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KO^{t}Bu-Mediated, Three-Component Coupling Reaction of Indoles, [60]Fullerene, and Haloalkanes: One-Pot, Transition-Metal-Free Synthesis of Various 1,4-(3-Indole)(organo)[60]fullerenes

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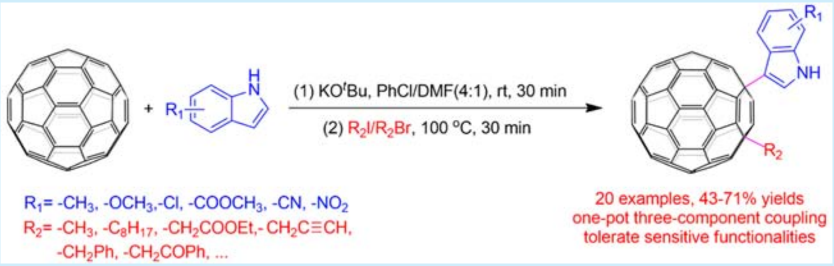
Supporting Information



ABSTRACT: The KO^{t}Bu-mediated three-component coupling reaction of indoles, [60]fullerene, and haloalkane has been developed as a practical and efficient protocol for the one-pot synthesis of various 1,4-(3-indole)(organo)[60]fullerenes. The reaction exhibits high regioselectivity at the 3-position of indoles and the 1,4-position on the [60]fullerene core. Furthermore, this methodology features excellent functional group tolerance, such as chloro, ester, cyano, and nitro on indole.

The 1,4-[60]fullerene bisadducts bearing two organic groups in a 1,4-relative regiochemistry on the fullerene core have been studied extensively and reported as excellent n-type acceptor materials for high-performance organic photovoltaics.[1−4] The two different organic addends of the unsymmetrical 1,4-fullerene adducts produce an increased absorption in the visible light region,[1] a higher LUMO energy level compared with the 1,2-adducts,[1−4] and an easy modification of materials' solubility in a variety of solvents.[1−4] Motivated by the special properties of 1,4-adducts, a number of methods have been developed for synthesizing various 1,4-fullerene derivatives.[5] The indole ring system represents a key structural element that occurs ubiquitously in optoelectronic functional materials.[6] However, to the best of our knowledge, synthesis of 1,4-(indole)(organo)[60]fullerenes remains unknown and very challenging.

During the past two decades, metal salt mediated or catalyzed reactions have emerged as one of the most important methodologies for the synthesis of novel fullerene derivatives.[7] Recently, we have been interested in developing new fullerene functionalization methods by using potassium *tert*-butoxide (KO^{t}Bu), which was recognized as an easily prepared, low-cost, and versatile base in organic synthesis. For example, we reported a method for synthesizing various 1,2-(3-indole)(hydro)[60]fullerenes via KO^{t}Bu-mediated coupling of indoles and [60]fullerene(C_{60}).[8] Inspired by our previous work, we focused on the transition-metal-free direct selective 1,4-difunctionalization of C_{60}. Herein, we present a novel KO^{t}Bu-mediated, three-component coupling reaction of indoles, [60]fullerene(C_{60}), and haloalkanes to afford various unsymmetrical 1,4-(3-indole)(organo)[60]fullerenes.

At the outset, the readily available indole (**1a**) and benzyl bromide (**2a**) were chosen as the model substrates. On the basis of our previous work,[8] we commenced our study by examining the reaction of representative indole **1a** (1 equiv) with C_{60} (0.05 mmol) in the presence of KO^{t}Bu (1.2 equiv) in chlorobenzene (PhCl)/DMSO(4:1). After the mixture was stirred for 30 min, the benzyl bromide (2 equiv) was added to the reaction system and stirred for other 30 min at room temperature (Table 1, entry 1), yet the desired product **3aa** could not be obtained. To our delight, raising the reaction temperature to 100 °C in the second step of the reaction led to an obvious increase in the yield of **3aa** (trace to 16%, Table 1, entry 2 vs 4). Further condition optimization showed the molar ratio of the reactants plays a key role in achieving high efficiency formation of product **3aa**. Increasing the amount of KO^{t}Bu from 1.2 to 2 equiv led to an increase in the yield of **3aa** to 21% (Table 1, entry 5), while increasing the amount of indole to 2 equiv led to a dramatic improvement of product yield to 62% (Table 1, entry 7). A notable cosolvent effect was observed on this present reaction. It was found that the absence of a polar cosolvent under other identical conditions did not produce any **3aa** (Table 1, entry 8).

