Article

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Regioselective Synthesis of Pyranone-fused Indazoles *via* Reductive Cyclization and Alkyne Insertion

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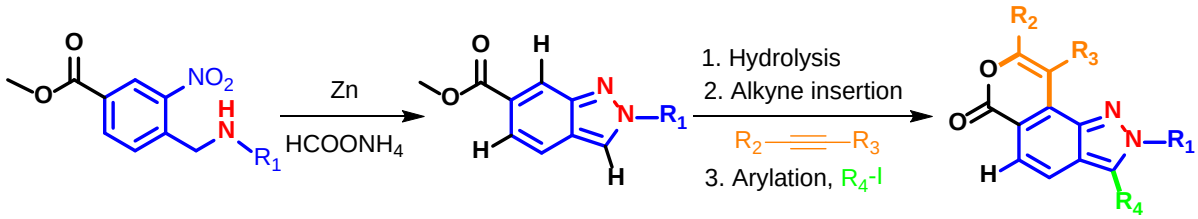
Graphic abstract



Abstract

A novel and efficient method for the one-pot synthesis of 2*H*-indazole from readily available building blocks is reported. The reaction of 2-nitrobenzylamines with zinc and ammonium formate underwent partial reduction to nitroso benzylamine followed by an intramolecular cyclization to afford 2*H*-indazole via N-N bond formation. The carboxylic acid moiety of indazole was proceeded to regioselective alkyne insertion under ruthenium catalysis to form pyranone-fused indazoles. The regioselectivity is influenced by the weak co-ordination of indazole ring nitrogen to the metal center.

Introduction

The indazole scaffold is a ubiquitous structural motif found in many natural products, agrochemicals and pharmaceutically important molecules.[1] In particular, 2*H*-indazole has been recognized as a privileged pharmacophore with a broad range of physiological and

pharmacological activities and it also acts as a bioisosteric replacement for other heterocycle structures such as indoles and benzimidazole.[2] For example, Niraparib is a known PARP inhibitor for the treatment of ovarian cancer.[3] 2-Benzyl-3-phenyl-7-(trifluoromethyl)-2*H*-indazole has been used a selective liver X receptor modulator. A substituted indazole with pyrazine and azetidine is identified as a glucokinase K activator.[4-5]

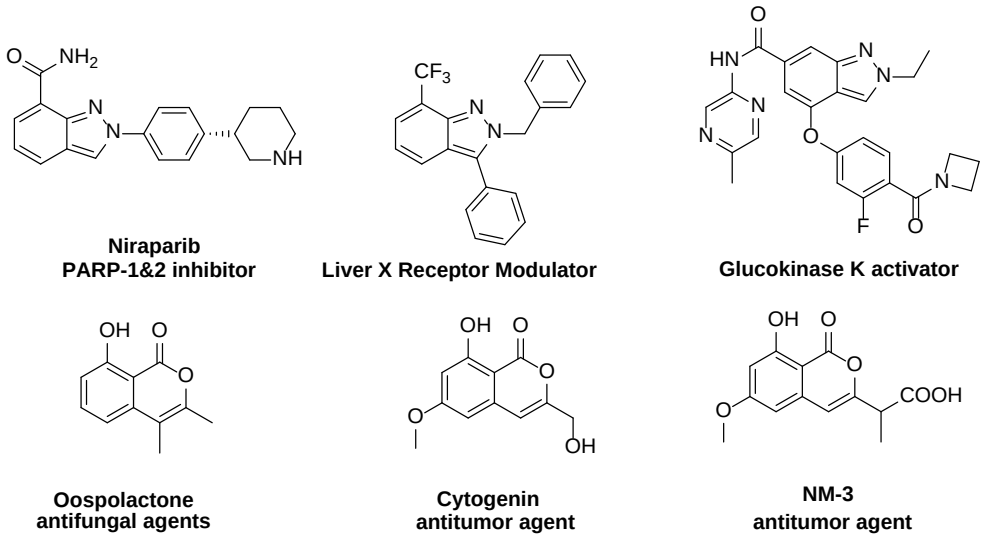
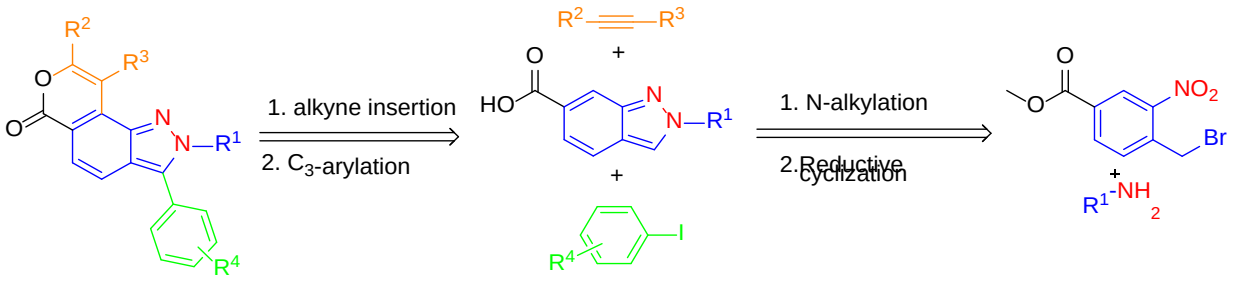


