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Diversity-Oriented Synthesis of oxacyclic spirooxindole derivatives through ring-closing enyne metathesis and intramolecular Pauson−Khand (2 + 2 + 1) cyclization of oxindole enynes

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Abstract: An efficient approach for a reagent-based Diversity-Oriented Synthesis (DOS) of novel fused spiro-oxindole scaffolds have been reported from oxindole enynes. The reaction involves a metal-catalyzed *C*-3 allylation/vinylation/homoallylation of *N*-substituted isatins gives rise to corresponding alcohols that can be converted into required enynes, further transformed to a diverse complex molecular scaffolds *via* subsequent Ruthenium catalyzed ring-closing enyne metathesis (RCEYM), or Cobalt catalyzed intramolecular Pauson−Khand (2 + 2 + 1) cyclization reaction (IPKR). This strategy provided a facile approach to various spirooxindole-vinyl dihydropyrans/tetrahydrooxepines and spirocyclic fused cyclopentenones in good to excellent yields.

Keywords: Diversity-Oriented Synthesis, Ring-closing enyne metathesis, intramolecular Pauson−Khand (2 + 2 + 1) cyclization, Oxindole enynes, Oxacyclic spirooxindoles, Fused cyclopentenones

Introduction

The discovery of new chemical entities for drug discovery has received considerable attention during the last few decades. In this context, Diversity-Oriented Synthesis (DOS) has emerged as a powerful tool to get the maximum structural variability from simple starting materials.[1,2] Especially, oxygen- and nitrogen-containing heterocycles have attracted the attention of synthetic and medicinal chemists because of the widespread occurrence of such structural motifs in natural and unnatural products and their use as building blocks.[3] Moreover, spirooxindoles have become a privileged skeleton given their broad and promising activities in various therapeutic areas.

Spirooxindole frame-work has drawn tremendous interest of researchers in the area of synthetic organic chemistry and medicinal chemistry worldwide because they occur in many natural products such as spirotryprostatins, horsfiline, gelsemine,[4] gelseverine,[4] (Figure 1) rhynchophylline, and elacomine, etc. and have been reported to have various types of bioactivity.[5] Some of the bioactive spirocyclic oxindole derivatives, for example (Figure 1) XEN907,[6] compound A (luminescent),[7] CB2 receptor antagonist,[8] progesterone receptor modulators,[9] anti-HIV,[10] anticancer,[11] antitubercular,[12] antimalarial,[13,14] and MDM2 inhibitors[15] were found in the literature. Therefore, the construction of spirooxindole skeleton has attracted great attention of synthetic chemists[16].

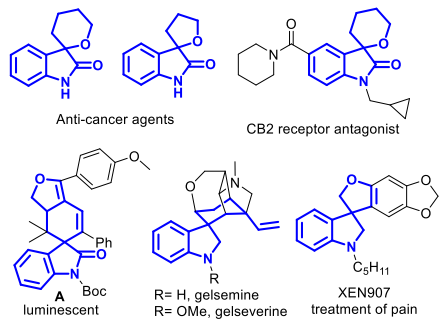

Figure 1: Examples of some natural and bioactive compounds containing spirocyclic oxindole scaffolds

Additionally, interesting and biologically active natural products containing bicyclic fused

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cyclopentenones are also common.[17-18] These are demonstrated in Figure 2. Among these, bicyclo[4.3.0]nonane,[17] and bicyclo[3.3.0]octane[18] frameworks are normally originate in bioactive natural products. For example, alisol-L,[17a] minwaninone,[17c] jiadifenin,[17c] hirsutanol A,[18a] incarnal,[18a] chondrosterin A[18a] are some of the representative natural products bearing 5,6-bicyclic, and 5,5-bicyclic cyclopentenone motifs in their structures.

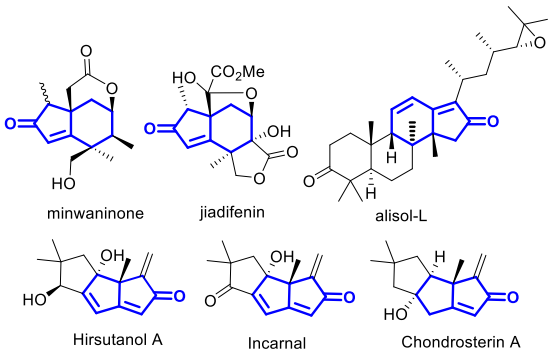
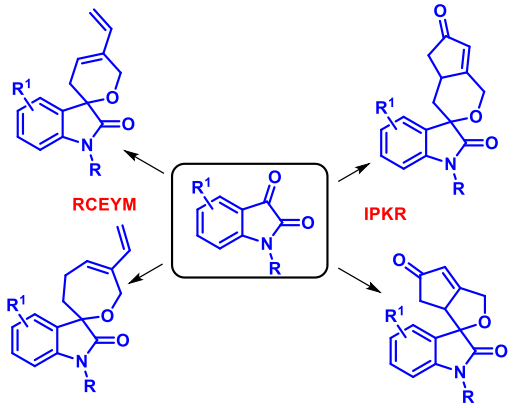


Figure 2: Natural products having a bicyclic fused cyclopentenone system.

