# Facile synthesis of 3,3-diallyl isoindolones via a indium-mediated double allylation of *ortho*-cyanobenzoates

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A B S T R A C T

Various 3,3-diallyl isoindolones were synthesized via a indium-mediated Barbier type double allylation reaction of *ortho*-cyanobenzoates in good yields in short time. The reactivity of nitrile group toward allylindium is sufficient to form a cyclic compound when a suitable electrophilic center is present in the same molecule to trap the imine intermediate.

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Allylindium reagents have been used extensively for the introduction of allyl group in a Barbier type manner to various electrophiles.[1–3] Although many electrophiles including aldehydes, ketones, imines, and *N*-tosylimines have been used in the indium-mediated allylations,[1] the reaction of a less reactive electrophile such as nitrile has not been used in organic synthesis. The first successful results of indium-mediated allylation of nitriles have been reported by Yamamoto and co-workers a decade ago (vide infra, Scheme 1),[2a,b] although allylation of nitrile with allylindate instead of allylindium was reported by Butsugan and co-workers in 1993.[2c] However, the allylation of nitrile with allylindium was limited to substrates having an electron-withdrawing substituent and an α-proton.[2a,b]

Very recently, we reported indium-mediated Barbier type allylations of the nitrile group in γ-cyanoesters (vide infra, Scheme 1),[3a] γ-ketonitriles,[3b] and δ-ketonitriles.[3c] The intrinsic reactivity of the nitrile group toward allylindium species was sufficient to form the corresponding imine or enamine intermediates, and the corresponding δ-valerolactams,[3a] pyrroles,[3b] and isoquinolines[3c] were obtained in good to moderate yields via the subsequent cyclization of the intermediates with an electrophilic moiety in the same molecule. During the studies we have found that the nitrile group can react with allylindium even in the absence of both an EWG and an α-proton when the intermediate can react with nearby electrophile in the same molecule such as an ester[3a] or a sterically hindered ketone.[3b,c] In addition, we also found that even

aromatic nitrile can react with allylindium.[3c] In these contexts, we envisioned that *ortho*-cyanobenzoates could afford 3,3-diallyl isoindolone scaffold via indium-mediated double allylation strategy, as shown in Scheme 1. The first results of Yamamoto in this area[2a,b] and ours of γ-cyanoesters[3a] are also depicted in Scheme 1 for comparison.
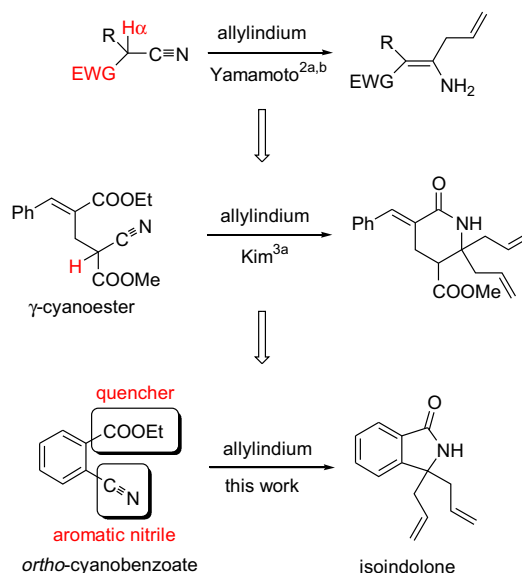


**Scheme 1.** Development of In-mediated allylation of nitrile.

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Various isoindolone derivatives have been known to possess interesting biological activities[4–6] including MDM2-p53 interaction inhibitory activity,[4a] mixed lineage kinase activity,[4b] CNS-related disorders treating activity,[4c] and HIV-1 integrase inhibitory activity.[4e] Especially, various spiro-isoindolones have received much attention due to their interesting biological activities.[4c,f,6d,e,g,h] Thus various synthetic approaches of isoindolone scaffold have been developed.[5,6] In some examples, a copper-catalyzed addition of nucleophile to carbonyl-ene-nitrile system,[5a] a palladium-catalyzed intramolecular C-arylation,[5b] and an addition of transiently-generated methyl o-lithiobenzoate to imine[5c] have been reported. Xu and co-workers reported the synthesis of 3-monoallyl isoindolone derivatives via the In-mediated allylation of N-tert-butanesulfinyl imines.[7] The synthesis of Xu and co-workers is the only paper describing the preparation of isoindolone scaffold by using indium chemistry, to the best of our knowledge.