Figure 1. Biologically active indazoles and coumarin derivatives

Similarly, iscoumarin is a well-known heterocycle for its diverse physiological and medicinal applications. Oosponal and Oospolactone have demonstrated their potent antifungal and antibiotic activities.[6] Cytogenin exhibits significant immunomodulating, antitumor and antiarthritic activities.[7] Moreover, the synthetic drug NM-3 is in the clinical trials for its potent antitumour function.[8] Owing to their biological significance, numerous synthetic methods have been reported in the literature. Among them, the direct *N*-alkylation or arylation of indazole is quite challenging due to the preferential formation of the thermodynamically more stable 1*H*-indazole or a mixture of 1*H*-indazole and 2*H* -indazole through their tautomeric forms.[9] In addition, the separation of N1 and N2 alkylated mixtures is laborious and tedious. As an alternative, one of the first methods to prepare 2*H*-indazole was reductive cyclization of ortho-imino-nitrobenzenes mediated by excess of triethyl phosphite at high temperature.[10] Subsequently, many other methods such as transition metal

catalyzed cyclization of iminonitroaromatics and 2-azidoimines were developed.[11] A variety of other methods including benzyne [3+2] cycloaddition, zincate addition to diazonium salts, and alkylation of 1*H*-indazoles have also been reported.[12] Among them, reductive cyclization of 2-nitrobenzylamines by using Sn, Ti, Zn and In have attracted considerable attention because of the readily available starting material.[13] Nevertheless, these methods still suffer from setbacks such as unsatisfying yields, longer and harsh reaction conditions. Consequently, there is still a need to develop an operationally simple and easy means to access this important class of heterocycles. In our strategy, N2-substituted indazole was obtained selectively with appropriately substituted *ortho*-nitro benzyl amines *via* partial reduction followed by intramolecular N-N bond formation. Similarly, among many available synthetic methods for the preparation of isocoumarin, transition-metal catalyzed protocols are proven to be a concise and efficient strategy. Especially, less expensive ruthenium (II) catalyzed, chelation assisted C-H activation/annulation of aromatic carboxylic acid with internal alkynes has received much attention in the recent years.[14]

Fused heterocycles containing two or more pharmacophores have played a very important role in both medicinal chemistry and organic synthesis.[15] While indazoles and coumarin are well presented, indazole fused with pyranone bi-heterocycle is rarely reported in the literature and no attempt has been made to the synthesize of pyranone-fused indazoles. In continuation with our research interest on the development of efficient methods for hybrid heterocycles,[16] we report herein a novel, atom economic and regioselective synthesis of indazole fused pyranone via a sequential, stepwise pathway as shown in Scheme 1. In our methodology, methyl 4-(bromomethyl)-3-nitrobenzoate acts as a basic substrate to build an indazole skeleton by nucleophilic aliphatic substitution with primary amines followed by reductive cyclization. Later, the strategically positioned methyl ester is hydrolyzed to a carboxylic acid which subsequently undergoes regioselective alkyne insertion through ruthenium catalysis to furnish pyranone-fused indazoles. To the best of our knowledge, construction of indazole fused pyranone via step-wise reductive cyclization and alkyne insertion has never been reported.

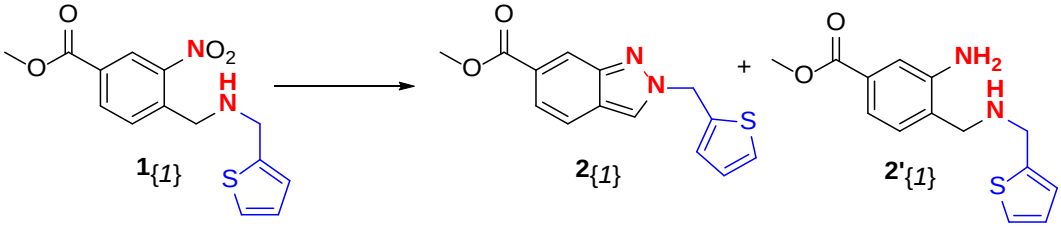


Scheme 1. A proposed synthetic route for the synthesis of pyranone-fused indazoles

Result and Discussion

Our preliminary investigation began with the reaction of methyl 4-(((thiophene-2-ylmethyl)amino)methyl)-3-nitrobenzoate **1**{*1*} in the presence of zinc and ammonium formate in methanol to prepare diamine product **2´**{*1*}(Table 1) for the possible synthesis of quinazoline with aldehydes.

