Extensive Screening of Green Solvents for Safe and Sustainable UiO-66 Synthesis

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ABSTRACT. Zirconium based Metal-Organic Framework UiO-66 is to date considered one of the benchmark compound among stable MOFs and it has attracted a huge attention for its employment in many strategic applications. Large scale production of UiO-66 for industrial purposes requires the use of safe and green solvents, fulfilling the green chemistry principles and able to replace the use of N,N-Dimethyl-Formamide (DMF), which, despite its toxicity, is still considered the most efficient solvent for obtaining UiO-66 of high quality. Herein we report on a survey of about 40 different solvents with different polarity, boiling point and acidity, used for the laboratory scale synthesis of high quality UiO-66 crystals. The solvents were chosen according the European REACH Regulation 1907/2006 among those having low cost, low toxicity and fully biodegradable. Concerning MOF synthesis, the relevant parameters chosen for establishing the quality of the results obtained are the degree are the crystallinity, microporosity and specific
surface area, yield and solvent recyclability. Taking into account also the chemical physical properties of all the solvents, a color code was assigned in order to give a final green assessment for the UiO-66 synthesis. Defectivity of the obtained products, the use of acidic modulators and the use of alternative Zr-salts have been also taken into consideration. Preliminary results lead to conclude that GVL (γ-valerolactone) is among the most promising solvents for replacing DMF in UiO-66 MOF synthesis.

INTRODUCTION

After a decade focused on fundamental synthetic and structural aspects, the chemistry of Metal-Organic Frameworks (MOFs) is rapidly moving towards industrial application and large-scale commercialization. Zirconium based MOFs are today considered benchmark compounds for their high stability in different media, low cost and for their high structural versatility which allows to employ them in a vast number of strategic applications in the field of catalysis\textsuperscript{1-4}, gas\textsuperscript{5} and solvent sorption\textsuperscript{6,7}, separation\textsuperscript{8,9}, proton conductivity\textsuperscript{10} and for biomedical purposes.\textsuperscript{11,12} The archetypal Zr-MOF is the UiO-66 phase of general formula \(\text{Zr}_6\text{O}_4(\text{OH})_4(\text{BDC})_6\cdot n\text{DMF} \) (\(\text{H}_2\text{BDC} = \text{benzene dicarboxylic acid}\)) first synthesized in 2008 by Lillerud et al.\textsuperscript{13} From its discovery to date, the number of papers citing UiO-66 overcomes 1500. UiO-66 has a cubic face centred symmetry and it is constituted by hexanuclear \(\text{Zr}_6\text{O}_4(\text{OH})_4^{12+}\)-twelve connected inorganic building units (IBUs) linked by the BDC ligand. Porosity of UiO-66 is variable (BET surface area in the 900 to 1600 m\(^2\)/g range) owing to the possibility to generate a defective structure by using monocarboxylic acid modulators during synthesis, which lead the formation of missing linker or missing cluster defects.\textsuperscript{14-18} The early stage synthesis of UiO-66 involved the use of \(\text{ZrCl}_4\) as \(\text{Zr}^{4+}\)
source and DMF as solvent able to well dissolve H$_2$-BDC and Zr salt. The formation of zirconium oxo-clusters required the presence of oxygen sources which can arise from water present in DMF, in the hydrated salts or from direct addition of water during synthesis. The use of acidic modulators and of proton scavengers have been also extensively investigated.$^{19,20}$ During the last years, several synthetic strategies have been tried for the synthesis of DMF-free UiO-66, involving the use of alternative methods such as mechanochemical approaches$^{21}$, accelerated aging$^{22}$ and microwaves$^{23}$ or the use of non-toxic solvents such as water, green solvents from biomasses and from industrial production waste.$^{24}$ Water based syntheses were found to be effective for UiO-66 MOFs based on substituted X-BDC ligands (with X = F, Cl, Br, NO$_2$) or nitrogen-containing BDC-like linkers such as 2,5-piryidine or 2,5-pirazine dicarboxylic acids (H$_2$-PDC, H$_2$-PyDC) with higher acidity than simple H$_2$-BDC acid, which increased the solubility in water.$^{25,26}$ However, the use of water has proven to be not suitable for the preparation of H$_2$-BDC UiO-66 due to its low solubility in water, while the zirconium salt is highly soluble. This difference in the “solution-state” make the crystals growth very difficult.$^{27}$ In fact, solvents play a dramatic role in influencing the chemical and environmental efficiency of a process, and also the preparation of MOF materials is tremendously affected by the medium used both on the properties of the material obtained and on its applicability. In almost every chemical production, it is urgent the need for developing new, safer, and cleaner synthetics routes in agreement to the regulatory requirements in the European Union aiming at reducing or banning the use of chemicals that may be harmful to human health or the environment. Representative is the case of the European REACH Regulation 1907/2006 that envisages a mechanism which forces companies to apply for an authorization if they
want to use or distribute chemicals (including solvents) identified as Substances of Very High Concern (SVHC).\textsuperscript{28} Equivalent rules apply to the manufacturing, the commercialization and use SVHC, and especially to largely used solvents. Health and safety regulations have nowadays a major impact on solvent selection and in particular, chlorinated hydrocarbons, aromatics, and dipolar aprotic solvents such as $N,N$-dimethylformamide (DMF), are identified as hazardous due to their well-known chronic toxicity effects.\textsuperscript{28} In this context, it is fundamental the identification of safer media to replace those highly toxic and most of the fundamental and industrial research is looking for novel safe solvent candidates with a special attention to those deriving from waste of large manufacturing process or from biomasses.\textsuperscript{29-39} The ideal solvent for the synthesis of H$_2$-BDC UiO-66 is responsible to perform in many different directions. An effective solvent should be able to completely dissolve the reagents whilst playing a fundamental role in the formation of the crystalline structure. As an example, the commonly used DMF, has an active role in H$_2$-BDC UiO-66 synthesis by entering the coordination sphere of the zirconium steering the formation of the crystal lattice formation.\textsuperscript{40} In this contribution, we report an extensive study on the screening of solvents that could be eventually be selected as alternative for the synthesis of BDC-UiO-66. Based on our previous studies,\textsuperscript{24,41-46} we have considered several different classes of solvents and grouped in terms of their chemical-physical features, \textit{e.g.} dielectric constant ($\varepsilon$) and boiling point (Bp). We have compared their efficiency to produce BDC-UiO-66 using a standard protocol and classified their performance based the ability to actually form the desired UiO-66 MOF, the full width at half maximum (FWHM) of (111) diffraction peak, the crystal size, the BET surface area achieved and the yield. The screening allowed to identify a small number of selected
solvents which afforded high quality UiO-66 crystals as pure phase without the formation of co-products whereas those yielding co-products or MOFs with low crystallinity degree will be object of future dedicated studies.

