Microwave-Assisted N- Allylation/Homoallylation-RCM Approach: Access to Pyrrole-, Pyridine-, or Azepine-Appended (Het)aryl Aminoamides

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ABSTRACT: A facile and diversity-oriented approach has been developed for the synthesis of pyrrole-, pyridine-, or azepine-appended (het)aryl aminoamides via the N-allylation/homoallylation-ring-closing metathesis (RCM) strategy. Microwave condition was efficiently utilized for N-allylation of (het)aryl aminoamides to synthesize di-, tri-, and tetra-allyl/homoallylated RCM substrates in good yields. All of the RCM substrates were successfully converted to respective pyrroles 6a–h, 13a,b, 15a,b, pyridines 11a–d, 13c, and azepines 7a,b via RCM. All of the five-, six-, and seven-membered N-heterocycles were synthesized in shorter reaction times with excellent yields without isomerization products. A one-pot reaction to synthesize compounds 6a and 6b without isolating corresponding RCM substrates was achieved successfully. The synthetic utility of the compound 6b has been demonstrated by synthesizing biaryl derivatives 17a,b under the microwave Suzuki coupling reaction condition.

INTRODUCTION

Among the various N-heterocycle compounds, pyrroles, pyridines, and azepines are the most predominant constituents in many natural products, pharmaceuticals, and functionalized organic molecules.1–6 Particularly, many drug molecules and alkaloids possess dihydro pyrroles, tetrahydro pyridines, and tetrahydroazepines as their core moiety (Figure 1).7–13

Thus, various expedient routes have been developed for their synthesis. Individually, dihydro pyrroles have been synthesized from intramolecular hydroamination of homoallylic aminols,14 cyclization of 4-amino butynols,15 amines with 1,4-dichloro-2-butene under microwave condition,16 reaction of Huisgen zwitter ion with benzoyl chlorides,17 and Nb-catalyzed ring-closing metathesis (RCM) of N,N-diallylsulfonamides,18 as well as from allyl alcohols with amines followed by RCM.19

On the other hand, tetrahydro pyridines have been synthesized via the reaction of vinyl silanes with iminium/acyl iminium ion,20 allyne-aza-Prins cyclization of tosyl amines and aldehydes,21 radical cyclization of 1,6-enzymes,22 reaction of amine aldehydes and esters via the multicomponent reaction (MCR) approach,23–24 and chemoenzymatic one-pot cascade approach of diallylamines,25 as well as from diallyl aniline using additives via RCM.26

Tetrahydroazepines have been synthesized from cyclohexanone oxime,27 Overman rearrangement–RCM pathway of allylic alcohols,28 vinylation of imine–RCM pathway,29 and the reaction of methyl acrylate and allyl amine via RCM.30

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Figure 1. Biologically important compounds with pyrrole, pyridine, and azepine heterocycles as cores.
In recent years, the microwave (MW) irradiation method has emerged as a complementary tool to classical synthesis.\cite{36,31} And the ring-closing metathesis (RCM)\cite{32-35} has been proved as a key step in synthesizing five- and six-membered N-heterocycles. The methods developed for the synthesis of five-, six-, and seven-membered nitrogen heterocycles\cite{34-29} require longer and harsh reaction conditions, and more importantly, they suffer isomerization of the product, which impacts the yield of the desired product. To overcome these difficulties and also in continuation to our previous efforts,\cite{36} we have developed the microwave-assisted N-allylation/homoallylation-RCM approach to synthesize five-, six-, and seven-membered nitrogen heterocycles. The details of the study are presented in this manuscript.

## RESULTS AND DISCUSSION

Initially, a mixture of 1 equiv of 2-aminobenzamide (1a) and 2.2 equiv of allyl bromide (2a), with Et$_3$N as base in CH$_3$CN was microwave-irradiated (100 W) for 4 min. The reaction afforded 2-(diallylamino)benzamide (3a) in 60% yield (Table 1, entry 1).

