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# An expedient synthesis of poly-substituted pyrroles from γ-ketonitriles via indium-mediated Barbier reaction strategy

Sung Hwan Kim, Se Hee Kim, Ka Young Lee, Jae Nyoung Kim *

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

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Dedicated to the memory of the late Professor Eung Kul Ryu whose vision and passion in organic and medicinal chemistry was an inspiration for all

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Indium
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ABSTRACT

We developed an efficient synthetic strategy of poly-substituted pyrroles via an indium-mediated Barbier type allylation from γ-ketonitriles. Initial attack of allylindium species occurred at the nitrile group selectively to form the enamine intermediate, which reacted with the ketone group intramolecularly to furnish the pyrroles.



Allylindium reagents have been used extensively for the introduction of allyl group in a Barbier type manner.[1–3] Although allylindium reagents can be added to many reactive functional groups including aldehyde, ketone, and activated imine with acyl or tosyl group,[1,2] the reaction with nitrile has not been reported much except for recent Yamamoto's paper.[3] According to the results introduction of allylindium can be carried out with only nitrile compounds having both an α-hydrogen atom and an α-EWG group.[3,4]

Recently we reported an efficient synthesis of diallylated δ-valerolactam derivatives via an indium-mediated successive double Barbier type allylations (Scheme 1).[4] In the reaction, diallylated δ-valerolactam was formed via the sequential processes; (i) first Barbier allylation of nitrile to produce enamine intermediate, (ii) cyclization to cyclic *N*-acylimine derivative, and (iii) second Barbier allylation to imine, as shown in Scheme 1.[4]

During the study we reasoned that poly-substituted pyrrole derivatives could be synthesized from γ-ketonitriles, if the reactivity of allylindium toward nitrile surpasses that of allylindium to ketone. Suitably substituted pyrroles are the basic skeleton of many biologically important substances,[5,6] and numerous methods for the synthesis of pyrrole derivatives have been investigated extensively.[5,6] In these contexts we prepared γ-ketonitrile such as **1a**[7] and examined the reaction with allylindium species as shown in Scheme 2.

We chose **1a** as a model compound based on the following expectations: (i) the nitrile group of **1a** and allylindium can produce the enamine intermediate (**II**) easily as reported[3,4] and (ii) the reactivity of the ketone group of **1a** toward allylindium was expected low due to the steric interference of nearby phenyl substituent (vide infra). Compound **1a** was prepared from desyl chloride and methyl cyanoacetate ($K_2CO_3$, DMF, rt, 2 h) in 75% yield as a *syn*/*anti* mixture (3:1).[7,8] The reaction of **1a** and allyl bromide in the presence of indium powder (THF, reflux, 30 min) produced poly-substituted pyrrole **2a** in 55% yield as expected.[8] In the reaction, we separated lactone derivative **3a** in trace amount (3%) as a *syn*/*anti* mixture (1:1).[8,9] The plausible mechanism for the formation of **2a** is depicted in Scheme 2. Allylindium species attacked the nitrile group first to produce enamine intermediate (**II**) which underwent intramolecular condensation to form the pyrrole **2a**. Compound **3a** might be produced via the sequential processes: (i) reaction of allylindium to the ketone first to produce hydroxyester (**III**), (ii) lactonization to γ-butyrolactone (**IV**), and (iii) second allylation at the nitrile of (**IV**).[3,4]

Encouraged by the results we prepared various γ-ketonitriles **1b**–**j** and examined the synthesis of poly-substituted pyrrole derivatives **2a**–**j** and the results are summarized in Table 1 and Table 2. Starting materials **1b**–**j** were prepared as a *syn*/*anti* mixture from methyl (or ethyl) cyanoacetate and the corresponding α-chloro

