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ABSTRACT

Various spirofluorenyl oxindoles and spiroindeno[1,2-*b*]indolyl oxindoles were synthesized in good yields in one-pot reaction by $TiCl_4$-catalyzed sequential inter- and intramolecular Friedel-Crafts reactions of isatins with *meta*-arylphenols and 2-arylindoles in 1,2-dichloroethane.



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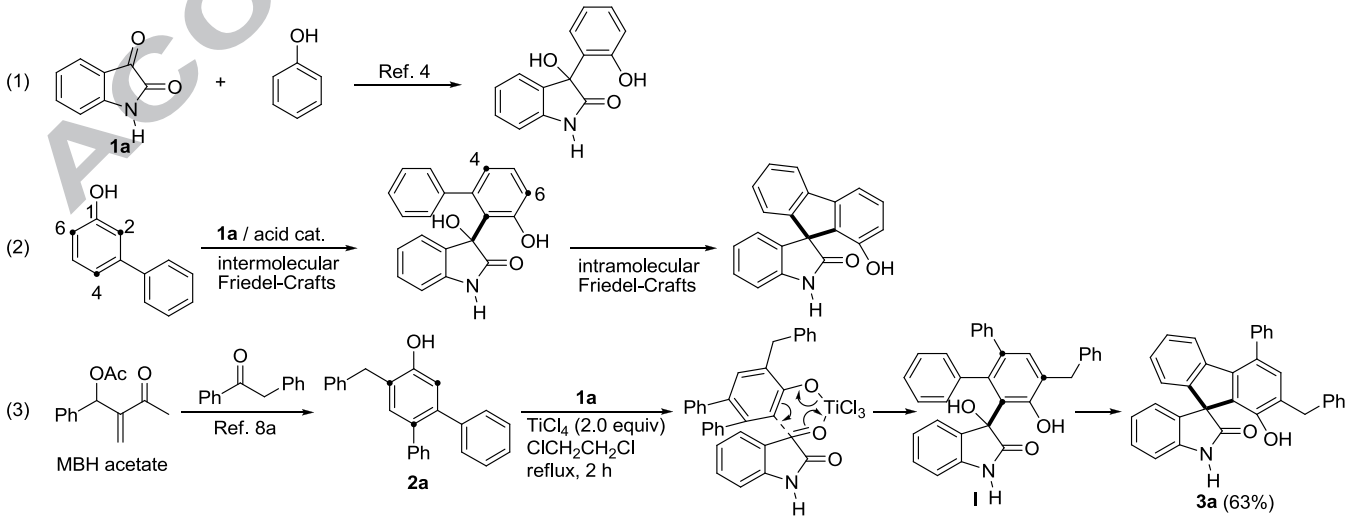
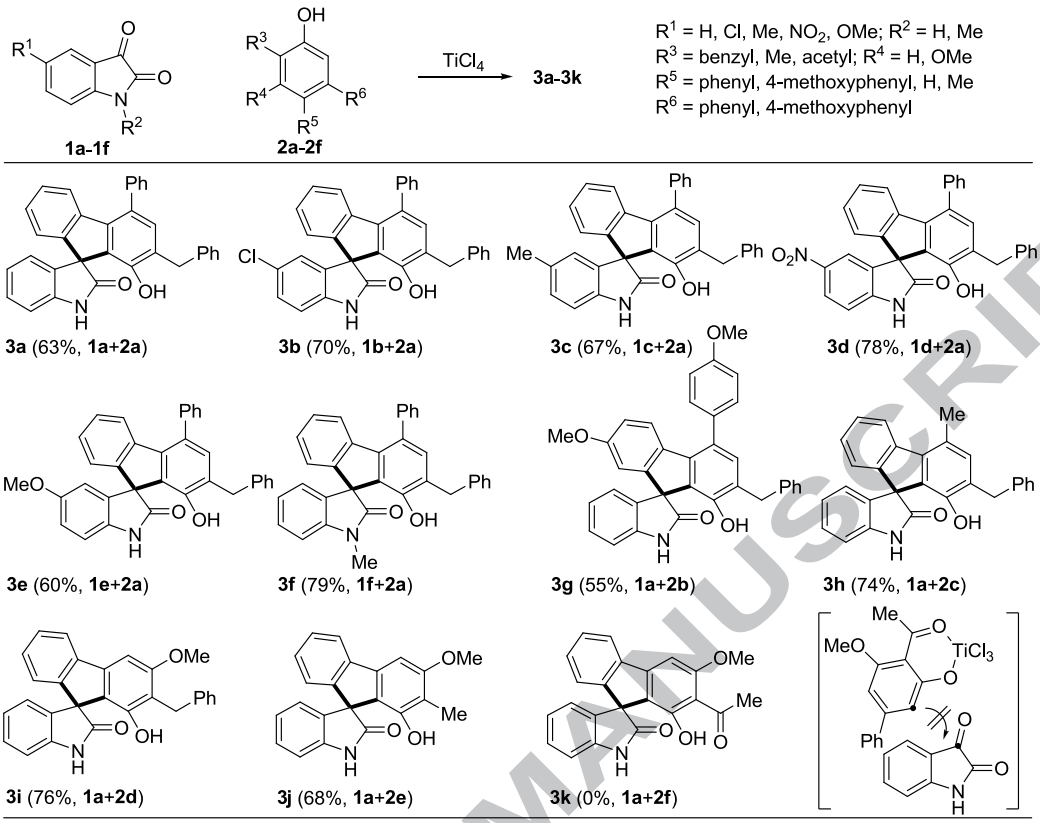
The oxindole framework bearing a spirocyclic quaternary stereocenter at the C3 position is a significant privileged heterocyclic scaffold, appears in a plethora of natural and synthetic compounds.[1-3] The synthesis of five-membered carbocycle-containing spirooxindoles has also been reported such as spirocyclopentadienyl-, spiroindenyl-, and spirofluorenyl oxindoles.[2]




