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Metathetic approach to naphthoxepin and spirocyclic molecular frameworks ☆

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Abstract—An efficient method for the synthesis of naphthoxepin and spirocyclic skeletons starting from β-naphthol has been developed. The Claisen rearrangement and the ring-closing metathesis reaction are used as key steps for their assembly.
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1. Introduction

Oxepin is an important structural element present in numerous biologically active molecules. For example, there are many naphthoxepin derivatives such as **1** and **2**, which are used as antipsychotic drugs (Fig. 1).[1]

Similarly, the spirocyclic cyclopentanoid core is present in a variety of pharmacologically active terpenoids such as stemaranes[2] and scopadulanes. A broad pharmacological profile has been observed for scopadulan diterpenes.[3] Scopadulcic acid B, and scopadulciol are powerful inhibitors of H^+ and K^+ adenosine triphosphate. Conformationally constrained analogs of *N*-phenyl-*N*′-aralkylurea **3** act as potential ACAT inhibitors.[4]

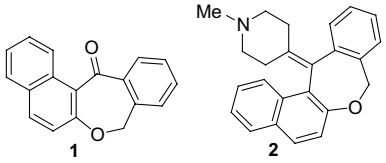

Figure 1. Naphthoxepin derivatives used as antipsychotic drugs.

The spirocyclic model compound **4** binds with remarkable efficiency to bulged DNA oligonucleotides, offering potential for the design of therapeutic agents (Fig. 2).[5]

Herein, we report a simple approach for the synthesis of naphthoxepin and spirocyclic cyclopentanoid molecular frameworks from readily available β-naphthol based on microwave-assisted Claisen rearrangement and ruthenium catalyzed ring-closing metathesis (RCM) as key steps.[6]

Recently, the RCM reaction using Grubbs' catalysts[7] **5** and **6** (Fig. 3) has become a useful tool for synthetic chemists and has been applied for the preparation of various heterocyclic, carbocyclic, and macrocyclic molecules.[8]

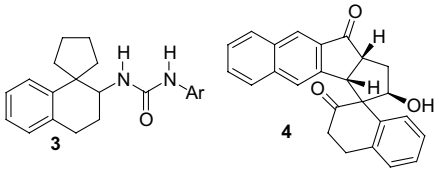

Figure 2. Various biologically active spiro analogs.

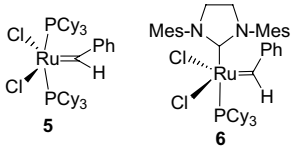

Figure 3. Grubbs' catalysts used for RCM.

Keywords: Claisen rearrangement; Metathesis; Oxepins; Spiro compounds.

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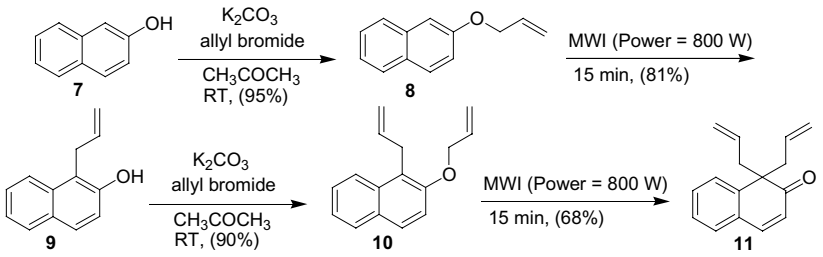


Scheme 1.

For the synthesis of our targets, the required starting materials **10** and **11** were prepared by O-allylation of β-naphthol derivatives (**7** and **9**) using potassium carbonate, acetone, and allyl bromide at rt. The Claisen rearrangement of compounds **8** and **10** was carried out using microwave irradiation conditions without using any solvent and the products **9** and **11** were obtained within 15 min (Scheme 1). We found that the Claisen rearrangement of **8** and **10** using microwave irradiation (MWI) has advantages over conventional conditions[9] in several aspects. Some of them include shorter reaction times, cleaner products, and simpler work-up procedures.

