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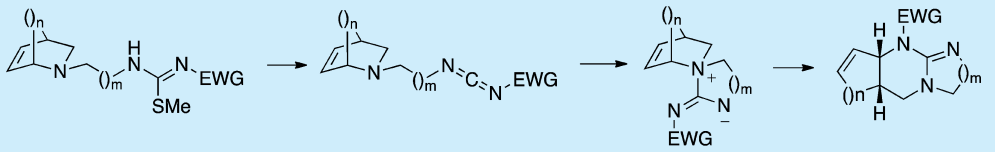
Intramolecular Formation of Zwitterionic Intermediates in 1,3-Diaza-Claisen Rearrangements

Joel D. Walker, Rebecca Watson, Stevenson Flemer, Yanbo Yang, and José S. Madalengoitia*

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

Supporting Information



ABSTRACT: Isothioureas tethered to bridged-bicyclic tertiary allylic amines can be converted to carbodiimides through reaction with Hg(II) salts. Intramolecular cyclization of the tethered tertiary allylic amines to the carbodiimides afford zwitterionic intermediates that undergo 1,3-diaza-Claisen rearrangements, affording highly substituted tricyclic guanidines.

We have previously described methodology for the synthesis of highly substituted guanidines through the in situ generation of an electron-deficient carbodiimide from an isothiourea, thiourea, or urea followed by the addition of a tertiary allylic amine to the carbodiimide affording a zwitterionic intermediate that in turn undergoes a 1,3-diaza-Claisen rearrangement.[1−5] In previously reported examples of the 1,3-diaza-Claisen rearrangement, the overall process involved the intermolecular reaction of the tertiary allylic amine with the carbodiimide. In this work, we investigate systems in which the carbodiimide and tertiary allylic amine are tethered and thus form the zwitterionic intermediate through the intramolecular reaction of these species. Originally, we envisioned the conversion of thioureas **1** into carbodiimides **2** (Figure 1). Attack of the tertiary

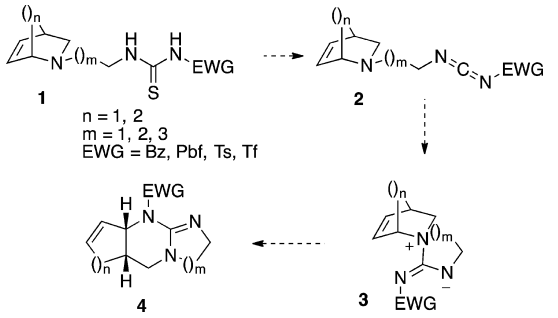


Figure 1. Proposed transformation of thioureas **1** into carbodiimides **2** followed by cyclization to zwitterionic intermediates **3** and rearrangement to guanidines **4**.

allylic amine on the carbodiimide would result in intramolecular formation of zwitterionic intermediate **3** that would in turn rearrange into the tricyclic guanidine **4**. The advantage of the tethered tertiary allylic amine and carbodiimide lies in the formation of an additional ring and thus in an increase in molecular complexity as part of the overall process.

The new proposed rearrangement brought up an interesting electronic/regioisomeric issue. Specifically, in the intermolecular reaction of thiourea **6** with aza-norbornene **5**, the only regioisomer isolated is isomer **7**, in which the electron withdrawing Ts-group results on the imine nitrogen of the guanidine (Figure 2).[1,2] We have never observed the other

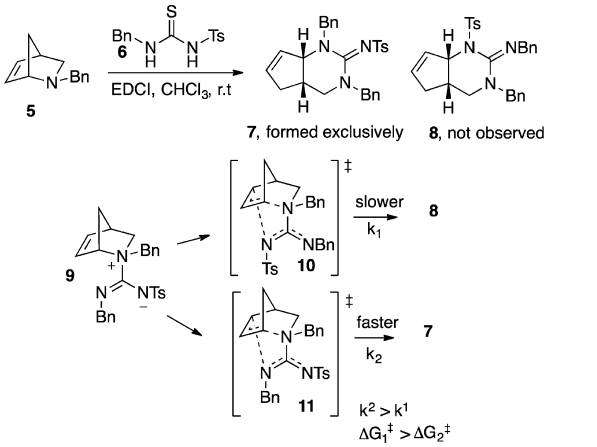


Figure 2. Reaction of aza-norbornene **5** and thiourea **6** affords only regioisomer **7** indicating a higher energy of activation for transition state **10**.

possible regioisomer **8**. This result suggests that isomer **7** forms faster than isomer **8** and that the energy of activation for the formation of **8** is higher than for the formation of **7**. In the proposed intramolecular rearrangement, by necessity, the electron-withdrawing group is constrained by the system to not end up on the imine nitrogen. It was thus unknown at the start of

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the project whether the intramolecular rearrangement would be feasible due to the less than ideal electronics.