MATERIALS AND METHODS.

Chemicals

All chemicals are commercially available and used without further purification.

1-(2-hydroxyethyl)-2-pyrrolidone, 2-ethylhexylacetate, Cyclohexanone, 2-Methyl-tertahydrofuran, Ethyl-L-lactate, γ-valerolactone (GVL), Zirconium Chloride and terephthalic acid were purchased by Sigma Aldrich. Diethyl succinate i-Butylacetate, Diethyl carbonate, Dimethyl carbonate, Propylene carbonate, 1,3-Dioxolane and 1,2-isopropylidene glycerol (Solketal) were purchased by Alfa Aesar. Dimethyl adipate, Dimethyl succinate, Ethylene glycole diacetate, i-Propylacetate, Isoamyl acetate, Methyl laurate, Methyl tetradecanoate, Anisole, 2-Ethylhexylacetate, Triacetine, p-Cymene, n-Amyl acetate, Cyclopentylmethyl ether (CPME), and Zirconyl chloride octahydrate were purchased by Thermo Fisher Scientific. Rhodiasolv® IRIS, Rhodiasolv® Polarclean were purchased by Solvay. Esterol® F were purchased by Arkema. Loxanol®, Plurafac® LF120, Plurafac® LF221, Plurafac® LF303, Plurafac® LF771, Dehypon® LS54, Agnique® AMD 810 were purchased by BASF. Synperonic® LF30 was purchased by CRODA. Purasolv® EHL was purchased by Corbion Purac. Steposol® MET-10U was purchased by Stepan. Tert-amyl methyl ether (TAME) was purchased by IMCD and 4-methyltetrahydropyran was purchased by Kurakay. Acetic Acid was purchased by Carlo Erba.
Synthetic procedures

DMF synthesis of UiO-66

First, DMF synthesis without modulator of UiO-66 was tried according to literature\textsuperscript{11}: ZrCl\textsubscript{4} (0.5 mmol), one equivalent of H\textsubscript{2}-BDC and three equivalents of water were dissolved in 100 mL of DMF in a Teflon reactor and the mixture was sonicated until complete dissolution of reagents occurred. After this, the reactor was put in thermostated oven at 120°C. After 16 hours MOF was soaked in DMF, water and acetone to remove unreacted starting materials and the reaction media. At the end the UiO-66 was put in oven at 80°C to remove the solvent used to soak. Figure 1 shows the general reaction scheme.

