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Expanded Chemistry of Formamidine Ureas

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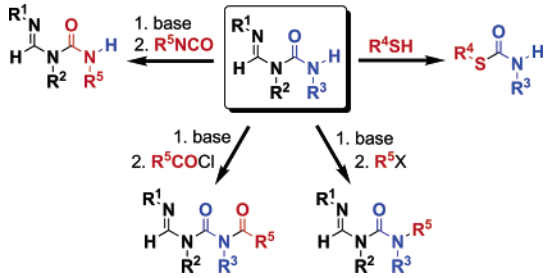
ABSTRACT



Formamidine ureas display a rich manifold of reactivity. Thiols induce substitution at the carbonyl carbon to give thiolcarbamates; base-mediated alkylation and acylation occurs at the terminal urea nitrogen, and a new fragmentation/acylation pathway has been uncovered with isocyanates.

We have recently described a facile entry to the formamidine urea skeleton **1** and the tunable electrophilicity of the formamidine center in such compounds.[1,2] Thus, primary amine nucleophiles undergo exchange (Scheme 1), and rates

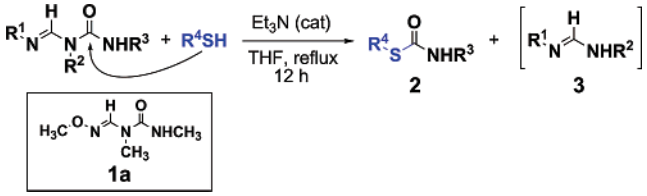
Scheme 1

1

of hydrolysis vary over 3 orders of magnitude depending on the steric and electronic properties of the R^1 substituent.[2] We report here several additional modes of reactivity of these multifunctional structures. In addition to standard alkylation of the distal urea nitrogen, thiols have been found to react much differently than nitrogen nucleophiles and a new formamide fragment exchange process has been uncovered.

In contrast to the exchange reaction observed with amines, which requires nucleophilic attack on the formamidine carbon, thiols cleave the central *N*-acyl bond to generate thiolcarbamates in good yields (Scheme 2); the putative

Scheme 2



2 **3**

1a

amidine byproduct **3** was not characterized. Neither 1,3-disubstituted ureas nor several *N*-acylureas underwent any trace of the corresponding reaction, demonstrating that the amidine group is activating. Note also that treatment of *N*,*N*′-diphenylformamidine with thiols did not give nitrogen substitution, in contrast to the facile reactivity of this group with amines.[3] When made electron-rich by a heteroatom donor in R^1, as in the oxime ether **1a**, the formamidine urea

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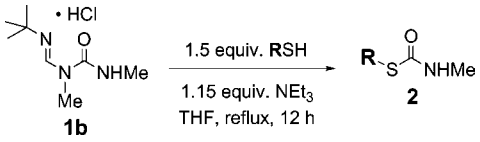
was rendered inert to thiols, similar to its stability toward attack at the formamidine carbon in hydrolysis.[2]

The reaction of formamidine ureas and thiols is catalyzed by base and gave the best yields in THF or CH_3CN. Table 1 outlines the scope of the reaction with 1-(*tert*-butylimino-methyl)-1,3-dimethyl urea hydrochloride **1b**, which is conveniently available in large quantities.[1] Triethylamine (1 equiv) was used to neutralize the starting hydrochloride salt. The process allows the introduction of side chains bearing other reactive functionalities, including halide, ester, alcohol, amine, and thiol groups (entries 6−10).

Table 1. Reactions of **1b** with Thiols[a]



entry	R	% yield[a]	product
1	*p*-X−C_6H_4 (X = H, Me, OMe, Br, Cl, OH)	66−70	**2a−f**
2	2-naphthyl	68	**2g**
3	CH_2CH_2Ph	69	**2h**
4	CH_2Ph	67	**2i**
5	*n*-C_6H_{13}	71	**2j**
6	$CH_2CH_2CH_2Cl$	62	**2k**
7	$CH_2CH_2CO_2Et$	70	**2l**
8	$(CH_2)_4OH$	61	**2m**
9	$CH_2CH_2NH(n\text{-}C_4H_9)$	63	**2n**
10	$(CH_2)_8SH$	67	**2o**

[a] Yields are reported for pure products after column chromatography and are based on **1b**.

