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Six-Component Reactions for the Stereoselective Synthesis of 3-Arylidene-2-oxindoles via Sequential One-Pot Ugi/Heck Carbocyclization/Sonogashira/Nucleophilic Addition

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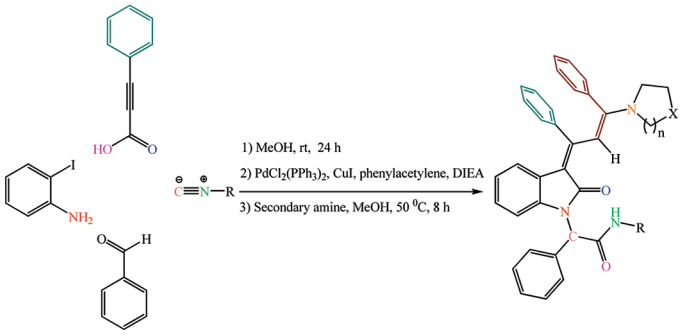

An efficient palladium-catalyzed protocol for the synthesis of 3-arylidene-2-oxindoles has been developed. In this approach, a sequential one-pot six-component reaction via Ugi/Heck carbocyclization/Sonogashira/nucleophilic addition was used for the synthesis of the desired skeleton.

Introduction

Designing novel multicomponent reactions (MCRs) leading to the formation of multiple bonds with a high bond-forming efficiency (BFE) as well as synthesizing macromolecules in one operation is among the most challenging objectives in modern organic synthesis.[1] Transition metals have been used for catalyzing transformations in tandem processes, and significant progress has been made in this regard,[2] including the efficient use of palladium catalysts in different tandem reactions in an attempt at constructing biologically active heterocyclic compounds.[3]

The 2-oxindole unit represents an important structural motif found in natural products and biologically relevant compounds.[4] Molecules containing this motif benefit from a broad range of therapeutic activity, including oncology, inflammation, and CNS immunology.[5] 3-Arylidene-2-oxindole derivatives also have a range of medicinal and biological activities, such as antiangiogenic and anticancer activities.[6] Many 3-arylidene-2-oxindole analogues have been extensively evaluated for kinase inhibitory activities,

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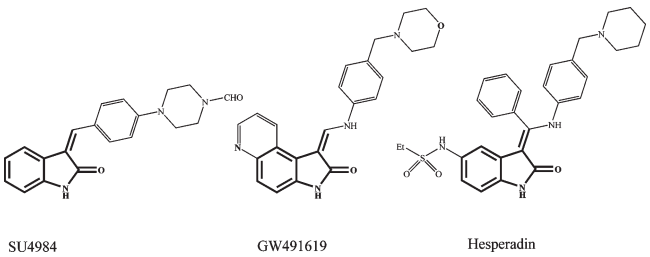


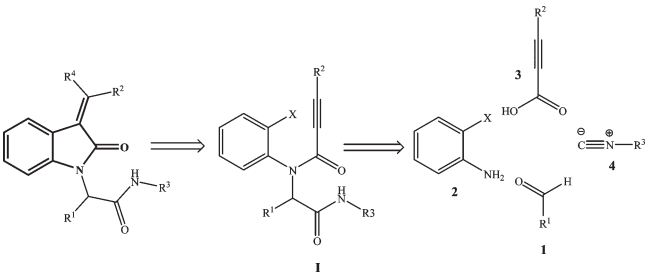
FIGURE 1. Representative 3-arylidene-2-oxindoles.

e.g., SU4984[7] and GW491619.[8] Recently, hesperadin has been identified as an Aurora B inhibitor that is tetrasubstituted in the exocyclic olefin[9] (Figure 1).

