) was added to a solution of the _exo_-ethoxycarbonyl aza-norbornene derivative **3b** (0.27 g, 1.05 mmol) at room temperature. After stirring for 1 h, the reaction mixture was concentrated in vacuo and dissolved in EtOAc (15 mL). The organic layer was washed with water (2 × 15 mL) and brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification of the crude product over silica gel, eluting with 3:2 (hexanes–EtOAc), gave (0.22 g, 47%) of the urea **35** and (0.20 g, 44%) of isourea **36** as a white solid. **35**: mp 125- 127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.7 Hz, 2H), 7.34 (d, J = 8.3 Hz, 2H), 7.29–7.23 (m, 3H), 7.14 (d, J = 7.8 Hz, 2H), 6.12–6.06 (m, 1H), 5.77–5.73 (m, 1H), 5.27–5.23 (m, 1H), 4.97 (d, J = 14.6 Hz, 1H), 4.01–3.90 (m, 2H), 3.88 (d, J = 15.1 Hz, 1H), 3.65 (d, J = 5.8 Hz, 1H), 2.94–2.86 (m, 1H), 2.67–2.59 (m, 1H), 2.55–2.44 (m, 1H), 2.44 (s, 3H), 1.14 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 169.2, 152.7, 143.9, 137.4, 135.6, 133.4, 130.9, 129.2, 128.6, 128.5, 128.2, 127.7, 63.6, 61.7, 57.8, 50.1, 39.1, 32.8, 21.5, 13.8 ppm; IR

dx.doi.org/10.1021/jo401810p | J. Org. Chem. 2013, 78, 11772–11782

(ATR) υ_{max} 1738, 1557, 1298, 733 cm^{-1}; MS (ESI-TOF) calcd for $C_{24}H_{26}N_2O_5S$ $[M + Na]^+$ 477.1460, found 477.1462.

3-Benzyl-2-(toluene-4-sulfonylimino)-2,3,4,4a,5,7a-hexahydro- cyclopent[*e*][1,3]oxazine-4-carboxylic acid ethyl ester (36). Yield 44%: mp 54−56 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J = 8.3 Hz, 2H), 7.30−7.26 (m, 5H), 7.25 (d, J = 9.2 Hz, 2H), 5.89−5.84 (m, 1H), 5.63−5.58 (m, 1H), 5.31−5.26 (m, 1H), 5.01 (d, J = 14.8 Hz, 1H), 4.33 (d, J = 14.8 Hz, 1H), 3.90−3.84 (m, 2H), 3.81−3.74 (m, 1H), 3.04−2.98 (m, 1H), 2.61 (d, J = 15.4 Hz, 1H), 2.46−2.40 (m, 1H), 2.38 (s, 3H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 167.4, 157.3, 141.7, 140.7, 135.1, 134.3, 128.8, 128.7, 128.6, 128.5, 128.2, 126.9, 85.5, 61.7, 56.7, 52.6, 38.7, 33.4, 21.3, 13.4 ppm; IR (ATR) υ_{max} 1735, 1676, 1168, 663 cm^{-1}; MS (ESI-TOF) calcd for $C_{24}H_{26}N_2O_5S$ $[M + Na]^+$ 477.1460, found 477.1452.

2-Benzyl-2-aza-bicyclo[2.2.2]oct-5-ene-3-carboxylic acid ethyl ester (4a, 4b). The same procedure was followed as in the synthesis of **3a**, **3b** except 1,3-cyclohexadiene (21 g, 0.26 mmol) was used instead of cyclopentadiene. Purification of the crude product over silica gel, eluting with 70:30 (hexanes−EtOAc), gave (22.7 g, 42%) of the exoisomer and (8.1 g, 23%) of the endoisomer. The spectral data was consistent with published data.[8c]