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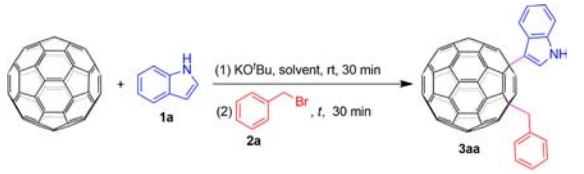
Table 1. Optimization of Reaction Conditions[a]



entry	molar ratio[b]	solvent (v/v)	temp[c] (°C)	yield[d] (%)
1	1:1:1.2:2	PhCl/DMSO (4:1)	rt	NR
2	1:1:1.2:2	PhCl/DMSO (4:1)	50	trace
3	1:1:1.2:2	PhCl/DMSO (4:1)	80	10 (71)
4	1:1:1.2:2	PhCl/DMSO (4:1)	100	16 (58)
5	1:1:2:2	PhCl/DMSO (4:1)	100	21 (55)
6	1:1.5:2:2	PhCl/DMSO (4:1)	100	54 (66)
7	1:2:2:2	PhCl/DMSO (4:1)	100	62 (62)
8	1:2:2:2	PhCl	100	NR
9	1:2:2:2	PhCl/DMF (4:1)	100	67 (67)
10	1:2:2:2	PhCl/CH_3CN (4:1)	100	NR
11	1:2:2:2	PhCl/DME (4:1)	100	NR
12	1:2:2:2	PhCl/1,4-dioxane (4:1)	100	NR
13	1:2:2:2	PhCl/$CHCl_3$ (4:1)	100	NR

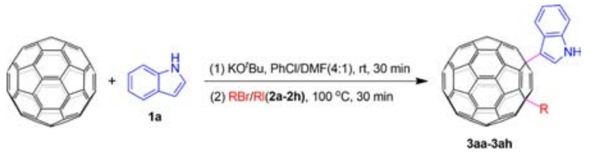
[a]The reactions were carried out with C_{60}/indole/KOᵗBu in a designated molar ratio in Schlenk tubes under Ar atmosphere for 30 min. Benzyl bromide was added, and the mixture was stirred for another 30 min. The mixture was cooled to room temperature, and then 20 mL of carbon disulfide was added. The resulting dark-yellow solution was washed with water and then evaporated in vacuo. The residue was separated on a silica gel column with carbon disulfide as the eluent to give **3aa**. [b]Molar ratio refers to C_{60}/indole/KOᵗBu/benzyl bromide. [c]Oil temperature. [d]Isolated yield by column chromatography. Values in parentheses were based on consumed C_{60}.

Various cosolvents were screened to optimize the reaction conditions, and the representative results are summarized in Table 1 (entries 8−13), proving the cosolvent DMF was the most efficient one, promoting the yield of **3aa** to 67% (Table 1, entry 9). Other cosolvents, such as CH_3CN, DME, 1,4-dioxane, and chloroform, display no influence in facilitating the reaction (Table 1, entries 10−13). The reaction did not provide any product **3aa** under air, leading us to assume that the oxygen may oxidize the fullerene anion intermediate and the moisture in air will also quench the base.[8]

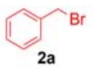
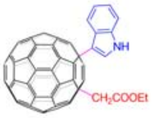
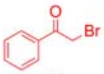
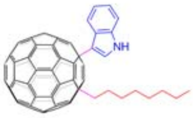
With the optimized reaction conditions in hand, the substrate scope was investigated by employing different haloalkanes. As shown in Table 2, a variety of haloalkanes reacted efficiently with indoles and C_{60} to afford the desired products in good yields. Reactions of various bromoalkanes such as benzyl bromide (**2a**), propargyl bromide (**2b**), ethyl bromoacetate (**2c**), and 2-bromoacetophenone (**2d**) proceeded efficiently and furnished the desired products **3aa**−**ad** in 55−71% yields (Table 2, entries 1−4). Iodoalkanes were also successfully applied in this reaction, providing **3ae**−**af** in 48−62% yields, although larger amounts of haloalkanes and higher reaction temperatures were required (Table 2, entries 5−8). It is important to note that all of the reactions are regioselective, giving products substituted at the 3-position of the indoles. Additionally, the N−H bonds on the indoles were easily recovered by washing with water, thus realizing the efficient three-component coupling reaction of free (N−H) indoles, C_{60}, and haloalkanes.

