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

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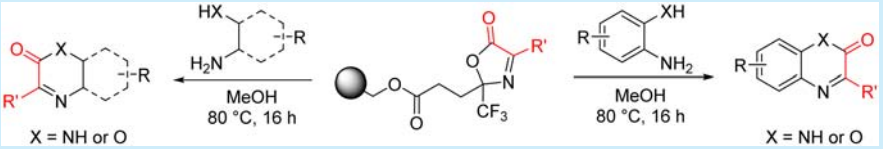
Supporting Information



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.

Oxazol-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(2*H*)-oxazolones or 2,2-bis(trifluoromethyl)-5-(2*H*)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-2-ones 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 antiviral[9] effects, they have been shown to act as enzyme inhibitors[10] 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 organic chemistry and show potential in affecting biological model systems.[12]

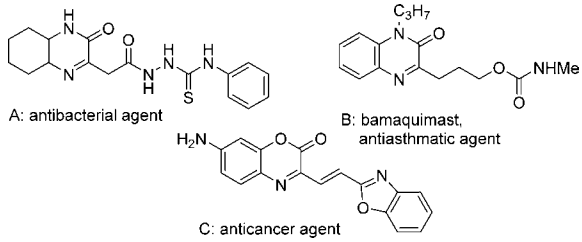


Figure 1. Biologically active molecules containing a dihydropyrazinone (A), quinoxaline (B), or benzoxazin-2-one moiety (C).

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 4-substituted 2-trifluoromethyl oxazolones **2a**–**e** was synthesized in good purity and yield. The attachment of the oxazolones to the

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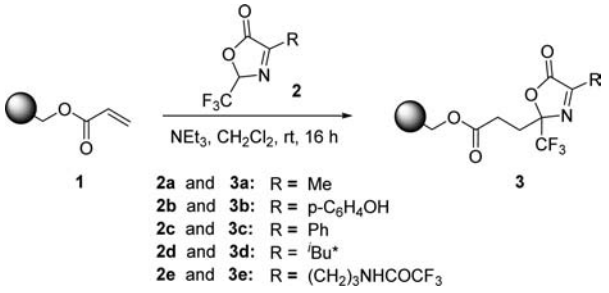
solid supported material was achieved via installation of an acrylic acid linker on Merrifield resin and followed by Michael addition of the oxazolone in 2-position (Scheme 1).[2a] Independent of the

Scheme 1. Synthesis of Oxazolone-Modified Resins 3a−e[a]



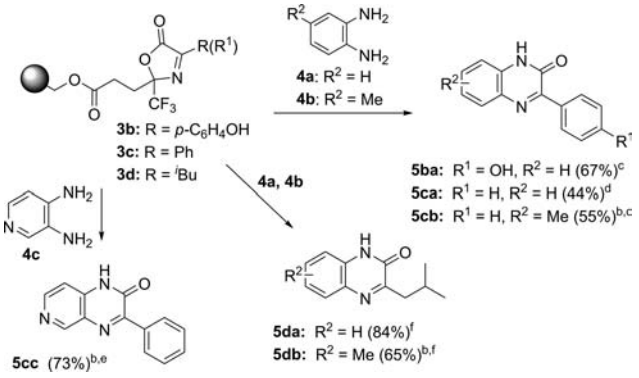
[a]Conditions: **2** (3−4 equiv), NEt_3, CH_2Cl_2, rt, 16 h. *Use of DMAP as base.

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 dihydroxazinones. We were pleased to observe that the literature procedure using the activated 2,2-bis- or 2-mono(trifluoromethyl)-5-oxazolones as starting material[3] 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., **5cc**.

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-oxazolidinones with 1,2-diaminobenzene.[3] Encouraged by these

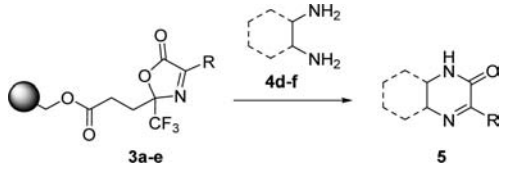
Scheme 2. Cleavage of Immobilized Oxazolones 3b−d Giving Quinoxalin-2-ones 5 (Yield Calculated over 3 Steps)[a]



[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 NEt_3, 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 (1*R*,2*R*)-(−)-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