Our initial studies focused on the synthesis of the aza-norbornene tethered through a three-carbon chain to the thiourea (Figure 3). LAH reduction of the commercially available

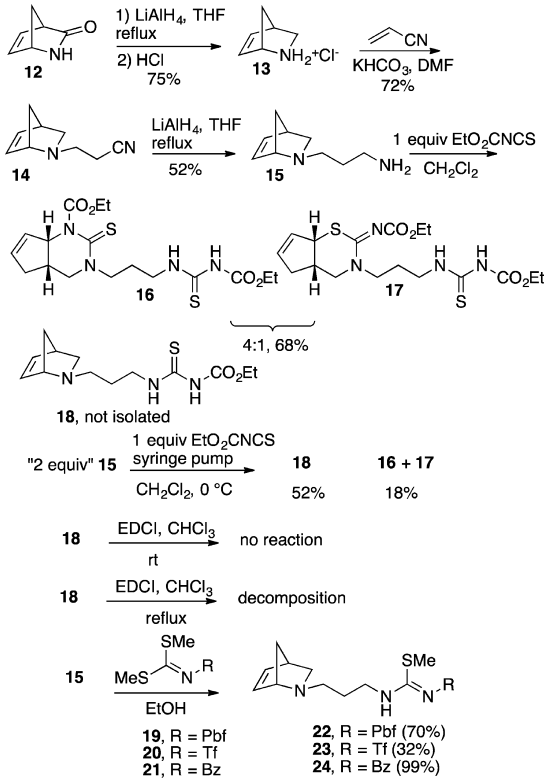

Figure 3. Synthesis of amine **15** from lactam **12**. Reaction of a 1:1 stoichiometry of **15** with EtO_2NCS did not afford the desired thiourea **18** but rather the isomers **16** and **17**. Reaction of a 2:1 stoichiometry of **15** to EtO_2CNCS afforded the thiourea **18** in 52% yield. Attempted carbodiimide formation from **18** with EDCI did not afford any rearrangement product. However, isothioureas **22**–**24** could be synthesized from the reaction of **15** with carbodithioimidates **19**–**21** as alternative carbodiimide precursors to the corresponding thioureas.

lactam **12** in THF at reflux followed by isolation of the amine as the hydrochloride salt afforded the salt **13** in 75% yield.[6] In situ generation of the free base of the hydrochloride salt **13** with $KHCO_3$ in DMF followed by conjugate addition to acrylonitrile afforded the nitrile **14** in 72% yield with the requisite three-carbon chain appropriately functionalized for conversion to the urea. Reduction of the nitrile **14** with LAH in Et_2O at reflux afforded the primary amine **15** in 52% yield. However, the attempted reaction of amine **15** with ethoxycarbonyl isothiocyanate did not afford any of the desired thiourea **18**. Instead, the regioisomeric products **16** and **17** in which isothiocyanate had reacted with aza-norbornene at both the primary and tertiary amine were isolated as a 4:1 mixture, respectively, in 68% yield.

The isolation of products **16** and **17**, resulting from the reaction of amine **15** with 2 equiv of isothiocyanate, prompted us to investigate an alternative strategy. The reaction was run by syringe pump addition of ethoxycarbonyl isothiocyanate to a solution of 2 equiv of amine in CH_2Cl_2 at 0 °C. The idea behind this strategy was that under these reaction conditions, as thiourea **18** begins to form, the slowly added isocyanate would react with amine **15** preferentially over the thiourea **18** due to the higher concentration of amine **15**. Indeed, this experimental setup resulted in the isolation of thiourea **18** in 52% yield. However, products **16** and **17** were still formed in 18% combined yield. With thiourea **18** in hand, we subjected **18** to carbodiimide formation conditions (EDCI, $CHCl_3$), but thiourea **18** did not undergo any reaction. This was surprising to us since the transformation of thioureas to carbodiimides by EDCI and the subsequent trapping of carbodiimides by amines is, from our experience, a fast process (usually complete in less than 15 min).[7] The reaction was also attempted under forcing conditions (heating at reflux), but this resulted in decomposition. Attempted formation of the carbodiimide with the Mukayiama salt at room temperature and at elevated temperatures also failed to yield any rearrangement product (data not shown). We have also investigated the reaction of amine **15** with the more reactive TsNCS using the syringe pump addition of TsNCS to 2 equiv of amine **15**, but with this more reactive isocyanate, the corresponding thiourea was only obtained in 24% yield and attempted rearrangements of this thiourea also failed (data not shown). All these combined results suggested that perhaps we needed a different, less reactive, carbon(IV) source than an isocyanate and a different carbodiimide precursor than a thiourea. Aryl sulfonyl *S*,*S*-dimethyl carbodithioimidates seemed ideal reagents for our purposes as they are far less reactive than isothiocyanates and react with amines to give isothioureas that can be readily converted to carbodiimides with thiophilic metals.[8−11] Indeed, the amine **15** reacted with carbodithioimidates **19**–**21** to give the corresponding isothioureas **22**–**24** bearing a range of electron withdrawing groups to allow determination of the electron-withdrawing group effect on the rearrangement.[12,13]

