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Three-Component Reaction toward Polyannulated Quinazolinones, Benzoxazinones, and Benzothiazinones

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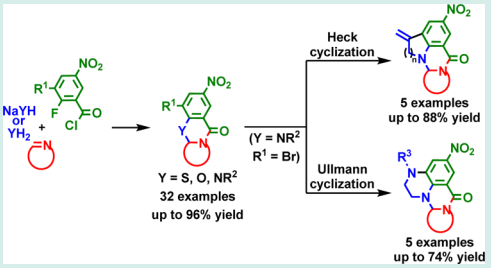
Supporting Information

ABSTRACT: An efficient conversion of readily accessible cyclic imines with acid chlorides, that are able to take part in nucleophilic aromatic substitution (S_NAr) reactions is realized in a new three-component, one-pot reaction, giving at least tricyclic annulated quinazolinones, benzoxazinones, and benzothiazinones as a result of the employed nitrogen, oxygen, or sulfur nucleophiles, respectively. Especially in the case of quinazolinones, this convenient strategy enables the access to heterocycles of heightened diversity, which offer the development of efficient derivatizations of the elaborated heterocyclic scaffolds. In a subsequent Heck or Ullmann cyclization, further annulations to the mentioned quinazolinones can be carried out.



KEYWORDS: *multicomponent reaction, heterocycles, polyannulation, cyclic imines, Heck, Ullmann*

INTRODUCTION

Multicomponent reactions (MCRs) have become a helpful toolkit in organic synthesis since Laurent and Gerhardt first described the formation of cyanohydrin imines in 1838.[1] Nowadays, MCRs are omnipresent in organic synthesis[2] and can be found in natural product synthesis[3] as well as combinatorial[4] or polymer chemistry.[5] Multiple interesting heterocyclic motifs can be realized using MCRs. One of them is 3-thiazolidine, which is a five-membered ring that contains a sulfur atom and a nitrogen atom in its ring system. The structure of 3-thiazolidine and its oxygen analog 3-oxazolidine can be found in natural as well as in pharmaceutical products.[6,7] This scaffold is easily accessible by addition reactions at the reactive imine double bond of 2,5-dihydro-1,3-thiazole (3-thiazoline) and 2,5-dihydro-1,3-oxazole (3-oxazoline).[8] Hence, we would like to describe the synthesis of six-membered quinazolinones, benzothiazinones, and benzoxazinones by the conversion of 3-thiazolines, 3-oxazolines, and 1,4-benzothiazines, respectively. These classes of heterocyclic compounds show interesting characteristics as biologically active substances. Benzothiazinones, for example, are known anti-inflammatory agents,[9] sodium channel blockers,[10] and antimycobacterial agents,[11] whereas benzoxazinones have been described as modulators of neurotransmitters in the human brain.[12] Quinazolinones are considered as a frequently encountered heterocyclic structure in medicinal chemistry because of their broad bandwidth of biological properties. Besides anti-inflammatory, antihypertensive, and anticonvulsant activities, quinazolinones have shown anti-HIV, anticancer, and anti-mutagenic activities, to name but a few.[13] Furthermore, quinazolinones are a main component in numerous bioactive natural alkaloids.[14] On the basis of the many-faceted applications, there is an unexpectedly high number of synthetic routes to realize the quinazolinone structure. Predominantly, quinazolinones synthesis developments have only been enabled in recent years with the emergence of catalytic methodologies, microwave-enhanced processes, and synthesis through combinatorial chemistry.[15]

To develop a synthesis route that combines the heterocyclic structure of 3-thiazolidines, 3-oxazolidines, and benzothiazines each with six-membered quinazolinones, benzoxazinones, and benzothiazinones, respectively, our group published a two-component reaction in 2010.[16] In a continuation of these efforts, we next focused on a convenient reaction that allows the use of three components, leading to products with an increased diversity in the case of quinazolinones. Notably, in this connection, a wide range of amines should be tolerated with the perspective of further derivatizations.

