chemistry proceedings

MDPI

Proceeding Paper

Regioselective Synthesis of Spiro-Oxindoles by Ruthenium Catalyzed Metathesis Reaction †

Pradip Debnath

Department of Chemistry, Maharaja Bir Bikram College, Agartala, Tripura 799004, India; pradipchem78@gmail.com; Tel.: +91-381-2526607; Fax: +91-381-2516728

† Presented at the 27th International Electronic Conference on Synthetic Organic Chemistry (ECSOC-27), 15–30 November 2023; Available online: https://ecsoc-27.sciforum.net/.

Abstract: Spiro-oxindoles are important heterocyclic motifs found in various alkaloids and many of which exhibited pharmacological properties. Due to the remarkable biological activity of spiro-oxindoles, significant effort has been paid towards the synthesis of substituted spirooxindoles. In this paper, the preliminary results towards the synthesis of 3,3′-spiro pentacyclo-oxindole derivatives by the ring-closing metathesis of 3,3-diallyl oxindoles has been 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

Citation: Debnath, P. Regioselective Synthesis of Spiro-Oxindoles by Ruthenium Catalyzed Metathesis Reaction. **2023**, *14*, x. https://doi.org/10.3390/xxxxx

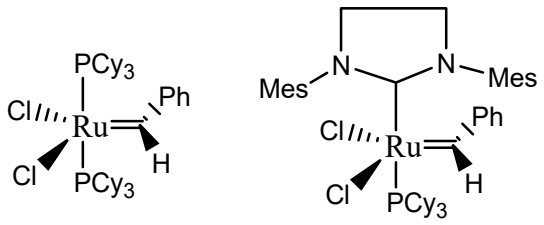
Academic Editor(s):

Published: 15 November 2023

Introduction

Indoles and its annulated derivatives are very important heterocyclic compounds found a variety natural products [1] and several of which exhibited remarkable biological activities including antimalarial, anti-inflammatory, antiasthmatic, antibacterial, antihypertensive, anti-cancer and tyrosine kinase inhibiting agents [2]. Spirocycloxindoles also have wide applications in medicinal chemistry and pharmacological fields.[3] Several functionalized spirocycloalkyloxindoles has been used as an active intermediate for the preparation of complex molecules of biological interest [4]. This core moiety is the basic skeleton of various natural alkaloids including coerulescine, horsfiline, welwitindolinone A, spirotryprostatin A, elacomine, alstonisine, surugatoxin, etc [5]. Due to the remarkable biological activity of spiro-oxindoles, significant effort has been paid towards the synthesis of substituted spirooxindole derivatives [4,6]. However, application of ring closing metathesis [7] for the synthesis of spirocyclo-oxindole derivatives has not been reported.

During the last decades, the 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 [8]. The RCM has been considered as a highly effective and practical method in organic synthesis. In our previous works [9], we have reported the synthesis of some annulated heterocycles by RCM using ruthenium carbene catalyst-I and **II** (Figure 1) [10]. In this paper, we reported the preliminary results of the ring closing metathesis reaction involving indole moiety. The ring-closing metathesis reaction of 3,3-diallyl oxindoles leading 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.



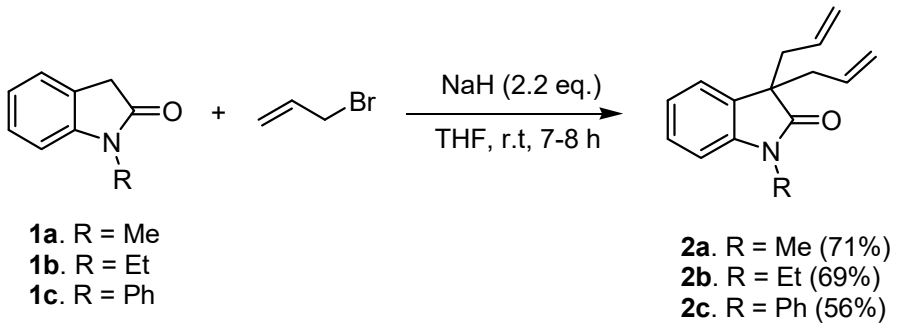
Cat-I **Cat-II**

Figure 1. Structures of Grubb's catalysts)

Figure 1.

Result and Discussion

We have chosen 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 to give the requisite starting materials 3,3′-diallyl oxindoles (Scheme 1).



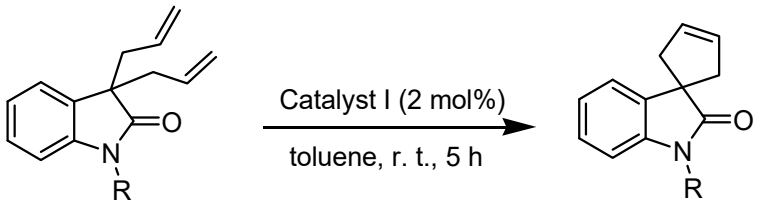
1a. R = Me
1b. R = Et
1c. R = Ph

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

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

Scheme 1.

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**.** The RCM on diene **2a** with 2 mol% of catalyst-**I** in CH_2Cl_2 at room temperature under 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 of the reaction at 60 °C led to considerable decomposition of the starting materials. The ring-closing metathesis reactions with compounds **2b** and **2c** were 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 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.

Scheme 2.

Conclusions

In conclusion, we have 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 short reaction of time.

Experimental

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 internal standard. Silica gel [(60–120 mesh), Spectrochem, India] was used for chromatographic separation. Pre-coated Aluminum plate [Merck(India)] is used for thin layer chromatography

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), NaH was stirred in dry THF (20 mL) for 7 h at room temperature. The reaction mixture was quenched with water and resulted 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.**

Compound 2a.

Yield: 71 %; colourless 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^+].

Compound 2b.

Yield: 69 %; colourless 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^+].

Compound 2c.

Yield: 56 %; colourless 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^+].

Typical Procedure for the Enyne RCM:

The 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 N_2 atmosphere. The reaction mixture was stirred at room temperature for 5 h. After completion of reaction time, the solvent was removed under reduced pressure and the residue was subjected to column chromatography over silica gel using petroleum ether-ethyl acetated (4:1) as eluent to give **3a** in 92 % yield. Similar treatment of compound **2b** and **2c** provided **3b** and **3c** in 90 % and 84 % yields, respectively.

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^+].

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^+].

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^+].

Acknowledgement: The author is thankful to Maharaja Bir Bikram College, Agartala for providing infrastructural facilities and Tripura University for spectroscopic facilities.

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