Table 1. Cleavage of Oxazolones 3a−e with Aliphatic 1,2-Diamines Giving Dihydropyrazine-2-ones 5



entry	resin	nucleophile	pyrazine-2-one	yield (%)[a]
1	**3a**	**4d**	**5ad**	51
3	**3b**	**4d**	**5bd**: R^2 = OH	90
2	**3c**	**4d**	**5cd**: R^2 = H	86
4	**3d**	**4d**	**5dd**	57
5	**3e**	**4d**	**5ed**	54
6	**3d**	**4e**	**5de**	quant
7	**3b**	**4e**: R^1 = H	**5be**: R^1 = H	86
8	**3b**	**4f**: R^1 = Me	**5bf**: R^1 = Me	89[b]
9	**3c**	**4e**: R^1 = H	**5ce**: R^1 = H	quant
10	**3c**	**4f**: R^1 = Me	**5cf**: R^1 = Me	84[b]

[a]Yield calculated over 3 steps. Conditions: **4** (3 equiv), methanol, 80 °C, 16 h. [b]Product 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

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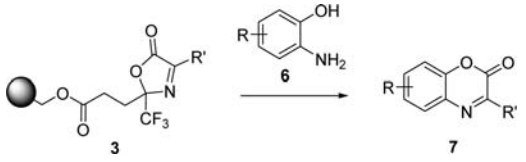
comparison to the results obtained via cleavage with 1,2-diaminobenzenes (up to 85% yield calculated for three steps) (Table 2). The yield of the reaction depends on both, the

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



entry	resin	nucleophile	benzoxazin-2-one	yield (%)[a]
1	3a	6a: R = H	7aa: R = H	34
2	3a	6b: R = ^{t}Bu	7ab: R = ^{t}Bu	53
3	3b	6a: R = H	7ba: R = H	62
4	3b	6b: R = ^{t}Bu	7bb: R = ^{t}Bu	85
5	3b	6c: R = Cl	7bc: R = Cl	63
6	3b	6d: R = Ph	7bd: R = Ph	50
7	3b	6e	7be	68
8	3c	6b	7cb	26
9	3d	6a: R = H	7da: R = H	37
10	3d	6b: R = ^{t}Bu	7db: R = ^{t}Bu	38
11	3e	6a: R = H	7ea: R = H	47
12	3e	6b: R = ^{t}Bu	7eb: R = ^{t}Bu	65
13	3e	6c: R = Cl	7ec: R = Cl	42

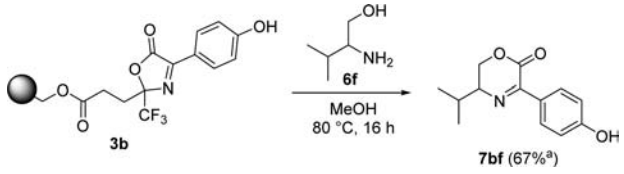
[a]Yield calculated over 3 steps. Conditions: **6** (3 equiv), methanol, 80 °C, 16 h.

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 (**7bf**, 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.,

Scheme 3. Cleavage of Immobilized Oxazolone 3b Giving Dihydro-1,4-oxazin-2-one 7bf

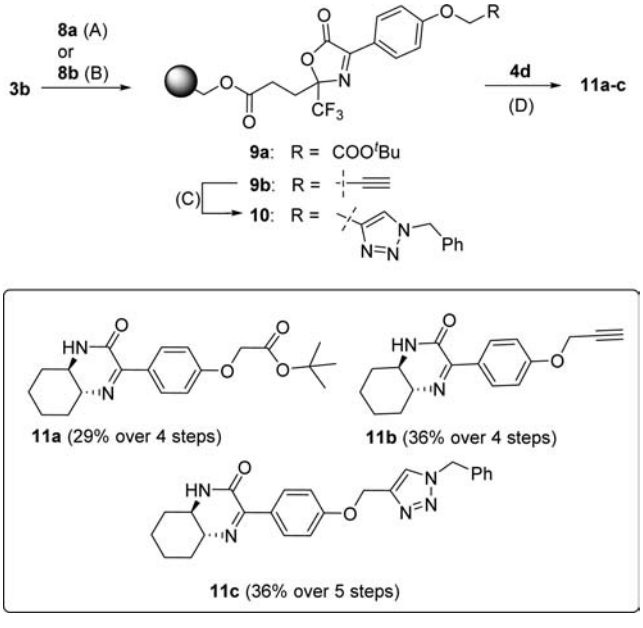


[a]Yield calculated over 3 steps.

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 (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (**4d**) to give the modified quinoxalin-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 6-membered heterocycles via a solid-supported procedure using immobilized oxazoles in combination with difunctional

Scheme 4. On-Bead Functionalization of Immobilized Oxazolones and Cleavage[a]



[a]Reagents: **8a**, ^{t}Bu-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, CH_2Cl_2, rt, 2 h. D: (1*R*,2*R*)-(−)-1,2-diaminocyclohexane (**4d**), methanol, 80 °C, 16 h.

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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.

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