HETEROCYCLES, Vol. 100, No. 12, 2020, pp. 2050 - 2060. © 2020 The Japan Institute of Heterocyclic Chemistry
Received, 21st August, 2020, Accepted, 9th September, 2020, Published online, 23rd September, 2020
DOI: 10.3987/COM-20-14340

STEREOSELECTIVE SYNTHESIS OF (*Z*)-3-ARYLIDENE-2-OXINDOLES VIA A PALLADIUM-CATALYZED TANDEM REACTION

Sunhwa Park, Kye Jung Shin, and Jae Hong Seo*

Integrated Research Institute of Pharmaceutical Sciences, College of Pharmacy, The Catholic University of Korea, 43 Jibong-ro, Wonmi-gu, Bucheon, Gyeonggi-do 14662, Republic of Korea; E-mail: jaehongseo@catholic.ac.kr

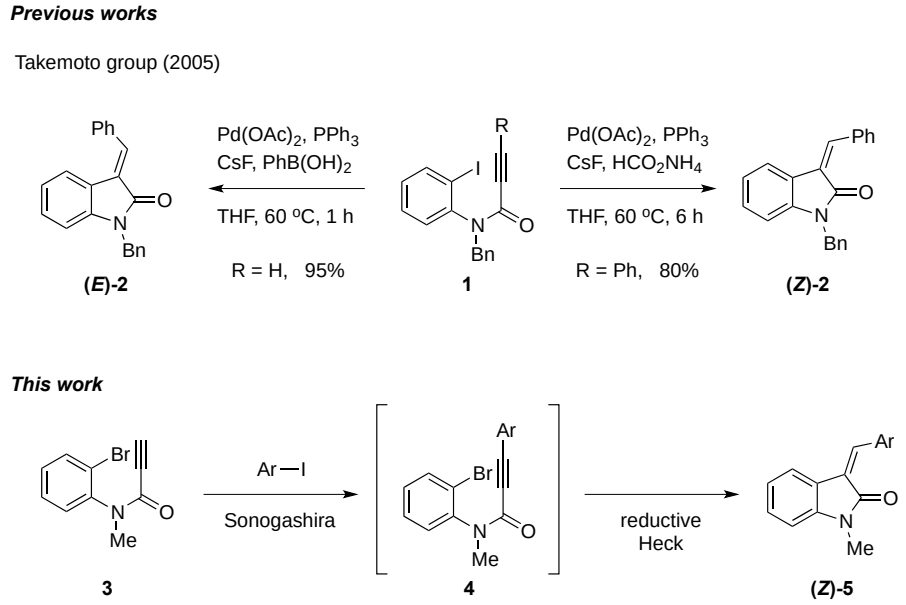
Abstract - A novel and efficient synthetic method for the stereoselective preparation of (*Z*)-3-arylideneoxindoles from simple propiolamide has been developed utilizing a palladium-catalyzed tandem reaction. Two Sonogashira and reductive Heck reactions were successfully combined under microwave irradiation. The *E*/*Z* stereoselectivity of the reaction was enhanced by solvent control.

INTRODUCTION

The 3-methyleneoxindole skeleton is an important structure found in various natural products,[1] synthetic intermediates[2] and drugs.[3] Among them, 3-arylideneoxindole derivatives have attracted the attention of synthetic chemists due to their unique biological activities.[4]

Among the various synthetic approaches to 3-arylideneoxindoles,[5] the most common and simple way is the Knoevenagel reaction of oxindoles and aryl aldehydes.[6] However, the *E*/*Z* stereoselectivity of this reaction system is generally low. In 2005, Takemoto and coworkers reported an elegant palladium-catalyzed approach for the stereoselective synthesis of (*E*)- and (*Z*)-3-arylideneoxindoles respectively (Scheme 1).[7] (*E*)-3-Arylideneoxindoles were obtained in good yield from a non-substituted propiolamide (**1**, R=H) via successive palladium-catalyzed reactions, the Heck and Suzuki-Miyaura reactions. The synthesis of (*Z*)-3-arylideneoxindoles was also achieved by the reductive Heck cyclization of substituted propiolamides (**1**, R=aryl). However, the substrate scope of these methods has not been fully evaluated. Thus, a novel stereoselective method for 3-arylideneoxindole synthesis remains in demand. (*Z*)-3-Arylideneoxindoles, which are dominant over (*E*)-isomers in biologically active compounds, are especially intriguing target.[8] As a part of our ongoing efforts to develop efficient and novel synthetic methods for 3-methyleneoxindole derivatives,[9] we evaluated one-pot conditions for the

Z-selective synthesis of 3-arylidenoxindoles from non-substituted propiol amide **3** by combining the Sonogashira and reductive Heck reactions.

