Formamidine Ureas as Tunable Electrophiles

David D. Díaz and M. G. Finn*[a]

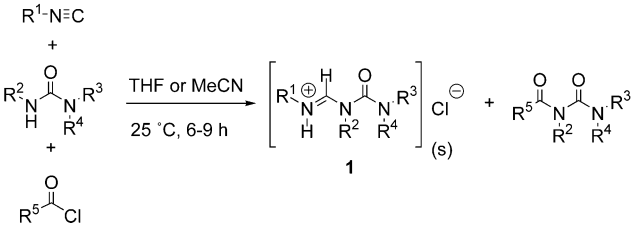
Abstract: Formamidine urea compounds exchange imine fragments with primary nitrogen nucleophiles, allowing the preparation of a variety of derivatives from a single precursor. The reactivities of these species are governed primarily by the electron-donating power of the substituents and are tunable over a range of $>10^3$ in first-order rates of hydrolysis.

Keywords: electrophiles · formamidines · hydrolysis · synthesis design · ureas

Introduction

Formamidines are of interest in synthetic chemistry[1] and have been used extensively as pesticides (e.g., amitraz, chlordimeform, formetanate)[2] and as pharmacological agents.[3] The reported biochemical targets of formamidines include adrenergic, histamine, and neurochemical receptors,[2a–c,3a,3b,4] monoamine oxidase,[2e,5] and prostaglandin E_2 synthesis.[6] Their use as ligands in transition-metal complexes has also been noted.[7] Recently, well-defined polymeric structures containing large numbers of amidine groups were reported.[8] The uses of formamidines in organic synthesis have been quite diversified, including such roles as auxiliaries in asymmetric synthesis,[9] protecting groups for primary amines,[10] electrophiles,[11] and linkers in solid-phase synthesis.[12] General routes to formamidines and related compounds are dominated by condensation (amine + formamide)[13] and exchange (amine + formamidine acetals)[10,14] processes.

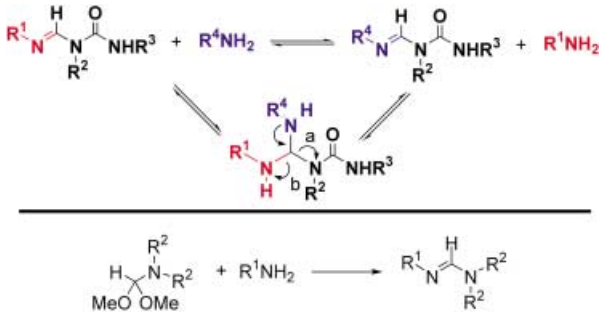
We recently reported an efficient preparation of formamidine ureas **1** from isonitriles and ureas in the presence of acid chlorides (Scheme 1).[15] The previously known methods of formamidine synthesis had not been applied to, or were ineffective in, the incorporation of the urea moiety, which may be expected to enhance the biological activity of such structures. Here we describe a facile exchange reaction[16] with nucleophilic amines, which provides access to formamidine ureas of wide scope at the formamidine position.



Scheme 1.

Results and Discussion

Formamidines are electrophilic at the central carbon atom, and we anticipated that the carbamoyl substituent would perhaps enhance this reactivity relative to simple alkyl- or arylformamidine structures. We observed that the freebase form of formamidine ureas **1** undergo clean exchange with primary nitrogen nucleophiles at room temperature (Scheme 2). The reaction presumably proceeds through a



Scheme 2.

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Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author. Representative ^{1}H NMR and ^{13}C NMR spectra for the compounds described in the Experimental Section and full details of kinetics measurements.

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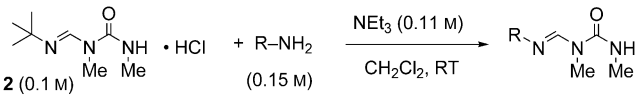
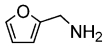
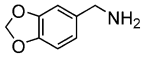
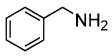
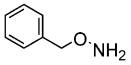
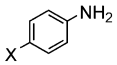
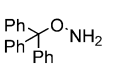
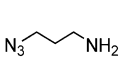
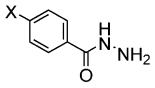
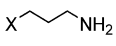
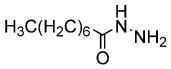
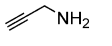
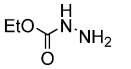
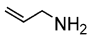
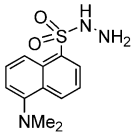
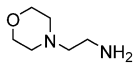
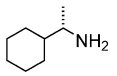
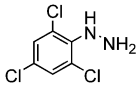
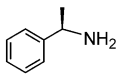
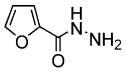
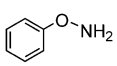
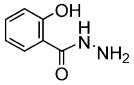
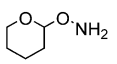
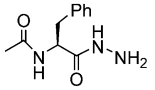
tetrahedral intermediate,[11,17] which ejects amine in preference to urea (Scheme 2), establishing an equilibrium between formamidine urea species. Similar substitution reactions have been described with diaryl- and *N*-acylformamidines,[18] but these are less efficient than the process described here. The formamidine urea is therefore analogous in its electrophilicity to formamidine acetals,[10,14] shown at the bottom of Scheme 2. Since we have been unable to capture formamidine acetals with substituted ureas, the methodology of Schemes 1 and 2 represents the best way so far developed to prepare structurally diverse formamidine urea compounds.

Among the formamidine ureas reported earlier,[15] 1,3-dimethyl-1-*tert*-butyliminomethylurea hydrochloride (**2**, see scheme in Table 1) emerged as the most effective starting material for the exchange process. This compound can be conveniently obtained from *tert*-butylisocyanide on a 40 g scale, and the bulky nature of the *tert*-butyl group makes its substitution irreversible. Table 1 summarizes a set of exchange reactions between **2** and a variety of aromatic and aliphatic primary amines, hydroxylamines, hydrazines, and hydrazides. Triethylamine was employed to neutralize the starting hydrochloride salt, and the use of 1.5 equivalents of nucleophile gave slightly better yields than 1.0 equivalent.

Table 1. Nucleophilic substitution of **2** under standard conditions.



R–NH_2	Product	Yield [%][a]	R–NH_2	Product	Yield [%][a]
	**3**	67		**21**	83
	**4**	69		**22**	81
	**5**	73		**23**	78
	**6** (X = H) **7** (X = Me) **8** (X = OMe) **9** (X = NMe_2)	32–49		**24**	66
	**10**	61		**25** (X = H) **26** (X = Me)	66
	**11** (X = Br) **12** (X = Cl)	62		**27**	67
	**13**	68		**28**	62
	**14**	65		**29**	66
	**15**	63	$MeNHNH_2$	**30**	48
	**16**	79		**31**	53
	**17**	74		**32**	59
	**18**	77		**33**	34
	**19**	80		**34**	51[b]
$MeO–NH_2$	**20**	76			

[a] Yields of analytically pure compounds after chromatography. [b] Obtained under more dilute conditions (0.01 M in **2**), after 20 h at reflux.

