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New Efficient RCM-Mediated Synthesis of Pyrrolidine Derivatives

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Abstract: Fast and effective ring-closing olefin metathesis (RCM) of diallyamine derivatives of coumarin, quinolone, pyridine, and substituted benzene, using first-generation RCM ruthenium-based catalyst, leads to corresponding pyrrolidine derivatives in 70–95% yields under very mild conditions.

Keywords: Diallylamine derivatives, pyrrolidine, ring-closing metathesis

INTRODUCTION

Ring-closing metathesis (RCM) has emerged as one of the most powerful tools for the construction of carbo- and heterocyclic compounds, as demonstrated by the numerous total syntheses of complex molecules and natural products that include this versatile technique as the key synthetic step.[1] Consequently, the RCM of olefinic ethers, esters thioethers, allylic phosphanes, and allyl phosphonamides has been well established using various catalytic systems.[2] Very few examples are known where less basic *N*,*N*-diallyl amine derivative[3] or Lewis acid–assisted[4] RCM gave pyrrolidine derivatives. In view of the wide range of biological activities, pyrrolidine derivatives have received much attention. For example, pyrrolidine-3-carboxylate has been utilized as a β-turn motif in GP II b/III an antagonist.[5] Some of these derivatives have been proven to be neurotransmitters.[6] They can also be incorporated as a 3,4-dehydro-isoproline-peptidomimetic scaffold to be used as intermediates to construct alkaloid natural products and drug candidates.[7] On the other hand, coumarin, quinolone, and pyridine are structural

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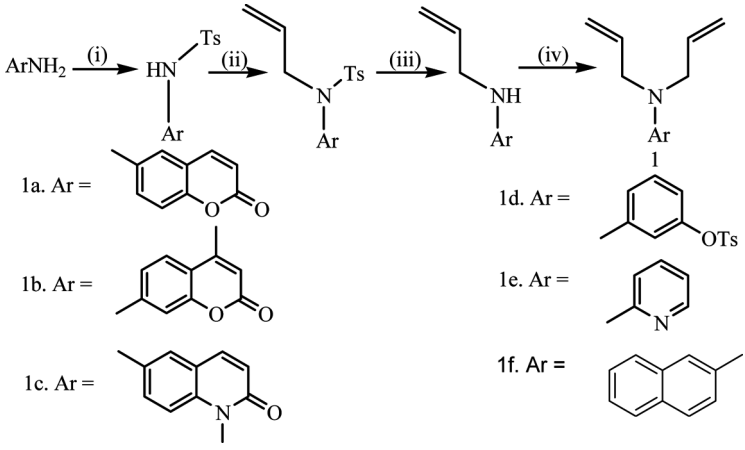
subunits in numerous natural products that exhibit a wide range of biological activities such as antibacterial, antifungal, anti-allergic, and DNA-gyrase inhibition.[8] In connection with our studies, directed toward the syntheses of heterocycles using metathesis,[9] we became interested in accessing hitherto unreported pyrrolidine derivatives containing coumarin, quinolone, pyridine, substituted benzene, and naphthalene moiety using Grubbs 1 catalyst.

RESULTS AND DISCUSSION

The requisite precursor *N,N*-diallylamine may be accessed by allylation of the amine. Direct allylation of the amines gives only mono-allylated product in moderate yields under prolonged refluxing condition. Furthermore, 2-aminopyridine on direct allylation gives only the pyridinum salt. So, we have chosen a four-step process to prepare the precursors **1a–f** as depicted in (Scheme 1). All the corresponding amines were first converted into their *N*-tosyl derivatives by heating at 70–80 °C with tosylchloride and pyridine for about 3–4 h. The *N*-tosyl derivatives were then subjected to allylation with allylbromide (1.2 equiv) in refluxing dry acetone in the presence of anhydrous K_2CO_3 to afford *N*-allyl-*N*-tosyl derivative of the corresponding amines. The reaction takes place within 3–4 h, and the yield of the product is quantitative. Detosylation of *N*-allyl-*N*-tosyl derivatives were carried out with a mixture of acetic acid and sulfuric acid (3:1), by heating on a water bath for about 3–4 h. Monoallyl derivatives



Scheme 1. Reagents and conditions: (i) TsCl, pyridine, heat 3–4 h; (ii) allyl bromide, anhy. K_2CO_3, dry acetone, reflux, 3–4 h; (iii) AcOH, H_2SO_4 (3:1), heat, 3–4 h; (iv) allyl bromide, anhy. K_2CO_3, reflux, 12–24 h.

of the corresponding amines on refluxing with allylbromide (1.2 equiv) and anhydrous K_2CO_3 in dry acetone for about 12–24 h afforded compounds **1a–f** in good yields (Table 1).

