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First Practical Synthesis of Formamidine Ureas and Derivatives

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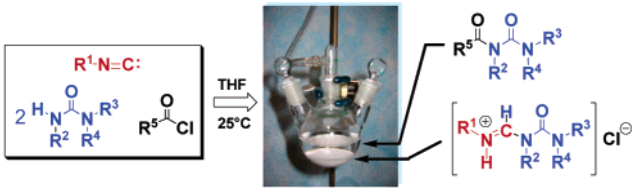
ABSTRACT

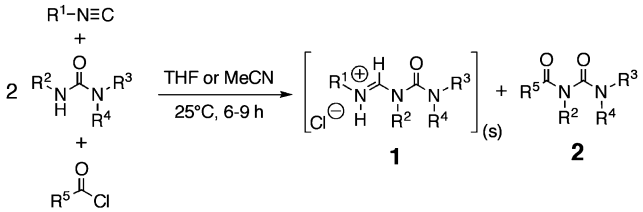


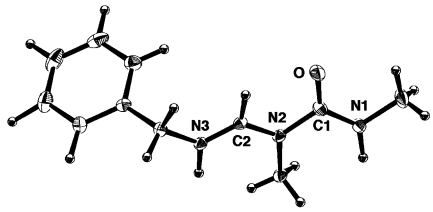
Isonitriles and ureas undergo a condensation reaction in the presence of acid chlorides to give formamidine ureas, for which no general synthetic routes currently exist. A mechanism is proposed in which the key intermediate is an electrophilic adduct of isonitrile and acid chloride. The process is tolerant 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
$R^1 = CH_2Ph$
$R^2 = R^3 = Me$
$R^4 = H$

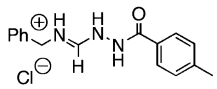


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Figure 1. (Top) Formamidine and *N*-acyl urea formation. (Middle) X-ray crystal structure of **1a**. (Bottom) Formamidine derived from a hydrazide instead of urea.

(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]

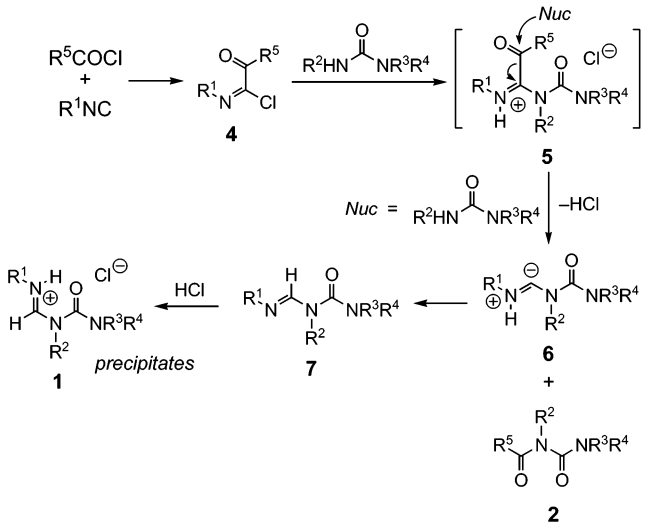
[a] Isonitrile (0.8 M); 1.1 equiv of acetyl chloride, 3.0 equiv of urea. [b] 1,3-Dimethylthiourea was used. [c] Only 1.1 equiv of urea was used due to poor solubility, which probably accounts for the relatively low yield. [d] Ad = 1-adamantyl. [e] Ar = *p*-tolyl. [f] 1,6-Diisocyanohexane; 4 equiv of 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.

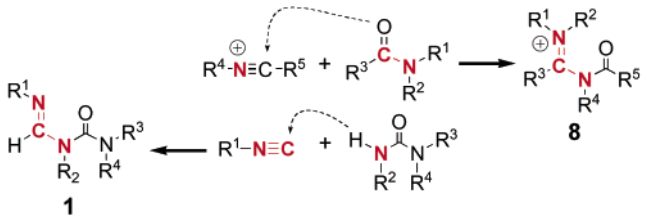
(7) Hegarty, A. F.; Chandler, A. *Tetrahedron Lett.* **1980**, *21*, 885−888.

(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.

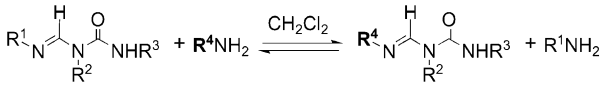
Scheme 2



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



Acknowledgment. We thank The Skaggs Institute for Chemical Biology for support of this work and Dr. Michal Sabat (University of Virginia) for X-ray crystallography of compound **1a**. D.D. thanks the Spanish MECD (Ministerio de Educación, Cultura y Deportes; Secretaria de Estado de Educación y Universidades) for a postdoctoral fellowship cofinanced by the Fondo Social Europeo.

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.

OL034287R

(9) (a) Orr, G. L.; Orr, N.; Cornfield, L.; Gole, J. W. D.; Downer, R. G. H. *Pestic. Sci.* **1990**, *30*, 285−294. (b) Ismail, S. M. M.; Matsumura, F. *Insect Biochem. Mol. Biol.* **1992**, *22*, 713−720. (c) Longtine, C. A.; Zehnder, G. W.; Radcliffe, E. B. *J. Entomol. Sci.* **1996**, *31*, 89−101.

(10) (a) Glocker, M. O.; Shrestha-Davadi, P. B.; Küchler-Krischun, J.; Hofmann, J.; Fischer, H.; Jochims, J. C. *Chem. Ber.* **1993**, *126*, 1859−1865. (b) Jochims, J. C.; Glocker, M. O. *Chem. Ber.* **1990**, *123*, 1537−1544

(11) (a) Glocker, M. O.; Shrestha-Davadi, P. B.; Küchler-Krischun, J.; Hofmann, J.; Fischer, H.; Jochims, J. C. *Chem. Ber.* **1993**, *126*, 1859−1865. (b) Jochims, J. C.; Glocker, M. O. *Chem. Ber.* **1990**, *123*, 1537−1544. (c) Bitter, I.; Kárpáti-Ádám, E.; Tóke, L. *Acta Chim. Acad. Sci. Hung.* **1979**, *102*, 235−246. (d) Csuros, Z.; Soos, R.; Bitter, I.; Karpati-Adam, E. *Acta Chim. (Budapest)* **1972**, *73*, 239−246.

