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One-step synthesis of *N*,*N*′-substituted 4-imidazolidinones by an isocyanide-based pseudo-five-multicomponent reaction†

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A pseudo-five-multicomponent reaction involving an isocyanide, a primary amine, two molecules of formaldehyde and water is reported, which gives *N*,*N*′-substituted 4-imidazolidinones when trifluoroethanol is used as the solvent. The reaction proceeds with good yields and with a wide variety of amines and isocyanides, providing an efficient new entry to these heterocycles. A preliminary study of the reaction mechanism suggests that trifluoroethanol, although acting as the solvent, is directly involved as a reagent in the reaction pathway.

Multicomponent reactions (MCRs) have become increasingly popular as powerful tools for the rapid generation of small-molecule libraries. However, in further pursuit of molecular diversity and complexity, novel and more versatile MCRs prove necessary. Despite the existence of rational design strategies for discovering new MCRs, serendipity continues to be an important source.[1] It is not surprising that MCRs, where three or more molecules must react in sequential steps in a defined succession, will be affected by changes in the conditions in which they are performed. It is known, for example, that the use of catalysts, solvents, or additives may redirect the course of a reaction along different pathways, thus producing alternative scaffolds.[1]

In this context, several recent reports provide evidence on the use of 2,2,2-trifluoroethanol (TFE) as a solvent in MCRs. This highly fluorinated alcohol has several properties such as low nucleophilicity, high ionizing power and high hydrogen bonding ability, which make it a unique solvent capable of inducing profound changes in the reaction outcome. As an interesting example, when ammonia is added in a four-component Ugi reaction as the amine component, the use of methanol as the solvent leads to a six-component coupling product with low yields, whereas TFE efficiently gives the expected α-aminoacylamide.[2,3]

During our work on the use of MCRs as key synthetic steps for the generation of bioactive molecules, we turned our attention toward the Ugi–Smiles reaction, which gives an *N*-aryl carboxamide **1** from an acidic phenol (**2**), an amine (**3**), an isocyanide (**4**) and an aldehyde (**5**).[4] Preliminary optimization experiments were performed using the particular components shown in Scheme 1 and different solvents and reaction temperatures. Taking into account the reports mentioned on the use of TFE as a solvent for the classic Ugi reaction, we decided to include it along with toluene and ethanol.

Unexpectedly, whereas the latter solvents yielded the desired product **1**, the use of TFE rendered the formation of 4-imidazolidinone **6a**. To the best of our knowledge, and although the synthesis of the 4-imidazolidinone ring has been widely explored, no reports are available on the preparation of this scaffold through a MCR.

The 4-imidazoline ring is a biologically relevant scaffold, as it occurs in natural compounds such as oxaline, neoxaline[5] and hetacillin,[6] isolated from *Penicillium* spp., which exhibit antibacterial, antifungal, and antitumoral activities. In addition, this ring is present in some bioactive synthetic compounds such as spiperone and mosapramine, which are known to interact with the dopamine receptor[7] and are clinically useful antipsychotic agents[8] (Fig. 1).

Numerous synthetic methods have been reported for obtaining 4-imidazolidinones which are in general multistep routes involving harsh conditions.[9–17] A typical procedure starts with the construction of a linear α-amino amide followed by a cyclization reaction. In several cases, the use of a protective group is needed. Furthermore, additional substitution reactions are required if the target compound is an *N*-substituted ring.

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† Electronic supplementary information (ESI) available: Detailed experimental procedures and NMR spectra (^{1}H, ^{13}C, and ^{19}F) for all the new compounds. 2D-NMR and mass spectra for selected compounds. See DOI: 10.1039/c8ob02229a

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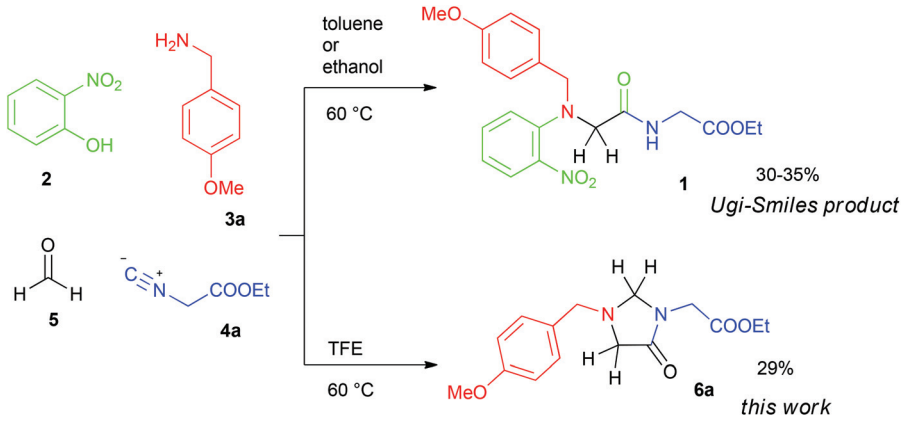


Scheme 1 TFE induces a new multicomponent condensation.

