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Synthesis of highly substituted ureas and thioureas through 1,3-diaza-Claisen rearrangements

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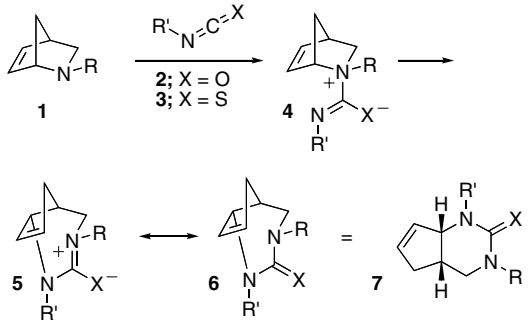
Abstract—Isocyanates and isothiocyanates that are not activated by an electron withdrawing group react with azanorbornenes in benzene at reflux to afford ureas and thioureas through the corresponding 1,3-diaza-Claisen rearrangements. At higher temperatures, a triazinone byproduct is observed. Isocyanates and isothiocyanates that are activated by an electron-withdrawing group react at room temperature to give the corresponding ureas and thioureas. The reactions of the activated isocyanates and isothiocyanates are also accompanied by the formation of isoureas and isothioureas. Interestingly, while benzoyl isocyanate reacts with *N*-benzyl azanorbornene at room temperature to give a 2:1 mixture of urea to isourea, in benzene at reflux the only product observed is the urea. A crossover experiment rules out the possibility that the products are formed through a retro-Diels–Alder, [4+2] cycloaddition sequence instead of a 1,3-diaza-Claisen rearrangement. Competition experiments between isocyanates and isothiocyanates with limiting azanorbornene indicate that isothiocyanates react faster to give the rearrangement product. Since isocyanates are shown to be more electrophilic, these data are consistent with a fast addition step and a rate-determining rearrangement step.

We have recently reported that in situ generated *N*-alkyl-*N*′-tosyl carbodiimides react with azanorbornenes through a zwitterionic 1,3-diaza-Claisen rearrangement to afford guanidines.[1] Because isocyanates and isothiocyanates (**2**, **3**, and Scheme 1) are isoelectronic with carbodiimides, it seemed plausible that they may react in a similar manner with azanorbornenes (**1**) to give a zwitterionic intermediate **4** that could in turn undergo a 1,3-diaza-Claisen rearrangement to give ureas and thioureas **7**. As the analogous rearrangement of ketenes with azanorbornenes (and other tertiary allylic amines) is well precedented by the work of Roberts, MacMillan, Nubbemeyer and co-workers,[2] we were surprised that a survey of the literature revealed no examples of a zwitterionic 1,3-diaza-Claisen rearrangement involving isocyanates or isothiocyanates. This paucity of data prompted us to investigate the scope and limitations of the 1,3-diaza-Claisen rearrangements that affords ureas and thioureas.

Table 1 details the reactions of isocyanates and isothiocyanates with azanorbornenes. The reaction of *N*-benzyl azanorbornene **8a** with benzyl isothiocyanate **9a** in toluene at reflux afforded the expected rearrangement product **10a** in 64% yield and the triazinone **11** in a 4:1 ratio. This is clearly a positive result in that it demonstrated the first example of a 1,3-diaza-Claisen rearrangement that affords ureas. However, the formation of triazinone **11** was surprising.



Scheme 1.

Scheme 2 describes the proposed mechanism for the formation of triazinone **11**. The zwitterionic intermediate **13** may proceed to product **10a** as expected or it may undergo a retro-Diels–Alder reaction to afford cyclopentadiene and the 1,4-dipole **14**. Precedent for the retro-Diels–Alder reaction is provided by Grieco et al.

Keywords: [3,3]-Sigmatropic rearrangements; Ureas; Thioureas; Isocyanates; Isothiocyanates.
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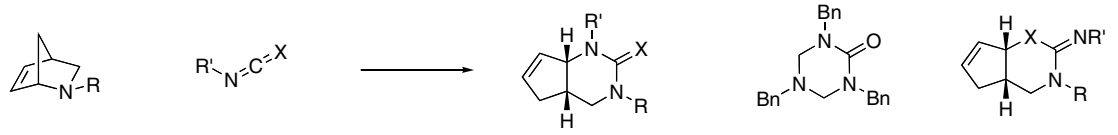
Table 1. Reaction of unactivated isocyanates and isothiocyanates with azanorbornenes



8a; R = Bn
8b; R = CH_2CO_2t-Bu
8c; R = *i*-Pr

9a; R' = Bn, X = O
9b; R' = Ph, X = O
9c; R' = Cy, X = O
9d; R' = Bn, X = S
9e; R' = Bz, X = O
9f; R' = Bz, X = S
9g; R' = SO_2Ph, X = O