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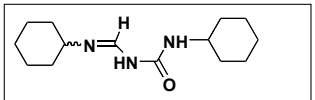
Supporting Information

EXPANDED DISCUSSION

Literature precedents

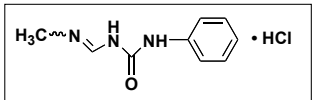
Four formamidine urea structures (bearing H-atom substitution at the central amidine carbon atom) are reported in the Beilstein database, as shown in Scheme S1. The only preparative details available (from the paper by Jentzsch & Seefelder) describe the elaboration of formamidines (RNHCOH) with oxalyl, phosphoryl, or sulfuryl chloride, to imidoyl halide (chloroiminium) species with subsequent capture by amines.

Scheme S1



Beilstein number: 2653437
CAS Registry number: 1220-02-6

Reference: Jentzsch, W.; Seefelder, M. *Chem. Ber.* **1965**, *98*, 274-279



Registry number: 4016773
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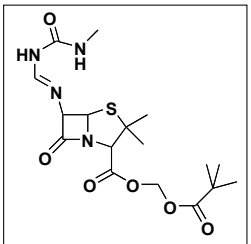
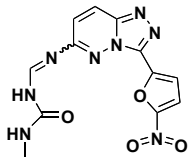


Beilstein number: 1054729
not found in CAS database



Beilstein number: 1046519
CAS Registry number: 49715-74-4

Reference: Berger, H.; Gall, R.; Merdes, H.; Stach, K.; Sauer, W.; Voemel, W. In *Ger. Offen.*; (Boehringer Mannheim G.m.b.H.). De, 1973, p 15 pp. Addn. to Ger. Offen. 12,030,218 (CA 076;72536w).

The vast majority of other amidine urea structures known have alkyl or aryl substitution at the central amidine carbon. The chemistry used to construct them is dominated by Vilsmeier-type sequences using $COCl_2$ or $SOCl_2$. Early examples include: Schwenker; Kolb. *Tetrahedron* **1969**, *25*, 5549-5551; Jentzsch, W.; Seefelder, M. *Chem. Ber.* **1973**, *106*, 105-114; Lecher, Gubernator *J. Am. Chem. Soc.* **1953**, *75*, 1087-1091 (activation using Hg^{II}). Thus, the process that we describe here is new and quite a bit more convenient than previous methods.

The more general amidine nucleus [R^1HN-$C(R^2)$=NR^3, with R^2 usually H] is available from isonitriles and amines under a variety of conditions. Prominent among these is mediation by electrophilic "soft" metals such as Cu, Hg, and Ag,[1-10] and more recently In.[11] This general scheme has also been applied to hydrazide and sulfonamide nucleophiles.[12,13] A very early report describes the simple addition of amines to isonitriles in the presence of carboxylic acids.[14]

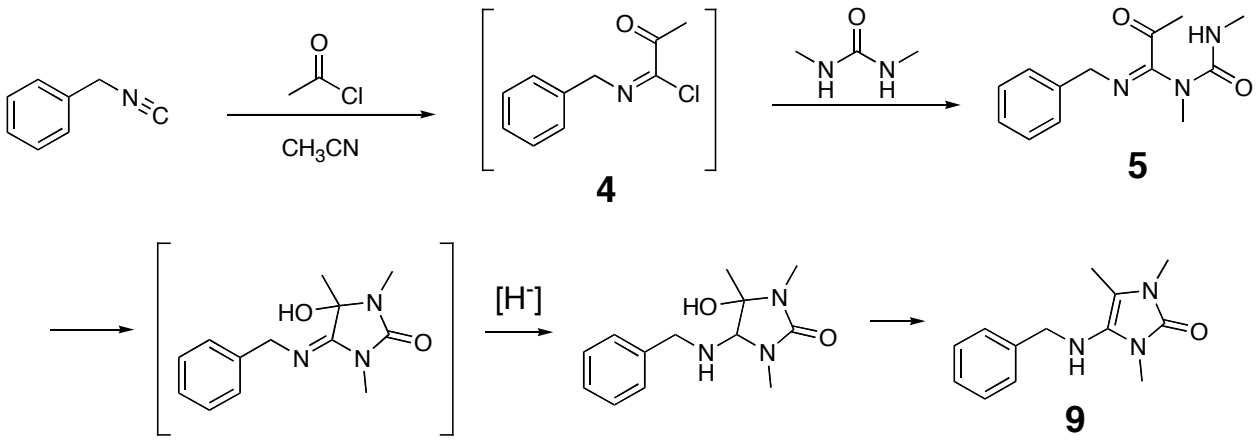
Other entries to amidines from isonitriles include the following.

– Pd-catalyzed assembly of isonitriles, aryl halides, and tin alkoxides, followed by amine displacement to give C-aryl amidines.[15]
– Electrophilic activation by *N*-halobenzotriazoles (via intermediate imidoyl benzotriazoles).[16]
– Uncatalyzed attack by secondary amines on electron-deficient isonitriles, such as α-cyano-β-carboxylate or α-cyano-β–phosphonate varieties.[17,18]
– Oxidative activation by (and incorporation of) chloramines T,[19,20] sulfenyl chlorides,[21] or elemental selenium.[22]

Reaction design

Our initial target, shown in Scheme S2, was a convenient synthesis of the imidazolone ring as a scaffold for displaying the urea functionality. Following the precedents of Ugi[23] and Livinghouse,[24-27] reaction of benzyl isocyanide with acetyl chloride was expected to form acetyl imidoylchloride **4**, which would be captured by urea to give the acetyl imidourea **5**. We hoped that **5** would be sufficiently stable to be treatable with reducing agent to provide the desired imidazalone **9**. Of course, the observed course of the reaction suggests that **5** is sufficiently electrophilic to be attacked by another equivalent of urea. Furthermore, the rate of reaction of **5** with urea must be substantially faster than the reaction of **4**, since the use of one equivalent of urea gives formamidine **1** rather than a buildup of intermediate **5**.

Scheme S2



Preliminary Survey of Reaction Conditions

A preliminary survey of reaction conditions was undertaken in order to establish the dependence of the process on solvent, reactant stoichiometries, and acyl halide. The results are shown in Table S1 and were summarized in the text, but are repeated here for convenience. Yields were found to be highest in THF, and the use of three equivalents of urea is significantly superior to one equivalent. No additional benefit was provided by the use of greater amonts of urea (data not shown). Reaction yields were similar among the five acid chlorides used; note that none of them are particularly hindered. In each case, the corresponding *N*-acylurea **6** was

detected as the major byproduct in solution, in >60% yield with respect to acyl chloride used (R^2 = Ph is known[28]). The use of acetyl chloride in catalytic amounts (0.1 equiv.) in CH_3CN or THF gave no precipitated product.