**Scheme 1**. (1) known process, (2) synthetic rationale of spirofluorenyl oxindole, (3) synthesis of spirofluorenyl oxindole **3a**.

**Table 1**. Synthesis of spirofluorenyl oxindoles from *meta*-arylphenols.[a,b]



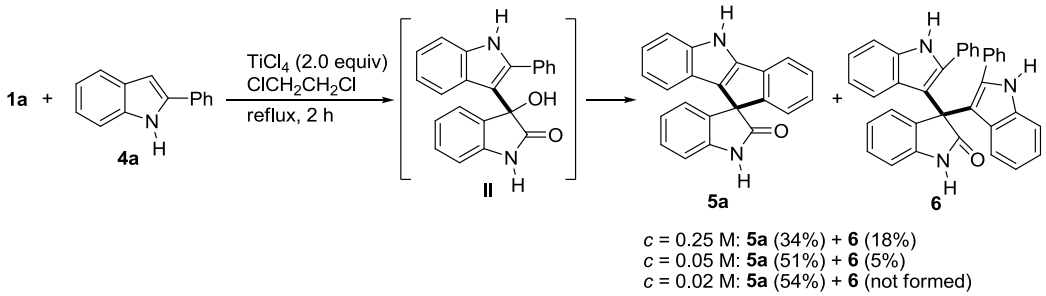

[a]Conditions: isatin (0.5 mmol), phenol (0.5 mmol), $ClCH_2CH_2Cl$ (2.0 mL), $TiCl_4$ (1.0 mmol), reflux, 2 h.
[b]**1a**: isatin; **1b**: 5-chloroisatin; **1c**: 5-methylisatin; **1d**: 5-nitroisatin; **1e**: 5-methoxyisatin; **1f**: *N*-methylisatin.
**2a**: 2-benzyl-4,5-diphenylphenol; **2b**: 2-benzyl-4,5-di(*p*-methoxyphenyl)phenol; **2c**: 2-benzyl-4-methyl-5-phenylphenol;
**2d**: 2-benzyl-3-methoxy-5-phenylphenol; **2e**: 2-methyl-3-methoxy-5-phenylphenol; **2f**: 2-acetyl-3-methoxy-5-phenylphenol.

The reaction of isatin (**1a**) and electron-rich arenes such as phenol and naphthol provides 3-aryl-3-hydroxy-2-oxindoles.[4,5] A selective C-C bond formation occurred at the *ortho*-position of phenol or naphthol due to stabilizing hydrogen bonding effect between the phenolic OH and the carbonyl group of oxindole (Eq. 1, Scheme 1).[4a-f] We reasoned out a phenol derivative bearing an aryl group at the *meta*-position could be used for the synthesis of spirofluorenyl oxindole via sequential inter- and a following intramolecular Friedel-Crafts reactions,[6] as shown in Eq. 2. Since the three positions (positions 2, 4 and 6) of *meta*-arylphenol can react with isatin, the two positions (positions 4 and 6) of *meta*-arylphenol should be blocked with a substituent in order to synthesize spirofluorenyl oxindole.[7] As shown in Eq. 3, *meta*-arylphenols such as 2-benzyl-4,5-diphenylphenol (**2a**) could be used for this purpose. The reaction of **1a** and **2a** in the presence of suitable acid catalyst would provide an intermediate **I**, and a subsequent intramolecular Friedel-Crafts reaction under the same reaction condition could form **3a**.