**Figure 1.** DMF synthesis of UiO-66 (3a) without modulator. Reaction condition [ZrCl\textsubscript{4}] = 0.125M (1a), 1 equivalent of 2a, and 3 equivalents of water.

In the second step the reaction was scaled down to verify the viability of the process using a lower amount of solvent and therefore a higher concentration of reagents to improve the efficiency of the process. The procedure was the same as reported above but the volume of the solvent amount was 2 mL and the ZrCl\textsubscript{4} 0.5 mmol. The final concentration of zirconium salt was 0.25M. Finally, the procedure was optimized by adding 30 equivalents of acetic acid (AcOH).
Synthesis of UiO-66 using green solvents at the optimized conditions

The synthetic procedures were standardized in the following way: In a screw capped 4 mL vial, H$_2$-BDC (83 mg, 0.5 mmol) was dissolved in the *chosen solvent* (4 mL), followed by the addition of water (27 μL, 3 eq), acetic acid (860 μL, 30 eq) and ZrCl$_4$ (116 mg, 0.5 mmol). The mixture was sonicated until dissolution. The vial was then put inside a Teflon reactor and placed in a thermostated oven at 120°C for 16 h. After completion of the reaction, the solid was centrifuged and washed with MeOH (two time one-hour soaking), water (one times one-hour soaking) and acetone (one time one-hour soaking, one-time overnight soaking). The solids were dried at 80 °C for two hours.

* see table 1

Table 1. Molecular structure of the solvent used.

RESULTS AND DISCUSSION

DMF synthesis was preliminary performed in order to have a term of comparison with the results arising from the successive solvent screening. XRPD patterns of the syntheses without (exp. a) and with modulator (exp. b) are shown in figure S1. The optimized synthesis (b) was performed by increasing the reagent concentration (from 0.05 M of literature synthesis to 0.125 M). The addition of 30 eq of AcOH allowed to improve the degree of crystallinity. This synthetic condition was employed for all the solvents tested. Table 2 reports the list of solvents used for the synthesis of UiO-66. The solvents are divided in classes (alcohols, esters, carbonates, ketones, aromatics, ethers and dipolar aprotic solvents). To this end, a classical color code (green, yellow, red) has
been used for each general area of assessment (i.e. solvent greenness, boiling point requirement for safety/processing, viscosity for the crystallization/purification steps). According to a classification reported in a recent paper of Vaccaro et al., on the use of green solvents for organic
thin-film transistor processing, the solvent color code is inspired by the GlaxoSmithKline, GSK, and CHEM 21 solvent selection guides for the pharmaceutical industry.\textsuperscript{48-51} These guides account for the physical and (eco)toxicity properties of solvents by transforming them into a scale to determine their greenness. The color codes for bps, viscosity and crystal size of MOFs are reported in the table 3. Other than the parameters already used in previous work for the green assessment we added here a color code also for the crystallinity degree of the obtained MOF. DMF is also included as reference entry. These codes are also combined in a composite color incorporating all these requirements, to give a ranking by default and “ranking after discussion” of each solvent. Particularly, the preferred solvents, i.e. solvents presenting a few issues, are displayed with the green color code; the yellow color code has been used for problematic solvents, i.e. solvents that can be used but their implementation may present issues or uncertainties; not recommended solvents are identified with red color code, i.e. the constraints on the solvent use are very high.

