Tetrahedron Letters 51 (2010) 860–862

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

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

Sung Hwan Kim, Se Hee Kim, Ko Hoon Kim, Jae Nyoung Kim *

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

ARTICLE INFO

Article history:
Received 10 November 2009
Revised 1 December 2009
Accepted 7 December 2009
Available online 16 December 2009

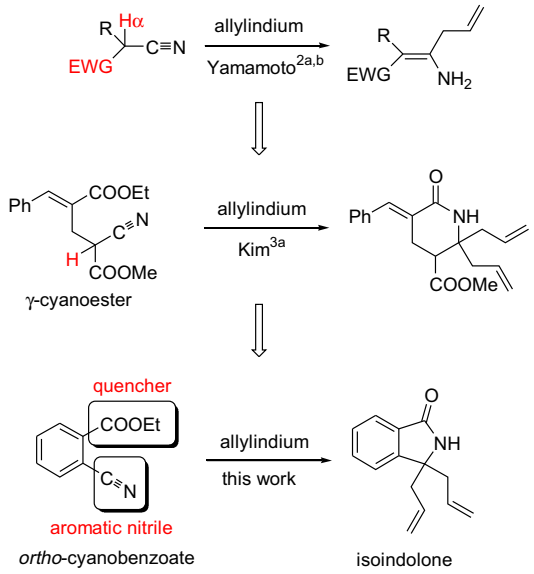
Keywords:
Isoindolones
Indium
Barbier reaction
Double allylation
ortho-Cyanobenzoates

ABSTRACT

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.

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.



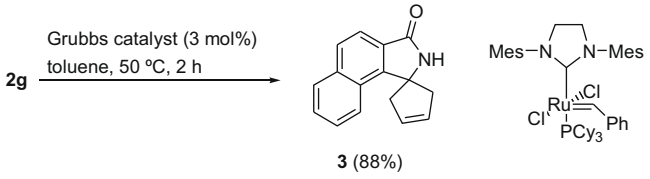
Scheme 1. Development of In-mediated allylation of nitrile.

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

0040-4039/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2009.12.034

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]



3 (88%)

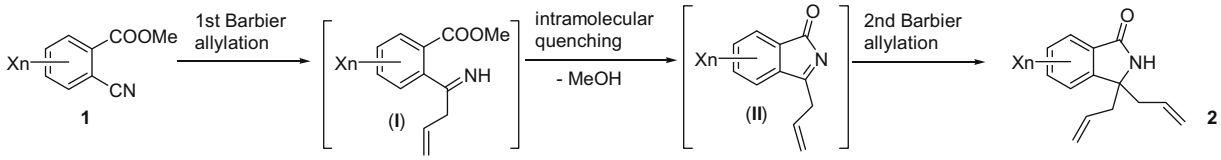
Scheme 2.

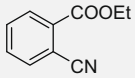
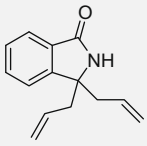
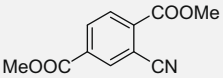
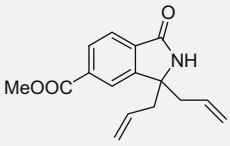
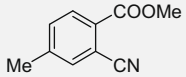
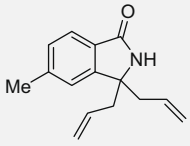
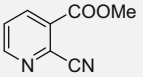
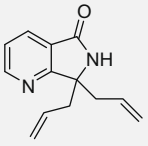
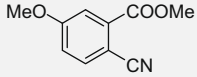
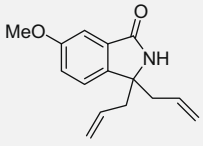
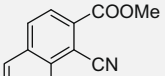
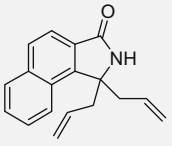
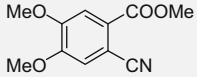
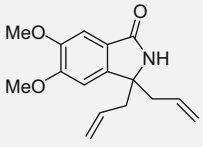
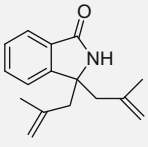
During the studies we observed an interesting solvent effect. The product **2a** was formed in THF at refluxing temperature in 71% as described above; however, the reaction in DMF (70–80 °C) was failed completely and **1a** was recovered. Similarly, the reaction failed in 1,4-dioxane, aqueous THF, PEG-3400, 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

This research was supported by Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education, Science and Technology (2009-0070633). Spectroscopic data was obtained from the Korea Basic Science Institute, Gwangju branch.

