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A facile synthesis of (*Z*)-1, 6-disubstituted-7*H*-benzo[*b*][1,5]diazonin-7-one derivatives via arylation-allylation-RCM pathway of anthranilamide and isatoic anhydride

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ABSTRACT

A facile and efficient method has been developed for the synthesis of (*Z*)-6-allyl-1-phenyl-1,2,5,6-tetrahydro-7*H*-benzo[*b*][1,5]diazonin-7-one and (*Z*)-1,6-diphenyl-1,2,5,6-tetrahydro-7*H*-benzo[*b*][1,5]-diazonin-7-one from anthranilamide via *N*-arylation/*N*-allylation and from isatoic anhydride via ring opening/*N*-arylation/*N*-allylation followed by ring closing metathesis using Grubbs-II catalyst as a key step. Grubbs-II catalyst was found to be superior over Grubbs-I catalyst in terms of reaction time and yield of the product, and the routes developed were suitable to synthesize benzo fused nine membered nitrogen heterocycles. The requirement of diallylated substrates with protected amine and amide nitrogen is suitable for RCM has been established for the synthesis of diazoninone derivatives.

Introduction

Among medium size ring heterocycles, nine membered azoninones and diazoninones are important due to their existence in the biologically active natural products (Fig. 1) [1], as drug candidates [2], as materials [3] and as catalyst [4]. Several synthetic strategies have been developed for the synthesis of azoninones / diazoninones. The methods include gold catalyzed intramolecular Ugi hydroarylation [1h], copper catalyzed intramolecular *N*-arylation of phosphoramidates and carbamates [5], C-N coupling of β-lactam and arylhalides followed by trans amidation [6], alkylation followed by ring closing metathesis (RCM) [7], Beckmann rearrangement of cyclooctenone oxime [8], Ugi multicomponent reaction (MCR) followed by RCM [9], cross coupling of allyl/homoallyl amino acids followed by RCM [10], aza-Claisen rearrangement of 2-vinylpyrrolidines [11], photochemical reaction of chromium carbene complex and 3°-allyl amines followed by aza-Cope rearrangement [12]. The RCM have been demonstrated as one of the powerful tool as an efficient synthetic protocol to synthesize functionalized carbo- and heterocycles. Most of these compounds have been found to be part of natural products or acts as peptide mimics with a ring size from five to large complex macrocycles [13]. furthermore, synthesis of unsaturated / fused bicyclic lactams have been achieved via RCM [14]. Both anthranilamide [15] and isatoic anhydride [16] have been utilized synthons for the synthesis of biologically important nitrogen and oxygen heterocyclic compounds.

Despite several methods were reported [5–12] for the construction of azoninones/diazoninones, it suffers by by-product formation, lower yields, longer reaction time and harsh reaction conditions and hence better synthetic methods are still in demand. Therefore, to overcome the difficulties, we have developed two different pathways for the construction of benzo-fused diazoninones starting from readily available anthranilamide **1** and isatoic anhydride **10** via a sequence of reactions viz. arylation/allylation-RCM reaction. The reaction sequence has advantages such as shorter reaction time and excellent yields. The details of the synthesis, optimization, scope and limitation of the methodology is outlined in this manuscript.

Our initial effort to achieve the synthesis of benzo[*b*][1,5]diazonin-7-one **A**, a retrosynthetic analysis is proposed in Scheme 1. Thus, the benzo fused diazoninone derivative **A** could be obtained from anthranilamide diallyl derivative **B** via a RCM. The diallyl derivative **B** could be prepared by direct *N*, *N*-diallyaltion of anthranilamide **C** with ally bromide under basic conditions.

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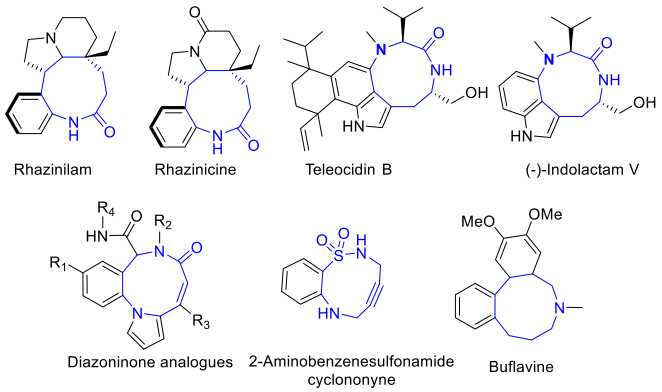
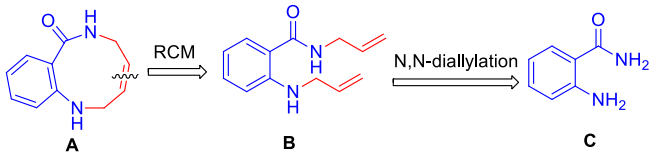


Fig. 1. Natural products with heterononine cores.



