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Tandem Claisen rearrangement and ruthenium catalyzed enyne bond reorganization as a route to the synthesis of tricyclic 1,8-naphthyridinones

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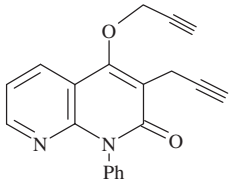
Abstract—A novel procedure for the synthesis of substituted 1,8-naphthyridinones via tandem Claisen rearrangement and ring-closing enyne metathesis is reported.

Naphthyridine derivatives are important due to the exceptionally broad spectrum of their biological activities. Substituted 1,8-naphthyridine derivatives are used for diagnostic and therapy of human diseases including AIDS and for combating exo- and endoparasites in agriculture.[1] The attractive biological activities of these 1,8-naphthyridines, for example, the anti-allergic agents[2] **1** and **2**, and the cytoprotective, anti-inflammatory and anti-allergic activity of some 2,3-fused and 3,4-fused furo and pyrano tricyclic compounds,[3] explains the great interest in the naphthyridinone moiety as a target in organic synthesis. However, there is no general synthesis of medium-sized, oxacycle fused, naphthyridinone derivatives. In recent years, ring-closing enyne metathesis[4] has become useful for the synthesis of small and medium ring dienes[5] using the first generation Grubbs catalyst[6] (**A**). In ring-closing enyne metathesis (RCEYM), being an intramolecular reaction, catalyst turnover is usually fast enough to compete with and overcome coordination by functional groups at the allylic and propargylic positions. Hence, it appeared to us that a combination of a Claisen rearrangement and ring-closing enyne metathesis could be useful to access hitherto unknown medium-sized, oxacycle-annulated, 1,8-naphthyridinone derivatives.



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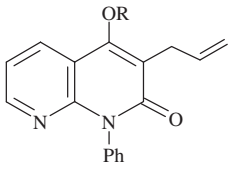
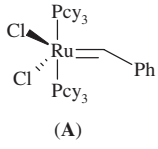


2 R = -COCH$_3$
3 R = H



(**A**)

Here we report a general methodology for the regiocontrolled synthesis of substituted 1,8-naphthyridinones.

4-Allyloxy-1-phenyl-1,8-naphthyridin-2(1*H*)-one has been reported[2] earlier. 3-Allyl-4-hydroxy-1,8-naphthyridinone **3** has been prepared[2] by refluxing 4-allyloxy-1,8-naphthyridinone in acetic anhydride followed by hydrolysis of the resulting acetate **2**. We observed that this two-step protocol for the synthesis of **3** could be avoided if the Claisen rearrangement of 4-allyloxy-1,8-naphthyridinone was carried out in refluxing chlorobenzene. Product **3** was obtained directly under these conditions. The isolation of the product is easy and the yield of the product is better. Alkylation of **3** with propargyl bromide (2 equiv) and 1-aryloxy-4-chlorobut-2-yne (1.5 equiv) in refluxing acetone in the presence of anhydrous potassium carbonate for 2–3 h afforded the corresponding ene–yne derivatives **4a–d** in good yields (Scheme 1).

When a dichloromethane solution of **4a** and 10 mol % of **A** was stirred at room temperature for 2 h under a

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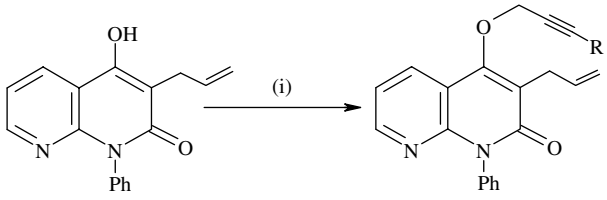
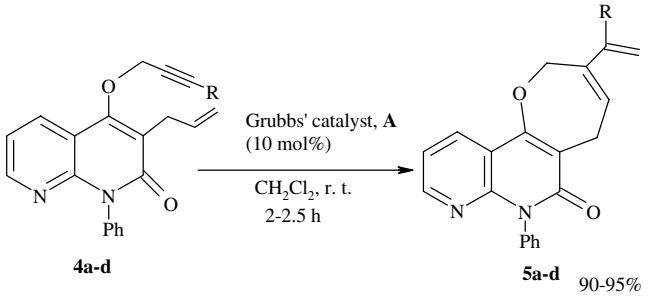


	Ar	yields (%)
4b	4-Me-C_6H_4	52
4c	2,4-Cl_2-C_6H_3	53
4d	4-Cl-C_6H_4	50

Scheme 1. Reagents and conditions: (i) propargyl bromide/chloride, dry acetone, K_2CO_3, reflux, 2–3 h, yields; 50–55%.

nitrogen atmosphere, we found that ring-closing enyne metathesis proceeded smoothly to afford the oxepine derivative **5a** in 92% yield. The tricyclic compound **5a** was identified from its elemental analysis and spectroscopic data. The enynes **4b**, **4c** and **4d** were treated in a similar manner and the desired RCEYM products **5b**, **5c** and **5d** were obtained in 90%, 95% and 94% yields, respectively (Scheme 2).