Table 1. Optimization of the reaction conditions[a]



Entry	Reductive agents	Yield (%) 2{*1*}	2´{*1*}
1	Zn (2 equiv)/ $HCOONH_4$ (1 equiv)	45	19
2	Pd/C (2 equiv) / H_2	0	85
3	Pd/C (2 equiv)/ $HCOONH_4$ (1 equiv)	0	82
4	Zn (3 equiv)/ $HCOONH_4$ (1 equiv)	62	9
5	Zn (5 equiv)/ $HCOONH_4$ (1 equiv)	76	0

[a] Reaction conditions: the reaction was carried out in 0.165 mmol scale with various reductive agents in methanol at room temperature for 1 h.

However, to our surprise the reaction furnished an unknown compound (45%) as the major product together with the diamine **2´**{*1*} (19%). The absence of benzyl methylene peak and the appearance of characteristic signal of C(3)-H as a sharp singlet in the aromatic region (7.95 ppm) confirmed the formation of 2*H*-indazole **2**{*1*}. Further, the structure of **2**{*1*} was ascertained by X-ray single crystallography (Figure 2) which indicates the N-N bond formation.

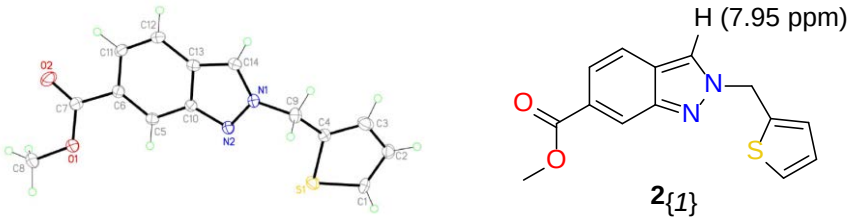


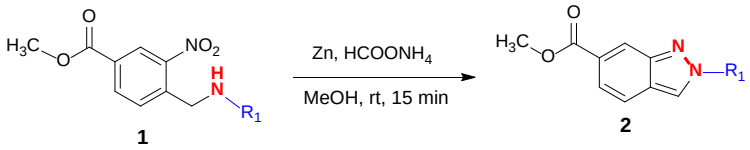
Figure 2. ORTEP diagram of compound **2**{*1*}

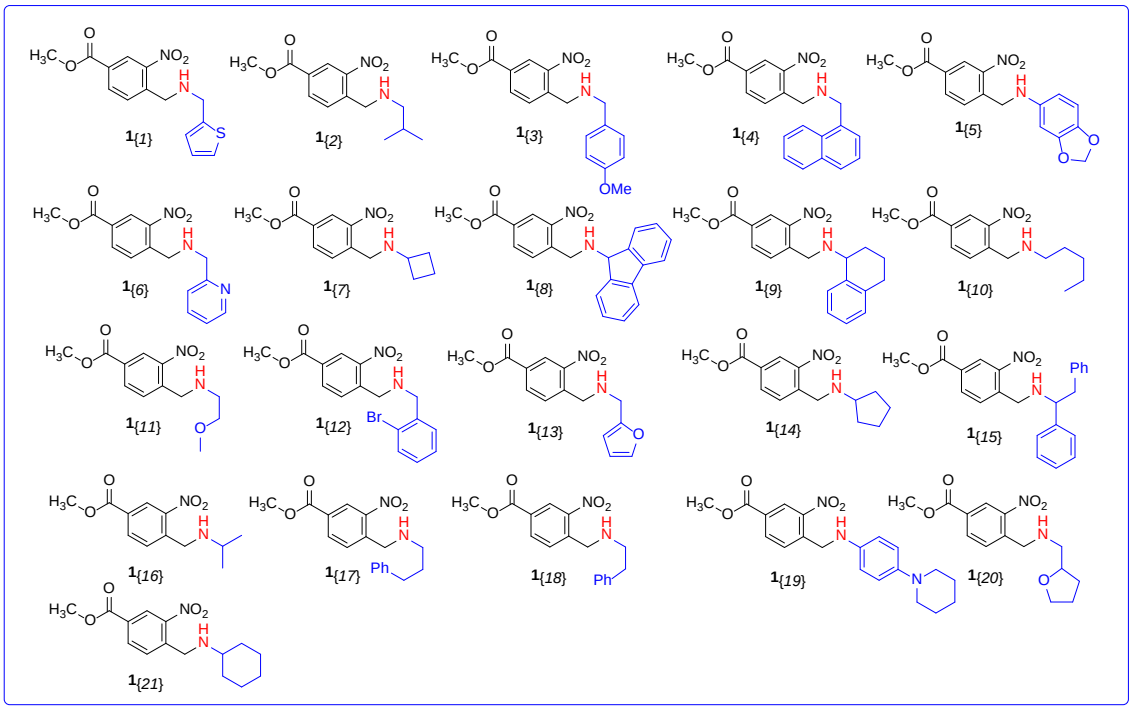
We reasoned that under reductive condition, the nitro group underwent partial reduction to nitroso benzyl amine which cyclized intramolecularly to furnish indazole *via* N-N bond formation. This unprecedented result encouraged us to develop an exclusive method to selectively synthesize indazole ring owing to their notable biological property. In order to study the formation of **2**{*1*} exclusively, the reaction conditions were optimized with various reducing agents as shown in Table 1. When the same reaction was carried out in the presence of palladium on charcoal with hydrogen gas or ammonium formate, only diamine **2´**{***1***} (entries 2 and 3) was obtained. Increasing the amount of zinc, significantly increases the yield of **2**{*1*} with the diminished formation of **2´**{*1*} (entries 4 and 5). However, an exclusive formation of **2**{*1*} in 76% yield was accomplished when ammonium formate in methanol was added drop wise to the reaction mixture (entry 5).