Phenol **2a** was synthesized via [4+2] annulation protocol from Morita-Baylis-Hillman (MBH) adducts according to the reported method.[8a] At the outset of our experiment, the reaction of **1a** and **2a** was examined in refluxing AcOH; however, no reaction was observed. When we carried out the reaction in AcOH in the presence of $H_2SO_4$ (2.0 equiv), a trace amount of **3a** was formed along with many intractable side products. The use of $AlCl_3$ (2.0 equiv) in AcOH showed a similar result with that of $H_2SO_4$/AcOH. To our delight, **3a** was formed in a reasonable yield (63%) by using $TiCl_4$ (2.0 equiv) in 1,2-dichloroethane (reflux, 2 h).[4d,e,5] The yield of **3a** decreased slightly by using lesser amount of $TiCl_4$ (1.2-1.5 equiv.), and the use of $Ti(O^iPr)_4$ showed completely no reaction.

Encouraged by the successful result, various *meta*-arylphenols **2b-f** were prepared according to the reported methods,[8] and the syntheses of spirooxindoles were examined. The results are summarized in Table 1. The reactions of isatins **1b-1f** and **2a** afforded the corresponding spirooxindoles **3b-3f** in good yields (60-79%).[9] The reactions of **1a** and *meta*-arylphenols **2b-2e** afforded **3g-3j** in moderate to good yields (55-76%). However, the reaction of **1a** and the phenol **2f**, bearing an *ortho*-acetyl moiety, failed completely. A preferential intramolecular chelation of titanium phenolate with acetyl group would be the reason for the failure, as shown in Table 1.

The mechanism for the formation of **3a** could be proposed, as shown in Scheme **1**. Thermalization of phenol **2a** and $TiCl_4$ afforded titanium phenolate $[TiCl_3(OAr)]$.[10] The coordination between the oxygen atom of isatin and $[TiCl_3(OAr)]$ makes close




**Scheme 2.** Synthesis of spirooxindole **5a** bearing indeno[1,2-*b*]indole moiety.

the two reaction centers, *ortho*-position of phenol and the 3-position of isatin. Thus, the first intermolecular Friedel-Crafts type bond-formation occurs readily to form **I**. A subsequent intramolecular Friedel-Crafts cyclization of **I** proceeds readily under the same reaction condition to afford **3a**, thus **I** cannot be isolated.

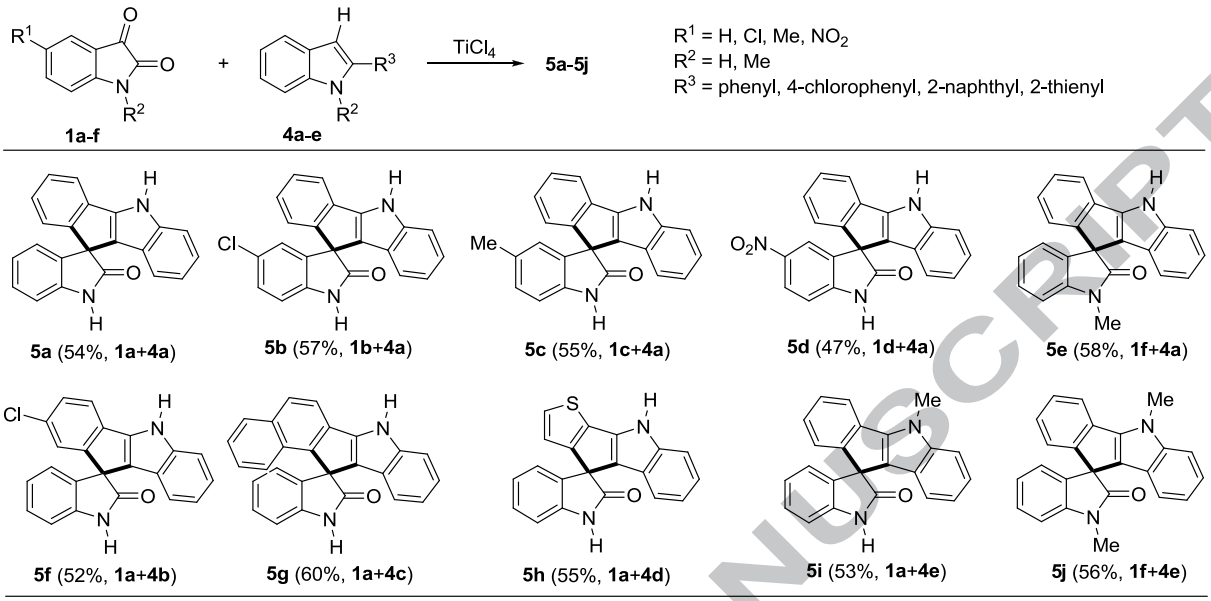
Spirooxindoles bearing an indole moiety has been received special attention due to their abundance in natural and synthetic drug candidates.[11] The reaction of indole and isatin has been studied extensively.[12-14] 3,3-Diindolyl-2-oxindole derivatives were obtained as major products in the presence of an acid catalyst.[12] The synthesis of 3-hydroxy-3-indolyl-2-oxindole has also been reported in a few reports;[13] however, mono-indolylization of isatin with 2-arylindoles has not been reported, to the best of our knowledge.[14] In these respects, we were not confident with the successful synthesis of spiroindeno[1,2-*b*]indolyl oxindole **5a**; however, we decided to examine the synthesis of **5a** due to importance of spirooxindoles bearing an indole moiety.[11]