Thus, we are initiating our investigations by preparing 3-thiazolines, 3-oxazolines, and 1,4-benzothiazines. However, the five-membered cyclic imines can be obtained by a modified Asinger four-component reaction (A-4CR).[17] On the basis of the obtained imines, we envisioned that a reaction with an eligible acid chloride and the respective nitrogen, oxygen, or sulfur nucleophiles could lead to the desired products.

RESULTS AND DISCUSSION

The intended synthetic route required the synthesis of heterocyclic imines bearing the scaffolds of thiazolidine, oxazolidine, and benzothiazine. The monocyclic five-membered thiazolidine and oxazolidine structures were converted from the 3-thiazoline **1**{*1*−*3*} and 3-oxazoline **1**{*4*−*5*}, for instance. Both

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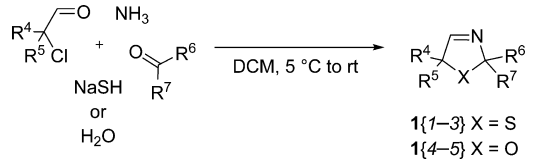
Scheme 1. Synthesis of 3-Thiazolines 1{*1*−*3*} and 3-Oxazolines 1{*4*−*5*}



Scheme 2. Synthesis of 1,4-Benzothiazines 1{*6*−*7*}

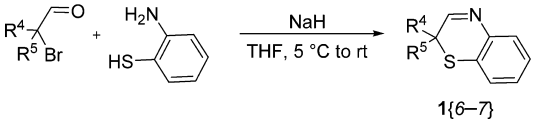
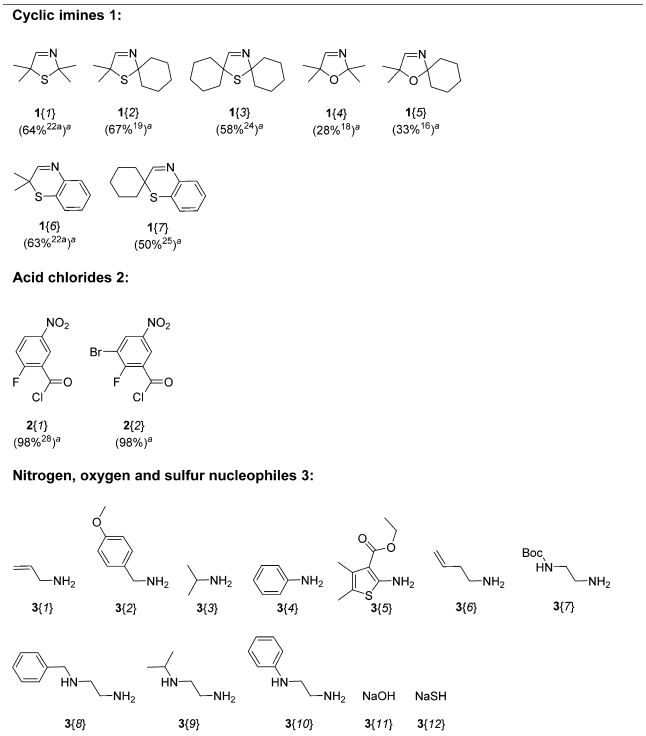


Table 1. Diversity Elements Used for Library Synthesis



[a]Isolated yield.

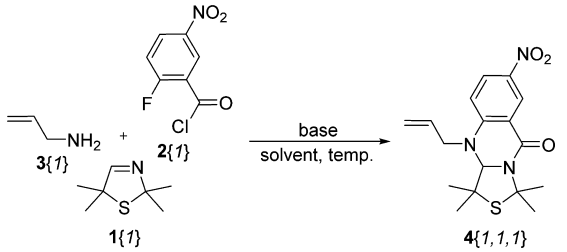
substance classes were prepared by a modified A-4CR.[17,18] This MCR uses an α-halogen aldehyde, a carbonyl compound (aldehyde or ketone), ammonia, and sodium hydrosulfide or, in the case of 3-oxazolines, water (Scheme 1). Owing to the wide scope of useable α-halogen aldehydes and carbonyl compounds, this MCR is well-known for its facile preparation of manifold cyclic imines.[19]

By means of the modified A-4CR, three known 3-thiazolines and two known 3-oxazolines were prepared in moderate-to-good yields of up to 67%.

