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Multicomponent Reactions of Isocyanides for the Preparation of Low Molecular Weight Gelators: Preliminary Studies †

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Abstract: Low molecular weight gelators, LMWGs, are small molecules that can self-associate in organic solvents or in water to form fibrous supramolecular architectures and three-dimensional networks that present important applications in several fields. Although various strategies are known for the synthesis of these type of compounds, these are commonly hampered by the use of long multistep processes that include the protection and deprotection of functional groups. Therefore, it is essential to find direct and robust reactions that allow introducing the complexity and structural diversity necessary to obtain tailor-made functional materials in a simple and efficient way. A promising approach to this end is the use of multicomponent reactions. Based on our experience in this field, we report our studies aimed at the use of multicomponent reactions of isocyanides to prepare LMWGs.

Keywords: hydrogel; gelator; LMWGs; multicomponent reactions; isocyanides; microwave; new materials; supramolecular chemistry

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1. Introduction

Low molecular weight gelators, LMWGs, are small molecules that form fibrous supramolecular architectures and three-dimensional networks able to trap and immobilize solvents, either organic solvents (organogelators) or water solvents (hydrogelators). The driving forces of gelation are noncovalent interactions, such as hydrogen bonds, van der Waals forces, π-π stacking, and donor−acceptor interactions. The gelation process is reversible and can be activated by light, ultrasound, pH variations, or the addition of small molecules [1–4].

LMWGs present applications in several fields, such as analyte sensing, optoelectronics, organo-catalysis, and biomedicine [5,6]. Applications in tissue engineering [7], drug delivery, and antibacterial agents are especially important [8].

Many LMWGs of natural or synthetic origin are known. However, the development of novel smart materials with defined tailor-made properties is of crucial importance. To reach this aim, it is essential to have powerful synthetic tools that can provide the structural diversity necessary to finely control the physical properties of the products. Although the gelation abilities are complex to predict, and many LMWGs have been discovered by serendipity [6], rational design is still possible if key structural features are considered. Thus, for a compound to be able to form supramolecular gels, it is essential that it be at least partially soluble in the solvent to be gelled and that it contains groups capable of forming noncovalent intermolecular interactions.

Gelators derived from biological molecules, such as amino acids or carbohydrates, have been classically used in medicine and tissue engineering as they are biocompatible materials [9]. In particular, peptide-based hydrogelators show great potential in biomedical

applications, due to the presence of complementary functional groups that form directional noncovalent bonds responsible for the formation of supramolecular fibers [10]. A drawback of LMWG peptides is that they are rapidly degraded in vivo by proteases. Thus, the development of peptidomimetic hydrogelators has emerged as a valuable alternative since they maintain the activity of the model peptide and exhibit superior stability in a biological environment [11–14].

Multicomponent reactions are powerful tools for the synthesis of tailor-made LMWGs [15] as they allow the easy introduction of structural modifications that lead to the desired characteristics. Prototypically, the Ugi four-component condensation [16] enables the synthesis of peptoids in a highly convergent process and has been used for the synthesis of tripeptoid gelators [17]. Here, we report some novel approaches to the synthesis of peptide-like LMWGs using multicomponent reactions developed by our group.

2. Results and Discussion

Our research group has great experience in the use of the isocyanide-based multicomponent reaction, IMCR, for the synthesis of molecular libraries. IMCRs allow rapid access to functionalized molecules with a high degree of diversity simply by varying the different starting components. Thus, IMCRs constitute a promising strategy for preparing libraries of compounds capable of acting as gelators.

To prove this idea, we performed gelification essays on different compounds we previously prepared using IMCR protocols. We chose two very different structural types: simple 1,3-dicarbonyl compounds (1) and pyrrolinodione derivatives (2) (Figure 1). In both cases, we were able to introduce different substituents through the multicomponent reaction, which allowed us to assess their influence on the gelation properties.

