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A 1,3-Diaza-Claisen Rearrangement that Affords Guanidines

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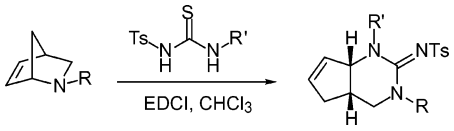
ABSTRACT

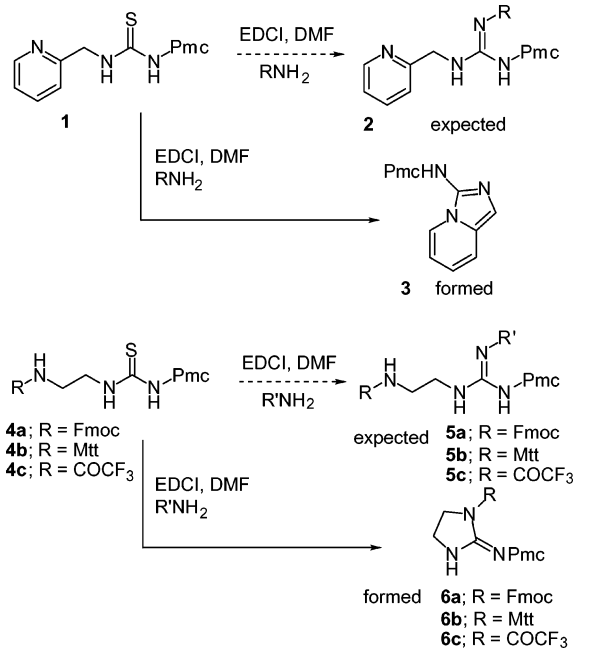


***N*-Alkyl-*N*′-tosylthioureas activated by EDCI react with azanorbonenes at room temperature through a 1,3-diaza-Claisen rearrangement, affording highly substituted, bicyclic guanidines in moderate to good yields.**

The synthesis of guanidines from thioureas is one of the most commons strategies used for the construction of the guanidine functionality.[1−3] In this transformation, a thiourea is activated through reaction with DIC, EDCI, Hg(II), 2-chloro-1-methylpyridinium iodide, 2,4-dinitrofluorobenzene, etc. While we were attempting the synthesis of guanidines **2** and **5a**−**c** from thioureas **1** and **4a**−**c**, respectively, in a reaction mediated by EDCI, we noticed a remarkable reactivity (Scheme 1). In all instances, an intramolecular cyclization pathway was preferred, affording the cyclic guanidines **3** and **6a**−**c**. In particular, the cyclization of **4b** and **4c** in which the nitrogens are highly deactivated through protection with methyltrityl (Mtt) and trifluoromethylacyl groups, respectively, indicates that the activation of the thioureas affords a highly electrophilic intermediate.

The most commonly accepted mechanism for the activation of thioureas involves the transformation of thioureas into carbodiimides. We thus hypothesized that the highly electrophilic intermediate involved in the reactions of Scheme 1 was an *N*-alkyl-*N*′-sulfonyl carbodiimide.[4,5] We further hypothesized that an *N*-alkyl-*N*′-tosyl thiourea (**8**, Scheme 2) would also afford a highly electrophilic *N*-alkyl-*N*′-tosyl carbodiimide **9** on activation with EDCI. We expected that the carbodiimide **9** might be reactive enough to undergo a reaction with azanorbornene **7**, affording the zwitterionic intermediate **10**. In turn, the intermediate **10** would then be

Scheme 1



(1) For examples, see: (a) Atwal, K. S.; Ahmed, S. Z.; O'Reilly, B. C.; *Tetrahedron Lett.* **1989**, *30*, 7313. (b) Poss, M. A.; Iwanowicz, E.; Reid, J. A.; Lin, J.; Gu, Z. *Tetrahedron Lett.* **1992**, *33*, 5933. (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) Linton, B. R.; Carr, A. J.; Orner, B. P.; Hamilton, A. D. *J. Org. Chem.* **2000**, *65*, 1566.

(2) For a review, see: Manimala, J. C.; Anslyn, E. V. *Eur. J. Org. Chem.* **2002**, 3909.

(3) For an alternative synthesis of guanidines from thioureas, see: Ostresh, J. M.; Schoner, C. C.; Hamashin, V. T.; Nefzi, A.; Meyer, J.-P. Houghten, R. A. *J. Org. Chem.* **1998**, *63*, 8622.