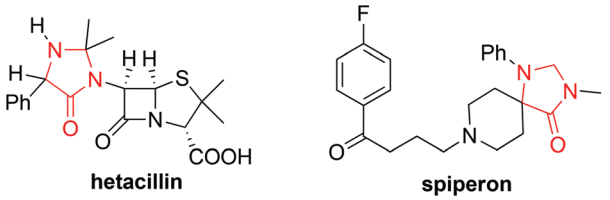
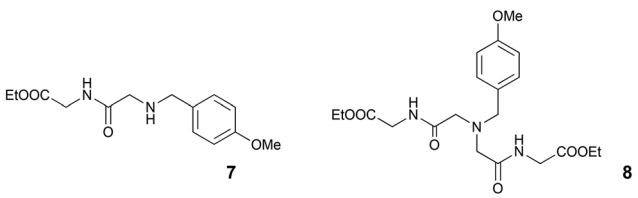


Fig. 1 Natural and synthetic compounds possessing the 4-imidazolidinone scaffold in their structures.

Table 1 Identification of the best-suited conditions for the synthesis of **6a**

Entry	T (°C)	2-Nitrophenol	CH_2O[a]	H_2O[a]	Yield[b] (%)
1	25	1	1.1	3.6	15[c]
2	60	1	1.1	3.6	29
3	90	1	1.1	3.6	21[d]
4	60	0	1.1	3.6	31
5	60	0	5	15	75
6	60	0	5	5	41[c]
7	60	0	5	100	72

[a] Equivalents with respect to isocyanide **6a**. [b] Isolated yields. [c] No completion of the reaction after 96 h by TLC. [d] By-products **7** and **8** were also isolated (4% and 6%, respectively).



In this context, and in light of our unexpected result, we decided to further identify the conditions leading, if possible, to an improvement of the reaction yield. Table 1 gives an overview of the most relevant screening results. Firstly, we determined that the reaction was best performed at 60 °C, as the formation of **6a** proceeded slowly at room temperature (entry 1), whereas a lower yield and the formation of some by-products, mainly the α-aminoamide Ugi-like intermediate **7**, probably originated by water attack on the intermediate nitrilium ion,[18,19] and **8**, likely formed through an over-Ugi reaction,[20] were observed at 90 °C (entry 3). Most importantly, we found that 2-nitrophenol **2** was not required for the reaction to proceed (entry 4).

In another set of experiments, and as two equivalents of formaldehyde are required to give the cyclization product, an experiment starting with an excess of this component was attempted. In this case, the yield could be improved to reach 75% by the addition of five equivalents of formaldehyde (as formalin, a 37% aqueous solution, entry 5). Finally, the effect of water on the outcome of the reaction was assessed by replacing formalin with paraformaldehyde, and adding variable amounts of water. When the quantity of water was reduced to 5 equivalents, to be equimolar to formaldehyde, the reaction proceeded slowly and no completion of the reaction was observed after 96 h (entry 6). On the other hand, an excess of water (entry 7) does not prove to increase the yield. Thus, we choose the conditions reported under entry 5 as the best-suited for the formation of the 4-imidazolidinone **6a**.

Having these improved conditions in hand, we tested the reaction with different isocyanides and amines. Our preliminary assays confirmed that in these cases the *N*,*N*′-substituted 4-imidazolidinones **6b**, **6c** and **6d** were also formed with good yield (Fig. 2), suggesting that this procedure may have a broad general scope.

As in other isocyanide-based MCRs, we were limited by the availability of this family of reactants. Furthermore, as isocyanides usually have unpleasant odors, we decided to overcome these drawbacks by synthesizing them *in situ* from the corresponding formylamides following Dömling's procedure,[21,22] which involves the slow addition of a triphosgene solution to a solution of formylamide **8** and triethylamine (TEA) in dichloromethane at 0 °C (Scheme 2). In order to test this strategy, we prepared compounds **6c** and **6d** starting from formylamides **9c** and **9d**, which were converted into isocyanides and used without prior isolation in our MCR. It is worth highlighting