Much effort has been made in investigating the synthesis of derivatives of these compounds to deduce structure−activity relationships and discovering new analogues with improved properties, as well as finding novel methods for the synthesis of this skeleton.[10]

There are several approaches for the synthesis of 3-arylidene-2-oxindoles, such as (i) nucleophilic addition of oxindoles to carbonyl compounds,[11] (ii) Heck reaction,[12] (iii) radical cyclization,[13] (iv) transition-metal-catalyzed domino processes with α,β-acetylenic amides derived from 2-haloanilines[14] or anilines (proceeding with arene ortho C−H bond activation),[15] (v) carbonylation of 2-alkynylanilines,[16] (vi) carbopalladation Stille coupling reaction with carbamoyl chlorides,[17]and (vii) Pd- or Rh-catalyzed cyclization of 2-alkynylaryl isocyanates in the presence of an external nucleophile.[18] Some of the aforementioned methods have restrictions due to the lack of generality, poor functional group tolerance, lengthy synthetic sequences, and also complex starting materials.

SCHEME 1. Retrosynthetic Pathway for the Synthesis of 3-Arylidene-2-oxindoles



Because of the significant biological activities of these derivatives, stereoselective syntheses of 3-arylidene-2-oxindoles remain an interesting subject in organic synthesis. Pd catalysts are of considerable importance because they are used in the synthesis of many biologically active 3-arylidene-2-oxindoles. *N*-Substituted-2-alkynamides were generally used as starting materials for the synthesis of 2-oxindole derivatives.[10a,b,12,14a−c,15,19]

In our retrosynthetic analysis, the formation of the exocyclic double bond in 3-arylidene-2-oxindoles was investigated by ring-closure procedure of *N*-substituted-2-alkynamides (**I**) resulting from the four-component reaction of aldehydes, 2-haloanilines, propiolic acids, and isocyanides, using Pd-catalyst (Scheme 1).

In continuation of our research for the construction of new heterocyclic skeletons via one-pot reactions, we became interested in the synthesis of 3-arylidene-2-oxindols. Herein, we wish to report a novel type of Ugi/Heck carbocyclization/Sonogashira/nucleophilic addition reaction sequences for the synthesis of 3-arylidene-2-oxindoles **7a−j** via one-pot six-component reactions in the presence of palladium catalyst in high yields and bond-forming efficiency. The reactions were carried out in one pot in three steps in MeOH (Scheme 2).

Results/Discussions

Müller and co-workers assembled a tandem Heck carbonylation/Sonogashira cross coupling approach for the reaction of *N*-(2-iodophenyl) alkynamides with terminal alkynes, which led to oxindoles possessing exocyclic conjugated enynes that could enter the subsequent cascade of reactions to yield rigid spirocycles.[14a] In our strategy, a novel six-component reaction of benzaldehyde (**1**), 2-iodoaniline (**2**), phenylpropiolic acid (**3**), isocyanides (**4**), phenylacetylene (**5**), and secondary amines (**6**) was used for the synthesis of 3-arylidene-2-oxindoles **7a−j** in

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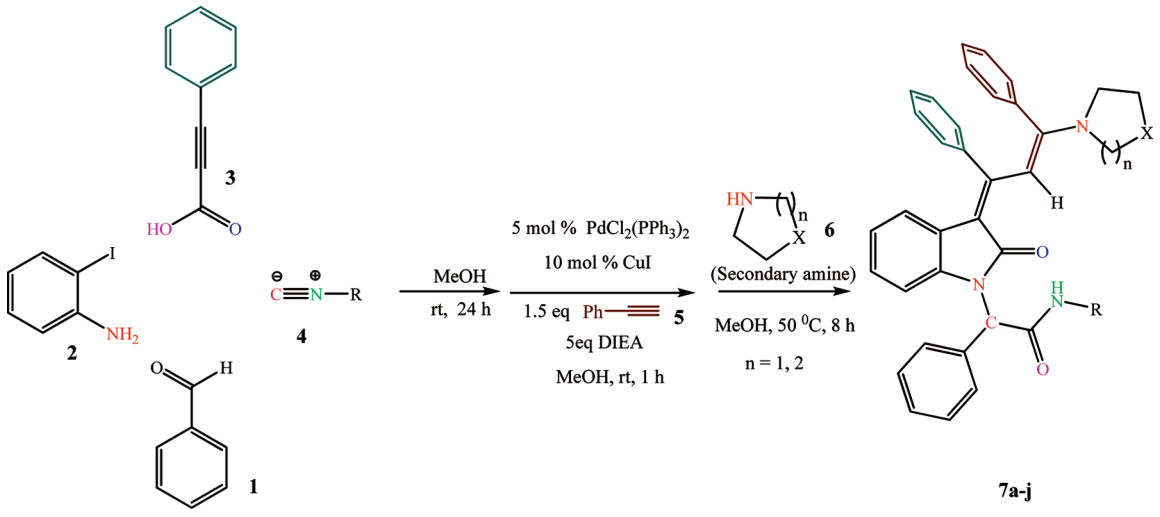
SCHEME 2