With the synthesis of the analogues with a three-carbon-tether between aza-norbornene and the isothiourea complete, attention was refocused on completing the synthesis of the two- and four-carbon-tethered analogues. Reaction of glycine methyl ester hydrochloride with aqueous formaldehyde and cyclopentadiene afforded aza-norbornene **25** in 83% yield through the hetero-Diels–Alder reaction (Figure 4).[14] Ammonolysis of the ester in a saturated methanol solution afforded the amide **26** in 89% yield. Finally, LAH reduction of the amide in THF at reflux followed by reaction of the subsequent amine **27** with carbodithioimidate **19** afforded the isothiourea **28** in 55% yield for both steps. It is worth noting that we found the amine **27** volatile and was best used

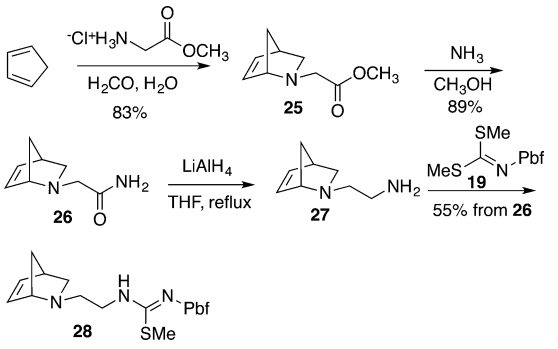

Figure 4. Hetero-Diels–Alder of cyclopentadiene with in situ generated iminium ion from formaldehyde and glycine methyl ester hydrochloride affords the aza-norbornene **25**. Ammonolysis of **25** affords the amide **26** that is reduced to the amine **27** with LAH. Reaction of amine **27** with **19** affords the isothiourea **28**.

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immediately after the Fieser workup without removing the THF solvent under vacuum.

The synthesis of the four-carbon-tethered analogue was completed by an analogous strategy used above (Figure 5).

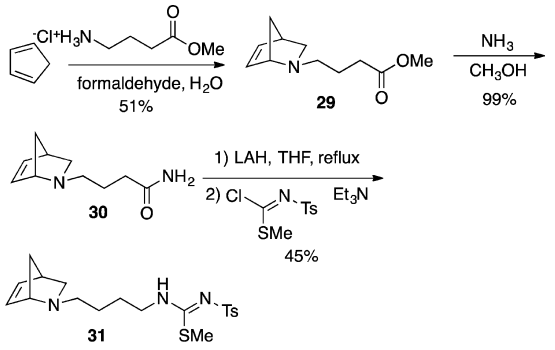

Figure 5. Hetero-Diels–Alder reaction of cylcopentadiene with in situ generated iminium ion derived from formaldehyde and methyl 4-amino butyrate hydrochloride affords aza-norbornene **29**. Ammonolysis of ester affords amide **30**. LAH reduction of amide and reaction of amine with Pbf-carbonochloridoimidothioate affords isothiourea **31**.