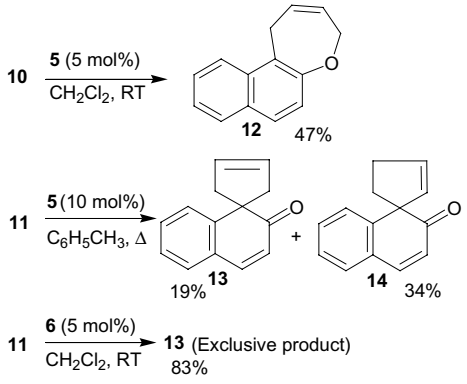
Ruthenium catalyzed RCM of compounds **10** and **11** gave the corresponding naphthoxepin and spirocyclic skeletons, respectively. Naphthoxepin derivative **12** was obtained in the presence of catalyst **5** (5 mol%) at rt using dichloromethane as solvent whereas, RCM of compound **11** was found to be very slow. Two products **13** and **14** were obtained when the compound **11** was refluxed for 7 days in toluene in the presence of the Grubbs' catalyst **5**. Both the products exhibited characteristic dienone absorption bands at 1663 and 1664 cm^{-1}, respectively, and showed molecular ion peaks at m/z 196 in the mass spectrum. ^1H NMR spectral data for **14** exhibited two different multiplets, which corresponded to the two nonequivalent olefinic protons and the presence of 14 lines in the proton decoupled ^{13}C NMR spectral data indicated that **14** was an isomer of **13** (Scheme 2).

Palladium/carbon catalyzed hydrogenation of both the isomers **13** and **14** gave the same reduced products **15**[10] and **16** in a 1:1 ratio, which further confirmed that compound **14** was the double bond isomer of **13**.

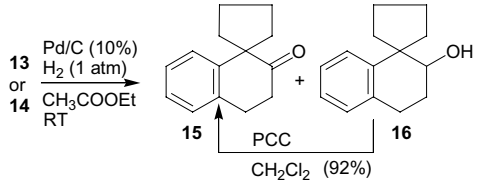
The structure of the alcohol **16** appears to be the result of complete reduction of compounds **13** or **14**. The structure of **16** was confirmed by its conversion into the corresponding ketone **15** (Scheme 3). The ketone was converted into the corresponding known hydrazone derivative and its identity was confirmed by melting point comparison.

Compound **13** was refluxed in toluene in the absence of Grubbs' catalyst for 7 days leading to no isomerized product **14**. This clearly indicates that thermal isomerization of **13** to **14** is not feasible in the absence of Grubbs' catalyst. However, in the presence of Grubbs' catalyst **5** (10 mol%) under the above conditions, isomerized product **14** was obtained in good yield (66%) (Scheme 4). Treatment of compound **11** with the more active second generation Grubbs' catalyst **6** gave the required compound **13** as the exclusive product in DCM under rt stirring conditions. No isomerized product was observed (Scheme 2).

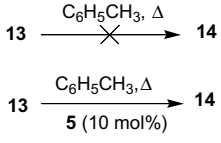
Recent literature reports dealing with olefin isomerization using Grubbs' catalyst are limited to substrates, which contain oxygen or nitrogen substituents in the allylic or homoallylic position.[11] We have observed that in the presence of Grubbs' catalyst, isomerization of the double bond is also feasible under thermal conditions without alcohol, ether or amide functional groups in the allylic or homoallylic positions.



Scheme 2. Synthesis of oxepin and spirocyclic enones via RCM.



Scheme 3.



Scheme 4.

