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Cyclizations of *N*-carbamoyl and *N*-thiocarbamoyl iminium ions leading to ring-fused heterocycles

Ahmad Qarah, Douglas A. Klumpp *

Department of Chemistry and Biochemistry, Northern Illinois University, DeKalb, IL 60115, United States

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ABSTRACT

γ-Ureidoacetals react in excess acid to give ring-fused heterocycles (12 examples, 46–93% yields) by intramolecular cyclizations. A mechanism is proposed involving *N*-carbamoyl iminium ions and related species. The mechanism is further examined by DFT calculations.

Introduction

The synthetic utility of *N*-acyl iminium ions is well known.[1] These electrophiles have been used in numerous synthetic methods via intra- and intermolecular reactions and they have been useful in natural product syntheses. *N*-Carbamoyl iminium ions have also been used in synthetic methods. For example, Gazizov and co-workers showed that γ-ureidoacetals react in CF_3CO_2H with arenes to provide aryl-substituted pyrrolidines.[2] This chemistry involves formation of *N*-carbamoyl iminium ions—for example, ion **1**—and subsequent reaction with an arene nucleophile (Scheme 1). Cyclization reactions of *N*-carbamoyl iminium ions have also been described, such as in the formation of the ion **2** and cyclization with the 3-thienyl group to give **3**.[3,4] Although *N*-carbamoyl iminium ions have been utilized in synthetic methodologies such as those described above, their chemistry is not as well developed as the *N*-acyliminium ion chemistry. In the following manuscript, we describe new cyclization chemistry involving *N*-carbamoyl and *N*-thiocarbamoyl iminium ions. The chemistry provides access to novel ring-fused 3,4-dihydroquinazolin-2(1*H*)-ones.

Results

Our studies began with the preparation of a series of γ-ureidoacetals. As previously reported by Gazizov et al.[2a] these substrates are readily prepared from aminoacetals and the appropriate aryl isocyanate or isothiocyanate (Scheme 2). Both the urea (**4**) and thiourea (**5**) were prepared in good yields using this chemistry. When the γ-ureidoacetals are reacted with strong or superacidic media, the cyclization products are observed (Tables 1 and 2). For example, urea **6** provides the tetrahydropyrrolo[1,2-*c*]quinazolin-5(6*H*)-one (**7**) in good yields from excess superacidic CF_3SO_3H. The yield of **7** drops off considerably with decreasing amounts of CF_3SO_3H. Likewise, a modest to large decrease in yields is seen in less acidic solutions. While CF_3SO_3H (H_o −14.1) gives product **7** about 90% yield, CF_3SO_3H-CF_3CO_2H, H_2SO_4, and CH_3SO_3H, are strong acids—but not superacids ($H_o > -12$)—and the yields of these conversions are in the 39–70% yield range.[5] We also attempted the cyclization with Lewis acids, $BF_3{\cdot}Et_2O$ and $TiCl_4$. Product **7** was isolated, but the yield obtained was less than the Brønsted acid-promoted reactions.

Using the optimum procedure, a series if urea and thiourea derivatives were reacted with superacid (Table 2). The cyclization chemistry is found to work best with alkyl-substituted aryl and 1-naphthyl groups. Both urea and thiourea substrates are found to give cyclization products. For example, compounds **4** and **5** provide compounds **15** and **16**—substance possessing the aza-steroid ring system. Despite the superacidic conditions, there is no evidence for alkyl group migration or transalkylation processes. Following the cyclization, the products themselves may further reduced (Scheme 3). Compound **15** is converted to the hexahydro benzo[*h*]pyrrolo[1,2-*c*]quinazoline (**18**) by reacting with $LiAlH_4$, while the thiocarbonyl derivative (**16**) is converted to the same

* Corresponding author.