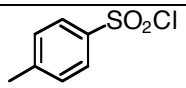
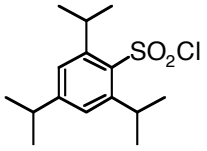
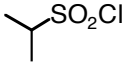
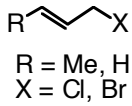
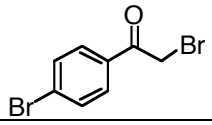
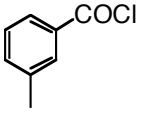
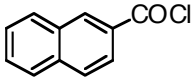
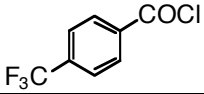
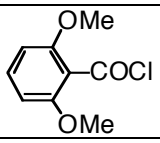
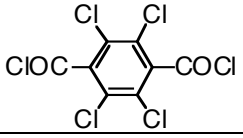
Table S1. Isolated yields of **1a** or **1b** under various conditions. In all cases, 1.1 equivalents of acyl chloride was used relative to isonitrile; except for the results shown in the last column, all reactions were performed with 1.0 equivalent of 1,3-dimethylurea.

R^1	R^2	solvent					3 equiv. urea
		MeCN	THF	Et_2O	toluene	DMF	THF
t-Bu	CH_3	43%	45%				73%
t-Bu	cyclopropyl	27%	50%				74%
t-Bu	isobutyl	21%	47%				62%
t-Bu	Ph	35%	46%				57%
t-Bu	CH_2Ph						56%
t-Bu	*n*-pentyl						63%
CH_2Ph	CH_3	46%	47%	23%	42%	0%	73%
CH_2Ph	cyclopropyl	41%	49%	22%	40%	0%	63%
CH_2Ph	isobutyl	46%	49%	25%	44%		63%
CH_2Ph	Ph	12%	50%	21%	33%		79%
CH_2Ph	CH_2Ph						62%
CH_2Ph	*n*-pentyl						60%

Survey of Electrophiles

Among the most intriguing of the mechanistic questions posed by these results is the role of the acyl chloride. To probe this, the electrophilic scope of the process was explored as shown in Table S2. Yields are constant for a variety of aliphatic (entries 1-7), simple aromatic (entries 9-12), and vinylic (entries 15-18) acyl chlorides. Pivaloyl chloride fails (entry 8), presumably for steric reasons, and 2,6-dimethoxybenzoyl chloride is similarly poor (entry 13). Both steric and electronic factors may play a role in the latter case, since the hindered but electron deficient tetrachloroterephthaloyl dichloride gives the desired product (entry 14). Ineffective are oxalyl and sulfuryl chloride (entries 19-20), sulfonyl chlorides (entries 21-23), an acyl fluoride (entry 24), several activated alkyl chloride and bromide electrophiles (entries 25–27), a silyl chloride (entry 28), and protic acids (entry 29). Acyl bromides give lower yields (and require longer reaction times) than acyl chlorides (entries 30-31). Most interestingly, triphenylmethyl (trityl) chloride promotes the reaction in modest yield (entries 32-33); trityl bromide is less effective (entry 34). Note that little change in yield with trityl chloride is observed when only one equivalent of urea is employed (31%) instead of the normal three equivalents (37%), in contrast to the behavior of the reaction mediated by acid chlorides (Table S1). The electron-rich compound crystal violet shows no activity (entry 35).

Table S2. Isolated yields of **1a** from the following reaction conditions: 1.0 equiv. benzyl isocyanide, 3.0 equiv.; 1,3-dimethylurea; 1.1 equiv. of the indicated electrophile; 0.8 M total solute in the indicated solvent; 9 h at room temperature.

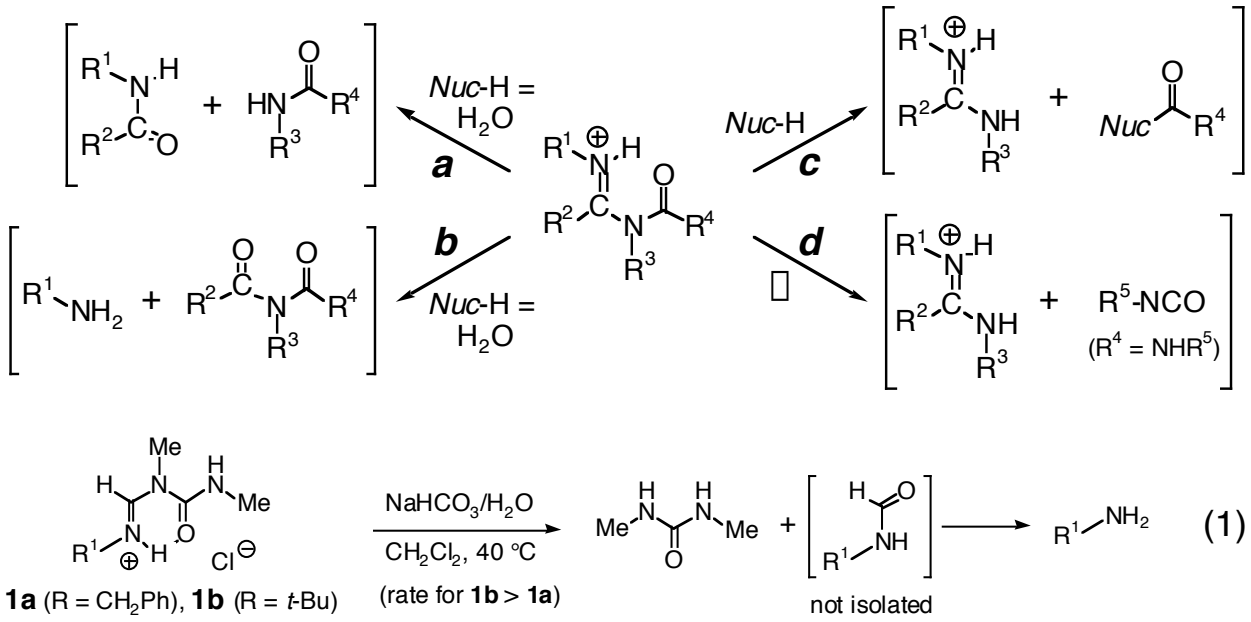
Entry	Electrophile	Solvent	Yield	Entry	Electrophile	Solvent	Yield
1	MeCOCl	THF	73	19	$(COCl)_2$	MeCN	0
2		THF	75	20	SOCl2	MeCN	0
3	*i*-PrCOCl	THF	74	21		MeCN	0
4	*n*-C_5H_{11}COCl	THF	72	22		THF	0
5	$PhCH_2COCl$	THF	71	23		MeCN	0
6	$ClCH_2COCl$	THF	69	24	PhCOF	MeCN	0
7	*t*-$BuCH_2COCl$	MeCN	60	25	 R = Me, H X = Cl, Br	MeCN	0
8	*t*-BuCOCl	MeCN	0	26	$PhCH_2Cl$	MeCN	0
9	PhCOCl	THF	72	27		MeCN	0
10		MeCN	70	28	Me_3SiCl	MeCN	4
11		THF	68	29	protic acid [a]	MeCN	0-5
12		MeCN	61	30	MeCOBr	MeCN	10
13		MeCN	0	31	$BrCH_2COBr$	MeCN	28
14		THF	68	32	Ph_3CCl	THF	37 [b]
15	CH_2=CHCOCl	MeCN	70	33	Ph_3CCl	THF	31 [b,c]
16	*trans*-MeCH=CHCOCl	MeCN	69	34	Ph_3CBr	THF	12
17	*trans*-PhCH=CHCOCl	MeCN	67	35	(*p*-$Me_2NC_6H_4)_3CCl$	THF	0
18	Me_2C=CHCOCl	MeCN	72				