The biological properties of thiolcarbamates have received much attention,[4] including their use in herbicides,[4b−f] pesticides,[4g−i] antifertility agents,[4j] and antivirals.[4k] The cleavage of the acyl−S bond of thiolcarbamates by protic solvents and nucleophiles is well-known[5,7a] and may be related to the biological activity of these compounds.[4k] Early routes to thiolcarbamates included acid-mediated addition of alcohols to thiocyanates,[6] the Newman−Kwart rearrangement,[7] and various procedures involving phosgene[8] or other highly energetic reagents.[9] More recently, a variety of methods have been reported, including aminolysis of cyclic thioxocarbonates,[10] carbonate-mediated addition of alkyl halide to carbon disulfide,[11] elaboration of activated carbamoyl derivatives[5a,12] and thiocarbonates,[13] O-to-S allylic rearrangement,[14] rearrangement of *N*-alkyl carbonimidodithionates,[15] various carbonylation and thiocarbonylation reactions,[16] and thiolation of isocyanates,[4k] the last being the most general. The process described here is notable for its convenience and lack of hazardous reagents.

Given the differing apparent sites of attack of amines and thiols on thiolcarbamate electrophiles, the internal competition offered by a nucleophile containing both groups was of interest. As shown in Scheme 3, *L*-cysteine ethyl ester hydrochloride and formamidine **1b** gave enantiomerically pure thiazoline[17] (+)-**4** and 1,3-dimethylurea as the only observed products, the former in 78% isolated yield. The absence of racemization was confirmed by reduction to the known[18] hydroxymethyl derivative. The nature of the product allows us to propose that amine substitution at the formamidine carbon (path **a**) is initially favored, followed by intramolecular cyclization of thiol (or thiolate) in the formamidine urea intermediate **5**. It is difficult to propose a reasonable mechanism for the formation of **4** from initial thiol addition to **1b** (path **b**) to give intermediate **6**. A similar reaction is observed in the interaction of acyclic 1,2-diamines with formamidine ureas. Thus, enantiomerically pure (*R*,*R*)-1,2-diphenylethylenediamine **7** smoothly afforded the corresponding chiral imidazoline **8** (Scheme 3),[19] presumably

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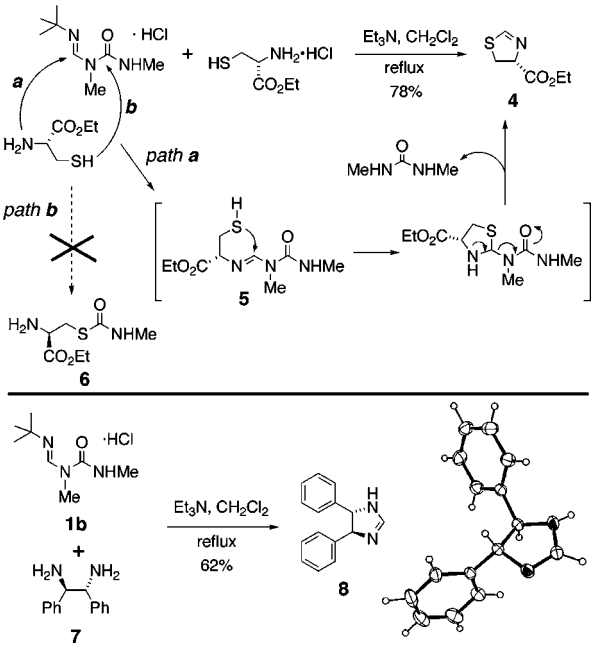
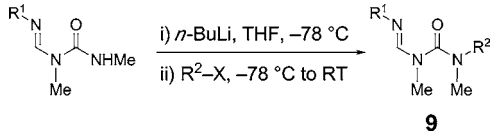
Scheme 3



by an analogous mechanism. The X-ray crystal structure of **8** is shown in Scheme 3.

Formamidine ureas of the type **1** were deprotonated by a strong base and trapped with alkyl or acyl halides at the distal urea nitrogen to give the N-alkylated/acylated products **9** (Table 2), thus extending the range of formamidine urea

Table 2. Alkylation of Formamidine Ureas[a]

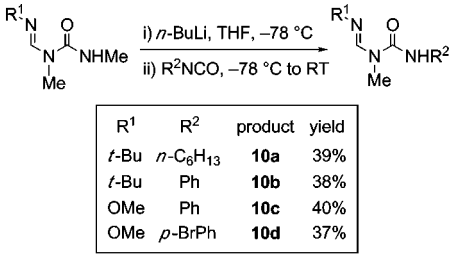


entry	R^1	R^2–X	% yield[b]	product
1	*t*-Bu	MeI	68	**9a**
2	*t*-Bu	*n*-$C_8H_{17}Br$	69	**9b**
3	*t*-Bu	$HC{\equiv}CCH_2Br$	71	**9c**
4	*t*-Bu	PhCOCl	67	**9d**
5	$PhCH_2$	MeI	66	**9e**
6	$PhCH_2O$	MeI	70	**9f**
7	$PhCH_2O$	*n*-$C_5H_{11}COCl$	72	**9g**
8	MeO	MeI	69	**9h**
9	MeO	PhCOCl	67	**9i**