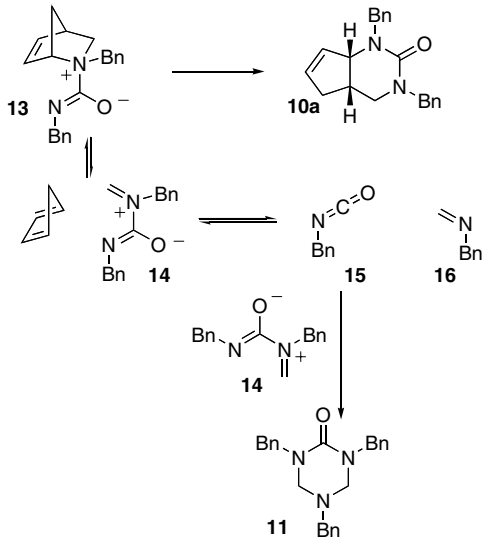
10a; R = Bn, R' = Bn, X = O
10b; R = Bn, R' = Ph, X = O
10c; R = CH_2CO_2t-Bu, R' = Ph, X = O
10d; R = Bn, R' = Bn, X = S
10e; R = Bn, R' = Bz, X = O
10f; R = Bn, R' = Bz, X = S
10g; R = Bn, R' = SO_2Ph, X = O
10h; R = *i*-Pr, R' = Bz, X = O

11

12e; R = Bn, R' = Bz, X = O
12f; R = Bn, R' = Bz, X = S
12g; R = Bn, R' = SO_2Ph, X = O

Azanorbornene	Iso(thio)cyanate	Conditions[a]	Product	Ratio	%Yield
8a	**9a**	Toluene, reflux	**10a**, **11**	4:1	64 (**10a**)
8a	**9a**	Benzene, reflux	**10a**	—	71
8a	**9b**	benzene, reflux	**10b**	—	80
8a	**9c**	Benzene, reflux	NR	—	—
8b	**9b**	Benzene, reflux	**10c**	—	82
8a	**9d**	Benzene, reflux	**10d**	—	77
8a	**9e**	$CHCl_3$, rt	**10e**, **12e**	2:1	90
8a	**9e**	Benzene, reflux	**10e**	—	90
8a	**9f**	$CHCl_3$, rt	**10f**, **12f**	2:1	96
8a	**9f**	Benzene, reflux	Complex mixture	—	—
8a	**9g**	$CHCl_3$, rt	**10g**, **12g**	1:1	91
8c	**9e**	Benzene, reflux	**10h**	—	73

[a] In a typical experiment, 1–2 equiv of iso(thio)cyanate were used. In all instances the reaction was complete within 12 h with the exception of the reaction of **8b** with **9b** and **8c** with **9e** that required 24 h.



Scheme 2.

who have shown that azanorbornenes that bear a positive charge can easily undergo a retro-Diels–Alder reaction.[3] The 1,4-dipole may then eliminate most likely in a reversible manner to afford the isocyanate **15** and the imine **16**. Cycloaddition of the 1,4-dipole **14** and the imine **16** then affords the triazinone **11**. A survey of the literature reveals that this is a plausible transformation as there are reports that isocyanates react with imines to give triazinones.[4] Since the product distribution is determined by the competing rates of rearrangement versus retro-Diels–Alder reaction from the intermediate **13**, the possibility existed of modifying the conditions to optimize the rearrangement pathway. The highly ordered transition state of the rearrangement is expected to have a negative entropy of activation, while the retro-Diels–Alder transition state is expected to have a positive entropy of activation. In this scenario, lower temperatures should favor the rearrangement pathway. Indeed, when azanorbornene **8a** and isocyanate **9a** were allowed to react in benzene at reflux, (instead of in toluene at reflux) the rearrangement product **10a** was formed in 71% yield without any detectable formation of triazinone.

With the reaction conditions optimized, additional examples of this transformation were investigated. Phenyl isocyanate **9b** also reacted with azanorbornene **8a** to give the urea **10b** in 80% yield. The reaction appears to be sensitive to sterics as the cyclohexyl isocyanate failed to react with azanorbornene **8a**. The reaction of the azanorbornene **8b** with benzyl isocyanate demonstrates that even electron-withdrawing groups are tolerated on the azanorbornene. Benzyl isothiocyanate also reacts with azanorbornene **8a** to afford the bicyclic thiourea **10d** in 77% yield. Thus, isothiocyanates are also suitable substrates for zwitterionic 1,3-diaza-Claisen rearrangements.

