Diastereoselective one pot five-component reaction toward 4-(tetrazole)-1,3-oxazinanes†

Ajay L. Chandgude, a Daniele Narducci, a Katarzyna Kurpiewska, b Justyna Kalinowska-Tłuścik b and Alexander Dömling a

A diastereoselective one pot five-component reaction toward the synthesis of 4-(tetrazole)-1,3-oxazinanes has been reported. The sonication-accelerated, catalyst-free, simple, general and highly time efficient, Asinger–Ugi–tetrazole reaction was used for the synthesis of diverse 4-(tetrazole)-1,3-oxazinanes. The reaction exhibit excellent diastereoselectivity and broad substrate scope.

Introduction

The oxazine motif attained significant attention due to their widespread availability in natural products, such as aragupe-trosine, bujeine, pagicerine, quimbeline, and upenamide. The oxazines scaffold is present in many pharmacologically active agents and drugs, such as pranlukast, dirithromycin, and dolutegravir. It is also used as intermediate for the synthesis of drugs like oxacephem antibiotics.

On the other hand, the tetrazole is a highly important synthetic scaffold for a wide range of areas and applications. It is extensively used in medicinal and organic chemistry, also in industries such as explosives, agrochemicals, materials, and polymers. Their use as a carboxylic acid isostere and cis-amide bond isostere in peptides have many advantages, such as extra lipophilicity, metabolic stability, and hydrogen bonding to increase potency. Heterocycles are important in drug design and are present in half of the top 200 drugs. Thus, recently the use of heterocycle linked tetrazole scaffolds got major attention as a privileged core structure for the development of drug candidates. This combination is an effective strategy to balance drug-like properties. Owning the importance of heterocycles linked tetrazoles resulted into reports of many examples of bioactive agents, such as pyridine-tetrazole, Akt1 and Akt2 dual inhibitors; pyrazole-tetrazole, antileishmanial or as cardiotonic agents; pyridine-tetrazole, antibacterial; piperazines-tetrazole, type 2 diabetes; isoaxazole-tetrazole, for AMPA receptors; and also for ionotropic glutamate receptors. Moreover, in non-medical applications, use of cyclic ketimines-tetrazoles as organocatalysts, and pyridine-tetrazoles in lanthanide-based applications are also well known.

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Results and discussion

We envisioned the use of Asinger–Ugi-tetrazole union for the first time to synthesize an oxazines-tetrazole scaffold. We start our optimization by using isobutyraldehyde, ammonium hydroxide, 3-hydroxypivaldehyde, benzyl isocyanide and TMSN₃. The reaction in methanol at room temperature resulted in only trace product formation (Table 1, entry 1). Union of an Asinger reaction with other MCRs is known to be low yielding. Therefore we move our attention towards the use of sonication in MCR which can be highly effective. Further optimization was carried out with sonication at room temperature.

First, we optimized the ammonia source. We screened different ammonia sources, like NH₄OH, NH₄Cl, and NH₄OAc. NH₄OH in 1.5 equivalent was found to be the best. When the reaction was performed in MeOH, a promising 51% yield was obtained (Table 1, entry 2). Next, we move our attention towards solvent screening. Use of MeOH : H₂O solvent systems, such as 3 : 1, 1 : 1 or 1 : 3 resulted in less product formation, like 21%, 17%, and 15% respectively (Table 1, entries 3–5). However, EtOH as solvent gave the desired product only in trace amounts. When water was used as a solvent, the reaction did not proceed further probably due to the water insolubility of the reactants (Table 1, entry 7). Use of dioxane and THF provided a similar
Previous methods

This method

One-pot 5-component reaction

Fig. 1 In situ bis-heterocycle synthesis.

yield of ~30% (Table 1, entries 8–9). TFE and DCM gave lower yields. Toluene turned out to be the best solvent with 60% yield (Table 1, entry 13). However, an attempt to make the protocol

Table 1 Optimization of reaction conditions

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<td>3</td>
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Table 2 Substrate scope

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The reaction was carried out with isobutyraldehyde (1 mmol), ammonium hydroxide (1.5 mmol), 3-hydroxyvaleraldehyde (1 mmol), benzyl isocyanide (1.2 mmol) and TMSN₃ (1.2 mmol) in 0.5 ml solvent. YIELD of isolated product. „dr ratio determined by NMR analysis.