With the optimized conditions in hand, the scope of the reaction was evaluated. As shown in Table 2, various substituted 2-nitrobenzylamines were tested for this unique transformation. For alkyl substituted substrates, the corresponding *2H*-indazoles were obtained in good to excellent yields. However, moderate yields were obtained in the case of aromatic substituted (**2**{*5*} and **2**{*19*}) and bulky substituted (**2**{*8*} and **2**{*9*}) 2-nitrobenzylamine accompanied with compounds **2´**{*5*}, **2´**{*19*}, **2´**{*8*}, and **2´**{*9*}. The

moderate yields of indazole formation may be due to the resonance stabilization of nitrogen lone pair of aniline type amine within the aromatic ring in the nitroso form (Scheme 2, A).

Table 2. Synthesis of 2*H*-indazoles *via* reductive cyclization



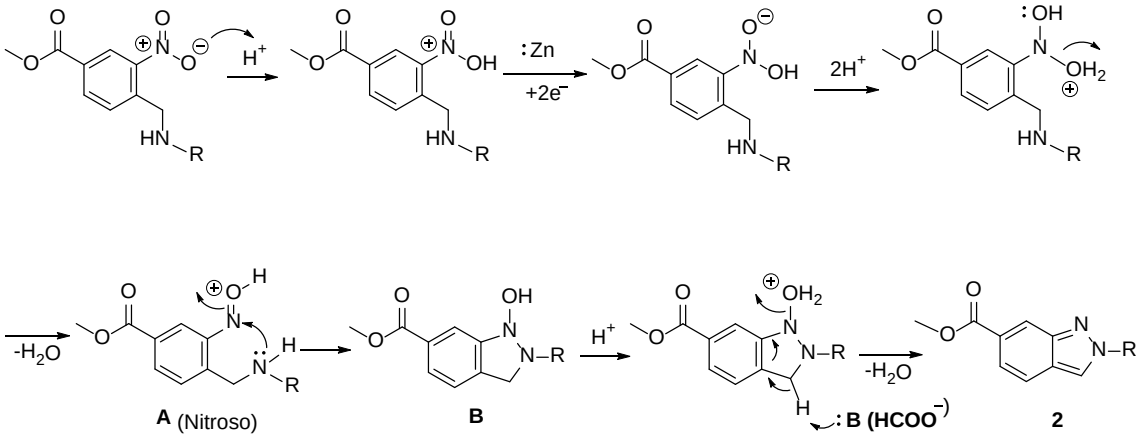


Entry	Product	Isolated yield (%)	Entry	Product	Isolated yield (%)
1	**2**{*1*}	76	11	**2**{*11*}	70
2	**2**{*2*}	79	12	**2**{*12*}	66
3	**2**{*3*}	62	13	**2**{*13*}	75
4	**2**{*4*}	65	14	**2**{*14*}	75
5	**2**{*5*}	47	15	**2**{*15*}	72
6	**2**{*6*}	49	16	**2**{*16*}	78
7	**2**{*7*}	71	17	**2**{*17*}	68
8	**2**{*8*}	53	18	**2**{*18*}	71

9	**2**{*9*}	51	19	**2**{*19*}	45
10	**2**{*10*}	80	20	**2**{*20*}	65
			21	**2**{*21*}	79

Based on the literature reports, a tentative mechanism for the synthesis of *2H*-indazole is depicted in Scheme 2. Initially, 2-nitrobenzylamine was reduced to nitroso compound **A** in the presence of zinc and ammonium formate via reductive addition of two hydrogen atoms. It is noteworthy that, because of the presence of nucleophilic benzyl nitrogen at the *ortho*-position, the reduction of nitro group with zinc under acidic condition stop at nitroso state for the possible formation of N-N bond. Then, an intramolecular nucleophilic addition of benzyl amine on nitroso group delivered intermediate **B**, upon elimination of water to produce *2H*-indazoles. The driving force for the proton elimination in the final step is due to the formation of the more stable, aromatic like 2*H*-indazole.