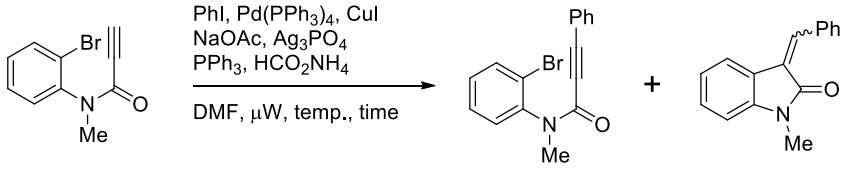


Scheme 1. Synthetic approaches for 3-arylidene-2-oxindoles

RESULTS AND DISCUSSION

To identify the optimal conditions for the synthesis of (*Z*)-3-arylideneoxindoles we began with our previous tandem Sonogashira/Heck/Suzuki-Miyaura reaction conditions.[9] As an alternate route, arylboronic acid was exchanged with HCO_2NH_4 as the hydride source (Table 1, Entry 1) in the Sonogashira/reductive Heck reaction. Under these conditions, the desired product **5a** was obtained in 67% yield (*E*/*Z* = 2:1) with the remaining intermediate **4a** in 22% yield (Entry 1). In our previous study of tandem Sonogashira, Heck and Suzuki-Miyaura reactions, we found that Sonogashira step proceeded smoothly at low temperature while the following Heck and Suzuki-Miyaura reactions required higher reaction temperature.[9a] Thus, the incomplete reaction of entry 1 implies that the second reductive Heck reaction needs more harsh conditions rather than the first Sonogashira step. To complete the reaction, the temperature was increased to 180 °C, which provided the desired product **5a** in 77% yield (*E*/*Z* = 2:1), although a small amount of the Sonogashira adduct **4a** remained (Entry 2). At 250 °C the reaction proceeded to completion but with a slightly decreased yield of 64% (*E*/*Z* = 2:1) (Entry 3). The reaction without Ag_3PO_4, key additive for high stereoselectivity,[9] resulted in slightly lower yields (Entry 4, 66%, *E*/*Z* = 2:1). Changing the hydride source from HCO_2NH_4 to HCO_2Na resulted in low yields. (Entry 5, 63%, *E*/*Z* = 2:1). Interestingly, all of the above reaction conditions gave the same *E*/*Z* stereoselectivity (*E*/*Z* = 2:1). This implies that *E*/*Z*-isomerization of products occurs quickly to reach an equilibrium ratio of 2:1.

Table 1. First optimization of the tandem Sonogashira/ reductive Heck reaction[a)]



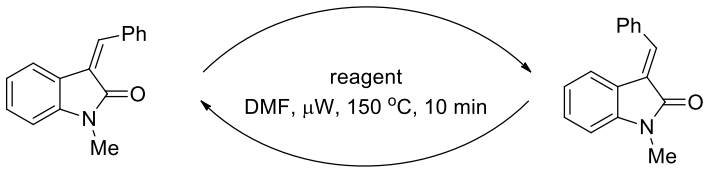
3 **4a** **5a**

Entry	Temp (°C)	Time (min)	**4a** (%)	**5a**	
				Yield[b)] (%)	*E*/*Z* ratio
1	150	10	22	67	2:1
2	180	10	3	77	2:1
3	250	10	-	64	2:1
4[c)]	180	10	-	66	2:1
5[d)]	180	10	-	63	2:1

[a)]Reagents and conditions: **3** (0.17 mmol), phenyl iodide (1.1 eq), $Pd(PPh_3)_4$ (10 mol%), CuI (5 mol%), NaOAc (3.0 eq), Ag_3PO_4 (1.1 eq), PPh_3 (30 mol%), HCO_2NH_4 (1.2 eq), DMF (3.0 mL), μW, temp., time. [b)]Combined isolated yield of *E*- and *Z*-isomers. [c)]Without Ag_3PO_4. [d)]HCO_2Na instead of HCO_2NH_4 was added.

To elucidate the reason(s) for this isomeric equilibration under all of these reaction conditions, an *E*/*Z* isomerization study was conducted for each reagent (Table 2). In all cases, each pure isomer was partly isomerized into the other. **(*Z*)-5a** isomerized into **(*E*)-5a** to give *E*/*Z* ratios of 1.1:1 to 2.3:1 (Entries 1–4). **(*E*)-5a** was slightly less prone to isomerization, resulting in *E*/*Z* ratios of 2:1 to 2.7:1 (Entries 5–8). Interestingly, even without any reagent, isomerization occurred in the DMF solvent under microwave irradiation (150 °C, 10 min) (Entries 4 and 8). These results are consistent with those of Li's group, where (*Z*)-isomer was isomerized into the (*E*)-isomer by heating in toluene (140 °C, 10 h).[10]

Table 2. *E*/*Z* Isomerization[a)]