Hetero-Diels–Alder reaction of methyl 4-aminobutyrate hydrochloride with aqueous formaldehyde and cyclopentadiene afforded the aza-norbornene **29** with the requisite four-carbon tether in 51% yield. Ammonolysis of the ester smoothly gave the amide **30** in 99% yield. LAH reduction of the amide afforded the amine that was carried on to the following reaction without purification. Curiously, while we had had success in the reaction of primary amines with *S*,*S*-dimethyl carbodithioimidate **19** to make isothioureas, the amine derived from the reduction of amide **30** failed to afford any of the corresponding isothiourea. We investigated several reaction conditions, including different solvents, elevated temperatures as well as neat conditions without any success. As such, we explored the reaction of the amine with methyl tosylcarbonochloridoimidothioate which did afford the corresponding isothiourea **31** in 45% yield from the amide **30**.[15,16] While in the series of homologues **22** and **28** we have been working with Pbf-protected isothioureas, the tosylisothiourea **31** breaks this trend. The synthesis of methyl Pbf-carbonochloridoimidothioate was attempted by heating **29** with sulfuryl dichloride in CH_2Cl_2, but instead of the desired product, the product obtained was consistent with free-radical chlorination of a benzylic position of the Pbf group. We expect the Pbf and Ts to behave similarly, despite the many more electron-releasing groups on the aromatic group.

The final rearrangement precursor was synthesized as described in Figure 6. Reduction of the known lactam **32** with

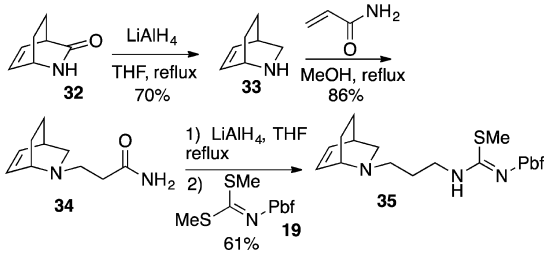

Figure 6. LAH reduction of lactam **32** affords amine **33**. Conjugate addition of **33** to acrylamide gives amide **34**. LAH reduction of the amide and subsequent reaction of the amine with **19** yields isothiourea **35**.

LAH in THF according the procedure of Malpass gave the amine **32** in 70% yield.[17] Conjugate addition of the amine **32** to acrylamide was accomplished by heating in MeOH at reflux for 3 h to afford the isoquinuclidene **33** with the three-carbon tether in 86% yield. LAH reduction of the amide and subsequent reaction of the corresponding amine with carbodithioimidate **19** afforded the isothiourea **35** in 61% yield for both steps.

With the synthesis of the series of representative isothioureas complete, effort was focused on the critical one pot carbodiimide formation, cyclization to form the zwitterionic intermediate, followed by rearrangement to afford the corresponding guanidines. Reaction of isothiourea **28** with $HgCl_2$ in the presence of Et_3N in DMF gratifyingly afforded the tricyclic guanidine **36** in 82% yield (Figure 7). We had originally thought

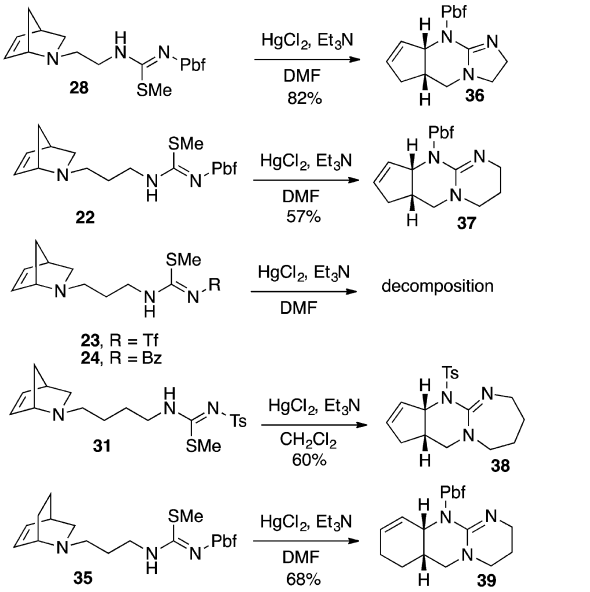

Figure 7. Activation, cyclization, and rearrangement of isothioureas.

that this rearrangement would be challenging because examination of models suggested that for a suprafacial–suprafacial rearrangement, the orbital alignment was not optimal for such a rigid framework (Figure 8). This suboptimal orbital arrangement,

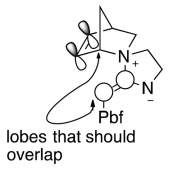

Figure 8. Orbital overlap necessary for rearrangement.

however, may be compensated for by the coupling of bond breakage to the release ring strain in the transition state. It is also noteworthy that the rearrangement proceeded in spite of the less than ideal electronics (noted in Figure 2) in which the electron-withdrawing group cannot end up on the imine nitrogen. This result suggests that while transition state **11** may have a higher energy of activation than transition state **10**, the energy of activation for transition state **11** is still lower than for a transition state not possessing an electron-withdrawing group.