As shown in Scheme 2, desired spiroindeno[1,2-*b*]indolyl oxindole **5a** was obtained in moderate yield (34%) by the reaction of **1a** and 2-phenylindole (**4a**), under the same reaction condition for the synthesis of **3**, to our delight. However, the formation of 3,3-diindolyl derivative **6**,[12c,14] albeit in low yield (18%), lowers the yield of **5a**. Spirooxindole **5a** must be formed by an intramolecular Friedel-Crafts reaction of intermediate **II**, while **6** could be produced by intermolecular Friedel-Crafts reaction between **II** and **4a**. Thus, we presumed that the formation of **6** could be reduced by carrying out the reaction in dilution conditions. As expected, the yield of **5a** increased to 51% in 0.05 M concentration and further improved to 54% in 0.02 M concentration.[15,16]

Encouraged by the successful synthesis of spiroindeno[1,2-*b*]indolyl oxindole, the reactions of some representative isatins **1a**-**1f** and 2-arylindoles **4a**-**4e** were examined. The results are summarized in Table 2. The reactions of **1b**-**1d** and **1f** with **4a** afforded the corresponding spirooxindoles **5b**-**5e** in moderate yields (47-58%). The reactions of **1a** with 2-(4-chlorophenyl)indole (**4b**), 2-(2-naphthyl)indole (**4c**), 2-(2-thienyl)indole (**4d**), and *N*-methyl-2-phenylindole (**4e**) afforded the corresponding spirooxindoles **5f**-**5i** in reasonable yields (52-60%). It is interesting to note that the intramolecular Friedel-Crafts cyclization occurred selectively at the 1-position of naphthalene ring during the synthesis of **5g**. The formation of a regioisomeric product was not observed. The selective Friedel-Crafts reaction is due to a small loss of resonance energy of the naphthalene ring during the Friedel-Crafts reaction.[17] The reaction of **1f** and **4e** also gave **5j** in a similar yield (56%).

In summary, the reactions of various *meta*-arylphenols and 2-arylindoles with isatins provided spirofluorenyl- and spiroindeno[1,2-*b*]indolyl oxindoles in the presence of $TiCl_4$ in moderate to good yields in one-pot reaction. The reaction proceeds via a consecutive inter- and intramolecular Friedel-Crafts reactions.

**Table 2.** Synthesis of spirooxindoles from 2-arylindoles.[a,b]




[a]Conditions: isatins (0.6 mmol), indoles (0.5 mmol), $TiCl_4$ (1.0 mmol), $ClCH_2CH_2Cl$ (25 mL), reflux, 2 h.
[b]**4a**: 2-phenylindole; **4b**: 2-(4-chlorophenyl)indole; **4c**: 2-(2-naphthyl)indole; **4d**: 2-(2-thienyl)indole; **4e**: *N*-methyl-2-phenylindole.