![Reaction Scheme](image)

Table 1. Optimization of the Synthesis of Compound 3a$^{a,b,c,d}$

| entry | base     | solvent | MW power (W) | irradiation time (min) | % yield |
|-------|----------|---------|--------------|------------------------|---------|
| 1     | Et$_3$N  | CH$_3$CN | 100          | 4                      | 60      |
| 2     | Et$_3$N  | CH$_3$CN | 100          | 6                      | 75      |
| 3     | Et$_3$N  | CH$_3$CN | 100          | 8                      | 65      |
| 4     | Et$_3$N  | CH$_3$CN | 200          | 2                      | 60      |
| 5     | Et$_3$N  | CH$_3$CN | 200          | 4                      | 85      |
| 6     | Et$_3$N  | CH$_3$CN | 200          | 6                      | 82      |
| 7     | Et$_3$N  | CH$_3$CN | 300          | 2                      | 65      |
| 8     | Et$_3$N  | CH$_3$CN | 300          | 4                      | 80      |
| 9     | K$_2$CO$_3$ | CH$_3$CN | 200          | 4                      | 92$^d$  |
| 10    | Na$_2$CO$_3$ | CH$_3$CN | 200          | 4                      | 87      |
| 11    | CaH$_2$  | CH$_2$CN | 200          | 4                      | 85      |
| 12    | K$_2$CO$_3$ | DMP   | 200          | 4                      | 90      |
| 13    | K$_2$CO$_3$ | toluene | 200          | 4                      | 90      |
| 14    | K$_2$CO$_3$ | CH$_3$CN | 83          | 200        | 90      |

$^a$Reaction conditions: All of the reactions were carried out on a CEM Discover-300 microwave synthesizer. $^b$Power mode, 50 psi. $^c$Optimized yield. $^d$Refux for 12 h.

The structure of compound 3a (N$_2$,N$_2$-diallylated product) was confirmed after thorough characterization by the spectroscopic method. It should be noted that the other possible N$_1$,N$_1$-diallylated and N$_1$/N$_2$-monoallylated products were not observed under this condition.

To improve the yield of 3a, an optimization study was undertaken and the parameters such as microwave power, irradiation time, base, and solvent were considered. Thus, a reaction of compounds 1a and 2a in a 1:2.2 ratio was microwave-irradiated at 100 W for 6 min showed a slight improvement of yield of 3a (75%) (Table 1, entry 2). However, upon prolonging the irradiation time to 8 min, a decreased yield of 3a was noted (Table 1, entry 3). Further, improved yields of 3a up to 80% were observed by increasing the microwave power level to 200 and 300 W (Table 1, entries 4–8). Significantly, screening the base afforded compound 3a in excellent yield of up to 92% (Table 1, entries 9–11). The solvent effect in improving the yield of 3a was minimal (Table 1, entries 12 and 13). A reaction under conventional heating yielded the desired product 3a in 83% yield in a longer reaction of 12 h (Table 1, entry 14). Thus, conditions shown in entry 9 of Table 1 were found to be optimum.

Encouraged by the preliminary results, and to expand the scope and diversity of the reaction, various (het)aryl aminoamides 1a–h and alkyl halides 2a–c were screened and the reaction afforded respective diallylated/homoallylated products 3a–h, 4a,b, and 5a (Figure 2). Aminoamides 1a–h with allyl bromide 2a afforded diallylated products 3a–h in good to excellent yields, whereas the reaction with 2b and 2c afforded products 4a,b and 5a in relatively lower yields. This may be due to the reactivity and stability of the corresponding carbocation of allylation/homoallylation reagents 2a–c. Variable yields were observed for the products 3a, 3f, and 3g as the position of the amine group in the substrate is changed. Thus, the alkylation of substrates 1a (ortho-NH$_2$) and 1g (para-NH$_2$) afforded 3a (92%) and 3g (91%), respectively. While the alkylation of 1f (meta-NH$_2$) afforded product 3f in a slightly decreased yield of 80% (Figure 2). All of the synthesized compounds were thoroughly characterized by spectroscopic data, including single-crystal X-ray diffraction (XRD) data of representative compound 3d (Figure 3).