(*Z*)-5a **(*E*)-5a**

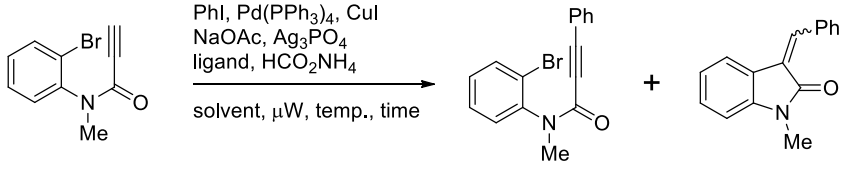
Entry	Starting Material	Reagent	*E*/*Z* ratio[a)]
1	**(*Z*)-5a**	$Pd(PPh_3)_4$ (10 mol%)	1.7:1
2	**(*Z*)-5a**	PPh_3 (30 mol%)	1.2:1
3	**(*Z*)-5a**	NaOAc (3.0 eq)	2.3:1
4	**(*Z*)-5a**	none	1:1.1

5	**(*E*)-5a**	$Pd(PPh_3)_4$ (10 mol%)	2:1
6	**(*E*)-5a**	PPh_3 (30 mol%)	2.7:1
7	**(*E*)-5a**	NaOAc (3.0 eq)	2.2:1
8	**(*E*)-5a**	none	2.2:1

[a)] Ratio was determined by ^{1}H NMR of the crude mixture.

Because *E/Z* isomerization occurred easily in DMF at high temperatures, the next step in finding optimal conditions was solvent screening (Table 3). The same reaction in acetonitrile (ACN) provided the desired product in a low yield but with slightly higher *E/Z* stereoselectivity (Entry 1: 35% yield, *E/Z* = 1:2). Tetrahydrofuran (THF) as a solvent dramatically increased the *E/Z* stereoselectivity to 1:7 with a moderate 51% yield (Entry 2). Higher reaction temperature (180 ℃) in THF improved yields up to 60%, but resulted in much lower stereoselectivity (Entry 3: *E/Z* = 1:3.5). Interestingly, the absence of the phosphine ligand slightly improved both yield and *E*/*Z* stereoselectivity (Entry 4: 61% yield, *E*/*Z* = 1:8). Elongation of the reaction time to 20 min increased yield at the expense of *E*/*Z* stereoselectivity (Entry 5: 70% yield, *E*/*Z* = 1:6). Performing the reaction at 130 ℃ resulted in high stereoselectivity, but the reaction did not rut to completion, resulting in low yields (Entry 6: 53% yield, *E*/*Z* = 1:8). Using none or only a small amount (0.5 eq) of silver salt dramatically reduced both yield and stereoselectivity, which proved the essential role of silver salt in our system (Entries 7 and 8).[9] As the amount of HCO_2NH_4 was increased to two equivalents, yields also increased to 87% with moderate *E*/*Z* stereoselectivity (Entry 9: *E*/*Z* = 1:5). Using three equivalents of HCO_2NH_4 resulted in 95% yield with an *E*/*Z* = 1:4 (Entry 10).

Table 3. Second optimization of the tandem Sonogashira/ reductive Heck reaction[a)]



3 **4a** **5a**

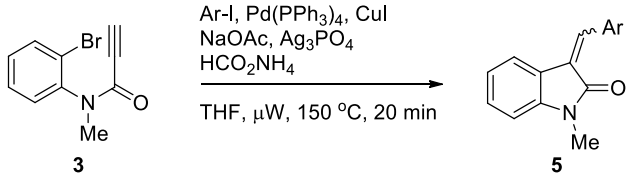
Entry	Solvent	Ligand	Temp (℃)	Time (min)	**4a** (%)	**5a**	
						Yield[b)] (%)	*E*/*Z* ratio
1	ACN	PPh_3	150	10	35	35	1:2
2	THF	PPh_3	150	10	28	51	1:7
3	THF	PPh_3	180	5	26	60	1:3.5
4	THF	-	150	10	26	61	1:8
5	THF	-	150	20	15	70	1:6
6	THF	-	130	20	27	53	1:8
7[c)]	THF	-	150	10	28	-	-

8[d)]	THF	-	150	10	41	38	1:3
9[e)]	THF	-	150	20	11	87	1:5
10[f)]	THF	-	150	20	4	95	1:4

[a)]Reagents and conditions: **3** (0.17 mmol), phenyl iodide (1.1 eq), $Pd(PPh_3)_4$ (10 mol%), CuI (5 mol%), NaOAc (3.0 eq), Ag_3PO_4 (1.1 eq), PPh_3 (30 mol%), HCO_2NH_4 (1.2 eq), solvent (3.0 mL), μW, temp., time. [b)]Combined isolated yield of *E*- and *Z*-isomers. [c)]without Ag_3PO_4. [d)]0.5 eq of Ag_3PO_4 was added. [e)]2.0 eq of HCO_2NH_4 was added. [f)]3.0 eq of HCO_2NH_4 was added.