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7. Actually, the reaction of 3-phenylphenol and isatin (**1a**) under optimized reaction conditions did not afford any trace amount of spirooxindole. One of the three possible 3,3-diarylation products was obtained selectively in moderate yield (52%, see Supplementary data).
8. For synthesis of starting materials, see: (a) Kim, S. J.; Kim, S. H.; Kim, K. H.; Kim, J. N. *Bull. Korean Chem. Soc*. **2008**, *29*, 876; (b) Ramachary, D. B.; Kishor, M. *J. Org. Chem*. **2007**, *72*, 5056; (c) Kim, J. M.; Lee, K. Y.; Kim, J. N. *Bull. Korean Chem. Soc*. **2003**, *24*, 1057.
9. **Typical procedure for the synthesis of 3a**: To a stirred solution of **1a** (74 mg, 0.5 mmol) and **2a** (168 mg, 0.5 mmol) in 1,2-dichloroethane (1.5 mL) was added dropwise a solution of $TiCl_4$ (190 mg, 1.0 mmol in 0.5 mL 1,2-dichloroethane) at room temperature over 2 min, and the reaction mixture was heated to reflux for 2 h. After the usual extractive aqueous workup and column chromatographic purification process (hexanes/EtOAc, 2:1) compound **3a** was obtained as a white solid, 147 mg (63%). Other compounds were synthesized similarly, and the selected spectroscopic data of **3a**, **3h**, **3i**, **5a**, **5h**, and **5i** are as follows.

*Compound **3a***: 63%; white solid, mp 144-146 °C; IR (KBr) 3270, 1697, 1618, 1470 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 3.90 (d, *J* = 15.3 Hz, 1H), 4.01 (d, *J* = 15.3 Hz, 1H), 6.56 (d, *J* = 7.2 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.85-6.92 (m, 3H), 7.02 (d, *J* = 7.8 Hz, 1H), 7.05-7.29 (m, 8H), 7.39-7.55 (m, 5H), 8.96 (s, 1H), 10.84 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 34.60, 61.90, 109.54, 121.70, 121.97, 122.74, 123.05, 125.96, 127.27, 127.43, 127.46, 128.00, 128.35, 128.56, 128.91, 128.97, 129.19, 131.41, 132.62, 132.65, 138.11, 140.19, 140.21, 141.38, 143.76, 146.79, 150.44, 176.76 (one carbon was overlapped); ESIMS *m/z* 466 $[M+H]^+$. Anal. Calcd for $C_{33}H_{23}NO_2$: C, 85.14; H, 4.98; N, 3.01. Found: C, 85.02; H, 5.09; N, 2.93.

*Compound **3h***: 74%; pale yellow solid, mp 172-174 °C; IR (KBr) 3261, 1697, 1275, 1260 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 2.55 (s, 3H), 3.84 (d, *J* = 15.3 Hz, 1H), 3.95 (d, *J* = 15.3 Hz, 1H), 6.45 (d, *J* = 7.2 Hz, 1H), 6.78 (t, *J* = 7.2 Hz, 1H), 6.82-6.95 (m, 2H), 6.99 (d, *J* = 7.2 Hz, 1H), 7.20-7.32 (m, 7H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.85 (d, *J* = 7.2 Hz, 1H), 8.58 (s, 1H), 10.77 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 19.59, 34.58, 62.03, 109.47, 121.65, 122.60, 122.73, 122.95, 123.62, 125.85, 126.83, 127.21, 127.87, 128.04, 128.26, 128.75, 131.67, 132.59, 133.13, 139.34, 140.60, 142.42, 143.73, 146.61, 149.07, 176.88; ESIMS *m/z* 404 $[M+H]^+$. Anal. Calcd for $C_{28}H_{21}NO_2$: C, 83.35; H, 5.25; N, 3.47. Found: C, 83.46; H, 5.11; N, 3.45.

*Compound **3i***: 76%; pale yellow solid, mp 120-122 °C; IR (KBr) 3321, 1695, 1492 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 3.87 (s, 3H), 3.93 (s, 2H), 6.46 (d, *J* = 7.5 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 7.05-7.13 (m, 3H), 7.13-7.22 (m, 5H), 7.38 (t, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 8.75 (s, 1H), 10.74 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 28.21, 56.02, 61.91, 95.49, 109.48, 115.27, 120.34, 121.63, 122.59, 122.83, 124.81, 125.45, 127.42, 127.88, 127.93, 128.17, 131.46, 140.79, 141.73, 142.05, 143.67, 146.69, 151.77, 159.28, 176.94 (one carbon was overlapped); ESIMS *m/z* 420 $[M+H]^+$. Anal. Calcd for $C_{28}H_{21}NO_3$: C, 80.17; H, 5.05; N, 3.34. Found: C, 80.34; H, 5.33; N, 3.19.