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

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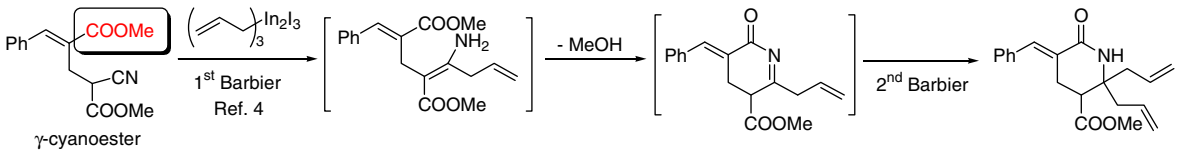
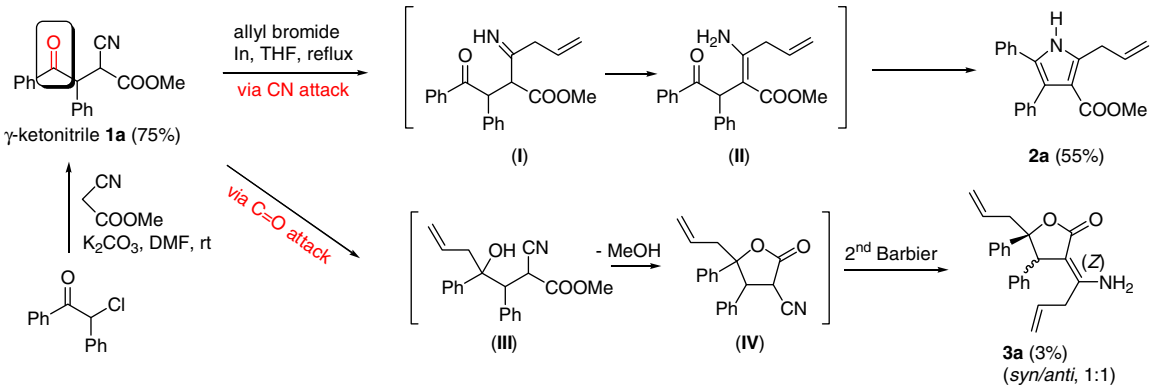



**Scheme 1.**




**Scheme 2.**

**Table 1**
Synthesis of poly-substituted pyrroles **2a–f**

| Entry | Nitrile **1**[a] (%) | Pyrrole **2**[b] (%) |
|---|---|---|
| 1 | **1a** (75) | **2a** (55)[c] |
| 2 | **1b** (76) | **2b** (63) |
| 3 | **1c** (70) | **2c** (55) |
| 4 | **1d** (78) | **2d** (57) |
| 5 | **1e** (66) | **2e** (53) |
| 6 | **1f** (60) | **2f** (62) |

[a] *Syn/anti* mixture (1:1–6:1).
[b] Conditions: nitrile **1** (1.0 mmol), allyl bromide (2.0 mmol), In (1.0 mmol), THF, reflux, 30–60 min.
[c] Compound **3a** was isolated together (3%, see Table 2).

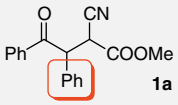
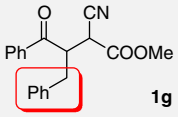
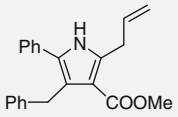
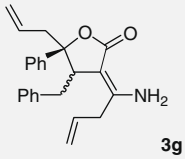
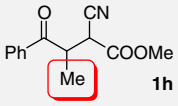
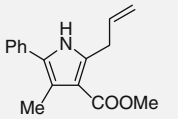
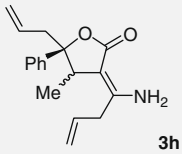
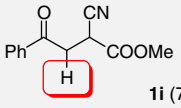
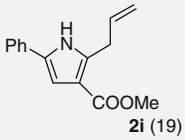
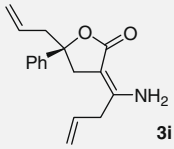
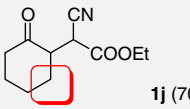
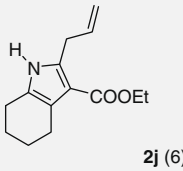
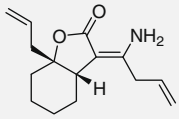
(or bromo) ketone derivatives in the presence of $K_2CO_3$ in DMF at room temperature.[7]