With the optimal reaction conditions in hand, we investigated the substrate scope of the tandem Sonogashira/reductive Heck reaction (Table 4). Regardless of the substitution position or electronic properties of the substituents on the aryl group, all of the reactions gave the corresponding 3-arylideneoxindoles in good yields with moderate (*Z*)-stereoselectivities (Entries 1–8). However, placing an electron-donating methoxy group at the 4-position of aryl iodide resulted in low yields and low stereoselectivity (Entry 1: 72% yield, *E*/*Z* ratio = 1:2.5). Reducing the amount of HCO_2NH_4 to two equivalents recovered the stereoselectivity (*E*/*Z* ratio = 1:5) with a slight decrease in yield (66%) (Entry 2). The introduction of a heteroaryl group also resulted in good yield and stereoselectivity (Entry 8).

Table 4. Substrate scope of the tandem Sonogashira/ reductive Heck reaction[a)]



3 **5**

Entry	Ar	**5**	Yield[b)] (%)	*E*/*Z* ratio
1	4-$MeOC_6H_4$	**5b**	72	1:2.5
2[c)]	4-$MeOC_6H_4$	**5b**	66	1:5
3	4-ClC_6H_4	**5c**	99	1:4.5
4	4-$NO_2C_6H_4$	**5d**	99	1:4
5	3-$MeOC_6H_4$	**5e**	83	1:4.5
6	3-ClC_6H_4	**5f**	99	1:4
7	3-$NO_2C_6H_4$	**5g**	97	1:3.5
8	3-pyridinyl	**5h**	99	1:4

[a)]Reagents and conditions: **3** (0.17 mmol), Ar-I (1.1 eq), $Pd(PPh_3)_4$ (10 mol%), CuI (5 mol%), NaOAc (3.0 eq), Ag_3PO_4 (1.1 eq), HCO_2NH_4 (3.0 eq), THF (3.0 mL), μW, temp., time. [b)]Combined isolated yield of *E*- and *Z*-isomers. [c)]2.0 eq of HCO_2NH_4 was added.

In conclusion, we have developed a novel and efficient synthetic method, featuring a palladium-catalyzed tandem reaction consisting of the Sonogashira and reductive Heck reactions, for the stereoselective synthesis of (*Z*)-3-arylideneoxindoles in excellent yields. Our method provides a quick synthetic approach to diverse (*Z*)-3-arylideneoxindoles from the simple propiol amide **3** and can be used in diversity-oriented syntheses of various derivatives for a wide range of applications.

EXPERIMENTAL

All reactions were performed under an argon atmosphere with dry solvents, unless otherwise stated. Dry tetrahydrofuran (THF), and methylene chloride (CH_2Cl_2) were obtained from Ultimate Solvent Purification System (JC Meyer Solvent System, Laguna Beach, CA, USA). Other dry solvents were purchased as anhydrous grade. All commercially available reagents were purchased and used without further purification. Microwave reaction was conducted on microwave reactor of Biotage Initiator$^+$. Reactions were monitored by thin-layer chromatography (TLC) on silica gel plates (Merck TLC Silica Gel 60 F_{254}, Darmstadt, Germany) using UV light, PMA (an ethanolic solution of phosphomolybdic acid) as visualizing agent. Purification of products was conducted by column chromatography through silica gel 60 (0.060−0.200 mm). Melting points of all solid compounds were determined by Buchi M-565. IR spectra were recorded on a Jasco P-2000 FT-IR spectrometer. NMR spectra were obtained on Bruker AVANCE III 500 MHz (Bruker Corporation, Billerica, MA, USA) using residual undeuterated solvent or TMS (tetramethylsilane) as an internal reference.

General Procedure for Tandem Sonogashira/Reductive Heck Reaction

A microwave reaction vial was charged with **3** (0.168 mmol, 1.0 equiv.), aryl iodide (0.185 mmol, 1.1 equiv.), HCO_2NH_4 (0.504 mmol, 3.0 equiv.), NaOAc (0.504 mmol, 3.0 equiv.), CuI (0.0084 mmol, 5 mol%), $Pd(PPh_3)_4$ (0.0168 mmol, 10 mol%), Ag_3PO_4 (0.185 mmol, 1.1 equiv.) and THF (3 mL). The reaction vial was sealed and exposed to microwave irradiation conditions with indicated time and temperature (150 °C, 20 min). The mixture was cooled to 25 °C and diluted with EtOAc (100 mL). Organic layer was washed with H_2O (20 mL×3), then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexane:EtOAc or CH_2Cl_2:MeOH) to afford 3-arylidene-2-oxindoles **5a-h**.