3-Benzyl-1-(toluene-4-sulfonyl)-3,4,4a,5,6,8a-hexahydro-1*H*-quinazolin-2-one (37). The same procedure was followed as in the synthesis of **30** except *p*-TsNCO (0.19 g, 0.96 mmol) was added to the aza-bicyclooctene **4a** (0.1 g 0.5 mmol) at room temperature. The resulting mixture was heated at 80 °C for 12 h under solvent-free conditions. Purification of the residue over silica gel, eluting with 65:35 (hexanes−EtOAc), gave (0.09 g, 48%) of the urea **37** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) 7.97 (d, J = 8.5 Hz, 2H), 7.33 (d, J = 8.5 Hz, 2H), 7.26−7.24 (m, 3H), 7.14−7.12 (m, 2H), 5.72 (m, 2H), 5.11 (d, J = 15 Hz, 1H), 5.02 (s, 1H), 4.22−4.11 (m, 2H), 3.82 (d, J = 15 Hz, 1H), 2.68−2.64 (m, 1H), 2.44 (s, 3H), 1.95−1.68 (m, 4H), 1.26 (t, J = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) 170.6, 151.7, 144.0, 137.6, 135.3, 129.2, 128.9, 125.9, 61.9, 58.5, 52.9, 49.9, 36.3, 24.1, 21.5, 20.8, 14.1 ppm; IR (ATR) υ_{max} 1619, 903 cm^{-1}; MS (ESI-TOF) calcd for $C_{25}H_{28}N_2O_5S$ $[M + Na]^+$ 491.1617, found 491.1621.

1-Benzoyl-3-benzyl-1,3,4,4a,5,7a-hexahydro-cyclopentapyrimidin-2-one (47). The same procedure was used as in the synthesis of **6** except that benzoyl isocyanate (0.17 g, 1.1 mmol) was used instead of *p*-TsNCO. Purification of the residue over silica gel, eluting with 2:3 (hexanes−EtOAc), gave 0.35 g (90%) of **47** as a colorless oil: ^1H NMR (500 MHz, $CDCl_3$) δ 7.59−7.24 (m, 10 H), 5.97−5.82 (m, 2H), 5.50−5.36 (m, 1H), 4.61 (d, J = 14.6 Hz, 1H), 4.36 (d, J = 14.6 Hz, 1H), 3.62−3.46 (m, 1H), 3.20−3.09 (m, 1H), 3.03−2.93 (m, 1H), 2.68−2.50 (m, 1H), 2.03−1.88 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) 173.0, 156.7, 137.1, 136.6, 134.0, 131.1, 130.1, 128.6, 128.5, 128.0, 127.9, 127.7, 63.2, 52.0, 48.8, 37.4, 36.5 ppm; FTIR (film) 1712, 1656 cm^{-1}; MS (ESI-ion trap) calcd for $C_{21}H_{20}N_2O_2$ $[M+H]^+$ 333.1603, found 333.1598.

***N*-(Benzylcarbamothioyl)trifluoromethanesulfonamide (5).** A solution of $TfNH_2$ (500 mg, 3.35 mmol) in THF (3 mL) was added dropwise to a suspension of NaH (148 mg, 3.68 g, 60% dispersion in mineral oil) in THF (2 mL) at 0 °C. The cooling bath was removed, and the mixture was maintained at rt for 1 h. BnNCS (0.44 mL, 3.4 mmol) was added, and the mixture was heated at reflux overnight. The reaction mixture was allowed to cool to rt, and H_2O (2 mL) was added. The THF was removed on a rotary evaporator. The residue was taken up in H_2O (8 mL) and washed with CH_2Cl_2 (2 × 15 mL). Aqueous 2 M HCl (3 mL) was added to the aqueous layer, and a precipitate formed. This mixture was extracted with CH_2Cl_2 (3 × 15 mL). The last three organic fractions were combined, dried over Na_2SO_4, and concentrated to afford thiourea **5** (840 mg, 88%), which was used without further purification. Note that thiourea **5** is unstable and undergoes rapid decomposition, and it exhibited decomposition on flash chromatography over silica gel: ^1H NMR (500 MHz, $CDCl_3$) 7.41−7.29 (m, 5H), 4.80 (d, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 175.9, 134.6, 128.9, 128.3, 127.7, 119.2 (q, J = 320 Hz), 50.2 ppm; IR (ATR) 3007, 1543, 1497 cm^{-1}.