For a series of anilines (giving **6**–**9**), yields were low due to poor nucleophilicity, increasing slightly with increasing electron-donating power of the *para*-substituent; 4-nitroaniline was entirely unreactive. The process allows the introduction of amines bearing other reactive functionalities (compounds **10**–**15**), chiral groups (compounds **16**, **17**), and a solid support (from aminomethylpolystyrene, not shown). While the crude reaction mixtures with hydrazines and hydrazides giving **30**–**33** appeared to be quite clean, these compounds were difficult to elute from silica gel and so suffered some losses in yield upon purification. Reactions with $RONH_2$ and $RNHNH_2$ nucleophiles were generally effective, even when incorporating sterically hindered components (**22**, **24**, **31**). When solubility was poor, as with the *N*-acetylphenylalanine hydrazide which gave **34**, reaction in refluxing CH_2Cl_2 was required, often at higher dilution, to obtain acceptable yields. Most of the reactions shown benefit in terms of speed and yield from reaction at elevated temperatures, but were performed at room temperature for convenience.

The exchange process gave the best results in chlorinated solvents, with the order of effectiveness being CH_2Cl_2, 1,2-dichloroethane, $CHCl_3$, $CCl_4 \gg$ THF, $CH_3CN \gg$ toluene, benzene, $Et_2O \gg$ pyridine > 1,4-dioxane > DMSO, DMF $\gg$ acetone, MeOH. No byproducts or other impurities were observed in any solvent. Use of the secondary amine mor-

pholine instead of primary amines gave a mixture of as yet uncharacterized compounds, and secondary amines did not appear to catalyze the substitution of primary amines.

The biological activity of formamidine ureas and their derivatives is likely to be limited by their rates of hydrolysis.[19] In our initial report, we described the relatively rapid hydrolysis of the parent compounds to urea and amine.[15] This process is presumed to begin with nucleophilic attack of water or hydroxide on the formamidine carbon to give a hemiorthoamide intermediate, and can be promoted by either acid or base. Both type of mechanisms have been implicated in the hydrolysis of formamidines and *N*-acylformamidines, with a direct relationship between the electron-withdrawing power of substituents and the hydrolysis rate observed.[17,18] With a variety of formamidine ureas in hand, we examined the rates of hydrolysis as a function of the electron-donating ability of the formamidine substituent and, therefore, the electrophilicity of the formamidine carbon.

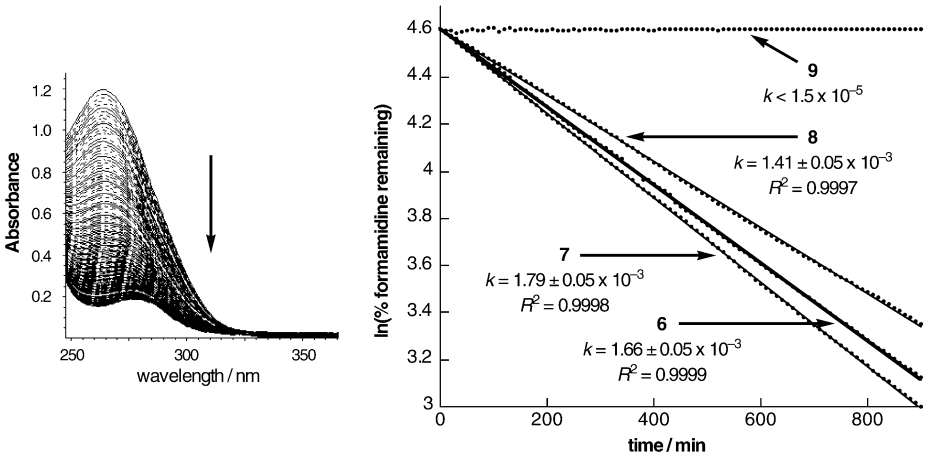


Figure 1. Left: UV-visible spectrum of compound **6** in 0.1 M phosphate buffer, pH 7.0; arrow indicates increasing time. Right: first-order kinetics plots for the hydrolysis of compounds **6–9** in 0.1 M phosphate buffer, pH 7.0, monitored every 10 min over 15 h at 23 ± 1 °C. Rate constants are in units of min^{-1}.

Hydrolysis of formamidine ureas was accompanied by a loss in intensity of the main absorbance band at approximately 280 nm (Figure 1); this made for the convenient monitoring of aqueous hydrolytic stability as a function of pH. Figure 1 shows first-order kinetics plots for the disappearance of aniline-substituted compounds **6–9** at pH 7.0. Stability was found to be enhanced by electron-donating *para*-substituents in the order: $NMe_2 \gg OMe > Me \approx H$. The dimethylamino compound **9** was far more stable at neutral pH than would be expected on the basis of Hammett type considerations, showing a reduction in hydrolysis rate of at least two orders of magnitude relative to the methoxy derivative **8**.

Kinetic analyses of formamidine urea hydrolysis were similarly performed for 11 additional compounds spanning a range of stabilities. Figure 2 shows these results in the form of a plot of half-life in three different buffers, calculated from the experimentally determined first-order rate constants, for those compounds for which appreciable hydrolysis was observed within 16 h at room temperature. The rates of hydrolysis were neither dependent on the nature of the buffer nor its concentration. Not shown are data for the other compounds **22**, **27**, **30**, **32**, and **34**, which were observed to be highly resistant to hydrolysis. The hydrolysis rate constants for these compounds are therefore estimated to be less than $1 \times 10^{-4}\ min^{-1}$ (half-life > 116 h). Full details

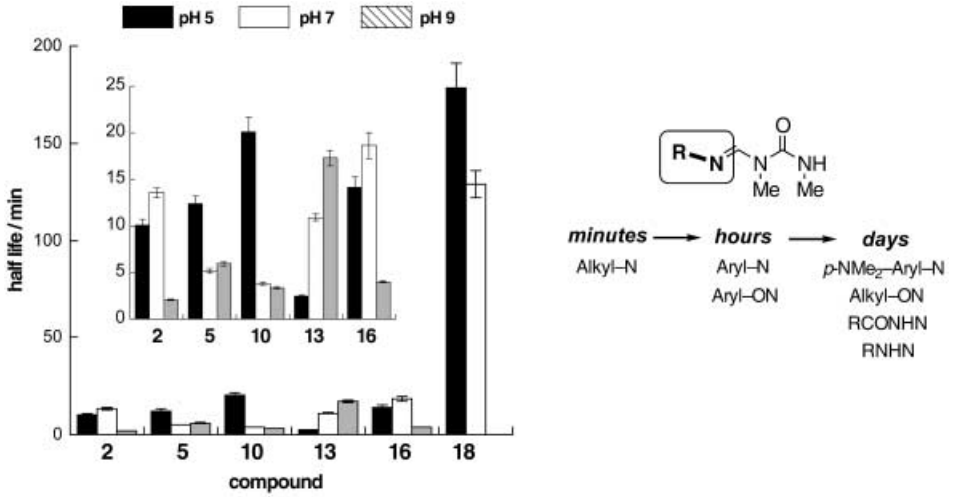
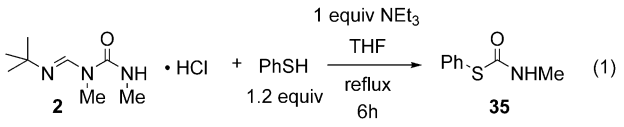