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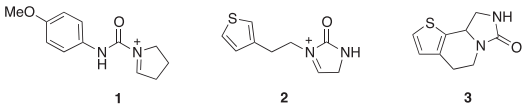
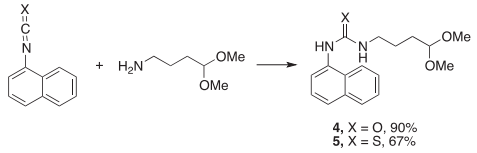
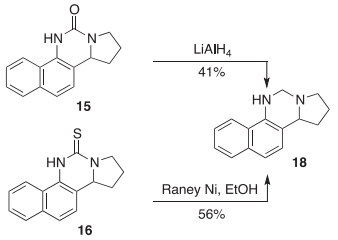


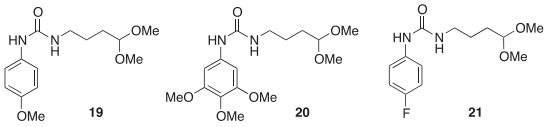
Scheme 1.



Scheme 2.

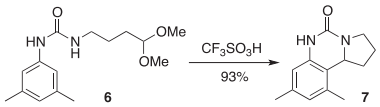


Scheme 3.



Scheme 4.

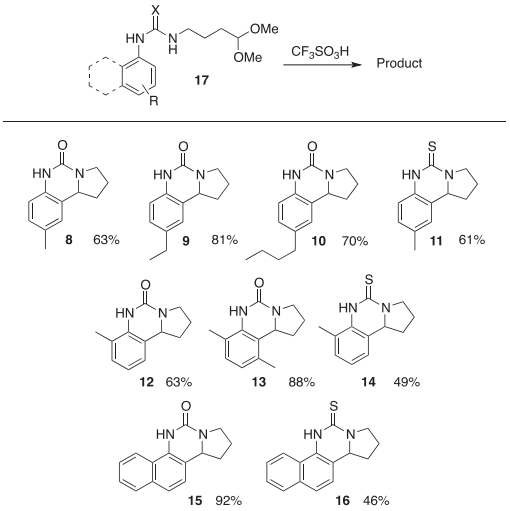
Table 1
Reactions and yields for the conversion of urea **6** to **7**



Acid	Yield[a] (%)	Acid	Yield[a] (%)
CF_3SO_3H (50 equiv)	93 88[b]	CF_3CO_2H (100 equiv)	65
CF_3SO_3H (5 equiv)	22	H_2SO_4 (50 equiv)	51
CF_3SO_3H (1 equiv)	11	CH_3SO_3H (50 equiv)	39
CF_3SO_3H:CF_3CO_2H (1:1 v:v, 50 equiv)	70	$BF_3{\cdot}Et_2O$ (20 equiv)	29
		$TiCl_4$ (5 equiv)	65

[a] Reaction conditions: 25 °C, 24 h.
[b] Reaction conditions: 25 °C, 2 h.

Table 2
Products (**8**–**16**) and yields from cyclizations of acetals **17**



[a]Reaction conditions: 50 equiv. CF_3SO_3H, 25 °C, 24 h.

product (**18**) with Raney nickel. Several methoxy-substituted and halogen-substituted aryl ureas (i.e., **19**–**21**) were also prepared and reacted with superacid, but no tetrahydropyrrolo[1,2-*c*]quinazolin-5(6*H*)-one products were obtained (Scheme 4).

Based on the observed products, a mechanism is proposed invoking *N*-carbamoyl iminium ion intermediates (Fig. 1). Reaction of the γ-ureidoacetal (**9**) provides the *N*-carbamoyl iminium ion **25** by cationic reactions at the acetal group. The cyclization could occur by two conceivable paths: an intramolecular Friedel–Crafts type reaction of the ion **25** or through a 6π electrocyclization involving the tautomeric ion **26**. Theoretical calculations estimate that **25** is about 10 kcal/mol more stable than the tautomer **26** (gas phase structures at the B3LYP 6-311G (d,p) level)—suggesting the electrocyclization is unlikely for the monocationic ion.[6] However, urea and thiourea functional groups are somewhat strong base sites ($pK_a = 0.2$)[7] and an equilibrium with the dicationic species (**29**) is a possibility. Olah and co-workers have previously found evidence for deprotonated urea under superacidic conditions.[8] Efforts to directly observe intermediate species using NMR and stable ion conditions (FSO_3H) were not successful. It should be noted that formation of the dication **29** might facilitate reaction by the electrocyclization pathway. Dication **29** is expected to have a large resonance contribution from the delocalized structure **29′**. Theoretical calculations reveal that the C–N bond shortens upon protonation of the urea oxygen. In the optimized structures, the OC–NH bond length decreases from 1.49 Å in **25** to 1.31 Å in **29**, consistent with a greater degree of π-bond character. This dicationic π-system should be more favorably disposed to undergo the 6-π electrocyclization to give product **10**, as previous theoretical and experimental studies have shown that delocalization of charge may facilitate electrocyclizations in dicationic systems.[9]