These bicyclic fused cyclopentenone derivatives serve as valuable building blocks in the synthesis of various natural products,[19] such as (+)-propindilactone G,[19c] (+)-ryanodol,[19d] (+)-Penostatin E,[19e] (+)-Sieboldine A[19f] and Paecilomycine A.[19g]

The ring closing enyne metathesis (RCEYM),[20] has attracted attention due to its synthetic potential in the generation of ring structures with 1,3-diene moieties, which can subsequently be further functionalised. While, the Pauson-Khand reaction (PKR)[21] is widely used as a powerful method for the synthesis of cyclopentenone ring systems. The intramolecular version of the reaction has gained much popularity because it can afford cyclopentenone-fused ring systems, which are difficult to construct. Due to their important roles, we have utilized these two synthetic methods to construct spirocyclic oxindole based compounds from oxindole enynes.

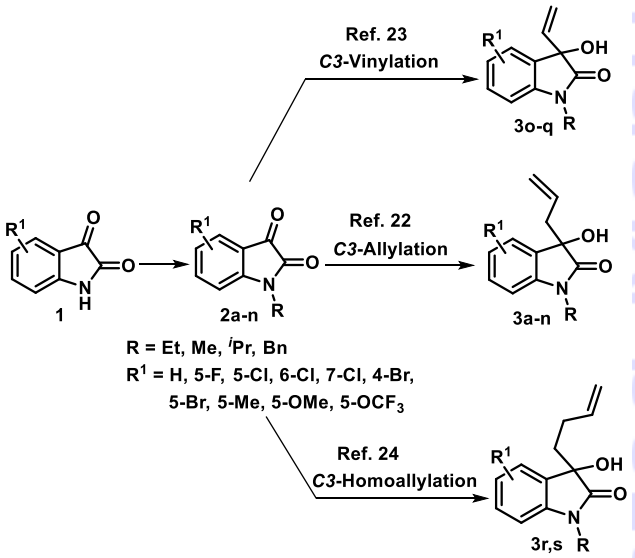


Scheme 1: DOS strategy

Herein, we wish to report our results on the synthesis of diverse spirooxindole-vinyl dihydropyran/tetrahydrooxepines and spirooxindole-5,6-bicyclic/5,5-bicyclic cyclopentenone derivatives (Scheme 1) from oxindole enynes, which are constructed from isatins.

We started our investigation with the preparation of the desired oxindole alcohols **3a-s** from isatins (Scheme 2). For this, first we synthesized *N*-alkylated isatins **2a-n** by treating various isatins (**1**) with K_2CO_3 and different alkyl halides. Then these were subjected to a metal-mediated Nucleophilic addition to ketone group at *C3*-position to get variety of transformations such as *C3*-Allylation[22] **3a-n**, *C3*-Vinylation[23] **3o-q**, *C3*-Homoallylation[24] **3r**,**s** with good yields as illustrated in Scheme 2.

Scheme 2: Diverse synthesis of oxindole alcohols starting from isatins



Results and Discussion

Now, the desired enyne intermediates, 3-allyl-1-substituted-3-prop-2-ynyloxy)-indolin-2-ones (1,7-enynes, **4a-n**) could be accessed in 89-99% yields by *O*-propargylation of the homoallylic alcohols **3a-n** with propargyl bromide in the presence of NaH and a catalytic amount of TBAI in dry THF at 0 °C-rt. Under similar conditions, propargylation of **3o-q** and **3r,s** yielded 1-substituted-3-(prop-2-ynyloxy)-3-vinylindolin-2-ones (1,6-enynes, **4o-q**) and 1-benzyl-3-(but-3-enyl)-3-(prop-2-ynyloxy)indolin-2-ones (1,8-enynes, **4r,s**) respectively as shown in Scheme 3.

These enynes **4a-s** would in turn become suitable substrates for selected transition metal catalyzed transformations (ring-closing enyne metathesis RCEYM, intramolecular Pauson−Khand reaction

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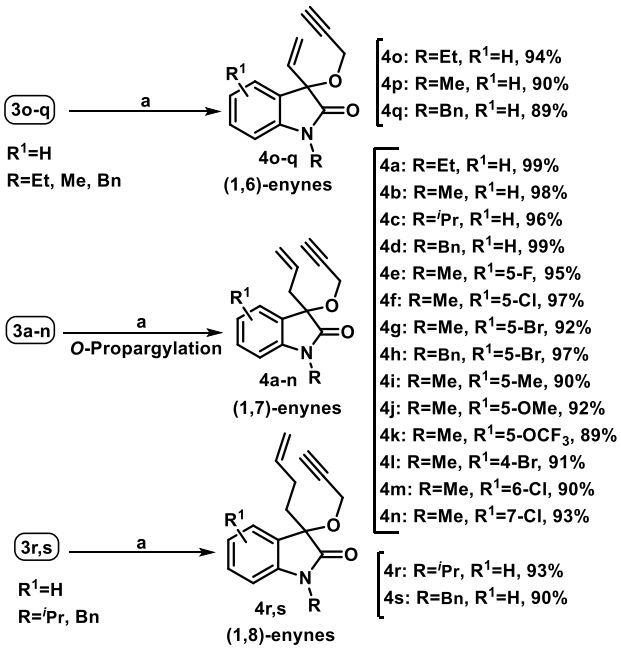
IPKR), aimed at obtaining a small collection of structurally diverse molecules in a single step.