Figure 2. Left: Chart showing half-lives calculated from first-order kinetics plots of hydrolysis of formamidine ureas in 0.1 M acetate buffer (pH 5.0), 0.1 M phosphate buffer (pH 7.0), and 0.1 M bicarbonate buffer (pH 9.0), each at 23 ± 1 °C. Omitted are bars corresponding to the > 116 h half-lives of **22**, **27**, **30**, **32**, and **34**. Right: Summary of the range of half-lives toward hydrolysis in aqueous solution versus the nature of the terminal formamidine substituent in derivatives of 1,3-dimethylurea.

are given in the Supporting Information. The stable compounds comprise adducts of an oxime (**22**), hydrazine (**30**), and three hydrazides (**27**, **32**, **34**). Their resistance to hydrolysis is presumably due to the stabilization provided to the formamidine carbon atom by the electron-donating ability of the highly nucleophilic nitrogen centers of each of these substituents. Note especially that oxime adduct stability is substantially diminished with aromatic conjugation (**18**). Thus, the reactivities of formamidine ureas can be tuned over a wide range with changes in the formamidine substituent, as summarized by the scheme on the right-hand side of Figure 2.

With the exception of propargylamine derivative **13**, hydrolysis was observed to occur slowest at pH 9. Both acid- and base-mediated mechanisms may be operative,[17,20] but these data suggest that acidic catalysis may be more common for formamidine ureas. Indeed, amidines and *N*-acylamidines have been shown to be fairly strong hydrogen-bond acceptors.[21] Furthermore, the Brønsted basicities of *N*,*N*-dimethylformamidines $R^1N{=}CH{-}NMe_2$ in ethanol are only approximately five orders of magnitude less than the corresponding primary amines R^1NH_2.[22] Formamidine ureas are likely to be somewhat less basic than this, but still basic enough to respond to mild acid catalysis. Hydrazide adduct **33**, bearing an *ortho*-phenolic group, was as stable as the other hydrazide compounds examined (no decomposition observed for 12 h at pH 5 and 7, although a full kinetic analysis was not performed), indicating that its phenolic hydroxyl group does not participate intramolecularly in formamidine hydrolysis.

The reaction of **2** with a thiol nucleophile resulted not in exchange at the formamidine position, but rather attack at the urea carbonyl to give thiolcarbamate **35**,[23] and presumably *N*-*tert*-butyl-*N*′-methylformamidine, which would be expected to hydrolyze upon workup [Eq. (1)]. Thiolcarbamates are not available by direct substitution of ureas with thiols, so the observed reaction is of some theoretical and practical interest and is under current investigation.



2 **35** (1)

In summary, we have described a general exchange reaction between formamidine ureas and nitrogen nucleophiles, allowing the synthesis of compounds bearing a wide variety of substituents from a single isonitrile precursor (which is used to gain entry to the formamidine urea skeleton). Formamidine ureas, being related to biologically active formamidines and bearing multiple sites for potential hydrogen-bonding interactions, are of interest for the design of novel pharmacophores. We have also shown that the electrophilic reactivity of formamidine ureas can be tuned over a wide range, which may make them useful as covalent or reversible inhibitors of certain classes of enzymes.

Experimental Section

General: ^1H and ^{13}C NMR spectra were recorded on Bruker DRX-500, AMX-400, or Varian Mercury 200 spectrometers in $CDCl_3$ or CD_3OD as solvent. 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. Melting points were measured in a Thomas Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a MIDAC EM200 instrument with horizontal attenuated total reflectance accessory from Pike Instruments. UV-visible measurements were performed on a HP 845x UV-visible spectrophotometer in the 190–1100 nm range, in quartz cells with 1 cm path length. Optical rotations were determined for solutions in chloroform on an Autopol® III polarimeter (Rudolph Research). Column chromatography was performed on EM Science silica gel, 40–63 micron mesh. 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. Purification of some compounds was performed by preparative TLC on UNIPLATE™ 20×20 cm plates (2000 microns, silica gel GF) plates. CH_2Cl_2 was dried by passage through activated alumina columns;[24] dry Et_3N and other solvents used in this work were purchased from Aldrich. Reactions requiring anhydrous conditions were performed under nitrogen. Buffer (0.1 M) and amine solutions were prepared immediately before use.

General procedure for formamidine urea substitution: Et_3N (2.6 mmol, 1.1 equiv) was added to a solution of 1,3-dimethyl-1-*tert*-butyliminomethylurea hydrochloride (**2**) (2.4 mmol, 1.0 equiv) in dry CH_2Cl_2 (25 mL) at room temperature under a nitrogen atmosphere. The reaction mixture was stirred for 5 min, and then the nucleophilic amine (3.6 mmol, 1.5 equiv) was added. In cases in which the nucleophile was used as its hydrochloride salt (**18**, **20**, **21**, **22**, **23**), an additional equivalent of triethylamine was used. The reaction mixture was stirred at room temperature for 12 h, diluted with CH_2Cl_2, washed with brine, dried ($MgSO_4$), filtered, concentrated, and purified by column chromatography to yield the formamidine–urea derivative. The hygroscopic products were dried under vacuum and stored under nitrogen. Note that in many cases, the reactions may be heated to obtain equal or slightly better yields than those reported above with shorter reaction time. Note that aniline derivatives **6**–**9** are somewhat unstable in the solid state at room temperature, but are stable in CH_2Cl_2 or methanol solution for extended periods. The remaining formamidine ureas are more stable in the solid state, but should be stored under nitrogen in a refrigerator for extended periods.

General procedure for measurement of hydrolysis kinetics: Stock solutions of each compound of interest were prepared in 3 mL MeOH immediately before use. The stock solution was then diluted into the indicated buffer (minimum dilution was 1:100) to a concentration giving an absorbance value at λ_{max} of 1.1 ± 0.1. The reaction mixture was immediately transferred to a quartz cuvette, sealed, and monitoring at λ_{max} was commenced, with spectra acquired every 10 minutes for 16 h. Each sample was then checked daily until the absorbance value varied by less than $\pm$ 0.005 for two successive days, at which point the sample was judged to have been fully hydrolyzed. These data were used to construct plots of ln(% formamidine urea remaining) versus time, which were linear over a substantial portion of the reaction. The slopes of these lines are the observed first-order rate constants for hydrolysis. See Supporting Information for details.