The annulated six-membered 1,4-benzothiazines 1{*6*−*7*} were synthesized by a protocol using an α-bromo aldehyde, 2-aminothiophenol, and sodium hydride in anhydrous THF (Scheme 2).[20]

All three types of cyclic imines 1{*1*−*7*} are well-known for their reactivity. The reactive imine double bond enables multiple conversions to different types of amides[18,21] and polycyclic[16,22] structures.[23]

Table 2. Reaction Optimization.[a]



entry	solvent	base	temperature	yield[b] (%)
1	DMF	Et_3N	rt	31
2	DMF	K_2CO_3	rt	trace
3	DMF	Cs_2CO_3	rt	trace
4	DMF	*t*-BuOK	rt	0
5	DMF	Et_3N	100 °C	36
6	**DCM**	**Et_3N**	**rt**	**69**/42[c]
7	DCM	K_2CO_3	rt	16
8	DCM	Cs_2CO_3	rt	15
9	DCM	*t*-BuOK	rt	0
10	THF	Et_3N	rt	trace
11	THF	Et_3N	65 °C	trace
13	$CHCl_3$	Et_3N	rt	55
14	$CHCl_3$	Et_3N	61 °C	63

[a]All reactions were performed under an argon atmosphere using 0.50 mmol 1{*1*}, 0.55 mmol 2{*1*}, 0.65 mmol allylamine (3{*1*}), 1.25 mmol base in 4 mL solvent, followed by column chromatography on silica gel. [b]Isolated yield after column chromatography. [c]Et_3N was added to the reaction mixture 1 h after all of the other compounds were added.

Herein, we initially present the synthesis of tricyclic quinazolinones 4{*1,1,1*}−4{*1,2,10*}, a class of six-membered ring lactams with a secondary amine function in the γ position. An effective method, allowing the formation of an amide based on the reactive imine bond, is the addition of an acyl chloride.[26] To form the target quinazolinones 4{*1,1,1*}− 4{*1,2,10*} in a three-component, one-pot reaction, we were compelled to use an acyl chloride that enables nucleophilic aromatic substitution (S_NAr) by amines, thiols, or alcohols. A Communication from Tempest and Hulme's group reported the employment of a combination of the Ugi condensation with a post S_NAr cyclization based on 2-fluoro-5-nitrobenzoic acid.[27] The acid chloride formation of this commercially available compound using thionyl chloride easily provided a 98% yield (2{*1*}).[28] Furthermore, the unknown, 3-bromo-2-fluoro-5-nitrobenzoic acid, was synthesized by bromination via 1,3-dibromo-5,5-dimethylhydantoin in fuming sulfuric acid in very good yield (85%). The corresponding acid chloride 2{*2*} was also generated in excellent yield (98%) by means of the method mentioned above.[28]

The last of the three compounds needed for the reaction was a primary amine that could take part in a S_N and S_NAr reaction. We started our investigation with allylamine (3{*1*}), 2-fluoro-5-nitrobenzoyl chloride (2{*1*}), and cyclic imine 1{*1*} to establish optimal conditions for the conversion to quinazolinone 4{*1,1,1*} (Table 2).

Alcohols are nonqualified solvents for the planned synthesis. They are inappropriate because of their nucleophilic character and, therefore, they offer the possibility to take part in S_NAr reactions or conversions with acid chlorides.[29] In preliminary studies by our group, DCM was found to be the solvent of choice for a wide range of addition reactions involving the