Scheme 1. Retrosynthesis analysis for 5,6-dihydro-benzo[*b*][1,5]diazonin-7(2*H*)-one **A**.

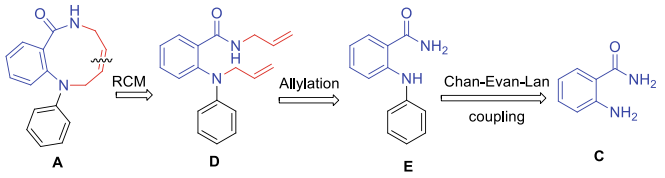
Thus, anthaliniamide **1** in DMSO upon treatment with excess of allyl bromide **2** and KOH/alumina at 70 °C for 24 h provided three products namely, amine *N*-allylated product **3**, amide *N*-allylated product **4** and *N*, *N*-diallylated product **5** in 20%, 60% and 10% yields, respectively (Scheme 2). Although the most suitable RCM substrate **5** was obtained only in 10%, the same was obtained in 90% from the second allylation of mono allylated compound **4** by the treatment of allyl bromide, and sodium carbonate at 70 °C for 12 h. To our dismay, the key RCM reaction of diallylated compound **5** in CH_2Cl_2 with 5 mol% Grubbs I/II catalysts failed to provide the benzodiazinone derivative and the unreacted starting material was recovered quantitatively.

The failure of RCM reaction of *N*,*N*-diallylated compound **5** prompted us to find the reason for it. Literature revealed that the synthesis of medium size ring products mainly depend on the conformational and stereochemical feature of the double bonds in the starting material when the RCM reactions is concerned [6,17]. Thus, we assumed of introducing a substitution at amine nitrogen prior to allylation would provide a diallylated product with a substitution would be a conformationally favoured and suitable substrate for RCM to provide target nine membered benzodiazoninones. Thus, we revised the retrosynthetic pathway as shown in Scheme 3.

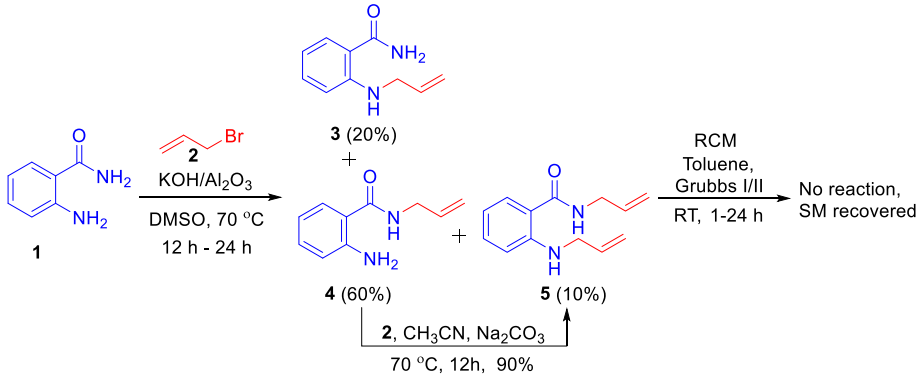
Accordingly, the benzodiazoninone derivative **A** could be obtained from *N*-phenyl, *N*, *N*-diallyl derivative **D** via RCM. The *N*-phenyl, *N*, *N*-diallyl derivative **D** can be achieved by allylation of *N*-arylated anthranilamide **E**. While intermediate **E** could be obtained from Cha-Evans-Lam coupling reaction of anthanilamide **C** with aryl boronic acid under copper catalyst conditions (Scheme 3).