a) R= Cyclohexyl
b) R= *t*-Bu

MeOH in the presence of palladium catalyst in one-pot reaction conditions. The reactions could be carried out in the presence of 5% $PdCl_2(PPh_3)_2$, 10% CuI, and DIEA as the base in MeOH. The results have been summarized in Table 1.

Control experiments indicate that this sequential reaction could proceed in three steps, namely, (i) Ugi 4-MCR between benzaldehyde, 2-iodoaniline, phenylpropiolic acid, and isocyanides that is the presumed first step of this tandem process leading to *N*-substituted-2-alkynamides **I** (**a, b**), (ii) Heck carbocyclization/Sonogashira cross-coupling of *N*-(2-iodophenyl) alkynamides with phenylacetylene as a domino insertion, coupling sequence, and finally (iii) the formation of the intermediates **8** (*E* isomer) and **9** (*Z* isomer) and nucleophilic addition of secondary amines to activated triple bond in dihydroindolones **8** and **9** to form the 3-arylidene-2-oxindoles **7a**−**j**.The proposed mechanism is shown in Scheme 3. The following steps show the role of palladium catalyst in the formation of 3-arylidene-2-oxindoles (Scheme 3).

The second step of the proposed mechanism is a known domino Heck/Sonogashira reaction process, and the reaction procedure could be categorized, respectively, as follows: (1) Occurence of oxidative addition of haloarene to Pd(0) (intermediate **A**). (2) Insertion reaction to alkyne moiety and formation of intermediate **B** (carbopalladation). (3) Transmetalation with copper and the addition of copper phenylacetylide to intermediate **B** and formation of intermediate **C**. (4) Final reductive elimination leads the formation of the mixture of *E* and *Z* isomers of dihydroindolones **8** and **9**. Nucleophilic addition of the secondary amines to the electrophilic carbon center in the alkynyl moiety of the intermediate **8** or **9** would produce the zwitterionic intermediates **10** and **11**. The intermediate **10** leads to product **12**, which has a strong steric hindrance. As is shown, the intermediate **10** could be converted to the intermediate **11** as a result of steric hindrance in the structure of **12** compared to **7a**−**j**. Rotation of the newly formed bond between the indole core and the allenyl moiety and subsequent tautomerization leads to stereoselective synthesis of **7a**−**j**. In all cases, the *Z* isomers of compounds **7a**−**j** were obtained as the sole product because of the phenyl group participation.