Having demonstrated the success of the reaction with a broad range of haloalkanes, we next assessed the scope of indoles. As shown in Scheme 1, a variety of indoles reacted efficiently with C_{60} and haloalkanes to afford the desired products in good yields.

Table 2. KOᵗBu-Mediated Three-Component Coupling Reaction of Indole, C_{60}, and Haloalkanes[a]

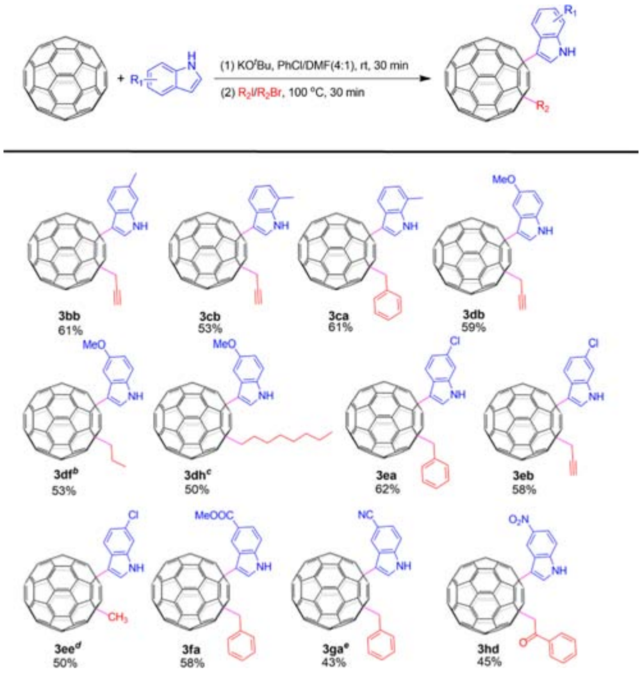


3aa-3ah

entry	substrate **2**	product **3**	yield[b](%)
1	 **2a**	 **3aa**	67
2	 **2b**	 **3ab**	60
3	$BrCH_2COOEt$ **2c**	 **3ac**	71
4	 **2d**	 **3ad**	55
5[c]	CH_3I **2e**	 **3ae**	48
6[d]	 **2f**	 **3af**	62
7[e]	 **2g**	 **3ag**	57
8[f]	 **2h**	 **3ah**	54

[a]Unless otherwise specified, all of the reactions were carried out with C_{60} (0.05 mmol), **1a** (0.10 mmol, 2.0 equiv), KOᵗBu (0.10 mmol, 2.0 equiv), and haloalkane **2** (0.10 mmol, 2.0 equiv) in a mixture of PhCl (8 mL) and DMF (2 mL) in Schlenk tubes under Ar atmosphere for the indicated time. The mixture was cooled to room temperature, and then 20 mL of carbon disulfide was added. The resulting dark-yellow solution was washed with water and evaporated in vacuo followed by separation on a silica gel column. [b]Isolated yield by column chromatography. [c]The reaction was carried out with methyl iodide (**2e**) (0.25 mmol, 5 equiv). [d]To the reaction mixture was added 1-iodopropane (**2f**) (0.20 mmol, 4 equiv) followed by stirring at 120 °C for 30 min. [e]To the reaction mixture was added 1-iodo-2-methylpropane (**2g**) (0.20 mmol, 4 equiv) followed by stirring at 150 °C for 60 min. [f]To the reaction mixture was added 1-iodooctane (**2h**) (0.20 mmol, 4 equiv) followed by stirring at 150 °C for 15 h.

