

Modular synthesis of formamidines and their formation of stable organogels†

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An improvement in the practical aspects of formamidine synthesis has resulted in the discovery of a class of compounds which produce organogels in protic solvents, presumably through intermolecular hydrogen bonding and π - π stacking interactions.

Formamidines have claimed the interest of many research groups for their biological activity and pharmacological potential.¹ Formamide acetals **1** have been widely used in the synthesis of amidines from amines and amides, providing **2** under mild conditions in high yields (Scheme 1).² Recently, we reported that formamidine urea compounds (**3**) undergo exchange reactions of their imine fragments with primary nitrogen nucleophiles, giving derivatives of varying electrophilicity determined primarily by the electronic-donating power of the substituents.¹ We anticipated that this behavior could be extended to the simple *N,N*-dimethyl formamidines **2**, in order to access a wider array of simple formamidines **4**. Several reports in the literature describe the exchange of the dimethylamine fragment of **2** with nucleophiles such as aliphatic³ and aromatic⁴ amines, hydrazines,⁵ and hydroxylamines.⁶ Most of these reactions are carried out in protic solvents (e.g. MeOH, EtOH) at elevated temperatures, but the scope and limitations of this important exchange process have not yet been explored. Here we describe the use of polar nonprotic solvents, allowing for the convenient isolation of pure compounds by precipitation and therefore access to a much wider array of structures than was previously possible. In the course of our efforts to take advantage of this development, a molecule displaying highly efficient properties as a gelator of organic solvents was discovered.

Our interest in the chemistry of the formamidine nucleus^{1,7} prompted us to explore first the conversion of dimethylformamidine **5**⁸ into **6** by amine exchange (Scheme 1). The best yields were

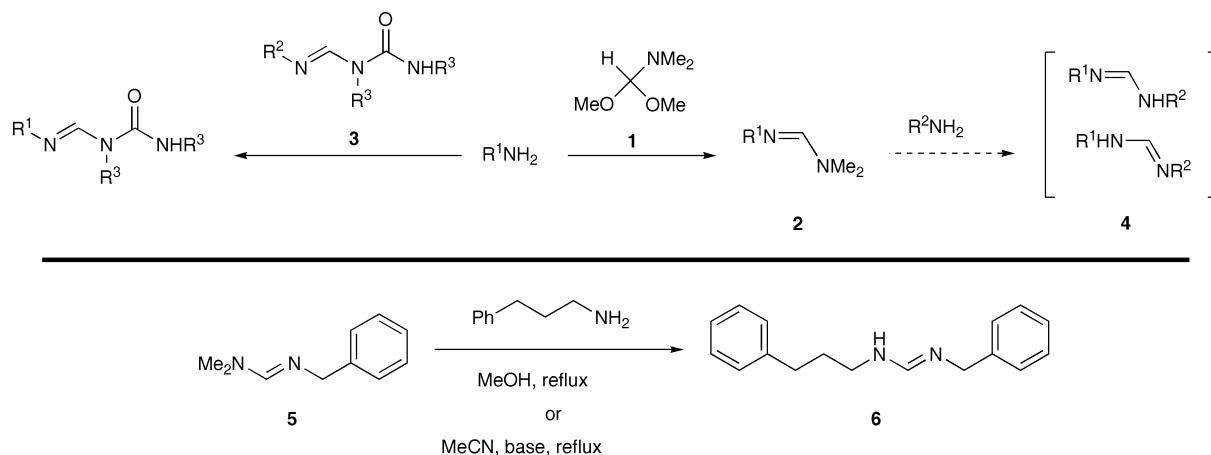
achieved in methanol with the use of 3 equivalents of nucleophile, but reactions in nonprotic polar solvents such as acetonitrile were found to be fairly effective with 1.5 equivalents of amine and the addition of organic base (Et₃N, *i*Pr₂NET, DMAP).⁹ A broader study of the general method was then performed with an eye toward the preparation of formamidines of tunable electrophilicity¹ at the central carbon.