A possible mechanism for the isomerization reaction involving a 16 electron Ru complex, may involve intramolecular hydrogen transfer followed by β-elimination as illustrated in Scheme 5.[12]

In summary, we have developed an efficient method for the synthesis of naphthoxepin **12** and spirocyclic skeletons such as **13**, **14**, **15**, and **16** from the readily available β-naphthol **7** as starting material using Claisen rearrangement and RCM reactions as the key steps. Non-metathetic behavior of Grubbs' catalyst has been observed beyond the metathesis reaction.

2. Experimental

2.1. General procedure for the Claisen rearrangement

The compound was added to a sealed glass tube and placed in a Ken Star 800 W microwave oven (Model OM-992E). Typical reactions were run using 100% of power (800 W) for 3 × 5 min in solvent-free conditions. The resulting reaction mixture was then directly (without any work-up) purified by flash chromatography.

2.2. General procedure for the RCM reaction

The diallyl compound (1 equiv) in dry DCM (or toluene) was degassed for 10 min. Grubbs' catalyst **5** or **6** (5–10 mol %) was then added and the reaction mixture was refluxed for 24 h. The resulting reaction mixture was concentrated under reduced pressure and the crude product was purified by silica gel flash chromatography. Elution of the column with ethyl acetate and petroleum ether mixture gave the required compound.

2.3. 1,4-Dihydronaphtho[2,1-*b*]oxepin 12

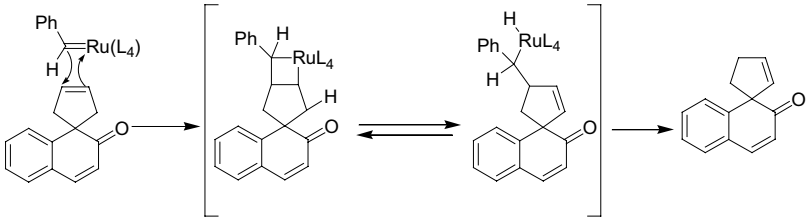
To a solution of compound **10** (97 mg, 0.43 mmol) in dry degassed DCM (12 mL) was added Grubbs' catalyst **5** (18 mg, 0.02 mmol, 5 mol %). The reaction mixture was refluxed for 24 h. Then, the reaction mixture was concentrated and the crude product was purified by silica gel column chromatography. Elution of the column with 1.5% EtOAc/petroleum ether gave **12** as a white crystalline solid (40 mg, 47%). Mp 84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 3.91$ (d, 2H, $J = 3$ Hz), 4.63 (s, 2H), 5.5 (d, 1H, $J = 11.4$ Hz), 5.96 (dt, 1H, $J = 11.4$, 5.2 Hz), 7.23 (d, 1H, $J = 8.4$ Hz), 7.35 (dd, 1H, $J = 7.8$, 6.9 Hz), 7.45 (dd, 1H, $J = 7.2$, 8.4 Hz), 7.67 (d, 1H, $J = 8.7$ Hz), 7.77 (d, 1H, $J = 8$ Hz), 7.98 (d, 1H, $J = 8.4$ Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 24.7$, 70.6, 121.8, 123.1, 124.3, 126, 126.1, 128.1, 128.7, 130.5, 131.2, 131.8, 156.2. Mass: m/z 196 (M^+). Anal. calcd for $C_{14}H_{12}O$: C, 85.68; H, 6.16. Found: C, 85.28; H, 6.51.

