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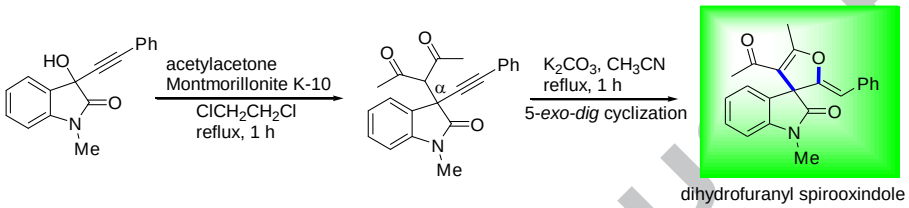

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An efficient synthesis of dihydrofuranyl spirooxindoles from isatin-derived propargylic alcohols and 1,3-dicarbonyls

Hwa Jung Roh, Su Yeon Kim, Beom Kyu Min, Jae Nyoung Kim*

Department of Chemistry and Institute of Basic Science, Chonnam National University, Gwangju 500-757, Republic of Korea

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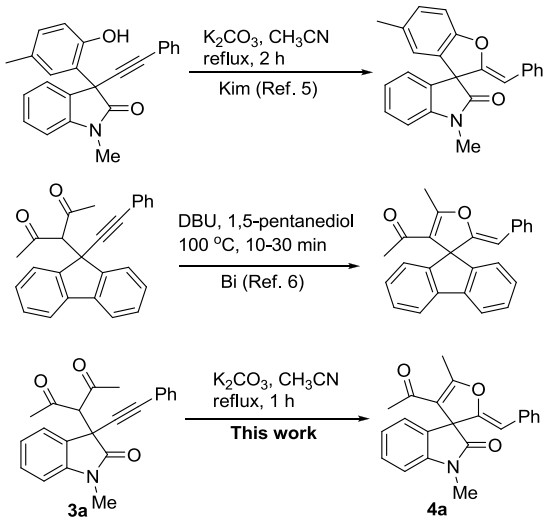
ABSTRACT

Various dihydrofuranyl spirooxindoles have been synthesized via montmorillonite K-10-catalyzed propargylation of 1,3-dicarbonyl compounds with isatin-derived propargylic alcohols and subsequent base-mediated 5-*exo*-*dig* cyclization.

Various types of spirooxindoles exist in a large number of natural products and biologically interesting compounds.[1] Thus, developments of efficient synthetic protocols to access these important motifs have received much attention over the past years.[1-4] Especially, spirooxindoles bearing five-membered oxacycles have been found in many biologically important synthetic and natural compounds.[3,4] The five-membered oxacyclic moieties found in reported spirooxindoles include 2,3-dihydrofurans,[3a-e,r] 2,5-dihydrofurans,[3f-q] γ-butyrolactones,[4a-c] α-methylene-γ-butyrolactones,[4d-h] tetrahydrofurans,[4i-k] butenolides,[4l,m] and 1,3-dioxolanes.[3o,p]

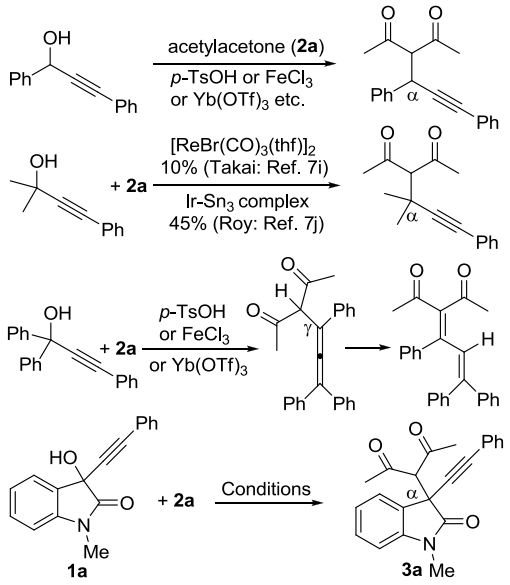
During our recent synthesis of 3-naphtho[2,1-*b*]furanyl-2-oxindoles, we found that 2,3-dihydrofuranyl spirooxindole could be synthesized readily from 3-(*ortho*-hydroxyaryl)-2-oxindole by base-catalyzed cyclization reaction,[5] as shown in Scheme 1. Bi and co-workers also reported the synthesis of spirodihydrofurans by base-catalyzed cyclization reaction of the propargylated acetylacetone derivative.[6] In these contexts, we envisioned that dihydrofuranyl spirooxindole **4a** could be synthesized by base-mediated 5-*exo*-*dig* cyclization reaction of propargylated acetylacetone derivative **3a**, as also shown in Scheme 1.

