Transition metal and base-free synthesis of 3,3-diaryl-2-oxindoles from 2,2,\textit{N}-triarylacetamides

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Abstract

A transition metal and base-free synthesis of 3,3-diaryl-2-oxindoles has been developed from 2,2,\textit{N}-triarylacetamides in the presence of montmorillonite K-10 in 1,2-dichlorobenzene under \textit{O}_2 balloon atmosphere.

Numerous 3,3-disubstituted oxindole derivatives including spirooxindoles showed interesting biological activity.\textsuperscript{1,2} Thus, various synthetic methods of this scaffold have been developed.\textsuperscript{3,9} The synthesis has been carried out from various starting materials such as \textit{N}-arylamides, \textit{N}-arylacrylamides, oxindoles, and isatins. Palladium-catalyzed synthesis from \textit{N}-(ortho-haloaryl)amides has been reported by Hartwig, Ackermann, and other groups.\textsuperscript{3} The synthesis via a direct oxidative coupling method of \textit{N}-arylamides has been reported by Kundig and Taylor.\textsuperscript{4} Bolm and co-workers used a nucleophilic aromatic substitution (S\text{\textit{N}}Ar) pathway using \textit{N}-(ortho-haloaryl)amides.\textsuperscript{5} Various radical-triggered cyclizations of \textit{N}-arylacrylamides have also been reported.\textsuperscript{1,6} In addition, palladium-catalyzed arylation of oxindoles has been reported by Sammakia and co-workers and Buchwald and co-workers.\textsuperscript{7b,c} The Friedel–Crafts type arylation of 3-hydroxyoxindoles or diarylations of isatins has been reported.\textsuperscript{8}

Many 3,3-diaryl-2-oxindoles showed interesting biological activities such as laxatives,\textsuperscript{20} antioxidant,\textsuperscript{21} and anticancer activity,\textsuperscript{22} as shown in Figure 1. Although numerous 3,3-disubstituted oxindoles have been synthesized as noted above, the synthesis of 3,3-diaryl derivatives is rather limited. Synthesis of 3,3-diaryl-2-oxindoles with same arenes could be carried out from isatin and arenes in the presence of strong acid.\textsuperscript{2a,b,8d–g} Differently substituted 3,3-diaryl-2-oxindoles were prepared generally by synthesis of 3-aryl-3-hydroxy-2-oxindoles from isatin and aryl Grignard reagents and subsequent Friedel–Crafts reaction with arenes in the presence of an acid catalyst.\textsuperscript{2a,b,8d–g} Recently, Maruoka and co-workers reported phase-transfer-catalyzed asymmetric synthesis of 3,3-diaryl-2-oxindoles from 3-aryl-2-oxindoles by S\text{\textit{N}}Ar approach.\textsuperscript{9} In these respects, an efficient synthesis of 3,3-diaryl-2-oxindoles from readily available starting material is highly required.

Very recently, we reported an efficient transition-metal-free synthesis of 1\textit{H}-indazoles from arylhydrazones with montmorillonite K-10 under \textit{O}_2 atmosphere.\textsuperscript{10} An aerobic oxidation of 2,7a-dihydro-1\textit{H}-indazole intermediate to 1\textit{H}-indazole occurred efficiently under \textit{O}_2 atmosphere in the presence of K-10. As a continuous study, we presumed that \textit{N}-methyl-2,2,\textit{N}-triphenylacetamide (1\textit{a}) could be converted to 3,3-diphenyl-2-oxindole (2\textit{a}) in the presence of montmorillonite K-10 under \textit{O}_2 atmosphere, as shown in Scheme 1.

Thus \textit{1a} was prepared from diphenylacetic acid and \textit{N}-methyl-aniline using 1,3-dicyclohexylcarbodiimide (DCC),\textsuperscript{5,9d,11} and the synthesis of \textit{2a} was examined in the presence of K-10 under \textit{O}_2 balloon atmosphere. To our delight, \textit{2a} was obtained in moderate yield (60%) in ODCB (reflux, 36 h) as shown in entry 3 (Table 1, vide infra). As compared to the reported methods of direct oxidative coupling of \textit{N}-aryl-amides\textsuperscript{8} involving the use of CuCl\textsubscript{2}/NaO\textsubscript{Bu}\textsuperscript{2a–c} or Cu(OAc)\textsubscript{2}/KO\textsubscript{Bu},\textsuperscript{4d} the synthesis of \textit{2a} does not require the use of transition metal catalyst or strong base.