(*Z*)-3-Benzylidene-1-methylindolin-2-one ((*Z*)-5a)

Yellow solid; mp 100.8 °C (lit.[11] 106 °C); R_f = 0.32 (silica gel, hexanes:EtOAc 6:1); IR (film) 2930, 2371, 1686, 1468, 1090, 751, 688 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.30 (d, *J* = 6.8 Hz, 2H), 7.54−7.52 (m, 2H), 7.47−7.40 (m, 3H), 7.29 (td, *J* = 7.7, 1.0 Hz, 1H), 7.06 (td, *J* = 7.6, 0.9 Hz, 1H), 6.81 (d, *J* = 7.8

Hz, 1H), 3.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 142.5, 137.2, 134.0, 132.1, 130.6, 129.0, 128.4, 126.2, 124.5, 121.9, 119.1, 108.0, 26.1 ppm.

(*E*)-3-Benzylidene-1-methylindolin-2-one ((*E*)-5a)[12]

Yellow oil; R_f = 0.21 (silica gel, hexanes:EtOAc 6:1); IR (film) 3054, 2930, 1704, 1606, 1468, 1101, 777, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (s, 1H), 7.64 (t, *J* = 7.8 Hz, 3H), 7.48−7.42 (m, 3H), 7.27 (t, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 3.29 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 144.4, 137.3, 135.2, 129.9, 129.6, 129.4, 128.8, 127.4, 122.9, 121.9, 121.3, 108.3, 26.3 ppm.

(*Z*)-3-(4-Methoxybenzylidene)-1-methylindolin-2-one ((*Z*)-5b)[11]

Yellow solid; mp 124.0 °C; R_f = 0.31 (silica gel, hexanes:EtOAc 4:1); IR (film) 3056, 2929, 1683, 1588, 1249, 1179, 742 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41−8.38 (m, 2H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.49 (s, 1H), 7.26 (td, *J* = 7.5, 1.1 Hz, 1H), 7.05 (td, *J* = 7.6, 0.9 Hz, 1H), 6.98−6.95 (m, 2H), 6.81 (d, *J* = 7.8 Hz, 1H), 3.88 (s, 3H), 3.29 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 161.7, 142.0, 137.2, 134.6, 128.3, 127.2, 125.0, 123.7, 121.8, 118.6, 113.9, 107.9, 55.5, 26.1 ppm.

(*E*)-3-(4-Methoxybenzylidene)-1-methylindolin-2-one ((*E*)-5b)[11]

Yellow oil; R_f = 0.19 (silica gel, hexanes:EtOAc 4:1); IR (film) 3055, 2932, 1698, 1599, 1250, 1174, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.81 (s, 1H), 7.75 (d, *J* = 7.6 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 6.93−6.90 (m, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 3.88 (s, 3H), 3.29 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.0, 161.0, 144.2, 137.5, 131.6, 129.5, 127.5, 125.5, 122.5, 121.8, 121.6, 114.2, 108.2, 55.5, 26.3 ppm.

(*Z*)-3-(4-Chlorobenzylidene)-1-methylindolin-2-one ((*Z*)-5c)

Yellow solid; mp 151.4 °C (lit.[13] 151-152 °C); R_f = 0.27 (silica gel, hexanes:EtOAc 6:1); IR (film) 2787, 2318, 1686, 1605, 1087, 829, 745 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.26 (d, *J* = 8.5 Hz, 2H), 7.50 (d, *J* = 7.5 Hz, 1H), 7.44 (s, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.30 (td, *J* = 7.7, 0.8 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 3.26 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 142.6, 136.5, 135.5, 133.4, 132.5, 129.3, 128.6, 126.7, 124.3, 122.1, 119.1, 108.1, 26.1 ppm.

(*E*)-3-(4-Chlorobenzylidene)-1-methylindolin-2-one ((*E*)-5c)

Yellow solid; mp 105.0 °C (lit.[8c] 107-109 °C); R_f = 0.25 (silica gel, hexanes:EtOAc 4:1); IR (film) 3729, 2928, 1706, 1607, 1469, 1095, 777 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.77 (s, 1H), 7.58 (t, *J* = 7.4 Hz, 3H), 7.44 (d, *J* = 8.5 Hz, 2H), 7.28 (td, *J* = 7.8, 0.7 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 3.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.4, 144.6, 135.6, 135.5, 133.6, 130.8, 130.2, 129.1, 127.9, 122.9, 122.0, 121.0, 108.5, 26.3 ppm.