Having diallylated products in hand, we then performed a preliminary RCM reaction of the diallylated product 3a in dichloromethane (DCM) with 5 mol % Grubbs I catalyst. The reaction afforded the cyclized product 6a in 87% yield in 5 min (Table 2, entry 1). Further, an optimization study was undertaken by varying the parameters such as catalyst, catalyst loading, temperature, and solvent. Thus, repeating the reaction by increasing the reaction time did not alter the yield (Table 2, entries 2 and 3). Further, the RCM of compound 3a was carried out in DCM and a slight improvement in the yield was observed (Table 2, entry 4). Subsequent reactions with increased reaction time did not improve the yield of 6a (Table 2, entries 5 and 6). The RCM of 3a was carried out in different solvents such as DCM, toluene, and tetrahydrofuran (THF). The results revealed that toluene was found to be a suitable solvent with an optimum yield of 98% (Table 2, entry 7). The reactions at elevated temperature did not alter the yield, and a slight decrease in the yield was observed after 30 min at 120 °C (Table 2, entry 11). To optimize the catalyst load, RCM reactions with 3 and 10 mol % Grubbs II catalyst were carried out and it was found that 3 mol % catalyst would be sufficient to produce optimum yield (Table 2, entries 12 and 13). Thus, the condition shown in entry 12 of Table 2 was found to be optimum.

To demonstrate the scope of the reaction, under optimized condition, diallylated products 3b–h and 4a,b afforded the corresponding dihydro pyrrole derivatives 6b–h and tetrahydropyrazine derivatives 7a,b in excellent yield (Figure 4). The RCM reaction of 2-(di-(pent-4-en-1-yl)amino)benzamide 5a was unsuccessful to yield the cyclic product, which might be due to free –NH groups in the substrate.\cite{38}

After the successful synthesis of five- and seven-membered N-heterocycles via a two-step procedure, we then explored the possibility of one-pot procedure to synthesize 6a,b directly from 1a,b. Thus, the reaction of 1a/1b with 2a under optimized condition (Table 1, entry 9) and the crude reaction...
mixture further subjected to RCM (Table 2, entry 12) afforded compounds 6a and 6b in 55 and 63% yields, respectively (Scheme 1).

The fruitful results shown in Scheme 1 prompted us to explore the synthesis of six-membered N-heterocycle from the sequential reaction of 1a with allyl bromide 2a, followed by homoallyl bromide 2b and finally RCM cyclization. To achieve the synthesis of six-membered N-heterocycles, as shown in Scheme 2, we have proposed two synthetic routes for the synthesis of 2-(allyl(but-3-en-1-yl)amino)-benzamide 10a. According to route 1, the first N₁-allylated product 8a was synthesized from 1a and allyl bromide 2a, and then, N₁-allyl,N₁-homoallylated product 10a was synthesized in 90% yield from the reaction of 8a and homoallyl bromide 2b under basic condition. In route 2, N₁-homoallylated product 9a was synthesized from 1a and homoallyl bromide 2b and compound 10a was synthesized in 95% yield from 9a and 2a. In both routes 1 and 2, 1 equiv of allyl halide 2a/2b was used (Table 1, entry 9). It has been observed that N₁-allyl,N₁-homoallylated product 10a synthesized via route 2 has a slight edge over route 1 in terms of yield. Further, the scope of the reaction was...
extended by synthesizing \( \text{N}_1\)-allyl, \( \text{N}_1\)-homoallylated products 10b, c from 1f, 1g, and 1e via route 2 (Scheme 2).

To achieve six-membered \( \text{N}\)-heterocycles, the RCM reaction of compounds 10a−d under optimized condition (Table 2, entry 12) was carried out to synthesize 1,2,3,6-tetrahydropyridine-substituted aminoamides 11a−d in very good yields (Scheme 3). All of the new compounds were thoroughly characterized by spectroscopic data including single-crystal XRD data of compound 11b (Figure 5).37