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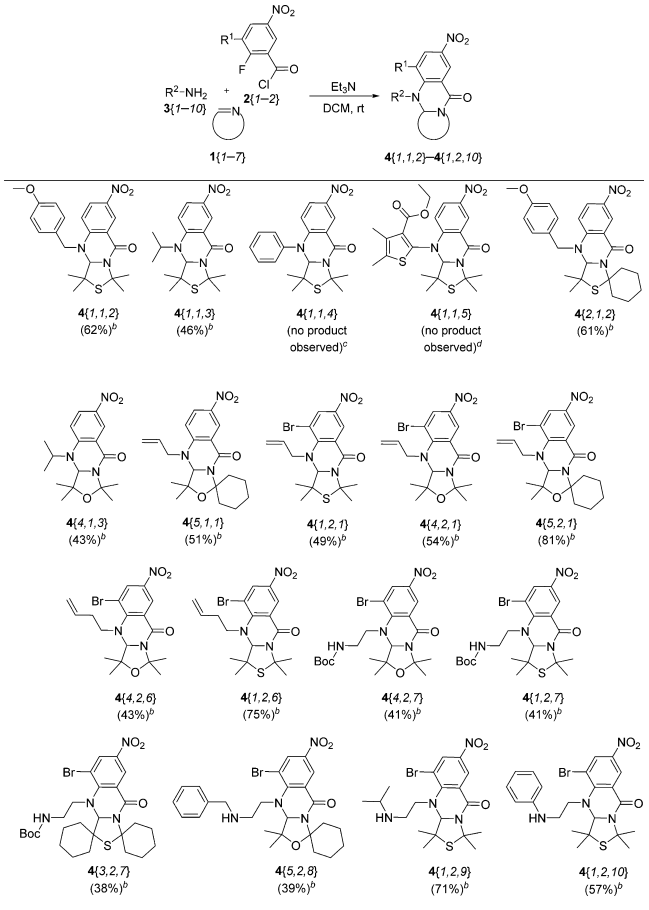
Table 3. Synthesis of Quinazolinones 4{*1,1,2*}−4{*1,2,10*} Using a Three-Component Reaction[a]



[a]The reaction was performed under an argon atmosphere with imine 1{*1*−*7*} (1.00 equiv), acyl chloride 2{*1*−*2*} (1.10 equiv), amine 3{*1*−*10*} (1.50 equiv), and Et_3N (2.50 equiv) in DCM at rt for 48 h. [b]Isolated yield after column chromatography. [c]α-Aminoamide (*RS*)-4-(phenyl)amino-3-(2-fluoro-5-nitrobenzoyl)-2,2,5,5-tetramethyl-1,3-thiazolidine (5{*1,1,4*}) was isolated as the product in 28% yield. [d]α-Aminoamide (*RS*)-4-(ethyl-4,5-dimethylthiophene-3-carboxylate)-amino-3-(2-fluoro-5-nitrobenzoyl)-2,2,5,5-tetramethyl-1,3-thiazolidine (5{*1,1,5*}) was isolated as the product in 32% yield.

conversion of acid chlorides to cyclic imines with a following nucleophilic substitution.[22a] In all cases, Et_3N was used to trap the liberated hydrogen chloride.[22a] In addition, S_NAr reactions could, for example, be performed using potassium carbonate or ps-morpholine in DMF.[27,29] To optimize the synthesis, we examined a series of solvents and bases that lead to the desired product 4{*1,1,1*}. First, we tested DMF and DCM. Looking at Table 2, it is evident that Et_3N was the most effective base in both cases (Table 2, entries 1, 5 and 6). The carbonate bases and potassium *tert*-butoxide did not lead to satisfactory yields (Table 2, entries 2−4 and 7−9). On the basis of these results, we examined THF and $CHCl_3$ exclusively in combination with Et_3N (Table 2, entries 10−14). THF turned out to be inappropriate even when the reaction temperature was increased (Table 2, entry 11). When $CHCl_3$ was used as the solvent, product 4{*1,1,1*} was obtained in 55% yield. Increasing the reaction temperature to 61 °C led to a yield of 63% (Table 2, entry 14). The highest yield of 69% was obtained when Et_3N in DCM was used at rt (Table 2, entry 6). It is also important to add Et_3N prior to the amine. A modified order led to an extenuated yield of 42% (Table 2, entry 6).

In order to explore the scope of the reaction under the optimized conditions, a number of primary amines 3{*1*−*10*} and cyclic imines 1{*1*−*7*} were investigated (Table 3).