Boiling points are already considered in the overall greenness assessment but, a separate column was included in Table 2 listing the solvent b.ps, to take specifically into account their suitability for UIO-66 synthesis. The associated color codes are based on the ranges defined in Table 3a.

| Solvent                          | Structure                                      | Code                              |
|----------------------------------|------------------------------------------------|-----------------------------------|
| Plurafac LF 120                  | ![Structure](image1)                           | Trade secret                      |
| Propylene carbonate              | ![Structure](image2)                           |                                   |
| Purasolv EHL                     | ![Structure](image3)                           |                                   |
| Solketal                         | ![Structure](image4)                           |                                   |
| Steposol                         | ![Structure](image5)                           |                                   |
| Synperonic LF 30                 | Ethylene oxide/propylene oxide copolymer based on C12-C15 alcohol |                                   |
| β-amyl methyl ether              | ![Structure](image6)                           |                                   |
| Triacetin                        | ![Structure](image7)                           |                                   |
| γ-Valerolacton                   | ![Structure](image8)                           |                                   |
| Polarclean                       | ![Structure](image9)                           |                                   |

![Chemical Structures](image10)
Extremely low boiling point solvents (T ≤ 50°C) may not be suitable for MOF processing and cannot be used both for technical and safety issues. Table 3a also reports the value ranges for the solvent viscosity (η, mPa·s) coding, reflecting again the general solvent appropriateness for MOFs synthesis. The crystal size and the surface area has been also scored. These two parameters have prime importance to evaluate the morphological quality and the adaptability of the synthesized UIO-66 for example for gas storage and catalysis.

Consequently, the ranking “by default” color code is dominated by the crystal size (Table 3b). Finally, a ranking “after discussion” was assessed (Table 2, last column), as the result of an overall evaluation of the solvent greenness, MOFs crystal size and surface area, and so on further improvement and possible applications based on the obtained morphological features. First, in the ranking “after discussion” DMF, despite the quality of the MOF obtained, is listed as “not recommended” due to its critical toxicological profile. We did not modify the ranking by default for “preferred” solvents (“green” code) leading to UIO-66 MOFs with crystal size higher than 450 Å, an arbitrary value we chosen in order to establish a good crystallinity degree. Moreover, we assigned the color “green“ to those solvents leading to a “green” crystal size but that featured present an intermediate BET surface area (yellow code). The reason for this choice is the fact that further enhancement in the MOF synthesis could lead to higher values.

Furthermore, we assigned “yellow code” to the combination “green” crystal size/ “red” surface area and “red” code to the combination “yellow” crystal size/ “red” surface area and vice versa. Crystal size values lower than 300 Å regardless of the BET surface area value achieved a red score.
Table 2. Solvent assessment for the synthesis of UiO-66 and quality indicators of MOF. Reaction conditions: 3 eq H₂O, 30 eq AcOH, 120°C; * 3 eq H₂O, 120°C.

| Classification | Solvent                        | Overall Green Ass. | B.p. (°C) | Viscosity | Presence of characteristic UiO66 peaks | Crystal size (Å) | BET surface area (m²/g) | Default rank | Ranking after discussion |
|----------------|--------------------------------|---------------------|-----------|-----------|----------------------------------------|------------------|-------------------------|--------------|--------------------------|
| Alcohol        | Solketal                       | 188-189             | other phase | -         | -                                      | -                | -                       | -            | -                        |
|                | 1-(2-HE)-2-P                   | 140-142             | yes        | 731       | 1407                                    | -                | -                       | -            | -                        |
|                | 1,3-propanediol                | 214                 | yes        | 653       | 838                                     | -                | -                       | -            | -                        |
| Ester          | 2-ethylhexylacetate            | 199-200             | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | Diethyl succinate              | 216-218             | other phase | -         | -                                      | -                | -                       | -            | -                        |
|                | 2-ethylhexylacetate            | 216-218             | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | Dimethyl adipate               | 109-110             | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | 2-ethylhexylacetate            | 109-110             | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | Diethyl succinate              | 216-218             | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | 2-ethylhexylacetate            | 216-218             | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | Ethylene glycol diacetate      | 186-187             | yes        | 132       | 115                                     | -                | -                       | -            | -                        |
|                | Ethyl-L-lactate                | 154                 | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | g-valerolactone                | 207-208             | yes        | 655       | 930                                     | -                | -                       | -            | -                        |
|                | 2-ethylhexylacetate            | 216-218             | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | 2-ethylhexylacetate            | 216-218             | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | IRIS                           | 215.6               | No REACT   | -         | -                                      | -                | -                       | -            | -                        |
|                | Isoamyl acetate                | 142                 | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | Loxanol                        | > 300               | No REACT   | -         | -                                      | -                | -                       | -            | -                        |
|                | Methyl laurate                 | 261-262             | yes        | 112       | 257                                     | -                | -                       | -            | -                        |
|                | n-amyl acetate                 | 149                 | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | Purasolv EHL                   | 246                 | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | n-amyl acetate                 | 149                 | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | triacetin                      | 258                 | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|                | Plurafac LF711                  | >300                | No REACT   | -         | -                                      | -                | -                       | -            | -                        |

