An expedient synthesis of 3-alkylideneoxindoles by Ti(O\textsuperscript{\textit{i}}Pr\textsubscript{4})/pyridine-mediated Knoevenagel condensation

Hyun Ju Lee, Jin Woo Lim, Jin Yu, 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 7 November 2013
Revised 6 December 2013
Accepted 25 December 2013
Available online 4 January 2014

Keywords:
3-Alkylideneoxindoles
Titanium enolates
Ti(O\textsuperscript{\textit{i}}Pr\textsubscript{4})/pyridine
Knoevenagel condensation

ABSTRACT

3-Alkylideneoxindoles have been prepared in excellent yields from oxindole and carbonyl compounds via an in situ generated titanium enolate of oxindole. (Z)-3-Alkylideneoxindoles could be synthesized selectively as major products from unsymmetrical ketones.

At the outset of our experiment, the reaction of oxindole (1\textit{a}) and acetophenone was examined in the presence of Ti(O\textsuperscript{\textit{i}}Pr\textsubscript{4}) (3.0 equiv) and pyridine (2.0 equiv) in THF at room temperature, as shown in Table 1. The reaction afforded 2\textit{a} in high yield (95%) in short time (entry 1). When we reduced the amount of Ti/pyridine (entry 2), the yield of 2\textit{a} was not changed. However, the reaction was not completed with lesser amount of Ti/pyridine (entries 3 and 4) even at elevated temperature. Although the yield was satisfactory in the case of acetone, we examined the optimum conditions for three representative carbonyl compounds, benzophenone (entries 5–7), acetonophenone (entries 8–11), and benzaldehyde (entries 12–18).

The reaction of sterically hindered benzophenone was not effective even in the presence of an excess amount of Ti/pyridine and a long reaction time (entries 5 and 6), while the reaction at 60 °C afforded the product 2\textit{d} in high yield in short time (entry 7). The reaction of acetonophenone afforded good yield of 2\textit{e} in THF or toluene (entries 8–10), while the use of TiCl\textsubscript{4} was not effective (entry 11). It is interesting to note that Z-isomer was formed selectively (2\textit{e}-\textit{Z}: 2\textit{e}-\textit{E} = 5:1), as compared to the selective formation of E-isomer by the amine-catalyzed Knoevenagel condensation method.\textsuperscript{1c,3d} The structures of 2\textit{e}-\textit{Z} and 2\textit{e}-\textit{E} were confirmed by comparison with the reported. A methyl proton of 2\textit{e}-\textit{E} appeared downfield (\textit{\delta} = 2.80 ppm) than the Z-form (\textit{\delta} = 2.63 ppm) due to deshielding anisotropic effect of the carbonyl proton of 2\textit{e}-\textit{E}.
group of oxindole moiety (vide infra, Scheme 1). In addition, the proton at the C-4 position of 2e-E appeared quite upfield (δ = 6.13 ppm) due to shielding effect of the phenyl ring.

The reaction of benzaldehyde in the presence of 1.5 equiv of Ti catalyst (entry 12) gave moderate yield of product 2l, to our surprise, due to the formation of some intractable side products. When we reduced the amount of catalyst (entry 13) the reaction produced 2l in high yield (92%). However, more stable E-isomer was isolated as a major product presumably due to rapid isomerization of the initially formed Z-isomer (vide infra). The reaction with lesser amount of catalyst (entry 14) was not completed. In order to reduce the isomerization, we carried out the reaction in the absence of pyridine (entry 15), in the presence of other base such as Et3N and 2,6-lutidine (entries 16 and 17), or at low temperature (entry 18). However, 2l-E was obtained as a major product in all entries.

According to the brief optimization results we examined the reactions of various carbonyl compounds, and the results are summarized in Table 2. The reactions of 1a and cyclohexanone and N-benzylpiperidine afforded 2b and 2c, respectively, in high yields. The reaction of benzophenone afforded 2d in high yield (88%) by using Ti/pyridine (3:2) system at 60 °C. As for the reaction of aceto phenone, the reactions with 4-nitroacetophenone, 2-ace tynaphthone, 2-acetyltiophene afforded 2f-h in good yields (88–94%). The reactions of 3-chlorooxindole (1b) and 5-methoxy oxindole (1c) with aceto phenone gave the corresponding products 2i and 2j in good yields (86–95%) with a similar E/Z selectivity. The reaction of propiophenone also showed a similar reactivity to give 2k (87%). In all cases, Z-isomer was isolated as a major product.