However, with the exception of benzothiazines 1{*6*−*7*}, all of the 3-thiazolines 1{*1*−*3*} and 3-oxazolines 1{*4*−*5*} could take part in the reaction on which we are focusing. We first studied the reaction between different primary amines and the cyclic imine 1{*1*} and acid chloride 2{*1*}. Allylamine (3{*1*}) and 4-methoxybenzylamine (3{*2*}) were shown to be more reactive (giving 4{*1,1,1*}, 4{*1,1,2*}). The aliphatic amines seemed to react reluctantly. The isopropylamine derivative 4{*1,1,3*} was maintained in 46% yield. Even if other cyclic imines were used, the benzylic and allylic amines seemed to be more reactive than the aliphatic amines (4{*2,1,2*}−4{*5,1,1*}). With a view for further derivatization in a subsequent Heck cyclization reaction, we used the synthesized acid chloride 2{*2*}, different cyclic imines 1{*1*−*5*}, as well as allylamine (3{*1*}) or 3-butenylamine (3{*6*}) to form the quinazolinones 4{*1,2,1*}−4{*1,2,6*}. The structure of 4{*1,2,1*} was confirmed by X-ray diffraction analysis (see Figure S2 in the Supporting Information). The conversion of 3-oxazoline 1{*5*} with allylamine 3{*1*} and 2{*2*} to form the corresponding product 4{*5,2,1*} afforded the highest yield (81%). Furthermore, the utilization of monoprotected and mono-*N*-substituted diamines 3{*7*−*10*} was examined. Under the optimized conditions, all reactions involving diamines proceeded successfully to afford the corresponding quinazolinones 4{*4,2,7*}−4{*1,2,10*}. For instance, products 4{*4,2,7*}−4{*3,2,7*} based on mono-Boc-protected ethylendiamine 3{*7*} were obtained in yields from 38 to 41%. Surprisingly, the cyclic lactams 4{*5,2,8*}−4{*1,2,10*} obtained using mono-*N*-substituted diamines 3{*8*−*10*} could be generated as analogs (4{*5,2,8*}, 39%) and with higher yields (4{*1,2,9*}, 71% and 4{*1,2,10*}, 57%).

But not all amines led to the desired quinazolinones 4{*1,1,1*}−4{*1,2,10*}. Instead of the targeted derivatives 4{*1,1,4*} and 4{*1,1,5*}, α-aminoamides 5{*1,1,4*} and the respective 5{*1,1,5*} were formed. This is presumably the result of steric interactions that preclude nucleophilic attack. Therefore, it is necessary to use amines with at least the α-methine group. In other circumstances, the steric features of the amine prevent a successful outcome. In combination with a mechanistic NMR study (see Figure S1 in the Supporting Information), the isolated compounds 5{*1,1,4*} and 5{*1,1,5*} underline the intermediate formation of an α-substituted amide. Until then ring closing takes place via the S_NAr reaction.

As outlined in Scheme 3, cyclic imine 1{*1*−*5*} first reacts in an acyl chloride addition to generate α-chloroamide **A**, which is in equilibrium with the *N*-acyliminium ion **B**.[26a,b] The equilibrium position lies toward the covalent structure **A**.[30] Through nucleophilic substitution with an amine, α-aminoamide **5** is formed. With the exception of isolated 5{*1,1,4*} and 5{*1,1,5*}, all α-aminoamides directly undergo a S_NAr to form tricyclic quinazolinones **4**.

To underline the diversity of the reaction products, we examined the synthesis of the six-membered oxa and thia analogs. Benzoxazinones 6{*2,1,11*}−6{*6,1,11*} and benzothiazinones 7{*3,1,12*}−7{*6,1,12*} were prepared by a similar way, using sodium hydroxide 3{*11*} and sodium hydrosulfide 3{*12*}, respectively. Owing to the solubility of the sodium salts, the solvent was changed to DMF. A comparison of the yields of the

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Scheme 3. Mechanism for Quinazolinone Formation

