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Transition metal and base-free synthesis of 3,3-diaryl-2-oxindoles from 2,2,*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,*N*-triarylacetamides in the presence of montmorillonite K-10 in 1,2-dichlorobenzene under O_2 balloon atmosphere.

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

Many 3,3-diaryl-2-oxindoles showed interesting biological activities such as laxatives,[2h] antioxidant,[2f] and anticancer activity,[2b–e,g] 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.[2a,b,8a–c] 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.[2d,e,g,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_NAr approach.[9l] 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*H*-indazoles from arylhydrazones with montmorillonite K-10 under O_2 atmosphere.[10] An aerobic oxidation of 2,7a-dihydro-1*H*-indazole intermediate to 1*H*-indazole occurred efficiently under O_2 atmosphere in the presence of K-10. As a continuous study, we presumed that *N*-methyl-2,2,*N*-triphenylacetamide (**1a**) could be converted to 3,3-diphenyl-2-oxindole **2a** in the presence of montmorillonite K-10 under O_2 atmosphere, as shown in Scheme 1.

Thus **1a** was prepared from diphenylacetic acid and *N*-methylaniline using 1,3-dicyclohexylcarbodiimide (DCC),[5,9d,11] and the synthesis of **2a** was examined in the presence of K-10 in ODCB under O_2 balloon atmosphere. To our delight, **2a** was obtained in moderate yield (60%) in the presence of K-10 (300%, *w*/*w*) 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 *N*-arylamides[4] involving the use of $CuCl_2$/NaO^{t}Bu[4a–c] or $Cu(OAc)_2$/KO^{t}Bu,[4d] the synthesis of **2a** does not require the use of transition metal catalyst or strong base.

The reaction mechanism for the formation of **2a** could be proposed as shown in Scheme 1. The reaction of molecular oxygen and the enol form of **1a**, present in the presence of acidic K-10 albeit in a small amount,[12] produced hydroperoxide intermediate

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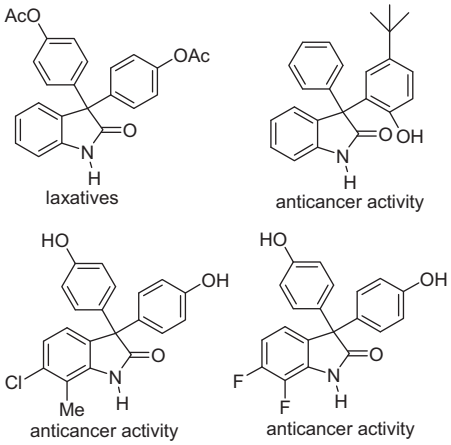


Figure 1. Biologically active 3,3-diaryl-2-oxindoles.

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

Entry	Conditions[a]	**2a**[b] (%)
1	K-10 (100%, *w*/*w*), ODCB, reflux, 36 h	22
2	K-10 (200%, *w*/*w*), ODCB, reflux, 36 h	41
3	K-10 (300%, *w*/*w*), ODCB, reflux, 36 h	60
4	K-10 (500%, *w*/*w*), ODCB, reflux, 14 h	88[c]
5	K-10 (500%, *w*/*w*), ODCB, 130 °C, 60 h	37
6	K-10 (500%, *w*/*w*), *p*-xylene, reflux, 60 h	24
7	K-10 (500%, *w*/*w*), N_2 balloon, ODCB, reflux, 14 h	<5
8	KSF (500%, *w*/*w*), ODCB, reflux, 14 h	0
9	H_2SO_4 (1.0 equiv), ODCB, 130 °C, 5 h	0[d]

[a] All reactions were carried out with **1a** (0.5 mmol) under O_2 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.