According to Scheme 3, the Cham-Evans-Lam coupling reaction of anthranilamide **1** in MeOH upon treatment with phenyl boronic acid, CuCl/TEA at room temperature afforded *N*-arylated compound **7** in 87% yield. Further, reaction of *N*-arylated compound **7** in DMSO with allyl bromide and KOH at 70 °C for 12 h provided *N*-arylated-*N*, *N*-diallylated product **8a** and *N*-arylated-triallylated product **8b** in 25% and 70% yield, respectively (Scheme 4). RCM reaction of compound **8a** in toluene with 5 mol% Grubbs I catalyst for 24 h failed to provide benzodiazoninone and the unreacted starting material was recovered quantitatively. Repeating the above reaction with Grubbs II also failed to provide the desired product. The free -NH group of compound **8a** might coordinate with catalyst, thus interrupts the catalytic cycle leading to failed RCM reaction [17]. However, RCM reaction of the triallylated product **8b** in toluene with 5 mol% Grubbs I catalyst afforded the desired benzodiazoninone derivative **9a** in 70% yield within five minutes. The structure of product **9a** was confirmed by analysis of spectroscopic data (See SI).

In the quest to optimise the condition and to improve the yield of **9a,** parameters such as solvent, catalyst, catalyst loading, temperature and reaction time were considered. Thus, RCM reaction of compound **8b** was carried out using Grubbs II catalyst and observed a slight improvement in the yield of **9a** up to 80% (Table 1, entry 2). Hence, Grubbs II catalyst was used for all the subsequent optimization reactions. The reactions with prolonged reaction time and increased catalyst loading did not altered the yield of **9a** (Table 1, entries 3–5). Among the reactions in different solvents such as DCM, benzene, toluene, THF, toluene was found to be suitable solvent with improved yield (90%) of compound **9a** (Table 1,



Scheme 3. Revised retrosynthesis from anthranilamide.



Scheme 2. Synthesis and attempted RCM of *N*-allyl-2-(allylamino)benzamide **5.**

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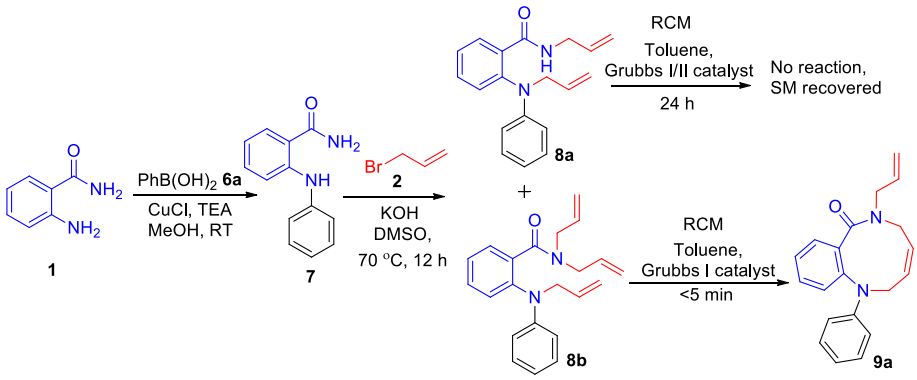
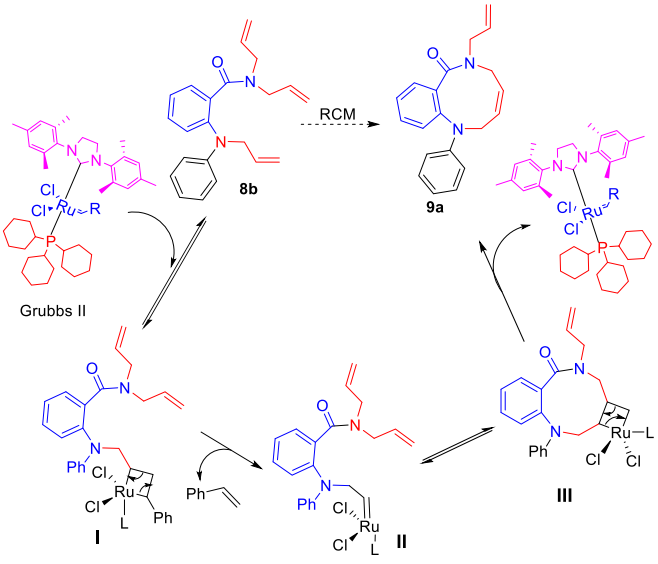


Scheme 4. Synthesis of 6-allyl-1-phenyl-5,6-dihydro-1*H*-benzo[*b*][1,5]diazonin-7(2*H*)-one **9a.**