Precursor molecules **1a–f** were then subjected to RCM condition (catalyst 1, CH_2Cl_2) at room temperature as depicted in (Scheme 2).

This led to the corresponding pyrrolidine derivatives **2a–d** in good to excellent yields within a very short time (Table 1). Unfortunately, all attempts to prepare the corresponding pyrrolidine derivative of **1e** under the same condition were unsuccessful, the starting material was recovered. The problem associated with pyridine nitrogen and the compatibility of the olefin metathesis catalyst has been reported many times. Perhaps the pyridine nitrogen interferes with the catalytic cycle by coordinating with ruthenium.[10]

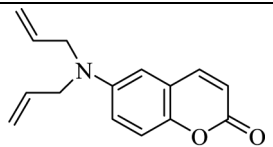
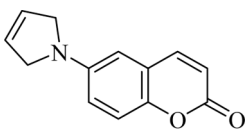
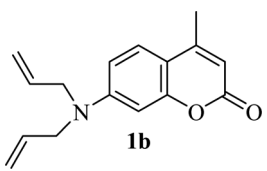
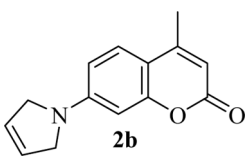
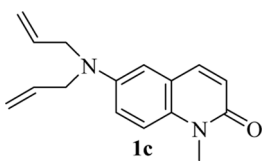
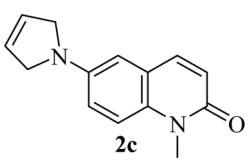
To circumvent this problem, we have blocked the nitrogen functionality by the formation of pyridinium salt with 4-toluenesulfonic acid so that it cannot interfere with the ruthenium. Pyridinium salt on treatment with Grubbs catalyst for 30 min followed by a basic workup gave the desired pyrrolidine derivative **2e** in good yield. The hydrogenated product of **2e** has been reported in poor yield by cycloaddition of ethylene with 2*H*-pyrrole-1(5*H*)-carbonitrile under high pressure and moderate temperature in the presence of cobaltocene catalyst.[11] However, this can be achieved very easily by hydrogenation of **2e**. On the other hand, under the same set of conditions as describe for **1a–d,** compound **1f** gives **2f**, the usual pyrrolidine derivative, and unusual pyrrole derivative **2g.** The pyrrole formation can be explained through an RCM followed by in situ oxidation. Amines with an electron-withdrawing group on the nitrogen atom did not dehydrogenate to the pyrrole but to the expected pyrrolidine derivative, so it is clear that oxidation is dependent upon nitrogen basicity.

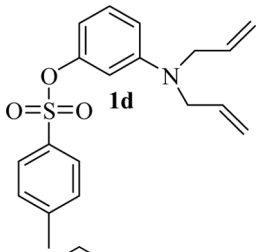
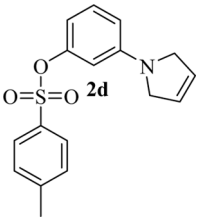
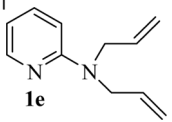
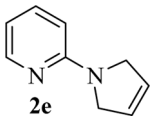
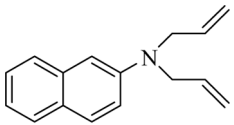
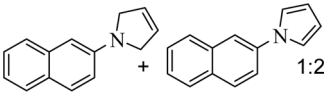
In conclusion, we have successfully extended the RCM to the synthesis of coumarin, quinolone, pyridine, substituted benzene, and naphthalene-containing pyrrolidine derivatives. The process is quite general and afforded good to excellent yields of the desired product.

EXPERIMENTAL

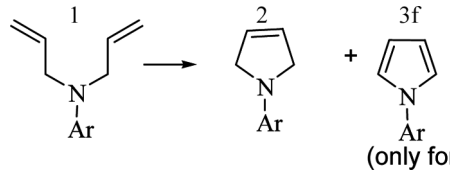
Melting points were determined in open capillaries and are uncorrected. IR spectra were recorded on a Perkin-Elmar L 120–000A spectrometer (γ_{max} in cm^{-1}) using samples as neat liquids, and solid samples were recorded in KBr disks. ^1H NMR (400-MHz) spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ (chemical shift in δ) with TMS as internal standard. Silica gel [(60–120, 230–400 mesh), Spectrochem,

Table 1. Summarized results of the RCM reaction

Entry	Percursor	Method[a]	Time (h)	Product	Yield (%)
1	 **1a**	A	0.20	 **2a**	95
2	 **1b**	A	0.25	 **2b**	90
3	 **1c**	A	0.30	 **2c**	85

4	 **1d**	A	0.25	 **2d**	95
5	 **1e**	B	12	 **2e**	70
6	 **1f**	A	6	 **2f** + **3f** 1:2	

[a]Method A: Grubbs 1, dry CH_2Cl_2, rt: method B: Grubbs 1, dry CH_2Cl_2,4-toluenesulphonic acid (cat.), rt.