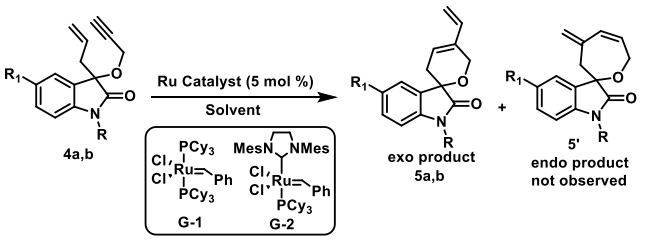
Scheme 3: Diverse synthesis of oxindole enynes



Reagents and conditions: (a) Propargyl bromide, NaH, TBAI (cat.), Dry THF, 0 °C-rt, 8-12 h.

To evaluate the feasibility of RCEYM (ring closing enyne metathesis) reaction,[20] 3-allyl-1-ethyl-3-(prop-2-ynyloxy)indolin-2-one (**4a)** was chosen as a model substrate and was initially treated with Grubbs-I (containing PCy_3 ligand) and Grubbs-II (containing *N*-heterocyclic carbene (NHC) ligand) catalysts in THF at room temperature for 48 h and 72 h, a vinyl dihydropyran derivative, 1-ethyl-5'-vinyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one (**5a**) was obtained in 55% and 50% yields respectively (Table 1, entry 1 & 2). To improve the efficiency, different solvents (toluene and DCM), temperatures and timings were tried (entries 3−6). Among them, DCM as the reaction medium at reflux temperature for 12 h was the most efficient. The reaction with Grubbs-II catalyst was less efficient than Grubbs-I in promoting this reaction (entries 2 & 6). Since triple bond is more electron donating than a double bond, the RCEYM reaction occurs successfully with the less active first-generation Grubbs catalyst and proceeds under mild conditions. For consistency, we performed the reaction of **4b** with 5 mol% of Grubbs-I catalyst in DCM (40 °C, 12 h), which yielded **5b** in 92 % (Table 1, entry 7). In summary of the optimization study, we observed only the *exo* product **5a** formation over the *endo* product **5'** with both Grubbs-I and Grubbs-II catalysts[25] as shown in Table 1. The structure of **5a** was confirmed by NMR analysis and also finally confirmed by NOE analysis.

Table 1: Optimization of RCEYM Reaction[a]



entry	substrate	Catalyst/conditions	yield(%)[b]
1	4a	G-1/THF, rt, 48 h	55
2	4a	G-2/THF, rt, 72 h	50
3	4a	G-1/Toluene, rt, 40 h	45
4	4a	G-1/Toluene, 50 °C, 24 h	65
5	4a	G-1/DCM, reflux, 12 h	90
6	4a	G-2/DCM, reflux, 20 h	76
7	4b	G-1/DCM, reflux, 12 h	92

[a]All reactions performed under Ar atmosphere, Reaction conditions: **4** (0.539 mmol, 1.0 eq), G-1 (5 mol %), DCM (25 mL), reflux, 12 h. [b]Yields refer to pure products after column chromatography

The *exo* compound **5a** was determined by using detailed NMR experiments. The observed characteristic n*O*e cross-peaks between H_1−H_6, H_5-H_6, $H_{1'}$-H_3 and H_2−H_4 indicates that the six membered ring contains vinyl group as represented in Figure 3.

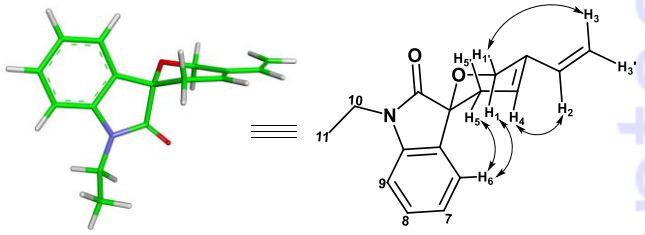


Figure 3: Chemical and energy-minimized structures of compound **5a**.

With these optimized reaction conditions at hand, we surveyed the substrate scope by varying the structure of (1,7)-enynes (**4a-n)**. As shown in Scheme 4, (1,7)-enynes bearing an alkyl substituent on the nitrogen, including Et, Me, ^{i}Pr, Bn **4a-d** performed well in RCEYM optimal conditions provided **5a-d** in excellent yields and we were delighted to find that the reaction also accommodated several substituents, including electron-donating and electron-withdawing groups such as 5-Me, 5-OMe, 5-OCF_3, 5-F, 5-Cl, 6-Cl, 7-Cl, 4-Br, 5-Br on the oxindole moiety, **4e-n** giving the corresonding spirooxindole-vinyl dihydropyrans **5e-n** in 84%-90% yields.