Table 1
Optimization of synthesis of compound **9a.**

Entry	Solvent	Catalyst (mol%)	Temp (°C)	Time (min.)	% Yield **9a**[a]
1	CH_2Cl_2	Grubbs I (5)	RT	5	70
2	CH_2Cl_2	Grubbs II (5)	RT	5	80
3	CH_2Cl_2	Grubbs II (5)	RT	30	80
4	CH_2Cl_2	Grubbs II (5)	RT	60	80
5	CH_2Cl_2	Grubbs II (10)	RT	5	80
6	DCM	Grubbs II (5)	RT	5	85
7	C_6H_6	Grubbs II (5)	RT	5	87
8	Toluene	Grubbs II (5)	RT	5	90[b]
9	THF	Grubbs II (5)	RT	5	80
10	Toluene	Grubbs II (5)	50	5	90
11	Toluene	Grubbs II (5)	100	5	90
12	Toluene	Grubbs II (5)	120	60	87

[a] Isolated yield.
[b] Optimised condition.



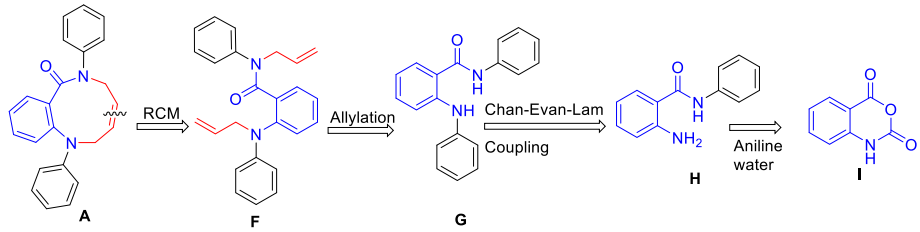
Scheme 5. Plausible mechanism for the formation of compound **9a.**

entries 6–10). The reactions with elevated temperatures in toluene did not improved the yield. A slight decrement in the yield was observed in a reaction after 60 min at 120 °C (Table 1, entries 11–12). Thus, condition shown in entry 8, Table 1 was found to be optimum condition.

A plausible mechanism for the formation of product **9a** is shown in Scheme 5. Accordingly, initial reaction of terminal allyl and methylene group of Grubbs II catalyst lead to the formation of metallacyclobutane intermediate **I,** which upon cycloreversion leads to metal-carbene intermediate **II** with the elimination of ethene. Subsequently the metal-carbene intermediate **II** forms a second metallacyclobutane intermediate **III** with the second terminal allyl group. The final cyclo reversion of intermediate **III** leads to the formation of desired product **9a**.

The failed RCM reaction of substrates **5** and **8a** and successful substrate **8b** suggested that the only tetrasubstituted anthranilamide substrates are suitable for RCM reaction to afford benzodiazoninone. Hence, we again revised the retrosynthetic approach for the general synthesis of *N*, *N*-diphenyl benzodiazoninone starting from isatoic anhydride (Scheme 6). As shown in Scheme 6, the benzodiazoninone derivative **A** could be derived from *N*, *N*-diphenyl, *N*, *N*-diallyl derivative **F** via RCM. The *N*, *N*-diphenyl, *N*, *N*-diallyl derivative **F** in turn can be achieved by allylation of *N*, *N*-arylated anthranilamide **G.** While intermediate **G** could be obtained from Cha-Evans-Lam coupling reaction of *N*-arylated anthranilamide **H** with aryl boronic acid/copper catalyst conditions. Compound **H** could obtained from isatoic anhydride **I** by a known procedure [18].

The amide *N*-arylated product **12** was obtained from a known reaction of isatoic anhydride **10** with aniline **11a** in water at room temperature [18]. Subsequent Cham-Evans-Lam coupling [19] reaction of compound **12a** with phenyl boronic acid **6a**, CuCl/TEA at room temperature afforded *N*, *N*-diarylated compound **13a** in 85% yield. Subsequent reaction of compound **13a** with allyl bromide/KOH at 70 °C for 12 h provided *N*, *N*-diallylated product **14a** in 89% yield (Scheme 7). Similarly, compounds **14b** and **14c** were prepared from compounds **13b** and **13c** in 92% and 90% yields, respectively.



Scheme 6. Revised retrosynthesis from isatoic anhydride.