All of the five-, six-, and seven-membered \( \text{N}\)-heterocycles were synthesized via diallylated/homoallylated RCM substrates. However, we envisaged the possibility of synthesis of tri- and tetra-allylation substrate followed by the RCM cyclization approach to construct the title compounds. Initially, to achieve the synthesis of triallylated RCM substrates, a reaction of 3a with 1 equiv of compound 2a was carried out, although the expected triallylated product 12a was obtained only in 10% yield. The reaction was optimized by varying base, substrate ratio, and solvent. Among the different conditions explored, the reaction of 3a and 2a in a 1:1.2 ratio in dimethyl sulfoxide (DMSO) using NaH as base and microwave power level of 200 W and 4 min irradiation was found to be optimum with 85% yield of 12a (see Table S1, entry 5).
Under similar conditions, triallylated products 12b,c were obtained from 3e and 10d, respectively. All of the triallylated RCM substrates 12a–c were converted to N$_1$-allylated 2,5-dihydro-1H-pyrral-1-yl-substituted aminoamides 13a,b and N-allyl-2-(5,6-dihydropyridin-1(2H)-yl)benzenesulfonamide 13c under optimized RCM cyclization (Scheme 4). We did not observe other possible cyclized products from cyclization of N$_1$ and N$_2$ allyl groups.\(^{21}\)

Scheme 4. Synthesis of N$_1$-Allylated 2,5-Dihydro-1H-Pyrral-1-yl and 5,6-Dihydropyridin-1(2H)-yl-Substituted Aminoamides 13a–c

To begin with, the tetra-allylated RCM substrate 14a was obtained in 20% yield from compounds 3a and 2a (2 equiv) using 1,4-dioxane as solvent and NaH as base. The reaction was carried out at 50 W power level and 50 psi pressure under microwave condition over 5 min (see Table S2, entry 1). To improve the yield of compound 14a, an optimization study was conducted. To begin with, a slight increase in the yield was observed by increasing the irradiation time and equivalence of 2a (see Table S2, entries 2–5). Interestingly, a sharp increase in the yield of compound 14a to 82% was observed when the KOH was used as base (see Table S2, entry 6). Repeating the reaction with base NaOH did not improve the yield (see Table S2, entry 7). Thus, the condition shown in entry 6 of Table S2 (see Supporting Information) was found to be optimum. Similarly, compound 14b was synthesized in 85% yield from substrate 3b. Under optimized RCM condition, the synthesized tetra-allylated RCM substrates 14a,b were converted to respective cyclic (2,5-dihydro-1H-pyrral-1-yl)-(2,5-dihydro-1H-pyrral-1-yl)aryl)methanones 15a,b in excellent yield. Notably, the diazadione derivative 15b' was isolated in 10% yield along with 15b from the RCM reaction of 14b, which might be due to the metathesis of N$_1$ and N$_2$ allyl groups (Scheme 5).

To demonstrate the synthetic utility of the products, the microwave-assisted Suzuki reaction of 6b with aryl boronic acids 16a,b was successfully attempted to afford 4-(2,5-dihydro-1H-pyrral-1-yl)-4’-methyl-[1,1’-biphenyl]-3-carboxamide 17a and 4’-cyano-4-(2,5-dihydro-1H-pyrral-1-yl)-[1,1’-biphenyl]-3-carboxamide 17b in 82 and 78% yields, respectively (Scheme 6).

### EXPERIMENTAL SECTION

**Materials and Methods.** All of the reactions were carried out in oven-dried glassware. A CEM Discover-300 microwave synthesizer was used for all of the microwave irradiation reactions. All of the chemicals, including (het)aryl aminooamides (1a–g), alkyl halides (2a–c), aryl boronic acids (16a,b), Grubbs II catalyst, and palladium reagent were purchased from Sigma-Aldrich and used as received. Thin-layer chromatography (TLC) monitored the progress of the reactions, while purification of crude compounds was done by column chromatography using silica gel (mesh size, 100–200). The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker-400 MHz NMR spectrometer (400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR) with CDCl$_3$ or (CD$_3$)$_2$SO as the solvent and tetramethylsilane (TMS) as an internal reference. Integrals are in accordance with assignments; coupling constant ($J$) was reported in hertz (Hz). All $^{13}$C NMR spectra reported are proton-decoupled. Multiplicity is indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), and m (multiplet).
(quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). High resolution mass spectrometry (HRMS) analyses were conducted using Q-T of a Micro mass spectrometer (different mass analyses based on the availability of instruments). Yields refer to quantities obtained after chromatography. All of the commercial solvents were purified before use.