A preliminary survey of nucleophiles demonstrated that a two-step exchange process followed a predictable set of rules. Thus, the formamide acetal **1** readily accepted primary amines, amides, hydroxylamines, hydrazides, and hydrazines. However, the second step, displacement of the dimethylamine fragment from formamidines **7**, was blocked when the imine component was strongly electron donating (derived from hydrazines, hydrazides, or hydroxylamines), a trend also observed with formamidine ureas.¹ Furthermore, with all reactive examples of **7**, the entering nucleophile in the second step must be more nucleophilic than an amide. Aside from these limitations, a modular exchange route to diverse mixed formamidines **8** was found to be straightforward, as shown in Scheme 2.⁹

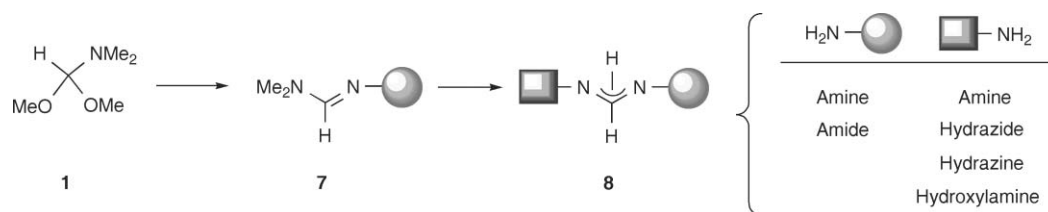
When highly polar amines were used in protic solvents, the isolation and purification of the final amidine products was tedious, requiring the use of HPLC or complex crystallization procedures. However, base catalysis in acetonitrile allowed analytically pure compounds to be obtained as precipitates,¹⁰ the modest nature of the yields being more than outweighed by the convenient nature of the procedure. Fig. 1 shows a set of formamidines made in this fashion. All products were isolated as pure white solids by filtration.

As the biological activity of formamidines is likely to be influenced by their rates of hydrolysis,¹¹ we examined the stabilities of simple model compounds representing combinations of amine-amine, amine-hydrazide, amide-hydrazide, and amide-amine fragments, in aqueous methanol solutions at three different pH values.⁹ These compounds were found to be far more stable toward hydrolysis than formamidine ureas,¹ displaying half lives from 1 to more than 200 h. Both acid- and base-mediated hydrolysis

† Electronic supplementary information (ESI) available: Experimental details, expanded discussion and compound characterization. See <http://www.rsc.org/suppdata/cc/b4/b406704e/>



Scheme 1 Exchange reactions in the preparation of formamidines and formamidine ureas.



Scheme 2 General exchange process for the synthesis of formamidines from formamide acetals.

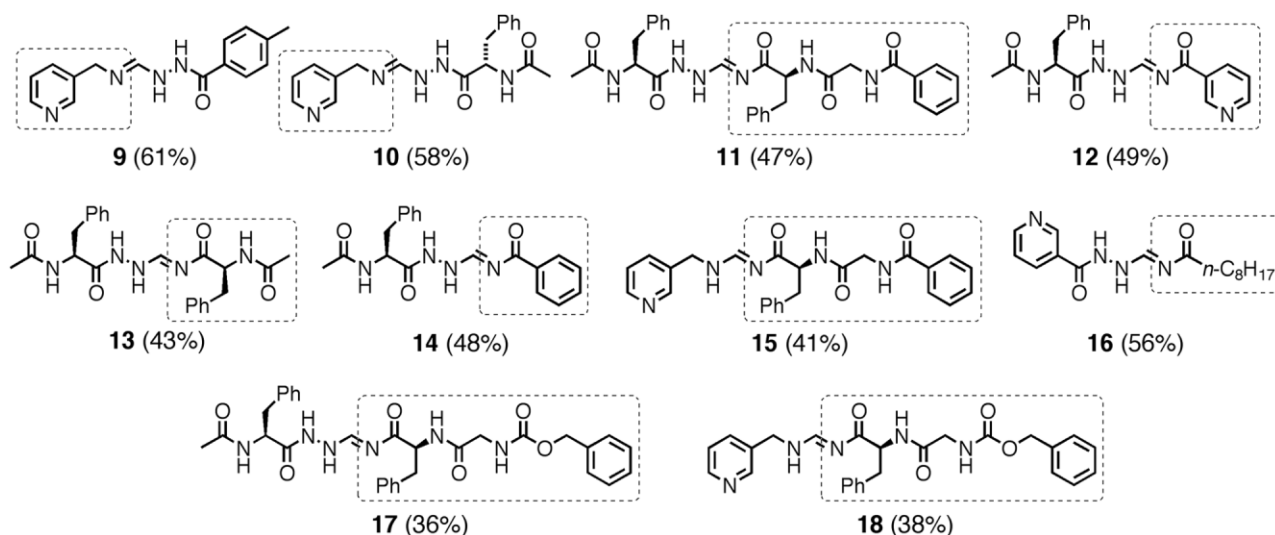


Fig. 1 Compounds obtained by the two-step exchange process shown in Scheme 2, using acetonitrile as solvent and DMAP as catalytic base. The boxed fragment was introduced in the first step; isolated yields of analytically pure material are given in parentheses.

