

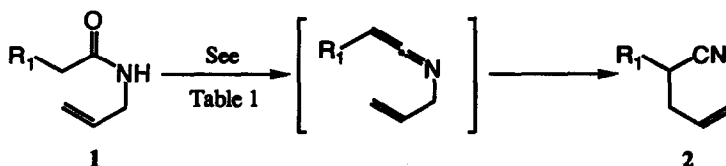
## An Extremely Mild 3-Aza-Claisen Reaction. 2. New Conditions and the Rearrangement of $\alpha$ -Heteroatom Substituted Amides.

M. A. Walters,\* A. B. Hoem, H. R. Arcand, A. D. Hegeman, and C. S. McDonough

Dartmouth College, 6128 Burke Laboratory, Department of Chemistry, Hanover, NH 03755-3564

**Abstract:** Several new and potentially useful reaction conditions for the 3-aza-Claisen rearrangement of N-allyl amides have been developed. These new conditions have been successfully applied to the rearrangement of  $\alpha$ -heteroatom substituted species forming  $\alpha$ -amino nitriles and protected cyanohydrins as products.

The utility of sigmatropic rearrangements such as the Claisen and Cope has been widely documented, and several recent investigations have focused on milder methods for effecting this class of carbon-carbon bond-forming reactions.<sup>1</sup> We recently reported the development of an extremely mild, essentially neutral, room temperature 3-aza-Claisen reaction for the conversion of simple N-allyl amides **1** to pentenitriles **2** (Scheme 1).<sup>2</sup> As part of our continuing studies we have sought to expand the flexibility of this reaction by developing alternative reaction conditions. Herein we report both our success along these lines and the first application of this new methodology to the unprecedented rearrangement of  $\alpha$ -heteroatom substituted N-allyl amides.



Scheme 1.

The principal aims of this study were three-fold. First, it was desirable to increase the flexibility of this reaction so that a wide variety of conditions would be available for the rearrangement of any given compound. Second, we wanted to develop reagents that would effect the reaction at lower temperatures than the room temperature conversion originally reported to establish an effective temperature range for this methodology. Third, a practical goal was to avoid the formation of the large amounts of triphenylphosphine oxide that the original conditions produced as side products. By studying the rearrangement of the N-allylamide **3** we have found that a variety of simple dehydrating reagents effect the desired transformation efficiently at room temperature or below, many giving water soluble by-products which facilitate reaction work-up. (Table 1). Of particular note along these lines are the reactions which employ the reagents P(OMe)<sub>3</sub>, P(OEt)<sub>3</sub>,<sup>3</sup> and triphosgene<sup>4</sup> as activating agents, each of which produces the pure pentenitrile product **4**.

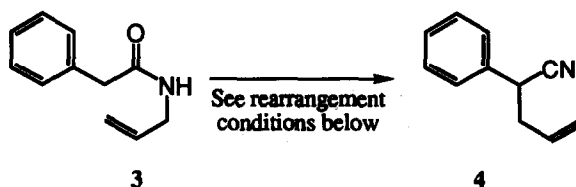


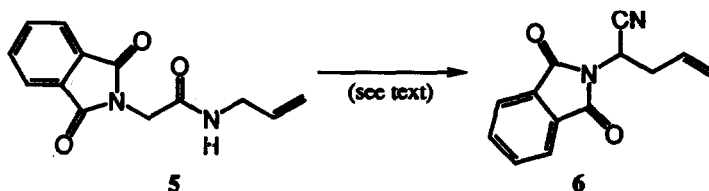
Table 1. New Reaction Conditions for the 3-aza-Claisen Rearrangement.

