Synthesis of 5-Carboxamide-oxazolines with a Passerini−Zhu/Staudinger−Aza−Wittig Two-Step Protocol

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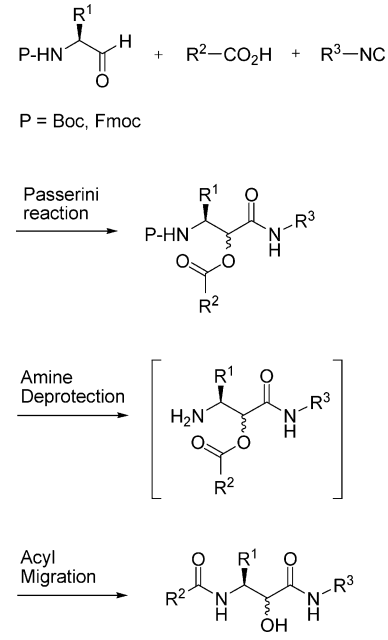
Our research group has been active during the past decade to discover novel applications of isocyanide-based multicomponent reactions (I-MCRs), such as the Passerini[1] and Ugi[2] condensations. Specifically, we have reported the PADAM (Passerini reaction−amine deprotection−acyl migration) strategy that, starting from N-protected α-aminoaldehydes, employs a Passerini reaction to straighforwardly generate *β*-acylamino-α-hydroxyamides (Scheme 1).[3] This strategy has been employed by us and by others to assemble biologically active peptidomimetic compounds.[4]

During the search for variations of this methodology, we attempted to replace the *N*-Boc- or *N*-Fmoc-protected aminoaldehyde with the corresponding α-azidoaldehyde, having in mind to employ the azido group as a surrogate of a protected amine. α-Azidoaldehydes have been very rarely reported in the literature, the only examples being related to sugar chemistry[5] and would be very precious and versatile building blocks in I-MCRs; we, therefore, decided to investigate their synthesis.

Our first attempts started from α-azidoacid **1**, prepared according to a known procedure;[6] this was converted into the corresponding Weinreb amide and reduced to aldehyde **2** with lithium aluminum hydride. Although the crude aldehyde was far to be pure, we attempted a Passerini reaction with benzylisocyanide and benzoic acid, obtaining adduct **3**{*1*,*1*,*1*} in 18% yield as a mixture of two diastereoisomers. To prove whether compound **3**{*1*,*1*,*1*} could be transformed into *β*-benzoylamino-α-hydroxyamide **4** according to the PADAM protocol, it was reacted with triphenylphosphine, known to reduce azides to amines via phosphazene formation and subsequent hydrolysis. The reaction proceeded smoothly in dichloromethane and water but, instead of **4** furnished oxazoline **5**{*1*,*1*,*1*} according to a Staudinger−Aza−Wittig (SAW) reaction (Scheme 2).

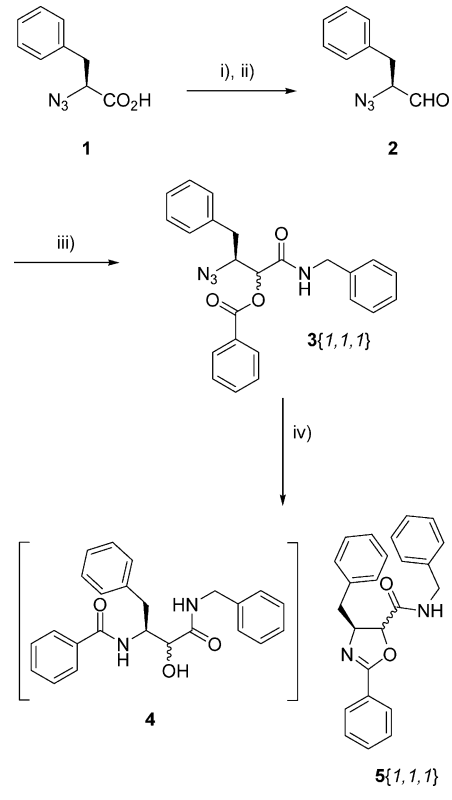
The SAW reaction is a very common strategy to assemble medium-size heterocycles.[7] However, this strategy is typically carried out using carbonyl compounds and leading to imines; on the contrary, there are fewer examples of intramolecular SAW with the less reactive esters or amides,

Scheme 1. PADAM Strategy



and it has been used in a limited number of cases to prepare selected oxazolines.[8]

Scheme 2. Outcome of the PADAM Strategy Applied to α-Azidoaldehydes[a]



[a] Reagents and conditions: (i) *N*,*O*-dimethylhydroxylamine hydrochloride, DCC, HOBt, Et_3N, DCM, rt, 76%; (ii) LAH, Et_2O, 0 °C, for the yield see text; (iii) benzoic acid, benzyl isocyanide, DCM, rt, 18%; (iv) triphenylphosphine, DCM, H_2O, rt, 99%.