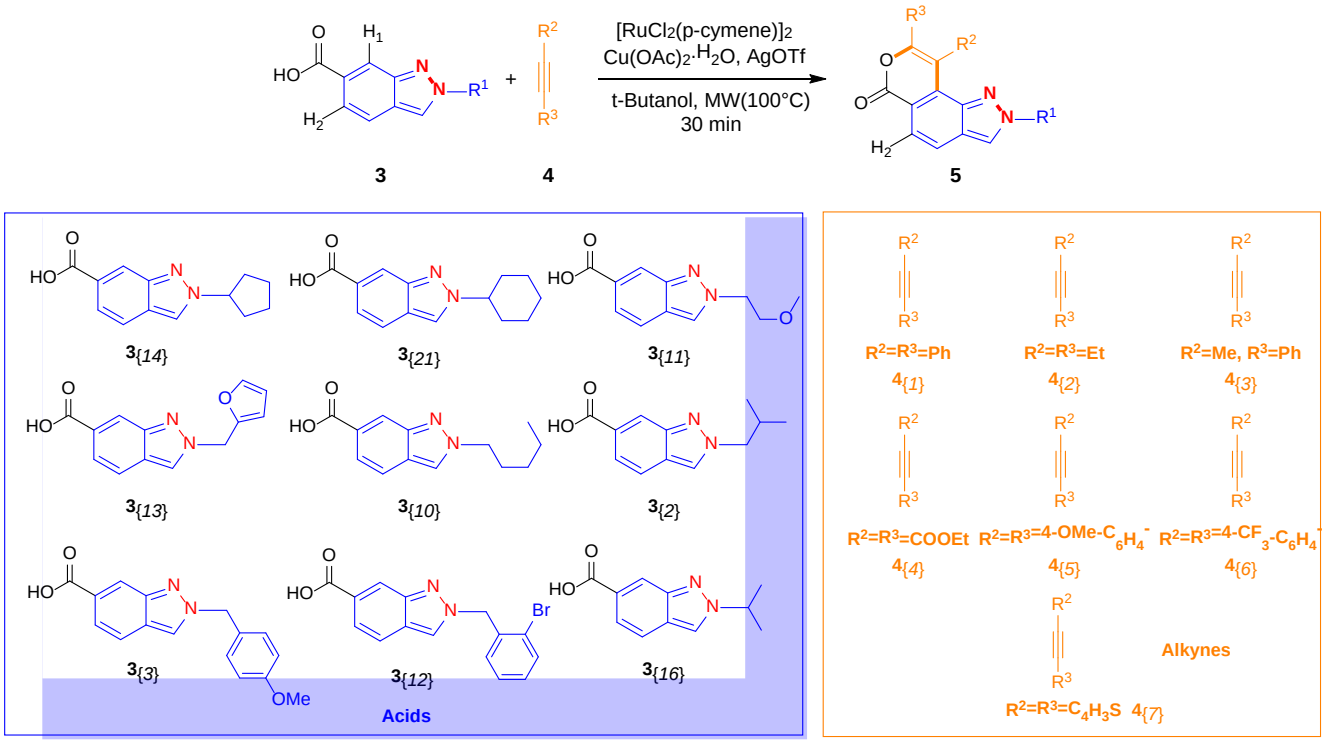
Scheme 2. A plausible mechanism for the formation of *2H*-indazoles



In light of a successful reductive cyclization process for the regioselective synthesis of 2*H*-indazoles, the next task is aiming to build a pyranone framework by utilizing an acidic form of indazole through metal mediated alkyne insertion. Our attempt was initiated by the base hydrolysis (*aq.* NaOH) of indazole esters to the corresponding acid derivatives. After synthesizing these acids, we carried out an oxidative coupling of **3**{*14,1*} with

diphenylacetylene **4**{*1*} in the presence of $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $Cu(OAc)_2.H_2O$ (2 equiv) as an oxidant and AgOTf (20 mol %) as an additive in refluxing p-xylene (5 mL) for 12 h to deliver the desired product **5**{*14,1*} in 45% yield (see Supporting Information, Table S1, entry 1). Encouraged by this promising result, further screening of the reaction conditions was carried out as shown in see Supporting Information File in Table S1. From these results, we concluded that $[RuCl_2(p\text{-cymene})]_2$ (5 mol %), $Cu(OAc)_2.H_2O$ (2 equiv) as an oxidant and AgOTf (20 mol %) as an additive in *t*-butanol under microwave irradiation at 100 °C for 30 minutes provided the optimal results. (See Supporting Information, Table S1).

Table 3. Indazole-directed regioselective synthesis of fused bi-heterocycles



Entry	Product	Isolated yield (%)	Entry	Product	Isolated yield (%)
1	**5**{*14,1*}	82	12	**5**{*2,1*}	77

2	**5**{*21,2*}	79	13	**5**{*2,2*}	75
3	**5**{*21,3*}	68	14	**5**{*2,3*}	69
4	**5**{*11,1*}	77	15	**5**{*3,1*}	67
5	**5**{*11,2*}	81	16	**5**{*12,1*}	65
6	**5**{*11,3*}	69	17	**5**{*9,1*}	74
7	**5**{*13,1*}	82	18	**5**{*16,3*}	71
8	**5**{*13,2*}	79	19	**5**{*17,4*}	ND
9	**5**{*13,3*}	68	20	**5**{*17,5*}	79
10	**5**{*10,1*}	85	21	**5**{*17,6*}	74
11	**5**{*10,3*}	72	22	**5**{*17,7*}	81

