ORGANIC LETTERS

2009
Vol. 11, No. 3
575−578

Facile 1,3-diaza-Claisen Rearrangements of Tertiary Allylic Amines Bearing an Electron-Deficient Alkene

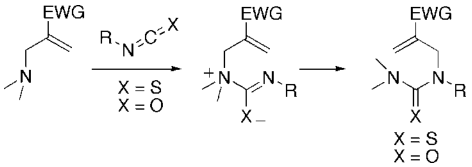
Rachel M. Aranha, Amy M. Bowser, and Jose S. Madalengoitia*

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

jmadalen@uvm.edu

Received November 7, 2008

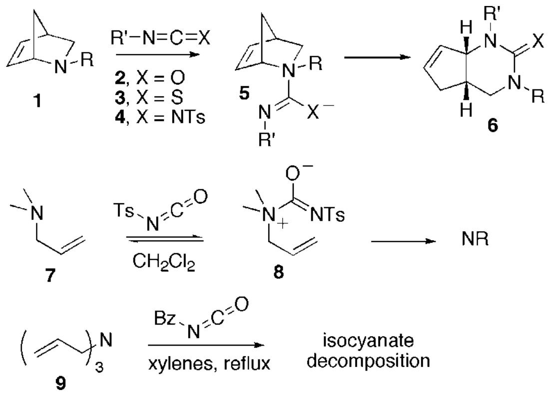
ABSTRACT



Tertiary allylic amines with an electron-deficient alkene react with isocyanates and isothiocyanates to give highly substituted ureas and thioureas arising from formal 1,3-diaza-Claisen rearrangements. Isocyanates and isothiocyanates with strong electron-withdrawing groups are more reactive. Similarly, the data suggest that a stronger electron-withdrawing substituent on the alkene favors a faster reaction, but this may be offset by sterics in the cyclic transition state.

We have previously reported that isocyanates, isothiocyanates, and *N*-sulfonyl-*N*′-alkyl carbodiimides (generated in situ from *N*-sulfonyl-*N*′-alkyl-thioureas) react with azanorbornenes **1** to transiently form zwitterionic intermediates **5** that in turn undergo a 1,3-diaza-Claisen rearrangement to give ureas, thioureas, and guanidines **6**, respectively (Scheme 1).[1−3] Interestingly, attempts to effect this transformation with simpler tertiary allylic amines did not afford the rearrangement product. For example, the attempted reaction of *N*,*N*-dimethylallylamine **7** with TsNCO at rt did not afford the rearrangement product. The evaluation of more forcing conditions (e.g., triallylamine, BzNCO, in xylenes at reflux) resulted only in isocyanate decomposition. These results indicate that 1,3-diaza-Claisen rearrangements with simple tertiary allylic amines are not as facile.

Scheme 1



Since we have previously provided evidence that the rate-determining step appears to be the rearrangement step,[2] our focus became devising a strategy that would lower the energy of activation of the rearrangement step. A review of the Claisen rearrangement literature indicated that an electron-withdrawing group at the 5-position accelerates the rate of the Claisen rearrangement (Figure 1).[4] We therefore hypothesized that

---

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

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

(3) For examples of zwitterionic 3-aza-Claisen rearrangements see: (a) 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. (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. (e) Vedejs, E.; Gingras, M. *J. Am. Chem. Soc.* **1994**, *116*, 579.