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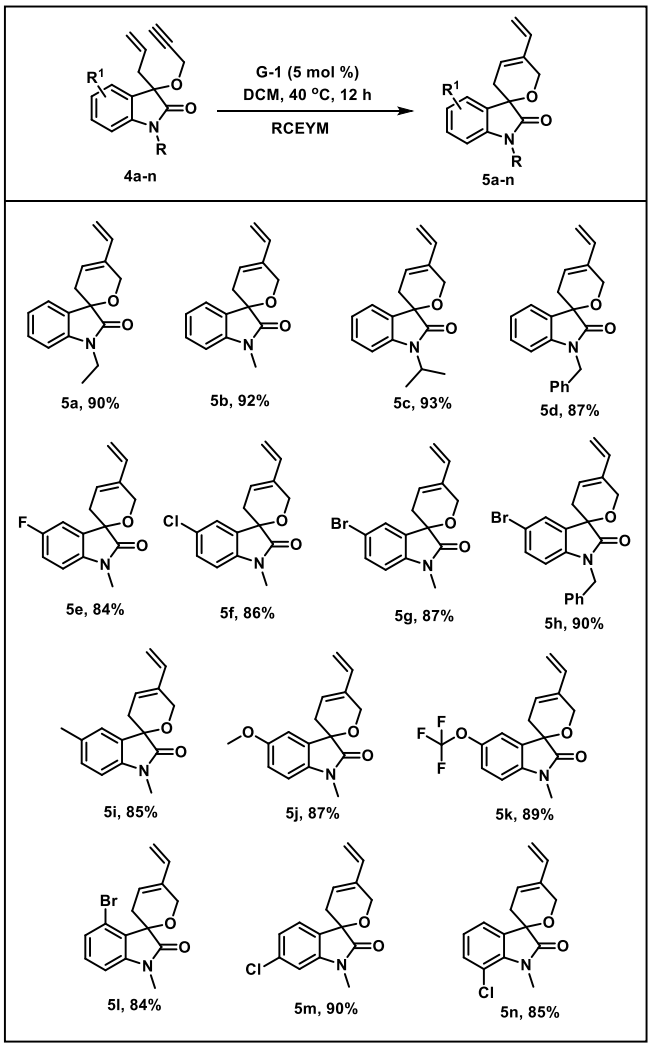
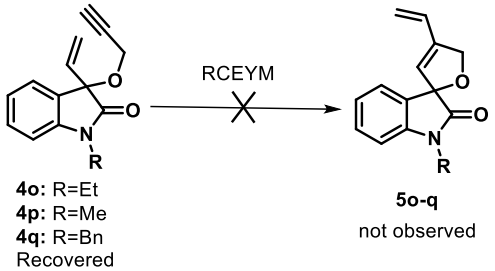
Scheme 4: Scope of RCEYM Reaction of (1,7)-enynes[a]



[a]Reaction conditions: **4** (0.539 mmol, 1.0 eq), G-1 (5 mol %), DCM (25 mL), reflux, 12 h. [b]Yields refer to pure products after column chromatography.

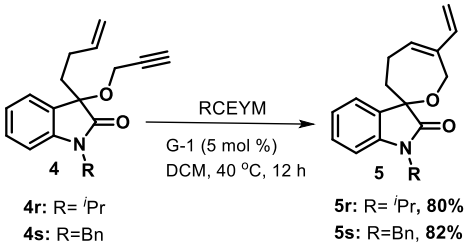
To investigate the applicability of this method to other ring systems, **4o-q** were subjected to RCEYM reaction. Unfortunately, RCEYM of **4o-q** with both Grubbs I & II in various solvents such as DCM, toluene, THF at different temperatures (rt-reflux) and time did not work to give the expected 1'-benzyl-4-vinyl-5H-spiro[furan-2,3'-indolin]-2'-ones 5**o-q** (Scheme 5). All the (1,6)-enynes **4o-q** were intact and recovered by column chromatography. One possible reason for this lack of reactivity in the RCEYM step is the steric hindrance of the oxindole in the starting material.

Scheme-5: RCM of (1,6)-enynes 4o-q



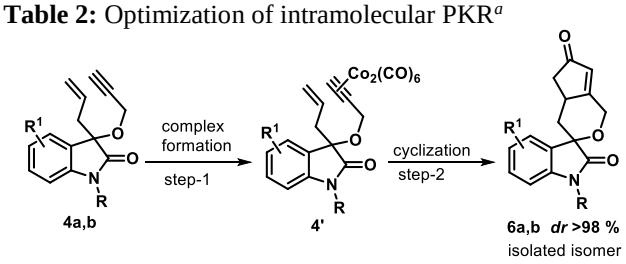
Further investigations demonstrated with 1,8-enynes (**4r,s**). Gratifyingly, RCEYM reaction of **4r,s** with Grubbs-I catalyst in refluxing DCM successfully provided 1-benzyl-6'-vinyl-4',7'-dihydro-3'H-spiro[indoline-3,2'-oxepin]-2-ones (**5r,s**) in 80% & 82% yields (Scheme 6).

Scheme 6: RCM of (1,8)-enynes (4r,s)



Next, we turned our attention towards IPKR.[21] The Pauson-Khand reaction generates three new carbon bonds as it forms a cyclopentenone in one step. The intramolecular route is reliable for the synthesis of [3.3.0] and [3.4.0] bicyclic systems. Recently, Schreiber et al. used these kind of small molecules in drug-discovery.[26] We carried out an optimization of the reaction conditions, the results of which are summarized in Table 2. Initially, complexation of $Co_2(CO)_8$ to the alkyne was best achieved in CH_2Cl_2 or THF,[27] occurring quantitatively within 2 h at rt (entry 1-7, Table 2, The alkyne-$Co_2(CO)_8$ complex formation was monitored by TLC), while the cycloaddition could be effected either in refluxing toluene within 2 h or in DCM at room temperature for 12 h using *N*-methylmorpholine *N*-oxide (NMO)[28] or Trimethylamine *N*-oxide (TMANO)[28] as the promotor. The use of DCM instead of toluene gave rise to a noticeable increase in chemical yield and accompanied by the formation of a isolated isomer **6a** (*dr* up to >98 %) (entry 5-7, Table 2). The structure of **6a** was established by NMR & NOE analysis.