(a) Introduced in the form of 4N HCl in dioxane, conc. HCl, or acetic acid. (b) reaction time 48 h. (c) One equivalent of urea used instead of three.

Previously reported chemistry of acylamidinium compounds and observed hydrolysis of formamidine ureas.

The known reactivity of acylamidinium compounds with nucleophiles is outlined in Scheme S3. Hydrolysis at the electrophilic iminium carbon atom has been observed to take two paths (*a* and *b*), while other nucleophiles can also attack the carbonyl carbon and thereby react according to paths *a–c*.[29-32] Our observed hydrolysis of **1a** and **1b** is shown in Equation 1.

Scheme S3. Reported routes of acylamidinium reactivity.



(1)

It should also be noted that allowing the urea-isocyanide condensation reaction to proceed too long causes a reduction in yield of formamidine urea. Thus, **1b** was isolated (from 1 equiv. *t*-BuNC, 1.1 equiv. MeCOCl, 3 equiv. 1,3-dimethylurea, THF; concentration = 0.6 M in isonitrile) in the following yields as a function of reaction time: 1.5 h, 25%; 3 h, 71%; 6 h, 70%; 9 h, 68%; 12 h, 55%; 16 h, 47%; 24 h, 45%; 36 h, 44%; 48 h, 42%. We do not yet know the fate of the presumably decomposed product at extended reaction times.

MATERIALS AND METHODS

General. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX–500 and/or AMX–400 spectrometer in $CDCl_3$, CD_3OD, CD_3CN or DMSO-d_6 as solvent, which is indicated in each case. Mass spectra were taken using a HP 1100 LC/MS spectrometer (model G1946A) with mobile phase composed of 90:10 CH_3OH:H_2O containing 0.1% CF_3CO_2H. Elemental analyses were performed by Midwest MicroLab, Inc. Melting points were measured in a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on MIDAC-FTIR or MAGNA-IR 550 spectrophotometers on solids dispersed on a CaF_2 disc (20 x 2 mm) or in KBr pellets. TLC analysis was facilitated by the use of the following stains in addition to UV light with fluorescent-indicating plates: phosphomolybdic acid, vanillin/EtOH, anisaldehyde/EtOH, or $KMnO_4$/H_2O. THF, acetonitrile, diethyl ether, and toluene were dried by passage through activated alumina columns;[33] dry DMF was purchased from Aldrich. Acid chlorides were purified by distillation immediately before use. Reactions requiring anhydrous conditions were performed under nitrogen.

General procedure for formamidine-urea formation (Table 2).

To a solution of isocyanide (1.6 mmol, 1.0 equiv) in dry CH_3CN or THF (2 mL) at room temperature under a nitrogen atmosphere was added sequentially freshly distilled acyl chloride (1.76 mmol, 1.1 equiv) and the corresponding urea (4.8 mmol, 3.0 equiv). The reaction mixture was vigorously stirred for 9 h, and the precipitate was filtered and washed carefully with a small amount of cold CH_3CN or THF to remove colored impurities. The resulting products were white in color and analytically pure, except for the presence of small amounts of adsorbed water. The solids were dried in a vacuum oven at 40 °C and stored under nitrogen.

Compound characterization.

General. Examination of spectroscopic data for compounds **1** (Table 1) reveals the following characteristic resonances. ^{1}H NMR: ca. 2.9 and 3.4 ppm (singlets, 3H each, urea NHMe), ca. 9.0 (broad s, 1H, C–H of formamidine group. ^{13}C NMR: ca. 153 ppm (C=O), ca. 150 ppm (C=N), ca. 33 and 26 ppm, (urea NHMe). IR: ca. 3300 cm^{-1} (N–H stretching vibration), ca. 1550 cm^{-1} (N–H bending vibration), 1650-1750 cm^{-1} (C=O); note that the characteristic 2300-2800 cm^{-1} band of isonitriles are absent from the spectra of the formamidine urea products

1-(Benzylimino-methyl)-1,3-dimethyl-urea hydrochloride (**1a**). White solid (hygroscopic): Mp 157–158 °C; ^{1}H NMR (CD_3OD) δ 2.96 (s, 3H), 3.41 (s, 3H), 4.91 (s, 2H), 7.47–7.54 (m, 5H), 9.19 (s, 1H); ^{13}C NMR (CD_3OD) δ 25.6, 29.6, 50.9, 126.9, 127.2, 127.5, 133.5, 151.4, 154.8; IR (KBr, cm^{-1}) 3235, 2979, 1728, 1538, 699; MS *m*/*z* (relative intensity) 207 $(M+2)^+$ (14), 206 $(M+1)^+$ (100), 108 (12). HMRS calcd for $C_{11}H_{16}N_3O$ $(M+1)^+$ 206.1293, found 206.1288.

1-(*tert*-Butylimino-methyl)-1,3-dimethyl-urea hydrochloride (**1b**). White solid (hygroscopic): Mp 180–181 °C; ^{1}H NMR (CD_3OD) δ 1.57 (s, 9H), 2.96 (s, 3H), 3.44 (s, 3H), 8.82 (br s, 1H); ^{13}C NMR (CD_3OD) δ 26.8, 27.3, 31.5, 58.1, 152.5, 153.5; IR (KBr, cm^{-1}) 3656, 3216, 3047, 1654; MS *m*/*z* (relative intensity) 173 $(M+2)^+$ (10), 172 $(M+1)^+$ (100), 115 (1). Anal. Calcd for $C_8H_{18}ClN_3O \cdot 1/4\ H_2O$: C, 45.28; H, 8.79; N, 19.80; Cl, 16.71. Found: C, 45.58; H, 8.71; N, 19.87; Cl, 16.66.