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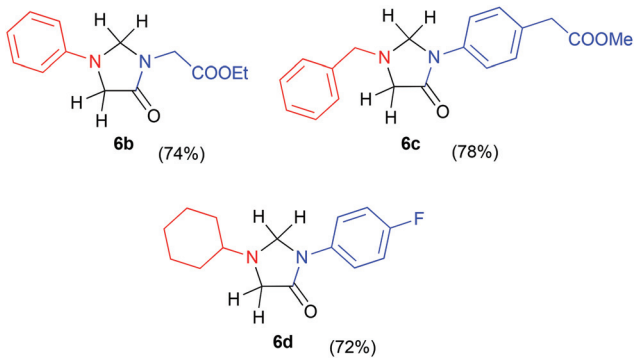


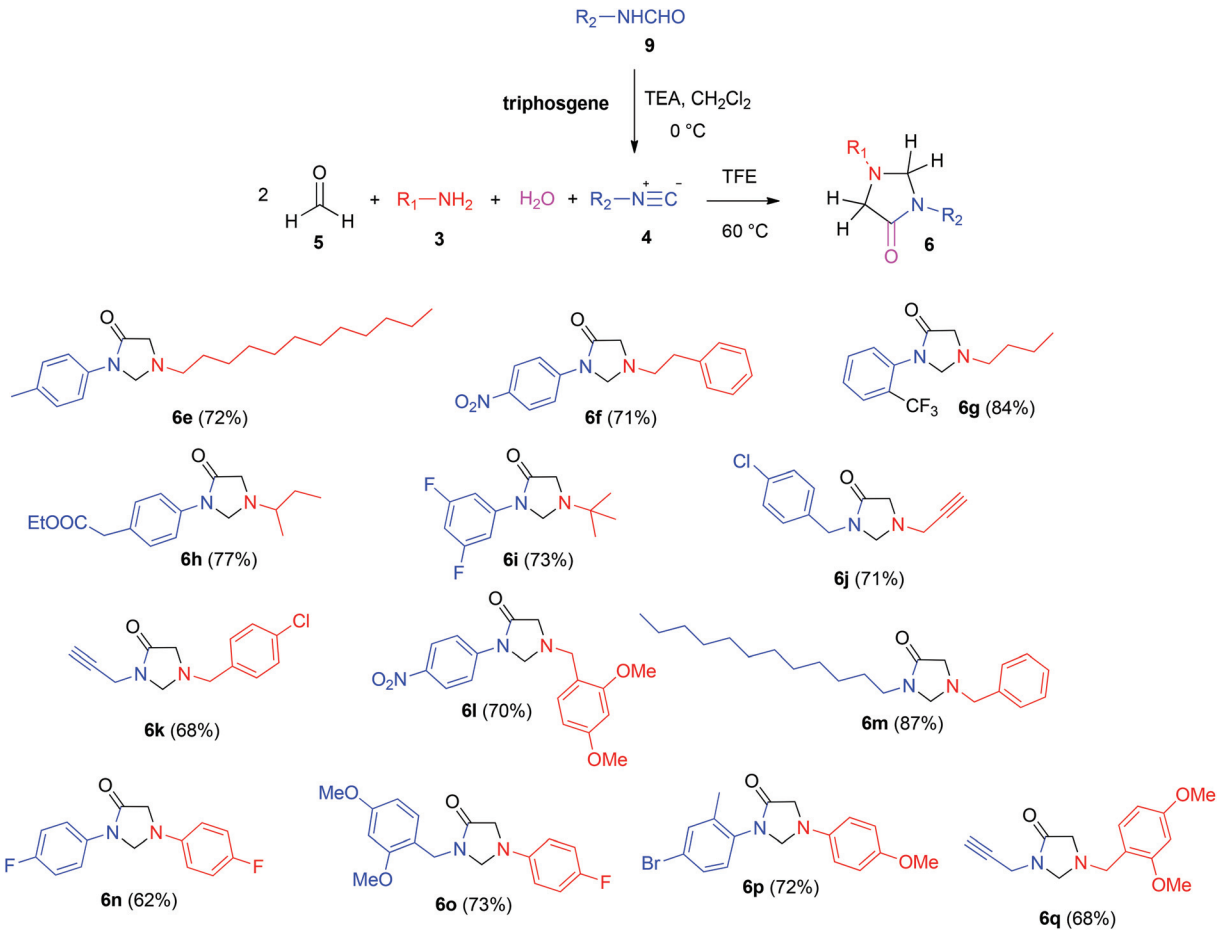
Fig. 2 Compounds obtained by the variation of the amine and the isocyanide.

that both compounds were formed with similar yields when compared to our previous experiments. Also of note is that the presence of dichloromethane, which was the solvent used in isocyanide synthesis, did not preclude the progress of this reaction.