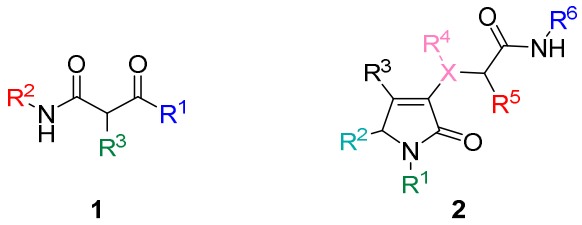


Figure 1. General structures of two type of structures tested in gelification essays.

2.1. Self-Assembling Properties of Dicarbonyl Compounds

Dicarbonylic compounds (1a–h, Figure 2) were prepared in a two-step sequence. A Passerini reaction between glyoxal derivatives (3), isocyanides (4), and acetic acid (5) produced 3-oxocarboxamides (6), which were then subjected to reduction or hydrolysis to produce alfa-unsubstituted or alfa-hydroxysubstituted 3-oxocarboxamides [18–20] (Scheme 1).

In order to modulate the potential intermolecular interactions in the supramolecular gel, substituents R^1 and R^2 were tuned by choosing the appropriate carbonyl compound (3) and isocyanide (4) components in the Passerini reaction. The best gelification results were obtained with the R^1 and R^2 hydrophobic groups, which favored van der Waals interactions, while the amide and carbonyl groups enabled the formation of hydrogen bonds. Thus, different aromatic and aliphatic substituents have been introduced in the R^1 and R^2 positions. Aromatic rings are capable of forming π-π interactions, which may be one of the main intermolecular forces leading to gelation.

The gelation capacity of dicarbonylic compounds 1a–h was tested in a water/EtOH system. Gelation was triggered by applying a heat−cold cycle to a suspension of the samples, by means of microwave irradiation.

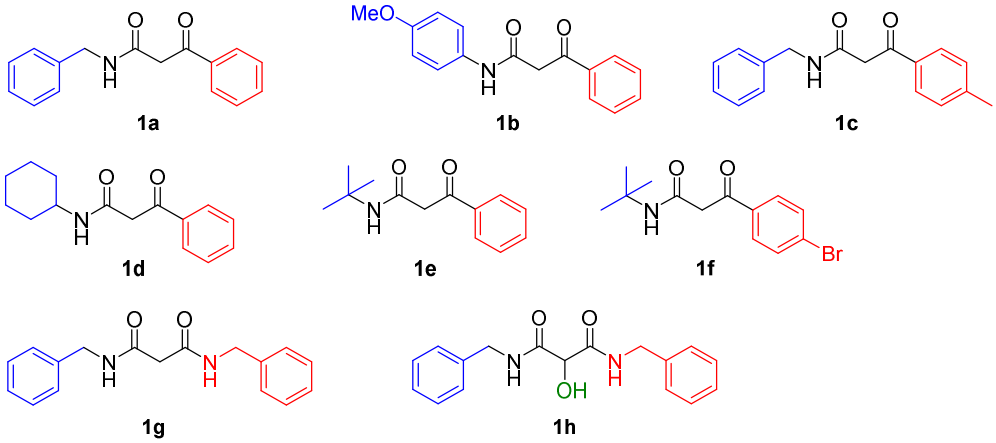
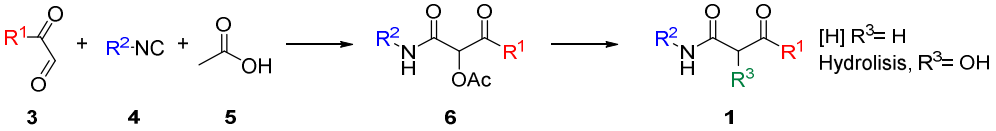


Figure 2. Dicarbonylic compounds tested as gelators.