The selective formation of Z-isomer could be explained, as shown in Scheme 1. Oxindole might be converted to the titanium enolate under the reaction conditions via the initially formed amide enolate, and the nucleophilic attack of aldehyde occurs preferentially from the Z-side. The reason for the observed pseudo-Z isomerization is possibly due to the steric hindrance of the phenyl ring.
of I toward the Si face of acetophenone via a six-membered transition state II, bearing a larger phenyl group at the equatorial position, would produce the Z-isomer as a major product. 6,9

It is interesting to note that the isolated 2f-Z of 4'-nitroacetophenone was isomerized slowly to 2f-E to some extent at room temperature in CDCl₃, 10 although 2f-Z was not isomerized during the reaction progress. Actually, the ratio of E/Z (ca. 1:9) was not changed when we let the reaction mixture for a long time (20 h). The initially formed 2f-Z might be present in its enolate form IV in the reaction mixture before acidic workup, as shown in Scheme 2. The indicated carbon atom of IV is not electrophilic. Thus a plausible isomerization, caused by some nucleophilic species such as water or pyridine, would not occur during the reaction progress. In contrast to the carbon atom of IV, the indicated carbon atom of 2f-Z is electrophilic and the isomerization would proceed slowly via an addition/elimination of a nucleophile. 10

The isomerization via rotation around the C–C single bond of the canonical structure V might contribute to some extent for the isomerization process. 10

The reactions of mesitaldehyde and cinnamaldehyde provided the corresponding products 2m and 2n in good yields (89–93%), and the ratio of E/Z was similar to that of benzaldehyde. Initially formed Z-isomer, via the chelation-controlled transition state, could be isomerized into more stable E-isomer via the same

---

**Table 2**

Synthesis of 3-alkylideneoxindoles

<table>
<thead>
<tr>
<th>2a (90%)</th>
<th>2b (94%)</th>
<th>2c (95%)</th>
<th>2d (88%)</th>
<th>2e-Z (78%)/2e-E (15%)</th>
<th>2f-Z (82%)/2f-E (9%)</th>
<th>2g-Z (85%/2g-E (9%)</th>
<th>2h-Z (80%)/2h-E (8%)</th>
<th>2i-Z (62%/2i-E (24%))</th>
<th>2j-Z (72%)/2j-E (23%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
<td>Si</td>
<td>Me</td>
<td>2.0/1.5, 4 h</td>
<td>2.0/1.5, 5 h</td>
<td>2.0/1.5, 5 h</td>
<td>2.0/1.5, 5 h</td>
<td>2.0/1.5, 5 h</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1.5/1.0, 2 h</td>
<td>3.0/2.0, 5 h</td>
<td>2.0/1.5, 4 h</td>
<td>2.0/1.5, 5 h</td>
<td>2.0/1.5, 5 h</td>
</tr>
<tr>
<td>2a</td>
<td>2b</td>
<td>2c</td>
<td>2d</td>
<td>2e-Z</td>
<td>2g-Z</td>
<td>2h-Z</td>
<td>2i-Z</td>
<td>2j-Z</td>
<td>2k-Z</td>
</tr>
<tr>
<td>(90%)</td>
<td>(94%)</td>
<td>(95%)</td>
<td>(88%)</td>
<td>Z</td>
<td>Z</td>
<td>Z</td>
<td>Z</td>
<td>Z</td>
<td>Z</td>
</tr>
<tr>
<td>1.5/1.0, 1 h</td>
<td>1.5/1.0, 1 h</td>
<td>1.5/1.0, 2 h</td>
<td>3.0/2.0, 5 h</td>
<td>2.0/1.5, 4 h</td>
<td>2.0/1.5, 5 h</td>
<td>2.0/1.5, 5 h</td>
<td>2.0/1.5, 5 h</td>
<td>2.0/1.5, 5 h</td>
<td>4.0/3.0, 12 h</td>
</tr>
</tbody>
</table>

---

a Oxindoles (0.5 mmol), carbonyl compounds (1.2 equiv), dry THF, and rt are common. Isolated yield and the equivalents of Ti/pyridine and reaction time are indicated below.

b At 60 °C.