(*Z*)-1-Methyl-3-(4-nitrobenzylidene)indolin-2-one ((*Z*)-5d)

Red solid; mp 187.6 °C (lit.[14] 187.6-189.1 °C); R_f = 0.53 (silica gel, CH_2Cl_2 only); IR (film) 3108, 3058,

2928, 1676, 1517, 1336, 742 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (d, *J* = 8.7 Hz, 2H), 8.28−8.25 (m, 2H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.52 (s, 1H), 7.35 (td, *J* = 7.7, 0.9 Hz, 1H), 7.09 (td, *J* = 7.6, 0.7 Hz, 1H), 6.84 (d, *J* = 7.8 Hz, 1H), 3.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 148.2, 143.3, 140.0, 133.2, 132.4, 130.4, 129.8, 123.6, 123.5, 122.4, 119.9, 108.4, 26.2 ppm.

(*E*)-1-Methyl-3-(4-nitrobenzylidene)indolin-2-one ((*E*)-5d)

Red solid; mp 230.4 °C (lit.[14] 167.6-168.5 °C); R_f = 0.31 (silica gel, CH_2Cl_2 only); IR (film) 3101, 2929, 1695, 1518, 1469, 1341, 780 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 8.8 Hz, 2H), 7.79−7.78 (m, 3H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 3.29 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.9, 148.1, 145.0, 141.9, 133.4, 131.1, 130.11, 130.10, 124.1, 123.0, 122.2, 120.5, 108.8, 26.4 ppm.

(*Z*)-3-(3-Methoxybenzylidene)-1-methylindolin-2-one ((*Z*)-5e)

Yellow solid; mp 139.9 °C (lit.[14] 106.9-108.4 °C); R_f = 0.38 (silica gel, hexanes:EtOAc 4:1); IR (film) 3094, 2944, 1684, 1568, 1257, 1050, 784, 746 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.36−8.35 (m, 1H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.53−7.51 (m, 2H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.29 (td, *J* = 7.7, 1.0 Hz, 1H), 7.06 (td, *J* = 7.6, 0.9 Hz, 1H), 7.00 (ddd, *J* = 8.2, 2.5, 0.7 Hz, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 3.92 (s, 3H), 3.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 159.6, 142.4, 137.2, 135.3, 129.2, 129.0, 126.3, 125.3, 124.6, 121.9, 119.0, 117.7, 116.0, 108.0, 55.6, 26.1 ppm.

(*E*)-3-(3-Methoxybenzylidene)-1-methylindolin-2-one ((*E*)-5e)

Yellow solid; mp 132.2 °C (lit.[15] 139-140 °C); R_f = 0.22 (silica gel, hexanes:EtOAc 4:1); IR (film) 3002, 2934, 1692, 1606, 1258, 1105, 693 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.83 (s, 1H), 7.67 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H), 7.29−7.23 (m, 2H), 7.16 (s, 1H), 6.97 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 3.84 (s, 3H), 3.29 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.6, 159.8, 144.5, 137.1, 136.5, 129.9, 129.8, 127.6, 123.1, 121.9, 121.8, 121.3, 115.6, 114.4, 108.3, 55.5, 26.3 ppm.

(*Z*)-3-(3-Chlorobenzylidene)-1-methylindolin-2-one ((*Z*)-5f)

Yellow solid; mp 105.8 °C (lit.[14] 106.9-108.4 °C); R_f = 0.35 (silica gel, hexanes:EtOAc 4:1); IR (film) 3059, 2929, 1685, 1468, 1093, 1041, 749 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (s, 1H), 8.14−8.12 (m, 1H), 7.51 (d, *J* = 7.5 Hz, 1H), 7.43 (s, 1H), 7.39−7.37 (m, 2H), 7.31 (t, *J* = 7.7 Hz, 1H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 142.8, 135.6, 135.1, 134.3, 131.6, 130.3, 130.1, 129.55, 129.54, 127.6, 124.1, 122.1, 119.3, 108.2, 26.1 ppm.

(*E*)-3-(3-Chlorobenzylidene)-1-methylindolin-2-one ((*E*)-5f)

Yellow solid; mp 130.0 °C (lit.[14] 80.4-81.6 °C); R_f = 0.28 (silica gel, hexanes:EtOAc 4:1); IR (film) 3053, 2929, 1697, 1606, 1473, 1106, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.75 (s, 1H), 7.61 (s, 1H), 7.54−7.50 (m, 2H), 7.40−7.39 (m, 2H), 7.29 (t, *J* = 7.7 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 6.83 (d, *J* = 7.8

Hz, 1H), 3.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.3, 144.6, 137.0, 135.2, 134.8, 130.4, 130.1, 129.5, 129.1, 128.5, 127.4, 123.0, 122.1, 120.9, 108.5, 26.3 ppm.