*Compound **5a***: 54%; white solid, mp 295-297 °C; IR (KBr) 3275, 3171, 1674, 1277 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 6.53 (d, *J* = 7.2 Hz, 1H), 6.77-6.84 (m, 2H), 6.89 (d, *J* = 7.2 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 7.02-7.17 (m, 3H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 1H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 7.2 Hz, 1H), 10.92 (s, 1H), 11.86 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 58.18, 109.95, 112.82, 117.25, 118.42, 119.86, 121.44, 121.58, 122.02, 122.36, 123.27, 123.43, 125.95, 128.16, 128.56, 130.17, 135.59, 140.70, 143.41, 144.67, 150.41, 177.02; ESIMS *m/z* 323 $[M+H]^+$. Anal. Calcd for $C_{22}H_{14}N_2O$: C, 81.97; H, 4.38; N, 8.69. Found: C, 81.68; H, 4.64; N, 8.52.

*Compound **5h***: 55%; white solid, mp 245-247 °C; IR (KBr) 3280, 3179, 1688, 1517 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 500 MHz) δ 6.39 (d, *J* = 7.5 Hz, 1H), 6.82 (t, *J* = 7.5 Hz, 1H), 6.86 (d, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 5.5 Hz, 1H), 6.98 (d, *J* = 7.5 Hz, 1H), 7.01-7.08 (m, 3H), 7.22 (d, *J* = 5.5 Hz, 1H), 7.58 (d, *J* = 7.5 Hz, 1H), 10.69 (s, 1H), 11.48 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$, 125 MHz) δ 58.43, 110.44, 117.81, 119.25, 120.44, 121.34, 121.91, 122.28, 122.49, 123.72, 124.06, 126.55, 129.05, 130.52, 135.70, 142.06, 143.85, 145.68, 150.89, 177.30; ESIMS *m/z* 329 $[M+H]^+$. Anal. Calcd for $C_{20}H_{12}N_2OS$: C, 73.15; H, 3.68; N, 8.53. Found: C, 73.41; H, 3.80; N, 8.59.

*Compound **5i***: 53%; white solid, mp 280-282 °C; IR (KBr) 3255, 3193, 1691, 1488 $cm^{-1}$; $^1H$ NMR (DMSO-$d_6$, 300 MHz) δ 4.13 (s, 3H), 6.55 (d, *J* = 7.5 Hz, 1H), 6.79-6.87 (m, 2H), 6.94 (t, *J* = 7.5 Hz, 1H), 6.96 (d, *J* = 7.5 Hz, 1H), 7.07-7.21 (m, 3H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.5 Hz, 1H), 10.94 (s, 1H); $^{13}C$ NMR (DMSO-$d_6$, 75 MHz) δ 31.19, 57.97, 110.00, 110.94, 117.37, 118.83, 120.00, 120.88, 121.47, 121.83, 122.05, 123.29, 123.63, 126.11, 128.17, 128.62, 130.07, 135.26, 141.61, 143.41, 145.24, 150.44, 176.87; ESIMS *m/z* 337 $[M+H]^+$. Anal. Calcd for $C_{23}H_{16}N_2O$: C, 82.12; H, 4.79; N, 8.33. Found: C, 82.03; H, 4.96; N, 8.16.
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15. When we reduced the amount of $TiCl_4$, the formation of **6** increased. When we carried out the reaction with 2.0 equiv. of **1a** in order to reduce the amount of **6**, the yield of **5a** increased to 41% ($c$ = 0.25 M). The use of other acid catalysts such as $AlCl_3$, $InCl_3$, $FeCl_3$, or $SnCl_4$ was less effective than $TiCl_4$. The use of $H_2SO_4$ produced **6** as a major product.

16. In order to reduce the formation of 3,3-diindolyl derivative, isatin was used in a slightly excess amount (1.2 equiv).

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**One-pot synthesis of spirofluorenyl- and spiroindeno[1,2-*b*]indolyl oxindoles via sequential inter- and intramolecular Friedel-Crafts reactions**

Jin Woo Lim, Hye Ran Moon, Su Yeon Kim, Jae Nyoung Kim*

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