Table 2: Optimization of intramolecular PKR[a]



entry	conditions for step-1/step-2	enone (%)[b]	dr[c]
1	4a, $Co_2(CO)_8$ (1.1 eq), DCM, rt, 2 h/ NMO (6.0 eq), $PhCH_3$, reflux, 2 h	56(**6a**)	95:5
2	4b, $Co_2(CO)_8$ (1.1 eq), DCM, rt, 2 h/ NMO (6.0 eq), $PhCH_3$, reflux, 2 h	45(**6a**)	95:5
3	4a, $Co_2(CO)_8$ (1.1 eq), THF, rt, 2 h/ NMO (6 eq), THF, rt, 20 h	72(**6a**)	5:1
4	4a, $Co_2(CO)_8$ (1.1 eq), THF, rt, 2 h/ Me_3NO (6.0 eq), THF, rt, 24 h	65(**6a**)	5:1
5	4a, $Co_2(CO)_8$ (1.1 eq), DCM, rt, 2 h/ NMO (6.0 eq), DCM, rt, 12 h	86(**6a**)	>98:2
6	4a, $Co_2(CO)_8$ (1.1 eq), DCM, rt, 2 h/ Me_3NO (6.0 eq), DCM, rt, 16 h	74(**6a**)	>98:2
7	4b, $Co_2(CO)_8$ (1.1 eq), DCM, rt, 2 h/ NMO (6.0 eq), DCM, rt, 12 h	85(**6b**)	>98:2

[a]Reaction conditions: step-1) **4** (0.623 mmol, 1.0 eq), $Co_2(CO)_8$ (0.685 mmol, 1.1 eq), DCM (15 mL), rt, 2 h; step-2) NMO (3.73 mmol, 6.0 eq), rt, 12 h. [b]Yields refer to pure products after column chromatography. [c]*dr* measured by NMR Spectroscopy.

The compound **6a** was determined by using detailed NMR experiments, such as 2D-NOESY, TOCSY and *J*-coupling analysis. The appearance of characteristic n*O*e cross-peaks between $H_{1'}$–H_2, H_1-H_4 and H_5-H_6 indicates that the isolated compound is having fused cyclopentenone ring as represented in Figure 4.

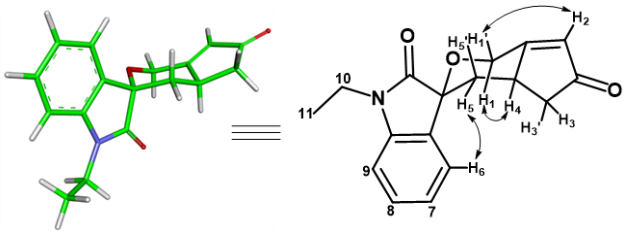
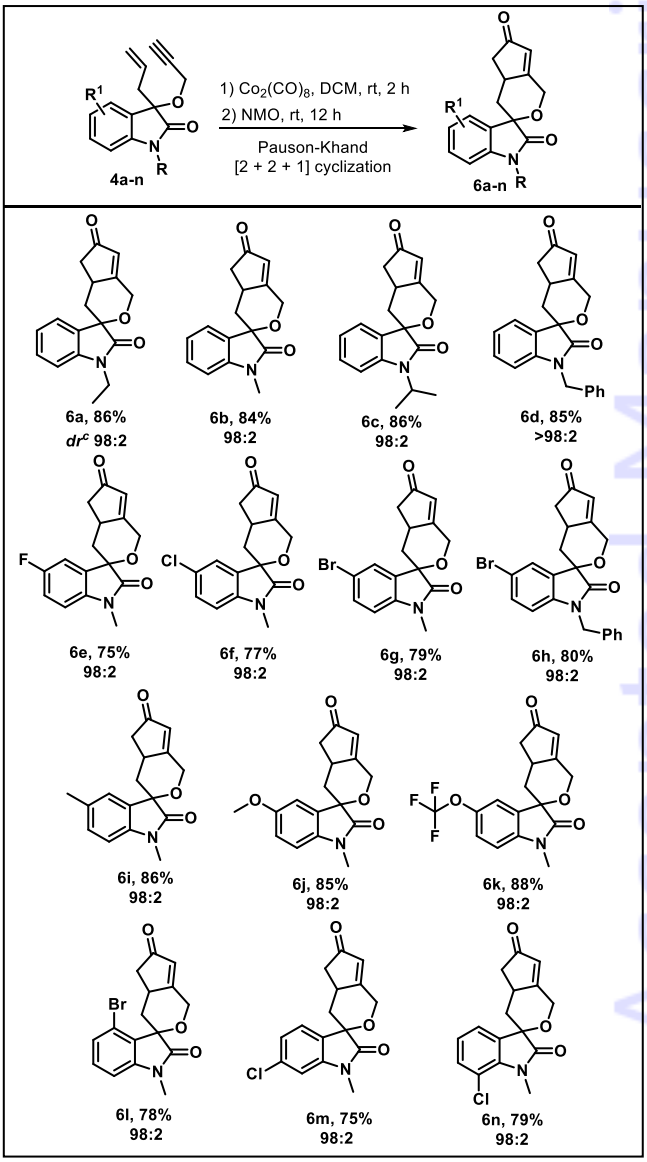