With this new, optimized procedure, a small library of 4-imidazolidinones was obtained with a variety of substitution patterns (Scheme 2).

Various alkylamines, both linear and branched, including sterically demanding *tert*-butylamine, reacted to afford the corresponding 4-imidazolidinones in good to excellent yields (**6e–q**). Amines with additional functional groups, such as propargylamine and benzylamines with different electrodemanding substituents, also proved useful in this reaction. Moreover, the fact that the isocyanides can be obtained from the corresponding amines, allows the same substituent to be introduced in each of the N atoms of the heterocycle (compare **6e** and **6m**, or **6j** and **6k**). However, some amines, especially those with lower nucleophilicity such as 4-nitroaniline, 3-aminopyridine or 1-(3-aminophenyl)ethanone failed to give the corresponding 4-imidazolidinones, yielding α-hydroxy amides instead, which are probably derived from the attack of the isocyanide on formaldehyde.[23,24]

On the other hand, chemically diverse isocyanides reacted correctly to provide the target compounds **6**, irrespective of their structure.



Scheme 2 4-Imidazolidinones obtained from isocyanides generated *in situ*. Reaction conditions: **9** (1.1 mmol), TEA (2.4 equiv.) and triphosgene (0.4 equiv.) in CH_2Cl_2 (1.0 mL) were stirred at 0 °C for 2 h, then **5** (37% aq, 5 eq.) and **3** (1.1 eq.) in TFE (1.5 mL) were added. The reaction was kept at 60 °C for 3 days; isolated yields after purification. Following this procedure, compounds **6c** and **6d** were obtained in 74% and 81% yields, respectively.

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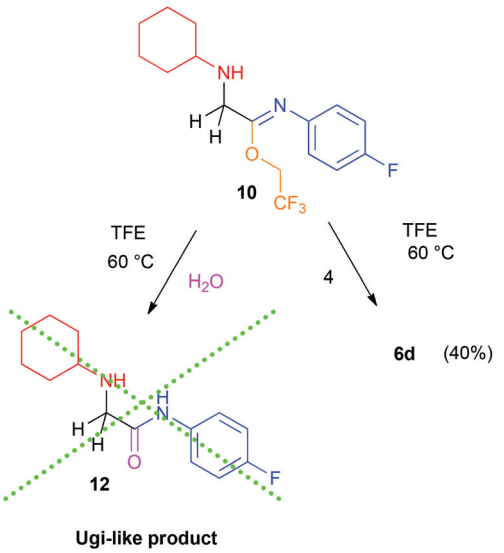
After having demonstrated the wide scope of this new MCR, we performed additional experiments in order to establish a preliminary proposal for its mechanism. Taking into account previous reports on isocyanide-based reactions,[25] and the fact that the formation of the 4-imidazolidinones involved the participation of two equivalents of aldehyde, we conducted the reaction with a lower amount of this component (1 equivalent with respect to amine), and at a lower temperature, with the aim of detecting possible intermediates. Fortunately, it was possible to isolate and fully characterize intermediate imidate[26] **10** depicted in Scheme 3. This suggests that the solvent does not only act as an acidic medium but also participates directly in the reaction as a reactant even when it is not present in the final product.

Interestingly, Saya *et al.* have observed very recently the formation of this kind of intermediate during a Passerini-type reaction when 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) was present as a cosolvent.[27] Thus, we performed some preliminary experiments in order to verify if this alternative fluorinated alcohol might also promote the formation of the 4-imidazolidinones reported herein. To our delight, both compounds **6a** and **6b** were obtained with good yields when TFE was replaced by HFIP following the same procedures described before (see the ESI† for details). Furthermore, when using the latter solvent, a small amount of the corresponding imidate **11** was also isolated at low temperatures.