Rearrangement Conditions <sup>a</sup>	Yield of Nitrile 4
1. 2 PPh <sub>3</sub> , 2 CCl <sub>4</sub> , 3 Et <sub>3</sub> N <sup>5</sup>	97%
2. 2 PPh <sub>3</sub> , 2 CBr <sub>4</sub> , 3 Et <sub>3</sub> N <sup>6</sup>	66%
3. PPh <sub>3</sub> , I <sub>2</sub> , 2 Et <sub>3</sub> N	56%
4. Br <sub>2</sub> •PPh <sub>3</sub> , 2 Et <sub>3</sub> N <sup>7</sup>	89%
5. 3 I <sub>2</sub> , 3 P(OEt) <sub>3</sub> , 3 Et <sub>3</sub> N <sup>3</sup>	86%
6. 3 I <sub>2</sub> , 3 P(OMe) <sub>3</sub> , 3 Et <sub>3</sub> N	36%
7. Tf <sub>2</sub> O, 2 (iPr) <sub>2</sub> NEt <sup>8</sup>	67%
8. Triphosgene (1/2), 2.5 Et <sub>3</sub> N <sup>4</sup>	78%
0 °C	85%
-78 °C	40%
9. (COCl) <sub>2</sub> , 2 Et <sub>3</sub> N <sup>9</sup>	31%
10. PhCH <sub>2</sub> NEt <sub>3</sub> <sup>+</sup> Cl <sup>-</sup> (.03%), CHCl <sub>3</sub> , 50% NaOH/H <sub>2</sub> O <sup>10</sup>	39%
11. TFAA, 2 Et <sub>3</sub> N <sup>11</sup>	b

<sup>a</sup>Numerals indicate relative stoichiometry. These reactions are usually run in dichloromethane and at room temperature.

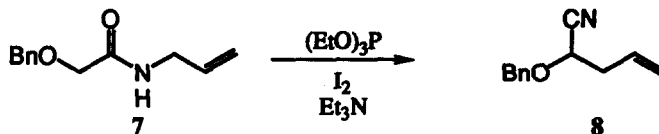
<sup>b</sup>Product formed, yield not determined.

These new reaction conditions have been applied to the rearrangement of  $\alpha$ -heteroatom substituted N-allyl amides as shown in Reactions 1 and 2. While these reactions have proven to be as efficient as those reported for the previous examples, they are also more sensitive to variations in reaction conditions. For example, the only acceptable yield of pentenitrile **6** was obtained when amide **5** was submitted to the reaction conditions which employ  $\text{PPh}_3 \cdot \text{Br}_2$  in  $\text{CH}_3\text{CN}$  (78%). This sensitivity to rearrangement conditions may be due, in part, to the relative insolubility of the  $\alpha$ -N-substituted amides in solvents commonly used for the reaction ( $\text{CH}_3\text{CN}$ ,  $\text{CH}_2\text{Cl}_2$ ,  $\text{CHCl}_3$ ,  $\text{Et}_2\text{O}$ ). A small amount of DMF (10%) cosolvent used in conjunction with  $\text{I}_2/\text{P}(\text{OEt})_3/\text{Et}_3\text{N}$  also gave a moderate amount (66%) of the desired product **6**.



Reaction 1.

In like fashion, the  $\alpha$ -oxygenated amide **7** gave a moderate yield (40%) of the protected cyanohydrin product **8** when treated with the conditions employing  $\text{I}_2/\text{P}(\text{OEt})_3/\text{Et}_3\text{N}$  as an activating agent.



Reaction 2.

We have found that our modified Brannock and Burpitt rearrangement<sup>12</sup> occurs with a wide variety of reagents, each of which presumably leads to the formation of a common 3-aza-1,2,5-hexatriene intermediate.<sup>13</sup> We are currently investigating the effect of  $\alpha$ -heteroatom substitution on the stereochemical outcome of this rearrangement.

### Acknowledgments

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10. Saraie, T.; Ishiguro, T.; Kawashima, K.; Morita, K. *Tetrahedron Lett.* **1973**, 2121-2124. These reaction conditions have been used to convert primary amides to nitriles.
11. TFAA = trifluoroacetic anhydride. For the conversion of primary amides to nitriles using these reaction conditions see: Campagna, F.; Carotti, A.; Casini, G. *Tetrahedron Lett.* **1977**, 1813-1816.
12. Brannock, K. C.; Burpitt, R. D. *J. Org. Chem.* **1965**, *30*, 2564-2565. This paper delineates the original conditions for the rearrangement of N-allylamides.
13. To our knowledge, the reaction conditions listed as entries 3, 5, 6, 7, 8, 9, 10, and 11 in Table 1 have not previously been employed to prepare simple ketenimines. The fact that they promote this rearrangement suggests that they may be useful for that purpose.

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