Scheme 2. Reagents and conditions: catalyst 1 (5 mol%), dry CH_2Cl_2.

India] was used for chromatographic separation. Silica gel G [E-Merck (India)] was used for thin-layer chromatography (TLC). Petroleum ether refers to the fraction boiling between 60 and 80 °C.

General Procedure for the Preparation of Diallyl Derivatives 1a–f

A mixture of corresponding monoallyl derivative of amines **1a–e** (2 mmol), allylbromide (2.4 mmol), and anhydrous K_2CO_3 (1 g) in dry acetone (75 mL) was refluxed for 12–24 h. The reaction mixture was cooled and filtered, and the solvent was removed. The residual mass was extracted with CH_2Cl_2 (3×20 mL). The CH_2Cl_2 extract was washed with water (3×15 mL) and dried(Na_2SO_4). The solvent was removed, and the residual mass was purified by column chromatography over silica gel using petroleum ether–ethylacetate as elutent.

Data

6-(Diallylamino)-2*H*-chromen-2-one (1a): Yellowish oil, yield 95%. IR (KBr): $\nu_{max} = 1721, 1568\,cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 7.58$ (d, 1H, $J = 9.5$ Hz), 7.15 (d, 1H, $J = 9.2$ Hz), 6.87 (dd, 1H, $J = 9.1$ Hz, $J = 3.0$ Hz), 6.62 (d, 1H, $J = 3.0$ Hz), 6.34 (d, 1H, $J = 9.6$ Hz), 5.82–5.88 (m, 2H), 5.14–5.18 (m, 4H), 3.92–3.93 (m, 4H) ppm; MS (m/z) = 241 (M^+). Anal. calcd. for $C_{15}H_{15}NO_2$; C, 74.67; H, 6.27; N, 5.81%. Found: C, 74.93; H, 6.13; N, 5.82%.

7-(Diallylamino)-4-methyl-2*H*-chroman-2-one (1b): Yellowish oil; yield 90%. IR (KBr): $\delta_{max} = 1716, 1605\,cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$): $d_H = 7.35$ (d, 1H, $J = 8.9$ Hz), 6.57 (dd, 1H, $J = 8.9$ Hz, $J = 2.6$ Hz), 6.53 (d, 1H, $J = 2.5$ Hz), 5.95 (d, 1H, $J = 0.7$ Hz), 5.78–5.87 (m, 2H), 5.13–5.20 (m, 4H), 3.96–3.98 (m, 4H), 2.32 (d, 3H, $J = 0.7$ Hz) ppm; MS (m/z) = 255 (M^+). Anal. calcd. for $C_{16}H_{17}NO_2$; C, 75.27; H, 6.71; N, 5.49%. Found: C, 75.30; H, 6.69; N, 5.60%.

6-(Diallylamino)-1-methylquinolin-2(1*H*)-one (1c): Yellow viscous liquid; yield 90%. IR (KBr): $\nu_{max} = 1650, 1440\,cm^{-1}$; ^1H NMR (400 MHz, $CDCl_3$):

$\delta_H = 7.55$ (d, 1H, $J = 9.4$ Hz), 7.45 (d, 1H, $J = 9.3$ Hz), 7.28 (dd, 1H, $J = 9.3$ Hz, $J = 2.9$ Hz), 6.73 (d, 1H, $J = 2.9$ Hz), 6.63 (d, 1H, $J = 9.4$ Hz), Hz), 5.82–5.90 (m, 2H), 5.16–5.20 (m, 4H), 3.94–3.95 (m, 4H), 3.66 (s, 3H) ppm. MS (m/z) = 254 (M^+). Anal. calcd. for $C_{16}H_{18}N_2O$; C, 75.56; H, 7.13; N, 11.01%. Found: C, 75.35; H, 7.01; N, 11.08%.