Compound characterization

General: Examination of spectroscopic data for the described compounds revealed the following characteristic resonances. ^1H NMR: δ = ca. 2.9 and 3.4 (s, 3H, urea NH*Me*), ca. 9.0 ppm (br s, 1H, C–H of formamidine group); ^{13}C NMR: δ = ca. 157(C=O), ca. 149 (C=N), ca. 30 and 26 ppm, (urea NHMe). IR: $\tilde{\nu}$ = ca. 3300 (N–H stretching vibration), ca. 1550 (N–H bending vibration), 1650–1750 cm^{-1} (C=O).

1,3-Dimethyl-1-*tert*-butyliminomethyl)urea (2): Compound **2** has been previously reported as the hydrochloride salt.[15] The freebase form exhibits the following characteristics. Gummy syrup (hygroscopic); ^1H NMR ($CDCl_3$): δ = 1.27 (s, 9H), 2.94 (s, 3H), 3.23 (s, 3H), 7.71 (s, 1H), 9.77 ppm (br s, 1H); ^{13}C NMR ($CDCl_3$): δ = 26.6, 30.7, 33.9, 54.9, 148.3, 157.2 ppm; IR (thin film): $\tilde{\nu}$ = 3350, 2964, 1669, 1554, 1323, 1222, 1077,

1001 cm^{-1}; MS: *m*/*z* (%): 194 (2) $[M+Na]^+$, 173 (10) $[M+2]^+$, 172 (100) $[M+1]^+$, 157 (55); elemental analysis calcd (%) for $C_8H_{17}N_3O{\cdot}0.5\,H_2O$: C 53.31, H 10.07, N 23.31; found: C 53.49, H 9.95, N 23.44.

1,3-Dimethyl-1-(2-furylmethyl)iminomethylurea (3): This compound was prepared from **2** and furfurylamine. Colorless oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.89$ (s, 3H), 3.20 (s, 3H), 4.51 (s, 2H), 6.21 (s, 1H), 6.34 (s, 1H), 7.92 (s, 1H), 9.06 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.6$, 30.8, 51.7, 107.2, 110.7, 142.4, 151.6, 153.3, 156.2 ppm; IR (thin film): $\tilde{\nu} = 3341$, 2951, 1679, 1534, 1309, 1076, 991 cm^{-1}; MS: *m*/*z* (%): 197 (10) $[M+2]^+$, 196 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_9H_{13}N_3O_2$: C 55.37, H 6.71, N 21.52; found: C 49.08, H 6.75, N 21.22.

1,3-Dimethyl-1-(*C*-benzo[1,3]dioxol-5-yl-methyl)iminomethylurea (4): This compound was prepared from **2** and piperonylamine. Light yellow oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.92$ (s, 3H), 3.31 (s, 3H), 4.52 (s, 2H), 6.18 (s, 2H), 6.72–6.76 (m, 3H), 7.93 (s, 1H), 9.27 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 26.9$, 32.7, 60.1, 101.3, 108.6, 120.7, 134.1, 146.9, 148.1, 148.4, 156.9 ppm; IR (thin film): $\tilde{\nu} = 3340$, 2946, 1671, 1534, 1309, 1249, 1072, 935 cm^{-1}; MS: *m*/*z* (%): 272 (9) $[M+Na]^+$, 251 (15) $[M+2]^+$, 250 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{12}H_{15}N_3O_3$: C 57.82, H 6.07, N 16,86; found: C 57.44, H 6.08, N 17.26.

1,3-Dimethyl-1-benzyliminomethylurea (5): This compound was prepared from **2** and benzylamine. Gummy syrup (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.93$ (s, 3H), 3.27 (s, 3H), 4.62 (s, 2H), 7.33–7.40 (m, 2H), 7.40–7.42 (m, 3H), 8.54 (s, 1H), 9.37 (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta =$ 32.7, 59.3, 127.0, 128.5, 140.3, 156.9, 163.1; IR (thin film): $\tilde{\nu} = 3340$, 2939, 1671, 1554, 1317, 1084 cm^{-1}; MS: *m*/*z* (%): 228 (6) $[M+Na]^+$, 207 (7) $[M+2]^+$, 206 (100) $[M+1]^+$, 149 (38); elemental analysis calcd (%) for $C_{11}H_{15}N_3O{\cdot}2\,H_2O$: C 54.76, H 7.94, N 17.42; found: C 55.03, H 7.66, N 17.67.

1,3-Dimethyl-1-phenyliminomethylurea (6): This compound was prepared from **2** and aniline. Colorless oil (hygroscopic): ^{1}H NMR ($CDCl_3$): $\delta =$ 3.02 (s, 3H), 3.37 (s, 3H), 7.08 (d, $J = 7.7$ Hz, 2H), 7.22–7.24 (m, 1H), 7.39–7.42 (m, 2H), 8.06 (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.3$, 30.8, 121.5, 125.2, 129.7, 149.5, 151.5, 156.4 ppm; IR (thin film): $\tilde{\nu} = 3353$, 2947, 1658, 1534, 1308, 1087, 1011 cm^{-1}; MS: *m*/*z* (%): 214$[M+Na]^+$ (17), 193$[M+2]^+$ (15), 192 $[M+1]^+$ (100); HRMS calcd for $C_{10}H_{14}N_3O$: 192.1137; found: 192.1139.

1,3-Dimethyl-1-*p*-tolyliminomethylurea (7): This compound was prepared from **2** and *p*-toluidine. Light yellow oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.40$ (s, 3H), 2.99 (s, 3H), 3.55 (s, 3H), 6.97 (d, $J = 6.6$ Hz, 2H), 7.19 (d, $J = 7.3$ Hz, 2H), 8.04 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta =$ 21.2, 27.2, 30.8, 121.2, 130.2, 134.8, 148.7, 151.2, 157.4 ppm; IR (thin film): $\tilde{\nu} = 3357$, 2959, 1655, 1526, 1300, 1078, 1007 cm^{-1}; MS: *m*/*z* (%): 228 (3) $[M+Na]^+$, 207 (15) $[M+2]^+$, 206 (100) $[M+1]^+$; HRMS calcd for $C_{11}H_{16}N_3O$: 206.1293; found: 206.1295.

1,3-Dimethyl-1-(4-methoxyphenyl)iminomethylurea (8). This compound was prepared from **2** and *p*-anisidine. Light yellow oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.93$ (s, 3H), 3.31 (s, 3H), 3.83 (s, 3H), 6.90 (d, $J =$ 9.0 Hz, 2H), 6.99 (d, $J = 10.0$ Hz, 2H), 8.50 (s, 1H), 9.06 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.0$, 32.7, 55.9, 142.7, 150.7, 154.6, 156.6ppm; IR (thin film): $\tilde{\nu} = 3349$, 2930, 1675, 1518, 1296, 1223, 1074 cm^{-1}; MS: *m*/*z* (%): 223 (13) $[M+2]^+$, 222 (100) $[M+1]^+$; HRMS calcd for $C_{11}H_{16}N_3O_2$: 222.1243; found: 222.1240.