1-(Cyclohexylmethylimino-methyl)-1,3-dimethyl-urea hydrochloride (**1c**). White solid (hygroscopic): Mp 192–193 °C; ^{1}H NMR (CD_3OD) δ 1.29–1.33 (m, 1H), 1.47–1.50 (m, 2H), 1.58–1.63 (m, 2H), 1.78–1.80 (m, 1H), 1.94–1.97 (m, 2H), 2.08–2.11 (m, 2H), 2.95 (s, 3H), 3.39 (s, 3H), 3.75 (m, 1H), 8.99 (s, 1H); ^{13}C NMR (CD_3OD) δ 24.3, 24.9, 26.1, 27.2, 30.8, 32.8, 60.1, 150.9, 153.2; IR (KBr, cm^{-1}) 3223, 1720, 1674, 1532; MS *m*/*z* (relative intensity) 199 $(M+2)^+$ (12), 200 $(M+1)^+$ (100), 141 (1). Anal. Calcd for $C_{10}H_{20}ClN_3O$: C, 51.39; H, 8.62; N, 17.98; Cl, 15.17. Found: C, 51.34; H, 8.46; N, 17.98; Cl, 15.02.

[(1,3-Dimethyl-ureidomethylene)-amino]-acetic acid methyl ester hydrochloride (**1d**). White solid (hygroscopic): Mp 149–150 °C; ^{1}H NMR (DMSO-d_6) δ 2.80 (s, 3H), 3.46 (s, 3H), 3.77 (s, 3H), 4.54 (s, 2H), 9.84 (br s, 1H), 9.15 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 28.4, 33.2, 48.3, 53.4, 153.1, 158.3, 169.4; IR (KBr, cm^{-1}) 3269, 2957, 1746, 1533; MS *m*/*z* (relative intensity) 189 $(M+2)^+$ (9), 188 $(M+1)^+$ (100), 119 (4), 106 (5). Anal. Calcd for $C_7H_{14}ClN_3O_3$ • 1/2 H_2O: C, 36.14; H, 6.50; N, 18.06; Cl, 15.24. Found: C, 35.78; H, 6.21; N, 17.96; Cl, 15.62.

The ethyl ester was also prepared from the appropriate isocyanide (yield 69%): [(1,3-dimethyl-ureidomethylene)-amino]-acetic acid ethyl ester hydrochloride. White solid (hygroscopic): Mp 96–97 °C; ^{1}H NMR (DMSO-d_6) δ 1.29 (t, *J* = 9.1 Hz, 3H), 2.81 (s, 3H), 3.44 (s, 3H), 4.22–4.26 (m, 2H), 4.52 (s, 2H), 8.58 (br s, 1H), 9.04 (br s, 1H); ^{13}C NMR (DMSO-d_6) δ 14.9, 28.4, 33.1, 48.5, 62.3, 153.1, 158.3, 169.3; IR (KBr, cm^{-1}) 3294, 1738, 1672, 1527; MS *m*/*z* (relative intensity) 203 $(M+2)^+$ (10), 202 $(M+1)^+$ (100), 119 (2), 104 (31). Anal. Calcd for $C_8H_{16}ClN_3O_3 \cdot H_2O$: C, 37.58; H, 7.10; N, 16.43; Cl, 13.87. Found: C, 37.26; H, 6.83; N, 15.99; Cl, 14.22.

1-Butyliminomethyl-1,3-dimethyl-urea hydrochloride (**1e**). White solid (hygroscopic): Mp 147–148 °C; ^{1}H NMR (CD_3OD) δ 1.06 (t, *J* = 7.3 Hz, 3H), 1.49 (m, 2H), 1.79 (m, 2H), 2.95 (s, 3H), 3.41 (s, 3H), 3.71 (br s, 2H), 9.01 (s, 1H); ^{13}C NMR (CD_3OD) δ 13.0, 19.6, 27.2, 31.3, 31.9, 49.9, 153.1, 155.9; IR (KBr, cm^{-1}) 3217, 2963, 1714, 1678, 1528; MS *m*/*z* (relative intensity) 173 $(M+2)^+$ (10), 172 $(M+1)^+$ (100), 115 (12). Anal. Calcd for $C_8H_{18}ClN_3O$ • 1/4 H_2O: C, 45.28; H, 8.79; N, 19.80; Cl, 16.71. Found: C, 45.36; H, 8.62; N, 19.99; Cl, 17.89.

1-(Benzylimino-methyl)-1,3-dimethyl-thiourea hydrochloride (**1f**). White solid (hygroscopic): Mp 160–161 °C; ^{1}H NMR (CD_3OD) δ 3.37 (s, 3H), 3.60 (s, 3H), 4.92 (s, 2H), 7.47–7.54 (m, 5H), 9.49 (br s, 1H); ^{13}C NMR (CD_3OD) δ 31.9, 36.1, 52.4, 128.5, 128.9, 129.1, 135.0, 157.1, 182.6; IR (KBr, cm^{-1}) 3156, 2974, 1669, 1549, 699; MS *m*/*z* (relative intensity) 223 $(M+2)^+$ (14), 222 $(M+1)^+$ (100), 175 (6), 144 (1). Anal. Calcd for $C_{11}H_{16}ClN_3S$ • 1/2 H_2O: C, 49.52; H, 6.42; N, 15.75; S, 12.02; Cl, 13.29. Found: C, 49.78; H, 6.43; N, 16.19; S, 12.26; Cl, 13.39.

1-(Benzylimino-methyl)-imidazolidin-2-one hydrochloride (**1g**). White solid (hygroscopic): Mp 182–183 °C; ^{1}H NMR (CD_3OD) δ 3.66 (t, *J* = 7.0 Hz, 2H), 3.88 (t, *J* = 7.0 Hz, 2H), 4.21 (s, 2H), 7.49–7.58 (m, 5H), 8.89 (br s, 1H); ^{13}C NMR (CD_3OD) δ 37.6, 39.3, 40.9, 43.4, 128.6, 128.9, 129.2, 133.5, 160.8, 166.6; IR (KBr, cm^{-1}) 3221, 2971, 1770, 1679, 700; MS *m*/*z* (relative intensity) 205 $(M+2)^+$ (14), 204 $(M+1)^+$ (100), 119 (5), 105 (1). Anal. Calcd for $C_{11}H_{14}ClN_3O$ • 1/4 H_2O: C, 54.10; H, 5.98; N, 17.21; Cl, 14.52. Found: C, 54.05; H, 5.98; N, 17.09; Cl, 14.02.