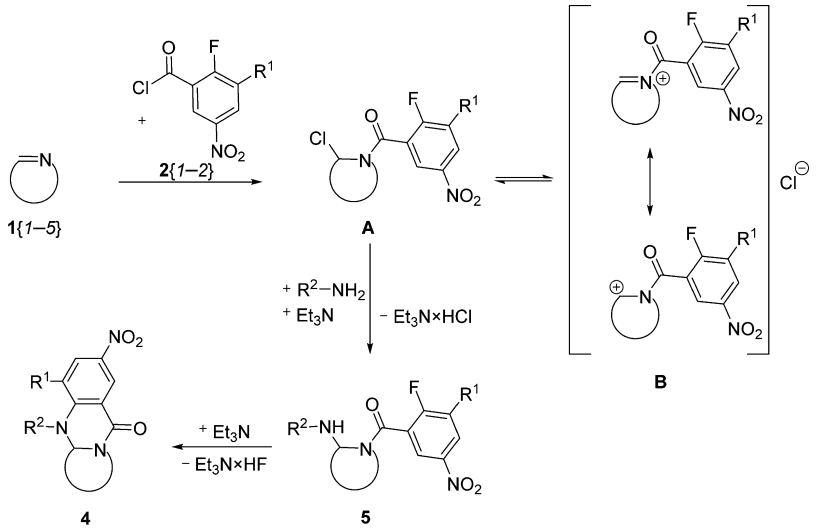
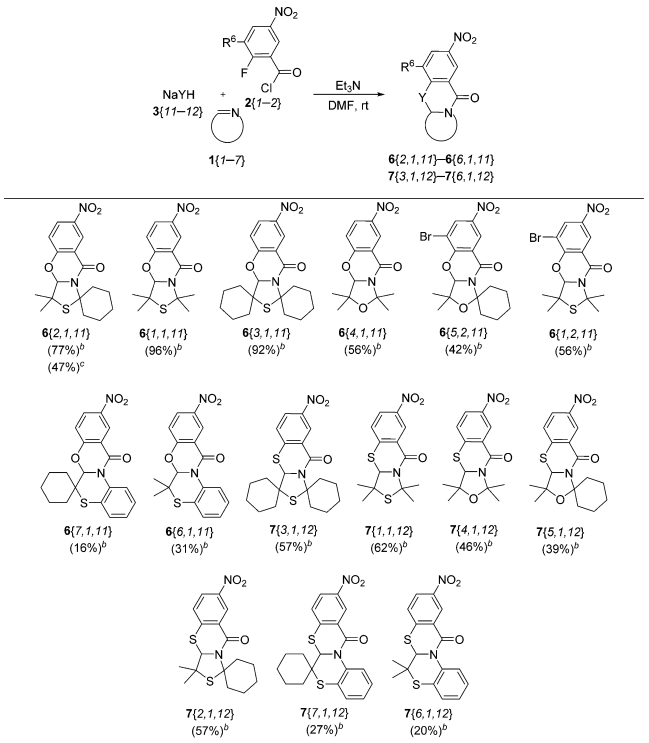


Table 4. Synthesis of Benzoxazinones 6{2,1,11}−6{6,1,11} and Benzothiazinones 7{3,1,12}−7{6,1,12} Using a Three-Component Reaction[a]

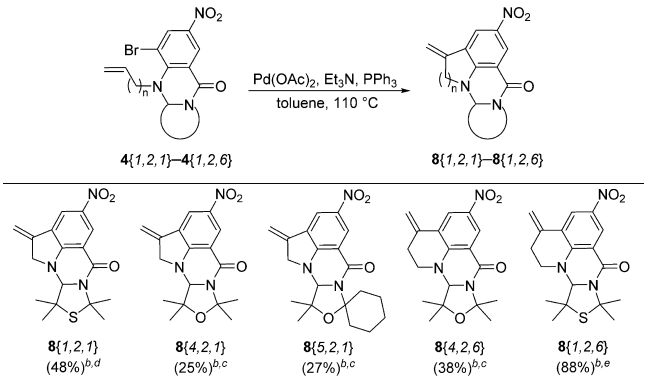


[a]The reaction was performed under an argon atmosphere with imine **1**{*1*−*7*} (1.00 equiv), acyl chloride **2**{*1*−*2*} (1.10 equiv), sodium salt **3**{*11*−*12*} (1.50 equiv), and Et_3N (2.50 equiv) in DMF at rt for 48 h. [b]Isolated yield after column chromatography. [c]The reaction was performed in DCM.

reaction, affording benzoxazinone **6**{*2,1,11*} in DMF (77%) and DCM (47%), approved this change to be reasonable.