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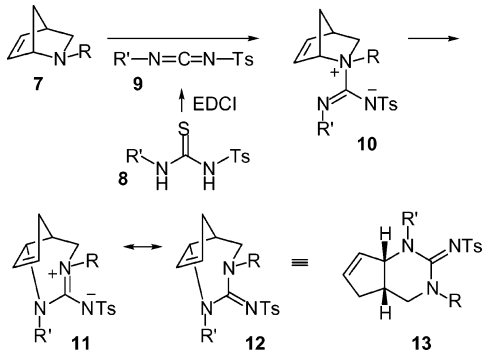
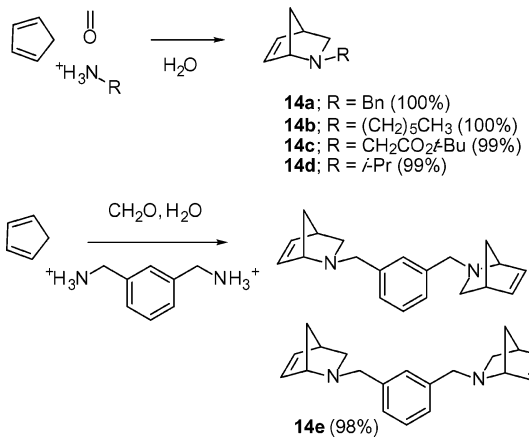
Scheme 2



poised for a 1,3-diaza-Claisen rearrangement, affording the bicyclic guanidine **13** in analogy to the reaction of azanorbornenes with ketenes.[6] Due to the novelty of the transformation and the ease with which it would increase chemical complexity, the feasibility of using highly electrophilic carbodiimides to mediate 1,3-diaza-Claisen rearrangements was investigated.

The synthesis of the azanorbornenes was accomplished as described by Grieco.[7] A solution of cyclopentadiene, formaldehyde, and an amine hydrochloride in water was maintained at room temperature, affording the azanorbornenes **14a**−**d** in uniformly excellent yields (Scheme 3). In addition,

Scheme 3



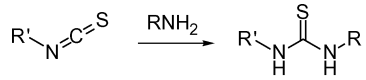
a bis-azanorbornene was synthesized from *m*-xylylenediamine hydrochloride, affording the bis-azanorbornenes **14e** as a mixture of diastereomers.[8] In all, the azanorbornenes are chosen to reflect a range of functionality, sterics, and complexity.

(4) Anslyn has reported that thioureas similar to **4a**, but bearing a benzoyl protecting group instead of a Pmc protecting group, do not undergo intramolecular cyclization on activation with EDCI. This provides further evidence that the unusual reactivity observed is due to the powerful electron-withdrawing nature of the sulfonyl group. Schneider, S. E.; Bishop, P. A.; Salazar, M. A.; Bishop, O. A. Anslyn, E. V. *Tetrahedron*, **1998**, *54*, 15063.

(5) For examples of *N*-sulfonylguanidines from *N*-sulfonylthioureas, see: (a) Zhang, J.; Shi, Y. *Tetrahedron Lett.* **2000**, *41*, 8075. (b) Li, J.; Zhang, G.; Zhang, Z.; Fan, E. *J. Org. Chem.* **2002**, *68*, 1611.

The *N*-alkyl-*N*′-tosyl thioureas **16a**−**e** were synthesized through reaction of either *N*-tosylisothiocyanate or *N*-Pmc-isothiocyanate with primary amines as shown in Scheme 4.[9,10]

Scheme 4

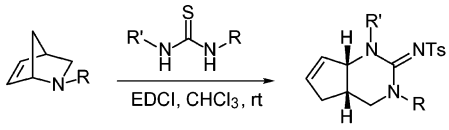


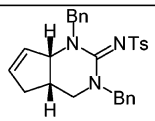
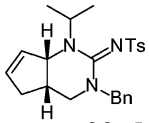
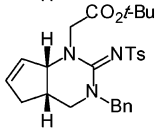
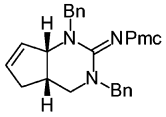
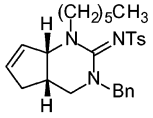
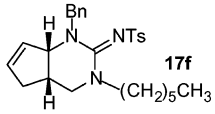
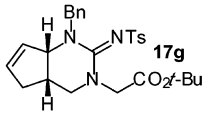
15a; R' = Ts
15b; R' = Pmc