The propargylation of acetylacetone (**2a**), as a typical 1,3-dicarbonyl compound, with propargylic alcohols has been extensively studied, as shown in Scheme 2.[7] Secondary propargylic alcohols afforded the corresponding α-adducts in good yields in most papers.[7a-i] However, the reaction with tertiary propargylic alcohols afforded different products depending on the substrates. Takai and co-workers reported the synthesis of α-adduct in low yield (10%) from 2-methyl-4-phenylbut-3-yn-2-ol by rhenium-catalyzed reaction.[7i] Roy and co-workers obtained the same α-adduct in moderate yield (45%) by using Ir-Sn catalyst.[7j] In contrast to the dimethyl derivative,[7i,j] the reaction with 1,1,3-triphenylprop-2-yn-1-ol gave allene or its isomerized diene derivative.[7a-e] Thus, at the outset of this study, we examined the synthesis of starting material **3a** from isatin-derived propargylic alcohol **1a**.



Scheme 1. Synthetic rationale of dihydrofuranyl spirooxindole **4a**.

*Corresponding author. Tel.: +82 62 530 3381; fax: +82 62 530 3389; *E-mail address*: kimjn@chonnam.ac.kr (J. N. Kim)



Scheme 2. Propargylation of **2a** with various propargylic alcohols.

The reaction of isatin-derived propargylic alcohol **1a** and acetylacetone (**2a**) was examined in the presence of some representative acid catalysts, as shown in Table 1. The reaction in the presence of *p*-TsOH (CH_3CN, reflux, entry 1) afforded **3a** in a low yield (14%) for 10 h. The reactions using $FeCl_3$ (toluene, 80 °C, entry 2) or $Yb(OTf)_3$ (CH_3NO_2, 80 °C, entry 3) provided **3a** in low yields. Trifluoroacetic acid was not an efficient catalyst for the reaction (entry 4). To our delight, the use of montmorillonite K-10 (MK10, 300%, *w/w*) in 1,2-dichloroethane (DCE, reflux, entry 5) afforded **3a** in moderate yield (47%) in short time (2 h).[8] The yield could be increased by using **2a** in an excess amount (3.0 equiv.) up to 64% (entry 6) in short time (1 h). When we used Boc carbonate of **1a**, the yield of **3a** increased slightly (entry 7). The same yield of **3a** was obtained by using 5.0 equiv. of **2a** (entry 8). From the results, we decided to use MK10 in DCE with 3.0 equiv. of **2a** (entry 6).[9]

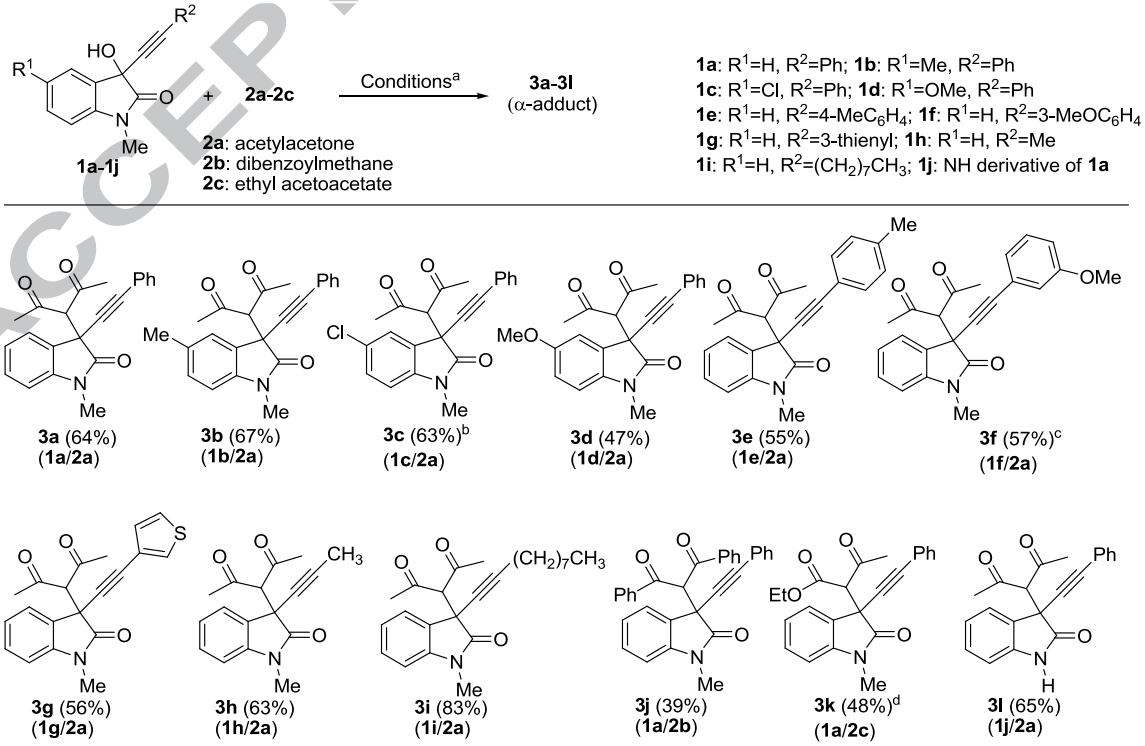
Table 1. Optimization study for the synthesis of α-adduct **3a**.