**General Experimental Procedure for the Synthesis of N,N,N-(*p*)-Dialkylated (Het)aryl aminoamides (3a–h, 4a,b) and 5a.** To a solution of (het)aryl aminoamides 1a–h (1 equiv) and allyl bromide 2a–c (2 equiv) in CH₂CN (1 mL) was added K₂CO₃ (2.5 equiv), and the reaction mixture was microwave-irradiated (power mode) at 200 W for 4 min. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with ethyl acetate and washed with HCl (0.25 M, 10 mL) followed by brine and distilled water, dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude product was purified on a silica gel column to afford the corresponding N,N-dialkylated (het)aryl aminoamides 3a–h in excellent yields, and 4a,b and 5a in good yields (eluent: n-hexane/EtOAc).

**Experimental Procedure for the Synthesis of N1-Monoalkylated Aminoamides (8a and 9a–d).** To a solution of (het)aryl aminoamides 1a–h (1 equiv) and allyl bromide 2a/2b (1 equiv) in CH₂CN (1 mL) was added K₂CO₃ (2.5 equiv), and the reaction mixture was microwave-irradiated (power mode) at 200 W for 4 min. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with ethyl acetate and washed with HCl (0.25 M, 10 mL) followed by brine and distilled water, dried over Na₂SO₄ and the solvent was evaporated under reduced pressure. The crude product was purified on a silica gel column to afford the corresponding N₁-monoalkylated aminoamides 8a and N₁-mono homomethylated aminoamides 9a–d in good yields (eluent: n-hexane/EtOAc).

**Experimental Procedure for the Synthesis of N1-, N2-, N3-Homoalkylated Aminoamides 10a–d. Synthesis from (Allylamino)benzene Amides (8a).** To a solution of (allylamino)benzene amides 8a (1 equiv) and 4-bromo-1-buten 2b (1 equiv) in CH₂CN (1 mL) was added K₂CO₃ (1.2 equiv), and the reaction mixture was microwave-irradiated (power mode) at 200 W for 4 min. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with ethyl acetate and washed with HCl (0.25 M, 10 mL) followed by brine and distilled water, dried over Na₂SO₄ and the crude product was purified on a silica gel column to afford the corresponding N₁-, N₂-, N₃-homoalkylated aminoamide 10a in good yield (eluent: n-hexane/EtOAc).

**Synthesis from (Homomlylamino)Benzene Amides (9a–d).** To a solution of (homomlylamino)benzene amides 13 (1 equiv) and allyl bromide 2a (1 equiv) in CH₂CN (1 mL) was added K₂CO₃ (1.2 equiv), and the reaction mixture was microwave-irradiated (power mode) at 200 W for 4 min. After completion of the reaction (monitored by TLC), the reaction mixture was extracted with ethyl acetate and washed with HCl (0.25 M, 10 mL) followed by brine and distilled water, dried over Na₂SO₄ and the crude product was purified on a silica gel column to afford the corresponding N₁-, N₂-, N₃-homoalkylated aminobenzamides 10a–d in excellent yields (eluent: n-hexane/EtOAc).

**Typical Experimental Procedure for the Preparation of Trialkylated Aminoamides 12a–c from 3a/3e/10d.** A mixture of N₁,N₂,N₃-trialkylated aminoamides 3a/3e/10d (1 equiv), allyl bromide 2a (1 equiv), and sodium hydride (1.5 equiv) in 1,4-dioxane (1 mL) was microwave-irradiated (power mode) at 200 W for 4 min. The reaction was quenched with cold water upon completion (monitored by TLC). The crude was extracted with ethyl acetate and washed with dilute HCl (0.25 M, 10 mL) followed by brine and distilled water. The combined organic layer was dried over Na₂SO₄ and the mixture was purified through silica gel column chromatography by gradient elution using EtOAc/hexane as eluent to afford N₁-allyl-2-(diallylamino)benzamide (12a)/sulfonamide (12b) and N-allyl-2-(allyl-(but-3-en-1-yl)-amino)benzenesulfonamide (12c) in very good yields.