General Procedure for BF_3·OEt_2 Catalyzed Isomerization. In a typical procedure, to a solution of aza-norbornene **1** (54.1 mg, 0.291 mmol) in dry benzene (3 mL) under nitrogen was added dropwise *p*-TsNCO (57.4 mg, 0.291 mmol) at ambient temperature. After stirring for 20 min, analysis by TLC indicated complete consumption of starting material and the presence of the urea/isourea isomers **6** and **7**, respectively. The solution was then cooled to 0 °C followed by the dropwise addition of BF_3·OEt_2 (4.1 mg, 0.029 mmol). After the addition was complete, the cooling bath was removed, and the reaction mixture was allowed to stir at room temperature. At the end of 15 min, TLC indicated complete disappearance of the isourea **7** and indicated the presence of only one isomer. The reaction mixture was then diluted with water (5 mL). The benzene was removed in vacuo, and the residue was diluted with EtOAc (5 mL) washed with water (2 × 5 mL). The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The residue was purified by coloumn chromatography on silica gel (20% ethyl acetate in hexanes) to afford **6** 96.5 mg, (87%) as a white foam identical to that prepared using the method for compounds in Table 1.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^1H and ^{13}C NMR spectra for all new compounds and X-ray crystallographic data (CIF) for compounds **19** and **21**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jmadalen@uvm.edu.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support for the discovery and early development of the 1,3-diaza-Claisen rearrangement was provided by Grant CHE-041283 from the NSF. Financial support for the mechanistic work was provided by CHE-1111694. Exact mass measurements were performed at the UCI Mass Spec Facility and the Vermont Genetics Network through Grant 8P20GM103449.

■ REFERENCES

(1) (a) Ishikawa, T.; Kumamoto, T. *Synthesis* **2006**, *8*, 737. (b) Berlinck, B. G. S.; Burtoloso, A. C. B.; Trindade-Silva, A. E.; Romminger, S.; Morais, R. P.; Bandeira, K.; Mizuno, C. M. *Nat. Prod. Rep.* **2010**, *27*, 1871. (c) Berlinck, R. G.; Burtoloso, A. C.; Kossuga, M. H. *Nat. Prod. Rep.* **2008**, *25*, 919. (d) Berlinck, R. G; Kossuga, M. H. *Nat. Prod. Rep.* **2005**, *22*, 516. (e) Berlinck, R. G. *Nat. Prod. Rep.* **1996**, *13*, 377.

(2) Bowser, A. M.; Madalengoitia, J. S. *Org. Lett.* **2004**, *6*, 3409.

(3) Bowser, A. M.; Madalengoitia, J. S. *Tetrahedron Lett.* **2005**, *46*, 2869.

(4) Aranha, R. M.; Bowser, A. M.; Madalengoitia, J. S. *Org. Lett.* **2009**, *11*, 575.

(5) Since our original disclosure of the 1,3-diaza-Claisen rearrangement, Saito has published its application to the ring expansion of vinyl aziridines and vinyl azetidines. (a) Kano, E.; Yamanoi, K.; Koya, S.; Azumaya, I.; Masu, H.; Yamasaki, R.; Saito, S. *J. Org. Chem.* **2012**, *77*, 2142. (b) Koya, S.; Kenichi, Y.; Yamasaki, R.; Azumaya, I.; Masu, H.; Saito, S. *Org. Lett.* **2009**, *11*, 5438.