Entry	Conditions	**3a** (%)
1	**2a** (1.0 equiv.), *p*-TsOH (5 mol%), CH_3CN, reflux, 10 h	14[a]
2	**2a** (1.0 equiv.), $FeCl_3$ (5 mol%), toluene, 80 °C, 10 h	18[a]
3	**2a** (1.0 equiv.), $Yb(OTf)_3$ (5 mol%), CH_3NO_2, 80 °C, 2 h	29
4	**2a** (1.0 equiv.), CF_3COOH (20 mol%), DCE, reflux, 10 h	<5[a]
5	**2a** (1.0 equiv.), MK10 (300%, *w/w*), DCE, reflux, 2 h	47
6	**2a** (3.0 equiv.), MK10 (300%, *w/w*), DCE, reflux, 1 h	64
7	**2a** (3.0 equiv.), MK10 (300%, *w/w*), DCE, reflux, 1 h	65[b]
8	**2a** (5.0 equiv.), MK10 (300%, *w/w*), DCE, reflux, 1 h	64

[a]Appreciable amount of **1a** remained.
[b]**1a**-Boc derivative was used.

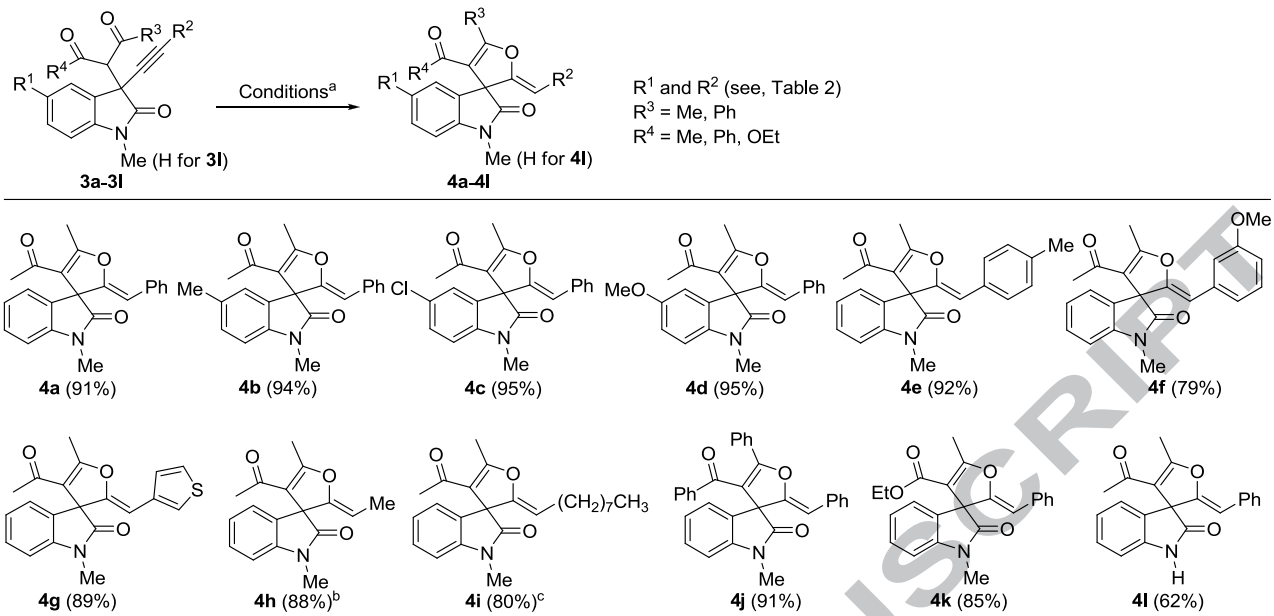
Thus, some representative α-adducts **3b**-**3l** were prepared in moderate to good yields by the reactions of isatin-derived propargylic alcohols **1a**-**1j** and 1,3-dicarbonyl compounds **2a**-**2c** under the optimized condition, as shown in Table 2.[10] Acetylacetone (**2a**), dibenzoylmethane (**2b**), and ethyl acetoacetate (**2c**) were used as representative 1,3-dicarbonyl compounds. The reactions of **1b** and **1c** with **2a** afforded **3b** (67%) and **3c** (63%) in moderate yields. However, the yield of 5-methoxyisatin derivative **3d** (47%) was somewhat lower than other entries. Three arylacetylene and two aliphatic alkyne derivatives **3e**-**3i** were synthesized in moderate to good yields (55-83%). The reactions of **1a** with **2b** and **2c** afforded **3j** (39%) and **3k** (48%) in low yields presumably due to steric reason. The reaction of *N*-unprotected derivative **1j** produced **3l** in a similar yield (65%) to that of *N*-methyl derivative **3a**.