3-(Diallylamino)phenyl 4-methylbenzenesulfonate (1d): Yellow liquid; yield 85%, IR (KBr) $\nu_{max} = 1632$, 1615 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 7.71$ (d, 2H, $J = 8.2$ Hz), 7.27 (d, 2H, $J = 8.0$ Hz), 7.00 (t, 1H, $J = 8.1$ Hz), 6.50–6.54 (m, 1H), 6.24–6.26 (m, 2H), 5.80–5.81 (m, 2H), 5.12–5.15 (m, 4H), 4.05–4.07 (m, 4H), 2.42 (s, 3H) ppm. MS (m/z) = 343(M^+). Anal. calcd. for $C_{19}H_{21}NO_3S$: C, 66.45; H, 6.16; N, 4.08%. Found: C, 66.69; H, 6.13; N, 4.05%.

N, N-Diallylpyridin-2-amine (1e): Yellow liquid; yield 70%. IR (KBr): $\nu_{max} = 2850$, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 8.13$ (m, 1H), 7.38–7.42 (m, 1H), 6.50–6.53 (m, 1H), 6.44 (d, 1H, $J = 8.6$ Hz), 5.80–5.89 (m, 2H), 5.11–5.15 (m, 4H), 4.09–4.10 (m, 4H) ppm. MS (m/z) = 174 (M^+). Anal. calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08%. Found: C, 75.77; H, 8.33; N, 16.26%.

N, N-Diallylnaphthalen-2-amine (1f): Yellow liquid; yield 80%. IR (KBr): $\nu_{max} = 2855$, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 7.65$ (d, 1H, $J = 8.9$ Hz), 7.60 (d, 1H, $J = 8.2$ Hz), 7.55 (d, 1H, $J = 8.2$ Hz), 7.30–7.33 (m, 1H), 7.10–7.15 (m, 1H), 6.90 (dd, 1H, $J = 8.9$ Hz, $J = 2.1$ Hz), 6.69 (d, 1H, $J = 2.1$ Hz), 5.75–5.82 (m, 2H), 5.13–5.17 (m, 4H), 3.98–4.05 (m, 4H), ppm. MS (m/z) = 223 (M^+). Anal. calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27%. Found: C, 85.96; H, 7.74; N, 6.23%.

General Procedure for Ring-Closing Metathesis of Diallyl Derivatives 1a–f

The ruthenium catalyst **1** (5 mol%) (and a catalytic amount 4-methylbenzenesulfonic acid for **1e** only) in dichloromethane (1 mL) was added under a nitrogen atmosphere to a solution of corresponding diallyl derivative (0.2 mmol) in dry dichloromethane (1.5 mL). The reaction mixture was stirred for 20–30 min (12 h for **1e**). The solvent was evaporated, and the residue was purified by flash chromatography over silica gel using petroleumether–ethylacetate as elutent.

Data

6-(2H-Pyrrol-1(5H)-yl)-2*H*-chromen-2-one (2a): Yellowish solid; yield 95%; mp 156–158 °C. IR (KBr): $\nu_{max} = 1714$, 1569 cm^{-1}; ^1H NMR (400 MHz,

$CDCl_3$): $\delta_H = 7.62$ (d, 1H, $J = 9.5$ Hz), 7.22 (d, 1H, $J = 9.2$ Hz), 6.71 (dd, 1H, $J = 9.0$, $J = 2.9$ Hz), 6.44 (d, 1H, $J = 2.8$ Hz), 6.37 (d, 1H, $J = 9.5$ Hz), Hz), 5.97 (s, 2H), 4.12 (s, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): $\delta c = 156.4$, 140.6, 139.1, 138.6, 121.3, 114.5, 112.5, 111.8, 110.5, 102.1, 49.7 ppm; HRMS: m/z calcd. for $C_{13}H_{11}NO_2$ $[M + H]^+$: 214.0859; found: 214.0863. Anal. calcd. for $C_{13}H_{11}NO_2$; C, 73.23; H, 5.20; N, 6.57%. Found: C, 73.47; H, 5.13; N, 6.71%.

4-Methyl-7-(2H-pyrrol-1(5H)-yl)-2*H*-chromen-2-one (2b): Light yellow solid; yield 90%, mp 156–158 °C. IR (KBr) $\nu_{max} = 1703$, 1605 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 7.40$ (d, 1H, $J = 8.8$ Hz), 6.44 (dd, 1H, $J = 8.8$ Hz, $J = 2.4$ Hz), 6.35 (d, 1H, $J = 2.4$ Hz), 5.96 (s, 2H), 5.95 (d, 1H, $J = 0.9$ Hz), 4.16 (s, 4H), 2.34 (d, 3H, $J = 0.9$ Hz) ppm; MS $(m/z) = 227$ (M^+). Anal. calcd. for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16%. Found: C, 73.87; H, 5.73; N, 6.05%.