The ring-closing enyne metathesis proceeds through the formation of a new C–C bond between the triple bond and the double bond to give the cyclized products **5a–d.**

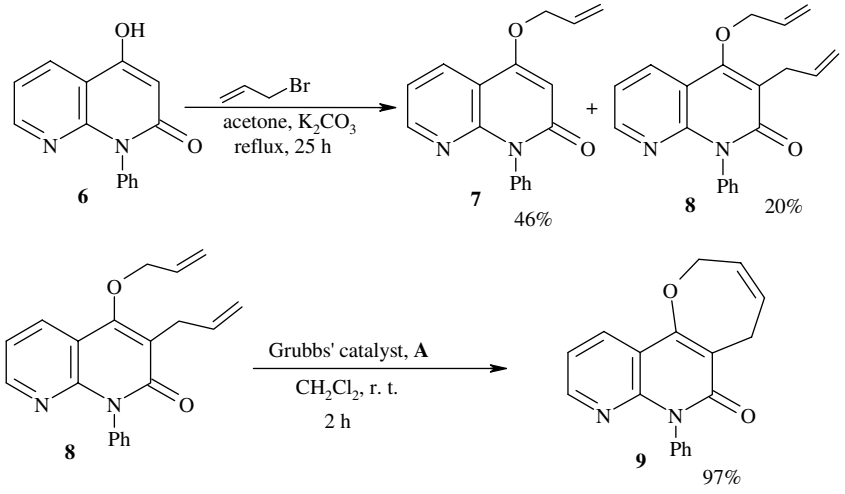


Scheme 2.

Another simple alkylation was performed on hydroxynaphthyridinone **3** with allyl bromide in place of propargyl bromide and the corresponding diallyl ether **8** was obtained. In fact, during the course of alkylation of naphthyridinone **6** with allyl bromide we found that a small amount of the O,C-diallylated product **8** was formed along with the O-allylated product **7**. However, formation of **8** from **6** in a single step was an advantageous outcome since it could be utilized directly in the subsequent step. The ring-closing metathesis[7] (RCM) of the O,C-diallylated product **8** using the commercially available ruthenium carbene complex **A** under a nitrogen atmosphere in dichloromethane solution smoothly provided the unsubstituted oxepine annulated 1,8-naphthyridin-2(1*H*)-one derivative **9** in an excellent yield (Scheme 3).

Several substituted and fused 1,8-naphthyridin-2(1*H*)-ones derivatives have useful levels of biological activities.[8] In conclusion, we have developed an efficient route to 1,8-naphthyridinone-fused polyheterocycles **5** using a Claisen rearrangement and ring-closing enyne metathesis.

Typical procedure for the ring-closing metathesis reactions: To a solution of substrate **4a** (50 mg, 0.158 mmol) in dry degassed CH_2Cl_2 (8 ml) under N_2 was added cat-



Scheme 3.

alyst **A** (10 mol %, 13 mg) and the reaction was stirred at room temperature for 2 h. After the removal of the solvent, the residue was purified by flash column chromatography on silica gel (pet ether/ethyl acetate, 4:1) to give **5a** in 92% yield. Diene **8** and dienynes **4b–d** were treated in a similar manner to give the corresponding cyclized products in excellent yields.

Compound **5a**—Yield 92%; solid; mp 184–186 °C; IR (KBr) ν_{max}: 2924, 1636, 1585 cm^{-1}; UV (EtOH), λ_{max}: 362, 331, 321, 216 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.75–3.77 (d, $J = 6.26$ Hz, 2H), 5.11–5.14 (d, $J =$ 10.9 Hz, 1H, exocyclic proton), 5.18 (s, 2H, $-OCH_2$), 5.29–5.33 (d, $J = 17.61$ Hz, 1H, exocyclic proton), 6.24–6.27 (t, $J = 6.26$ Hz, 1H), 6.36–6.43 (dd, $J =$ 10.9 Hz, 17.6 Hz, 1H), 7.10–7.13 (dd, $J = 4.69$ Hz, 7.84 Hz, 1H, ArH), 7.22–7.56 (m, 5H, ArH), 8.22–8.24 (dd, $J = 1.36$ Hz, 7.8 Hz, 1H, ArH), 8.38–8.39 (dd, $J = 1.32$ Hz, 4.29 Hz, 1H, ArH); MS: $m/z = 317$ (M^++1); Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.95; H, 5.06; N, 8.86. Found: C, 75.82; H, 5.15; N, 8.79.

Compound **9**—Yield 97%; solid; mp 142–144 °C; IR (KBr) ν_{max}: 2921, 1646, 1582 cm^{-1}; UV (EtOH), λ_{max}: 359, 330, 322, 219 nm; ^1H NMR (400 MHz, $CDCl_3$): δ_H 3.70 (d, $J = 5.45$ Hz, 2H), 4.91–4.93 (d, $J = 5.5$ Hz, 2H, $-OCH_2$), 6.00–6.05 (m, 1H, =CH), 6.20–6.26 (m, 1H, =CH), 7.11–7.14 (dd, $J = 4.7$ Hz, 7.8 Hz, 1H, ArH), 7.23–7.56 (m, 5H, ArH), 8.21–8.23 (dd, $J =$ 1.2 Hz, 7.8 Hz, 1H, ArH), 8.39–8.40 (dd, $J = 1.2$ Hz, 4.36 Hz, 1H, ArH); MS: $m/z = 291$ (M^++1). ^{13}C NMR (125 MHz, $CDCl_3$): 25.14, 68.00, 113.64, 114.13, 118.47, 127.00, 128.76, 129.33, 129.85, 132.13, 133.93, 138.00, 149.87, 150.31, 160.04 and 164.72. Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.48; H, 4.82; N, 9.65. Found: C, 74.62; H, 4.98; N, 9.51.

Acknowledgements

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