1,3-Dimethyl-1-(4-dimethylaminophenyl)iminomethylurea (9): This compound was prepared from **2** and *N*,*N*-dimethyl-*p*-phenylenediamine. Black gummy syrup (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.89$ (s, 3H), 2.96 (s, 6H), 3.25 (s, 3H), 6.90 (d, $J = 7.7$ Hz, 2H), 7.03 (d, $J = 7.6$ Hz, 2H), 8.55 (s, 1H), 9.23 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.2$, 32.7, 41.4, 113.9, 117.0, 145.2, 147.9, 148.9, 156.7 ppm; IR (thin film): $\tilde{\nu} = 3333$, 2922, 1650, 1513, 1300, 1083, 813 cm^{-1}; MS: *m*/*z* (%): 236 (16) $[M+2]^+$, 235 (100) $[M+1]^+$; HRMS calcd for $C_{12}H_{19}N_4O$: 235.1559; found: 235.1552.

1,3-Dimethyl-1-(3-azidopropyl)iminomethylurea (10): This compound was prepared from **2** and 3-azidopropylamine; note: this amine was used as a 0.62 M solution in toluene. Colorless oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 1.89$–1.94 (m, 2H), 3.23 (s, 3H), 3.43 (t, $J = 6.6$ Hz, 2H), 3.49 (t, $J = 6.6$ Hz, 2H), 7.82 (s, 1H), 9.21 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 26.9$, 30.9, 33.9, 152.7, 156.9 ppm; IR (thin film): $\tilde{\nu} = 3344$, 2944, 2101, 1662, 1534, 1312, 997 cm^{-1}; MS: *m*/*z* (%): 221 (22) $[M+Na]^+$, 200 (10) $[M+2]^+$, 199 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_7H_{14}N_6O{\cdot}1/3\,H_2O$: C 41.17, H 7.24, N 41.15; found: C 41.12, H 6.97, N 39.98.

1,3-Dimethyl-1-(3-bromopropyl)iminomethylurea (11): This compound was prepared from **2** and 3-bromopropylamine hydrobromide. Colorless oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.14$–2.23 (m, 2H), 2.90 (s, 3H), 3.29 (s, 3H), 3.51–3.58 (m, 2H), 3.81–3.89 (m, 2H), 8.48 (s, 1H), 9.35 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.6$, 30.4, 31.8, 32.7, 60.1, 152.9, 156.9 ppm; IR (thin film): $\tilde{\nu} = 3327$, 2941, 1686, 1527, 1308, 1075, 997 cm^{-1}; MS: *m*/*z* (%): 238 (100) $[M+2]^+$, 237 (10) $[M+1]^+$, 236 (94) $[M]^+$; elemental analysis calcd (%) for $C_7H_{14}BrN_3O{\cdot}1.5\,H_2O$: C 31.95, H 6.51, Br 30.37, N 15.97; found: C 31.86, H 6.43, Br 29.99, N 16.14.

1,3-Dimethyl-1-(3-chloropropyl)iminomethylurea (12): This compound was prepared from **2** and 3-chloropropylamine hydrochloride. Colorless oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.05$–2.19 (m, 2H), 2.90 (s, 3H), 3.31 (s, 3H), 3.52–3.59 (m, 2H), 3.65–3.70 (m, 2H), 8.51 (s, 1H), 9.23 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.3$, 30.5, 34.1, 43.0, 53.2, 152.9, 156.9 ppm; IR (thin film): $\tilde{\nu} = 3349$, 2951, 1668, 1539, 1310, 1069, 980 cm^{-1}; MS: *m*/*z* (%): 193 (11) $[M+2]^+$, 192 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_7H_{14}ClN_3O$: C 43.87, H 7.36, Cl 18.50, N 21.92; found: C 43.54, H 7.56, Cl 18.17, N 21.90.

1,3-Dimethyl-1-(prop-2-ynyl)iminomethylurea (13): This compound was prepared from **2** and propargylamine. Colorless oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.51$ (s, 1H), 2.95 (s, 3H), 3.27 (s, 3H), 4.28 (s, 2H), 8.09 (s, 1H), 9.02 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.1$, 62.9, 75.0, 79.9, 148.9, 156.8 ppm; IR (thin film): $\tilde{\nu} = 3354$, 2952, 1661, 1536, 1306 cm^{-1}; MS: *m*/*z* (%): 238 (97) $[M+Na]^+$, 217 (11) $[M+2]^+$, 216 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_9H_{17}N_3O_3$: C 50.22, H 7.96, N 19.52; found: C 49.93, H 7.51, N 19.23.

1,3-Dimethyl-1-allyliminomethylurea (14): This compound was prepared from **2** and allylamine. Colorless oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.91$ (s, 3H), 3.27 (s, 3H), 4.03 (d, $J = 17.0$ Hz, 2H), 5.12–5.14 (m, 2H), 5.84–6.18 (m, 1H), 8.53 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.0$, 32.8, 58.8, 115.7, 134.8, 148.7, 156.9 ppm; IR (thin film): $\tilde{\nu} = 3342$, 2964, 1656, 1552, 1073, 796 cm^{-1}; MS: *m*/*z* (%): 157 (9) $[M+2]^+$, 156 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_7H_{13}N_3O$: C 54.17, H 8.44, N 27.08; found: C 54.17, H 8.43, N 27.01.

1,3-Dimethyl-1-(2-morpholin-4-yl-ethyl)iminomethylurea (15):This compound was prepared from **2** and 4-(2-aminoethyl)morpholine. Colorless oil (hygroscopic); ^{1}H NMR ($CDCl_3$): $\delta = 2.12$–2.61 (m, 4H), 2.94 (s, 3H), 3.08 (s, 3H), 3.18 (s, 3H), 3.28–3.54 (m, 2H), 3.55–3.79 (m, 4H), 8.54 (s, 1H), 9.28 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 26.7$, 30.6, 53.6, 54.0, 60.1, 66.9, 152.5, 156.9 ppm; IR (thin film): $\tilde{\nu} = 3357$, 2950, 1675, 1583, 1321, 1111, 983 cm^{-1}; MS: *m*/*z* (%): 251 (7) $[M+Na]^+$, 230 (13) $[M+2]^+$, 229 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{10}H_{20}N_4O_2$ $\cdot 1.5\,H_2O$: C 47.04, H 9.08, N 21.94; found: C 47.04, H 8.88, N 22.14.