10.1021/ol802577z CCC: $40.75

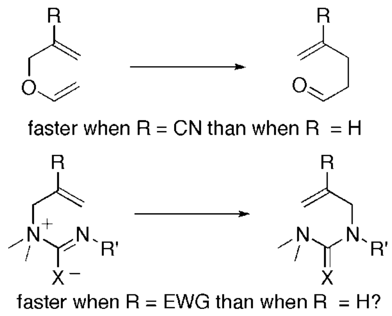
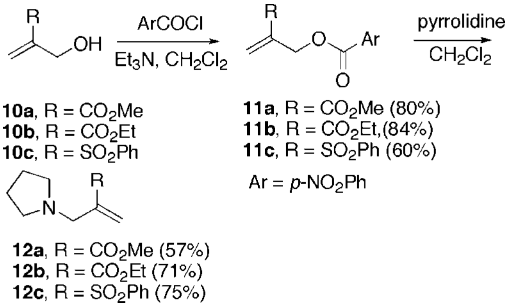


Figure 1. Do electron-deficient alkenes accelerate zwitterionic diaza-Claisen rearrangements in analogy to Claisen rearrangements?

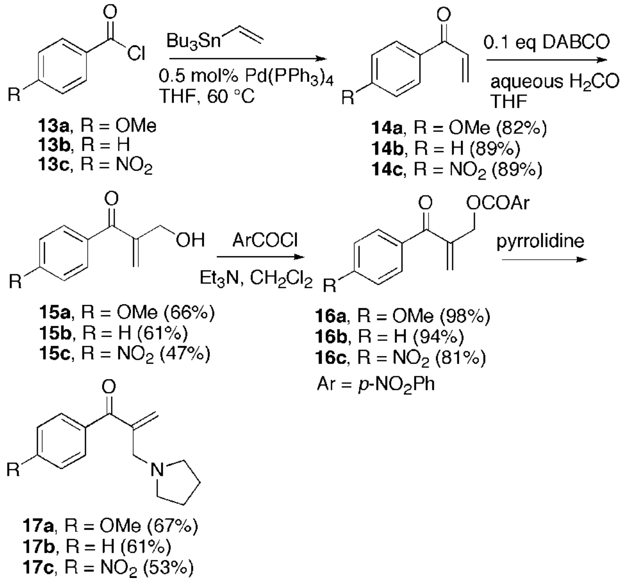
tertiary allylic amines bearing an electron-withdrawing substituent at the analogous position would be better substrates for zwitterionic 1,3-diaza-Claisen rearrangements.

The synthesis of the rearrangement precursors is shown on Schemes 2 and 3. The alcohols **10a**,**b** can be obtained by the Baylis–Hillman reaction of the respective Michael acceptors with formaldehyde.[5] The alcohol **10c** was synthesized by the procedure described by Carpino.[6] Acylation of the alcohol functionality with *p*-NO_2-benzoyl chloride and Et_3N gave the corresponding esters **11a**–**c**. Benzoate displacement in an S_N2'-type fashion with pyrrolidine afforded the rearrangement precursors **12a**–**c**.[5]

Scheme 2



Scheme 3



The synthesis of rearrangement precursors **17a**–**c** begins with the Stille reaction of the corresponding benzoyl chlorides **13a**–**c** with tri-*n*-butylvinyl stannane to give the arylvinylketones **14a**–**c**.[7] DABCO-catalyzed Baylis–Hillman reaction of the unsaturated ketones **14a**–**c** with formaldehyde afforded the alcohols **15a**–**c**. As before, acylation of the alcohols **15a**–**c** with *p*-NO_2-benzoyl chloride gave the esters **16a**–**c**. Finally, S_N2' displacement of the benzoate with pyrrolidine afforded the rearrangement precursors **17a**–**c**. We have found that the *p*-NO_2-benzoyl derived compound **17c** is highly unstable and must be used immediately.