For the substrates **1b–f**, desired poly-substituted pyrroles **2b–f** were produced as the major products and we isolated them in moderate yields (53–63%). We could not isolate the corresponding lactone derivatives **3b–f** in appreciable yields, although TLC observation implied the presence of the corresponding lactones in trace amounts (vide infra). However, benzyl derivative **1g** (entry 2 in Table 2) showed the formation of appreciable amounts of lactone **3g** (9%) together with pyrrole **2g** as the major product (52%). As we noted above (vide supra), the increased amount of lactone **3g** might be a result of increased reactivity of the ketone group of **1g** toward allylindium. When we used methyl-substituted substrate **1h** (entry 3 in Table 2), the yield of pyrrole **2h** was reduced to 43% and the lactone **3h** was formed in an increased yield (27%, 5:1 mixture). The ratio of pyrrole/lactone was reversed for the substrates **1i** and **1j**. In these cases, the yields of pyrroles (**2i** and **2j**) were low (6–19%) while those of lactones (**3i** and **3j**) were increased (38–53%). From the results, the reactivity of ketone moiety of **1a** and **1g–j** toward allylindium was increased by reducing the size of the substituent at the β-position of γ-ketonitrile.

The stereochemistry of double bond of enamine moiety of **3a** and **3g–j** might be *Z* as in the reported paper of Yamamoto.[3] In the $^1$H NMR spectrum of **3j** in $CDCl_3$, the $NH_2$ peak was so broad that we cannot read the chemical shift and this might be caused by the intramolecular hydrogen bonding between $NH_2$ and oxygen atom of lactone. However, two broad singlets of $NH_2$ appeared in DMSO-$d_6$ at $\delta = 6.65$ and 7.35 ppm.[8] Important NOE results of **3j** are shown in Figure 1. NOE results (when H at 3a-position was irradiated) between hydrogen and allyl group at the ring junction showed their cis-relationships. In addition, 2.5% increment of another allyl group stated that the double bond geometry of enamine is *Z*. Compounds **3a**, **3g,** and **3h** were isolated as an inseparable diastereomeric mixture (1:1–5:1 mixture) as shown in Table 2. It is interesting to note that compound **2f** can be aromatized easily by DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) oxidation to produce 1*H*-benzo[*g*]indole derivative **4** in good yield (88%) as shown in Scheme 3.

In summary, we developed an efficient synthetic strategy of poly-substituted pyrroles via an indium-mediated Barbier-type

**Table 2**
The effect of substituent at β-position of γ-ketonitrile **1**

| Entry | γ-Ketonitrile **1**[a] (%) | CN attack (%) | CO attack (%) |
|---|---|---|---|
| 1 |  **1a** | **2a** (55%) (entry 1 in Table 1) | **3a** (3)[b] (Scheme 2) |
| 2 |  **1g** (71) |  **2g** (52) |  **3g** (9)[b] |
| 3 |  **1h** (76) |  **2h** (43) |  **3h** (27)[c] |
| 4 |  **1i** (79) |  **2i** (19) |  **3i** (38)[d] |
| 5 |  **1j** (70) |  **2j** (6) |  **3j** (53)[d] |

[a] *Syn/anti* mixture (2:1–3:1).
[b] 1:1 Mixture.
[c] 5:1 Mixture.
[d] Single compound.

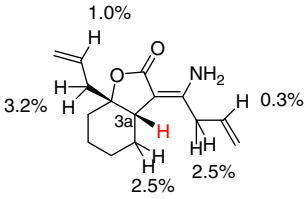
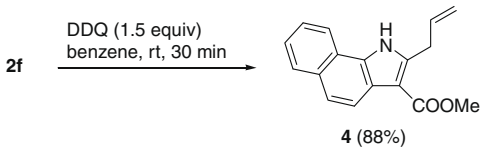



**Figure 1.** Important NOEs of 7a-allylhexahydrobenzofuran-2-one **3j** (H at 3a-position was irradiated).




**Scheme 3.**

allylation of γ-ketonitriles. The chemoselectivity between ketone and nitrile functionalities toward allylindium species could be controlled by providing some steric hindrance around the ketone group.

## Acknowledgments

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## References and notes

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3. (a) Fujiwara, N.; Yamamoto, Y. *Tetrahedron Lett.* **1998**, *39*, 4729–4732; (b) Fujiwara, N.; Yamamoto, Y. *J. Org. Chem.* **1999**, *64*, 4095–4101.
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6. For the synthesis and biological activities of pyrrole-containing compounds, see: (a) Thasana, N.; Worayuthakarn, R.; Kradanrat, P.; Hohn, E.; Young, L.;

Ruchirawat, S. *J. Org. Chem.* **2007**, *72*, 9379–9382; (b) Su, S.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2007**, *129*, 7744–7745; (c) Dhawan, R.; Arndtsen, B. A. *J. Am. Chem. Soc.* **2004**, *126*, 468–469; (d) Pandey, P. S.; Rao, T. S. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 129–131.