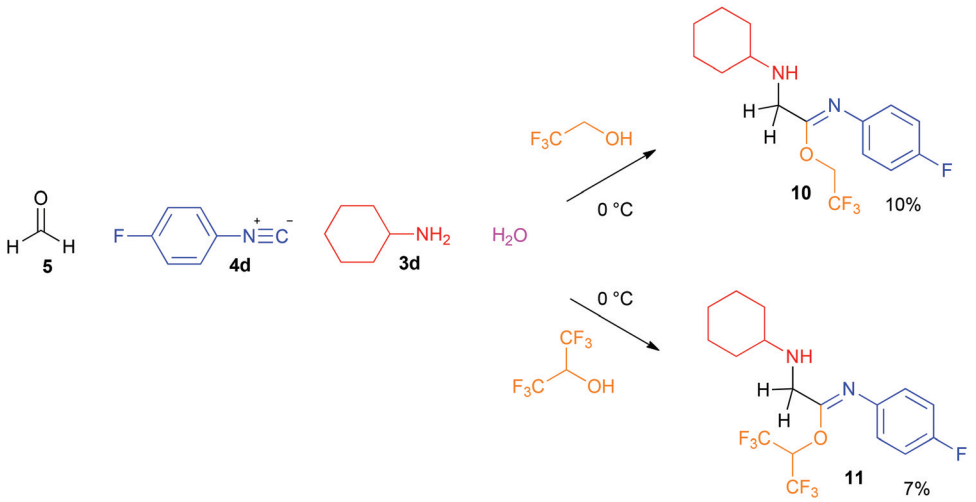
At this point, a possible pathway for the transformation of imidates such as **10** into the corresponding 4-imidazolidinone could be thought to involve the hydrolysis of **10** to give an α-aminoamide Ugi-like intermediate **12**, which might further react with formaldehyde to give the cyclic product. However, when **10** was treated with water in TFE at 60 °C, the starting material remained unchanged after 4 h of reaction. In contrast, when intermediate **10** was treated with an excess of aqueous formaldehyde, the cyclic final compound **6d** was obtained in good yields (Scheme 4). These findings reinforce



Scheme 4 Preliminary studies on the mechanism of the reaction.

our hypothesis that the procedure reported in this work constitutes a new MCR and not a combination of a previously known Ugi-like reaction followed by a post cyclization reaction.

Altogether, this information made it possible to conceive a reaction cycle leading to 4-imidazolidinone **6** (Fig. 3). This cycle may be initiated by the protonation of the imine **I** generated *in situ*, which suffers the attack of the isocyanide to give a nitrilium ion. This intermediate could be trapped by the nucleophilic trifluoroethanol to give the imidate **II**, which is stable enough to be isolated. We propose that **II** could react with a second molecule of formaldehyde to give the enamine **III**, which undergoes an intramolecular nucleophilic attack to form the cyclic intermediate **IV**. Finally, water reacts with **IV** to generate the hemi-orthoamide **V**, which in turn fragments to 4-imidazolidinone **6**, regenerating the solvent molecule **VI**.



Scheme 3 Isolation of the reaction intermediates.

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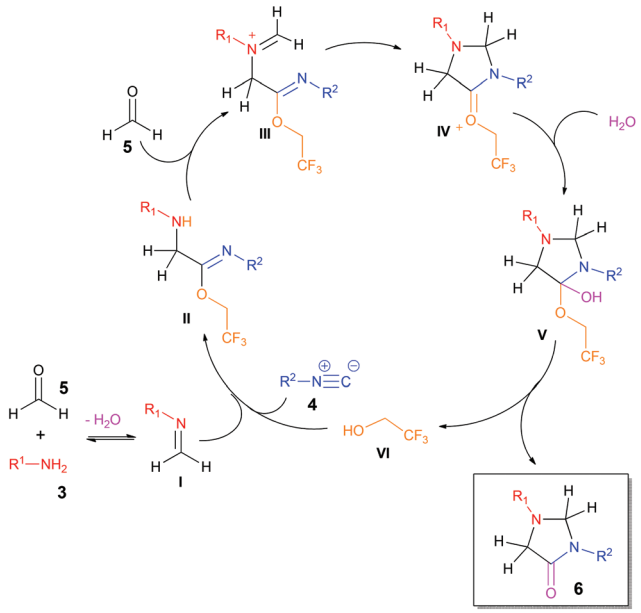

Fig. 3 Proposed mechanism for the formation of 4-imidazolidinones.

This proposed mechanism is supported in part by the mechanistic studies of Satterthwait and Jencks[28] on the aminolysis of acetate esters, and by those of Brace,[29] which suggest that the expulsion of a leaving group from a tetrahedral intermediate such as **V** in neutral or acidic media involves the relatively good leaving group, trifluoroethanol, and not water.

In summary, we describe a MCR which is an efficient methodology for the synthesis of *N*,*N'*-substituted 4-imidazolidinone derivatives. The reaction proceeds in good to excellent yields starting from a variety of electronically and structurally different amines and isonitriles. Furthermore, this new method offers a new entry to these types of interesting heterocycles with important advantages over existing methods, such as avoiding the use of protecting groups or catalysts, shorter reaction times, ease of product isolation and purification, and lower global costs and simple operation. Further studies aiming at extending the scope of this method and completely elucidating the mechanism involved are currently underway.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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