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greener by using toluene : water solvent system resulted in a lowering to 25% yield (Table 1, entries 14–16); while xylene did not ameliorate the reaction yield.

With optimized conditions in hand, next, we tested the scope and limitations of this reaction by reacting various aldehydes and isocyanides (Table 2). Different linear and branched aliphatic aldehydes such as isobutyraldehyde, propanal, butyraldehyde, and valeraldehyde provide moderate to good yields of 21% to 60% (Table 2, entries 2–7). Good to excellent yield were obtained with aliphatic-aromatic aldehydes like benzyl and phenylacetaldehyde. Benzaldehyde and 2-chloro benzaldehyde are valid substrates in this reaction with providing moderate yields of 35% and 45% respectively (Table 2, entries 12 and 13). However, the reaction with a ketone resulted in only trace product formation. It is important to mention that, the preformation of imine from aldehyde and ammonium hydroxide is needed to get high yield which normally requires 30 minutes to 1 hour preincubation. The slow addition of 3-hydroxypivalaldehyde over 30 min also helped to get a clean reaction. After the addition of isocyanide and TMSN₃, the reaction completes within 2–4 hours.

Further, we screened different isocyanides. Aliphatic isocyanides like tert-octyl isocyanide and cyclohexyl isocyanide worked well (Table 2, entries 3 and 9). Aromatic isocyanides like benzyl and phenylethyl isocyanide with different aldehydes, product yields were good. The glycine isocyanide provided the excellent yield of 83% (Table 2, entry 11). The functional group protected isocyanide, diethoxy-acetaldehyde was also compatible in this reaction, which is interesting for further postmodification condensation or for unions with other MCR (Table 2, entry 6). Also, a tolerance of a 2-bromo benzyl isocyanide is interesting for potential postreaction (Table 2, entry 4).

In all examples a higher diastereoselectivity was observed. Aliphatic, aromatic aldehydes and also all isocyanides show more than 90 : 10 diastereoselectivity. However with benzyl isocyanide and 2-bromo benzylisocyanides low diastereoselectivity was observed.

The structures have been confirmed by NMR, MS (low and high resolution) and also by X-ray crystallography (Fig. 2).

**Proposed mechanism**

Based on the previous reports we proposed the following mechanism and which could also explain the high diastereoselectivity of this reaction. In this reaction, first aldehyde, ammonia and 3-hydroxypivalaldehyde react together to form the asymmetrically substituted Asinger reaction product, 5,6-dihydro-2H-1,3-oxazines. With the reference of reported articles and study we assume that out of the two possible half-chair conformations with minimal energy I and II, the energetically preferred half-chair conformation conformer I is strongly favoured. As the strong steric interactions between one of the methylene protons in 6-position and substitution on the position 2 unfavoured the conformer II. However, in conformer I this steric repulsion is reduced by position 6 (Scheme 1).

Next, as per previously published research, isocyanide will preferentially attack axially on the six membered, 5,6-dihydro-2H-1,3-oxazines to reduce the steric stain to form the intermediate III. Followed by azide attack on this intermediate III formed the final product in high diastereoselectivity as per above mentioned reasons like preferable conformers of 5,6-dihydro-2H-1,3-oxazines and preferred axial attack of isocyanides.

**Conclusions**

In conclusion, we have developed a diastereoselective one-pot five component reaction for the oxazinane-tetrazoles synthesis. This sonic-assisted, novel, and general reaction has many advances, such as high time efficiency, catalyst-free, diverse scope, and excellent diastereoselectivity.
Moreover, due to diverse substrate compatibility, this reaction has a significant potential for postcondensation reactions to get more complex and diverse oxazine-tetrazole structures. Studies towards this area are in progress and will be reported in due course.

**Conflicts of interest**

There are no conflicts to declare.

**Acknowledgements**

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**Notes and references**


