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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, LMWG, 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 this 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 in our experience in this field, here we report our studies aimed at the use of multicomponent reactions of isocyanides to prepare LMWG.

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

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1. Introduction

Low molecular weight gelators, LMWG, are small molecules that form fibrous supramolecular architectures and three-dimensional networks able to trap and immobilize solvents, either organic solvents (organogelators) or water (hydrogelators). The driving forces of gelation are non-covalent 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]

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

Many LMWG 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 contain groups capable of forming non-covalent 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 have great potential in biomedical applications, due the presence of complementary functional groups that form directional non-covalent 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 keep the activity of the model peptide exhibiting superior stability in a biological environment. [11–14]

Multicomponent reactions are powerful tools for the synthesis of tailor-made LMWG, [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 LMWG using multicomponent reactions developed in our group.

2. Results and Discussion

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

To prove this idea, we have performed gelification essays on different compounds previously prepared by us using a IMCR protocols. We have chosen 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.

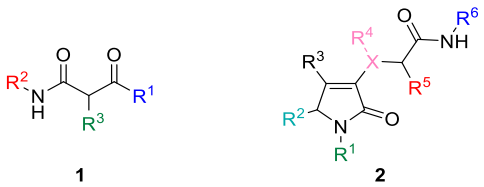
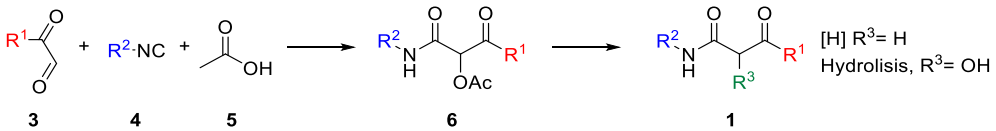


Figure 1. General structures of two type of structures tested in gelification essays.

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**) gave 3-oxocarboxamides (**6**), which were then subjected to reduction or hydrolysis to give alfa-unsubstituted or alfa-hydroxysubstituted 3-oxocarboxamides [18–20] (Scheme 1).



Scheme 1. Synthesis of dicarbonylic compounds **1**.

In order to modulate the potential intermolecular interactions in the supramolecular gel, substituents R^1 and R^2 can be tuned by choosing the appropriate carbonyl compound (**3**) and isocyanide (**4**) components in the Passerini reaction. The best gelification results were obtained with R^1 and R^2 hydrophobic groups, which favor van der Waals interactions, while the amide and carbonyl groups enable the formation of hydrogen bonds. Thus, different aromatic and aliphatic substituents have been introduced in R^1 position

and R^2 positions. Aromatic rings are capable to form π-π interactions, which may be one of the main intermolecular forces leading to gelation.

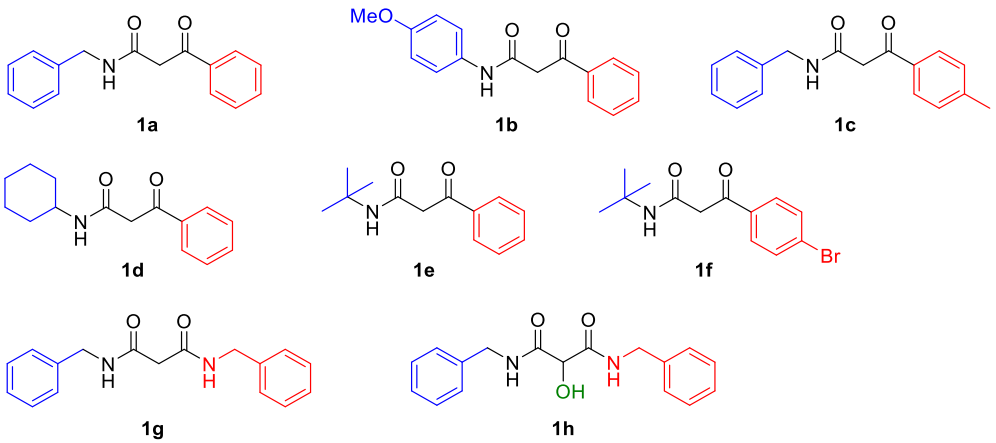


Figure 2. Dicarbonylic compounds tested as gelators.

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.

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 semi-gel led to irreversible precipitation of **1f** (Table 1, entry 7, Figure 3a). Successfully, compound **1g**, containing two benzylamide groups 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.**

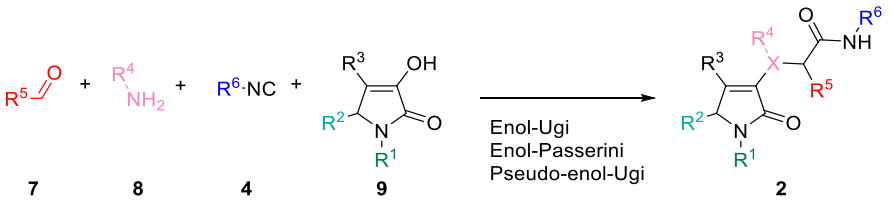
Entry	Compound	H_2O:EtOH	c (mg/mL)	Gelation
1	**1a**	1:0.1	12	NO
2	**1b**	1:0.1	5	NO
3	**1c**	1:1	14	NO
4	**1c**	1:0.1	6	NO
6	**1d**	1:0.1	6	NO
5	**1e**	1:0.1	12	NO
7	**1f**	1:0.1	9	PARTIAL
8	**1g**	1:0.1	8	YES
9	**1h**	1:0.1	9	NO

(**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 pyrrolidonodiones (**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 will permit modulation of the intermolecular interactions in the potentially formed gels could be achieved by controlling the six functionalization positions in the enol-derivatives **2a–h**.