Reaction of isothiourea **22** (possessing a three-carbon tether) with $HgCl_2$ and Et_3N in DMF afforded the tricyclic guanidine **37** in 57% yield. We have additionally investigated the desulfuriza-

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tion of isothiourea **22** with AgCl as a greener alternative to $HgCl_2$ and have found that the guanidine **37** is obtained in comparable yield (data not shown). Interestingly, it appears that an aryl sulfonyl group is close to an optimal electron-withdrawing group for these rearrangements with the mismatched electronics since the attempted rearrangement of isothiourea **23** with a more powerfully electron-withdrawing trifluoromethylsufonyl group afforded a complex mixture, and the attempted reaction of isothiourea **24** with the less powerfully electron-withdrawing benzoyl group also ended in decomposition. The reaction of the four-carbon tethered isothiourea **31** with $HgCl_2$ and Et_3N in CH_2Cl_2 smoothly afforded the tricyclic guanidine **38** in 60% yield. Finally, the reaction of isothiourea **35** with Hg(II) in DMF gave the guanidine **39** in 68% yield. This last result is quite significant as in the intermolecular reaction of *N*-benzyl isoquinuclidene with *N*-benzyl-*N*′-tosyl thiourea under no conditions studied was the rearrangement product observed.[2] To undergo the 1,3-diaza-Claisen rearrangement, *N*-benzylisoquinuclidene required *N*-benzyl-*N*′-Tf thiourea and heating at 60 °C overnight (Figure 9).[2] In contrast, isothiourea **35** converted to

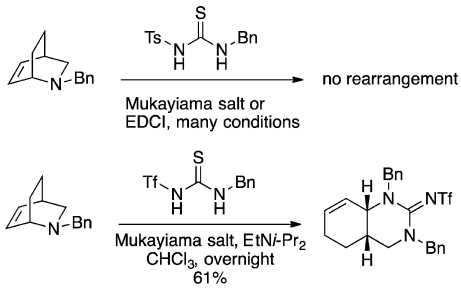

Figure 9. *N*-Bn isoquinuclidene does not undergo rearrangement with carbodiimides generated from arysulfonyl thioureas but does with Tf-substituted carbodiimides.

guanidine **39** at room temperature after treatment with $HgCl_2$. These data suggest that if the zwitterionic intermediate is formed intramolecularly, in some instances the overall reaction may proceed even if the analogous intermolecular process fails. We suspect that this may be due to the high reactivity of the in situ-generated *N*-sulfonyl carbodiimides. In the intermolecular reaction, the zwitterionic intermediate is in equilibrium with the carbodiimide and the carbodiimide can then dimerize or trimerize or perhaps participate in other processes other than undergo the 1,3-diaza-Claisen rearrangement.[3,18,19] In contrast, in the intermolecular reaction the formation of the zwitterionic intermediate is much more entropically favored, and thus, the carbodiimide form has less opportunity to trimerize or undergo other reactions before undergoing the 1,3-diaza-Claisen rearrangement.

In conclusion, we have developed methodology for the synthesis of bridged-bicyclic-tertiary allylic amines tethered to isothioureas which when converted to carbodiimides react intramolecularly with the tethered tertiary allylic amines to afford zwitterionic intermediates. The zwitterionic intermediates in turn undergo a 1,3-diaza-Claisen rearrangement to afford highly substituted, tricyclic guanidines. While the tricyclic ring systems of guanidines **36**–**39** do not correspond to the ring systems of any currently known guanidine natural products the 6,6-guanidine ring system contained in **37** and **39** would be analogous to the 6,6-guanidine ring system in some batzelladine alkaloids and the 5,6-guanidine ring system in **36** would be analogous to the 5,6-guanidine ring system in cylindrospermopsin.[20] It is thus possible that the application of the strategy of intramolecular formation of zwitterionic intermediate followed by 1,3-diaza-Claisen rearrangement on the appropriate substrates may be applicable the synthesis of these natural products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01746.

^{1}H NMR spectra for compounds **16**, **18**, and **23**. ^{1}H NMR and ^{13}C NMR spectra for compounds **14**, **15**, **19**, **22**, **24**, **26**, **28**–**30**, **35**–**39** (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jmadalen@uvm.edu.

ORCID

José S. Madalengoitia: 0000-0002-9999-1216

Notes

The authors declare no competing financial interest.

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