The reaction mechanism for the formation of \textit{2a} could be proposed as shown in Scheme 1. The reaction of molecular oxygen and the enol form of \textit{1a}, present in the presence of acidic K-10 albeit in a small amount,\textsuperscript{12} produced hydroperoxide intermediate.
Optimization for the synthesis of 2a and hydroxyl radical. 10,13 The reaction of 2a synthesis of in ODCB in the presence of K-10 (100%, 1a reaction of hydroxyl radical and 1a intramolecular Friedel–Crafts reaction. 8h,i,15 except for entry 7.

### Table 1
Optimization for the synthesis of 2a from 1a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Conditionsa</th>
<th>2a (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>K-10 (100%, w/w), ODCB, reflux, 36 h</td>
<td>22</td>
</tr>
<tr>
<td>2</td>
<td>K-10 (200%, w/w), ODCB, reflux, 36 h</td>
<td>41</td>
</tr>
<tr>
<td>3</td>
<td>K-10 (300%, w/w), ODCB, reflux, 36 h</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>K-10 (500%, w/w), ODCB, reflux, 14 h</td>
<td>88</td>
</tr>
<tr>
<td>5</td>
<td>K-10 (500%, w/w), ODCB, 110 °C, 60 h</td>
<td>37</td>
</tr>
<tr>
<td>6</td>
<td>K-10 (500%, w/w), p-xylene, reflux, 60 h</td>
<td>24</td>
</tr>
<tr>
<td>7</td>
<td>K-10 (500%, w/w), N2 balloon, ODCB, reflux, 14 h</td>
<td>&lt;5</td>
</tr>
<tr>
<td>8</td>
<td>KSF (500%, w/w), ODCB, reflux, 14 h</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>H2SO4 (1.0 equiv), ODCB, 130 °C, 5 h</td>
<td>0f</td>
</tr>
</tbody>
</table>

a All reactions were carried out with 1a (0.5 mmol) under O2 balloon atmosphere except for entry 7.

b Isolated yield (%) and variable amounts of 1a was remained except for entry 9.

c Starting material was completely consumed.

d Severe decomposition was observed.

I. K-10-assisted homolysis of 1 produced O-centered radical II and hydroxyl radical.10,13 The reaction of 1a and 1a gave III and C-centered radical IV. Otherwise, IV could be formed via the reaction of hydroxyl radical and 1a.10 The radical IV was converted to 2a via radical cyclization and a following loss of hydrogen radical.14 α-Hydroxamido radical III could also be converted to 2a via intramolecular Friedel–Crafts reaction.8h,i,15

In order to optimize the reaction conditions, we examined the synthesis of 2a under selected conditions (Table 1). The reaction of 1a in ODCB in the presence of K-10 (100%, w/w) produced 2a in low yield (22%) for 36 h (entry 1). The yield of 2a was improved gradually by increasing the amount of K-10 (entries 2–4). An optimum yield (88%) of 2a was obtained using 500% (w/w) K-10 in refluxing ODCB for 14 h (entry 4). The use of a large excess amount of K-10 (1000%, w/w) did not increase the yield although reaction time could be shortened slightly (12 h) for the completion. The reactions at lower temperature (130 °C) and the use of p-xylene as solvent were less effective (entries 5 and 6). As expected, the reaction under N2 atmosphere showed almost no reaction (entry 7). It is interesting to note that the use of montmorillonite KSF (entry 8) and H2SO4 (entry 9) was completely ineffective.

Encouraged by the result various 2,2,2-triarylacetamides 1b–1o were prepared,11 and the syntheses of 3,3-diaryl-2-oxindoles 2b–2o were examined.16 As shown in Table 2, N-phenyl derivative 2b was obtained in good yield (89%). The reaction of N-unsubstituted amide 1c was somewhat sluggish, and 2c was obtained in moderate yield (57%) for a long time (140 h). The enol content of N-unsubstituted amide 1c would be small compared to N-substituted substrates due to the presence of amide–imidic acid tautomerization,12,20 and this would be the reason for sluggish reactivity of 1c. The nature of N-aryl moiety did not affect the reactivity, and compounds 2d–2h were synthesized in good yields (78–92%). Variation of diarylmethyl moiety also did not affect the reactivity, and the corresponding oxindoles 2i–2k were obtained in good yields (80–91%). Spirooxindole derivative 2l could also be synthesized in good yield (84%). However, the reaction of 1m gave 2m in very low yield (14%) while the reaction of 1n failed completely, presumably due to the steric hindrance. In addition, the pyridine derivative 1o also failed to produce 2o presumably due to preferential acid–base interaction between the pyridine moiety of 1o and K-10.

