

Solid Phase Synthesis of (Benzannelated) Six-Membered Heterocycles via Cyclative Cleavage of Resin-Bound Pseudo-Oxazolones

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Supporting Information



ABSTRACT: A solid supported procedure for the synthesis of benzoxazinones, dihydropyrazinones, quinoxalinones, and dihydrooxazinones using immobilized oxazolones in combination with difunctional nucleophiles as cleavage agent is presented. The scope of the novel method has been demonstrated through subsequent modification of the parent oxazolone scaffold on solid supports using conversions with electrophiles or CuAAC reactions to give functionalized pyrazin-2-ones. The described method allows the synthesis of the target heterocycles in good yields via three to five steps on solid phases with only one chromatographic purification step.

xazol-5-ones are well-known heterocycles with manifold citations in the chemical literature as they occur as parts of natural products, pharmaceuticals, and intermediates in chemical reactions.¹ The conversion of the oxazol-5-one core has been investigated only in very few studies even though the high reactivity of the 5-membered heterocycle in the presence of nucleophiles and the good availability of those compounds allows diverse transformations. For example, ring opening reactions to give amino acids,^{2a} N-arylpyruvamides,^{2b} and α keto carbonyls^{2b,c} have been published. In addition, it has been shown for a few examples that the reaction of 2-(trifluoromethyl)-5(2H)-oxazolones or 2,2-bis(trifluoromethyl)-5-(2H)oxazolones as activated starting materials with difunctional nucleophiles can be used for the synthesis of heterocyclic compounds.³ The products of such reactions are interesting targets since quinoxalines and their derivatives the quinoxalin-2ones and dihydropyrazin-2-ones are prominent in synthetic chemistry^{4,5} and possess a wide range of biological activities (Figure 1).⁶ They are known as compounds with antimicrobial,⁷ anti-inflammatory,⁸ and antiviral⁹ effects, they have been shown to act as enzyme inhibitors¹⁰ and are potent candidates for antitumor therapeutics.¹¹ Until now, the condensation of oxazolones with 1,2-diaminobenzenes to quinoxalinones remains the unique application of this strategy as source for chemical diversity. Other compound classes, like, e.g. benzoxazin-2-ones or dihydrooxazin-2-ones, have not been gained in a similar manner although they are well-known as building blocks in



Figure 1. Biologically active molecules containing a dihydropyrazinone (A), quinoxaline (B), or benzoxazin-2-one moiety (C).

organic chemistry and show potential in affecting biological model systems.¹²

Our group has recently identified the oxazolone core as intermediate for the generation of many interesting heterocycles including quinoxalinones and benzoxazinones. In contrast to former well-known approaches toward the synthesis of those heterocycles,¹³ we were interested in the potential of oxazolones as solid supported building blocks that enable the formation of heterocycles in a combinatorial manner. According to a previously published protocol,² a set of five different 4substituted 2-trifluoromethyl oxazolones 2a-e was synthesized in good purity and yield. The attachment of the oxazolones to the

Received: June 3, 2016

solid supported material was achieved via installation of an acrylic acid linker on Merrifield resin and followed by Michael addition of the oxazolone in 2-position (Scheme 1).^{2a} Independent of the



^{*a*}Conditions: **2** (3–4 equiv), NEt₃, CH₂Cl₂, rt, 16 h. *Use of DMAP as base.

calculated loadings of the obtained resins 3a-e, which correspond to almost quantitative conversion for all of the immobilization experiments (detailed calculation given in Supporting Information), we observed that the oxazolone 2e should be purified via chromatography to reach high purity of the cleaved compounds in the end (see Tables 1 and 2).

The resins 3a-e were then used for the formation of quinoxalinones, pyrazin-2-ones, benzoxazoles, and dihydrooxazinones. We were pleased to observe that the literature procedure using the activated 2,2-bis- or 2-mono(trifluoromethyl)-5-oxazolones as starting material³ could be transferred successfully to a solid supported procedure. Thus, when the immobilized oxazoles 3b-d were reacted with aromatic diamines 4a and 4b the desired quinoxalinones 5 could be obtained in 44– 84% overall yield (linker attachment, oxazolone immobilization, and cyclative cleavage, Scheme 2). Additionally it was shown by one selected example that the procedure can be adapted successfully to the formation of pyridopyrazin-2-ones, as, e.g., Scc.

These results show that the solid supported procedure (Scheme 2) is as efficient as the known alternatives in solution with yields of 66-86% for the reactions of phenyl-, isopropyl, benzyl-, and methyl-substituted 2,2-bis(trifluoromethyl)-5-ox-azolidinones with 1,2-diaminobenzene.³ Encouraged by these

Scheme 2. Cleavage of Immobilized Oxazolones 3b-d Giving Quinoxalin-2-ones 5 (Yield Calculated over 3 Steps)^{*a*}