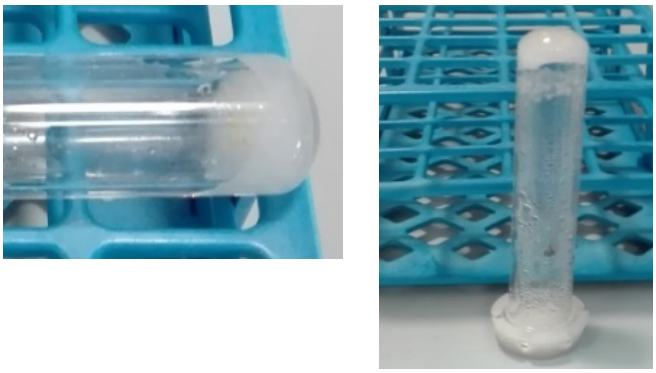


Scheme 1. Synthesis of dicarbonylic compounds 1.

Compound 1a, containing phenylketone and benzylamide moieties, precipitated in the solvent medium (Table 1, entry 1). The introduction of a methoxy group in the isocyanide subunit (1b) or a methyl group in the glyoxylic subunit (1c) did not make significant changes. Substitution of the amide aromatic ring by a cyclohexyl group (1d) also led to a precipitate. However, the *tert*-butyl derivative 1e showed some signs of gelification although it precipitated after cooling to room temperature. The introduction of a bromine substituent on the aromatic ring of 1e led to a poor gelation of compound 1f, which partially remained in suspension. Further sonication of this semigel led to the irreversible precipitation of 1f (Table 1, entry 7, Figure 3a). Compound 1g, containing two benzylamide groups, successfully and readily led to the formation of a stable gel (Table 1, entry 8, Figure 3b). We assumed that the introduction of an additional hydroxyl group could enhance water solubility and increase gelification driving forces. Disappointingly, compound 1h did not lead to the formation of any gel under our experimental conditions (Table 1, entry 9). A possible explanation of the lack of gelling capability of 1h is that the hydroxy group interferes in the intermolecular hydrogen bonds between the amide groups or that it disfavors the enolic tautomer, which can be key for the gelation of compound 1g.

Table 1. Gelation test under microwave irradiation of dicarbonyl compounds 1a–h.

Entry	Compound	H_2O:EtOH	c (mg/mL)	Gelation
1	1a	1:0.1	12	NO
2	1b	1:0.1	5	NO
3	1c	1:1	14	NO
4	1c	1:0.1	6	NO
6	1d	1:0.1	6	NO
5	1e	1:0.1	12	NO
7	1f	1:0.1	9	PARTIAL
8	1g	1:0.1	8	YES
9	1h	1:0.1	9	NO

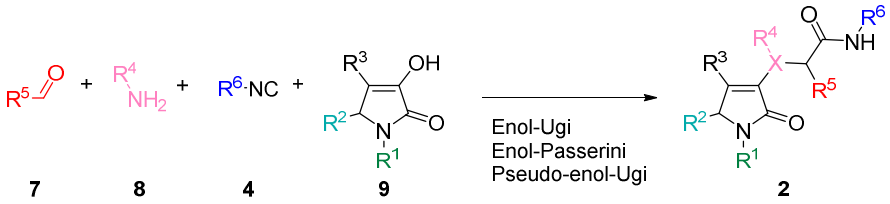


(**a**) (**b**)

Figure 3. Pictures of hydrogels: (**a**) compound 1f; (**b**) compound 1g.

2.2. Self-Assembling Properties of Enol-Ugi and Enol-Passerini Adducts

Peptidomimetic pyrrolidinone derivatives 2a–c and 2i (Figure 3, Scheme 2) were prepared by a enol-Ugi reaction [21] between aldehydes (7), amines (8), isocyanides (4), and pyrrolidinodiones (9). Alternatively, compounds 2d–2h (Figure 3, Scheme 2) were prepared by a pseudo-enol-Ugi reaction [22] of aldehydes (7), isocyanides (4), and enols (9). They permitted the modulation of the intermolecular interactions in the potentially formed gels that could be achieved by controlling the six functionalization positions in the enol derivatives 2a–h.



Scheme 2. Synthesis of enol derivatives 2.