Table 2. Synthesis of α-adduct **3**.



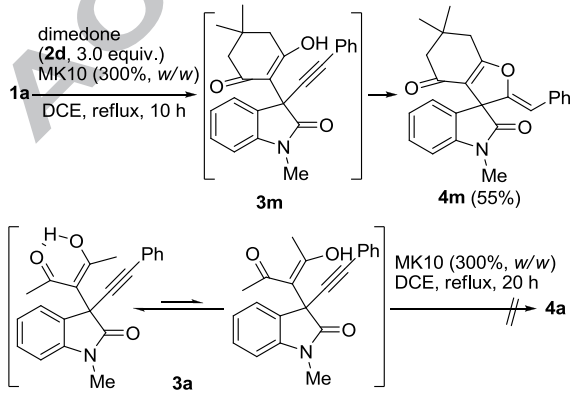
[a]Conditions: Propargyl alcohol **1** (1.0 mmol), 1,3-dicarbonyls **2** (3.0 mmol), montmorillonite K-10 (300%, *w/w*), DCE, reflux, 1 h.
[b]Reaction time was 8 h. [c]Reaction time was 2 h. [d]Inseparable 1:0.9 diastereomeric mixture.

Table 3. Synthesis of spirooxindoles **4**.



[a]Conditions: substrate **3** (0.5 mmol), K_2CO_3 (0.5 mmol), CH_3CN, reflux, 1 h.
[b]Reaction time was 3 h. [c]Reaction time was 8 h.

A following base-mediated cyclization of **3a** to **4a** was examined under the optimized reaction condition in our previous cyclization reaction of 3-(*ortho*-hydroxyaryl)-2-oxindoles.[5] To our delight, the reaction of **3a** in CH_3CN in the presence of K_2CO_3 (1.0 equiv.) afforded spirooxindole **4a** in good yield (91%) in short time (1 h), as shown in Table 3.[10,11] The spirooxindole **4a** was obtained as a single isomer, and the stereochemistry of the benzylidene moiety would be Z-form presumably due to steric hindrance between the oxindole moiety and the phenyl group of benzylidene moiety, as previously reported by Bi[6] and us[5] in a similar system. Three 5-substituted isatin derivatives **3b**-**3d** afforded the corresponding spirooxindoles **4b**-**4d** in high yields (94-95%). Spirooxindoles **4e**-**4i** were synthesized in good yields (79-92%) from the corresponding α-adducts **3e**-**3i** bearing various arylacetylene and aliphatic alkyne moieties. The cyclization of **3h** and **3i** required somewhat longer reaction time (3-8 h) than other entries. In addition, sterically congested compounds **4j** (91%) and **4k** (85%) were produced in good yields. The reaction of *N*-unprotected derivative **3l** afforded **4l** in somewhat lower yield (62%) than other entries.



Scheme 3. Synthesis of spirooxindole **4m**.

