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First Practical Synthesis of Formamidine Ureas and Derivatives

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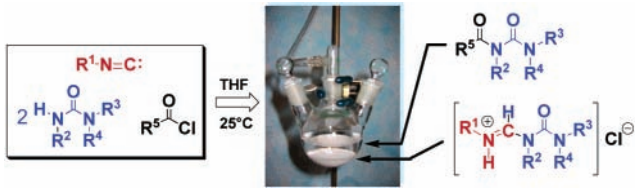
ABSTRACT

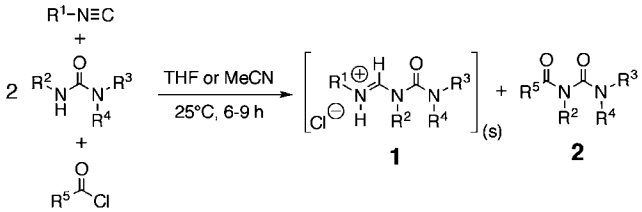


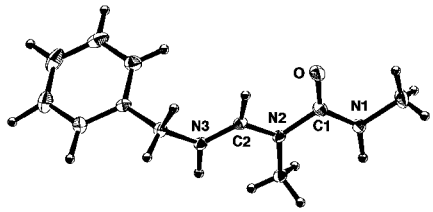
Isonitriles and ureas undergo a condensation reaction in the presence of acid chlorides to give formamidine ureas, for which no general synthetic routes currently exist. A mechanism is proposed in which the key intermediate is an electrophilic adduct of isonitrile and acid chloride. The process is tolerant of moderate variability in the nature of the components, and access to formamidine ureas of varying substitution patterns is further enhanced by a facile exchange reaction with amines.

Ureas are important components of biologically active molecules, having greater hydrogen bonding potential than amides while being less acidic than sulfonamides.[1] They have found use as amide bond surrogates,[2] allowing for a β-sheet-like display of functionality.[3] The development of new urea derivatives is therefore of practical interest. Here we report a novel and convenient condensation reaction that assembles formamidine ureas from readily available precursors.

Figure 1 outlines the process, in which the addition of a substituted urea to a mixture of isocyanide and acid chloride gives formamidine urea salts **1** in pure form. The structure of **1a** was established by X-ray crystallography (Figure 1) as well as appropriate spectroscopic data. The mother liquor contains *N*-acylureas **2**, identified by comparison to authentic compounds, in amounts approximately equimolar to the formamidine precipitates.[4]

The yields of **1** are maximized by the use of 3 equiv of urea, and THF provides the best results in general (except when the urea is not soluble, in which case acetonitrile is often preferred).[4] The reaction is easy to perform, and in most cases the solid formamidine hydrochloride salts can be isolated by filtration and washing to remove excess urea





1a
$R^1 = CH_2Ph$
$R^2 = R^3 = Me$
$R^4 = H$

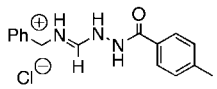


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Figure 1. (Top) Formamidine and *N*-acyl urea formation. (Middle) X-ray crystal structure of **1a**. (Bottom) Formamidine derived from a hydrazide instead of urea.

(1) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456−463.
(2) (a) Burgess, K.; Linthicum, D. S.; Shin, H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 907−909. (b) Burgess, K.; Ibarzo, J.; Linthicum, D. S.; Russell, D. H.; Shin, H.; Shitangkoon, A.; Totani, R.; Zhang, A. J. *J. Am. Chem. Soc.* **1997**, *119*, 1556−1564
(3) Nowick, J. S. *Acc. Chem. Res.* **1999**, *32*, 287−296.
(4) See Supporting Information.

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and the soluble byproduct **2**. With a standard set of reaction conditions, the process was found to be tolerant of substantial variations in the isocyanide and urea components, as shown in Table 1.

Table 1. Isolated Yields of Formamidine Urea Adducts Formed under a Standard Set of Reaction Conditions[a]

entry	R^1	R^2	R^3	R^4	solvent	product	% yield
1	CH_2Ph	Me	Me	H	THF	**1a**	73
2	*t*-Bu	Me	Me	H	THF	**1b**	71
3	cyclohexyl	Me	Me	H	THF	**1c**	68
4	CH_2CO_2Me	Me	Me	H	THF	**1d**	71
5	*n*-Bu	Me	Me	H	THF	**1e**	79
6	CH_2Ph	Me	Me	H	THF	**1f**[b]	52
7	CH_2Ph	$-CH_2CH_2-$		H	MeCN	**1g**	77
8	CH_2Ph	Me	H	H	MeCN	**1h**	38[c]
9	CH_2Ph	Ad[d]	H	H	MeCN	**1i**	27[c]
10	CH_2Ph	Ph	H	H	MeCN	**1j**	37[c]
11	CH_2Ph	CH_2Ph	H	H	MeCN	**1k**	23[c]
12	CH_2SO_2Ar[e]	Me	Me	H	THF	**1l**	77
13	$-(CH_2)_6-$[f]	Me	Me	H	THF	**1m**	68
14	2,6-Me_2Ph	Me	Me	H	THF	**1n**	66
15	CH_2Ph	allyl	allyl	H	MeCN	**1o**	72[g]
16	CH_2Ph	allyl	H	H	MeCN	**1p**	49[g]