Our previous work on the 1,3-diaza-Claisen rearrangement that affords guanidines had suggested the need for a strong electron-withdrawing group on the in situ generated carbodiimides. As such, it was interesting to determine if the isocyanates and isothiocyanates that are activated by an electron-withdrawing group reacted under milder conditions. Indeed, benzoyl isocyanate **9e** reacted with azanorbornene **8a** at room temperature to give 2:1 mixture of the urea **10e** and the isourea **12e** in

90% yield. The formation of the isourea **12e** is attributed to the benzoyl electron-withdrawing group that in the zwitterionic intermediate more closely distributes the electron density between the nitrogen and oxygen atoms. Interestingly, when the reaction was heated at reflux in benzene, the only product obtained was the urea **10e** in 90% yield. To rule out the possibility that the exclusive formation of **10e** at higher temperatures was due to a thermodynamic equilibration of **10e** and **12e**, the mixture of **10e** and **12e** was resubjected to the reaction conditions. However, the **10e/12e** ratio remained unchanged (data not shown). Benzoyl isothiocyanate **9f** also reacted with azanorbornene **8a** at room temperature furnishing the thiourea **10f** and isothiourea **12f** in a 2:1 ratio and in 96% yield. This reaction was also attempted in benzene at reflux to determine if at higher temperatures only the thiourea was formed. However, under these conditions, a complex mixture was obtained. Benzenesulfonyl isocyanate also reacted with azanorbornene **8a** at room temperature giving a 1:1 mixture of urea **10g** and isourea **12g** in 91% yield. Finally, benzoyl isocyanate reacted with the fairly sterically hindered *N*-isopropyl azanorbornene in benzene at reflux to afford the urea **10h** in 73% yield.

The possibility that the 'rearrangement' product could be formed through an alternative mechanism was also investigated. Since the formation of the triazinone strongly suggests the provability of a retro-Diels–Alder pathway, it is possible that the intermediate **4** (Fig. 1) could undergo a retro-Diels–Alder reaction to afford the 1,4-dipole **14** and cyclopentadiene. The 1,4-dipole could in turn act as the diene and undergo a [4+2] cycloaddition reaction with cyclopentadiene as the dieneophile to furnish the 'rearrangement' product. To rule out this alternate mechanistic path, a crossover experiment was undertaken. The azanorbornene **8a** and benzyl isothiocyanate **9a** were heated at reflux in benzene with 1 equiv of 1,3-cyclohexadiene with the expectation that if the 1,4-dipole were formed it would react with 1,3-cyclohexadiene in a manner analogous to cyclopentadiene. However, this reaction led to the formation of **10a** exclusively. This experiment rules out the possibility that the rearrangement product is formed from an alternate mechanistic pathway involving a retro-Diels–Alder, [4 + 2] cycloaddition sequence.

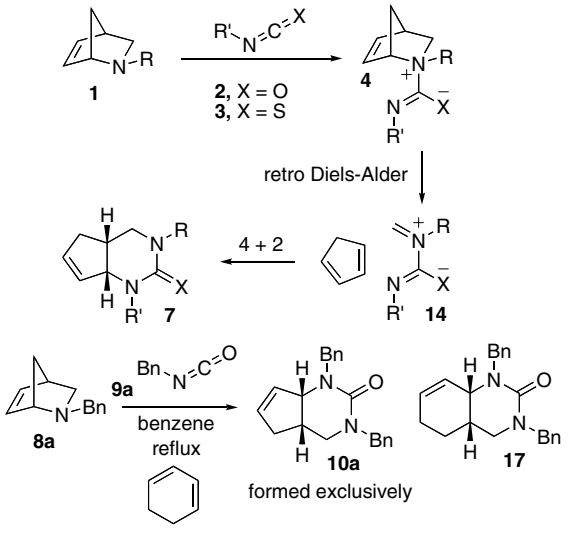


Figure 1. Alternate mechanistic path and crossover experiment.

We next turned our attention to investigating some of the mechanistic details of these transformations. In particular, it would be useful to know if the rate-determining step is the addition to form the zwitterionic intermediate, or the rearrangement step. In addition, it would be useful to shed some light on the observed reactivity differences between the activated and unactivated iso(thio)cyanates. For example, it is clear that the isocyanates and isothiocyanates that are activated by an electron-withdrawing group react faster (under the same conditions) than the unactivated iso(thio)cyanates. While it is logical to expect that the activated iso(thio)cyanates should be more reactive toward the addition step due to their increased electrophilicity, it is unclear if the electron-withdrawing groups bear any effect on the rearrangement step.