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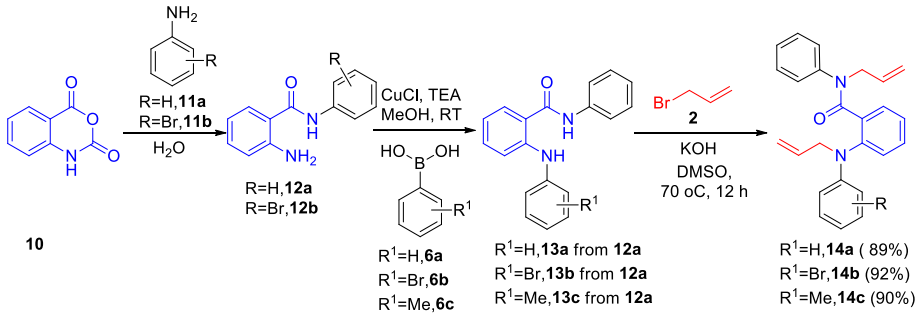
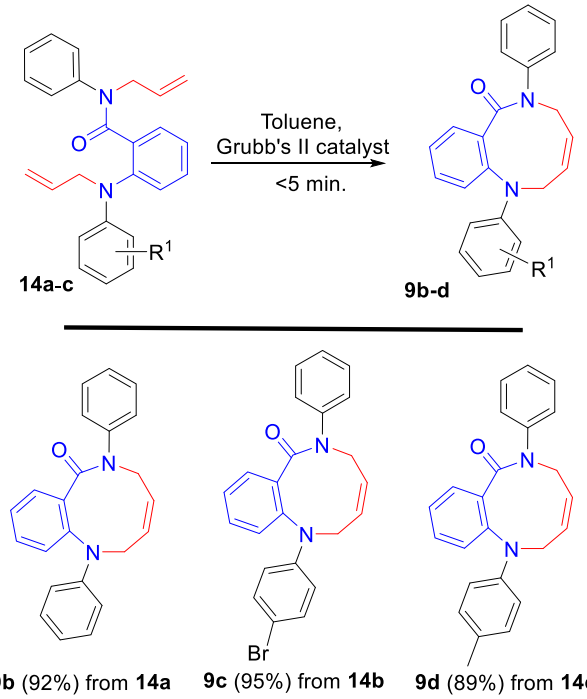


Scheme 7. Synthesis of N_1, N_2-diaryl N_1, N_2-diallyl aminoamides**14a-c** from isatoic anhydride **10.**

As described for compound **9a**, the final RCM reaction of the diaryl-diallylated product **14a** in toluene with 5 mol% Grubbs II catalyst afforded the desired benzodiazoninone derivative **9b** in 92% yield within five minutes (Scheme 8). The other substrates **14b** and **14c** under similar conditions afforded benzodiazoninone derivatives **9c** and **9d** in excellent yields.

All the new compounds were characterised by spectroscopic data such as ^{1}H NMR, ^{13}C NMR, DEPT-135 and HRMS. The final structure proof of a representative compound **9c** was obtained from single-crystal XRD method (Fig. 2).

In conclusion, we have demonstrated a facile and efficient method for the synthesis of (*Z*)-6-allyl-1-phenyl-1,2,5,6-tetrahydro-7*H*-benzo[*b*][1,5]diazonin-7-one and (*Z*)-1,6-diphenyl-1,2,5,6-tetrahydro-7*H*-benzo[*b*][1,5]diazonin-7-one from anthranilamide via *N*-arylation/*N*-allylation and from isatoic anhydride via ring opening/*N*-arylation/*N*-allylation followed by ring closing metathesis using Grubbs-II catalyst as a key step. Further work in exploring the synthesis of medium size ring compounds utilising the synthetic strategy described in this manuscript is in progress.



Scheme 8. Synthesis of 5,6-dihydro-1*H*-benzo[*b*][1,5] diazonin-7(2*H*)-ones **9b-d** via RCM reaction of **14a-c**.

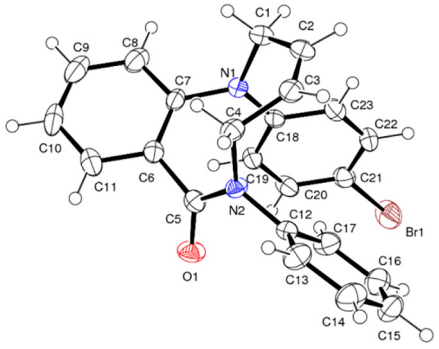


Fig. 2. ORTEP diagram of compound **9c** (CCDC 1920126) [20].

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.151163.

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[20] CCDC-1920126 (9c) contains the supplementary crystallographic data for this paper. This data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data request/cif.

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