1,3-Dimethyl-1-[(*S*)-α-cyclohexylethyl)iminomethylurea (16): This compound was prepared from **2** and (*S*)-(+)-1-cyclohexylethylamine. Colorless oil (hygroscopic); $[\alpha]_D^{23} = +71.1$ ($c = 2.5$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 0.94$–1.02 (m, 2H), 1.19 (d, $J = 6.6$ Hz, 3H), 1.29–1.32 (m, 3H), 1.73–1.83 (m, 5H), 2.91–2.93 (m, 1H), 2.94 (s, 3H), 2.96 (s, 3H), 7.68 (s, 1H), 9.65 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 20.8$, 26.5, 26.6, 26.8, 29.5, 30.1, 44.4, 67.2, 150.1, 157.1 ppm; IR (thin film): $\tilde{\nu} = 3357$, 2919, 2855, 1660, 1539, 1447, 1326, 1077, 996 cm^{-1}; MS: *m*/*z* (%): 248 (10) $[M+Na]^+$, 227 (14) $[M+2]^+$, 226 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{12}H_{23}N_3O{\cdot}1/3\,H_2O$: C 62.30, H 10.31, N 18.16; found: C 62.67, H 10.33, N 18.40.

1,3-Dimethyl-1-[(*R*)-α-phenethyl)iminomethylurea (17): This compound was prepared from **2** and (*R*)-α-methylbenzylamine. Colorless oil (hygroscopic); $[\alpha]_D^{23} = -49.7$ ($c = 1.5$ in $CHCl_3$); ^{1}H NMR ($CDCl_3$): $\delta = 1.61$ (d, $J = 7.0$ Hz, 3H), 2.92 (s, 3H), 3.21 (s, 3H), 4.40–4.44 (m, 1H), 7.21–7.23 (m, 5H), 7.84 (s, 1H), 9.42 ppm (brs, 1H); ^{13}C NMR ($CDCl_3$): $\delta = 27.1$, 30.0, 65.8, 126.5, 127.1, 128.9, 145.8, 151.6, 157.0 ppm; IR (thin film): $\tilde{\nu} =$ 3340, 2974, 1654, 1534, 1441, 1316, 1071 cm^{-1}; MS: *m*/*z* (%): 242 (9) $[M+Na]^+$, 221 (13) $[M+2]^+$, 220 (100) $[M+1]^+$, 130 (69); elemental analysis calcd (%) for $C_{12}H_{17}N_3O{\cdot}1/8\,H_2O$: C 65.06, H 7.85, N 18.97; found: C 65.03, H 8.11, N 18.64.

1,3-Dimethyl-1-phenoxyiminomethylurea (18): This compound was prepared from **2** and *O*-phenylhydroxylamine hydrochloride. White solid (hygroscopic); m.p. 96–97 °C; ^{1}H NMR (CD_3OD): $\delta = 2.89$ (s, 3H), 3.30 (s, 3H), 6.99–7.02 (m, 1H), 7.16 (d, $J = 8.0$ Hz, 2H), 7.32–7.35 (m, 2H),

9.02 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=26.7, 29.5, 113.7, 121.4, 129.2, 148.8, 156.6, 160.3 ppm; IR (thin film): $\tilde{\nu}$=3335, 3061, 2949, 1670, 1545, 1476, 1223, 933 cm^{-1}; MS: *m*/*z* (%): 230 (100) $[M+Na]^+$, 209 (5) $[M+2]^+$, 208 (39) $[M+1]^+$ elemental analysis calcd (%) for $C_{10}H_{13}N_3O_2$: C 57.96, H 6.32, N 20.28; found: C 57.56, H 6.09, N 19.95.

1,3-Dimethyl-1-(tetrahydro-*2H*-pyran-2-yloxy)iminomethylurea (19): This compound was prepared from **2** and *O*-(tetrahydro-2*H*-pyran-2-yl)hydroxylamine. Colorless oil (hygroscopic); ^{1}H NMR ($CDCl_3$): δ=1.65–1.77 (m, 4H), 1.85–1.90 (m, 2H), 2.95 (s, 3H), 3.22 (s, 3H), 3.66–3.69 (m, 1H), 3.96–4.00 (m, 1H), 5.20 (s, 1H), 6.65 (brs, 1H), 8.45 ppm (s, 1H); ^{13}C NMR ($CDCl_3$): δ=19.9, 25.6, 27.8, 29.2, 32.4, 62.8, 100.7, 148.8, 155.9 ppm; IR (thin film): $\tilde{\nu}$=3356, 2949, 1666, 1537, 1348, 1018 cm^{-1}; MS: *m*/*z* (%): 238 (97) $[M+Na]^+$, 217 (11) $[M+2]^+$, 216 (100)$[M+1]^+$; elemental analysis calcd (%) for $C_9H_{17}N_3O_3$: C 50.22, H 7.96, N 19.52; found: C 49.93, H 7.51, N 19.23.

1,3-Dimethyl-1-methoxyiminomethylurea (20): This compound was prepared from **2** and methoxylamine hydrochloride. White solid (hygroscopic); m.p. 107–108 °C; ^{1}H NMR (CD_3OD): δ=2.85 (s, 3H), 3.15 (s, 3H), 3.79 (s, 3H), 7.25 (brs, 1H), 8.63 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=26.6, 29.5, 61.01, 146.01, 156.9 ppm; IR (thin film): $\tilde{\nu}$=3339, 2949, 1642, 1529, 1348, 1058 cm^{-1}; MS: *m*/*z* (%): 168 (5) $[M+Na]^+$, 147 (6) $[M+2]^+$, 146 (96) $[M+1]^+$, 105 (38), 60 (100); elemental analysis calcd (%) for $C_5H_{11}N_3O_2$: C 41.37, H 7.64, N 28.95; found: C 41.64, H 7.76, N 28.59.

1,3-Dimethyl-1-allyloxyiminomethylurea (21): This compound was prepared from **2** and *O*-allylhydroxylamine hydrochloride. White solid (hygroscopic); m.p. 98–99 °C; ^{1}H NMR (CD_3OD): δ=2.85 (s, 3H), 3.15 (s, 3H), 4.48 (d, *J*=5.9 Hz, 2H), 5.24 (d, *J*=10.6 Hz, 1H), 5.34 (d, *J*=18.7 Hz, 1H), 6.01–6.09 (m, 1H), 8.66 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=26.6, 29.5, 74.7, 116.6, 134.8, 146.2, 156.9 ppm; IR (thin film): $\tilde{\nu}$=3344, 2922, 1647, 1538, 1345, 1047, 938 cm^{-1}; MS: *m*/*z* (%): 194 (13) $[M+Na]^+$, 173 (10) $[M+2]^+$, 172 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_7H_{13}N_3O_2$: C 49.11, H 7.65, N 24.54; found: C 49.46, H 7.29, N 24.09.