With the optimized reaction condition in hand, we probed the substrate scope of ruthenium catalyzed oxidative annulation with various substituted indazoles and internal alkynes (Table 3). A broad range of functional groups were well-tolerated and a variety of N2 substituted (alkyl, aryl, heterocyclic) indazoles were synthesized in excellent yields. Remarkably, the coupling reaction occurred regioselectively with C-H1 bond due to the possible chelation of indazole nitrogen to the metal center. We next investigated the scope of the reaction by using various disubstituted alkynes such as alkyl, aryl, and electron-rich and electron deficient symmetrical alkynes which converted to the products with moderate to excellent yields. However, with diethyl acetylenedicarboxylate, no conversion was observed under the same reaction condition.

The reaction of unsymmetrical alkyne (prop-1-yn-1-yl benzene) with indazoles **3** is highly regioselective in which the alkyne carbon bearing phenyl group is attached to the acid group site and the alkyne carbon bearing a methyl group is connected to the ortho-carbon of the acid to give the desired products (**5**{*21,3*}**, 5**{*11,3*}, **5**{*13,3*}, **5**{*10,3*}**, 5**{*2,3*} and **5**{*16,3*}) in good yields. The reason for the high regioselectivity would be the steric repulsion between the bulky phenyl group and the indazole ring. The observed regioselectivity is ascertained by X-ray single crystallography studies and the ORTEP diagrams of the representative compounds **5{***2,3***}** are shown in Figure 3. Interestingly, we

didn't observe any decarboxylative cyclization product in the present catalytic reaction system.

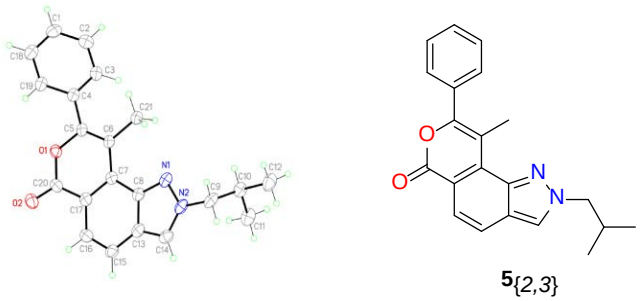
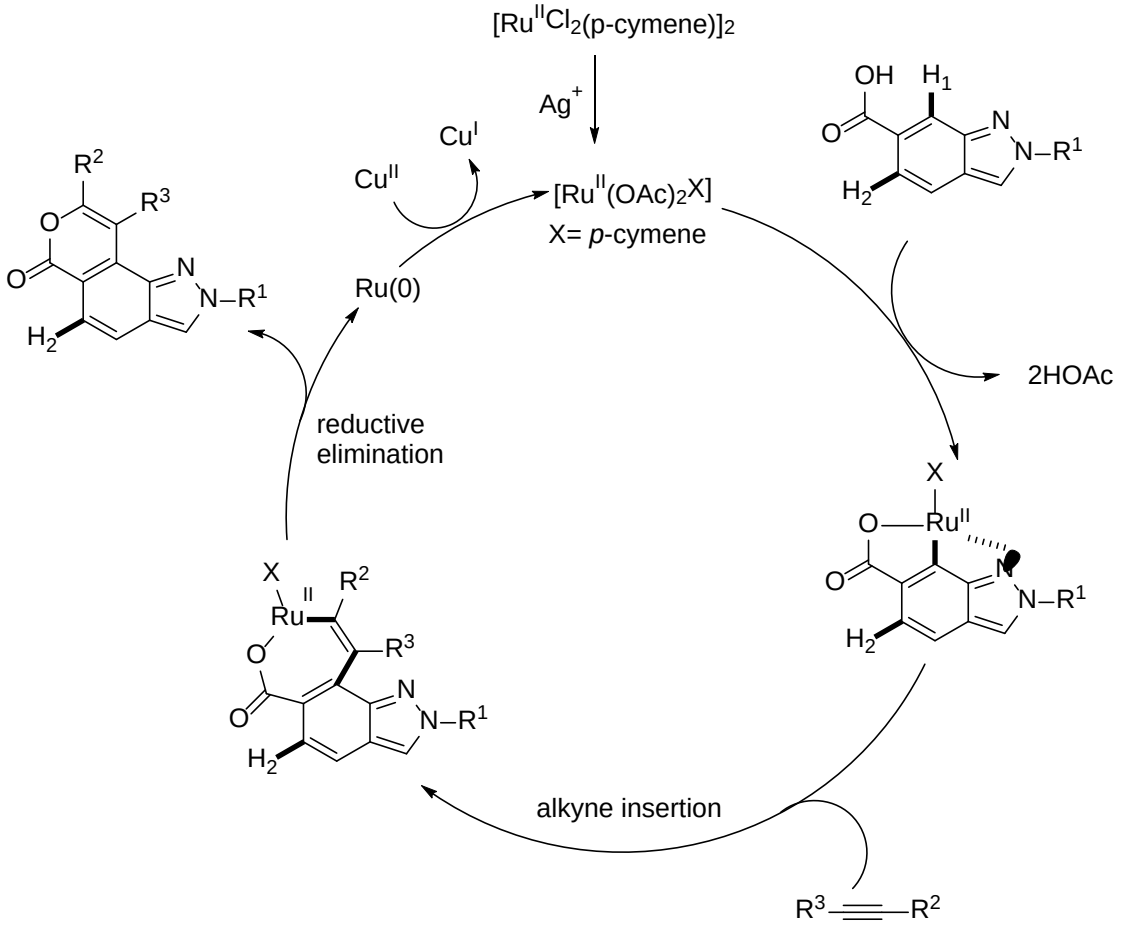