The reaction of N-benzyl derivative 1p showed a somewhat different reaction pathway under the standard condition, as shown in Scheme 2. N-Debenzylation proceeds to afford 1c in moderate yield (47%) along with a low yield of oxindole 2c (4%). It is interesting to note that an appreciable amount of 3 (37%) was formed presumably via C–N bond cleavage and recombination to the ortho-position of aniline moiety.9e,17

The reaction of N-allyl derivative 1q produced 2-azacyclopenta [a]inden-3-one derivative 4 (21%), N-deallylation amide 1c (17%), and many intractable side products, as shown in Scheme 3. Compound 4 could be formed via radical formation at the benzylic position and a cascade cyclization process, as observed by Li and co-workers in 5-exo-trig cyclization of 1,6-dienes with alkyl chlorides.18 Unwanted N-deallylation to 1c might occur through the migration of double bond to enamine intermediate and the cleavage by moisture under acidic reaction conditions.19

![Scheme 1. Proposed mechanism for the conversion of 1a to 2a.](image-url)
In summary, various 3,3-diaryl-2-oxindoles have been synthesized in good yields from 2,2,N-triarylacetamides in the presence of montmorillonite K-10 in 1,2-dichlorobenzene under O₂ balloon atmosphere. The reaction might proceed via a radical mechanism of the benzylic hydroperoxide intermediate. N-Benzyl and N-allyl derivatives showed somewhat different reaction pathways. In addition, the reaction conditions were found to be effective only for the synthesis of 3,3-diaryl-2-oxindoles.20

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data for the compounds 2a–2m, 3, and 4) associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.01.024.

References and notes


Actually, the reaction of 1a in the presence of tert-butylperoxy benzene (TBPB, 3.0 equiv) in ODCB (130 °C) for 30 h under O2 balloon atmosphere, a modified reaction condition of Duan,
afforded 2a in 78% yield presumably via C-centered radical IV.


Typical experimental procedure for the synthesis of 2a: A mixture of 1a (151 mg, 0.5 mmol) and montmorillonite K-10 (755 mg, 500x w/w) in ODCB (2.0 mL) was heated to reflux for 14 h. The reaction mixture was filtered through a pad of Celite and washed thoroughly with CH2Cl2. After removal of the volatiles and column chromatographic purification process (hexane/EtOAc, 1:10) 2a was obtained as a white solid, 132 mg (88%). Other compounds were prepared similarly, and the selected spectrophotometric data of 2d and 2f are as follows. Compound 2d: 91% white solid, mp 147–149 °C; IR (KBr) 1719, 1489, 1338 cm⁻¹; 1H NMR (CDCl3, 300 MHz) δ 3.30 (s, 3H), 5.87 (d, J = 8.4 Hz, 1H), 7.21–7.28 (m, 5H), 7.29–7.37 (m, 4H); 13C NMR (CDCl3, 75 MHz) δ 26.77, 62.62, 109.44, 126.40, 127.54, 127.89, 128.13, 128.33, 134.43, 141.18, 141.63, 177.08; ESI-MS m/z 334 [M+H]+, 336 [M+H+2]+. Anal. Calcd for C22H25CINO: C, 75.56; H, 4.83; N, 4.20. Found: C, 75.73; H, 4.91; N, 4.04.

Compound 2f: 92% white solid, mp 140–142 °C; IR (KBr) 1712, 1496, 1288 cm⁻¹; 1H NMR (CDCl3, 300 MHz) δ 3.25 (s, 3H), 3.73 (s, 3H), 6.81 (s, 1H), 6.82 (d, J = 8.1 Hz, 1H), 6.83 (d, J = 8.1 Hz, 1H), 7.18–7.32 (m, 10H); 13C NMR (CDCl3, 75 MHz) δ 26.73, 55.74, 62.91, 108.73, 112.33, 116.34, 127.25, 128.40 (2C), 134.13, 136.61, 141.82, 156.04, 177.19; ESI-MS m/z 330 [M+H]+. Anal. Calcd for C27H25N2O2: C, 82.20; H, 5.81; N, 4.25. Found: C, 82.03; H, 5.98; N, 4.17.


For similar cascade C–C bond formation, see: Liu, Y.; Zhang, J.-L.; Song, R.-J.; Li, J.-H. Eur. J. Org. Chem. 2014, 1177. The stereochemistry of 4 was confirmed by NOE experiment, see Supplementary data.


As a failed examples, the reactions of N-methyl-2,2-diphenylpropanamide (1r) and N-methyl-phenylisobutylamide (1s) under the optimized reaction conditions were ineffective. Most of starting material was remained in the reaction.