16a; R = Bn, R' = Ts (98%)
16b; R = *i*-Pr, R' = Ts (98%)
16c; R = CH_2CO_2t-Bu, R' = Ts (90%)
16d; R = Bn, R' = Pmc (97%)
16e; R = $(CH_2)_5CH_3$, R' = Ts (93%)

After the completion of the synthesis of a representative set of azanorbornenes and thioureas, the scope and limitations of the rearrangement were investigated (Table 1). The

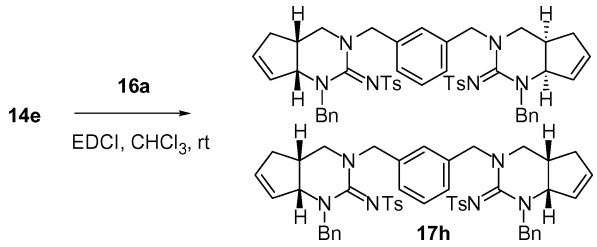
Table 1. EDCI-Mediated Reaction of Azanorbornenes with Thioureas



norbornene	thiourea	yield	product
14a	**16a**	67%	 **17a**
14a	**16b**	72%	 **17b**
14a	**16c**	71%	 **17c**
14a	**16d**	85%	 **17d**
14a	**16e**	77%	 **17e**
14b	**16a**	66%	 **17f**
14c	**16a**	66%	 **17g**
14d	**16a**		NR

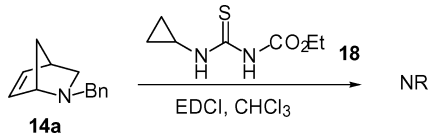
N-benzyl azanorbornene **14a** smoothly underwent reaction with thioureas **16a**−**e**, affording the rearrangement products **17a**−**e** in good to moderate yields. To the best of our knowledge, this work represents the first example of a zwiterionic 1,3-diaza-Claisen rearrangement. It is noteworthy that a set of diverse groups could be tolerated on the thiourea ranging from a fairly hindered isopropyl group (**16b**) to an ester functionality (**16c**). Furthermore, the reaction of the thiourea **16d** bearing a Pmc protecting group indicates that additional sulfonyl groups are also tolerated. We next investigated the reaction of azanorbornenes **14a**−**e** with *N*-benzyl-*N*′-tosylthiourea **16a**. In this instance, the reaction of the azanorbornenes **14b**−**c** with **16a** afforded the rearrangement products **17f** and **17g** in good yields. However, the reaction of the *N*-isopropyl azanorbornene **14d** with **16a** failed to afford any rearrangement product. The unreactivity of **14d** is most likely due to sterics since the nucleophilic tertiary nitrogen is now bonded to two secondary carbons and one primary carbon. Thus, a limitation of this reaction is that it cannot tolerate an azanorbornene substituent that has α-branching. The reaction of the bis-azanorbornenes **14e** with the thiourea **16a** smoothly afforded the diastereomeric guanidines **17h** in 75% yield (Scheme 5). This reaction may thus be useful in the synthesis of multivalent ligands.

Scheme 5



To further explore the scope of the reaction, we attempted the rearrangement of azanorbornene **14a** with the known carbamoyl-protected thiourea **18** (Scheme 6).[11] However, this reaction did not afford any rearrangement product. This suggests that the in situ-generated carbodiimides must bear a strongly electron-withdrawing substituent (such as sulfonyl) for the transformation to proceed. However, it is not known at this juncture if the strongly electron-withdrawing group

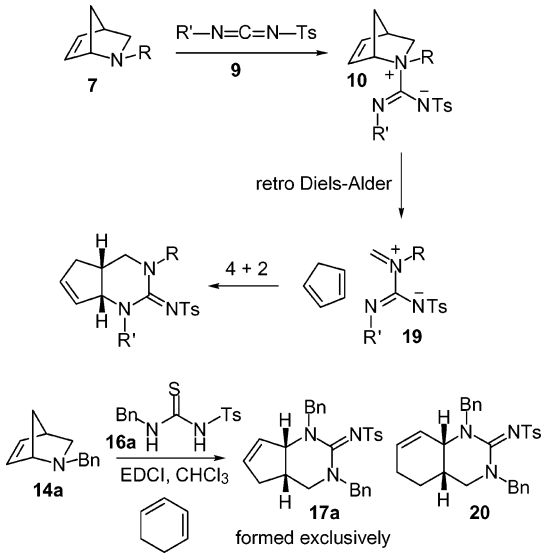
Scheme 6



is required for the addition step, the rearrangement step, or both steps.