1-(Benzylimino-methyl)-1-methyl-urea hydrochloride (**1h**). White solid (hygroscopic): Mp 168–169 °C; ^{1}H NMR (CD_3OD) δ 3.41 (s, 3H), 4.91 (s, 2H), 7.50–7.52 (m, 5H), 9.20 (br s, 1H); ^{13}C NMR (CD_3OD) δ 30.1, 56.3, 131.5, 132.2, 132.6, 132.9, 137.4, 156.3, 162.2; IR (KBr, cm^{-1}) 3274, 2829, 1732, 1687, 1359, 701; MS *m*/*z* (relative intensity) 193 $(M+2)^+$ (12), 192 $(M+1)^+$

(100), 149 (2), 119 (4), 101 (4). Anal. Calcd for $C_{10}H_{14}ClN_3O$ • 1/4 H_2O: C, 51.73; H, 6.29; N, 18.10; Cl, 15.27. Found: C, 51.95; H, 6.15; N, 18.57; Cl, 14.97.

1-Adamantan-1-yl-1-(benzylimino-methyl)-urea hydrochloride (**1i**). White solid (hygroscopic): Mp 171–172 °C; ^{1}H NMR ($CDCl_3$) 1.65 (br s, 6H), 1.66–2.06 (m, 9H), 4.48 (s, 2H), 5.31 (br s, 1H), 7.25–7.34 (m, 5H), 8.53 (s, 1H); ^{13}C NMR ($CDCl_3$) 30.8, 37.2, 42.3, 53.3, 129.2, 129.9, 130.3, 134.5, 149.4, 153.2; IR (KBr, cm^{-1}) 3240, 2918, 1747, 1686, 1555, 700; MS *m/z* (relative intensity) 334 $(M+Na)^+$ (11), 313 $(M+2)^+$ (22), 312 $(M+1)^+$ (100), 152 (18), 119 (8), 101 (8). Anal. Calcd for $C_{19}H_{26}ClN_3O$ • 1/2 H_2O: C, 63.94; H, 7.63; N, 11.77; Cl, 9.93. Found: C, 63.88; H, 7.46; N, 11.63; Cl, 10.18.

1-(Benzylimino-methyl)-1-phenyl-urea hydrochloride (**1j**). Yellow solid (hygroscopic): Mp 176–177 °C; ^{1}H NMR (DMSO-d_6) 7.10–7.58 (m, 10H), 9.12 (s, 1H), 10.92 (br s, 2H); ^{13}C NMR (DMSO-d_6) 48.0, 118.5, 119.7, 122.3, 127.9, 129.6, 130.1, 135.1, 138.2, 140.2, 155.2; IR (KBr, cm^{-1}) 3266, 2890, 1750, 1687, 1561, 1301, 700; MS *m/z* (relative intensity) 276 $(M+Na)^+$ (14), 255 $(M+2)^+$ (17), 254 $(M+1)^+$ (100), 225 (15), 119 (5). Anal. Calcd for $C_{15}H_{16}ClN_3O$: C, 62.18; H, 5.57; N, 14.50; Cl, 12.24. Found: C, 62.40; H, 5.57; N, 14.77; Cl, 12.39.

1-Benzyl-1-(benzylimino-methyl)-urea hydrochloride (**1k**). White solid (hygroscopic): Mp 177–178 °C; ^{1}H NMR (DMSO-d_6) 4.49 (s, 2H), 4.84 (s, 2H), 8.53 (br s, 2H), 7.33–7.54 (m, 10H), 9.03 (s, 1H); ^{13}C NMR (DMSO-d_6) 44.0, 48.0, 128.1, 129.6, 135.1, 139.0, 152.9, 158.0; IR (KBr, cm^{-1}) 3270, 2879, 1751, 1685, 1548, 1301, 699; MS *m/z* (relative intensity) 290 $(M+Na)^+$ (8), 269 $(M+2)^+$ (20), 268 $(M+1)^+$ (100), 119 (2). Anal. Calcd for $C_{16}H_{18}ClN_3O$: C, 63.26; H, 5.97; N, 13.83; Cl, 11.67. Found: C, 62.90; H, 5.91; N, 13.90; Cl, 11.42.

1,3-Dimethyl-1-[(toluene-4-sulfonylmethylimino)-methyl]-urea hydrochloride (**1l**). White solid (hygroscopic): Mp 114–115 °C; ^{1}H NMR (CD_3OD) 1.28-1.32 (m, 1H), 1.48 (ddd, J= 13.2, 13.2, 9.6 Hz, 2H),1.60 (ddd, J= 13.2, 13.2, 9.6 Hz, 2H), 1.78-1.80 (m,1H), 1.95 (d, J= 11.6 Hz, 2H), 2.09 (d, J= 11.7 Hz, 2H), 2.95 (s, 3H), 3.38 (s, 3H), 3.71-3.76 (m,1H), 9.0 (s,1H); ^{13}C NMR (CD_3OD) 26.3, 26.7, 35.1, 74.4, 124.7, 125.9, 128.9, 130.0, 135.4, 158.8, 162.3; IR (KBr, cm^{-1}) 3320, 1715, 1530, 1349, 703; MS *m/z* (relative intensity) 306 $(M+Na)^+$ (63), 285 $(M+2)^+$ (17), 284 $(M+1)^+$ (100), 177 (23), 157 (18), 105 (5). Anal. Calcd for $C_{12}H_{18}ClN_3O_3S$ • 1/2 H_2O: C, 43.83; H, 5.82; N, 12.78; Cl, 10.78; S, 9.75. Found: C, 43.99; H, 6.09; N, 13.15; Cl, 10.45; S, 9.62.

1-({6-[(1,3-Dimethyl-ureidomethylene)-amino]-hexylimino}-methyl)-1,3-dimethyl-urea *bis*-hydrochloride (**1m**). Beige solid (hygroscopic): Mp 153–154 °C; ^{1}H NMR (CD_3OD) 1.54 (m, 4H), 1.85 (m, 4H), 2.95 (s, 6H), 3.39 (s, 3H), 3.74 (br s, 4H), 9.02 (s, 2H); ^{13}C NMR (CD_3OD) 25.7, 26.4, 27.2, 29.5, 31.8, 49.8, 153.1, 156.0; IR (KBr, cm^{-1}) 3213, 2940, 1721, 1672, 1533; MS *m/z* (relative intensity) 335 $(M+Na)^+$ (35), 313 $(M+1)^+$ (63), 243 (31), 157 (100). Anal. Calcd for $C_{14}H_{30}Cl_2N_6O_2$ • 1/2 H_2O: C, 42.64; H, 7.92; N, 21.31; Cl, 17.98. Found: C, 42.35, H, 7.80; N, 21.53; Cl, 17.44.