These compounds present a peptidomimetic subunit linked to the pyrrolidinone core. The pyrrolidinone includes three variable substituents. R^3 must be an electron withdrawing group, such as CO_2Et, and, in all our examples, R^1 and R^2 contain aromatic rings. Moreover, the peptidomimetic subunit presents three further tunable positions. R^5 is usually also an aromatic ring, X can be either oxygen or nitrogen linked to aliphatic or benzylic group R^4, and R^6 can be aromatic or aliphatic.

The gelation capacity of enol derivatives 2a–i was tested in the same conditions as dicarbonylic compounds 1a–h.

Compound 2a precipitated as a gum in the media (Table 2, entry 1). Substituting a fluorine for a methoxy group on the aromatic ring R^2 and a *tert*-butyl for a cyclohexyl in R^6 did not appear to alter the gelling ability of 2b compared to 2a. In addition, no significant changes were observed for 2c, which contained an unsubstituted R^2 phenyl group and an electron-rich X-R^4 benzylic amine. Substituting R^4 cyclohexyl for a benzyl group (2d) also led to a gum precipitate. The introduction of a chlorine in derivative 2e led to the successful formation of a stable gel (Table 2, entry 5, Figure 4a). Compound 2f presented an oxygen atom in place of the N-R^4, and an R^2 methoxyphenyl group formed a precipitate after irradiation again. Likewise, analogous enol ether 2g also formed a precipitate (Table 2, entry 7). Structures 2h and 2i presnts R^2= H, and R^1 was a benzyl radical in place of a phenyl. When gelification conditions were applied, ether 2h formed a strong film on the solvent surface after which it was capable of supporting the aqueous phase (Table 2, entry 9, Figure 2b) while analogous amine 2i formed an insoluble precipitate (Figure 5).

Table 2. Gelation test of peptidomimetics 2a–i.

Entry	Compound	H_2O:EtOH	c (mg/mL)	Gelation
1	2a	1:0.2	10	NO
2	2b	1:0.2	12	NO
3	2c	1:0.2	12	NO
4	2d	1:0.2	14	NO
5	2e	1:0.2	12	YES
6	2f	1:0.2	10	NO
7	2g	1:0.2	10	NO
9	2h	1:0.2	11	FILM
10	2i	1:0.2	8	NO

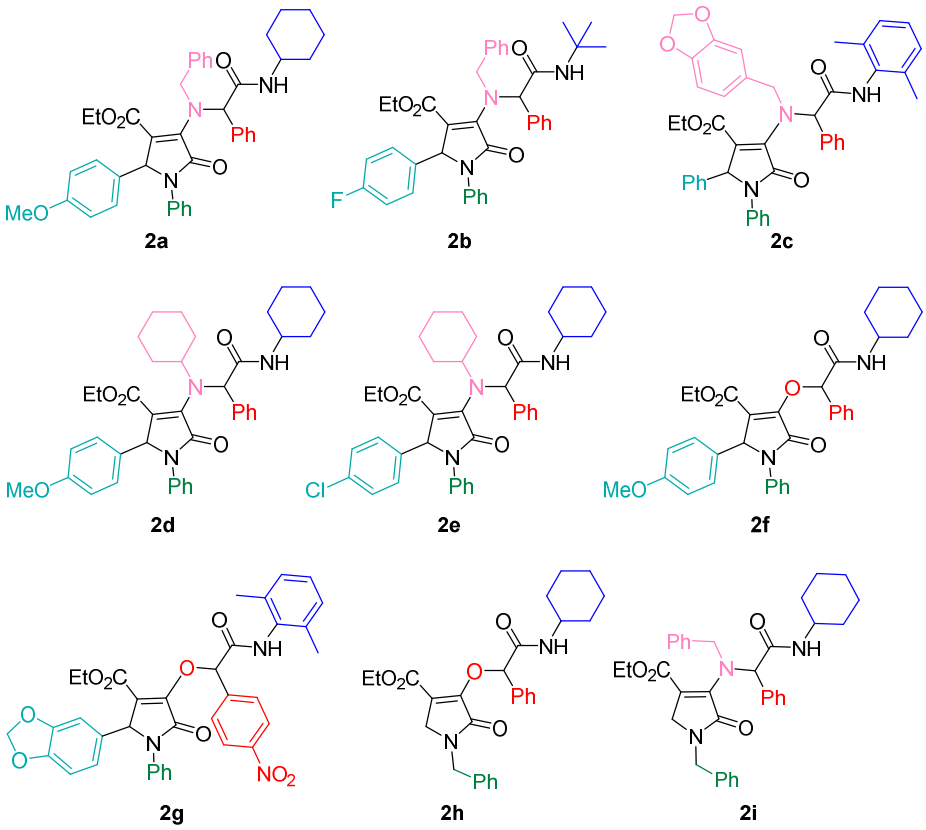
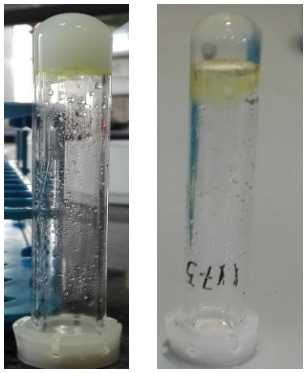


