An expedient synthesis of poly-substituted pyrroles from $\gamma$-ketonitriles via indium-mediated Barbier reaction strategy

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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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Barbier reaction
$\gamma$-Ketonitriles
Pyrroles

Abstract

We developed an efficient synthetic strategy of poly-substituted pyrroles via an indium-mediated Barbier type allylation from $\gamma$-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.

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Allylindium reagents have been used extensively for the introduction of allyl group in a Barbier type manner.1–4 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 $\alpha$-hydrogen atom and an $\alpha$-EWG group.3

Recently we reported an efficient synthesis of diallylated $\delta$-valerolactam derivatives via an indium-mediated successive double Barbier type allylations (Scheme 1).4 In the reaction, diallylated $\delta$-valerolactam was formed via the sequential processes; (i) first Barbier alylation 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.

During the study we reasoned that poly-substituted pyrrole derivatives could be synthesized from $\gamma$-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 $\gamma$-ketonitrile such as 1a7 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 reported3,4 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$_2$CO$_3$, 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 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 $\gamma$-butyrolactone (IV), and (iii) second allylation at the nitrile of (IV).3

Encouraged by the results we prepared various $\gamma$-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 $\alpha$-chloro...
Synthesis of poly-substituted pyrroles

**Scheme 1.**

**Scheme 2.**

**Table 1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Nitrile 1 (%)</th>
<th>Pyrrole 2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph COOEt</td>
<td>Ph COOMe</td>
</tr>
<tr>
<td>2</td>
<td>Ph COOMe</td>
<td>Ph COOMe</td>
</tr>
<tr>
<td>3</td>
<td>MeO</td>
<td>MeO</td>
</tr>
<tr>
<td>4</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>5</td>
<td>Cl</td>
<td>Cl</td>
</tr>
<tr>
<td>6</td>
<td>Ph COOMe</td>
<td>Ph COOMe</td>
</tr>
</tbody>
</table>

(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 K2CO3 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 moity 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. In the 1H NMR spectrum of 3j in CDCl3, the NH2 peak was so broad that we cannot read the chemical shift and this might be caused by the intramolecular hydrogen bonding between NH2 and oxygen atom of lactone. However, two broad singlets of NH2 appeared in DMSO-d6 at δ = 6.65 ppm and 7.35 ppm. 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 1H-benzo[γ]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
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

2. For the indium-mediated Barbier type allylation of imine, acylimine, and nitrile functionalities toward allylindium species could be controlled by providing some steric hindrance around the ketone group.
3. Scheme 3.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>γ-Ketonitrile 1 (%)</th>
<th>CN attack (%)</th>
<th>CO attack (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="1a.gif" alt="Image" /> 1a</td>
<td><img src="2a.gif" alt="Image" /> 2a (55%) (entry 1 in Table 1)</td>
<td>3a (3)\textsuperscript{b} (Scheme 2)</td>
</tr>
<tr>
<td>2</td>
<td><img src="1g.gif" alt="Image" /> 1g (71)</td>
<td><img src="2g.gif" alt="Image" /> 2g (52)</td>
<td><img src="3g.gif" alt="Image" /> 3g (9)\textsuperscript{c}</td>
</tr>
<tr>
<td>3</td>
<td><img src="1h.gif" alt="Image" /> 1h (76)</td>
<td><img src="2h.gif" alt="Image" /> 2h (43)</td>
<td><img src="3h.gif" alt="Image" /> 3h (27)\textsuperscript{c}</td>
</tr>
<tr>
<td>4</td>
<td><img src="1j.gif" alt="Image" /> 1j (79)</td>
<td><img src="2i.gif" alt="Image" /> 2i (19)</td>
<td><img src="3i.gif" alt="Image" /> 3i (38)\textsuperscript{d}</td>
</tr>
<tr>
<td>5</td>
<td><img src="1j.gif" alt="Image" /> 1j (70)</td>
<td><img src="2j.gif" alt="Image" /> 2j (6)</td>
<td><img src="3j.gif" alt="Image" /> 3j (53)\textsuperscript{d}</td>
</tr>
</tbody>
</table>

a Syn/anti mixture (2.1–3.1).
\textsuperscript{b} 5:1 Mixture.
\textsuperscript{c} Single compound.

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

Figure 3.
Prepared starting materials were identified by their IR, 1H NMR, and mass data. Compounds 1 and 2 were prepared according to the references, see: (a) Lev, I. J.; Ishikawa, K.; Bhide, N. S.; Griffin, C. W. J. Org. Chem. 1976, 41, 2654–2656. (b) Sakai, T.; Amano, E.; Kawabata, A.; Takeda, A. J. Org. Chem. 1980, 45, 43–47.

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 K2CO3 (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 mixture (hexanes/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 compounds 1, 2a, 3a, 3f, and 4 are as follows.

Compounds 1a, 2a, 3a, 3f, and 4 were synthesized similarly and the spectroscopic data of 1a, 2a, 3f, 3a, 3j, and 4 are as follows.