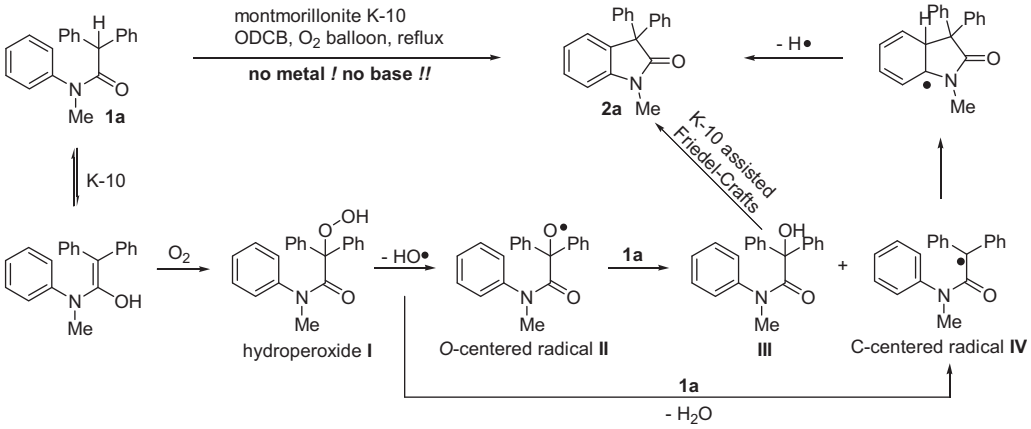
I. K-10-assisted homolysis of **I** produced *O*-centered radical **II** and hydroxyl radical.[10,13] The reaction of **II** and **1a** gave **III** and C-centered radical **IV**. Otherwise, **IV** could be formed via the reaction of hydroxyl radical and **1a**.[10] The radical **IV** was converted to **2a** via radical cyclization and a following loss of hydrogen radical.[14] α-Hydroxyamide **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 N_2 atmosphere showed almost no reaction (entry 7). It is interesting to note that the use of montmorillonite KSF (entry 8) and H_2SO_4 (entry 9) was completely ineffective.

Encouraged by the result various 2,2,*N*-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,[12b] 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.

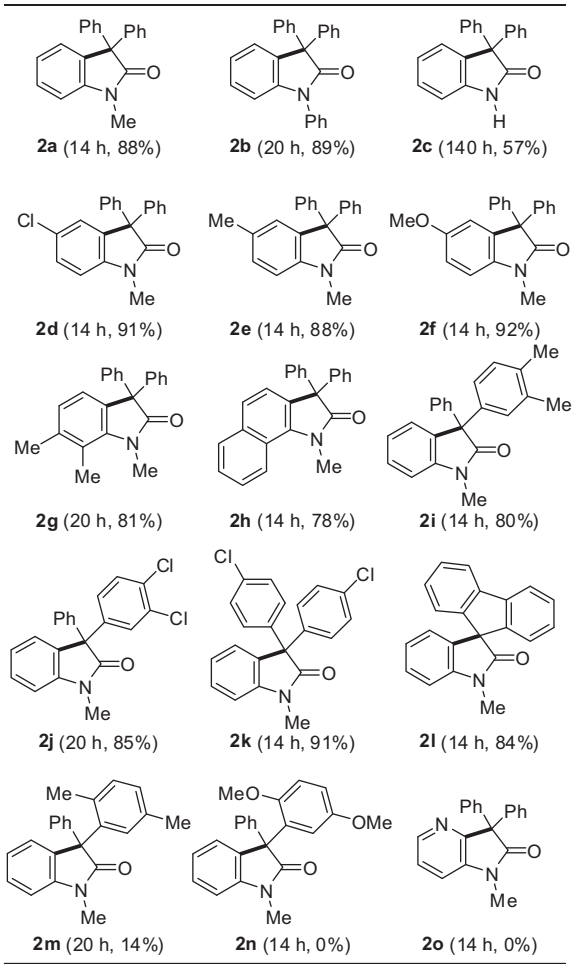
The reaction of *N*-benzyl derivative **1p** showed a somewhat different reaction pathway under the standard condition, as shown in Scheme 2. *N*-Debenzylation proceeds to afford **1c** in moderate yield (47%) along with a low yield of oxindole **2c** (4%). It is interesting to note that an appreciable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

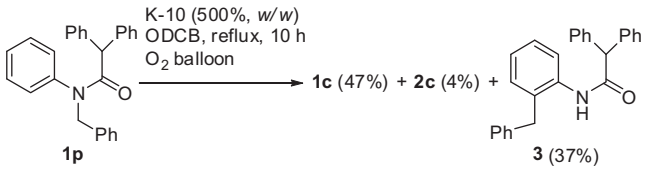


Scheme 1. Proposed mechanism for the conversion of **1a** to **2a**.