mechanisms were revealed, the former being favored for especially electron-rich systems.⁹

Two of the above structures were also found to be efficient gelators of protic organic solvents. Organogels are supramolecular materials of current interest;¹² to the best of our knowledge, we report here the first example of an organogel formed by a formamidine. The formamidine unit should be a potent building block in this regard, since linear arrays of hydrogen bonds are often crucial to the formation of the filamentous structures that comprise organogel networks.

Compounds **11** and **17** formed gels in alcohol solvents, with **11** being the more effective in terms of stability and efficiency (mass of gelator per unit volume of gel). A typical procedure involved heating a sample of **11** in MeOH, EtOH, 2-propanol, 1-propanol,

or 2,2,2-trifluoroethanol near the boiling point of the solvent, and then cooling the solution to 6 °C.¹³ The gel made from **11** in methanol could be dissolved by heating in extra solvent and then reformed upon cooling; this cycle could be repeated several times without affecting the gelation process. Complete gel formation using as little as 0.3 wt% of **11** in methanol was observed within 72 h and was confirmed by the inverted test-tube method (Fig. 2), although a turbid solution formed within minutes upon cooling.¹⁴ When the concentration of gelator was >0.7 wt%, heating accomplished the physical dispersion of the gel rather than its solubilization.

The gels formed by **11** were stable at room temperature for more than two months when stored in sealed glass vials. While requiring alcohol solvents to form, they remained immiscible and stable in

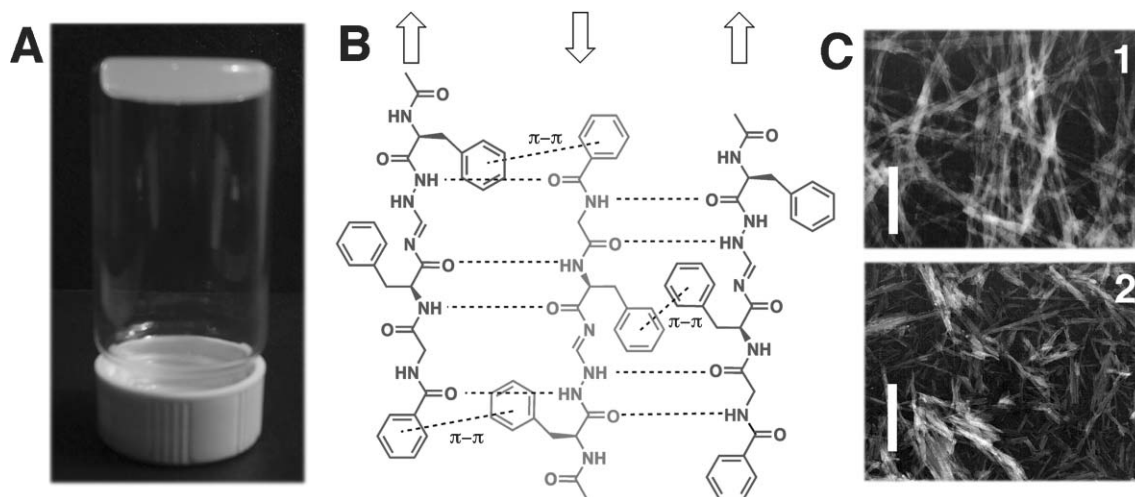


Fig. 2 (A) Organogel formed by 4 mg of **11** in 2 mL of MeOH and 0.2 mL of chlorobenzene. (B) Network of interactions proposed to promote gelation. (C) Negative stain TEM images of organogels formed from **11** (panel 1, 0.3 wt% in 10:1 MeOH:chlorobenzene; panel 2, 0.4 wt% in 1.2:1 DMA:H₂O); (scale bar 1 μm).

neutral aqueous solution for at least 4–5 days, after which time the consistency of the gel decreased.¹⁶ The fibrous nature of the gel material was demonstrated by transmission electron microscopy (Fig. 2). The gels made in protic solvents retain their form upon heating until temperatures are reached at which the trapped solvent boils, so we were unable to characterize gel-to-sol phase transition temperatures by differential scanning calorimetry.