It is interesting to note that the formation of α-adduct **3m** was not observed in the reaction of **1a** and dimedone (**2d**). The spirooxindole **4m** was obtained directly in moderate yield (55%), as shown in Scheme 3. The α-adduct **3a** might be present in its intramolecular hydrogen-bonded six-membered structure and the cyclization of **3a** to **4a** would be difficult, as shown in Scheme 3. Actually, **3a** was not converted to **4a** under the influence of MK10 (DCE, reflux) even after 20 h. As compared to **3a**, an intramolecular hydrogen-bond was not possible for the α-adduct **3m**. Thus, the cyclization of an α-adduct intermediate **3m** to the spirooxindole **4m** could proceed under the same acidic reaction condition.[12,13]

In summary, various dihydrofuranyl spirooxindoles have been synthesized via montmorillonite K-10-catalyzed propargylation of 1,3-dicarbonyl compounds with isatin-derived propargylic alcohols and subsequent base-mediated 5-*exo*-*dig* cyclization.

Acknowledgments

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9. The reaction of **1a** and **2a** under typical Mitsunobu reaction conditions (PPh_3, diethyl azodicarboxylate) in toluene at room temperature did not produce **3a** at all.
10. **Typical procedure for the synthesis of 3a and 4a**: A stirred mixture of **1a** (263 mg, 1.0 mmol), acetylacetone (**2a**, 300 mg, 3.0 mmol), montmorillonite K-10 (790 mg, 300%, *w/w*) in $ClCH_2CH_2Cl$ (3.0 mL) was heated to reflux for 1 h. The reaction mixture was filtered through a pad of Celite and washed thoroughly with $ClCH_2CH_2Cl$. After removal of solvent and column chromatographic purification process (CH_2Cl_2/EtOAc, 40:1) compound **3a** was obtained as a pale yellow solid, 221 mg (64%). A stirred mixture of **3a** (173 mg, 0.5 mmol) and K_2CO_3 (69 mg, 0.5 mmol) in CH_3CN (2.0 mL) was heated to reflux for 1 h. After the usual aqueous extractive workup and column chromatographic purification process (hexanes/EtOAc, 1:1) compound **4a** was obtained as a white solid, 157 mg (91%). Other compounds were synthesized similarly, and the selected spectroscopic data of **3a** and **4a** are as follows.

    Compound **3a**: 64%; pale yellow solid, mp 125-127 ^oC; IR (KBr) 1722, 1611, 1493, 1471, 1354 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.19 (s, 3H), 2.57 (s, 3H), 3.31 (s, 3H), 4.68 (s, 1H), 6.89 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 7.25-7.35 (m, 4H), 7.36-7.43 (m, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 27.1, 30.2, 33.3, 46.4, 70.4, 84.9, 85.1, 108.7, 121.9, 123.1, 124.5, 128.1, 128.3, 128.8, 129.1, 131.8, 143.6, 173.5, 200.5, 203.2; ESIMS *m/z* 346 $[M+H]^+$. Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.78; H, 5.81; N, 3.92.

    Compound **4a**: 91%; white solid, mp 230-232 ^oC; IR (KBr) 1720, 1690, 1631, 1610, 1493, 1385, 1370, 1345, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.03 (s, 3H), 2.59 (s, 3H), 3.30 (s, 3H), 5.08 (s, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.25 (t, *J* = 7.5 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 1H), 7.43 (d, *J* = 7.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 15.5, 27.1, 29.0, 62.8, 104.4, 108.6, 118.7, 123.5, 123.7, 127.0, 128.4, 128.6, 129.3, 131.9, 133.8, 144.1, 154.2, 167.8, 175.4, 191.4; ESIMS *m/z* 346 $[M+H]^+$. Anal. Calcd for $C_{22}H_{19}NO_3$: C, 76.50; H, 5.54; N, 4.06. Found: C, 76.58; H, 5.73; N, 4.17.
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13. The reaction of **1a** with other cyclic 1,3-dicarbonyl compounds such as 1,3-cyclohexanedione or *N*,*N*-dimethylbarbituric acid was very sluggish, and isolation of the corresponding α-adducts or spirooxindoles failed. The reason is not clear at this stage, and further studies are currently underway.

Supplementary Data

Supplementary data (experimental procedures and characterization data for compounds **1g-1i**, **3a-3l**, and **4a-4m**) associated with this article can be found, in the online version, at xxxxxxxxxxx.

Highlights

*Efficient synthesis of dihydrofuranyl spirooxindoles
*Montmorillonite-catalyzed propargylation of 1,3-dicarbonyls
*Synthetic usefulness of isatin-derived propargylic alcohols