7. Prepared starting materials were identified by their IR, $^1$H NMR, and mass data.[8] Compounds **1i** and **1j** were prepared according to the references, see: (a) Lev, I. J.; Ishikawa, K.; Bhacca, N. S.; Griffin, G. W. *J. Org. Chem.* **1976**, *41*, 2654–2656; (b) Sakai, T.; Amano, E.; Kawabata, A.; Takeda, A. *J. Org. Chem.* **1980**, *45*, 43–47.
8. *Typical procedure for the synthesis of compounds* **2a** *and* **3a**: A mixture of desyl chloride (346 mg, 1.5 mmol), methyl cyanoacetate (297 mg, 3.0 mmol), and $K_2CO_3$ (276 mg, 2.0 mmol) in DMF (3 mL) was stirred at room temperature for 2 h. After the usual aqueous workup and column chromatographic purification process (hexanes/EtOAc, 8:1), compound **1a** was obtained as colorless oil, 330 mg (75%) as a *syn/anti* mixture (3:1). A stirred mixture of compound **1a** (293 mg, 1.0 mmol), allyl bromide (242 mg, 2.0 mmol), and indium (115 mg, 1.0 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, 16:1:1), we obtained compound **2a** (175 mg, 55%) and compound **3a** (10 mg, 3%). Other compounds were synthesized similarly and the spectroscopic data of **1a**, **2a**, **2f**, **2g**, **3a**, **3j**, and **4** are as follows.
   *Compound* **1a** (*major/minor*, 3:1): 75%; colorless oil; IR (film) 2252, 1749, 1682, 1449, 1266 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.72 (minor, s, 3H), 3.81 (major, s, 3H), 4.06 (minor, d, $J$ = 7.2 Hz, 1H), 4.56 (major, d, $J$ = 10.2 Hz, 1H), 5.20 (major, d, $J$ = 10.2 Hz, 1H), 5.30 (minor, d, $J$ = 7.2 Hz, 1H), 7.27–7.41 (major and minor, m, 14H), 7.46–7.53 (major and minor, m, 2H), 7.88–7.95 (major and minor, m, 4H); ESIMS $m/z$ 294 [M+H]$^+$. Anal. Calcd for $C_{18}H_{15}NO_3$: C, 73.71; H, 5.15; N, 4.78. Found: C, 73.98; H, 5.37; N, 4.66.
   *Compound* **2a**: 55%; pale yellow solid, mp 135–136 °C; IR (KBr) 3302, 1681, 1460 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.60 (s, 3H), 3.82 (dt, $J$ = 6.6 and 1.2 Hz, 2H), 5.22–5.31 (m, 2H), 5.97–6.11 (m, 1H), 7.06–7.31 (m, 10H), 8.39 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 32.09, 50.53, 111.92, 118.26, 123.58, 126.38, 126.65, 126.88, 127.59, 127.89, 128.44, 130.68, 132.06, 134.20, 135.67, 136.58, 165.78; ESIMS $m/z$ 318 [M+H]$^+$. Anal. Calcd for $C_{21}H_{19}NO_2$: C, 79.47; H, 6.03; N, 4.41. Found: C, 79.54; H, 6.25; N, 4.31.
   *Compound* **2f**: 62%; pale yellow oil; IR (film) 3304, 1672, 1467 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.89–3.03 (m, 4H), 3.80–3.82 (m, 2H), 3.82 (s, 3H), 5.18–5.26 (m, 2H), 5.93–6.07 (m, 1H), 7.04–7.20 (m, 4H), 8.46 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 21.46, 29.46, 32.04, 50.65, 110.18, 117.94, 118.07, 121.82, 125.55, 126.38, 126.65, 128.28, 128.31, 134.35, 134.71, 137.47, 166.24; ESIMS $m/z$ 268 [M+H]$^+$. Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.12; H, 6.65; N, 5.11.