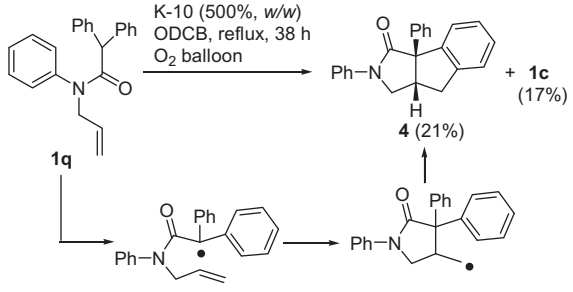
Table 2
Synthesis of 3,3-diaryl-2-oxindoles[a]



[a] Conditions: substrate **1a–o** (0.5 mmol), montmorillonite K-10 (500%, *w*/*w*), ODCB, reflux, O_2 balloon, given time.



Scheme 2. The reaction of *N*-benzyl derivative **1p**.



Scheme 3. The reaction of *N*-allyl derivative **1q**.

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 O_2 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]

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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.

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16. *Typical experimental procedure for the synthesis of 2a:* A mixture of **1a** (151 mg, 0.5 mmol) and montmorillonite K-10 (755 mg, 500% *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 CH_2Cl_2. After removal of the volatiles and column chromatographic purification process (hexanes/Et_2O, 10:1) **2a** was obtained as a white solid, 132 mg (88%). Other compounds were prepared similarly, and the selected spectroscopic data of **2d**, **2f** and **2h** are as follows.
Compound **2d**: 91%; white solid, mp 147–149 °C; IR (KBr) 1719, 1489, 1338 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.30 (s, 3H), 6.87 (d, J = 8.4 Hz, 1H), 7.21–7.28 (m, 5H), 7.29–7.37 (m, 7H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.77, 62.62, 109.44, 126.40, 127.54, 128.17, 128.29, 128.33, 128.56, 134.43, 141.18, 141.63, 177.08; ESIMS *m*/*z* 334 [M^++H], 336 [M^++H+2]. Anal. Calcd for $C_{21}H_{16}ClNO$: 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 ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.73, 55.74, 62.91, 108.73, 112.33, 113.64, 127.25, 128.40 (2C), 134.13, 136.61, 141.82, 156.04, 177.19; ESIMS *m*/*z* 330 [M^++H]. Anal. Calcd for $C_{22}H_{19}NO_2$: C, 80.22; H, 5.81; N, 4.25. Found: C, 80.13; H, 5.98; N, 4.17.
Compound **2h**: 78%; white solid, mp 156–158 °C; IR (KBr) 1711, 1493, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.92 (s, 3H), 7.22–7.34 (m, 10H), 7.38 (d, J = 8.4 Hz, 1H), 7.44–7.55 (m, 2H), 7.60 (d, J = 8.4 Hz, 1H), 7.84–7.91 (m, 1H), 8.46–8.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 31.22, 62.49, 121.38, 121.73, 123.20, 123.37, 125.75, 125.97, 127.37, 128.45, 128.56, 128.68, 129.42, 134.52, 138.07, 141.78, 179.32; ESIMS *m*/*z* 350 [M^++H]. Anal. Calcd for $C_{25}H_{19}NO$: C, 85.93; H, 5.48; N, 4.01. Found: C, 85.87; H, 5.67; N, 4.16.
17. For similar debenzylation and recombination process, see: (a) Hart, H.; Kosak, J. R. *J. Org. Chem.* **1962**, *27*, 116; (b) Anderson, L. L.; Arnold, J.; Bergman, R. G. *J. Am. Chem. Soc.* **2005**, *127*, 14542; (c) Sagrera, G.; Seoane, G. *Synthesis* **2009**, 4190; (d) Petchmanee, T.; Ploypradith, P.; Ruchirawat, S. *J. Org. Chem.* **2006**, *71*, 2892. The corresponding para-benzyl derivative could not be isolated in appreciable amount..
18. 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..
19. For *N*-deallylation, see: (a) Gigg, R.; Conant, R. *J. Carbohydr. Chem.* **1983**, *1*, 331; (b) Escoubet, S.; Gastaldi, S.; Timokhin, V. I.; Bertrand, M. P.; Siri, D. *J. Am. Chem. Soc.* **2004**, *126*, 12343; (c) Kajihara, K.; Arisawa, M.; Shuto, S. *J. Org. Chem.* **2008**, *73*, 9494.
20. As failed examples, the reactions of *N*-methyl-2,*N*-diphenylpropionamide (**1r**) and *N*-methyl-*N*-phenylisobutyramide (**1s**) under the optimized reaction conditions were ineffective. Most of starting material was remained in the reaction.