1-Methyl-6H-(2*H*-pyrrol-1(5H)-yl)quinolin-2(1*H*)-one (2c): Yellow solid; yield 85%; mp 94–96 °C. IR (KBr) $\nu_{max} = 1651$, 1446 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 7.57$ (d, 1H $J = 9.4$ Hz), 7.26 (d, 1H, $J = 9.0$ Hz), 6.83 (dd, 1H, $J = 9.1$ Hz, $J = 2.7$ Hz), 6.66 (d, 1H, $J = 9.4$ Hz), 6.57 (d, 1H, $J = 2.6$ Hz), 5.98 (s, 2H), 4.14 (s, 4H), 3.69 (s, 3H) ppm; MS $(m/z) = 226$ (M^+). Anal. calcd. for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38%. Found: C, 74.34; H, 6.07; N, 12.21%.

3-(2*H*-Pyrrol-1(5*H*)-yl)phenyl 4-methylbenzenesulfonate (2d): White solid; yield 95%; mp 78–80 °C. IR (KBr) $\nu_{max} = 1630$, 1610 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 7.73$ (d, 2H, $J = 8.2$ Hz), 7.28 (d, 2H, $J = 8.0$ Hz), 7.04 (t, 1H, $J = 8.1$ Hz), 6.34 (dd, 1H, $J = 8.2$, $J = 1.9$ Hz), 6.18 (dd, 1H, $J = 8.0$ Hz, $J = 1.7$ Hz), 6.14–6.15 (m, 1H), 5.90 (s, 2H), 3.99 (s, 4H), 2.43 (s, 3H) ppm.^{13}C NMR (125 MHz, $CDCl_3$): $\delta c = 146.0$, 143.0, 140.0, 127.8, 124.9, 124.6, 123.5, 121.1, 104.8, 103.7, 99.9, 49.4, 16.6 ppm; MS $(m/z) = 315$ (M^+). Anal. calcd. for $C_{17}H_{17}NO_3S$: C, 64.74; H, 5.43; N, 4.44%. Found: C, 64.86; H, 5.52; N, 4.36%.

2-(2H-Pyrrol-1(5*H*)-yl)pyridine (2e): Yellow liquid; yield 70%. IR (KBr) $\nu_{max} = 2851$, 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H =$ 8.15–8.17 (m, 1H), 7.42–7.47 (m, 1H), 6.52–6.55 (m, 1H), 6.32 (d, 1H, $J = 8.4$ Hz), 5.94 (s, 2H), 4.24 (s, 4H) ppm; MS $(m/z) = 146$ (M^+). Anal. calcd. for $C_9H_{10}N_2$: C, 73.94; H, 6.89; N, 19.16%. Found: C, 73.75; H, 6.90; N, 19.28%.

1-(Napthalen-2-yl)-2,5dihydro-1H-pyrrole (2f): Yellow viscous liquid; yield 30%. IR (KBr) $\nu_{max} = 2850$, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta_H = 7.70$ (d, 1H, $J = 8.96$ Hz), 7.66 (d, 1H, $J = 8.16$ Hz), 7.62 (d, 1H, $J = 8.28$ Hz), 7.32–7.36 (m, 1H), 7.13–7.17 (m, 1H), 6.93 (dd, 1H, $J = 8.92$ Hz, 2.0 Hz), 6.71 (d, 1H, $J = 2.0$ Hz), 5.99 (s, 2H), 4.22

(s, 4H), ppm; MS (m/z) = 195 (M^+). Anal. calcd. for $C_{14}H_{13}N$; C, 86.12; H, 6.71; N, 7.17%. Found: C, 86.25; H, 6.80; N, 7.25.

1-(Napthalen-2-yl)-1H-pyrrole (2g): Yellow viscous liquid; yield 60%. IR (KBr) $\nu_{max} = 2853$, 1598 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ_H = 7.89 (d, 1H, $J = 8.8$ Hz), 7.83 (d, 2H, $J = 8.16$ Hz), 7.78 (d, 1H, J = 2.0 Hz), 7.57 (dd, 1H, $J = 8.8$ Hz, 2.0 Hz), 7.41–7.53 (m, 2H), 7.22 (s, 2H), 6.40 (s, 2H) ppm; MS (m/z) = 193 (M^+). Anal. calcd. for $C_{14}H_{11}N$; C, 87.01; H, 5.74; N, 7.25%. Found: C, 87.15; H, 5.79; N, 7.20%.

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