2.4. RCM of 1,1-diallyl-1*H*-naphthalen-2-one 11 using the first generation Grubbs' catalyst

To a solution of compound **11** (150 mg, 0.7 mmol) in dry degassed toluene (15 mL) was added Grubbs' catalyst **5** (55 mg, 0.07 mmol, 10 mol %). The reaction mixture was refluxed for 7 days. Then, the reaction mixture was concentrated and the crude product was purified by silica gel column chromatography. Elution of the column with 2% EtOAc/petroleum ether gave unreacted starting material (11 mg). Further elution of the column with 2% EtOAc/petroleum ether gave compound **13** (23 mg, 19%, based on starting material recovered). IR (neat): ν_{max} 1663 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.62$ (d, 2H, $J = 13.8$ Hz), 3.17 (d, 2H, $J = 13.8$ Hz), 5.78 (s, 2H), 6.19 (d, 1H, $J = 9.9$ Hz), 7.27 (m, 2H), 7.35 (m, 2H), 7.43 (d, 1H, $J = 9.6$ Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 49.3$, 55.9, 125.1, 125.8, 126.8, 128.1, 128.7, 129.0, 130.5, 144.9, 149.6, 203.7. HRMS (EI): calcd for $C_{14}H_{12}O$: 196.0888; found: 196.0874. Continued elution of the column with the same solvent system gave **14** (41 mg, 34%, based on starting material recovered). IR (neat): ν_{max} 1664 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.01$–2.09 (m, 1H), 2.53–2.78 (m, 3H), 5.55–5.59 (m, 1H), 6.20 (d, 1H, $J = 10.2$ Hz), 6.22–6.24 (m, 1H), 7.20–7.36 (m, 4H), 7.46 (d, 1H, $J = 9.9$ Hz). ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 32.8$, 40.2, 65.9, 125.3, 127.2, 127.4, 129.1, 129.5, 130.4, 133.4, 135.6, 145.4, 146.4, 203.6. HRMS (EI): calcd for $C_{14}H_{12}O$: 196.0888; found: 196.0889.

2.5. RCM reaction of 1,1-diallyl-1*H*-naphthalen-2-one 11 using the second generation Grubbs' catalyst

To a solution of compound **11** (32 mg, 0.14 mmol) in dry degassed DCM (15 mL) was added Grubbs' catalyst **6** (7 mg, 0.008 mmol, 6 mol %). The reaction mixture was refluxed for 6 h. Then, the reaction mixture was concentrated and the crude product was purified by silica gel column chromatography. Elution of the column with 2% EtOAc/petroleum ether gave compound **13** (23 mg, 83%) as the exclusive product, showing the same



Scheme 5. Possible mechanism for the isomerization of the double bond in the presence of Grubbs' catalyst.

spectral data as that of **13** obtained by RCM of 1,1-diallyl-1*H*-naphthalen-2-one **11** using the first generation Grubbs' catalyst.

2.6. Palladium–charcoal catalyzed reduction of compound 13

To a three necked flask (25 mL) were added 10% Pd–charcoal (13 mg) and freshly distilled ethyl acetate (15 mL). The solvent was saturated with an atmospheric pressure of hydrogen for 30 min followed by addition of **13** (24 mg, 0.12 mmol) in ethyl acetate (1 mL). After completion of the reaction (1 h, TLC monitoring), the catalyst was removed by filtration and the filtrate was concentrated. Then the crude product was purified by silica gel column chromatography. Elution of the column with 2% EtOAc/petroleum ether gave compound **15** (12 mg, 48%). Mp (2,4-dinitrophenylhydrazone derivative of **15**): 118–119 °C (lit. 122–123 °C).[10] Continued elution of the column with the same solvent system gave **16** (11 mg, 45%). Mp 70 °C. IR (neat): ν_{max} 3377 cm^{-1} (br). ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.55$ (br s, 1H), 1.75–2.17 (m, 10H), 2.8 (dt, 1H, $J = 17.2$, 6 Hz), 3.15 (dt, 1H, $J = 16.6$, 8.1 Hz), 3.8 (d, 1H, $J = 4$ Hz), 7.04–7.27 (m, 4H). ^{13}C NMR (75.4 MHz, $CDCl_3$): $\delta = 25.7$, 26.3, 26.7, 27.7, 34.2, 41.9, 51.3, 74.5, 125.5, 126.4, 127.6, 128.6, 134.7, 145.0. Anal. calcd for $C_{14}H_{18}O$: C, 83.11; H, 8.97. Found: C, 82.78; H, 8.97.

Acknowledgements

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