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

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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.

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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 coworkers showed that of γ -ureidoacetals react in CF₃CO₂H 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 CF₃SO₃H. The yield of **7** drops off considerably with decreasing amounts of CF₃SO₃H. Likewise, a modest to large decrease in yields are seen in less acidic solutions. While CF₃SO₃H (*H*_o -14.1) gives product **7** about 90% yield, CF₃SO₃H-CF₃CO₂H, H₂SO₄, and CH₃SO₃H, 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, BF₃•Et₂O and TiCl₄. Product **7** was isolated, but the yield obtained was less than the Brønsted acid-promoted reactions.

Scheme 1.

Scheme 2.

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

Acid	Yield ^a	Acid	Yield
CF ₃ SO ₃ H (50 equiv)	93%	CF ₃ CO ₂ H (100 equiv)	65%
CF ₃ SO ₃ H (5 equiv)	22%	H ₂ SO ₄ (50 equiv)	51%
CF ₃ SO ₃ H (1 equiv)	11%	CH ₃ SO ₃ H (50 equiv)	39%
CF ₃ SO ₃ H:CF ₃ CO ₂ H (1:1 v.v, 50 equiv)	70%	BF ₃ ·Et ₂ O (20 equiv)	29%
		TiCl ₄ (5 equiv)	65%

^aReaction conditions: 25 °C, 2 hrs.^bReaction conditions: 25 °C, 2 hrs.**Table 2.** Products (**8-16**) and yields from cyclizations of acetals **17**.

8	63%	9	81%	10	70%	11	61%
12	63%	13	88%	14	49%		
15	92%	16	46%				

^aReaction conditions: 50 equiv. CF₃SO₃H, 25 °C, 24 h

Using the optimum procedure, a series of 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 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 reaction with LiAlH₄, while the thiocarbonyl derivative (**16**) is converted to the same 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 3. **Scheme 4.**

Based on the observed products, a mechanism is proposed invoking *N*-carbamoyl iminium ion intermediates (Figure 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 6 π electrocyclization involving the tautomeric ion **26**. Theoretical calculations estimate that **25** is about 15 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 coworkers have previously found evidence for deprotonated urea under superacidic conditions.⁸ Effort to directly observe intermediate species using NMR and stable ion conditions (FSO₃H) 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 coworkers 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

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

ion (**33**) having a trimethoxyphenyl group – an aryl group strongly activated towards 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 $\text{CF}_3\text{CO}_2\text{H}$, $\text{CH}_3\text{CO}_2\text{H}$, pTsOH , $\text{BF}_3 \cdot \text{Et}_2\text{O}$, 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.

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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