An alternative mechanistic pathway was also explored. Grieco has reported that the azanorbornenes are highly prone to a retro-Diels−Alder reaction when the nitrogen bears a positive charge.[12] Therefore, an alternative mechanistic pathway could be envisioned as arising from a retro-Diels−Alder reaction of the zwitterionic intermediate **10** (Scheme 7), affording cyclopentadiene and the 1,4-dipole **19**. The 1,4-

Scheme 7



dipole **19** and cyclopentadiene could in turn react by a 4 + 2 cycloaddition, furnishing the cyclic guanidine. To rule out this potential pathway, we designed a crossover experiment in which the rearrangement of **14a** was run in the presence of cyclohexadiene. If the retro-Diels−Alder pathway were viable, one would expect that **17a** would be formed along with its homolgue **20**. However, when the experiment was conducted, only **17a** could be detected. This result rules out the possibility that the "rearrangement" product arises from the retro-Diels−Alder pathway.

The regiochemistry of the rearrangement was also investigated, as two potential regioisomeric products are possible. It may be envisioned, for example, that a zwitterionic intermediate **21** may rearrange to afford the guanidine **24** or its thermodynamically more stable regioisomer **17d** (Scheme

(6) For examples of aza-Claisen rearrangements, see: (a) Maurya, R.; Pittol, C. A.; Pryce, R. J.; Roberts, S. M.; Thomas, R. J.; Williams, J. O. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1617. (b) Yoon, T. P.; Dong, V. M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **1999**, *121*, 9726. (c) Cid, M. M.; Pombo-Villar, E. *Helv. Chim. Acta* **1993**, *76*, 1591. (d) Cid, M. M.; Eggnauer, U.; Weber, H. P.; Pombo-Villar, E. *Tetrahedron Lett.* **1991**, *32*, 7233.

(7) (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.

(8) It is assumed that a ~1:1 mixture of diastereomers is formed. Neither the ^{1}H NMR and ^{13}C NMR spectra nor TLC indicate the presence of two diastereomers, but this is not surprising, as the diastereomers are expected to have very similar physical properties.

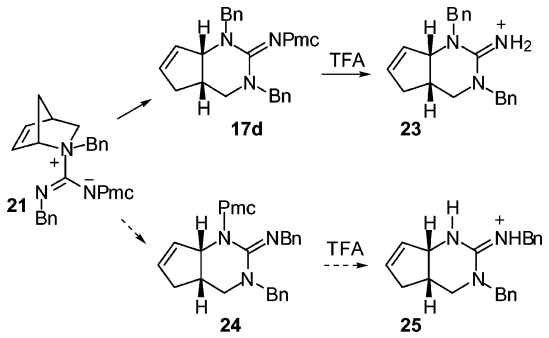
(9) (a) Compper, R.; Haegle, W. *Chem. Ber.* **1966**, *99*, 2885. (b) Barton, D. H. R.; Fontana, G.; Yang, Y. *Tetrahedron* **1996**, *52*, 2705.

(10) Synthesis of *N*-Pmc-isothiocyanate will be reported separately.

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

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

Scheme 8



8). In the reaction of ketenes, with azanorbornenes, the product is an amide, thus suggesting that the propensity in these rearrangements is for the most electronegative atom to end up double bonded and exocyclic in the product. This suggests that **17d** (in which NPmc is double bonded and exocyclic) should be the major product. To unambiguously establish this, the product of the reaction of **14a** with **16d** was subjected to Pmc deprotection with TFA. TOCSY spectroscopy of this sample revealed that the exchangeable protons did not exhibit a cross-peak with any other protons, indicating that the deprotected product is **23** and the rearrangement product is **17d**. It is expected by analogy that the reaction of the *N*-tosyl thioureas with azanorbornenes also proceeds with the same regiochemistry.

In conclusion, this paper describes a novel EDCI-mediated reaction between *N*-sulfonyl thioureas and azanorbornenes that we propose proceeds through a 1,3-diaza-Claisen rearrangement and affords guanidines. The reaction proceeds in modest to good yields and is fairly functional group tolerant.

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Supporting Information Available: Representative experimental conditions, characterization data, and copies of ^{1}H NMR and ^{13}C spectra for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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