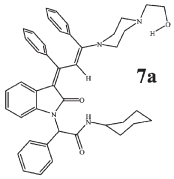
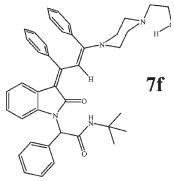
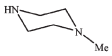
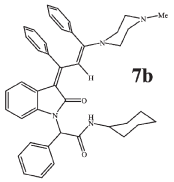
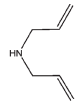
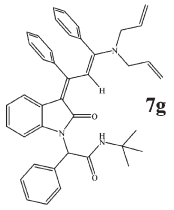
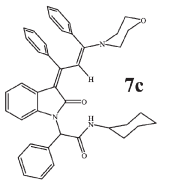
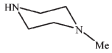
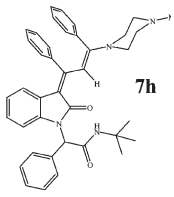
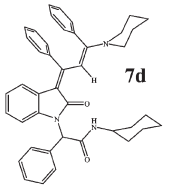
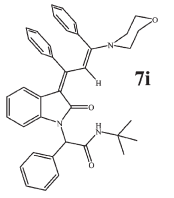
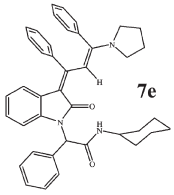
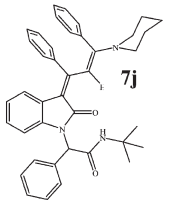
To gain more insight into the reaction mechanism, the Ugi adduct was allowed to react with phenylacetylene in the presence of palladium catalyst and cuprous iodide in catalytic amounts. The reaction of benzaldehyde, 2-iodoaniline, phenylpropiolic acid, and *tert*-butyl isocyanide in MeOH was selected as a model reaction (Scheme 4). After the formation of the desired *N*-substituted-2-alkynamide (**Ib**), phenyl acetylene (1.5 equiv) was also added to the mixture. The ^{1}H NMR study of the reaction mixture showed the formation of two *E* and *Z* isomers (**8b, 9b**) with a *E*/*Z* ratio of 41:59. The *E* isomer was recrystallized and its structure was also confirmed by X-ray crystallographic data as shown in Figure 2

The distinguished peaks for the *E* and *Z* isomers (**8b, 9b**) were observed as two doublets for the proton H-4 of oxindole ring at δ 8.49 and 6.51 ppm, respectively.

The solvent effect in the domino Heck/Sonogashira reaction (second step in Scheme 3) was examined by replacing THF with MeOH. Ugi 4-MCR was carried out in MeOH, and after evaporation of the solvent, without separation of the Ugi 4-MCR intermediate (**Ib**), addition of phenylacetylene (3 equiv) was performed in the presence of 5% $PdCl_2(PPh_3)_2$, 10% CuI, and 5 equiv of DIEA as the base in THF. Gratifyingly, the use of MeOH as the solvent resulted in a dramatic reduction of the reaction time (1 h) compared to that using THF (24 h). The yield of the reactions was better in MeOH than in THF. When THF was used as the solvent, 3 equiv of phenylacetylene should be used compared to MeOH as the solvent (1.5 equiv). The ratio of *E*/*Z* isomers (**8b/9b**) in THF was (65:35), whereas in MeOH it was (41:59). Meanwhile, 1,4-diphenyl-1,3-butadiyne was formed in THF as a byproduct.

The ratio of *E* and *Z* isomers for compounds **8b** and **9b** depends on the polarity of the solvent. In MeOH, the ratio of polar form (**9b**, *Z*) is higher (59%), and in THF, the dominate isomer is *E* (**8b**, 65%). There is a distinguished peak in the ^{1}H NMR spectra of the products. As a model compound, in the

TABLE 1. Stereoselective Synthesis of 3-Arylidene-2-oxindoles via Sequential Ugi/Heck Carbocyclization/Sonogashira/Nucleophilic Addition

R	Secondary amine	Product	Yield%[a]	R	Secondary amine	Product	Yield%
Cy[b]		 **7a**	62	*t*-Bu		 **7f**	67
Cy		 **7b**	71	*t*-Bu		 **7g**	65
Cy		 **7c**	70	*t*-Bu		 **7h**	73
Cy		 **7d**	68	*t*-Bu		 **7i**	70
Cy		 **7e**	68	*t*-Bu		 **7j**	70

[a]Isolated yield. [b]Cyclohexyl.

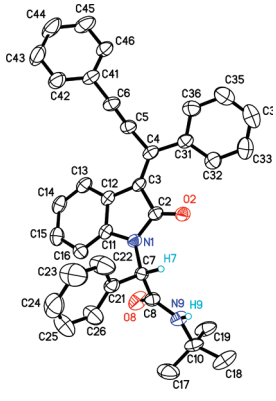


FIGURE 2. X-ray structure of compound **8b**.