(*Z*)-1-Methyl-3-(3-nitrobenzylidene)indolin-2-one ((*Z*)-5g)[6b]

Orange solid; mp 175.8 °C; R_f = 0.19 (silica gel, hexanes:EtOAc 4:1); IR (film) 3077, 2925, 1687, 1528, 1343, 1092, 671 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.11 (s, 1H), 8.59 (d, *J* = 7.8 Hz, 1H), 8.23 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.59 (t, *J* = 8.0 Hz, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.50 (s, 1H), 7.33 (td, *J* = 7.7, 0.9 Hz, 1H), 7.08 (td, *J* = 7.6, 0.6 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.9, 148.3, 143.0, 137.2, 135.4, 133.3, 130.1, 129.2, 129.0, 126.4, 124.5, 123.6, 122.3, 119.6, 108.4, 26.2 ppm.

(*E*)-1-Methyl-3-(3-nitrobenzylidene)indolin-2-one ((*E*)-5g)[6b]

Yellow solid; mp 145.3 °C; R_f = 0.32 (silica gel, hexanes:EtOAc 2:1); IR (film) 2921, 2851, 1713, 1610, 1530, 1351, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.51 (s, 1H), 8.28 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 7.80 (s, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.32 (td, *J* = 7.8, 0.9 Hz, 1H), 6.90 (td, *J* = 7.7, 0.8 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 3.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 148.6, 145.0, 137.0, 135.2, 133.3, 131.0, 130.0, 129.7, 124.1, 124.0, 122.8, 122.3, 120.5, 108.8, 26.4 ppm.

(*Z*)-1-Methyl-3-(pyridin-3-ylmethylene)indolin-2-one ((*Z*)-5h)[6a]

Orange oil; R_f = 0.24 (silica gel, 1% NH_4OH, hexanes:EtOAc 1:1); IR (film) 3053, 2932, 1693, 1607, 1471, 1091, 786, 704 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 9.14 (d, *J* = 8.1 Hz, 1H), 8.95 (brs, 1H), 8.61 (brs, 1H), 7.55 (d, *J* = 7.5 Hz, 1H), 7.47 (s, 1H), 7.40−7.38 (m, 1H), 7.32 (td, *J* = 7.7, 1.1 Hz, 1H), 7.08 (td, *J* = 7.6, 0.8 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 3.27 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 152.9, 150.7, 142.8, 138.3, 132.6, 130.1, 129.8, 128.6, 123.8, 123.3, 122.2, 119.5, 108.3, 26.1 ppm.

(*E*)-1-Methyl-3-(pyridin-3-ylmethylene)indolin-2-one ((*E*)-5h)[6a]

Orange oil; R_f = 0.24 (silica gel, 1% NH_4OH, hexanes:EtOAc 1:1); ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.90 (brs, 1H), 8.66 (brs, 1H), 7.92 (d, *J* = 7.9 Hz, 1H), 7.76 (s, 1H), 7.49 (d, *J* = 7.6 Hz, 1H), 7.42−7.41 (m, 1H), 7.28 (td, *J* = 7.7, 1.0 Hz, 1H), 6.89 (td, *J* = 7.7, 0.9 Hz, 1H), 6.84 (d, *J* = 7.7 Hz, 1H), 3.28 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 168.0, 150.3, 150.1, 144.7, 136.4, 132.7, 131.3, 130.6, 129.3, 123.6, 122.8, 122.2, 120.8, 108.6, 26.4 ppm.

ACKNOWLEDGEMENTS

This research was supported by Basic Science Research Program through the National Research Foundation of Korea(NRF) funded by the Ministry of Education(2018R1D1A1B07045653 and 2018R1A6A1A03025108)