(6) (a) Iwakawa, T.; Tamura, H.; Murabayashi, A.; Hayase, Y. *Chem. Pharm. Bull.* **1991**, *39*, 1939. (b) Wieland, G.; Simchen, G. *Liebigs Ann. Chem.* **1985**, 2178. (c) Barton, D. H. R.; Elliott, J. D.; Gero, S. D. *J. Chem. Soc., Chem. Commun.* **1981**, 1136. (d) Senning, A. *Acta Chem. Scand.* **1967**, *21*, 1293. (e) Bredereck, H.; Bredereck, K. *Chem. Ber.* **1961**, *94*, 2278. (f) Kessler, H.; Leibfritz, D. *Tetrahedron* **1970**, *26*, 1805. (g) Pruszynski, P. *Can. J. Chem.* **1987**, *65*, 626.

(7) For related 3-aza-Claisen rearrangements, see: (a) Baxter, E. W.; Labaree, D.; Ammon, H. L.; Mariano, P. S. *J. Am. Chem. Soc.* **1990**, *112*, 7682. (b) Mariano, P. S.; Mariano-Dunaway, D.; Huesmann, P. L. *J. Org. Chem.* **1979**, *44*, 124. (c) Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579. (d) Maruya, A.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Thomas, R. J.; Williams, J. O. *J. Chem. Soc,. Perkin Trans. 1* **1992**, 1617. (e) Edstrom, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6690. (f) Nubbemeyer, U. *J. Org. Chem.* **1996**, *61*, 3677. (g) Dong, V. M.; MacMillan, D. W.C. *J. Am. Chem. Soc.* **2001**, *123*, 2448. (h) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726.

(8) (a) Larsen, S. D.; Grieco, P. A. *J. Am. Chem. Soc.* **1985**, *107*, 1768. (b) Grieco, P. A.; Bahsas, A. *J. Org. Chem.* **1987**, *52*, 5746. (c) Bailey, P. D.; Brown, G. R.; Korber, F.; Reed, A.; Wilson, R. D. *Tetrahedron: Asymmetry* **1991**, *2*, 1263. (d) Bailey, P. D.; Wilson, R. D.; Brown, G. R. *Tetrahedron Lett.* **1989**, *30*, 6781.

(9) Flemer, S.; Madalengoitia, J. S. *Synthesis* **2007**, *12*, 1848.

(10) Hoekfelt, B.; Joensson, A. *J. Med. Pharm. Chem.* **1962**, *5*, 240.

(11) Barton, D. H. R.; Fontana, G.; Yang, Y. *Tetrahedron* **1996**, *52*, 2705.

(12) (a) Quin, C. Y.; Li, J. Z.; Fan, E. *Synlett* **2009**, *15*, 2465. (b) Atwal, K. S.; Ahmed, S. Z.; O'Reilly, B. C. *Tetrahedron Lett.* **1989**, *30*, 7313. (c) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540. (d) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677. (e) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933. (f) Yong, Y. F.; Kowalski, J. A.; Lipton, M. A. *J. Org. Chem.* **1997**, *62*, 1540. (g) Kim, K. S.; Qian, L. *Tetrahedron Lett.* **1993**, *34*, 7677. (h) Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D. *J. Org. Chem.* **2000**, *65*, 1566.

(13) Kessler, H.; Leibfritz, D. *Tetrahedron* **1970**, *26*, 1805.

(14) Grieco, P. A.; Parker, D. T.; Fobare, W. F.; Ruckle, R. *J. Am. Chem. Soc.* **1987**, *109*, 5859.

(15) Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83.

(16) Bonin, M.; Romero, J. R.; Grierson, D. S.; Husson, H.-P. *J. Org. Chem.* **1984**, *49*, 2392.

(17) Mamai, A.; Madalengoitia, J. S. *Org. Lett.* **2001**, *3*, 561.

(18) Expósito, A.; Fernádez-Suárez, M.; Iglesias, T.; Muñoz, L.; Riguera, R. *J. Org. Chem.* **2001**, *66*, 4206.