1,3-Dimethyl-1-*tert*-butoxyiminomethylurea (22): This compound was prepared from **2** and *O*-(*tert*-butyl)hydroxylamine hydrochloride. White solid (hygroscopic); m.p. 70–71 °C; ^{1}H NMR (CD_3OD): δ=1.32 (s, 9H), 2.86 (s, 3H), 3.18 (s, 3H), 8.55 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=25.2, 25.4, 28.3, 76.3, 143.3, 155.5 ppm; IR (thin film): $\tilde{\nu}$=3469, 3195, 3026, 1722, 1602 cm^{-1}; MS: *m*/*z* (%): 210 (5) $[M+Na]^+$, 189 (9) $[M+2]^+$, 188 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_7H_{11}N_3O$: C 54.89, H 7.24, N 27.43; found: C 54.57, H 7.25, N 27.80.

1,3-Dimethyl-1-benzyloxyiminomethylurea (23): This compound was prepared from **2** and *O*-benzylhydroxylamine. White solid (hygroscopic); m.p. 84–85 °C; ^{1}H NMR (CD_3OD): δ=2.84 (s, 3H), 3.13 (s, 3H), 5.01 (s, 2H), 7.35–7.43 (m, 5H), 8.67 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=26.6, 29.6, 75.9, 127.7, 128.3, 128.4, 138.3, 146.5, 156.8 ppm; IR (thin film): $\tilde{\nu}$=3370, 2931, 1652, 1527, 1350, 1036 cm^{-1}; MS: *m*/*z* (%): 244 (35) $[M+Na]^+$, 223 (12) $[M+2]^+$, 222 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{11}H_{15}N_3O_2$: C 59.71, H 6.83, N 18.99; found: C 59.62, H 6.64, N 18.64.

1,3-Dimethyl-1-trityloxyiminomethylurea (24): This compound was prepared from **2** and *O*-tritylhydroxylamine. White solid (hygroscopic); m.p. 100–101 °C; ^{1}H NMR (CD_3OD): δ=2.75 (s, 3H), 2.96 (s, 3H), 7.30–7.43 (m, 15H), 8.66 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=26.4, 30.3, 90.7, 127.4, 129.3, 144.8, 146.3, 156.8 ppm; IR (thin film): $\tilde{\nu}$=3351, 3061, 2948, 1669, 1537, 1283, 977 cm^{-1}; MS: *m*/*z* (%): 396 (100) $[M+Na]^+$, 375 (3) $[M+2]^+$, 374 (54) $[M+1]^+$; elemental analysis calcd (%) for $C_{23}H_{23}N_3O_2$: C 73.97, H 6.21, N 11.25; found: C 74.07, H 6.23, N 11.30.

1,3-Dimethyl-1-(benzoyl-hydrazonomethyl)iminomethylurea (25): This compound was prepared from **2** and benzhydrazide. White solid (hygroscopic); m.p. 155–156 °C; ^{1}H NMR (CD_3OD): δ=2.91 (s, 3H), 3.33 (s, 3H), 7.55–7.58 (m, 2H), 7.62–7.65 (m, 1H), 7.92–7.94 (m, 2H), 8.98 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=26.6, 29.4, 127.5, 128.7, 131.9, 133.5, 146.8, 157.0, 165.5 ppm; IR (thin film): $\tilde{\nu}$=3343, 2973, 1657, 1621, 1529, 1296 cm^{-1}; MS: *m*/*z* (%): 257 (100) $[M+Na]^+$, 236 (5) $[M+2]^+$, 235 (40) $[M+1]^+$; elemental analysis calcd (%) for $C_{11}H_{14}N_4O_2\cdot0.5H_2O$: C 54.31, H 6.22, N 23.03; found: C 54.75, H 6.31, N 22.82.

1,3-Dimethyl-1-(4-methylbenzoyl-hydrazonomethyl)iminomethylurea (26): This compound was prepared from **2** and *p*-toluic hydrazide. White solid (hygroscopic); m.p. 142–143 °C; ^{1}H NMR (CD_3OD): δ=2.48 (s, 3H), 2.90 (s, 3H), 3.33 (s, 3H), 7.38 (d, *J*=8.5 Hz, 2H), 7.83 (d, *J*=8.1 Hz, 2H), 8.96 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=19.1, 26.5, 30.0, 126.2, 127.9, 163.8, 131.9, 141.3, 145.4, 155.4 ppm; IR (thin film): $\tilde{\nu}$=3103, 2777, 2656, 1703, 1572, 1296, 1043 cm^{-1}; MS: *m*/*z* (%): 271 (28) $[M+Na]^+$, 249 (37) $[M+1]^+$, 192 (100); elemental analysis calcd (%) for $C_{12}H_{16}N_4O_2\cdot0.5H_2O$: C 54.12, H 6.81, N 18.02; found: C 54.23, H 7.19, N 17.76.

1,3-Dimethyl-1-(octanoyl)hydrazonomethyl)iminomethylurea (27): This compound was prepared from **2** and octanoic hydrazide. White solid (hygroscopic); m.p. 124–125 °C; ^{1}H NMR (CD_3OD): δ=0.98 (t, *J*=6.6 Hz, 3H), 1.39–1.42 (m, 8H), 1.68–1.75 (m, 2H), 2.28 (t, *J*=7.4 Hz, 3H), 2.88 (s, 3H), 3.26 (s, 3H), 8.75 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=13.4, 22.7, 26.0, 26.6, 29.1, 29.2, 29.3, 31.9, 34.5, 145.5, 157.1, 170.9 ppm; IR (thin film): $\tilde{\nu}$=3247, 2929, 1658, 1531, 1300 cm^{-1}; MS: *m*/*z* (%): 279 (100) $[M+Na]^+$, 258 (4) $[M+2]^+$, 257 (31) $[M+1]^+$; elemental analysis calcd (%) for $C_{12}H_{24}N_4O_2$: C 56.52, H 9.40, N 21.46; found: C 56.22, H 9.40, N 21.46.

Ethyl ester of *N*'-(1,3-dimethylureidomethylene)hydrazinecarboxylic acid (28): This compound was prepared from **2** and ethyl carbazate. White solid (hygroscopic); m.p. 72–73 °C; ^{1}H NMR (CD_3OD): δ=1.39 (t, *J*=7.4 Hz, 3H), 2.89 (s, 3H), 3.28 (s, 3H), 3.28–3.38 (m, 2H), 7.42 (brs, 1H), 8.75 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=13.4, 26.6, 29.2, 46.9, 145.5, 157.0, 170.9 ppm; IR (thin film): $\tilde{\nu}$=3307, 2928, 2859, 1653, 1536, 1299, 1077 cm^{-1}; MS: *m*/*z* (%): 225 (39) $[M+Na]^+$, 204 (8) $[M+2]^+$, 203 (100)$[M+1]^+$; elemental analysis calcd (%) for $C_7H_{14}N_4O_3$: C 41.58, H 6.98, N 27.71; found: C 55.89, H 7.32, N 27.56.