We are pleased to report that indeed tertiary allylic amines bearing an electron-deficient alkene undergo facile 1,3-diaza-Claisen rearrangements. The rearrangement reactions are summarized in Tables 1 and 2. Tertiary allylic amine **12a** smoothly undergoes reaction with *p*-TsNCO in benzene at reflux affording the urea **18** in 93% yield. Substrate **12b** also reacts with *p*-TsNCS in $CHCl_3$ at room temperature giving the thiourea **19** in 67% yield.[8] We have reported that in the case of azanorbornenes, isocyanates and isothiocyanates with stronger electron-withdrawing groups are more reactive, and the same trend is apparent with tertiary allylic amines bearing an electron-deficient alkene. As an example, *p*-nitrophenyl isothiocyanate reacts with substrate **12a** affording the thiourea **20** in 78% yield, while phenyl isothiocyanate failed to yield product under analogous conditions. The fact that none of the alkyl-isocyanates or isothiocyanates we investigated yielded the rearrangement product (data not shown) also supported this trend. These rearrangements thus require an electron-withdrawing substituent on the isocyanate or isothiocyanate.

In evaluating the scope of the reaction, we have found that substrate **25** yielded only decomposition products when subjected to rearrangement conditions with a number of isocyanates. We suspect that amine **25** does indeed rearrange, but the product eliminates and then undergoes decomposition. The failed rearrangement of substrate **26** highlights that the position of the electron-withdrawing substituent on the alkene significantly affects the rate of the rearrangement.[9] The ketones **17a**–**c** also undergo rearrangement affording the rearrangement products **21**–**24**. Similarly, the vinyl sulfone-based rearrangement precursor **12c** also underwent rear-

---

(4) Burrows, C. J.; Carpenter, B. K. *J. Am. Chem. Soc.* **1981**, *103*, 6983.

(5) Huang, H.; Liu, X.; Deng, J.; Qiu, M.; Zheng, Z. *Org. Lett.* **2006**, *8*, 3359.

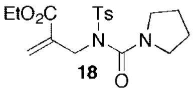
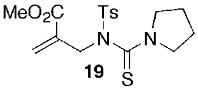
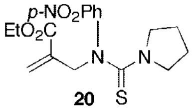
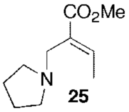
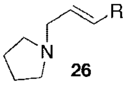
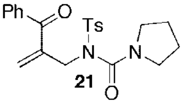
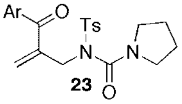
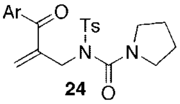
(6) Philbin, M.; Carpino, L. A. *J. Org. Chem.* **1999**, *64*, 4315.

(7) Labadie, J. W.; Tueting, D.; Stille, J. K. *J. Org. Chem.* **1983**, *48*, 4634.

(8) For the synthesis of TsNCS, see: Barton, D.H. R.; Fontana, G.; Yang, Y. *Tetrahedron* **1996**, *52*, 2705.

(9) Tsou, H.-R.; Overbeek-Klumpers, E. G.; Hallett, W. A.; Reich, M. F.; M. Floyd, M. B.; Johnson, B. D.; Michalak, R. S.; Nilakantan, R.; Discafani, C.; Golas, J.; Rabindran, S. K.; Shen, R.; Shi, X.; Wang, Y.-F.; Upeslacis, J.; Wissner, A. *J. Med. Chem.* **2005**, *48*, 1107.

Table 1. Reaction of Isocyanates and Isothiocyanates with Various Tertiary Allylic Amines

tertiary allylic amine	$R{-}N{=}C{=}X$	conditions	rearrangement product	yield
12b	TsNCO	benzene reflux	 **18**	93%
12a	TsNCS	$CHCl_3$, rt	 **19**	67%
12b	p-NO_2PhNCS	benzene reflux	 **20**	78%
12b	PhNCS	benzene reflux	decomposition	
 **25**	TsNCO	benzene reflux	decomposition	
 **26** R = CO_2t-Bu	TsNCO	benzene reflux	decomposition	
17b	TsNCO	$CHCl_3$ reflux	 **21**	73%
17b	BzNCO	100 °C neat	decomposition	
17a	TsNCO	100 °C neat	 **23** Ar = p-MeOPh	82%
17c	TsNCO	100 °C neat	 **24** Ar = p-NO_2Ph	68%

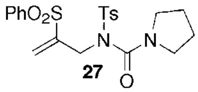
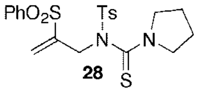
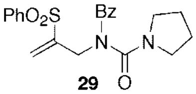
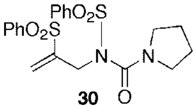
rangement with electron-deficient iso(thio)cyanates in modest to excellent yields (Table 2).