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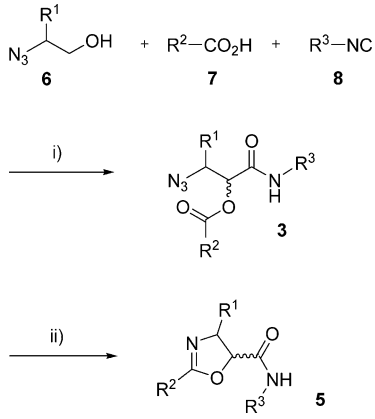
Scheme 3. Passerini−Zhu/Staudinger−Aza−Wittig Protocol[a]



[a] Reagents and conditions: (i) IBX, THF, MW (150 W), 100 °C; (ii) polymer supported triphenylphosphine, DCM, MW (150 W), 100 °C.

Oxazolines are privileged structures in medicinal chemistry; they have found applications as anti-inflammatory drugs,[9] dopaminergic agonists,[10] antibacterials,[11] cytotoxic,[12] and neuroprotective agents.[13] Different synthetic protocols are available to assemble the oxazoline ring, mainly based on cyclodehydration of amido alcohols,[14] haloamidation of alkenes,[15] and condensation of imidate hydrochlorides,[16] carboxylic acids,[17] esters,[18] imino ether hydrochlorides,[19] aminoacids,[20] nitriles,[21] and aldehydes[22] with amino alcohols. Some approaches involving multicomponent reactions have recently been reported.[23] These protocols allow for the introduction of various functional groups at the 2, 4, and 5 position of the oxazoline core; however, they mainly use starting materials where the substituents in positions 4 and 5 are already displayed by the starting aminoalcohol derivative, thus limiting the number of available building blocks; moreover, reports about the introduction of a carboxamide onto the 5 position are very rare, require multistep synthesis and are not amenable to combinatorial applications.[24] On the other hand, such compounds have found interesting biological properties as glucokinase activators or antibacterials.[25] A synthetic strategy able to assemble 2,4-substituted-5-carboxamideoxazolines in a very straightforward manner and, in a combinatorial fashion,[26] could open up the scenario to a novel class of molecules with specific biological properties.

Having this interesting strategy in hand, we moved to explore more efficient ways to prepare the α-azidoaldehyde building blocks, but we had to face with the intrinsic instability of such compounds, having heavily marked tendency to generate autocondensation adducts. On the other hand we were pleased to find that the azido group was rather stable, both under oxidative and reductive conditions, as judged by IR analysis of the products. This prompted us to investigate the synthesis of the corresponding α-azidoalcohols **6** with known procedures[27] and their in situ oxidation during the Passerini reaction, modifying a protocol recently introduced by Zhu[28] with different alcohols. With our delight this method afforded the desired adducts **3** in good yields (Scheme 3); after careful optimization of the reaction conditions, it was found that use of THF or EtOAc as the solvent under microwave heating (100 °C) with a slight excess of IBX as oxidating agent (1.3 equiv) resulted superior compared to the original conditions reported by Zhu. All Passerini adducts were then smoothly converted into the corresponding oxazolines **5**. We investigated the scope of the reaction employing three chemsets of azidoalcohols **6**{*1*−*4*}, carboxylic acids **7**{*1*−*7*}, and isocyanides **8**{*1*−*4* } (Figure 1), and the results are reported in Table 1. The final compounds, apart from entries b and c, were always obtained as a nearly 1:1 mixture of two diastereoisomers,

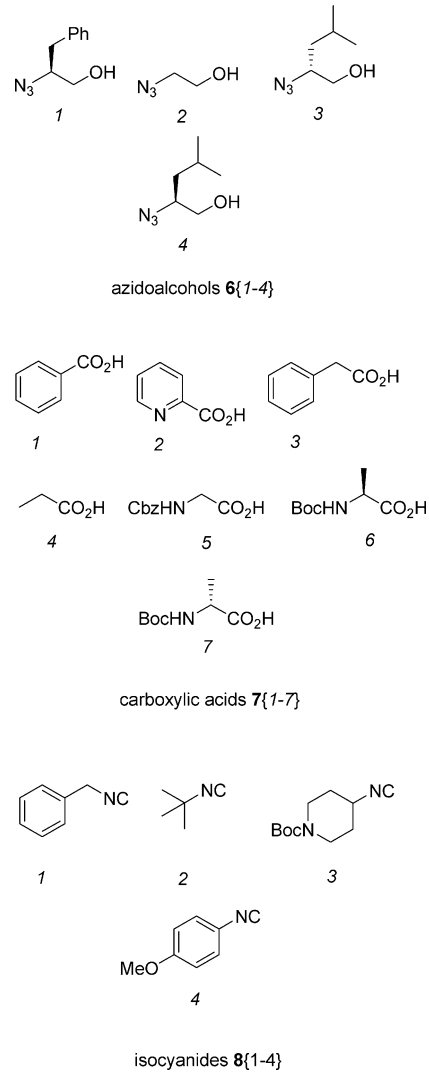


Figure 1. Chemsets employed in the Passerini−Zhu/Staudinger−Aza−Wittig Protocol.