1,3-Dimethyl-1-[(5-dimethylamino-1-naphthylsulfonyl)hydrazono]iminomethylurea (29): This compound was prepared from **2** and dansylhydrazine. Yellow solid (hygroscopic); m.p. 167–168 °C; ^{1}H NMR (CD_3OD): δ=2.76 (s, 3H), 2.95 (s, 6H), 2.97 (s, 3H), 7.34 (d, J=7.7 Hz, 1H), 7.62-7.68 (m, 2H), 8.30 (d, *J*=13.9 Hz, 1H), 8.50 (s, 1H), 8.53 (d, *J*=8.8 Hz, 1H), 8.65 ppm (d, *J*=8.8 Hz, 1H); ^{13}C NMR (CD_3OD): δ=26.4, 29.1, 44.8, 115.4, 120.0, 123.3, 128.0, 130.1, 130.5, 130.6, 134.7, 148.0, 152.1, 155.5, 156.8 ppm; IR (thin film): $\tilde{\nu}$=3403, 3118, 2945, 1658, 1537, 1465, 1320, 1143 cm^{-1}; MS: *m*/*z* (%): 386 (38) $[M+Na]^+$, 365 (24) $[M+2]^+$, 364 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_{16}H_{21}N_5O_3S$: C 52.88, H 5.82, N 19.27; S, 8.82; found: C 52.75, H 6.13, N 18.91; S, 8.56.

1,3-Dimethyl-1-(methylhydrazono)iminomethylurea (30): This compound was prepared from **2** and methylhydrazine. Gummy syrup (hygroscopic); ^{1}H NMR (CD_3OD): δ=2.90 (s, 3H), 3.09 (s, 3H), 3.16 (s, 3H), 6.13 (brs, 1H), 8.67 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=26.3, 31.9, 42.4, 145.6, 161.5 ppm; IR (thin film): $\tilde{\nu}$=3357, 2979, 1627, 1571, 1413, 1297, 1039 cm^{-1}; MS: *m*/*z* (%): 167 (10) $[M+Na]^+$, 146 (8) $[M+2]^+$, 145 (100) $[M+1]^+$; elemental analysis calcd (%) for $C_5H_{12}N_4O$: C 41.65, H 8.39, N 38.86; found: C 41.78, H 8.79, N 38.99.

1,3-Dimethyl-1-[(2,4,6-trichlorophenyl)hydrazono]iminomethylurea (31): This compound was prepared from **2** and 2,4,6-trichlorophenylhydrazine. Beige solid (hygroscopic); m.p. 141–142 °C; ^{1}H NMR (CD_3OD): δ=2.88 (s, 3H), 3.21 (s, 3H), 7.45 (s, 2H), 8.67 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=26.4, 29.9, 126.9, 127.0, 128.7, 128.8, 140.2, 145.0, 157.2 ppm; IR (thin film): $\tilde{\nu}$=3331, 3230, 2940, 1677, 1561, 1441, 1352, 1268, 1074 cm^{-1}; MS: *m*/*z* (%): 331 (18) $[M+Na]^+$, 310 (88) $[M+2]^+$, 309 (100) $[M+1]^+$, 261 (50); elemental analysis calcd (%) for $C_{10}H_{11}Cl_3N_4O$: C 38.80, H 3.58; Cl, 34.36, N 18.10; found: C 38.62, H 3.55; Cl, 33.98, N 18.53.

1,3-Dimethyl-1-[(furan-2-carbonyl)hydrazono]iminomethylurea (32): This compound was prepared from **2** and 2-furoic acid hydrazide. White solid (hygroscopic); m.p. 138–139 °C; ^{1}H NMR (CD_3OD): δ=2.90 (s, 3H), 3.31 (s, 3H), 6.69 (brs, 1H), 7.28 (brs, 1H), 7.78 (brs, 1H), 8.98 ppm (brs, 1H); ^{13}C NMR (CD_3OD): δ=26.6, 29.3, 112.0, 115.0, 145.6, 146.8, 147.0, 156.1, 157.0 ppm; IR (thin film): $\tilde{\nu}$=3374, 2968, 2605, 2493, 1620, 1539, 1302, 1177, 1029 cm^{-1}; MS: *m*/*z* (%): 247 (100) $[M+Na]^+$, 225 (10) $[M+1]^+$; elemental analysis calcd (%) for $C_9H_{12}N_4O_3$: C 48.21, H 5.39, N 24.99; found: C 48.63, H 5.72, N 24.59.

1,3-Dimethyl-1-[2-hydroxybenzoyl)-hydrazono]iminomethylurea (33): This compound was prepared from **2** and salicylhydrazide. Beige solid (hygroscopic); m.p. 184–185 °C; ^{1}H NMR (CD_3OD): δ=2.90 (s, 3H), 3.33 (s, 3H), 6.99–7.01 (m, 2H), 7.47 (m, 1H), 7.88 (d, *J*=7.7 Hz, 1H), 8.98 ppm (s, 1H); ^{13}C NMR (CD_3OD): δ=26.6, 29.3, 115.2, 117.5, 119.3, 127.8, 133.9, 147.0, 157.0, 160.0, 166.0 ppm; IR (thin film): $\tilde{\nu}$=3315, 3231, 3053, 2921, 1650, 1589, 1521, 1296, 1215 cm^{-1}; MS: *m*/*z* (%): 273 (89) $[M+Na]^+$, 251 (13) $[M+1]^+$, 65 (100); elemental analysis calcd (%) for

$C_{11}H_{14}N_4O_3 \cdot 0.5\,H_2O$: C 49.25, H 6.01, N 20.88; found: C 49.69, H 5.98, N 20.53.

***N*-{(1*S*)-1-benzyl-2-{(2*E*)-2-{{methyl[(methylamino)carbonyl]amino}methyllene}hydrazine}-2-oxoethyl}acetamide (34)**: This compound was prepared from the freebase form of **2** and acetyl-L-phenylalanine hydrazine. It was purified by preparative reversed-phase HPLC using a Polaris C18 A5µ column, eluting with a 0–100% gradient of CH_3CN in water. White solid; m.p. 109–110 °C; $[\alpha]_D^{23} = +28.3$ ($c = 0.12$ in H_2O); ^{1}H NMR (D_2O): $\delta = 1.94$ (s, 3H), 2.74 (s, 3H), 3.03 (dd, $J = 7.4$, 2.7 Hz, 2H), 3.08 (s, 3H), 4.43 (t, $J = 8.1$ Hz, 1H), 7.22?7.33 (m, 5H), 8.33 ppm (s, 1H); ^{13}C NMR (D_2O): $\delta =$ 21.9, 27.1, 29.8, 37.7, 54.8, 127.6, 129.1, 129.6, 136.5, 148.9, 157.8, 168.9, 174.3 ppm; IR (thin film): $\tilde{\nu} = 3276$, 3067, 1666, 1630, 1525, 1296 cm^{-1}; MS: *m*/*z* (%): 342 (34) $[M+Na]^+$, 321 (18) $[M+2]^+$, 320 (100) $[M+1]^+$; HRMS calcd for $C_{15}H_{22}N_5O_3Na$: 342.1537; found: 342.1544.

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