As the initial entry, we examined the reaction of ethyl 2-cyanobenzoate (1a) and allyl bromide in the presence of indium powder in THF and obtained 3,3-diallyl isoindolone (2a) in 71% yield (entry 1 in Table 1).[8] The reaction was very fast (30 min) and clean. Encouraged by the results, we prepared various ortho-cyanobenzoates 1b–g[9] and examined the syntheses of isoindolones 2b–h, as summarized in Table 1. The mechanism for the reaction can be proposed as follows: first allylation of 1 to produce the imine intermediate (I), cyclization of (I) to form cyclic N-acylimine (II), and second allylation of (II) to form 2, as shown in Table 1. As in entry 8, the reaction of 1a and methallyl bromide produced compound 2h in a similar yield (66%); however, the reaction with γ-substituted allylic bromides such as cinnamyl bromide or crotyl bromide did not produce appreciable amounts of the corresponding isoindolone derivatives, presumably due to steric problems.[10]
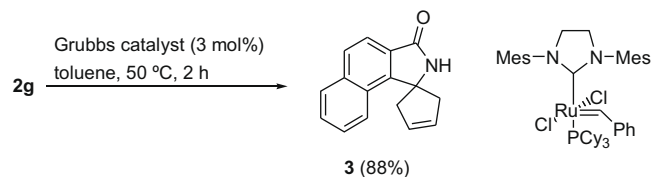


**Scheme 2.**

During the studies we observed an interesting solvent effect. The product 2a was formed in THF at refluxing temperature in 71% as described above; however, the reaction in DMF (70–80 °C) was failed completely and 1a was recovered. Similarly, the reaction failed in 1,4-dioxane, aqueous THF, PEG-3400, and DMSO, while 2a was obtained in moderate yields both in dichloroethane (51%) and ortho-dichlorobenzene (57%). From the results we could imagine that the reaction is effective in a solvent which does not disrupt the six-membered chelation transition state[1,2,10] and a decisive explanation deserved further studies.

As one of the synthetic applications of 3,3-diallylated isoindolones, we examined the ring-closing metathesis (RCM) reaction of 2g with 2nd generation Grubbs catalyst (3 mol %) in toluene (50 °C, 2 h) and obtained the corresponding spiro compound 3 in 88% yield, as shown in Scheme 2.

In summary, we synthesized various isoindolones via a indium-mediated double Barbier type allylation of ortho-cyanobenzoate derivatives in refluxing THF in moderate to good yields. We extended the scope of In-mediated allylation reaction toward nitrile-containing substrates which was hitherto regarded as unreactive.

**Table 1**
Synthesis of poly-substituted isoindolones[a]
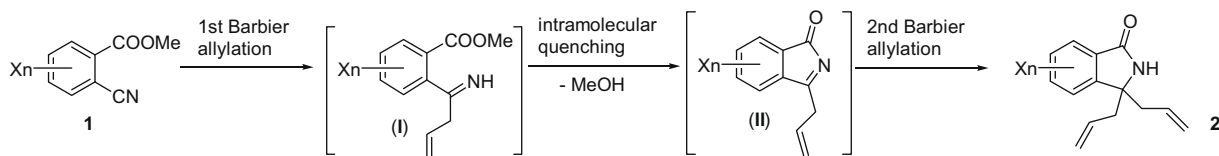


| Entry | Substrate | Product (%) | Entry | Substrate | Product (%) |
|---|---|---|---|---|---|
| 1 | 1a | 2a (71) | 5 | 1e | 2e (67) |
| 2 | 1b | 2b (73) | 6 | 1f | 2f (73) |
| 3 | 1c | 2c (70) | 7 | 1g | 2g (65) |
| 4 | 1d | 2d (69) | 8[b] | 1a | 2h (66) |

[a] Conditions: substrate (1.0 mmol), allyl bromide (4.0 mmol), In powder (2.0 mmol), THF, reflux, 30 min (60 min for entry 8).
[b] Methallyl bromide was used.