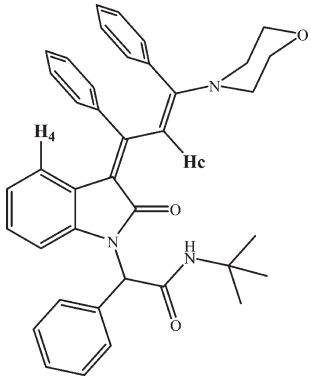
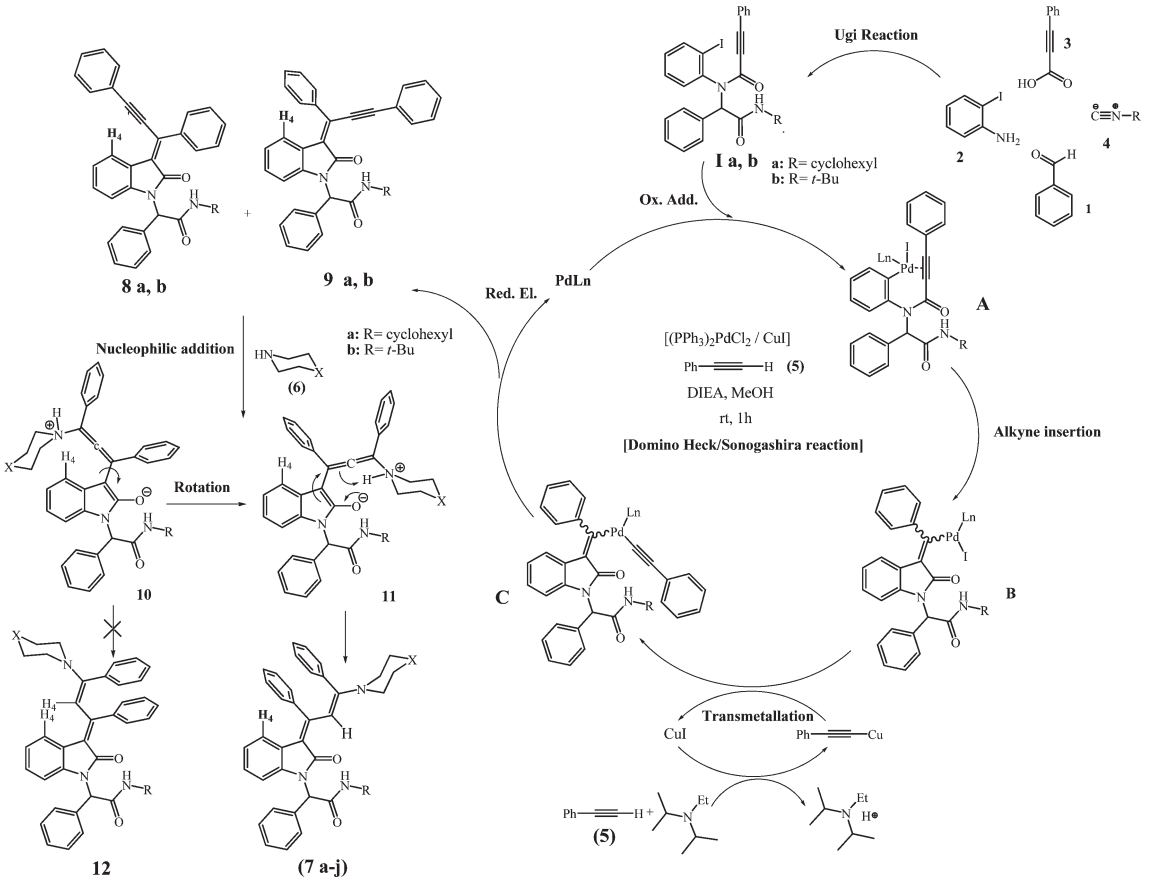