The best results for the formation of both classes are based on imine **1**{*1*} and acid chloride **2**{*1*} combined with the respective sodium salt **3**{*11*−*12*}. Benzoxazinone **6**{*1,1,11*} was obtained in 96% yield and benzothiazinone **7**{*1,1,12*} in 62% yield. It is evident that the average yields of benzoxazinones

Table 5. Synthesis of Indolines 8{1,2,1}−8{5,2,1} and Tetrahydroquinolines 8{4,2,6}−8{1,2,6} through a Pd-Catalyzed Heck Cyclization[a]



[a]The reaction was performed under an argon atmosphere with quinazolinone **4**{*1,2,1*}−**4**{*1,2,6*} (1.00 equiv), $Pd(OAc)_2$ (0.15 equiv), and triphenylphosphine (0.30 equiv) in a 3.90 M solution of Et_3N in toluene at 110 °C. [b]Isolated yield after column chromatography. [c]The reaction mixture was heated for 10 h. [d]The reaction mixture was heated for 20 h. [e]The reaction mixture was heated for 30 h.

6{*2,1,11*}−**6**{*6,1,11*} (16−96%) were higher than the yields of benzothiazinones **7**{*3,1,12*}−**7**{*6,1,12*} (20−62%). For example, a comparison of the yields of the cyclic oxavalerolactam **6**{*3,1,11*} (92%) with the corresponding thiavalerolactam **7**{*3,1,12*} (57%) distinguishes this observation. This may be reasoned with a more ideal conformation of the oxo derivative. It is worth mentioning that benzannulated imines **1**{*6*−*7*} could successfully be converted into the desired lactams. Benzoxazinones **6**{*7,1,11*} and **6**{*6,1,11*}, which are predicated on 1,4-benzothiazines, were obtained in 16% and 31% yields. The analog thiavalerolactams **7**{*7,1,12*} and **7**{*6,1,12*} could be isolated in 27 and 20% yields, respectively. The structures of tricyclic lactams **6**{*1,1,11*} and **7**{*4,1,12*}, such as the tetracyclic derivative **6**{*7,1,11*}, were verified by X-ray diffraction analysis (see Figures S3−5 in the Supporting Information).

On the basis of the described results concerning quinazolinones **4**{*1,1,1*}−**4**{*1,2,10*} and our ongoing interest in the construction of polyannulated heterocycles, we designed

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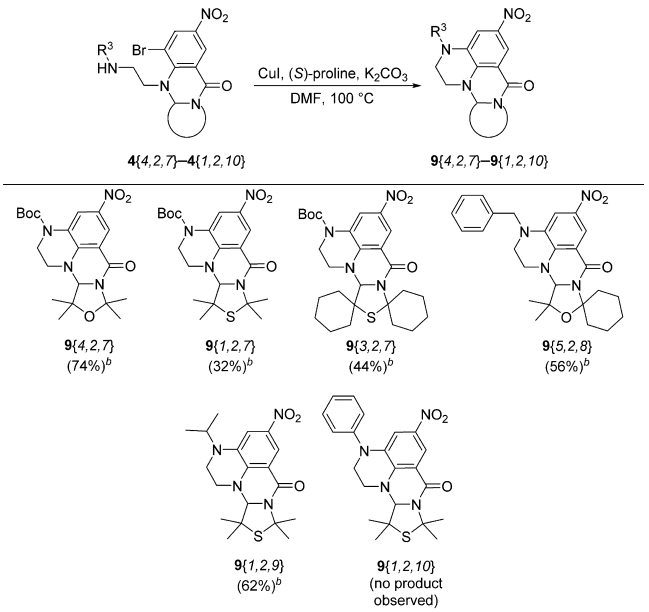
Table 6. Synthesis of Tetrahydroquinoxalines 9{4,2,7}−9{1,2,10} through the Cu-Catalyzed Ullmann Cyclization[a]