^{*a*}Conditions: 4 (3 equiv), methanol, 80 °C. ^{*b*}Mixture of isomers. ^{*c*}Reaction for 48 h. ^{*d*}Reaction for 20 d. ^{*e*}Conditions: 1.2 equiv of 4c and 0.3 equiv NEt₃₁ 13 d. ^{*f*}Reaction for 16 h. results, we extended the protocol to a conversion of the resins **3** with aliphatic 1,2-diamines. As far as we know, similar transformations are not known. Resins **3a**–**e** were reacted with different aliphatic nucleophiles, namely, the three diamines (1R,2R)-(-)-1,2-diaminocyclohexane (**4d**), 1,2-diaminoethane (**4e**), and propane-1,2-diamine (**4f**) for 16 h in methanol at 80 °C. The desired dihydropyrazin-2-ones **5** could be obtained mostly in good to excellent yields depending on the nature of the immobilized oxazolone. In only three cases (**5ad**, **5dd**, **5ed**) moderate yields (**51**–**57**%) were obtained (Table 1). In contrast





"Yield calculated over 3 steps. Conditions: 4 (3 equiv), methanol, 80 $^\circ$ C, 16 h. ^bProduct was obtained as a mixture of isomers.

to the condensations of (het)aromatic 1,2-diamines, which required up to 20 days to reach full conversion, condensations of aliphatic 1,2-diamines were completed within 16 h.

A further extension of the scope of the protocol was achieved by the reaction of resins 3a-e with several 2-amino-phenols. The average yield of the isolated benzoxazolones were lower in comparison to the results obtained via cleavage with 1,2diaminobenzenes (up to 85% yield calculated for three steps) (Table 2). The yield of the reaction depends on both, the

Table 2. Cleavage of Immobilized Oxazolones 3a-e Giving Benzoxazin-2-ones 7



^aYield calculated over 3 steps. Conditions: **6** (3 equiv), methanol, 80 $^{\circ}$ C, 16 h.

aminophenol and the immobilized oxazolone. Good results have been obtained for all compounds, which have been cleaved from the hydroxyphenylglycin-derived oxazolone resin **3b**, while benzoxazolone forming reactions with the phenylglycin-derived oxazolone resin **3c** or alanine-derived oxazolone resin **3a** resulted in general lower yields (entries 1, 2, and 8, Table 2).

To prove the applicability of the method to the preparation of dihydro-1,4-oxazin-2-ones, we selected the hydroxyphenylglycine-derived oxazolone resin **3b** for a conversion with commercially available 2-amino-3-methylbutan-1-ol (**6f**). As shown for the transformations of the parent *o*-aminophenols in Table 2, the reaction with an aliphatic *N*,*O*-nucleophile was successful as well. The target compound 3-(4-hydroxyphenyl)-5-isopropyl-5,6-dihydro-2*H*-1,4-oxazin-2-one (7**bf**, Scheme 3) was obtained in 67% yield (calculated over three steps).

As postcleavage derivatization suffers from the general disadvantages of combinatorial reactions in solution (e.g.,





workup and chromatography after each step), we were interested in further modifying of the immobilized oxazolone scaffold on solid supports. The hydroxyphenylglycin-derived oxazolone resin **3b**, offering a hydroxyl functionality suitable for derivation with alkyl bromides 8, was selected. The reactions with tert-butyl bromoacetic acid (8a) and propargyl bromide (8b) where performed using literature known procedures. The obtained intermediates, resins 9a and 9b, have been cleaved with (1R,2R)-(-)-1,2-diaminocyclohexane (4d) to give the modified guinoxalin-2-ones 11a and 11b in 29% and 36% yield calculated over 4 steps. The scope for further derivatization was shown by reacting the immobilized alkyne derivative 9b with benzylazide as a common model system for Cu-catalyzed alkyne azide cycloadditions (CuAAC). In accordance with the assumed quantitative conversion of terminal alkynes with benzyl azide in the so-called Click reaction, the obtained yield of the cleaved triazole-modified pyrazin-2-one 11c is comparable to the nonmodified precursor 11b (36% yield calculated over 5 steps, Scheme 4).

The herein described procedure allows the synthesis of 6membered heterocycles via a solid-supported procedure using immobilized oxazoles in combination with difunctional







^aReagents: **8a**, ^tBu-bromoacetate; **8b**, propargyl bromide. Conditions: A: **8a**, K_2CO_3 , DMF, 60 °C, 18 h. B: **8b**, K_2CO_3 , DMF, rt, 15 h. C: CuI, sodium ascorbate, benzyl azide, CH₂Cl₂, rt, 2 h. D: (1*R*,2*R*)-(-)-1,2-diaminocyclohexane (**4d**), methanol, 80 °C, 16 h. nucleophiles as cleavage agent. The new procedure has been used for the synthesis of substituted dihydropyrazin-2-ones and quinoxalin-2-ones as well as for the formation of two benzoxazin-2-ones and one dihydro-1,4-oxazin-2-one giving a set of 30 diverse heterocycles of which 20 are described for the first time. The scope of the novel method has been further demonstrated through subsequent modification of the oxazole scaffold on solid supports using conversion with electrophiles and CuAAC reactions giving functionalized pyrazin-2-ones **11a**– **11c**.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01609.

Experimental procedures and spectra (PDF)

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Notes

The authors declare no competing financial interest.

Supplementary crystallographic data for this paper (crystallographic data for compounds 7ba (CCDC-1442205) and 7be (CCDC-1442198)) can be obtained from the CCDC via www. ccdc.cam.ac.uk/data request/cif.

ACKNOWLEDGMENTS

This work was supported by the Helmholtz program Biointerfaces in Technology and Medicine (BIFTM). Research data have been stored and registered with support of the DFGfunded project Chemotion.

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