



100 years of isocyanide-based multicomponent reactions

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In 1921 Mario Passerini (1891–1962), who was holding a chair of organic chemistry at the University of Florence (Italy), published a report [1] where he described the first multicomponent reaction based on the peculiar chemistry of isocyanides. Isocyanides (also called isonitriles) are indeed “stable carbenes”, having a carbon atom that can act both as nucleophile and electrophile. In the reaction named after him, isocyanides react with carbonyl compounds and carboxylic acids to afford α -acyloxyamides.

In 1921, the term “multicomponent reaction” was not already used, and probably Passerini was not fully aware of the importance of his discovery. Nowadays, we define a multicomponent reaction as a process where three or more substrates react to give a product that contains essential parts of all starting materials. It was Ivar Ugi who, about 40 years after Passerini's discovery, [2] first understood the potential of multicomponent reactions in “diversity-oriented synthesis” [3] and in combinatorial chemistry. Ugi published his well-known reaction in 1960, 39 years later than the first report by Passerini. In consideration of the mechanistic similarity of the two reactions, it is surprising that so much time passed between the two discoveries. [4] This may be due to the fact that Passerini published his work in Italian that was not at the time the leading scientific language. The work of Passerini was indeed completely neglected until the early '50 s. Moreover, the mechanism initially proposed by Passerini, which was later found wrong, may have misled other researchers to simply substitute the carbonyl component with an imine.

In any case, both Passerini and Ugi reactions turned into high popularity only in the '90 s, when pharmaceutical companies became increasingly interested in combinatorial chemistry. It was soon clear that multicomponent reactions are exceptionally useful in this context. This is particularly true for those, like Passerini and Ugi reactions, which combine in a single step three or four real diversity inputs, represented by easily available reagents. Since then, the number of publications on multicomponent reactions (MCR) has grown up exponentially, and several new MCRs have been discovered in the last 30 years. However, isocyanide-based MCRs continue to maintain a leading role.

They have evolved along four main paths: (a) single-component replacements have generated numerous variants of Passerini and Ugi reactions; (b) coupling the classical reactions with post-MCR reactions (especially cyclizations) or with pre-MCR processes has allowed to widely explore scaffold diversity, for example, giving access to a huge variety of heterocycles; (c) new isocyanide-based chemistry has been investigated leading to the discovery of completely new IMCRs; (d) diastereoselectivity [5] and enantioselectivity of IMCRs have been studied. In particular, the very challenging issue of developing enantioselective catalytic Passerini [6] and Ugi reactions [7, 8] has been in part recently solved.

Meanwhile, new or old MCRs have demonstrated a wide utility not only in drug discovery [9], but also in the discovery of new functional materials [10]. More recently, they are also increasingly employed in target-oriented synthesis [11–13], also because their features respect some of the green chemistry principles [14]. More and more researchers all over the world are entering the field of multicomponent reactions. Since 2000 (the first event was held in Munich), they gather together periodically in dedicated MCR Conferences. The last one was in Burgos (Spain) in September 2023, where the excellent communications have further demonstrated the many opportunities offered by this strategy.

We, and all the other colleagues who share with us the passion for MCRs, are very indebted to the first discovery by Mario Passerini, made in 1921. The year 2021 does not

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represent only the anniversary of Passerini reaction [15], but also of all isocyanide-based multicomponent reactions (IMCRs), and is, more generally, a very important milestone for the whole MCR community.

For this reason, in late 2021, we have proposed to the editors in chief of Molecular Diversity to accept us as guest editors of a special issue named “100 years of isocyanide-based multicomponent reactions”. This journal seemed to us perfectly suited for this, because, as already said above, MCRs, and especially IMCRs, are one of the most powerful tools for achieving fast molecular diversity.

We were very happy that this proposal has been gladly accepted by several researchers in the field. Most of the papers have already been published in advance, but now we are finally ready to put together all these excellent contributions, hoping that all the readers will find in them inspiration for their future studies.

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