Synthesis of Cyclic Hydroxamic Acids by the Formal [2+4] Cycloaddition of Oximes and Homophthalic Anhydride

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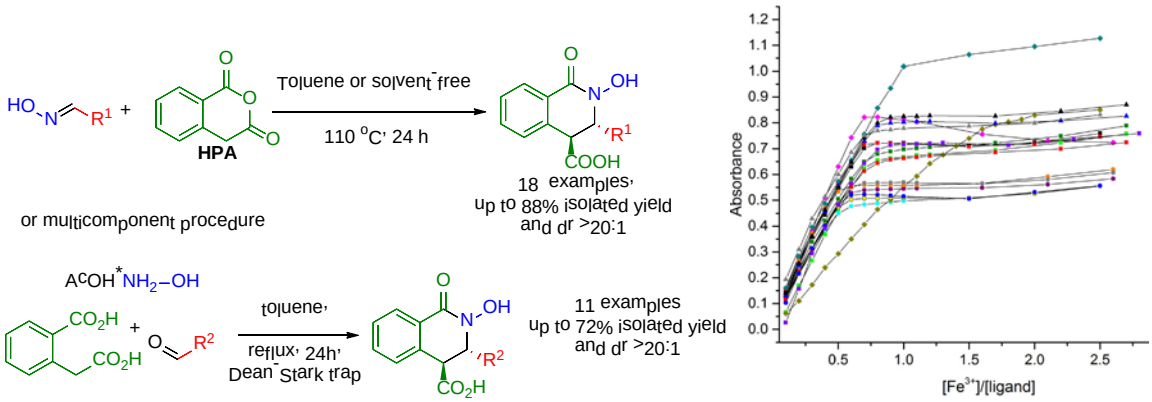
Cyclic hydroxamic acid (*N*-hydroxylactam) motifs are widely displayed in natural products as well as synthetic enzyme inhibitors. Hydroxamic acids have found utility as HIV integrase inhibitors[1], matrix metalloprotease inhibitors[2], histone deacetylase inhibitors[3] and analogs of bacterial siderophores[4]. The latter property was used to develop co-called 'troyan horse' strategy[5] for circumventing drug resistance of bacteria by designing of special carriers for antibiotics. The strategy was also successfully applied for improving fluorescent imaging *in vivo*.

The following study describes a novel practically convenient, approach to *N*-hydroxy tetrahydroisoquinoline (THIQ) acids via formal [2+4] cycloaddition of oximes and homophthalic anhydride (HPA)[6]. Recently a multicomponent procedure of this reaction has been developed in addition. A broad variety of O-unsubstituted and substitued oximes were tested in reaction with HPA, which delivered THIQs in high yields and diastereoselectivity. Some investigated mechanistical aspects of the reaction will be discussed. This new general approach was applied to design more simple and convenient synthesis of biologically active natural compound, 2-*N*-Hydroxy-3,4-dihydroisoqionol-2-one. All products demonstrated strong complexation with iron (III), which was studied spectrophotometrically. Perspectives of using obtained compounds as siderophores and precursors for fluorescent cationic chemosensors will be also discussed.



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Fragment-based and Multicomponent Synthesis of Polyphenols-Peptide Hybrids and their Evaluation as Amyloid Aggregation Inhibitors

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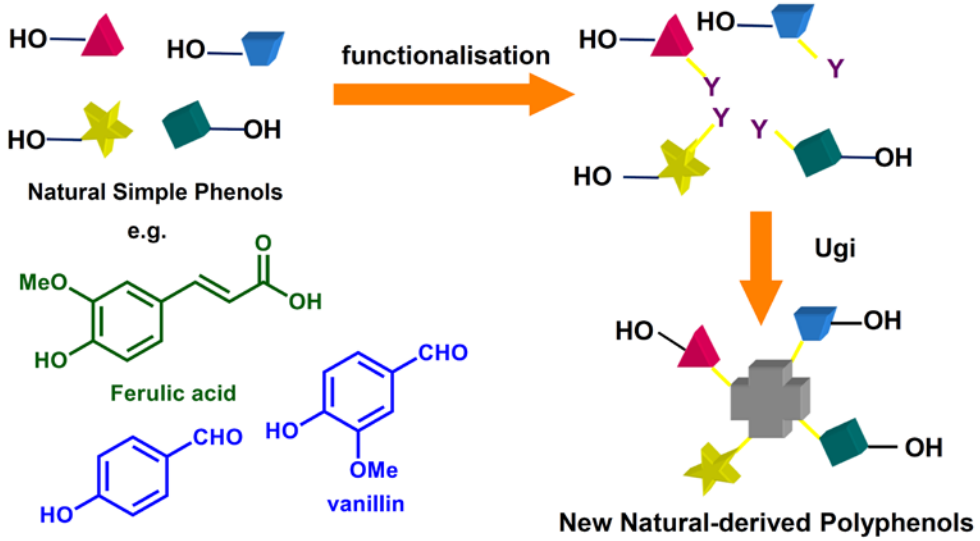
Alzheimer's disease (AD) is an irreversible and progressive neurodegenerative disorder and it is the most common cause of dementia. Although AD it is not clearly understood, it is strictly correlated to the presence in the brain of two types of aggregates: the intracellular neurofibrillary tangles and the extracellular amyloid plaques. The inhibition of amyloid aggregation is thus a promising therapeutic approach for the AD.
Recently, the ability of few natural and simple polyphenols (e.g. epigallocatechin gallate, curcumin) to inhibit the amyloid aggregation has been highlighted.[1] In addition, it is known that this class of compounds is endowed with antioxidant and anti-aging properties. However, their use as drugs is hindered by poor stability under physiological conditions and/or difficult blood-brain barrier permeability.
Aiming at overcoming this limitation, we have designed a very short synthetic sequence, based on the Ugi multicomponent reaction, to access a series of unnatural polyphenol-peptide hybrids. Most fragments used in this approach are bio-based phenols, that have been, in some cases, simply derivatized to afford the functionality needed for the Ugi reaction. Herein, the optimization of the synthetic strategy[2] and the *in vitro* and *in vivo* results of the most active compounds will be discussed.[3]