Table 1. Investigation of the Scope of the Synthetic Protocol

compound	yield[a] (%)	compound	yield (%)
3{*1,1,1*}	75[b]	**5**{*1,1,1*}	99[b]
3{*2,4,2*}	35	**5**{*2,4,2*}	84
3{*2,5,1*}	42	**5**{*2,5,1*}	93
3{*3,2,3*}	49[b]	**5**{*3,2,3*}	96[b]
3{*3,6,2*}	57[b]	**5**{*3,6,2*}	96[b]
3{*1,2,2*}	65[b]	**5**{*1,2,2*}	quantitative[b]
3{*3,3,2*}	65[b]	**5**{*3,3,2*}	98[b]
3{*1,3,4*}	74[b]	**5**{*1,3,4*}	93[b]
3{*1,7,1*}	50[b]	**5**{*1,7,1*}	91[b]
3{*1,3,3*}	66[b]	**5**{*1,3,3*}	96[b]
3{*3,4,4*}	81[b]	**5**{*3,4,4*}	97[b]
3{*3,2,1*}	74[b]	**5**{*3,2,1*}	97[b]
3{*4,2,1*}	77[b]	**5**{*4,2,1*}	98[b]

[a] Yields are referred to products purified by flash chromatography. [b] Yields are referred to the mixture of diastereoisomers.

which could be separated by standard chromatographic purification. This has to be ascribed to the well-known poor selectivity of the Passerini reaction when chiral aldehydes are employed; remarkably the diastereomeric Passerini adducts did not show difference in reactivity during the cyclization step and the diastereomeric ratio was conserved also in the oxazoline adducts. Identification of syn and anti diastereoisomers was made on the basis of *J* coupling constants between H-4 and H-5, being in the range 10−11 Hz in the case of the syn adduct and in the range 5−7 Hz in the case of anti adduct, in accordance with the Karplus equation and the geometry of the diastereomeric oxazolines. Furthermore, the correct configuration was confirmed also by NOE experiments.

To make this procedure amenable for large library production, we conducted parallel studies on model compound **5**{*1*,*2*,*2*}, finding that extractive work up and chromatographic purification after the Passerini step could be suppressed without significant decrease (<10%) of the final yield: simple filtration of IBX side products was sufficient to afford a crude material that could effectively undergo the cyclization to oxazolines; moreover, use of polymer supported triphenylphosphine in the SAW reaction facilitated the final purification, suppressing the formation of free triphenylphosphinoxide that often contaminated products **5**.

The obvious slower conversions observed with this supported reagent were overcome by performing this step under microwave heating, able to quantitatively transform Passerini adducts **3** into oxazolines **5** within 75 min (20 min were sufficient in most of the cases). Also use of polymer supported IBX was attempted; however, this was found to be not compatible with the reaction conditions required by the Passerini−Zhu step.

One concern was relative to the optical stability of the in situ generated α-azidoaldehydes under the rather harsh conditions required by the Passerini−Zhu protocol. Partial or total racemisation of this building block would indeed be a major drawback in view of the preparation of optically pure products. Compounds **5**{*3*,*6*,*2*} and **5**{*1*,*7*,*1*}, prepared with optically pure carboxylic acids, did not show any trace of epimerization and this seems to confirm that racemization did not occur. In order to rule out completely this side event, enantiomeric oxazolines **5**{*3*,*2*,*1*} and **5**{*4*,*2*,*1*} were analyzed by chiral HPLC analysis and absence of cross-contamination peaks (purity >99%) confirmed that racemization did not occur throughout the whole synthetic process.

In view of possible biological applications, we subsequently moved to investigate the stability of these novel oxazolines, finding that, although more acid labile than similar compounds without the carboxamide substituent, they were completely stable at pH 7.4. On the other hand some decomposition (10%) was observed under prolonged (24 h) exposure to pH 5 solutions and complete hydrolysis to compounds **4** was observed at pH 3.

Moreover, a DMSO solution of compound **5**{*1*,*1*,*1*} did not show any degradation either after 1 year storage at −20 °C in a sealed NMR tube or in an open vessel left for one month on the bench.

Furthermore, we conducted DSC analysis on azidoalcohols **6**{*1*} and **6**{*4*} to check their stability under microwave heating, finding a degradation temperature of 161 and 166 °C, respectively, with energy liberation of 1642 and 1906 J/g. This demonstrates that our synthetic protocol, requiring heating at 100 °C, is sufficiently safe on a multimilligram scale for automatized library production.

In conclusion, we have demonstrated that a novel class of oxazolines can be efficiently assembled in two steps from readily available building blocks using a Passerini-Zhu/SAW protocol. We are currently applying this methodology to the preparation of a 1000-member library that will be subjected to primary screening to determine the biological properties of such compounds. The results will be reported in due course.

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Supporting Information Available. General experimental procedures, full characterization and copies of ^{1}H and ^{13}C NMR spectra for compounds **3** and **5**. This information is available free of charge via the Internet at http://pubs.acs.org/

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