No gelation was observed when the hydrazide and amide fragments (Ac-Phe-NHNH₂ and Bz-Gly-Phe-NH₂, respectively) of **11** were dissolved individually or together. FT-IR of the gel showed N-H stretching bands in the 2800–3300 cm⁻¹ range and C=O bands at 1631 and 1540 cm⁻¹, characteristic of strong H-bonding interactions. A new weak signal at approximately 1760 cm⁻¹ was also observed, consistent with an antiparallel β -sheet arrangement (although this feature may also arise from a disordered structure).¹⁵ The CD spectra of **11** likewise changed dramatically in going from the solution phase at elevated temperature (little or no ellipticity) to the gel phase (substantial signal) upon cooling.⁹ The proposed intermolecular hydrogen-bonding pattern of **11** is shown in Fig. 2. In addition to hydrogen bonding, for which the formamidine function is crucial, dipolar interactions and π - π stacking may also play significant roles in promoting the efficient organization of **11** into aggregates and fibers.

In conclusion, the discovery of a simple procedure for the assembly of formamidine components has led to the synthesis of a range of structures showing good stability toward aqueous hydrolysis and potent hydrogen bonding activity in protic organic solvents and aqueous/organic mixtures. In addition to their demonstrated properties as organogel components, formamidines should engage in facile interactions with proteins. Their properties as biologically active agents are under current investigation in our laboratory.

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- 8 Compound **5** was synthesized by refluxing *N,N*-dimethylformamide dimethyl acetal with benzylamine for 13 h, see ref. 2.
- 9 See ESI† for details.
- 10 Typical procedure (preparation of **11**): a mixture of dimethylformamide dimethyl acetal (**1**, 46.7 μ L, 0.34 mmol) and Bz-Gly-Phe-NH₂ (100 mg, 0.31 mmol) in dry acetonitrile (5 mL) was heated at reflux and the reaction was monitored by mass spectrometry. The initial cloudy solution turned clear within 10 min of reaching reflux temperature and then dark orange shortly thereafter. After 1 h the reaction mixture was cooled, evaporated to dryness, and traces of remaining **1** were removed by two successive addition–evaporation sequences with toluene. The dried residue was dissolved in anhydrous acetonitrile (5 mL), heated for 5 min at 60 °C, and then treated while hot with Ac-Phe-NHNH₂ (68.6 mg, 0.31 mmol) and a catalytic amount of DMAP (3.8 mg, 0.1 equiv.) added in one portion. The initial cloudy solution turned clear within 1 min and was stirred under reflux. Within 1 h, compound **11** started to precipitate from the hot solution. After 15 h, the solution was cooled to room temperature and the precipitate was filtered and washed with anhydrous acetonitrile and diethyl ether. The solid was dried at 50 °C, yielding **11** in 47% yield as a white hygroscopic material, which was stored under nitrogen at –20 °C. Omission of catalytic base (DMAP in this case) requires the use of significantly longer reaction times to achieve comparable yields. Selected characterization data of new compounds are provided in the ESI†.
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- 16 The organogel prepared in 10:1 MeOH:PhCl was found to be stable for several days at neutral and acidic conditions (approximate pH as low as 2, and temperature as high as 65 °C). However, at pH > 8 the gel was almost completely dissolved within 1 h, suggesting either hydrolytic instability of the formamidine urea under these conditions or, more likely, an important role for amidine protonation in stabilization of the gel structure. The basicities of these compounds are under investigation; the conjugate acids of simple formamidines span a p*K*_a range of approximately 6.5 to 11 [E. D. Raczynska, M. Darowska, I. Dabkowska, M. Decouzon, J.-F. Gal, P.-C. Maria and C. D. Pollart, *J. Org. Chem.*, 2004, **69**, 4023–4030, and references therein]. No collapse of the gel was observed in the presence of organic solvents such as THF, CHCl₃, CH₂Cl₂, benzene, hexane or Et₂O for several days.