Figure 3. ORTEP diagram of compounds **5**{*2,3*}

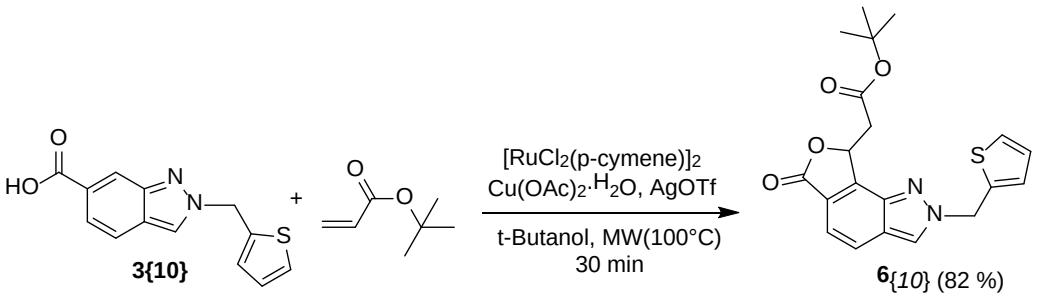
A plausible mechanism for the ruthenium-catalyzed regioselective C-H bond activation/annulation reaction is illustrated in Scheme 3. The catalytic cycle commences with the formation of five membered ruthenacycle A via acetate assisted irreversible C-H1 bond activation with the liberation of acetic acid. The regioselective C-H1 bond activation is governed by the weak co-ordination of indazole ring nitrogen to the metal center. Subsequently, an alkyne insertion furnished seven membered ruthenacycle which upon reductive elimination yields the desired pyranone-fused with indazole. The resulting Ru(0) is reoxidized to Ru(II) in the presence of Cu(II) salts to reinitiate the catalytic cycle.

Scheme 3. A plausible catalytic cycle for the regioselective alkyne annulation with acids



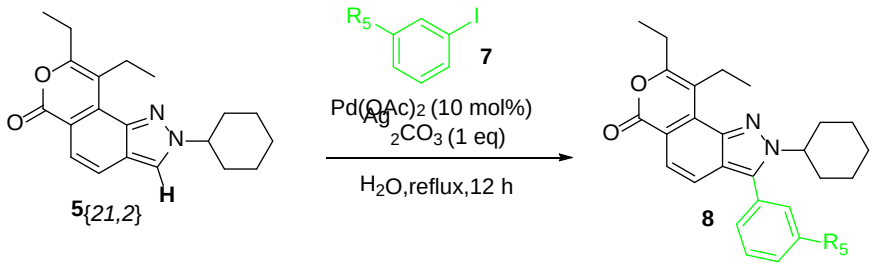
After the successful synthesis of pyranone-fused indazoles, we extended this methodology for alkene insertion to the synthesis of indazole-fused furanone scaffold. Gratifying, under the optimized condition, oxidative coupling with tert-butyl acrylate took place smoothly to produce the target molecule in 82% yield (Scheme 4).

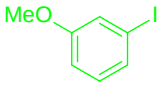
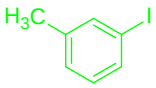
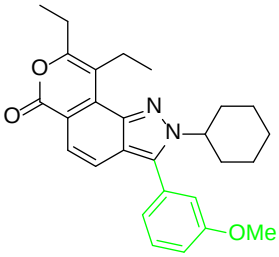
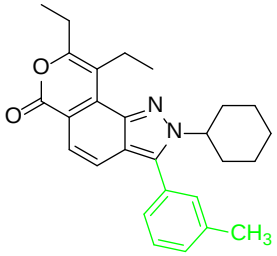
Scheme 4. Alkenylation/cyclization cascade for the synthesis of indazole-fused furanone



Similarly, we have successfully carried out selective C3-arylation of indazole fused pyranone with aryl halides in the presence of Pd/Ag catalytic system in water as shown in (Table 4).