1-[(2,6-Dimethyl-phenylimino)-methyl]-3-methyl-urea hydrochloride (**1n**). White solid (hygroscopic): Mp 167–168 °C; ^{1}H NMR (CD_3OD) 2.50 (s, 3H), 2.80 (s, 3H), 2.98 (s, 3H), 3.39 (s, 3H), 7.27–8.16 (m, 5H), 8.17 (s, 1H); ^{13}C NMR (CD_3OD) 17.2, 17.5, 26.1, 129.6, 132.0, 134.8; IR (KBr, cm^{-1}) 3310, 2869, 1654, 720, 697; MS *m/z* (relative intensity) 221 $(M+2)^+$

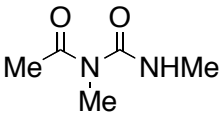
(14), 220 $(M+1)^+$ (100), 119 (2). Anal. Calcd for $C_{12}H_{18}ClN_3O \bullet 1/4\ H_2O$: C, 55.38; H, 7.17; N, 16.15; Cl, 13.62. Found: C, 55.54, H, 7.09; N, 13.74; Cl, 16.10.

1,3-Diallyl-1-(benzylimino-methyl)-urea hydrochloride (**1o**). Colorless oil: ^{1}H NMR (CD_3CN) δ 3.93 (d, J = 15.8 Hz, 2H), 4.45 (s, 1H), 4.83 (br s, 1H), 5.16–5.29 (m, 4H), 5.93–5.99 (m, 2H), 7.41–7.55 (m, 5H), 9.30 (br d, 1H); ^{13}C NMR (CD_3OD) δ 42.3, 45.9, 51.0, 114.3, 127.9, 129.1, 132.5, 136.0, 155.3; IR (CaF_2, cm^{-1}) 3305, 2986, 1703, 1562, 1241, 921; MS m/z (relative intensity) 259 $(M+2)^+$ (20), 258 $(M+1)^+$ (100), 183 (13), 141 (15). Anal. Calcd for $C_{15}H_{20}ClN_3O$: C, 61.32; H, 6.86; N, 14.30; Cl, 12.07. Found: C, 61.02, H, 7.01; N, 14.45; Cl, 11.75.

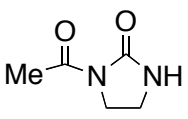
1-Allyl-1-(benzylimino-methyl)-urea hydrochloride (**1p**). Colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.91 (d, J = 15.9 Hz, 2H), 4.49 (s, 1H), 4.61 (s, 1H), 5.16–5.30 (m, 2H), 5.89–5.94 (m, 1H), 7.36–7.41 (m, 5H), 8.67 (s, 1H), 9.31 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 43.3, 45.8, 116.2, 127.8, 128.3, 129.2, 135.2, 137.5, 158.1; IR (CaF_2, cm^{-1}) 3307, 2950, 1715, 1563, 1245; MS m/z (relative intensity) 240 $(M+Na)^+$ (16), 219 $(M+2)^+$ (16), 218 $(M+1)^+$ (100), 150 (7), 136 (13), 101 (60). Anal. Calcd for $C_{12}H_{16}ClN_3O$: C, 56.80; H, 6.36; N, 16.56; Cl, 13.97. Found: C, 57.12, H, 6.48; N, 16.77; Cl, 13.58.

4-Methyl-benzoic acid N'-(benzylimino-methyl)-hydrazide hydrochloride (**3**). White solid (hygroscopic): Mp 169–170 °C; ^{1}H NMR ($CDCl_3$) δ 2.13 (s, 1H), 2.48 (s, 3H), 3.38 (s, 1H), 4.74 (s, 2H), 7.36–7.53 (m, 9H), 7.85–7.91 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 21.6, 50.3, 128.1, 128.7, 129.4, 143.2, 155.7; IR (KBr, cm^{-1}) 3062, 2924, 1707, 1652, 1495, 1269, 700; MS m/z (relative intensity) 290 $(M+Na)^+$ (14), 269 $(M+2)^+$ (18), 268 $(M+1)^+$ (100), 119 (5). Anal. Calcd for $C_{16}H_{18}ClN_3O$: C, 63.26; H, 5.97; N, 13.83; Cl, 11.67. Found: C, 62.93; H, 5.99; N, 13.80; Cl, 11.30.

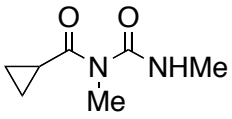
Acylurea Byproducts. In all cases in which the soluble portions of reaction mixtures were examined, the appropriate acylurea was detected in approximately equimolar amounts relative to the formamidine ureas formed. To support the assignment of acylurea structure, the examples were characterized as described below.



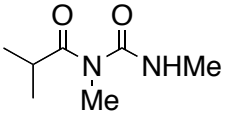
2



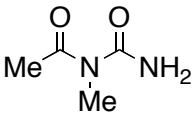
10



11



12



13

Compounds **2**[34-36] and **10**[37] were identified from comparison to literature values.

1-Cyclopropanecarbonyl-1,3-dimethyl-urea (**11**)**.** Colorless oil: ^{1}H NMR (CD_3OD) δ 1.03–1.07 (m, 4H), 2.18–2.20 (m, 1H), 2.89 (s, 3H), 3.48 (s, 3H); ^{13}C NMR (CD_3OD) δ 9.0, 14.1, 26.3, 31.4, 156.7, 177.8; IR (CaF_2, cm^{-1}) 3296, 2951, 1720, 1650; MS m/z (relative intensity) 179 $(M+Na)^+$ (16), 158 $(M+2)^+$ (9), 158 $(M+1)^+$ (100), 105 (2). Anal. Calcd for $C_7H_{12}N_2O_2$: C, 53.83; H, 7.74; N, 17.94. Found: C, 53.68, H, 7.70; N, 17.71.

1-Isobutyryl-1,3-dimethyl-urea (**12**). Colorless oil: ^{1}H NMR (CD_3OD) δ 1.21 (d, J = 2.2 Hz, 6H), 2.89 (s, 3H), 3.17–3.20 (m, 1H), 3.36 (s, 3H); ^{13}C NMR (CD_3OD) δ 18.7, 26.4, 31.2, 33.8, 157.1, 181.4; IR (CaF_2, cm^{-1}) 3297, 2974, 1720, 1658; MS m/z (relative intensity) 181 $(M+Na)^+$

(17), 160 $(M+2)^+$ (9), 159 $(M+1)^+$ (100), 105 (4). Anal. Calcd for $C_7H_{14}N_2O_2$: C, 53.15; H, 8.92; N, 17.71. Found: C, 53.21, H, 8.89; N, 17.72.