c E/Z (ca. 1:9 by 1H NMR mixture).
pathway in Scheme 2. The reaction of indole-3-carboxaldehyde gave 2o in good yield (92%); however, the E/Z ratio was converted and the reason might be ascribed to an intramolecular hydrogen-bond interaction between the carbonyl of oxindole and NH of indole moiety. As observed for the seven examples of unsymmetrical ketones in Table 2, Z-isomers (2e–k) were obtained as major products. As a next experiment, we expected the feasibility for the synthesis of E-isomer as a major product. We carried out the reaction of 1a and acetonophene in the presence of a limited amount of Ti catalyst (1.0 equiv) in order to obtain 2e–E as a major product, as shown in Scheme 3. According to our hypothesis in Scheme 2, we presumed that the initially formed 2e–Z would not be converted to its amide enolate intermediate (such as IV) without an excess Ti catalyst. Accordingly, an isomerization of 2e–Z would proceed to form 2e–E as a major product. As expected, 2e–E was formed selectively and could be isolated in good yield (71%) although the reaction was not completed even after 18 h at 60 °C. TAS-301 (3-bis-(4-methoxyphenyl)methylene-2-indolinone) has been synthesized in refluxing THF in the presence of an excess amount of NaH (2.5 equiv) for a long time (5 days) in moderate yield (55%). However, we could prepare TAS-301 in high yield (89%), as shown in Scheme 4. We also examined a palladium-catalyzed arylation of easily available p-methoxybenzylidene oxindole (E/Z, 4:1) with 4-iodoanisole or anisole according to our previous paper; however, the result was quite disappointing, as also shown in Scheme 4.

The reaction of N-methylindoxline (1d) and acetonophene was not completed under the standard condition (Ti/pyridine, 2.0/1.5). Thus the reaction was carried out in the presence of Ti/pyridine (4.0/3.0) for 7 h at room temperature, and the corresponding products 2q-Z (N-methyl 2e-Z, 70%) and 2q-E (N-methyl 2e-E, 13%) were obtained in reasonable yields. The sluggish reactivity of N-methyl derivative 1d as compared to 1a is not clear at this stage. More stable 2q-E could be prepared as a major product by carrying out the reaction at 60 °C, as in the case of 2e–E in Scheme 3 (vide supra). Actually, the reaction of 1d in the presence of Ti/pyridine (4.0/3.0) for 7 h at 60 °C produced 2q-E (72%) along with 2q-Z (15%).

As a limitation of this protocol, the reaction of 5-nitrooxindole (1e) and acetonophene failed completely to obtain the product 2r, as shown in Scheme 5. The reaction of 1e and Ti/pyridine might produce a nitronate VI instead of the Ti enolate. The fate of VI is not clear at this stage; however, many intraocular polar side spots were observed on TLC.

In summary, we prepared various 3-alkylidenoxindoles in high yields using in situ generated titanium enolate of oxindole. (Z)-3-Alkylidenoxindoles, which could not be synthesized by a traditional Knoevenagel condensation, could be obtained selectively as a major product from unsymmetrical ketones such as acetoephone.

Acknowledgments

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 (2012R1A1B3000541). Spectroscopic data were obtained from the Korea Basic Science Institute, Gwangju branch.

References and notes


and related

1H NMR (CDCl3

= 18.2) than the

13C NMR (CDCl3

8. For the Knoevenagel condensation involving the use of Ti(O

2013

2009

2004

2003

8. Typical procedure for the synthesis of 2e:

To a stirred solution of oxindole 1a, 67 mg (0.5 mmol), acetoephone (72 mg, 0.7 mmol), and pyridine (59 mg, 0.75 mmol) in dry THF (0.5 mL) was added dropwise a solution of Ti(O

242 [M+H]

270 [M+H]2

272 [M+H]

256 [M+H]

153.90, 155.50, 167.24; ESIMS m/z 256 [M+H]

2010

3. During the evaluation process, one of the referees asked to show an example of the isomerization of 3-alkylideneoxindoles, see: (a) Jiang, T.-S.; Tang, R.-Y.; Liao, S.-Z.; Liu, X.-J.; and (b) Murakami, M. Heteroatom Chem. 2007, 18, 113–120.

During the evaluation process, one of the referees asked to show an example of the isomerization of 3-alkylideneoxindoles, see: (a) Jiang, T.-S.; Tang, R.-Y.; Liao, S.-Z.; Liu, X.-J.; and (b) Murakami, M. Heteroatom Chem. 2007, 18, 113–120.

During the evaluation process, one of the referees asked to show an example of the isomerization of 3-alkylideneoxindoles, see: (a) Jiang, T.-S.; Tang, R.-Y.; Liao, S.-Z.; Liu, X.-J.; and (b) Murakami, M. Heteroatom Chem. 2007, 18, 113–120.

During the evaluation process, one of the referees asked to show an example of the isomerization of 3-alkylideneoxindoles, see: (a) Jiang, T.-S.; Tang, R.-Y.; Liao, S.-Z.; Liu, X.-J.; and (b) Murakami, M. Heteroatom Chem. 2007, 18, 113–120.

During the evaluation process, one of the referees asked to show an example of the isomerization of 3-alkylideneoxindoles, see: (a) Jiang, T.-S.; Tang, R.-Y.; Liao, S.-Z.; Liu, X.-J.; and (b) Murakami, M. Heteroatom Chem. 2007, 18, 113–120.