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3 This study was supported by the Fondazione Cariplo under the "Integrated Biotechnology and Bioeconomy" programme.

Donate-like mesoporous graphitic carbon nitride as a robust and heterogeneous organocatalyst for the one-pot synthesis of 2-amino-3-cyanopyridines

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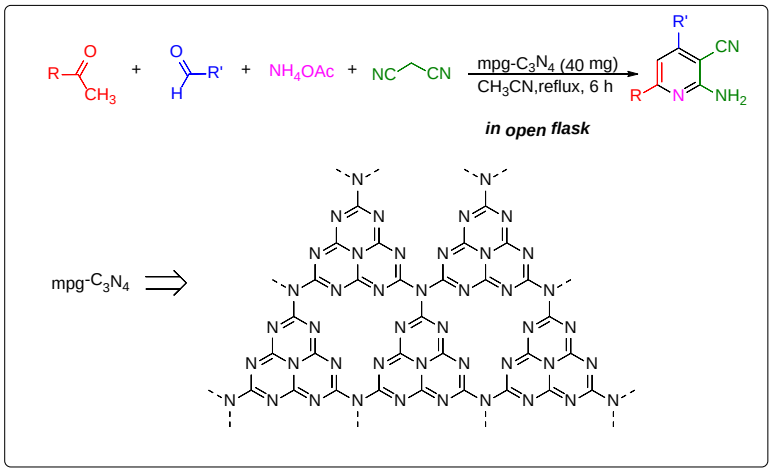
The pyridine substructure as one of the most prevalent heterocycles often play an indispensable role in chemical synthesis and the pharmaceutical industry.[1] Among them, 2-amino-3-cyanopyridines allowed an access to many demonstrated bio-active agents.[2] The prominence of these compounds has led to various methods for synthesizing such compounds in recent years.[3] The most common synthetic approach to these pyridine derivatives is the multicomponent reaction (MCR) of aldehydes, ketones, malononitrile, and ammonium acetate. However, most of these methods often involve the use of expensive reagents or metal-based catalysts. Considering both economic and environmental issues, the best option for catalyst-based synthesize of such compounds is heterogeneous catalysts and mesoporous graphitic carbon nitride (mpg-C_3N_4) can be an attractive candidate for this purpose. The incorporation of nitrogen atoms in the carbon nanostructure can enhance the basicity of this compound. Building on our previous research [3b] now, an efficient procedure for the synthesis of 2-amino-3-cyanopyridines via an mpg-C_3N_4 catalyzed four-component condensation is presented:



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HFIP as a Novel Acid Component in the Passerini Reaction: One-Pot Access to β-Amino Alcohols

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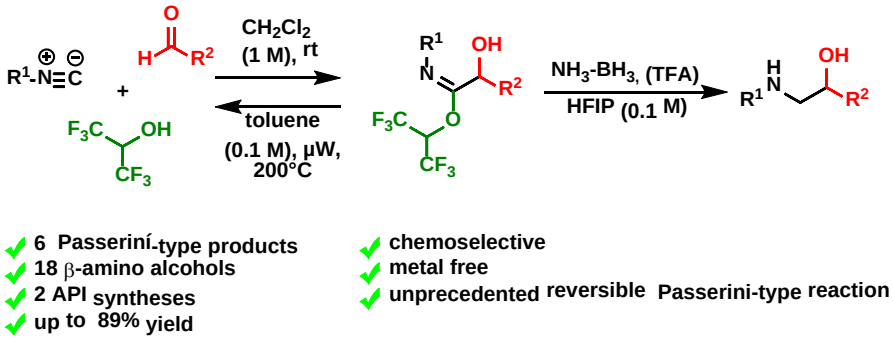
Isocyanide-based multicomponent reactions have received much interest over the past decades. Still, new discoveries continue to be made about these complex reactions. In addition to post-condensation modifications, new developments in this field are based on changing the nature of the traditional reaction pathway, either by single reactant replacement[1,2] or by interrupting the reaction mechanism.[3] Herein we report a new Passerini-type reaction in which HFIP functions as the acid component.[4] The reaction tolerates a broad range of isocyanides and aldehydes, and the resulting imidates can be reduced to medicinally important β-amino alcohols under mild, metal-free conditions. Moreover, the observation that the imidate products undergo an unprecedented retro- Passerini-type reaction under microwave irradiation provides valuable information about the general mechanism of the Passerini reaction and related reactions.



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