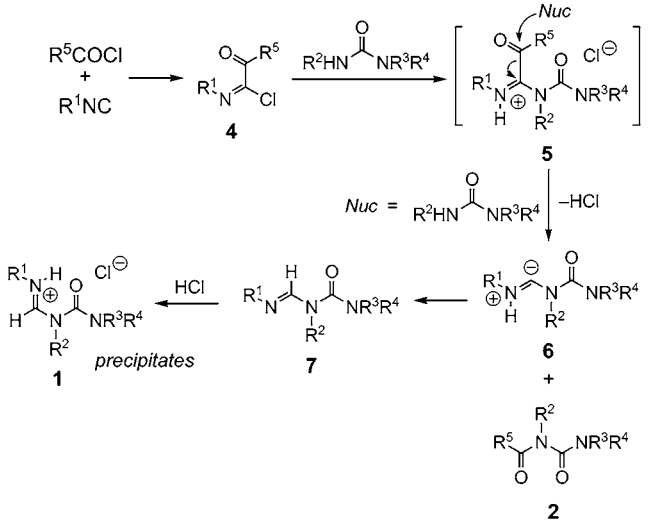
[a] Isonitrile (0.8 M); 1.1 equiv of acetyl chloride, 3.0 equiv of urea. [b] 1,3-Dimethylthiourea was used. [c] Only 1.1 equiv of urea was used due to poor solubility, which probably accounts for the relatively low yield. [d] Ad = 1-adamantyl. [e] Ar = *p*-tolyl. [f] 1,6-Diisocyanohexane; 4 equiv of urea and 2 equiv of acetyl chloride used per equivalent of diisocyanide. [g] Product does not precipitate and was isolated by column chromatography.

Yields were in the 50−80% range, except for cases in which the poor solubility of the urea forced its use in only stoichiometric amounts (entries 8−11). The process strongly favors monosubstituted urea nitrogen atoms in favor of unsubstituted (NH_2) or doubly substituted (NR_2) centers. Thus, monosubstituted ureas react at the substituted position exclusively (entries 8−11 and 16), even in the hindered adamantyl case, and *N*,*N*-dimethylurea is completely unreactive in both MeCN and THF. Other notable reactions include the facile formation of a bis(formamidine urea) (entry 13), the successful use of hindered isocyanides (entries 2 and 14), and the incorporation of allyl-substituted ureas (entries 15−16). Amides such as *N*-methylacetamide are unreactive, but *p*-tolylhydrazide was found to be converted to the corresponding formamidine adduct (**3**, Figure 1), although in low yield (39%) due to the relatively poor solubility of the hydrazide nucleophile. The preparation of **1b** has been scaled up to 0.1 mol with no difficulty.

An extensive survey of electrophiles[4] established that the reaction is restricted almost exclusively to acid chlorides: little or no yield was obtained with acyl bromides, oxalyl and sulfuryl chloride, sulfonyl chlorides, an acyl fluoride, several activated alkyl chlorides and bromides, trimethylsilyl chloride, and protic acids. In contrast, yields are independent of the nature of the acid chloride until steric hindrance becomes too great (e.g., pivaloyl chloride or 2,6-dimethoxybenzoyl chloride). Most interestingly, triphenylmethyl (trityl) chloride promotes the reaction, albeit in modest yield (37%).

A proposed mechanism is shown in Scheme 1. In the chemistry of Livinghouse and co-workers, isocyanide-acyl

Scheme 1



chloride adducts of the type **4** are treated with Ag^+ to generate highly electrophilic acylnitrilium ions, which are trapped intramolecularly to afford cyclization products in high yield.[5] We suggest that **4** is sufficiently electrophilic to undergo substitution by urea at the chloroiminium carbon to give **5**, analogous to Vilsmeier−Haack−Arnold chemistry.[6] (Note, however, that activation of isocyanide with excess HCl, giving the imidoyl chloride species $R^1N{=}CHCl$ and, presumably, its conjugate acid, is apparently not sufficient,[7] even though the Vilsmeier reagent $[Me_2N{=}CHCl]^+$ is reactive with ureas.[8]) Another equivalent of urea is then proposed to attack the electrophilic carbonyl center of **5** to release acylurea **2** and intermediate **6**. The latter species, an ylide (or a stabilized carbene resonance form, not shown), should undergo rapid proton transfer to give the formamidine **7**. An equivalent of HCl is extracted by precipitation of the hydrochloride salt **1**. Thus, when only 1 equiv of urea is used, a maximum of 50% yield can be expected, as is indeed observed.[4] Trityl chloride can presumably activate the isonitrile by formation of an analogous electrophilic adduct, although the nature of such a species is not yet clear. The efficiency and convenience of the reaction is governed by both the generation of the reactive adducts and the precipitation of the final product. Thus, the most effective solvents

