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Regioselective Synthesis of Spiro-Oxindoles via a Ruthenium-Catalyzed Metathesis Reaction †

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Abstract: Spiro-oxindoles are important heterocyclic motifs found in various alkaloids, many of which exhibit pharmacological properties. Due to the remarkable biological activity of spiro-oxindoles, significant effort has been made towards the synthesis of substituted spiro-oxindoles. In this paper, preliminary results regarding the synthesis of 3,3′-spiro pentacyclo-oxindole derivatives via the ring-closing metathesis of 3,3-diallyl oxindoles are reported. The ring-closing metathesis reaction proceeded smoothly with Grubb's catalyst-I (2 mol%) in toluene at room temperature. The desired products, 3,3′-spiro pentacyclo-oxindoles, were obtained in good to excellent yields under standard reaction conditions.

Keywords: oxindole; 3,3′-diallyl indoles; spirocyclo-oxindoles; ring-closing metathesis; grubb's catalyst

1. Introduction

Indoles and their annulated derivatives are very important heterocyclic compounds found in a variety of natural products [1,2], several of which exhibit remarkable biological activities, including antimalarial, anti-inflammatory, antiasthmatic, antibacterial, antihypertensive, anti-cancer, and tyrosine kinase-inhibiting agents [3,4]. Spirocycloxindoles also have wide applications in medicinal chemistry and pharmacological fields [5–11]. Several functionalized spirocycloalkyloxindoles have been used as an active intermediate for the preparation of complex molecules of biological interest [12]. This core moiety is the basic skeleton of various natural alkaloids, including coerulescine, horsfiline, welwitindolinone A, spirotryprostatin A, elacomine, alstonisine, surugatoxin, etc. [13–17]. Due to the remarkable biological activity of spiro-oxindoles significant effort has been paid towards the synthesis of substituted spiro-oxindole derivatives [12,18,19]. However, the application of ring-closing metathesis [20–22] for the synthesis of spirocyclo-oxindole derivatives has not been reported.

During the last decades, ring-closing metathesis (RCM) reactions have been widely used as a synthetic tool for the construction of a great variety of carbo- and heterocyclic systems [23–29]. RCM has been considered a highly effective and practical method in organic synthesis. In our previous study [30,31], we reported the synthesis of some annulated heterocycles via RCM using ruthenium carbene catalyst-I and II (Figure 1) [32,33]. In this paper, we report the preliminary results of the ring-closing metathesis reaction involving the indole moiety. The ring-closing metathesis reaction of 3,3-diallyl oxindoles leads to 3,3′-spiro pentacyclo-oxindole derivatives with 2 mol% of Grubb's catalyst-I in toluene solvent. The required starting materials, 3,3-diallyl oxindoles, were prepared by the simple alkylation of oxindoles with allyl bromide in the presence of NaH at room temperature.

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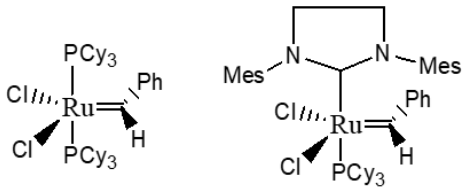
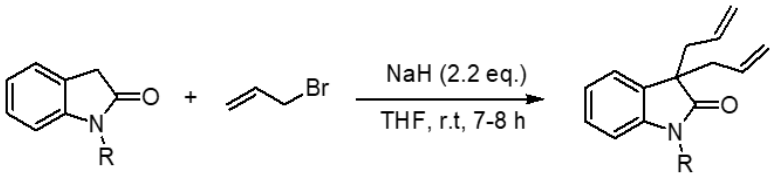


Cat-I **Cat-II**

Figure 1. Structure of Grubb's catalysts.

2. Result and Discussion

We chose 3,3-diallyl oxindoles (2) as starting materials for the preparation of 3,3′-spiro pentacyclo-oxindoles. The simple alkylation of oxindoles with allyl bromide in the presence of NaH at room temperature gives the requisite starting materials, 3,3′-diallyl oxindoles (Scheme 1).

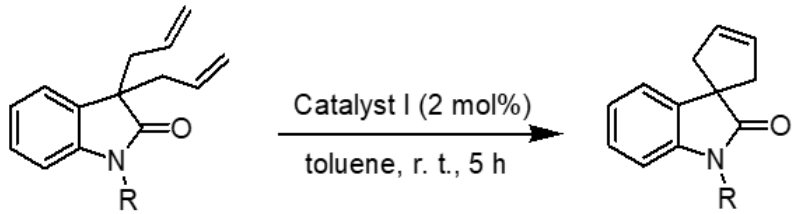


1a. R = Me
1b. R = Et
1c. R = Ph

2a. R = Me (71%)
2b. R = Et (69%)
2c. R = Ph (56%)

Scheme 1. Preparation of 3,3-diallyl *N*-substituted 2-oxindoles.

To examine the feasibility of the metathesis approach, we attempted the ring-closing metathesis (RCM) reaction of diene **2a** with 2 mol% of catalyst-I. RCM on diene **2a** with 2 mol% of catalyst-**I** in CH_2Cl_2 at room temperature under a nitrogen atmosphere led to 3,3′-spiro pentacyclo-oxindole (**3a**) in poor yield (37%). The use of 5 mol% of catalyst did not improve the yield of the product to any appreciable extent. However, the yield of the product was found to be raised to 92% by conducting the reaction in toluene at room temperature (Scheme 2). Heating the reaction at 60 °C led to considerable decomposition of the starting materials. The ring-closing metathesis reactions with compounds **2b** and **2c** also proceeded smoothly with 2 mol% of Grubb's catalyst-I in toluene solvent at room temperature. All the reactions were completed in 5h and provided a high yield of spiro-oxindole derivatives.