| Carbonate     | Diethyl carbonate             | 126-128             | yes        | 59        | 281                                     | -                | -                       | -            | -                        |
|               | Dimethyl carbonate            | 90                  | Yes (additional phases) | 345 | 132                                     | -                | -                       | -            | -                        |
|               | Propylene carbonate           | 240-243             | yes        | 813       | 771                                     | -                | -                       | -            | -                        |
| Ketone        | cyclohexanone                 | 155                 | No REACT   | -         | -                                      | -                | -                       | -            | -                        |
| Aromatic      | p-cymene                      | 176-178             | No REACT   | -         | -                                      | -                | -                       | -            | -                        |
| Ether         | 1,3-dioxolane                 | 74-75               | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|               | 2-methyl THF                  | 78-80               | Amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|               | Anisole                       | 154                 | No REACT   | -         | -                                      | -                | -                       | -            | -                        |
|               | 4-Me-THP                      | 107-108             | No REACT   | -         | -                                      | -                | -                       | -            | -                        |
|               | Cyclopentyl methyl ether      | 106                 | amorphous  | -         | -                                      | -                | -                       | -            | -                        |
|               | Plurafac LF711                | >300                | No REACT   | -         | -                                      | -                | -                       | -            | -                        |
| Solvent          | Boiling Point (°C) | Crystal Size (CS, Å) | BET Surface Area (m²/g) | Reactivity |
|------------------|--------------------|----------------------|--------------------------|------------|
| Plurafac LF221   | >300               | -                    | -                        | Amorphous  |
| Plurafac LF303   | 245-255            | No REACT             | -                        | -          |
| Plurafac LF120   | >300               | No REACT             | -                        | -          |
| Dehypon LS54     | >300               | No REACT             | -                        | -          |
| Syperonic LF30   | >300               | No REACT             | -                        | -          |
| T-amyl methyl ether | 85-86            | yes                  | 455                      | 813        |

Table 3. Ranking of a) boiling points (°C) and viscosity (η, mPa s), b) crystal size (CS, Å) and BET surface area (m²/g), c) presence of characteristic UiO66 peaks.

Despite the many experiments and the tentative optimization of specific conditions, most of the solvents screened were not able to successfully allow the MOF formation. In these cases, UiO-66...
failed to precipitate, amorphous phases or also unknown crystalline phases were formed. However, among the tested solvents, twelve were able to yield the UiO-66 phase whereas in six experiments the results were satisfying and, in some cases, much relevant. Selected solvents have quite high boiling point, higher than 80 °C, to avoid a massive evaporation during the reaction time that should conduct to an overly high-pressure in the vials. Among them, γ-valerolactone (GVL) and propylene carbonate (PC) are two environmentally benign and sustainable solvents. GVL showed to be an ideal and efficient alternative in that kind of transformation usually carried out in polar aprotic medium like Sonogashira and Heck coupling,\textsuperscript{52-53} while PC has been already used in the Suzuki-Miyaura coupling.\textsuperscript{54} Many other solvents have been selected using this selection strategy like, for example, pyrrolidones, amides, esters, ethers and alcohols. In general, addition of 30 eq. of AcOH yielded compounds with high crystallinity degree and porosity comparable to those found for UiO-66 of good quality.\textsuperscript{55} The exception is the experiment carried out in Steposol (ST) (entry 39bis) in which the best crystallinity was obtained without modulators. Syntheses at the optimized conditions which gave the best results are those made in the following solvents: γ-Valerolactone (entry 11) Propylene carbonate (PC) (entry 23) 1-(2-hydroxyethyl)-1-pyrrolidone (1-(2-HE)-2-P) (entry 2), t-amylmethylether (TAME) (entry 37) and 1,3-propandiol (1,3-PD) (entry 3). In two cases, those done in dimethyl carbonate (entry 22) and in dimethyl adipate (entry 6), the syntheses were successful but, due to the presence of other phases, the optimization was not done. Table 4 reports on the main features of obtained materials.