Mechanistic studies began with experiments aimed at determining if the isocyanates or isothiocyanates are more reactive in this transformation. To this end, competition experiments were designed in which isocyanates and isothiocyanates were allowed to compete for limiting azanorbornene. In the first experiment, a 1:1:1 ratio of benzoyl isocyanate, benzoyl isothiocyanate and *N*-benzyl azanorbornene were allowed to react at room temperature (Fig. 2). This reaction afforded a 2:1:1:0.5 mixture of thiourea **10f**, isothiourea **12f**, urea **10e**, and isourea **10e**. Since the products **10f** and **12f** arise from reaction of the isothiocyanate with the azanorbornene, isothiocyanates exhibit a 2:1 preferential reactivity over the isocyanates under these conditions. In the second experiment, a 1:1 mixture of benzyl isocyanate and benzyl isothiocyanate were allowed to compete for 1 equiv of azanorbornene in benzene at reflux. Under these conditions, the thiourea **10d** was the only product observed (within the detection limits). This result further highlights that the isothiocyanates react faster than the isocyanates on the path from azanorbornene to rearrangement product. It is also worth noting that the unactivated series exhibits more selectivity than activated series as this suggests that less reactive (unactivated) reagents react in a more selective fashion.

The result that isothiocyanates are more reactive in this transformation opened the possibility for determining whether the rate-determining step is the addition or the rearrangement. This is because if the isocyanates could be shown to be more electrophilic in the addition step, while in the overall reaction the isothiocyanates are more reactive this would be indicative that the rearrangement step is the rate-determining step. To determine the relative electrophilicities, a 1:1 mixture of isocyanate and isothiocyanate were allowed to compete for pyrrolidine as the nucleophile. These experiments assume that the addition step is negligibly reversible and is followed by a fast proton shuffle that leads to product. Interestingly, in these experiments the isocyanates were found to be more reactive (Fig. 2). These data are thus

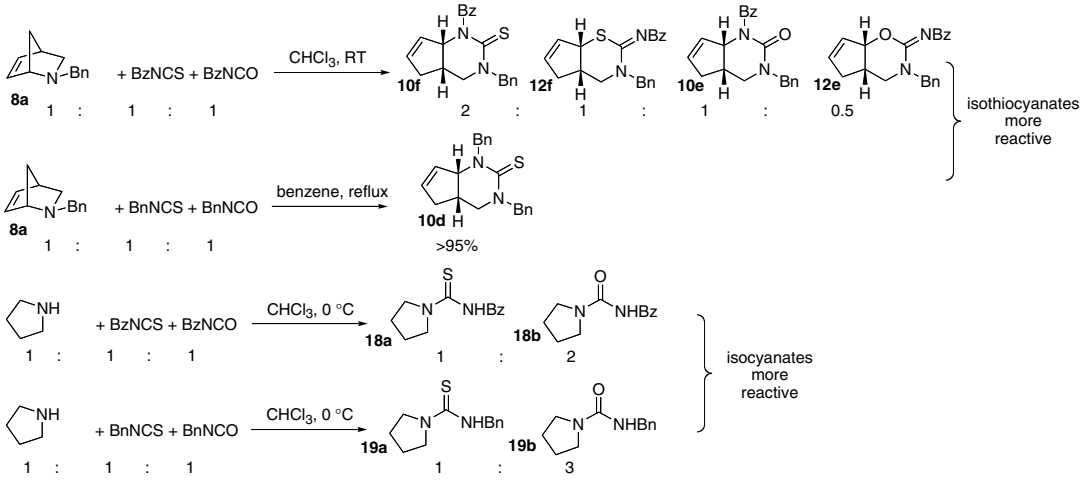


Figure 2. Competition experiments.

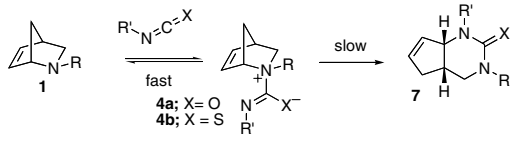


Figure 3. Proposed mechanistic model.

consistent with a fast (and most likely reversible) addition step and a rate-determining rearrangement step (Fig. 3). It is unclear at this juncture why the intermediate **4b** rearranges at a faster rate than **4a**. A trend that does become apparent, however, is that as the capacity of the zwitterionic intermediate to stabilize the negative charge increases so does the rate of rearrangement (i.e., when R′ = electron-withdrawing group, the rate from **4** to **7** is faster than when R′ = alkyl, and similarly when X = S the rate from **4** to **7** is faster than when X = O).

In conclusion, we have shown the first examples of 1,3-diaza-Claisen rearrangements of isocyanates and isothiocyanates with azanorbornenes. Isocyanates and isothiocyanates that are activated by an electron-withdrawing group react at a faster rate than unactivated isocyanates and isothiocyanates. Competition experiments are consistent with a fast addition step and a rate-determining rearrangement step. This information will be useful in the design of catalysts for this transformation as the goal of the catalyst must be to lower the energy of activation of the rate-determining rearrangement step instead of the addition step.

Acknowledgments

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