Table 4. Selective arylation of indazole-fused pyranone **5**{*21,2*}



Aryl halides(7)		
	7{*1*}	**7**{*2*}
		
	78%	**80%**
	8{*21,2,1*}	**8**{*21,2,2*}

Conclusion

In summary, a new synthetic route to prepare pyranone-fused indazole was explored by employing readily available substrates. The *2H*-indazole core is accomplished via reductive cyclization for N-N bond formation in the presence of zinc/ammonium format at ambient temperature. Subsequently, the strategically positioned carboxylic derivatives were successfully employed as a suitable substrate for the regioselective C-H bond activation /annulation with internal alkynes to deliver indazole-fused pyranones. The new protocol offers a concise route for the construction of these bi-heterocycles with diverse functionalization.

EXPERIMENTAL SECTION

Experimental procedure for the synthesis of Methyl 2-(thiophen-2-ylmethyl)-2*H*-indazole-6-carboxylate 2{*1*}.

To a solution of methyl 3-nitro-4-(((thiophen-2-ylmethyl)amino)methyl)benzoate **1**{*1*} (100 mg, 0.326 mmol) in methanol (6 mL) was added zinc (104 mg, 1.633 mmol) followed by ammonium formate (20 mg, 0.344 mmol) in methanol (1 mL) was added dropwise. The resulting reaction mixture was stirred at room temperature for 1 h. After the completion of the reaction, the reaction mixture was filtered through a pad of celite and washed with methanol (10 mL). The filtrate was evaporated and dissolved in CH_2Cl_2 (15 mL). The precipitated ammonium formate was filtered off. The resulting crude product was purified by silica gel column chromatography (EtOAc/Hexane = 3/10) to afford the desired product **2**{*1*} (67 mg, 76 %)

Methyl 2-(thiophen-2-ylmethyl)-2*H*-indazole-6-carboxylate 2{*1*}

Brown solid; yield 67 mg, 76%; mp 94-96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.53 (s, 1H), 7.96 (s, 1H), 7.71 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.64 (d, *J* = 8.8 Hz, 1H), 7.32 (dd, *J* = 5.2, 1.2 Hz, 1H), 7.16 (d, *J* = 3.6 Hz, 1H), 7.01 (dd, *J* = 5.2, 3.6 Hz, 1H), 5.79 (s, 2H), 3.95 (s, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.1, 167.9, 148.5, 137.1, 128.5, 128.3, 127.6, 127.4, 124.5, 123.1, 121.9, 121.8, 120.7, 52.6; IR (cm^{-1}, neat): 2948, 1714, 1502; MS (EI-MS) *m/z*: 272 (M^+); HRMS: calculated for $C_{14}H_{12}N_2O_2S$ *m/z*: 272.0619; found 272.0618.

Experimental procedure for the synthesis of 2-cyclopentyl-8,9-diphenylpyrano[3,4-*g*]indazol-6(2*H*)-one 5{*14,1*}.

To an oven dried microwave vial was added 2-cyclopentyl-2H-indazole-6-carboxylic acid (70 mg, 0.304 mmol), diphenyl acetylene (65 mg, 0.365 mmol), $[RuCl_2(p\text{-cymene})]_2$ (9 mg, 0.0152 mmol), $Cu(OAc)_2.H_2O$ (121 mg, 0.608 mmol) followed by AgOTf (16 mg, 0.0608 mmol) in *t*-BuOH (3 mL). The reaction tube was sealed and irradiated at a ceiling temperature of 100 °C using 150 W for 30 min. Upon completion of reaction, the residue was filtered through a pad of celite and the filtrate was concentrated in vacuo. The resulting crude product was purified by column chromatography (EtOAc/hexane= 1/5) on silica gel to afford compound **5**{*14,1*} (101 mg, 82 %)

2-cyclopentyl-8,9-diphenylpyrano[3,4-*g*]indazol-6(2*H*)-one 5{*14,1*}**.**

Brown semi solid; yield 62 mg, 71%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.8 Hz, 1H), 7.87 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.40–7.32 (m, 7H), 7.21–7.19 (m, 3H), 4.64 (quint, *J* = 7.4 Hz, 1H), 1.99–1.93 (m, 2H), 1.82–1.75 (m, 2H), 1.58–1.51 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.4, 153.0, 143.9, 136.9, 133.7, 132.6, 132.0, 129.8, 129.1, 128.3, 128.1, 127.8, 125.4, 122.2, 121.2, 120.6, 117.3, 117.1, 64.9, 33.9, 25.1;IR (cm^{-1}, neat): 2954, 1714, 1492; MS (EI-MS) *m/z*: 406 (M^+); HRMS: calculated for $C_{27}H_{22}N_2O_2$ *m/z*: 406.1681; found 406.1681.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI:
Full characterization and spectroscopic data (^{1}H and ^{13}C NMR, HRMS, FT-IR) of compounds **2, 5, 6** and **8**
X-ray crystallography of **2**{*1*} (CIF)
X-ray crystallography of **5**{*2,3*} (CIF)
X-ray crystallography of **5**{*3,1*} (CIF)

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Notes

The authors declare no competing financial interest.

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Regioselective Synthesis of Pyranone-fused Indazoles via Reductive Cyclization and Alkyne Insertion

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