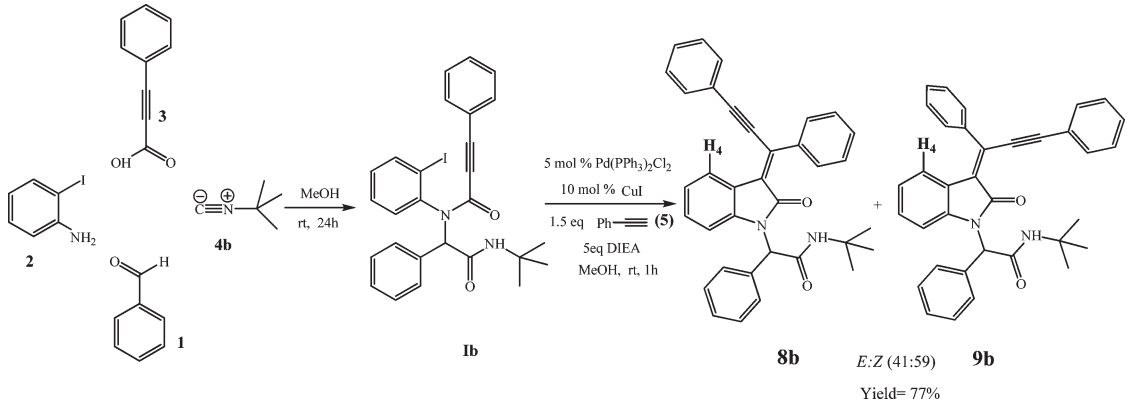
FIGURE 3. Structure of compound **7i**.

structure of compound **7i** (Figure 3), proton H-4 resonates at δ 5.49 ppm as a doublet, compared to H-4 in compound **8b** (δ 8.49 ppm). The shielding effect for this proton is related to the ring current of the aryl group. In fact, this proton lies in the diamagnetic region of the ring, which could be observed for all the products **7a**−**j**. Meanwhile,

SCHEME 3. Proposed Mechanism for the One-Pot Ugi/Heck Carbocyclization/Sonogashira/Nucleophilic Addition Reaction Sequences for the Synthesis of 3-Arylidene-2-oxidoles



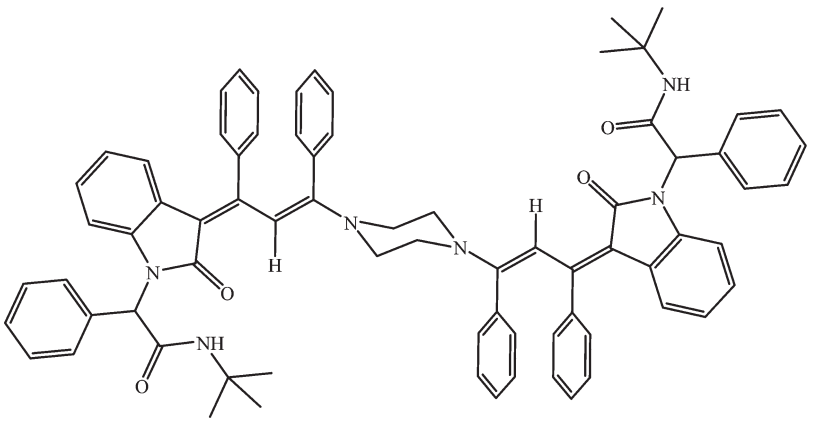
SCHEME 4



the structure of compound **7i** was unambiguously supported by NOE data. It should be mentioned that the decoupling of the H-4 proton at δ 5.49 ppm does not cause any changes in the singlet at δ 7.74 for the olefinic proton (H-c), and in this way, the geometry of the double bond could be confirmed.

The role of aryl group in the formation of 3-arylidene-2-oxindoles **7a**−**j** were investigated by using 2-butynoic acid instead of phenyl propiolic acid, and after the formation of the desired *N*-alkynamide **14** without separation, phenylacetylene was added to the mixture in the presence of palladium catalyst, cuprous iodide, and DIEA as the base (Scheme 5). ^{1}H NMR study of the crude reaction shows that the sole product is the *E* isomer (**15**). It seems that there is a strong steric hindrance between the methyl and hydrogen in compound **16**, but there is no such hindrance in compound **15**.The distinguished peak at δ 8.36 ppm in ^{1}H NMR spectrum of compound **15** is related to H-4 proton. The NOE experiment data could confirm the proposed *E* stereochemistry of compound **15**. The experiment was done by irradiation on CH_3 and H-4 at δ 2.777 and 8.385 ppm, respectively.