**Table 4** Comparison of the different syntheses performed (reaction conditions: 3 eq H\textsubscript{2}O, 30 eq AcOH, 120°C). Molecular formula calculated with \textsuperscript{1}H-NMR spectra and TGA analysis.
| Entry | Solvent                      | Yield | Crystallinity | Surface Area | Notes |
|-------|------------------------------|-------|---------------|--------------|-------|
| 0     | DMF                          | 0.11  | 85%           | 85%          | Zr₆O₄(OH)₄BDC₅.₇₄AA₀.₅₂ |
| 1     | GVL                          | 0.13  | 84%           | 930 m²/g     | Zr₆O₄(OH)₄(BDC)₅.₈₀(AA)₀.₄₀ |
| 2     | Steposol (ST)               | 0.16  | 82%           | 1440 m²/g    | Zr₆O₄(OH)₄(BDC)₅.₆₄Cl₂H₂O₁.₂ |
| 3     | Propylene carbonate (PC)    | 0.10  | 71%           | 771 m²/g     | Zr₆O₄(OH)₄(BDC)₅.₆₀(AA)₀.₆₂ |
| 4     | 1-(2-hydroxyethyl)-2-pyrrolidone (1-(2-HE)-2-P) | 0.11 | 94% | 1407 m²/g | Zr₆O₄(OH)₄(BDC)₅.₆₀(AA)₀.₆₂ |
| 5     | TAME                         | 0.18  | 83%           | 813 m²/g     | Zr₆O₄(OH)₄(BDC)₅.₇₆(AA)₀.₄₄ |
| 6     | 1,3-propandiol (1,3-PD)     | 0.13  | 63%           | 838 m²/g     | Zr₆O₄(OH)₄(BDC)₅.₄₂(AA)₁.₁₆ |
| 7     | Steposol (ST)               | 0.25  | -             | 366 m²/g     | - |
| 8     | Dimethyl adipate            | 0.13  | -             | 159 m²/g     | - |
| 9     | Ethylene glycol diacetate   | 0.60  | -             | 115 m²/g     | - |
| 10    | Dimethyl carbonate          | 0.23  | -             | 132 m²/g     | - |
| 11    | Diethyl carbonate           | 1.02  | -             | 281 m²/g     | - |
| 12    | Methyl laurate              | 0.72  | -             | 257 m²/g     | - |
| 13    | Polarclean                  | 1.00  | -             | 303 m²/g     | - |

*3 eq H₂O, 120°C*

Results shown in table 4 allow to have a direct comparison of the syntheses performed in DMF and the selected green solvents. We have chosen some comparative indices such as yield, crystallinity and surface area to estimate the potentiality of each solvent in replacing DMF. Entries
7-13 were not characterized owing to their low score, as indicated in table 2. Figure 2 shows the XRPD patterns and the N$_2$ adsorption and desorption analysis of the MOFs obtained (entries 1-6). The materials are pure phases with good degree of crystallinity and BET surface area values comparable to conventional UiO-66 syntheses. The MOF obtained in 1-(2-HE)-2-P presents the XRPD pattern having characteristic peaks of a defective structure, with broad signals in the low angle regions, as previously reported by Bordiga et al. This is also confirmed by the high specific surface area and micropore volume which is typical of defective UiO-66 with missing clusters defects. The experiment carried out in GVL is quite relevant since the MOF possesses a good crystallinity degree and it was obtained at a high yield (84%). Moreover, the GVL is a solvent which is rapidly replacing DMF, especially in the field of organic synthesis.

**Figure 2.** XRPD patterns (left) and N$_2$ adsorption and desorption isotherms (right) of the MOFs with the indicated solvents at the optimized conditions.

Another interesting result has been obtained by using Steposol (ST). Figure 3 shows the XRPD patterns and the BET analysis of the MOFs obtained with ST as solvent using the same reaction condition above reported except the use of acetic acid as modulator. As in the case of 1-(2-HE)-2-
P, in this solvent the MOF obtained has an XRPD pattern with characteristic broad low-angle peaks of a defective structure, as also confirmed by its higher specific surface area than the MOF obtained using DMF.