Besides the exact nature of the cyclization step, there remains one other unanswered question: why do the systems having activated aryl groups (i.e., **19** and **20**) not undergo cyclization? Gazizov and co-workers even trapped the *N*-carbamoyl iminium ion **1** with 2-naphthol,[1a] but no cyclization product was reported. Likewise, Chiou et al. showed that the *N*-acyliminium ion **31** undergoes efficient conversion to the cyclization product **32** (Scheme 5)—an observation consistent with highly activated nature of the trimethoxyphenyl ring.[10] Compound **20** is expected to generate an *N*-carbamoyl iminium ion (**33**) having a trimethoxyphenyl group—an aryl group strongly activated toward electrophilic attack. However when these systems react in superacidic media, very complex product mixtures are formed. Besides triflic acid, the cyclization of **20** was attempted with a wide variety of acids and conditions, including CF_3CO_2H, CH_3CO_2H, pTsOH, $BF_3{\cdot}Et_2O$, and $TiCl_4$. Among the observations from these attempts, a common product was 3,4,5-trimethoxyphenyl isocyanate. This suggests some *N*-carbamoyl iminium ions, such as **33**, have a tendency to undergo cleavage to the isocyanate starting material.

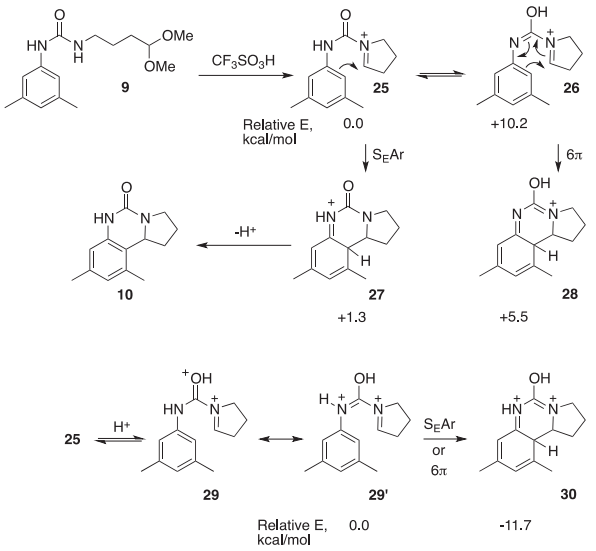
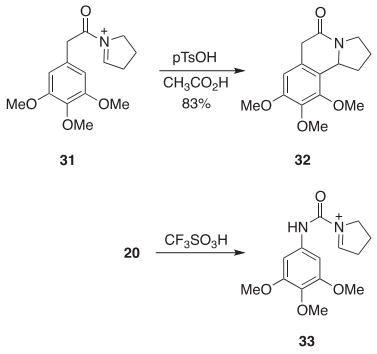


Figure 1. Proposed mechanism and B3LYP 6-311G (d,p) calculated relative energies for monocationic and dicationic intermediates (**25**–**30**).



Scheme 5.

Conclusions

We have found that γ-ureidoacetals may undergo acid-promoted cyclizations to provide ring-fused heterocycles. The reactions have been found to work best with alkyl-substituted aryl and 1-naphthyl groups. A mechanism is proposed involving formation of *N*-carbamoyl iminium ions followed by cyclization into the aryl group. Theoretical calculations indicate that a monocationic cyclization could occur as a slightly endothermic process, while the involvement of dicationic intermediates would lead to exothermic cyclization steps. The cyclization of the *N*-carbamoyl iminium ion is considered to be either a mono- or dicationic electrophilic aromatic substitution or a dicationic 6π electrocyclization.

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Supplementary data

Supplementary data (experimental procedure and characterization data available for new compounds; details regarding the computational studies) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.09.026.

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