[a]The reaction was performed under an argon atmosphere with quinazolinone 4{4,2,7}−4{1,2,10} (1.00 equiv), CuI (0.10 equiv), (*S*)-proline (0.20 equiv), and K_2CO_3 (2.00 equiv) in DMF at 100 °C. [b]Isolated yield after column chromatography.

derivatives 4{1,2,1}−4{1,2,6} for the preparation of annulated tetracyclic indolines 8{1,2,1}−8{5,2,1} and tetrahydroquinolines 8{4,2,6}−8{1,2,6}. Compounds 4{1,2,1}−4{1,2,6} include an aromatic halogen group and a terminal olefin, which are essential components for an intramolecular Pd-catalyzed Heck cyclization. After adaptation of the known protocol for Heck cyclization reactions, the procedure was performed using palladium(II) acetate, Et_3N, and triphenylphosphine in toluene.[31]

As shown in Table 5, all reactions proceeded successfully to form the annulated tetracycles 8{1,2,1}−8{1,2,6} in moderate-to-very good yields (up to 88%). The reactions to obtain the desired products 8{4,2,1}−8{4,2,6} were carried out by heating the reaction mixture for 10 h. This induced yields from 25 to 38%. In the case of compound 8{1,2,1}, heating the reaction mixture for 20 h increased the yield to 48%. However, compound 8{1,2,6} could be obtained in 88% yield in a reaction time of 30 h. In all cases, only the condensation product with an exocyclic alkene could be isolated. This could be confirmed through X-ray diffraction analysis of lactam 8{4,2,6} (see Figure S6 in the Supporting Information).

Furthermore, we focused on the annulation of another class of heterocycle, namely, tetrahydroquinoxalinones 9{4,2,7}−9{1,2,10}. Starting from quinazolinones 4{4,2,7}−4{1,2,10}, the required six-membered cycles 9{4,2,7}−9{1,2,10} could be prepared by means of a Cu-mediated Ullmann reaction. Therefore, we adapted a protocol for the synthesis of 1,2-disubstituted benzimidazoles using copper(I) iodide, (*S*)-proline, and potassium carbonate in DMF at 100 °C.[32]

With the exception of the transformation of 4{1,2,10} to tetrahydroquinoxaline 9{1,2,10}, all reactions proceeded and successfully formed the desired six-membered products 9{4,2,7}−9{1,2,9}. As shown in Table 6, the Boc-protected secondary amines 9{4,2,7}−9{3,2,7} were synthesized in a 32−74% yield. In addition, *N*-benzyl-substituted cycle 9{5,2,8} and *N*-isopropyl substituted derivative 9{1,2,9} could be obtained in 56 and 62% yields, respectively. Moreover, the structure of 9{4,2,7} was established by single-crystal X-ray structure analysis (see Figure S7 in the Supporting Information).

In conclusion, we have developed a MCR including a metal-free aromatic substitution step that can be used toward obtaining at least tricyclic annulated quinazolinones, benzoxazinones, and benzothiazinones. The combination of this new MCR with A-4CR allows us to obtain the composition of complex heterocycles with a high diversity in a fast and simple manner. With respect to the diversity of the amine input, in the case of quinazolinone formation, a wide range of further postdiversification reactions on the scaffold are possible. The conversions in Heck and Ullmann reactions to annulated tetracyclic indolines, tetrahydroquinolines, and tetrahydroquinoxalines exemplify this emphatically. To sum up, we have gained facile access to polyannulated heterocycles with a number of pharmaceutically interesting scaffolds.

■ ASSOCIATED CONTENT

Supporting Information

Selected ^1H NMR spectra (stacked) for the synthesis of compound 4{1,1,1}, together with explanations of the mechanism, and experimental details and copies of ^1H and ^{13}C NMR spectra for all new compounds, plus the X-ray crystal data of compounds 4{1,2,1}, 6{1,1,11}, 6{7,1,11}, 7{4,1, 12}, 8{4,2,6}, and 9{4,2,7}. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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