7 **8** **4** **9** **2**

Scheme 2. Synthesis of enol-derivatives **2**.

These compounds present a peptidomimetic subunit linked to pyrrolidonone core. Pyrrolidinone include 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 aromatic or benzylic groups 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**. Also, no significant changes were observed for **2c**, containing 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. Successfully, the introduction of a chlorine in derivative **2e** led to the formation of a stable gel (Table 2, entry 5, Figure 4a). Compound **2f**, presenting an oxygen atom in place of the N-R^4 and an R^2 methoxyphenyl group forms again a precipitate after irradiation. Likewise, analogous enol-ether **2g** also forms a precipitate (Table 2, entry 7). Structures **2h** and **2i** lack the aromatic ring R^2 and R^1 is a benzyl radical in place a phenyl. When applying gelification conditions, ether **2h** forms a strong film on the solvent surface, after which it is capable to support the aqueous phase (Table 2, entry 9, Figure 2b), while analogous amine **2i** forms an insoluble precipitate.

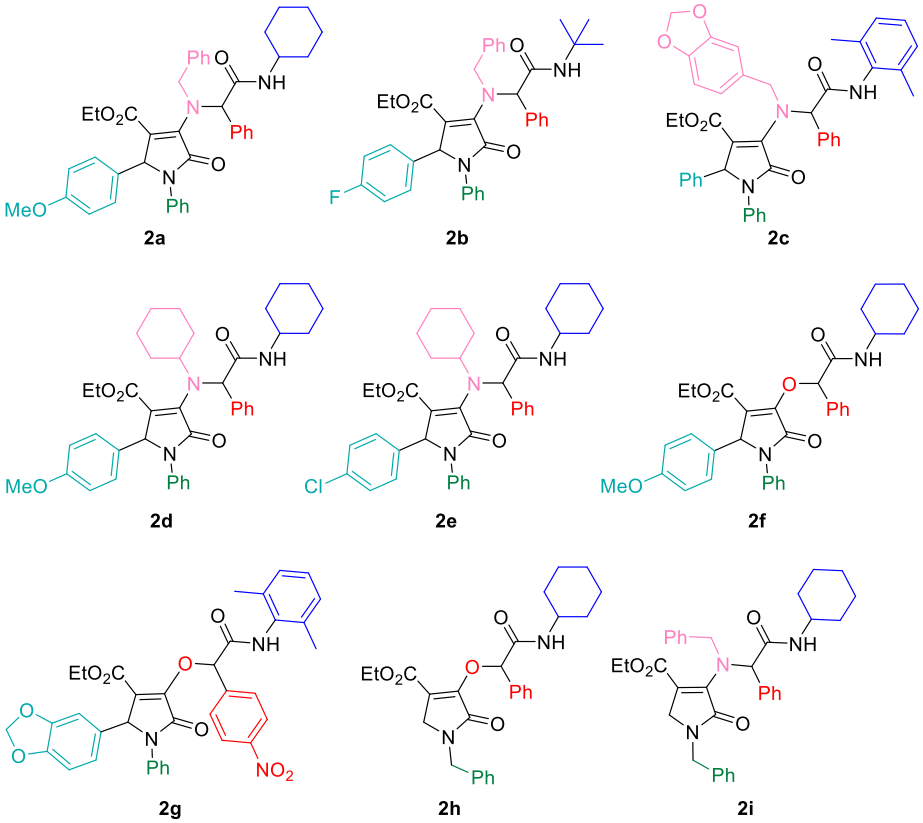
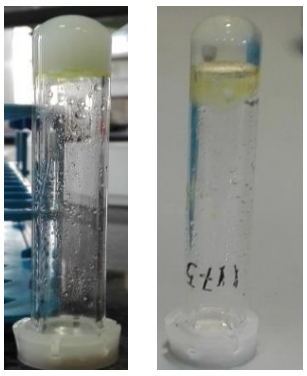


Figure 4. Peptidomitic pyrrolidinone derivatives tested as gelators.

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



(**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 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 derivatives **1h** was obtained through a Passerini 3-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 enol-Ugi reaction between imines, isocyanides (**4**), and pyrrolidine-2,3-diones (**9**). [21]

Compounds **2d** and **2e** were obtained by 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 gave **2f–h**. [22]

3.3. Gelation Protocol

Compounds **1a–h** and **2a–i** was suspended in water 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 allowed to cold at room temperature.

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

Gelation o formation 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 to obtain LMWG. Structures **1d** and **1g** are very simple and similar to others gelators, but pyrrolidino derivatives **2c** and **2h** present a novel structure in this kind of materials. The possibility to introduce fine changes in different positions of these compounds it would allow to obtain gelators with enhanced properties.

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

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