(5) (a) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1159−1165. (b) Westling, M.; Livinghouse, T. *Tetrahedron Lett.* **1985**, *26*, 5389−5392. (c) Westling, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1987**, *109*, 590−592. (d) Lee, C. H.; Westling, M.; Livinghouse, T.; Williams, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 4089−4095.

(6) Jutz, C. *Adv. Org. Chem.* **1976**, *9*, 225−342.

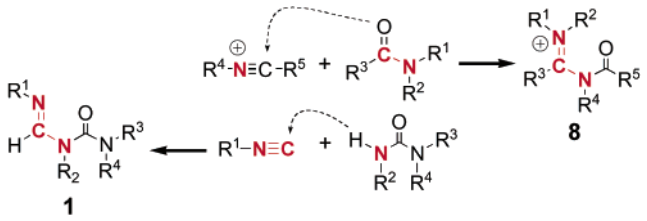
(7) Hegarty, A. F.; Chandler, A. *Tetrahedron Lett.* **1980**, *21*, 885−888.

(8) (a) Jentzsch, W.; Seefelder, M. *Chem. Ber.* **1965**, *98*, 274−279. (b) Bitter, I.; Kárpáti-Ádám, E.; Tóke, L. *Acta Chim. Acad. Sci. Hung.* **1979**, *102*, 235−246. (c) Csuros, Z.; Soos, R.; Bitter, I.; Karpati-Adam, E. *Acta Chim. (Budapest)* **1972**, *73*, 239−246.

(THF, MeCN) are those that can support charged or polar intermediates but also allow the formamidine urea salts to crystallize. Solvents either more (DMF) or less (Et_2O, toluene) polar are not as effective.

Although several *N*-arylformamidine compounds have been identified as insecticides,[9] formamidine ureas are little-known species. They may be regarded as a subset of acylamidinium compounds (**8**, Scheme 2), which are available by capture of nitrilium ions with amide nucleophiles.[10] In such reactions, the acylamidine nucleus is formed by a transfer of oxygen from the amide component (Scheme 2), a difficult process enabled by the highly reactive nature of the electrophilic nitrilium carbon. In contrast, our reaction accomplishes a formal H-atom transfer from a urea to the isonitrile carbon (Scheme 2). The overall transformation is made possible by the ability of the acid chloride to change the nature of the isonitrile carbon from nucleophile to electrophile. Such an *umpoulung* can also be accomplished with transition metals,[4] but apparently such routes have not employed ureas as the capturing nucleophiles.

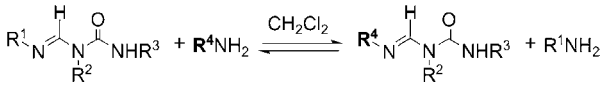
Scheme 2



Complete hydrolysis of **1a** or **1b** with aqueous $NaHCO_3$ in the presence of CH_2Cl_2 at 40 °C provides 1,3-dimethylurea and benzylamine or *tert*-butylamine, consistent with the reported reactivity of acylamidinium compounds with nucleophiles (including water) at both sp^2-hybridized carbon centers.[11] However, compounds **1** are somewhat stable in alcohol and water at neutral pH and ambient temperature, showing substantial hydrolysis only after 12−24 h. The salts are soluble and stable in polar organic solvents (DMF, THF, and CH_3CN), and are also unchanged upon heating in nonpolar solvents, showing no tendency to undergo the reported thermal fragmentation of amidine ureas to isocyanate and amidinium species.[11c,d]

We have also discovered that formamidine ureas in the unprotonated form undergo a facile exchange reaction with amine nucleophiles as shown in Scheme 3. The position and rate of the equilibrium depends on both steric and electronic factors, being driven to the right by large groups at R^1 and electron-rich groups at R^4. This exchange route offers very convenient access to different formamidine ureas from a single isonitrile precursor. Further explorations of the synthesis, reactivity, and biological activity of these and related compounds are in progress.

Scheme 3



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Supporting Information Available: Expanded discussion, experimental details, characterization of new compounds, and X-ray crystallographic details. This material is available free of charge via the Internet at http://pubs.acs.org.

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