In the course of these studies, we noted that when TsNCO was allowed to react with tertiary allylic amine **12a** at room temperature, a product other than urea **18** quickly formed within 15 min. We could not isolate this product but noted that at room temperature it slowly converted to the urea **18**, and if heated to 50 °C, it would convert to the urea **18** within 1 h (Figure 2). We propose that the initial product is the isourea **31** that in turn isomerizes to the urea **18**.[10] Thus, the urea **18** arises from two [3,3]-sigmatropic rearrangements, and it is possible that additional examples noted in Tables 1 and 2 also arise from two [3,3]-rearrangements.

We have additionally investigated the influence of the alkene electron-withdrawing substituent on the rate of the rearrangement. Although the studies above demonstrate that an electron-withdrawing group can significantly increase the rate of zwitterionic rearrangements, we sought to establish if a stronger electron-withdrawing group favored a faster rate of rearrangement.

To establish reactivity trends, we performed competition experiments (Figure 3). When substrates **12a** and **12c** were allowed to compete for limiting TsNCO, a 1.8:1 mixture of products **18** and **27** was formed. If product **27** had formed in excess, this would suggest that a stronger electron-withdrawing group (SO_2Ph > CO_2Et) favored a faster rearrangement rate. These results do not necessarily suggest that a weaker EWG favors a faster rearrangement because the steric differences between the substrates complicate the picture. For example, comparison of chair transition states **33** and **34** (Figure 4) predicts that transition state **33** would

Table 2. Reaction of Substrate **12c** with Iso(thio)cyanates

amine	$R{-}N{=}C{=}X$	conditions	rearrangement product	yield
12c	TsNCO	benzene reflux	 **27**	83%
12c	TsNCS	benzene reflux	 **28**	57%
12c	BzNCO	benzene reflux	 **29**	46%
12c	$PhSO_2NCO$	benzene reflux	 **30**	97%

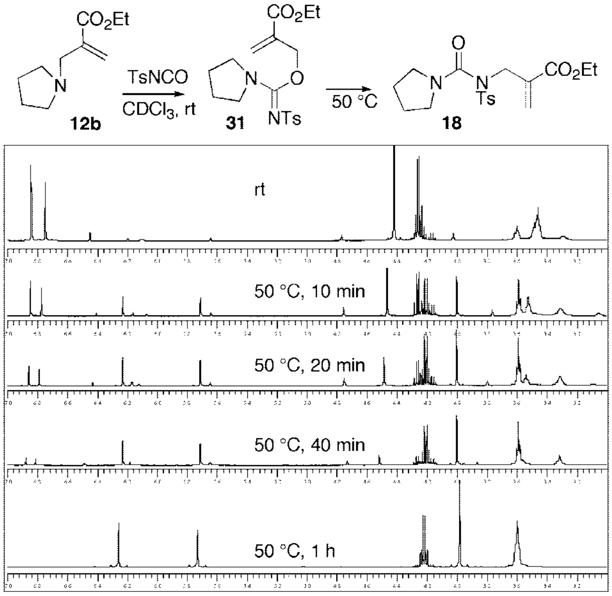


Figure 2. Room-temperature reaction of **12a** with TsNCO putatively affords isourea **31** that on mild heating rearranges to the urea **18**.