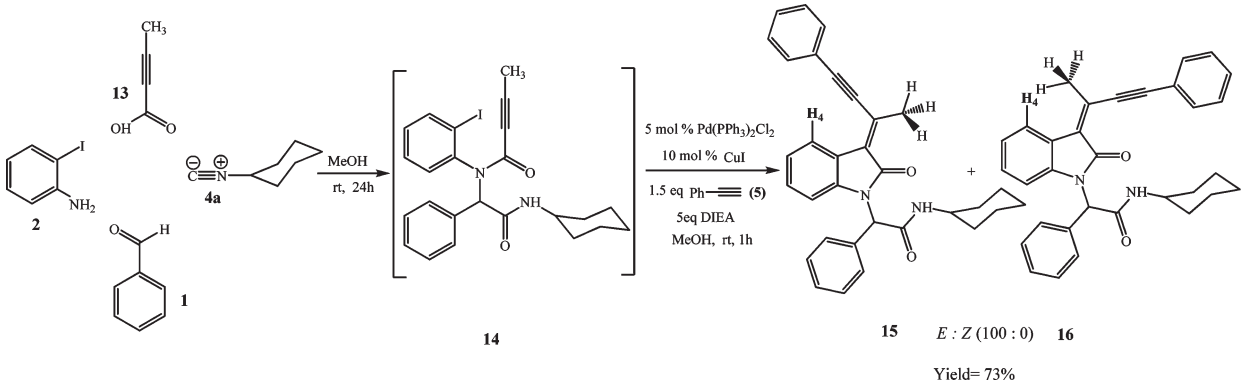
In another attempt, the one-pot six-component reaction of 2-iodoaniline, benzaldehyde, 2-butynoic acid, cyclohexyl



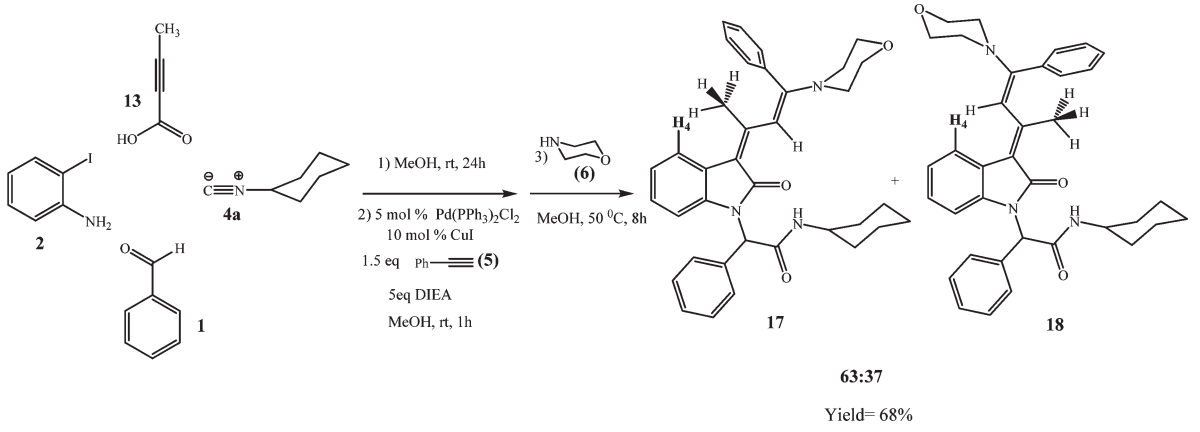
19

FIGURE 4. Synthesis of 1,4-disubstituted piperazine contained 3-arylidene-2-oxindole (**19**).

SCHEME 5



SCHEME 6



isocyanide, phenylacetylene, and morpholine was performed according to our reaction sequences. The products were **17** (*Z*) and **18** (*E*) with the ratio of 63:37 (Scheme 6). The H-4 protons in compounds **17** (isomer *Z*) and **18** (isomer *E*) were observed at δ 7.25 and 7.81 ppm, respectively.

Making a comparison between the chemical shift for H-4 in compounds **7a**−**j** and also compound **17** confirms the role of phenyl ring current effect on the chemical shift of H-4.

