Activation of Urea as a Leaving Group in Substitution Reactions of Formamidine Ureas

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The reactions of formamidine ureas with amines take different paths under protic vs. nonprotic conditions; loss of the urea fragment has been observed for the first time when protons are made available intra- or intermolecularly.

We have recently reported that easily accessible formamidine-urea compounds[1] exchange imine fragments with primary nitrogen nucleophiles in non-protic solvents, giving access to a variety of derivatives of tunable reactivity (Figure 1, path **a**).[2] Since the potential biological activity of formamidine ureas is likely to depend on their electrophilic properties,[3,4] the examination of their chemistry in protic solvents is of interest. We report here the unmasking of the alternative exchange pathway (Figure 1, **b**) in methanol and with amine nucleophiles bearing pendant hydroxy groups.

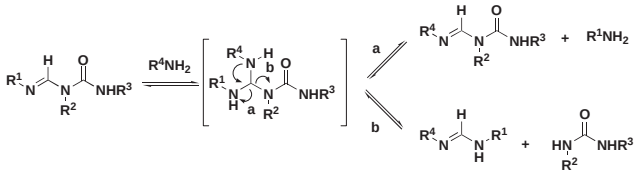

Figure 1. Pathways for amine reactions with formamidine ureas.

In our previous work,[2] we reported that the use of methanol as solvent gave no formamidine urea–amine exchange over 12 h at room temperature. We later detected small amounts of various species after 24-h reaction time under these conditions. For example, the reaction of 1-(*tert*-butyliminomethyl)-1,3-dimethylurea (**1**) with benzylamine in methanol provided three main products (Figure 2): the previously-reported exchange product **2** (pathway **a** in Figure 1), the unsymmetrical formamidine **3**, and the symmetrical formamidine **4**. That formamidine **4** can arise from either **2** or **3** was confirmed by testing of each compound separately;[5] the exchange with **2** appeared to be more facile.

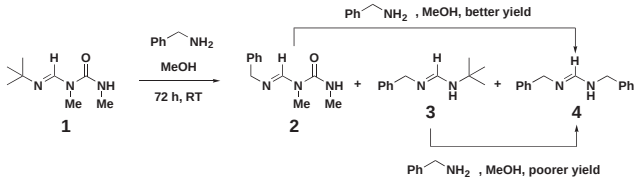

Figure 2. Distribution of species observed from **1**.

Compound **3** was found to be the major product from **1** after 72 h at room temperature, although the separation of the resulting mixture was difficult. This result is notable because it marks the first time that urea, rather than amine, has been found to be the leaving group from the presumed tetrahedral intermediate obtained by amine attack at the formamidine carbon (pathway **b** in Figure 1).

The observation of **3** and **4**, representing the activation of urea rather than amine as leaving group in protic solvent, raised new questions about the role of hydrogen bonding in the electrophilic chemistry of compounds such as **1**. The potential role of intramolecular H-bonding was explored by the treatment of **1** (1 equiv) with a series of aminoalcohols (1.1 equiv) neat or in methanol solution.[6] In most cases the disappearance of formamidine urea was accompanied by the formation of a mixture of products, from which pure compounds could be isolated and characterized. However, the required separations were too difficult for the analysis of more than a few reactions, and so we turned to electrospray ionization mass spectrometry (EIMS). Comparison of EIMS data of crude mixtures, an example of which is shown in Figure 3, and purified products established that the technique conveniently provides an accurate picture of the outcome of the process. Amidines are readily protonated and therefore detected with excellent selectivity by EIMS, without fragmentation,[7] under our conditions. Thus, the species detected by EIMS comprise at least 90% of the compounds in solution, as determined by comparison to the mass balance of isolated products.

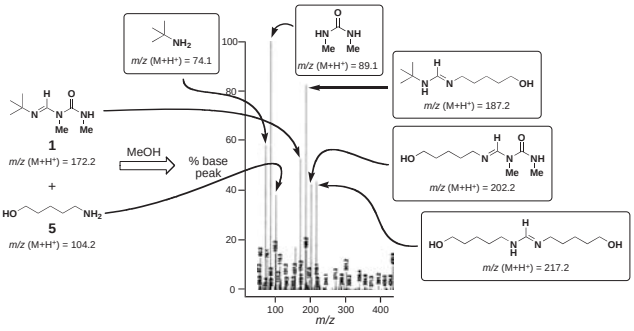

Figure 3. Direct EIMS analysis of an exchange reaction in methanol.

A summary of the results thus obtained is given in Figure 4. Structural type "**B**" was observed to be the major or dominant product for a wide variety of amino alcohol structures, involving chain lengths from two to six carbons and several types of functional groups. A few compounds of intermediate chain lengths gave disubstituted products (type **C**) as the major species. The methyl ethers of a representative set of compounds behaved as "normal" amines, giving only the original exchange products ("**A**") in CH_2Cl_2 solvent and slow reaction to formamidines of the **B** and **C** classes in methanol. It is therefore clear that the presence of an intramolecular hydroxy group largely redirects the exchange chemistry of these nucleophiles.