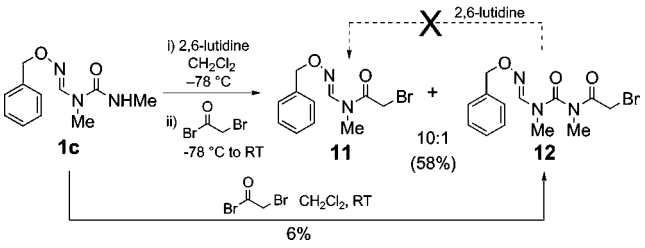
[a] Representative selection of these reactions was also found to work equally well with $LiN(SiMe_3)_2$, $NaN(SiMe_3)_2$, and NaH in place of *n*-BuLi; 2,6-lutidine was not effective [b] Yields are reported for pure products after column chromatography.

structures available beyond that provided by the original synthetic method. While such reactivity is unsurprising, being shared by simple ureas, the process took a different and unexpected course with isocyanate electrophiles. In these cases, the reaction mixtures were much less clean, but new formamidine ureas incorporating the elements of isocyanate in place of the original urea were the major isolable products (**10a**−**d**, Scheme 4). Similarly, the reaction of **1c** with

Scheme 4



R^1	R^2	product	yield
t-Bu	*n*-C_6H_{13}	**10a**	39%
t-Bu	Ph	**10b**	38%
OMe	Ph	**10c**	40%
OMe	*p*-BrPh	**10d**	37%



bromoacetyl bromide in the presence of a 2,6-lutidine (or *n*-BuLi, but in lower yield) gave the exchanged formamidine urea **11** along with a small amount of the expected acylated product **12** (Scheme 4). Compound **12**, obtained in very low yield in the absence of base, is stable to 2,6-lutidine and so is not an intermediate on the way to **11**.

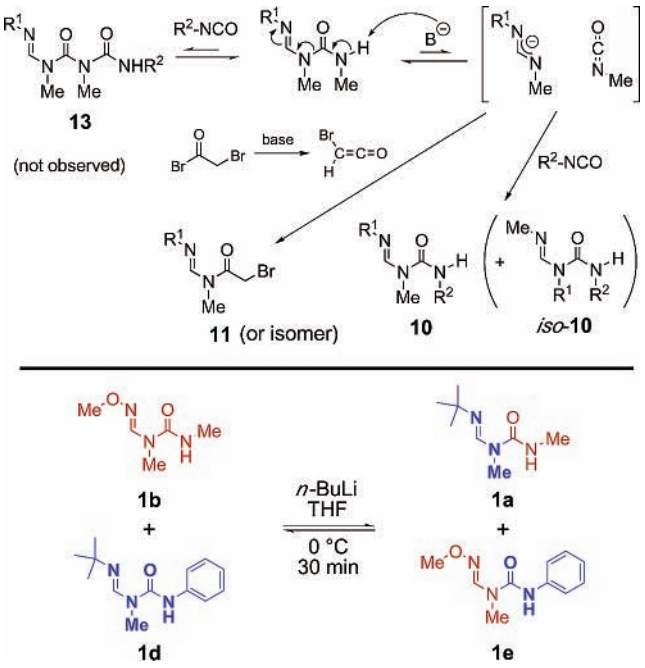


Figure 1. (Top) Proposed mechanism of formamidine urea fragmentation and trapping with isocyanate reagents. (Bottom) Crossover experiment.

Figure 1 shows a possible mechanism for the formation of products such as **10** and **11**. We suggest that structures **13** are unstable under the reaction conditions, allowing base-induced fragmentation of the formamidine urea to give amidine and isocyanate pieces. Capture of the former with added isocyanates or bromoketene (generated from bromoacetyl bromide and base[20]) would give **10** and **11**, respectively (Scheme 4). In the case of the *tert*-butyl and oxime formamidines used as starting materials, the expected product isomers (**10** and *iso*-**10**) could differ markedly in their energies or rates of formation; in the event, only one isomer of each compound was characterized. The proposed pathway was supported by the observation of crossover products **1a** and **1e** from treatment of a mixture of **1b** and **1d** with base (Figure 1) and by the observation of isocyanate from **1b** + *n*-BuLi by IR spectroscopy (Supporting Information).

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In summary, along with the amine exchange chemistry previously reported,[2] the carbonyl electrophilicity toward thiols, deprotonation/alkylation at nitrogen, access to thiazoline and imidazoline rings, and amide fragment exchange described here comprise a unique landscape of chemical reactivity of the formamidine urea unit. Current studies are directed toward the synthesis of new molecules with pharmacological and metal-binding properties.

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Supporting Information Available: Experimental procedures and full characterization of new compounds and selection of ^{1}H NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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