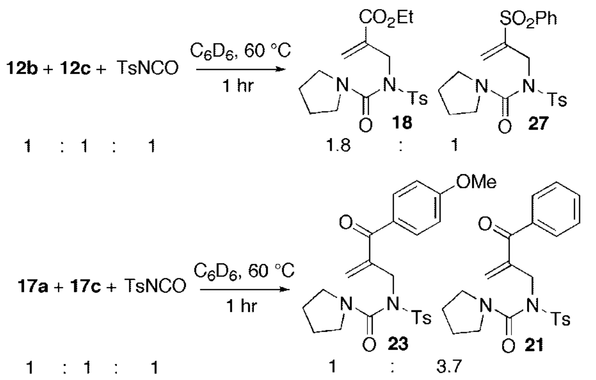


Figure 3. Competition experiments. Ratios were determined by integration of ^{1}H NMR spectra of product mixtures. All resonances in the crude spectra could be assigned to either product or starting material indicating minimal decomposition of products or starting materials under reaction conditions.

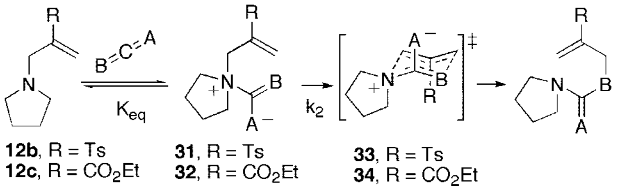


Figure 4. Proposed mechanism for the reaction of heterocumulenes with tertiary allylic amines **12b** and **12c**.

be higher in energy than TS **34** due to the 1,3-diaxial interaction of the larger SO_2Ph group with the pyrrolidine methylene. It is also worth noting that although the rearrangement is the rate-determining step the equilibrium for the formation of the zwitterionic intermediate can not be disregarded since the rate of formation of product = k_2[zwitterionic intermediate].[11] Due to the steric differences between **12b** and **12c**, it is expected that the concentration of zwitterionic intermediate **31** would be lower than **32** thus favoring faster formation of product **18**. These competition studies are inconclusive because electronic effects (due to the electron-withdrawing groups) may be offset by the steric effects noted above. When the substrates **17a** and **17b** (that are size matched) were allowed to compete for limiting TsNCO, a 1:3.7 mixture of products **23** to **21** was obtained.[12] These results thus suggest that a stronger electron-withdrawing group (benzoyl vs *p*-methoxybenzoyl) favors a faster rearrangement rate, but the results obtained with substrates **12b** and **12c** suggest that these electronic effects may be offset by sterics.

In conclusion, these studies demonstrate the tertiary allylic amines bearing electron-withdrawing substituents exhibit dramatic rate acceleration toward formal zwitterionic 1,3-diaza-Claisen rearrangements. The reasons for this acceleration are not clear at this juncture but will be the focus of future studies.

Acknowledgment. Support for this work was provided by CHE-041283 from the NSF.

Supporting Information Available: Experimental procedures for **14a**, **15a–c**, **16a–c**, **17a–c**, **18–21**, **23–25**, and **27–30** and ^{1}H and ^{13}C NMR spectra for representative compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802577Z

---

(10) A referee suggested that the rearrangement could proceed through an ionic mechanism in which the zwitterionic intermediate fragments to a urea anion/2-(ethoxycarbonyl)allyl cation pair that then recombines to give the isourea **31**. Although an ionic mechanism can not be ruled out for some of the rearrangements/conditions, an ionic mechanism for the rearrangement of **12b** with TsNCO at rt is unlikely since dimethylallylamine and TsNCO did not rearrange at rt and it could have proceeded through an allyl cation that would be more electron-rich than the 2-(ethoxycarbonyl)allyl cation.

(11) According to Figure 4, the rate of formation of rearrangement product = k_2[zwitterionic intermediate]. Thus, reaction conditions that increase the concentration of the zwitterionic intermediate (i.e., neat conditions, Table 1) should increase the overall rate of reaction.

(12) Although we initially synthesized the substrate **17c** for comparison with **17a** and **17b** in competition studies, its high lability made it unsuitable for these studies.