References and notes

1. For the general review on indium-mediated reactions, see: (a) Auge, J.; Lubin-Germain, N.; Uziel, J. *Synthesis* **2007**, 1739–1764; (b) Kargbo, R. B.; Cook, G. R. *Curr. Org. Chem.* **2007**, *11*, 1287–1309; (c) Lee, P. H. *Bull. Korean Chem. Soc.* **2007**, *28*, 17–28; (d) Li, C.-J.; Chan, T.-H. *Tetrahedron* **1999**, *55*, 11149–11176; (e) Pae, A. N.; Cho, Y. S. *Curr. Org. Chem.* **2002**, *6*, 715–737.
2. (a) Fujiwara, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 4729–4732; (b) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095–4101; For diallylation of benzonitrile with allylindate, see: (c) Jin, S.-J.; Araki, S.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1528–1532; For the indium(I) iodide-promoted allylation of α,β-unsaturated nitrile, see: (d) Ranu, B. C.; Das, A. *Tetrahedron Lett.* **2004**, *45*, 6875–6877.
3. (a) Kim, S. H.; Lee, H. S.; Kim, K. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 1696–1698; (b) Kim, S. H.; Kim, S. H.; Lee, K. Y.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 5744–5747; (c) Kim, S. H.; Lee, H. S.; Kim, K. H.; Kim, J. N. *Tetrahedron Lett.* **2009**, *50*, 6476–6479.
4. For the biological activities of isoindolone derivatives, see: (a) Riedinger, C.; Endicott, J. A.; Kemp, S. J.; Smyth, L. A.; Watson, A.; Valeur, E.; Golding, B. T.; Griffin, R. J.; Hardcastle, I. R.; Noble, M. E.; McDonnell, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 16038–16044; (b) Hudkins, R. L.; Johnson, N. W.; Angeles, T. S.; Gessner, G. W.; Mallamo, J. P. *J. Med. Chem.* **2007**, *50*, 433–441; (c) Jitsuoka, M.; Tsukahara, D.; Ito, S.; Tanaka, T.; Takenaga, N.; Tokita, S.; Sato, N. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 5101–5106; (d) Comins, D. L.; Schilling, S.; Zhang, Y. *Org. Lett.* **2005**, *7*, 95–98. and further references cited therein; (e) Fardis, M.; Jin, H.; Jabri, S.; Cai, R. Z.; Mish, M.; Tsiang, M.; Kim, C. U. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 4031–4035; (f) Wrobel, J.; Dietrich, A.; Woolson, S. A.; Millen, J.; McCaleb, M.; Harrison, M. C.; Hohman, T. C.; Sredy, J.; Sullivan, D. *J. Med. Chem.* **1992**, *35*, 4613–4627.
5. For the synthesis of isoindolone derivatives, see: (a Murai, M.; Miki, K.; Ohe, K. *J. Org. Chem.* **2008**, *73*, 9174–9176; (b) Salcedo, A.; Neuville, L.; Zhu, J. *J. Org. Chem.* **2008**, *73*, 3600–3603; (c) Campbell, J. B.; Dedinas, R. F.; Trumbower-Walsh, S. A. *J. Org. Chem.* **1996**, *61*, 6205–6211; (d) He, Z.; Yudin, A. K. *Org. Lett.* **2006**, *8*, 5829–5832; (e) Kobayashi, K.; Hase, M.; Hashimoto, K.; Fujita, S.; Tanmatsu, M.; Morikawa, O.; Konishi, H. *Synthesis* **2006**, 2493–2496; (f) Enders, D.; Braig, V.; Raabe, G. *Can. J. Chem.* **2001**, *79*, 1528–1535; (g) Sun, C.; Xu, B. *J. Org. Chem.* **2008**, *73*, 7361–7364; (h) Deville, J. P.; Behar, V. *Org. Lett.* **2002**, *4*, 1403–1405; (i) Araki, S.; Shimizu, T.; Johar, P. S.; Jin, S.-J.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538–2542.
6. For the synthesis of polycyclic- and spiro-isoindolone derivatives, see: (a Medimagh, R.; Marque, S.; Prim, D.; Marrot, J.; Chatti, S. *Org. Lett.* **2009**, *11*, 1817–1820; (b) Osante, I.; Lete, E.; Sotomayor, N. *Tetrahedron Lett.* **2004**, *45*, 1253–1256; (c) Bahajaj, A. A.; Vernon, J. M.; Wilson, G. D. *Tetrahedron* **2004**, *60*, 1247–1253; (d) Kang, S. W.; Kim, S. H. *Bull. Korean Chem. Soc.* **2006**, *27*, 153–154; (e) Kang, S. W.; Heo, E. Y.; Jun, J. G.; Kim, S. H. *Bull. Korean Chem. Soc.* **2004**, *25*, 1924–1928; (f) Majumdar, K. C.; Das, T. K.; Jana, M. *Synth. Commun.* **2005**, *35*, 1961–1969; (g) Bertus, P.; Menant, C.; Tanguy, C.; Szymoniak, J. *Org. Lett.* **2008**, *10*, 777–780; (h) Bertus, P.; Szymoniak, J. *J. Org. Chem.* **2003**, *68*, 7133–7136.
7. Sun, X.-W.; Liu, M.; Xu, M.-H.; Lin, G.-Q. *Org. Lett.* **2008**, *10*, 1259–1262.
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_2Cl_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}; ^1H 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}; ^1H 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}; ^1H 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}; ^1H 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}; ^1H 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}; ^1H 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}; ^1H 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).
10. For the mechanistic study of In-mediated allylation, see: (a) Isaac, M. B.; Chan, T.-H. *Tetrahedron Lett.* **1995**, *36*, 8957–8960; (b) Tan, K.-T.; Chng, S.-S.; Cheng, H.-S.; Loh, T.-P. *J. Am. Chem. Soc.* **2003**, *125*, 2958–2963; (c) Loh, T.-P.; Tan, K.-T.; Hu, Q.-Y. *Tetrahedron Lett.* **2001**, *42*, 8705–8708; (d) Loh, T.-P.; Tan, K.-T.; Yang, J.-Y.; Xiang, C.-L. *Tetrahedron Lett.* **2001**, *42*, 8701–8703.