Figure 4: Chemical and energy-minimized structures of compound **6a**

As the optimized reaction conditions were established, it was applied to a series of oxindole (1,7)-enynes (**4a-n**). These (1,7)-enynes **4a-n** bearing a different R/R^1 groups were subjected to a tertiary amine *N*-oxide promoted Intramolecular Pauson–Khand cyclization, which provided structurally diverse spirooxindole-5,6-bicyclic fused cyclopentenones (**6**) at high yields as shown in Scheme 7. (1,7)-Enyne with various *N*-substituted substituents such as Et, Me, ^{i}Pr, Bn delivered **6a-d** as only isolated isomers (ratio >98:<2) in good yields. In detail, the electronic nature of the oxindole enynes had no obvious effect on the yields and isomeric ratio. For example, in the case of

Scheme 7: Scope of intramolecular PKR of (1,7)-enynes[a]

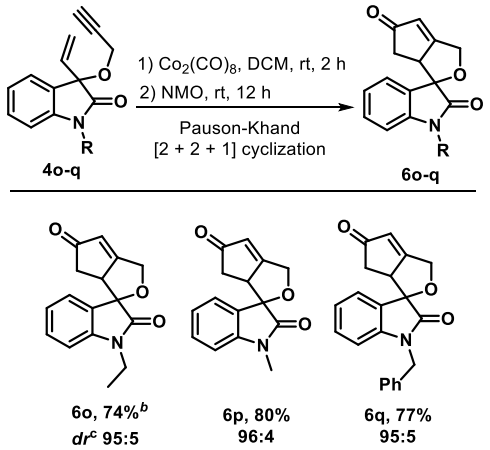


[a]Reaction conditions: step-1) **4** (0.623 mmol, 1.0 eq), $Co_2(CO)_8$ (0.685 mmol, 1.1 eq), DCM (15 mL), rt, 2 h ; step-2) NMO (3.73 mmol, 6.0 eq), rt, 12 h. [b]Yields refer to pure products after column chromatography. [c]*dr* measured by NMR Spectroscopy.

R^1 group at *C5*-position of oxindole moiety, both the electron-donating groups such as methyl (Me), methoxy (OMe) and electron-withdawing groups such as fluorine (F), chlorine (Cl), bromine (Br), trifluoromethoxy (OCF_3) proved to suitable substituents, which delivered the corresponding compounds **6e-k**. However, the other substrates having R^1 group at *C4*, *C6*, *C7*-position of the oxindole moiety, **4l-n** successfully participated in this reaction and afforded **6l-n** in good yields.

Later, we were encouraged to prepare a spirooxindole 5,5-bicyclic fused cyclopentenones.

Scheme 8: IPKR of (1,6)-enynes

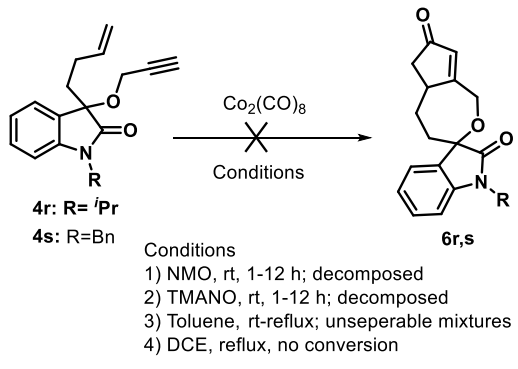


[b]Yields refer to pure products after column chromatography. [c]*dr* measured by NMR Spectroscopy.

For which, (1,6)-enynes **4o-q** were treated with $Co_2(CO)_8$ (1.1 eq) in DCM at rt for 2 h, followed by cyclization promoted with NMO (6.0 eq) at rt for 12 h (IPKR conditions) to obtain the spirooxindole 5,5-bicyclic cyclopentenones **6o-q** as a isomeric ratio >95:5 in 74-80% yields, which were shown in Scheme 8.

However, (1,8)-enynes of isatin (**4r,s)** were failed to give the respective PKR products **6r,s.** Compounds **4r,s** were transformed into the corresponding cobalt complexes**,** which was submitted to different IPKR reaction conditions as shown in Scheme 9. Unfortunately decomposition occured during cyclization in the presence of NMO and TMANO as the promotor at room temperature using DCM as solvent. Also, it was not successful in toluene and DCE under reflux conditions.

Scheme 9: IPKR of (1,8)-enynes



Based on the experimental results, the generality of these two methods (RCEYM and IPKR) were studied on a number of oxindole enynes for the synthesis of various oxacyclic spirooxindoles. As outlined in Schemes 4 and 7, both the methods can be used on (1,7)-enynes to obtain corresponding spirooxindole-vinyl dihydropyrans **5a-n** and spirooxindole-5,6-bicyclic fused cyclopentenone derivatives **6a-n** with good to excellent yields. At the same time, in the case of (1,6)-enynes successfully achieved 5,5-bicyclic fused cyclopentenones **6o-q** with good yields by using IPKR condition (Scheme 8). But, failed to cyclize with Grubbs catalysts I and II to produce **5o-q** (Scheme 5). Here, oxindole (1,6)-enynes may have steric hindrance and the starting material was recovered. However, the (1,8)-enynes easily cyclized with Grubbs catalyst to access spirooxindole-vinyl tetrahydrooxepines **5r,s** (Scheme 6). But, in the case of IPKR opposite results were shown (Scheme 9). Finally, although the difficulty to achieve ring sizes higher than five or six by using a Pauson-Khand reaction is familiar.[29] Here, we tried the reaction with various conditions as shown in Scheme 9 were not successful. Now, we are considering the scope of this IPKR for the formation of higher ring size. We will report on this and other aspects of this in due course.