Figure 4. Peptidomitic pyrrolidinone derivatives tested as gelators.



(**a**) (**b**)

Figure 5. Pictures of hydrogels: (**a**) compound 2e; (**b**) compound 2h.

3. Experimental

3.1. Materials and Methods

Liquid reagents were measured using positive displacement micropipettes with disposable tips and pistons.

Experiments under microwave irradiation were performed in closed vials, using a focused single-mode microwave reactor CEM Discover BenchMate.

3.2. Synthesis of Compounds Tested as Gelators

3.2.1. Synthesis of Dicarbonylic Compounds

β-Keto amides 1a–1f were prepared by a Passerini reaction between glyoxals (3), isocyanides (4), and acetic acid followed by reductive deacetoxylation with zinc [18].

Diamide 1g was prepared by reductive deacetoxylation of Passerini glyoxylamide adducts using photochemically activated SmI_2 [20].

Hydroxyglycine retropeptidic derivative 1h was obtained through a Passerini three-component reaction of glyoxyl amides (3), isocyanides (4), and acetic acid followed by an zinc catalyzed solvolysis [19].

3.2.2. Synthesis of Enol-Ugi and Enol-Passerini Adducts

Enol-Ugi derivatives 2a–c and 2i were prepared by an enol-Ugi reaction between imines, isocyanides (4), and pyrrolidine-2,3-diones (9) [21].

Compounds 2d and 2e were obtained by a reaction of aldehydes (7), amines (8), and pyrrolidine-2,3-diones (9) in methanol; the reaction of aldehydes (7), amines (8), and pyrrolidine-2,3-diones (9) in dichloromethane produced 2f–h [22].

3.3. Gelation Protocol

Compounds 1a–h and 2a–i were suspended in water, and then EtOH was added. The suspension irradiated at 150 W and 80 °C in a closed microwave vial for two minutes and was allowed to cool at room temperature.

The vial was removed from the microwave at 40–35 °C. In compounds 1f, 1g and 2e, we observed the gel formation or a film in 2h at this temperature. In cases where no gel was formed, no changes were observed when the temperature was below 35 °C.

The formation of a gel of a film was verified by the vial inversion method.

4. Conclusions

In this proof of concept, we confirm our idea that multicomponent reactions of isocyanides can be an effective method in obtaining LMWGs. Structures 1d and 1g are very simple and similar to other gelators, but the pyrrolidino derivatives 2c and 2h present a novel structure in these types of materials. The possibility to introduce fine changes in different positions in these compounds allows the obtainment of gelators with enhanced properties.

The complete characterization of the obtained gels and the use of computational tools [23] will provide information about the self-assembly mechanism and will help us rationalize the most convenient changes in these molecules to obtain new gelators with enhanced properties.

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