**Figure 3.** XRPD pattern (left) and N$_2$ adsorption isotherm (right) of the UiO-66 obtained in Steposol.

MOFs formulas are reported in table 4. These formulas were mainly obtained $^1$H-NMR analysis on the hydrolyzed compounds and from the TGA curves. Molecular weight (reported in SI) are calculated on the basis of the TGA curves: the weight losses at temperature higher than 200 °C where the solvent is supposed to be lost until the plateau formed over 600 °C where only ZrO$_2$ is present. All the TGA curves, except that of PC, display a variable weight loss in the 20-100 °C range, corresponding to the loss of a certain number of water molecules (see in SI) meaning that washing procedure fully exchange the most part of the tried solvents. Presence of chloride ions as monoanionic terminal group on the cluster structure, inducing defects, was verified by means of IC analysis. The presence of chlorides was sensibly detected only on the MOF synthesized in ST. (see table 3). The only case in which the solvent could be included in the compound formula is the UiO-66 synthesized in PC. As a matter of fact this solvent was not removed before starting
decomposition, as observed from the TGA curve (figure S8). The presence of the solvent could be also responsible of the low specific surface area if compared to the other syntheses. PC $^1$H-NMR peaks (figure S12) on the hydrolyzed MOFs confirmed this hypothesis. Figure S33 in SI reports on the FE-SEM images for the MOFs prepared in three different solvents. UiO-66 synthesized in GVL is constituted by nice octahedral nanocrystals of 200 nm average size. In the case of PC the UiO-66 has an octahedral shape but it results knobby. This observation, generally due to the presence of organic residues, can be ascribed to the presence of PC in the crystal structure and adsorbed on the crystal surface. The UiO-66 synthetized in the Steposol ® MET10U is constituted of nanocrystal with undefined shape and size. Stability of the reaction media was also tested with $^1$H-NMR analysis. A comparison was made between the NMR pattern of the neat solvent and that after the reaction. $^1$H-NMR spectra are reported in the SI (S8, S13 S18, S27, S32). In the case of GVL, the NMR profile (figure S8) is the same before and after the reaction, with the difference consisting in the presence of acetic acid in the second one and that the signals, in the reacted solvent, are less defined, this could be caused by the presence of other reagents in the reaction environment. In the case of PC the $^1$H-NMR profile is the same before and after the reaction (figure S13), but it presents some differences in the second one consisting in the presence of acetic acid (from the reaction) and some impurities that give signal at 1.21 ppm and between 3.31 and 3.69 ppm. The $^1$H-NMR profile of reacted 1-(2-HE)-2-P, compared with the clean one (figure S18), displays some differences consisting in the presence of acetic acid (from the reaction). The solvent peaks result broad and some impurities at 4.12 ppm and a broad singlet at 4.65 ppm which can be attributed the singlet of -OH in the solvent structure are also present. $^1$H-NMR spectra of TAME could be not recorded because of the solvent evaporation after reaction. 1,3-propandiol spectrum, after reaction, (figure S27) presents signals that could indicate the possible degradation of a part
of solvents. Steposol ® MET10U the $^1$H-NMR profile (figure S32) is quite similar before and after the reaction. In the reacted solvent the peaks are less defined and this could be due to the presence of other reagents in the reaction environment. Given the good results obtained with GVL as a solvent, different reaction conditions have been additionally tested (table 6) varying the zirconium source and the modulator.

**Table 6** reaction condition of synthesis of UiO 66 in GVL: Zr salt (0.5mmol), H$_2$-BDC (1eq), H$_2$O (3eq), 4 ml GVL

| Zr Salt          | Modulator        |
|------------------|------------------|
| **1a** ZrCl$_4$  | -                |
| **1b** ZrCl$_4$  | 30 eq AcOH       |
| **1c** ZrCl$_4$  | 30 eq HCOOH      |
| **2a** ZrOCl$_2$$\cdot8$H$_2$O | -          |
| **2b** ZrOCl$_2$$\cdot8$H$_2$O | 30 eq AcOH |
| **2c** ZrOCl$_2$$\cdot8$H$_2$O | 30 eq HCOOH |

![Graph a)](image1)

![Graph b)](image2)
Figure 4. XRPD patterns of a) UiO 66 synthesized in GVL whit ZrCl$_4$, 1a (black), 1b (red), 1c (blue) b) UiO 66 synthesized in GVL whit ZrOCl$_2$•8H$_2$O, 2a (black), 2b (red), 2c (blue)