Notably, to the best of our knowledge, this is the first approach to synthesize diverse spirooxindole-vinyl dihydropyran/tetrahydrooxepines and spirooxindole-5,6-bicyclic/5,5-bicyclic cyclopentenone derivatives from oxindole enynes proving the practical application of the methodology.

Conclusion

In summary, we have developed an efficient strategy for Diversity-Oriented Synthesis (DOS) of fused spiro-oxindole scaffolds from oxindole enynes via ring-closing enyne metathesis (RCEYM) and intramolecular Pauson−Khand (2 + 2 + 1) cyclization reaction (IPKR). Here, we disclose the synthesis of novel diverse spirooxindole-vinyl dihydropyran/tetrahydrooxepines and spirooxindole-5,6-bicyclic/5,5-bicyclic fused cyclopentenone derivatives from (1,6)/(1,7)/(1,8)-enynes with good to excellent yields. It provides the spirocycles that are of

increasing interest to the pharmaceutical industry. These kind of low molecular weight small libraries used in drug-discovery, including those relying on fragment-based drug discovery (FBDD), high-throughput screening (HTS) and realtime biological annotation.[26] We believe that the developed reaction approach will find the applications on relevant substrates to the synthesis of bioactive compounds.

EXPERIMENTAL SECTION

General Information. All the reactions were carried out in anhydrous solvents under inert atmosphere. ^{1}H NMR spectra were measured on 300 MHz, 400 MHz and 500 MHz spectrometers. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; dd = doublet of doublets; ddd = doublet of doublet of doublets; br = broad), coupling constant (Hz), integration, and assignment. ^{13}C NMR spectra were measured on 100 MHz and 125 MHz spectrometers. Chemical shifts were recorded in ppm from the solvent resonance employed as the internal standard (deuterochloroform at 77.0 ppm). 2D (TOCSY and NOESY) NMR spectra were recorded on Bruker Avance 400 MHz spectrometer in $CDCl_3$ at 298 K. High-resolution mass spectra (HRMS) were measured (ESI) on orbitrap mass spectrometers. Characteristic peaks in the infrared (IR) spectra were recorded in wave numbers, cm^{-1}. Melting points were determined on an Electro thermal melting point apparatus and are uncorrected. Thin-layer chromatography (TLC) was performed using 0.25 mm silica gel plates (60F-254). The products were purified by short column chromatography on silica gel 60-120 or 100−200 mesh. Commercially available $Co_2(CO)_8$ and NMO were used without further purification.

General procedure for the synthesis of (1,6)/(1,7)/(1,8)-enynes (4a-s, Scheme 3).

3a (1.58 mmol, 1.0 eq) was dissolved in dry THF (15 mL) at room temperature. NaH (60 %) (3.17 mmol, 2.0 eq) was added to the reaction at 0 °C and stirred for 20 min. Then propargyl bromide (80% w/w in toluene, 3.17 mmol, 2.0 eq) was added dropwise and allowed to rt and stirred for overnight. The reaction quenched with ice water and extracted with EtOAC. The crude residue purified by column chromatography (silica gel, 60-120) gave the compound **4a** in 99% yield.

***3-allyl-1-ethyl-3-(prop-2-yn-1-yloxy)indolin-2-one (4a)*:** R_f = 0.7 (petroleum ether/ethyl acetate, 9:1); yellow color liquid (399 mg, 99%); IR (neat) 3260, 3028, 2920, 2852, 2122, 1957, 1717, 1610, 1465, 1375, 1182, 1089, 992, 925, 749 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.24 (t, J = 7.2 Hz, 3H), 2.34 (t, J = 2.4 Hz, 1H), 2.65-2.72 (m, 1H), 2.76-2.83 (m, 1H), 3.64-3.73 (m, 1H), 3.76-3.85 (m, 2H), 3.92 (dd, J_1 = 14.6 Hz, J_2 = 2.4 Hz, 1H), 4.94-5.04 (m, 2H), 5.38-5.50 (m, 1H), 6.85 (d, J = 7.8 Hz, 1H), 7.10 (td, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H), 7.32-7.38 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.6, 34.6, 41.9, 53.5, 74.5, 79.2, 81.8, 108.5, 119.9, 122.7, 125.0, 126.1, 130.1, 130.2, 142.9, 174.4; HRMS calcd for $C_{16}H_{17}NO_2Na$ 278.1152 $[M + Na]^+$, found 278.1150.

General procedure for the RCEYM process: Preparation of Spirocyclic Oxindoles 5a-n (Scheme 4).

A solution of the corresponding enyne **4** (0.54 mmol, 1.0 eq) in dry DCM (25.0 mL) was degassed with Argon for 15 min. Then 1st generation Grubbs' catalyst (5 mol%) was added under inert atmosphere and again degassed with Argon for 5 min. Then the reaction mixture was heated at 40 °C for 10-12 h. Upon completion, the reaction was allowed to reach room temperature, solvents were removed under reduced pressure and the residue purified by flash chromatography using mixtures of *n*-hexanes:ethyl acetate (95:5) as eluent.