1-Acetyl-1-methyl-urea (**13**). White solid: Mp 159–160 °C; ^{1}H NMR (CD_3OD) δ 2.16 (s, 3H), 2.89 (s, 3H); ^{13}C NMR (CD_3OD) δ 22.6, 25.2, 155.4, 173.1; IR (KBr, cm^{-1}) 3221, 1715, 1559; MS *m/z* (relative intensity) 139 $(M+Na)^+$ (91), 118 $(M+2)^+$ (5), 117 $(M+1)^+$ (100). Anal. Calcd for $C_4H_8N_2O_2$: C, 41.37; H, 6.94; N, 24.12. Found: C, 41.52, H, 6.82; N, 23.82.

References and Notes

(1) Marmet, D.; Boullanger, P.; Descotes, G. *Tetrahedron Lett.* **1980**, *21*, 1459-1462.
(2) Hegarty, A. F.; Chandler, A. *Tetrahedron Lett.* **1980**, *21*, 885-888.
(3) Gottlieb, L.; Meyers, A. I. *Tetrahedron Lett.* **1990**, *31*, 4723-4726.
(4) Hashida, Y.; Imai, A.; Sekiguchi, S. *J. Heterocycl. Chem.* **1989**, *26*, 901-905.
(5) Meyers, A. I.; Bailey, T. R. *Journal of Organic Chemistry* **1986**, *51*, 872-875.
(6) Loewe, M. F.; Meyers, A. I. *Tetrahedron Letters* **1985**, *26*, 3291-3294.
(7) Smith, R.; Livinghouse, T. *Synthetic Communications* **1984**, *14*, 639-646.
(8) Ito, Y.; Inubushi, Y.; Saegusa, T. *Tetrahedron Letters* **1974**, 1283-1286.
(9) Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Yoshioka, H. *Bulletin of the Chemical Society of Japan* **1969**, *42*, 3310-3313.
(10) Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Yoshioka, H. *Tetrahedron Letters* **1966**, 6121-6124.
(11) Bertani, R.; Crociani, L.; D'Arcangelo, G.; Rossetto, G.; Traldi, P.; Zanella, P. *J. Organomet. Chem.* **2001**, *626*, 11-15.
(12) Jakobsen, P.; Treppendahl, S. *Tetrahedron* **1977**, *33*, 3137-3140.
(13) Jakobsen, P. *Acta Chemica Scandinavica, Series B: Organic Chemistry and Biochemistry* **1976**, *B30*, 847-852.
(14) Mitin, Y. V.; Glushenkova, V. R.; Vlasov, G. P. *Zh. Obshch. Khim.* **1962**, *32*, 3867-3871.
(15) Saluste, C. G.; Whitby, R. J.; Furber, M. *Tetrahedron Lett.* **2001**, *42*, 6191-6194.
(16) Katritzky, A. R.; Button, M. A. C.; Busont, S. *J. Org. Chem.* **2001**, *66*, 2865-2868.
(17) Simon, J. R. *Synthesis* **2001**, 2011-2014.
(18) Bergemann, M.; Neidlein, R. *Helv. Chim. Acta* **1999**, *82*, 909-918.
(19) Bossio, R.; Marcaccini, S.; Pepino, R. *J. Heterocycl. Chem.* **1995**, *32*, 1115-1116.
(20) Bossio, R.; Marcaccini, S.; Pepino, R. *Tetrahedron Lett.* **1995**, *36*, 2325-2326.
(21) Morel, G.; Marchand, E.; Foucaud, A.; Toupet, L. *Journal of Organic Chemistry* **1989**, *54*, 1185-1191.
(22) Witczak, Z. J. *Tetrahedron* **1985**, *41*, 4781-4785.
(23) Ugi, I. *Isonitrile Chemistry*; Academic Press: New York, 1971.
(24) Westling, M.; Smith, R.; Livinghouse, T. *J. Org. Chem.* **1986**, *51*, 1159-1165.
(25) Westling, M.; Livinghouse, T. *Tetrahedron Lett.* **1985**, *26*, 5389-5392.
(26) Westling, M.; Livinghouse, T. *J. Am. Chem. Soc.* **1987**, *109*, 590-592.
(27) Lee, C. H.; Westling, M.; Livinghouse, T.; Williams, A. C. *J. Am. Chem. Soc.* **1992**, *114*, 4089-4095.
(28) Newton, C. G.; Ollis, W. D.; Wright, D. E. *jcspt1* **1984**, *1*, 75-84.
(29) Glocker, M. O.; Shrestha-Davadi, P. B.; Küchler-Krischun, J.; Hofmann, J.; Fischer, H.; Jochims, J. C. *Chem. Ber.* **1993**, *126*, 1859-1865.

(30) Jochims, J. C.; Glocker, M. O. *Chem. Ber.* **1990**, *123*, 1537-1544.
(31) Bitter, I.; Kárpáti-Ádám, E.; Tóke, L. *Acta Chim. Acad. Sci. Hung.* **1979**, *102*, 235-246.
(32) Csuros, Z.; Soos, R.; Bitter, I.; Karpati-Adam, E. *Acta Chim. (Budapest)* **1972**, *73*, 239-246.
(33) Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.
(34) Egg, H.; Volgger, I. *Synthesis* **1982**, *12*, 1071-1073.
(35) Dmitrichenko, M. Y.; Rozinov, V. G.; Donskikh, V. I.; Ratovskii, G. V.; Sergienko, L. M.; Dolgushin, G. V.; Valeev, R. B. *Zh. Obsch. Khim.* **1988**, *58*, 2252-2261.
(36) Hamed, A.; Ismail, A.; Hitzler, M. G.; Jochims, J. C. *J. Prakt. Chem./Chem.-Ztg.* **1995**, *337*, 395-390.
(37) Greenhalgh, R.; Weinberger, M. A. *Can. J. Chem.* **1965**, *43*, 3340-3346.

X-RAY CRYSTALLOGRAPHY

Crystals of **1a** were obtained from acetonitrile solution.

DETAILS OF CRYSTALLOGRAPHY APPEAR IN A CIF FILE, AVAILABLE SEPARATELY FROM THE AUTHORS (mgfinn@scripps.edu).