   *Compound* **2g**: 52%; pale yellow oil; IR (film) 3304, 1676, 1465 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.63 (s, 3H), 3.80 (dt, $J$ = 6.9 and 1.2 Hz, 2H), 4.21 (s, 2H), 5.19–5.26 (m, 2H), 5.94–6.07 (m, 1H), 7.10–7.14 (m, 3H), 7.20–7.36 (m, 7H), 8.31 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 31.21, 32.17, 50.36, 111.56, 118.07, 119.98, 125.24, 127.09, 127.23, 127.90, 128.04, 128.77, 129.16, 132.34, 134.27, 137.23, 142.50, 165.93; ESIMS $m/z$ 332 [M+H]$^+$.
   *Compound* **3a** (*major/minor*, 1:1): 3%; pale yellow oil; IR (film) 3466, 3411, 3326, 1694, 1625, 1556, 1239 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 2.16–2.18 (m, 2H * 0.5), 2.41–2.92 (m, 6H * 0.5), 4.20 (s, 1H * 0.5), 4.28 (s, 1H * 0.5), 4.66–5.81 (m, 12H * 0.5), 6.81–7.07 (m, 8H * 0.5), 7.25–7.45 (m, 12H * 0.5); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 37.37, 37.40, 43.52, 47.76, 55.07, 57.17, 87.49, 88.82, 92.22, 94.51, 117.92, 118.87, 119.97, 120.19, 124.95, 126.13, 126.27, 127.00, 127.23, 127.43, 127.72, 128.31, 128.69, 128.86, 130.95, 131.14, 132.40, 132.87, 140.09, 141.08, 141.84, 145.83, 157.84, 158.10, 172.90, 173.29, and two carbon peaks were overlapped; ESIMS $m/z$ 346 [M+H]$^+$.
   *Compound* **3j**: 53%; colorless oil; IR (film) 3424, 3330, 1693, 1630, 1565, 1227 cm$^{-1}$; $^1$H NMR (DMSO-$d_6$, 600 MHz) $\delta$ 1.08–1.53 (m, 5H), 1.73–1.79 (m, 2H), 1.84–1.85 (m, 1H), 2.13–2.19 (m, 1H), 2.24–2.28 (m, 1H), 2.65 (dd, $J$ = 8.4 and 6.0 Hz, 1H), 2.86 (dd, $J$ = 14.4 and 6.0 Hz, 1H), 2.93 (dd, $J$ = 14.4 and 6.6 Hz, 1H), 5.03–5.19 (m, 4H), 5.70–5.77 (m, 1H), 5.81–5.88 (m, 1H), 6.65 (br s, 1H), 7.35 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 19.25, 20.48, 29.45, 30.51, 37.10, 40.72, 45.68, 83.25, 96.63, 118.47, 119.39, 132.30, 132.92, 154.59, 173.44; ESIMS $m/z$ 248 [M+H]$^+$. Anal. Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.89; H, 8.77; N, 5.48.
   *Compound* **4**: 88%; pale yellow solid, mp 208–210 °C; IR (KBr) 3324, 1713, 1466, 1314, 1180 cm$^{-1}$; $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 3.97 (s, 3H), 4.08 (dt, $J$ = 6.6 and 1.2 Hz, 2H), 5.30–5.37 (m, 2H), 6.04–6.17 (m, 1H), 7.43–7.48 (m, 1H), 7.52–7.57 (m, 1H), 7.64 (d, $J$ = 9.0 Hz, 1H), 7.93–7.99 (m, 2H), 8.23 (d, $J$ = 9.0 Hz, 1H), 8.99 (br s, 1H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 32.27, 50.93, 109.72, 118.75, 119.09, 120.87, 121.02, 122.45, 123.53, 124.29, 125.77, 128.93, 129.10, 130.43, 133.80, 142.33, 166.24; ESIMS $m/z$ 266 [M+H]$^+$. Anal. Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.07; H, 5.71; N, 5.09.
9. For the similar enaminobutyrolactones, see: (a) Duron, S. G.; Gin, D. Y. *Org. Lett.* **2001**, *3*, 1551–1554; (b) Bower, J. F.; Szeto, P.; Gallagher, T. *Org. Lett.* **2007**, *9*, 4909–4912.