2a. R = Me
2b. R = Et
2c. R = Ph

3a. R = Me (92%)
3b. R = Et (90%)
3c. R = Ph (84%)

Scheme 2. Ring-closing metathesis of diallyl indoles.

3. Conclusions

In conclusion, we carried out the ring-closing metathesis of 3,3-diallyl oxindoles with Grubb's first-generation catalyst for the synthesis of 3,3′-spirocyclic oxindoles. The reaction occurred smoothly at room temperature in a short amount of time.

4. Experimental

The melting points of the newly synthesized compounds were determined in open capillaries and are uncorrected. ^{1}H NMR (400 MHz) spectra were recorded on a Bruker DPX-400 spectrometer in $CDCl_3$ solvent with TMS as an internal standard. Silica gel [(60–120 mesh), Spectrochem, India] was used for chromatographic separation. Pre-coated aluminum plates [Merck (India)] were used for thin-layer chromatography.

4.1. Procedure for the Preparation of Compound **2a**

A mixture of *N*-methyl 2-oxyindole **1** (0.500 gm, 3.40 mmol), allyl bromide (2.5 eq., 8.5 mmol), and NaH was stirred in dry THF (20 mL) for 7 h at room temperature. The reaction mixture was quenched with water, and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined CH_2Cl_2 extract was washed with water and dried ($MgSO_4$). The residual mass after removal of CH_2Cl_2 was subjected to column chromatography over silica gel (60–120 mesh) using petroleum ether/ethyl acetate (9:1) as eluent to give compounds **2a.**

4.1.1. Compound **2a**

Yield: 71%; colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.51–2.62 (m, 4H), 3.74 (s, 3H), 4.83 (d, *J* = 10.1 Hz, 2H), 4.99 (d, *J* = 17.0 Hz, 2H)), 5.30–5.41 (m, 2H), 6.79 (d, *J* = 7.7 Hz, 1H), 7.17 (t, *J* = 7.1 Hz, 1H), 7.16–7.26 (m, 2H) ppm; MS: *m/z* for $C_{15}H_{17}NO$: 227 [M^+].

4.1.2. Compound **2b**

Yield: 69%; colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.19 (t, *J* = 7.2 Hz, 3H), 2.49–260 (m, 4H), 3.71 (q, *J* = 7.2 Hz, 2H), 4.86 (d, *J* = 10.2 Hz, 2H), 4.97 (d, *J* = 16.9 Hz, 2H), 5.32–5.42 (m, 2H), 6.81 (d, *J* = 7.76 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 7.19 (d, *J* = 7.3 Hz, 1H), 7.22–7.24 (m, 1H) ppm; MS: *m/z* for $C_{16}H_{19}NO$: 241 [M^+].

4.1.3. Compound **2c**

Yield: 56%; colorless solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.49–2.60 (m, 4H), 4.81 (d, *J* = 10.1 Hz, 2H), 4.98 (d, *J* = 17.0 Hz, 2H), 5.29–5.40 (m, 2H), 6.70 (d, *J* = 7.2 Hz, 1H), 7.13–7.18 (m, 3H), 7.77–7.33 (m, 3H), 7.41–7.43 (m, 1H) ppm; MS: *m/z* for $C_{20}H_{19}NO$: 289 [M^+].

4.2. Typical Procedure for the Enyne RCM

Grubb's catalyst-I (2 mol%) was added to a magnetically stirred solution of **2a** (114 mg, 0.5 mmol) in dry toluene (2 mL) under an N_2 atmosphere. The reaction mixture was stirred at room temperature for 5 h. After completion, the solvent was removed under reduced pressure, and the residue was subjected to column chromatography over silica gel using petroleum ether-ethyl acetate (4:1) as the eluent to give **3a** in 92% yield. Similar treatments of compounds **2b** and **2c** provided **3b** and **3c** in 90% and 84% yields, respectively.

4.2.1. Compound **3a**

Yield: 92%; solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.58 (d, *J* = 14.4 Hz, 2H), 2.98 (d, *J* = 14.9 Hz, 2H), 3.22 (s, 3H), 5.83 (s, 2H), 6.81 (d, *J* = 8.0 Hz, 1H), 7.01 (t, *J* = 7.44 Hz, 1H), 7.22–7.25 (m, 2H) ppm; MS: *m/z* for $C_{13}H_{13}NO$: 199.0987 [M^+].

4.2.2. Compound **3b**

Yield: 90%; solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.27 (t, *J* = 7.3 Hz, 3H), 2.57 (d, *J* = 14.6 Hz, 2H), 2.98 (d, *J* = 14.8 Hz, 2H), 3.76 (q, *J* = 7.2 Hz, 2H), 5.82 (s, 2H), 6.83 (d, *J* = 7.7 Hz, 1H), 6.99 (t, *J* = 7.3 Hz, 1H), 7.21–7.25 (m, 2H) ppm; MS: *m/z* for $C_{14}H_{15}NO$: 213.1172 [M^+].

4.2.3. Compound **3c**

Yield: 84%; solid; ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.58 (d, *J* = 14.7 Hz, 2H), 2.99 (d, *J* = 14.7 Hz, 2H), 5.83 (s, 2H), 6.82 (d, *J* = 7.7 Hz, 1H), 7.01 (t, *J* = 7.3 Hz, 2H), 7.21–7.25 (m, 4H), 7.28–7.31 (m, 2H) ppm; MS: *m/z* for $C_{18}H_{15}NO$: 261.1160 [M^+].

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