Figure 4 reported the XRPD patterns of the materials obtained using the reaction conditions of table 6. The patterns are similar and corresponded to compounds with similar degree of crystallinity even in absence of acid modulator. Therefore, it is possible to obtain a good UiO-66 phase both by using different two Zr- salts and two different modulators. Replacement of ZrCl$_4$ with ZrOCl$_2$•8H$_2$O leads to good results. Highly crystalline pure phases were obtained and more important, there is the advantage of using a zirconium salt which does not release toxic by-products. As illustrated in the figures below, all the most promising green solvents for the UiO-66 synthesis feature a relatively high boiling point, higher than commonly used DMF. While this corresponds to a higher energy demand for their removal by distillation, in the case of the preparation of UiO-66, the product is isolated by filtration and then residual solvent removed by water. Therefore, as in other applications, the higher boiling point corresponds to a minimized exposure to the solvent and a limited dispersion of the medium into the environment as it happens for VOCs. The new solvents proposed also feature a significantly higher flash point values, confirming an increased intrinsic process safety. TAME departs from this trend, which shows both a lower boiling point and flash point. An important parameter for the selection of the reaction medium for UiO-66 synthesis is the dielectric constant ($\varepsilon$) and in fact almost all the media selected share a high polarity comparable to that of DMF. Most important, the ecological profile of all the solvents proposed here as replacement for DMF is very good in contrast with that of DMF itself. In fact, they are biodegradable and with no bioaccumulation issues. All the solvents here proposed, show a better and less critical toxicological profile then DMF itself. Focusing on the dermal LD50
(rabbit) data listed in the table above, we can observe an important increase of this value in all the green solvents tested. Moreover GVL, PC and Steposol, are not considered to be potential carcinogenic by IARC, while DMF is classified as “possibly carcinogenic to humans” (IARC Group 2B), and for this reason is labelled as SVHC by the European REACH regulation.

The use of new solvents deriving from biomass and/or industrial waste is a definitely cleaner and safer opportunity, although currently it may result to be more expensive, especially in the case of biomass-derived chemicals. This is certainly related to the fact that their preparation is based on different transformations but also that this area of chemical production is still at its infancy and as the technologies related to this industrial sector will be optimized and the proper raw materials made available, the cost associated to processes is expected to decrease with the increase of the market requests.
CONCLUSION

In this paper an extensive screening of green solvents potentially suitable for substituting DMF for UiO-66 synthesis is presented. Due to the large number of parameters we have decided to optimize the synthesis in DMF, according to literature conditions, by increasing the reagents concentration and using AcOH as monocarboxylic modulator. The same synthetic conditions were also employed for screening over forty solvents chosen according to well established health and safety regulation protocols. Six experiments were successful, providing UiO-66 crystals with crystallinity, purity and porosity comparable to the standard DMF synthesis. The chosen solvents were also tested for their stability in reaction conditions and recyclability. Further studies are undergoing to study more in details the most promising solvents and the reasons for their efficiency (especially in the case of GVL) in the preparation of good MOF structures. These preliminary results bring to successive studies oriented to the synthesis optimization, like scaling-up, recyclability and use of other Zr-salts.
ASSOCIATED CONTENT

Supporting Information. Analytical and instrumental procedures, XRPD patterns, TGA analysis, $^1$H-NMR spectra, N$_2$ adsorption isotherms, ion chromatography analysis. The following files are available free of charge.

brief description (file type, i.e., PDF)

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Notes

Any additional relevant notes should be placed here.

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ABBREVIATIONS
MOF metal organic framework, SBU secondary building unit, UiO University of Oslo, H₂-BDC terephthalic acid or benzenedicarboxylic acid, NH₂-BDC amino-terephthalic acid, BDC-OH hydroxy-terephthalic acid, DMF N,N-dimethylformamide, 2-Me-THF 2- methyltetrahydrofuran, PC Propylene carbonate, 1-(2-HE)-2-P 1-(2-hydroxyethyl)-1-pyrrolidone, TAME 1,3-amylmethylether, 1,3-PD 1,3-propanediol, GVL γ-Valerolactone, CPME Cyclopentyl methyl ether, VOC Volatile organic compound, Bp Boiling point, Mp Melting point, AcOH or AA Acetic acid, HCOOH or FA Formic acid, REACH Registration, Evaluation, Authorisation and Restriction of Chemicals, SVHC Substances of Very High Concern.

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