## Acknowledgements

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8. *Typical procedure for the synthesis of compound* ***2a***: A stirred mixture of compound **1a** (175 mg, 1.0 mmol), allyl bromide (484 mg, 4.0 mmol), and indium powder (228 mg, 2.0 mmol) in THF (1.5 mL) was heated to reflux for 30 min. After the usual aqueous workup and column chromatographic purification process (hexanes/CH$_2$Cl$_2$/EtOAc, 5:1:1) we obtained compound **2a** (151 mg, 71%) as a white solid. Other compounds were synthesized similarly and the spectroscopic data of **2a**, **2c**, **2f**, **2g**, and RCM product **3** are as follows.
*Compound **2a***: 71%; white solid, mp 99–100 °C; IR (film) 3211, 1695, 1615, 1469 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.53–2.70 (m, 4H), 5.00–5.07 (m, 4H), 5.48–5.62 (m, 2H), 7.38 (dt, *J* = 7.5 and 0.9 Hz, 1H), 7.44 (td, *J* = 7.5 and 1.2 Hz, 1H), 7.56 (td, *J* = 7.5 and 1.2 Hz, 1H), 7.57 (br s, 1H), 7.82 (dq, *J* = 7.5 and 0.6 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 42.81, 64.07, 119.65, 121.63, 123.70, 128.07, 131.71, 131.74, 132.10, 149.66, 170.42; ESIMS *m/z* 236 (M$^+$+Na). Anal. Calcd for C$_{14}$H$_{15}$NO: C, 78.84; H, 7.09; N, 6.57. Found: C, 78.92; H, 7.31; N, 6.44.
*Compound **2c***: 70%; white solid, mp 103–104 °C; IR (film) 3217, 1694, 1621, 1493, 1435 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.51–2.67 (m, 4H), 3.86 (s, 3H), 5.00–5.07 (m, 4H), 5.49–5.63 (m, 2H), 7.11 (dd, *J* = 8.4 and 2.4 Hz, 1H), 7.27 (dd, *J* = 8.4 and 0.6 Hz, 1H), 7.30 (d, *J* = 2.4 Hz, 1H), 7.69 (br s, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 42.87, 55.55, 63.73, 106.28, 119.48, 120.00, 122.53, 131.85, 133.45, 141.89, 159.88, 170,36; ESIMS *m/z* 266 (M$^+$+Na). Anal. Calcd for C$_{15}$H$_{17}$NO$_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 74.40; H, 7.11; N, 5.49.
*Compound **2f***: 73%; white solid, mp 102–103 °C; IR (film) 3222, 1702, 1607, 1587, 1413 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.74 (d, *J* = 7.2 Hz, 4H), 4.96–5.06 (m, 4H), 5.46–5.60 (m, 2H), 7.38 (dd, *J* = 7.8 and 4.8 Hz, 1H), 7.77 (br s, 1H), 8.10 (dd, *J* = 7.8 and 1.5 Hz, 1H), 8.77 (dd, *J* = 8.1 and 1.5 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 41.46, 65.36, 119.79, 123.03, 125.99, 131.29, 131.79, 152.64, 168.50, 168.56; ESIMS *m/z* 237 (M$^+$+Na).
*Compound **2g***: 65%; white solid, mp 145–146 °C; IR (film) 3213, 1693, 1620, 1462, 1435, 1383 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.88–3.04 (m, 4H), 4.85–5.01 (m, 4H), 5.33–5.47 (m, 2H), 7.55 (br s, 1H), 7.59–7.68 (m, 2H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.99–8.02 (m, 1H), 8.08–8.11 (m, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 42.86, 65.73, 119.40, 119.79, 123.68, 126.98, 127.21, 127.46, 129.71, 129.85, 130.77, 131.35, 135.76, 146.43, 170.48; ESIMS *m/z* 286 (M$^+$+Na).
*Compound **3***: 88%; white solid, mp 160–161 °C; IR (film) 3211, 1693, 1620, 1462, 1383 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.86 (d, *J* = 16.2 Hz, 2H), 3.28 (d, *J* = 16.2 Hz, 2H), 6.00–6.06 (m, 2H), 7.54–7.64 (m, 2H), 7.74–7.77 (m, 1H), 7.87 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 8.4 Hz, 1H), 7.98–8.01 (m, 1H), 8.07 (br s, 1H); $^{13}$C NMR (CDCl$_3$, 125 MHz) δ 45.74, 66.96, 119.66, 123.33, 126.92, 127.00, 127.28, 128.94, 129.00, 129.26, 129.65, 135.80, 148.99, 170.10; ESIMS *m/z* 258 (M$^+$+Na). Anal. Calcd for C$_{16}$H$_{13}$NO: C, 81.68; H, 5.57; N, 5.95. Found: C, 81.82; H, 5.63; N, 5.69.

9. Starting material **1a** was purchased from the commercial source. Other compounds (**1b–g**) were synthesized from the corresponding bromides or chlorides via the Rosenmund-von Braun reaction with CuCN in DMF as reported, see: (a) Powers, J. J.; Favor, D. A.; Rankin, T.; Sharma, R.; Pandit, C.; Jeganathan, A.; Maiti, S. N. *Tetrahedron Lett.* **2009**, *50*, 1267–1269. (b) Wang, D.; Kuang, L.; Li, Z.; Ding, K. *Synlett* **2008**, 69–72. The spectroscopic data of unknown compounds **1b** and **1g** are as follows.
*Compound **1b***: 85%; white solid, mp 65–66°C; IR (film) 2228, 1711, 1604, 1436 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ 2.46 (s, 3H), 3.98 (s, 3H), 7.47 (ddd, *J* = 8.1, 1.8, and 0.6 Hz, 1H), 7.60–7.61 (m, 1H), 8.03 (d, *J* = 8.1 Hz, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 21.18, 52.61, 112.81, 117.64, 129.57, 131.14, 133.16, 135.23, 143.79, 164.51; ESIMS *m/z* 198 (M$^+$+Na).
*Compound **1g***: 85%; white solid, mp 109–110°C; IR (film) 2222, 1730, 1619, 1467 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 300 MHz) δ 4.06 (s, 3H), 7.66–7.76 (m, 2H), 7.91–7.95 (m, 1H), 8.07 (s, 2H), 8.39–8.42 (m, 1H); $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 52.86, 111.25, 115.73, 125.35, 126.40, 128.34, 129.19 (2C), 131.99, 132.61 (2C), 134.30, 164.79; ESIMS *m/z* 234 (M$^+$+Na).

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