**Experimental Procedure for the Synthesis of N,N-Diallyl-2-(diallylamino)-Substituted Benzamides 14a,b.** To a mixture of 3a/3b (1 equiv) and allyl bromide 2a (2 equiv) in 1,4-dioxane (1 mL) was added potassium hydroxide (KOH) (2.5 mmol) and microwave-irradiated (power mode) at 50 W for 7 min. The reaction was quenched with cold water upon completion (monitored by TLC). The crude was extracted with ethyl acetate and washed with dilute HCl and distilled water. The combined organic layer was dried over anhydrous Na₂SO₄. The solvent was removed under vacuum, and the crude was purified by silica gel column chromatography to afford pure N,N-diallyl-2-(diallylamino)-substituted benzamides 14a,b in excellent yields.

**General RCM Procedure for the Preparation of Compounds 2,5-Dihydro-1H-pyrrole-Substituted Aminoamides (6a–h, 13a,b, and 15a,b), 5,6-Dihydropyrindin-1(2H)-yl-Substituted Aminoamides (11a–d) and 2,3,6,7-Tetrahydro-1H-azepine-Substituted Aminoamides (7a,b).** To a solution of RCM substrates (3a–h/4a/b/5a/10a–d/13a–c/14a,b) in toluene, 3 mol % of Grubbs II catalyst (6 mol % Grubbs II catalyst was used for the substrates 14a,b) was added and stirred at RT for 3 min. After completion of the reaction, the solvent was removed under reduced pressure and the residue was purified by silica gel column chromatography using EtOAc/hexane as eluent to afford pure 2,5-dihydro-1H-pyrrole-substituted aminoamides (6a–h, 13a,b, and 15a,b), 5,6-dihydropyrindin-1(2H)-yl-substituted aminoamides (11a–d), and 2,3,6,7-tetrahydro-1H-azepine-substituted aminoamides (7a,b) in excellent yields.

**General Procedure for the Preparation of 2,5-Dihydro-1H-pyrrole-Substituted [1’,1’-biphenyl]-3-carboxamides 17a,b by Suzuki Coupling.** A mixture of 2-(2,5-dihydro-1H-pyrrol-1-yl)-5-iodo-benzamide 6b (1 equiv), aryloboric acids 16 (1.5 equiv), Pd(dppf)Cl₂/DCM (10 mol %), and 0.5 N K₂CO₃ (1 mL) in 4 mL of dioxygen=methanol (3:1) was microwave-irradiated (power mode) at 200 W for 10 min. After completion of the reaction (TLC), the solvent was removed in vacuo and the residue was extracted with ethyl acetate and washed with HCl (0.25 M, 20 mL) followed by brine. The combined organic layer was dried over Na₂SO₄ and the mixture was purified through silica gel column chromatography by gradient elution using EtOAc/hexane to afford 2,5-dihydro-1H-pyrrole-substituted [1’,1’-biphenyl]-3-carboxamides 17a,b in very good yields.

**One-Pot Preparation of 2,5-Dihydro-1H-pyrrole-Substituted Aminoamides 6a,b from 1a and 1b.** To a solution of (het)aryl aminoamides 1a/1b (1 equiv) and allyl bromide 2a (2 equiv) in toluene (1 mL) was added K₂CO₃ (2.5 equiv), and the reaction mixture was microwave-irradiated (power mode) at 200 W for 4 min. After 4 min, the reaction mixture was cooled to room temperature and a 3 mol % of Grubbs II catalyst was added and stirred at RT for 3 min. After completion of the reaction (monitored by TLC), the solvent...
was removed under reduced pressure and the residue was purified by silica gel column chromatography using EtOAc/hexane as eluent to afford pure 2,5-dihydro-1H-pyrrole-substituted aminoalcohols 6a,b in good overall yields.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.9b04038.

Optimization of synthesis of compounds 12a and 14a; copies of 1H NMR, 13C NMR, DEPT-135, and HRMS data for all of the new compounds; basic crystallographic data of compounds 3d and 11b (PDF)

Single-crystal XRD data for compound 3d (CIF)

Single-crystal XRD data for compound 11b (CIF)

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