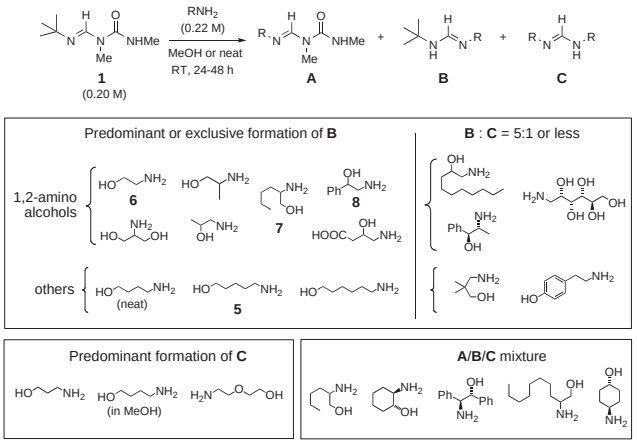

Figure 4. Summary of product distributions from the reactions of **1** with amino alcohols.

The reaction of **1** with 5-amino-1-pentanol (**5**) was examined in a variety of solvents. The process was quite slow in nonpolar solvents (benzene, Et_2O), with the amidine of type **B** being the major product. Alcohol solvents gave faster reactions and roughly equivalent amounts of **B** and **C**, with rates generally proportional to polarity (MeOH $\approx$ ethylene glycol $\approx$ glycerol $>$ EtOH $\approx$ phenol $>$ *i*-PrOH). Unusual behavior was found in diethylamine (dominant formation of amidine **B** from the primary amino alcohol) and 2,2,2-trifluoroethanol (TFE, exclusive formation of **C**). Reactions of **1** with **6**, **7**, and **8**, which gave the *tert*-butyl amidines **B** in methanol, also afforded **C** as the major products in TFE. Other than phenol, TFE was the most acidic solvent used; stronger acids such as acetic or propionic acid induced decomposition rather than substitution. It should also be noted that water can be used as a cosolvent or alone without causing a significant amount of hydrolysis of the formamidine urea moiety relative to amino alcohol substitution; in these cases mixtures of all three products (**A** + **B** + **C**) were obtained.

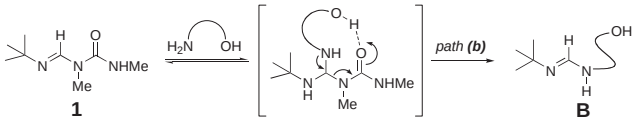

Figure 5. Proposed mechanism of intramolecular and intermolecular activation of urea as the leaving group in formamidine urea substitution.

The opening of a pathway in which the urea fragment is displaced by the entering amine nucleophile is likely to arise from hydrogen bonding activation of the urea as a leaving group. Such an intramolecular mechanism is shown in Figure 5. Protic solvents presumably engage in H-bonding to similar effect, though with variable efficiency depending on the properties of the solvent. The origin of the overall sluggishness of the reaction in protic solvents may be due to the better solvation, and therefore lower reactivities, of both reaction partners.

In conclusion, we have described here a new aspect of the interplay between nucleophile and leaving group in the exchange process of formamidine ureas with amines. If the nucleophilic amine is a primary amine, hydrazine, hydrazide or hydroxylamine, and the reaction is performed in aprotic solvents, the imine fragment is exchanged to give a new formamidine urea. In contrast, if the nucleophile is an amino alcohol and the reaction is carried out in protic solvents or under "solvent-free" conditions, the urea component becomes the leaving group giving formamidines as the major products. This chemistry is relevant to the potential biological activity of formamidine ureas and formamidine compounds in general. The pendant hydroxy group of the amino alcohols can be regarded as a crude mimic of a protic amino acid side chain in an enzyme binding site, and thus we anticipate that these formamidine-type electrophiles may be highly and selectively responsive to the binding pockets of certain proteins. Studies exploring such interactions are underway in our laboratory.

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References and Notes

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4 a) D. Díaz and M. G. Finn, *Chem. Commun.*, **2004**, 2514, and references therein. b) For other examples of fragment exchange in amidine electrophiles, see: D. M. Vyas, Y. Chiang, D. Benigni, and T. W. Doyle, *J. Org. Chem.*, **52**, 5601 (1987); S. Delarue, S. Girault, F. D. Ali, L. Maes, P. Grellier, and C. Sergheraert, *Chem. Pharm. Bull.*, **49**, 933 (2001); A. Donetti, E. Cereda, E. Bellora, A. Gallazzi, C. Bazzano, P. Vanoni, P. Del Soldato, R. Micheletti, F. Pagani, and A. Giachetti, *J. Med. Chem.*, **27**, 380 (1984).
5 Compound **3** was prepared independently by sequential treatment of *N*,*N*-dimethylformamide dimethylacetal with *tert*-butyl and benzyl amines, or from the commercially available dimethyl-*tert*-butyl formamidine intermediate.
6 Typical experimental procedure: To a solution of **1** (1.0 equiv, 0.2 M) in dry methanol was added 5-amino-1-pentanol (1.1 equiv). The mixture was stirred at room temperature for 24–48 h, after which time the mixture was analyzed by EIMS using an Agilent 1100 LC/MS spectrometer (model G1946A) with mobile phase composed of 90:10 CH_3OH:H_2O, and ionization current at a relatively low setting of 60. Product mixtures were invariant to storage in this solvent system for at least 15–30 min, which exceeds the duration of the EIMS analyses. Upon exposure to aqueous mixtures for longer periods, hydrolysis of formamidine ureas and, to a much lesser extent, formamidines, becomes evident.
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