***1-ethyl-5'-vinyl-3',6'-dihydrospiro[indoline-3,2'-pyran]-2-one (5a)*:** R_f = 0.7 (petroleum ether/ethyl acetate, 9:1); off white solid (124 mg, 90%), mp 101−103 °C; IR (KBr) 3062, 2930, 1717, 1610, 1489, 1452, 1372, 1281, 1170, 1107, 1026, 751, 692 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3H), 2.27 (dd, J_1 = 17.9 Hz, J_2 = 5.3 Hz, 1H), 2.86 (dd, J_1 = 18.0 Hz, J_2 = 2.7 Hz, 1H), 3.76 (qd, J_1 = 7.2 Hz, J_2 = 1.6 Hz, 2H), 4.54 (dd, J_1 = 16.0 Hz, J_2 = 2.0 Hz, 1H), 4.73 (d, J = 16.1 Hz, 1H), 5.00-5.10 (m, 2H), 5.97-6.04 (m, 1H), 6.38 (dd, J_1 = 17.8 Hz, J_2 = 11.1 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 7.02 (td, J_1 = 7.6 Hz, J_2 = 0.9 Hz, 1H), 7.28 (dd, J_1 = 7.5 Hz, J_2 = 0.9 Hz, 1H), 7.33 (td, J_1 = 7.7 Hz, J_2 = 1.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 12.5, 30.5, 34.6, 62.1, 74.2, 108.6, 111.7, 122.5, 122.6, 124.4, 129.2, 129.7, 134.3, 135.3, 142.6, 174.3; HRMS calcd for $C_{16}H_{17}NO_2Na$ 278.1157 $[M + Na]^+$, found 278.1168.

General Procedure for intramolecular Pauson−Khand Reaction: Preparation of Spirocyclic fused Cyclopentenones 6a-q (Scheme 7 & 8).

To a solution of $Co_2(CO)_8$ (0.685 mmol, 1.1 eq) in anhydrous CH_2Cl_2 (15 mL) at rt was added a solution of the corresponding enyne **4** (0.623 mmol, 1.0 eq) in anhydrous CH_2Cl_2 (5.0 mL). The mixture was stirred at rt for 2 h, and then *N*-methylmorpholine N-oxide (NMO) (3.73 mmol, 6.0 eq) was added onto the freshly prepared cobalt complex solution. The resulting mixture was stirred at rt for 12 h. The reaction was monitored by TLC. Upon transformation of the complex, the mixture was filtered through a Celite pad, and the solvent was evaporated. The crude residue was purified by flash column chromatography using a mixture of AcOEt/ hexane (20:80) as the eluent.

***1'-ethyl-4a,5-dihydro-1H-spiro[cyclopenta[c]pyran-3,3'-indoline]-2',6(4H)-dione (6a)*:** R_f = 0.3 (petroleum ether/ethyl acetate, 7:3); off white solid (152 mg, 86%), mp 142−144 °C; IR (KBr) 3065, 2932, 2821, 1709, 1622, 1491, 1469, 1334, 1190, 1065, 1010, 741, 691 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, J = 7.2 Hz, 3H), 1.91-2.08 (m, 2H), 2.23 (dd, J_1 = 13.7 Hz, J_2 = 5.9 Hz, 1H), 2.68 (dd, J_1 = 18.7 Hz, J_2 = 6.6 Hz, 1H), 3.74 (q, J = 7.2 Hz, 2H), 3.91-

4.02 (m, 1H), 4.64 (d, J = 13.6 Hz, 1H), 5.40 (d, J = 13.6 Hz, 1H), 6.08 (s, 1H), 6.85 (d, J = 7.8 Hz, 1H), 7.09 (td, J_1 = 7.6 Hz, J_2 = 0.8 Hz, 1H), 7.24-7.38 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 12.5, 33.6, 34.3, 39.6, 41.7, 62.7, 75.3, 108.6, 123.1, 123.7, 127.7, 129.1, 130.1, 141.9, 174.7, 175.2, 207.5; HRMS calcd for $C_{18}H_{18}NO_3$ 284.1287 $[M + H]^+$, found 284.1289.

Supporting Information Available

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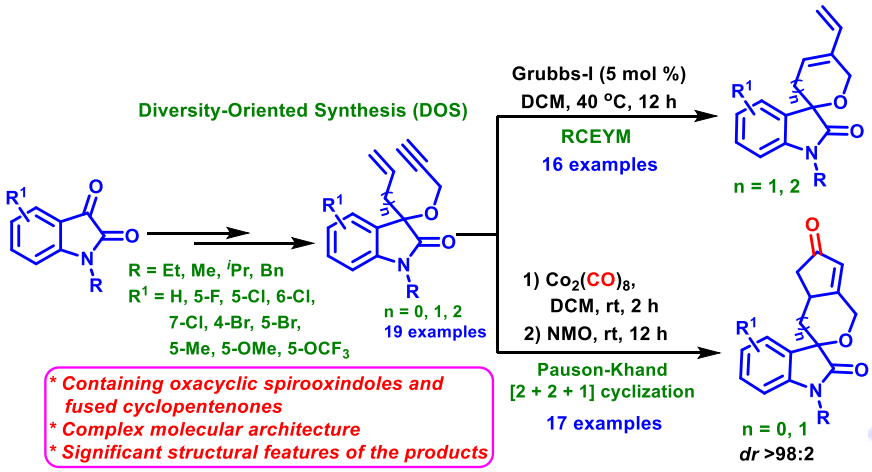
UPDATES

Diversity-Oriented Synthesis of oxacyclic spirooxindole derivatives through ring-closing enyne metathesis and intramolecular Pauson–Khand (2 + 2 + 1) cyclization of oxindole enynes



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