REFERENCES

1. (a) T. Hoshino, T. Kondo, T. Uchiyama, and N. Ogasawara, *Agric. Biol. Chem.*, 1987, **51**, 965; (b) M. S. C. Pedras, J. L. Sorensen, F. I. Okanga, and I. L. Zaharia, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 3015; (c) I. Fatima, I. Ahmad, I. Anis, A. Malik, and N. Afza, *Molecules*, 2007, **12**, 155.
2. (a) S. Lin, Z.-Q. Yang, B. H. B. Kwok, M. Koldobskiy, C. M. Crews, and S. J. Danishefsky, *J. Am. Chem. Soc.*, 2004, **126**, 6347; (b) B. M. Trost, N. Cramer, and H. Bernsmann, *J. Am. Chem. Soc.*, 2007, **129**, 3086; (c) A. Singh and G. P. Roth, *Org. Lett.*, 2011, **13**, 2118.
3. (a) L. Q. Chow and S. G. Eckhardt, *J. Clin. Oncol.*, 2007, **25**, 884; (b) C. A. London, P. B. Malpas, S. L. Wood-Follis, J. F. Boucher, A. W. Rusk, M. P. Rosenberg, C. J. Henry, K. L. Mitchener, M. K. Klein, J. G. Hintermeister, P. J. Bergman, G. C. Couto, G. N. Mauldin, and G. M. Michels, *Clin. Cancer Res.*, 2009, **15**, 3856; (c) L. Richeldi, R. M. du Bois, G. Raghu, A. Azuma, K. K. Brown, U. Costabel, V. Cottin, K. R. Flaherty, D. M. Hansell, Y. Inoue, D. S. Kim, M. Kolb, A. G. Nicholson, P. W. Noble, M. Selman, H. Taniguchi, M. Brun, F. Le Maulf, M. Girard, S. Susanne Stowasser, F. Schlenker-Herceg, B. Disse, and H. R. Collard, *N. Engl. J. Med.*, 2014, **370**, 2071.
4. (a) E. Vessally, R. Hosseinzadeh-Khanmiri, E. Ghorbani-Kalhor, M. Es'haghi, and A. Bekhradnia, *RSC Adv.*, 2017, **7**, 19061; (b) N. Kammasud, C. Boonyarat, S. Tsunoda, H. Sakurai, I. Saiki, D. S. Grierson, and O. Vajragupta, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 4812; (c) E. Rizzi, G. Cassinelli, S. Dallavalle, C. Lanzi, R. Cincinelli, R. Nannei, G. Cuccuru, and F. Zunino, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 3962.
5. (a) W. R. Bowman, H. Heaney, and B. M. Jordan, *Tetrahedron Lett.*, 1988, **29**, 6657; (b) R. Yanada, S. Obika, Y. Kobayashi, T. Inokuma, M. Oyama, K. Yanada, and Y. Takemoto, *Adv. Synth. Catal.*, 2005, **347**, 1632; (c) M. Arthuis, R. Pontikis, and J.-C. Florent, *Tetrahedron Lett.*, 2007, **48**, 6397; (d) S. Balalaie, H. Motaghedi, M. Bararjanian, D. Tahmassebi, and H. R. Bijanzadeh, *Tetrahedron*, 2011, **67**, 9134; (e) M. Arthuis, R. Pontikis, G. G. Chabot, J. Seguin, L. Quentin, S. Bourg, L. Morin-Allory, and J.-C. Florent, *ChemMedChem*, 2011, **6**, 1693.
6. Knoevenagel reactions: (a) A. A. Alkaev, E. V. Villemson, N. S. Vorobyeva, A. G. Majouga, E. M. Budynina, and M. Y. Melnikov, *J. Org. Chem.*, 2017, **82**, 5689; (b) M. Kiamehr, M. R. Khodabakhshi, F. M. Moghaddam, A. Villinger, and P. Langer, *ARKIVOC*, 2017, **v**, 20; (c) H. J. Lee, J. W. Lim, J. Yu, and J. N. Kim, *Tetrahedron Lett.*, 2014, **55**, 1183.
7. R. Yanada, S. Obika, T. Inokuma, K. Yanada, M. Yamashita, S. Ohta, and Y. Takemoto, *J. Org. Chem.*, 2005, **70**, 6972.
8. (a) R. Yanada, S. Obika, M. Oyama, and Y. Takemoto, *Org. Lett.*, 2004, **6**, 2825; (b) A. Millemaggi, A. Perry, A. C. Whitwood, and R. J. K. Taylor, *Eur. J. Org. Chem.*, 2009, 2947; (c) J. Lubkoll, A. Millemaggi, A. Perry, and R. J. K. Taylor, *Tetrahedron*, 2010, **66**, 6606; (d) F. A. Ross, S. A.

Hawley, F. R. Auciello, G. J. Gowans, A. Atrih, D. J. Lamont, and D. G. Hardie, *Cell Chem. Biol.*, 2017, **24**, 813.

9. (a) G. R. Dong, S. Park, D. Lee, K. J. Shin, and J. H. Seo, *Synlett*, 2013, **24**, 1993; (b) S. Park, K. J. Shin, and J. H. Seo, *Synlett*, 2015, **26**, 2296; (c) S. Park, J. Lee, K. J. Shin, E. Oh, and J. H. Seo, *Molecules*, 2017, **22**, 503; (d) Y. Yu, K. J. Shin, and J. H. Seo, *J. Org. Chem.*, 2017, **82**, 1864.
10. T.-S. Jiang, R.-Y. Tang, X.-G. Zhang, X.-H. Li, and J.-H. Li, *J. Org. Chem.*, 2009, **74**, 8834.
11. A. Teichert, K. Jantos, K. Harms, and A. Studer, *Org. Lett.*, 2004, **6**, 3477.
12. S. Ueda, T. Okada, and H. Nagasawa, *Chem. Commun.*, 2010, **46**, 2462.
13. P. Ivashkin, S. Couve-Bonnaire, P. Jubault, and X. Pannecoucke, *Org. Lett.*, 2012, **14**, 2270.
14. X.-H. Yang, K. Li, R.-J. Song, and J.-H. Li, *Eur. J. Org. Chem.*, 2014, 616.
15. W. Zhang and M.-L. Go, *Bioorg. Med. Chem.*, 2009, **17**, 2077.