To expand the applicability of this domino reaction, after optimization of experimental conditions, piperazine was used as the secondary amine in our one-pot reaction to afford compound **19** in 60% yield (Figure 4).

In conclusion, the aforementioned strategy presents a new and direct route to biologically relevant heterocyclic scaffolds by new one-pot Ugi/Heck carbocyclization/Sonogashira/nucleophilic addition reaction sequences. The high stereoselectivity, the ability of carrying out the reaction in mild conditions with high yields, and the introduction of the novel six-component reaction are the major advantages of this work.

Experimental Section

General Procedure for the Synthesis of 3-Arylidene-2-oxindoles 7a−j. 2-Iodoaniline (219 mg, 1 mmol) and benzaldehyde (106 mg, 1 mmol) were mixed together in MeOH (5 mL) and stirred for 30 min. Then, phenyl propiolic acid (146 mg, 1 mmol) and after 15 min isocyanide (1 mmol) were added, and the mixture was stirred for 24 h. CuI (20 mg, 0.1 equiv) $PdCl_2(PPh_3)_2$, (35 mg, 0.05 equiv), phenylacetylene (153 mg, 1.5 mmol), and DIEA (650 mg, 5 mmol) were simultaneously added to the solution of Ugi adduct in MeOH. The mixture was stirred at room temperature for 1 h. After this time, the secondary amine (1.5 mmol) was added as the sixth starting material in one portion, and the resulting solution was heated at 50 °C for 8 h. After cooling to room temperature, the reaction mixture was diluted with brine (30 mL) and extracted with ethyl acetate (3 × 20 mL). The combined organic layers were dried with sodium sulfate, concentrated to dryness in vacuo, and purified by column chromatography on silica gel (hexane/ethyl acetate) to give **7a−j** (yields 62−73%) as red solids.

***N*-Cyclohexyl-2-((3*E*)-3-((*E*)-3-(4-(2-hydroxyethyl)piperazin-1-yl)-1,3-diphenylallylidene)-2-oxoindolin-1-yl)-2-phenylacetamide (7a) (Table 1, entry 1).** Isolated yield 62%; mp 239−241 °C; IR (KBr, cm^{-1}) ν 3427, 3052, 2929, 1670, 1628; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.10−1.65 (m, 10H, $H_{Cyclohexyl}$), 2.55 (m, 5H, $2CH_2$ (CH_2N), OH), 2.57 (t, 2H, J = 5.3 Hz, CH_2N), 3.29 (s, 4H, $2CH_2$, CH_2NC=), 3.62 (t, 2H, J = 5.3 Hz, CH_2OH), 3.89 (m, 1H, CH, $H_{Cyclohexyl}$) 5.46 (d, 1H, J = 7.9 Hz, H_4), 6.23 (d, 1H, J = 7.8 Hz, NH), 6.41 (t, 1H, J = 7.6 Hz, H_{Ar}), 6.44 (s, 1H, CH), 6.70 (d, 1H, J = 7.9 Hz, H_{Ar}), 6.78 (t, 1H, J = 7.6 Hz, H_{Ar}), 6.81−7.41 (m, 15H, H_{Ar}), 7.76 (s, 1H, =CH); ^{13}C NMR (125 MHz, $CDCl_3$) δ 24.6, 24.7, 25.5, 32.7, 32.8, 48.6, 48.8, 49.2, 52.8, 53.0, 57.8, 58.0, 59.2, 106.3, 110.2, 113.7, 120.8, 121.3, 124.7, 124.9, 127.1, 127.6, 127.7, 127.9, 128.1, 128.3, 128.4, 129.3, 130.2, 135.2, 136.5, 138.0, 139.9, 157.1, 162.4, 167.4, 168.2; HR-MS (ESI) calcd for $C_{43}H_{47}N_4O_3$ $[M + 1]^+$ 667.36427, found 667.36427; calcd for $C_{43}H_{46}N_4NaO_3$ $[M + Na]^+$ 689.34732, found 689.34728.

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Supporting Information Available: Experimental procedures, complete analytical data, NOE results, X-ray crystallographic data, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.