Scheme 1. Synthesis of 1,4-Fulleroindoles[a]



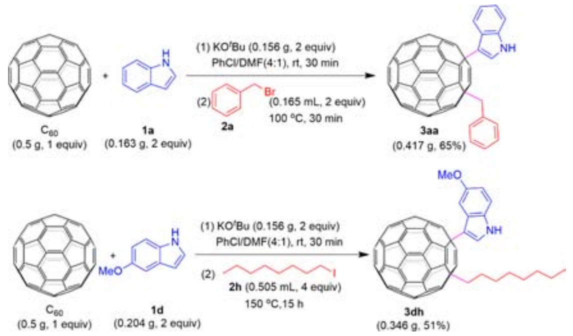
[a] Unless otherwise specified, the reactions were carried out with C_{60} (0.05 mmol), indole **1** (0.10 mmol, 2.0 equiv), KO^{t}Bu (0.10 mmol, 2.0 equiv), and haloalkane **2** (0.10 mmol, 2.0 equiv) in a mixture of PhCl (8 mL) and DMF (2 mL) in Schlenk tubes under Ar atmosphere for indicated time. The mixture was cooled to room temperature, and then 20 mL of carbon disulfide was added. The resulting dark-yellow solution was washed with water and evaporated in vacuo followed by separation on a silica gel column. [b] To the reaction mixture was added 1-iodopropane (**2f**) (0.20 mmol, 4 equiv) followed by stirring at 120 °C for 60 min. [c] To the reaction mixture was added 1-iodooctane (**2h**) (0.20 mmol, 4 equiv) followed by stirring at 150 °C for 15h. [d] The reaction was carried out with methyl iodide (**2e**) (0.25 mmol, 5 equiv). [e] The reaction was stirred at 140 °C for 30 min.

The substrates having an electron-donating methyl group at the 6- or 7-position of indole afforded the corresponding products **3bb−ca** in 53%−61% yields. Indoles with a strong electron-donating methoxy group at the 5-position exhibited slightly lower reactivity to afford the corresponding products **3db−dh** in 50−59% yields. Withdrawing halogen groups such as chloro at the 6-position of indole were also compatible with the reaction conditions, affording the desired products **3ea−ee** in 50−62% yields. To our delight, sensitive withdrawing groups such as ester, cyano, and nitro on the indole could be tolerated under the reaction conditions and gave the expected products **3fa−hd** in 43−58% yields.

After proving the wide substrate scope tolerance, the presented method was readily amenable to scale-up (Scheme 2). The reaction of C_{60} (0.5 g, 0.694 mmol) with indole (0.163 g, 1.389 mmol) and 5-methoxyindole (0.204 g, 1.389 mmol) in the presence of KO^{t}Bu (0.156 g, 1.389 mmol) under identical conditions afforded the corresponding products **3aa** and **3dh** in 65 and 51% yield, demonstrating that the efficiency of the present method remains high at a large scale.

The structures of **3aa−hd** were unambiguously characterized by MALDI-TOF MS, ^{1}H NMR, ^{13}C NMR, FT-IR, and UV−vis spectroscopy. All of the mass spectra of these products gave the correct molecular ion peaks. The ^{1}H NMR spectra of **3aa−hd** showed all expected signals. All the fulleroindoles **3aa−ah** and **3bb−hd** are 1,4-adducts, which are supported by the peak at ca. 445 nm in their UV−vis spectra and the C_1 molecular symmetry deduced from their ^{13}C NMR spectra.

Scheme 2. Scale-up Synthesis of 3aa and 3dh



The half-wave reduction potentials of representative products along with C_{60} and PCBM have been investigated by cyclic voltammetry (CV); the results and the estimated LUMOs are summarized in Table 3. The obtained 1,4-fulleroindoles exhibited essentially similar CV behaviors and showed two quasi-reversible redox processes under our conditions. It should be noted that the first reduction potentials of the 1,4-fulleroindoles were generally shifted negatively by adding stronger electron-donating groups. For instance, one *n*-propyl group on the 1,4-fulleroindoles reduces the first reduction potential from −1.157 V (**3ae**, a methyl group substituted 1,4-fulleroindole) to −1.162 V (**3af**), whereas one *n*-octyl group is decreased to −1.168 V (**3ah**). Furthermore, one methoxy group on the indole ring also steadily decreases the first reduction potential from −1.168 V (**3ah**) to −1.179 V (**3dh**). These 1,4-fulleroindoles possess higher LUMO energy levels than that of

Table 3. Reduction Potentials and LUMO Levels for 1,4-(3-Indolyl)(organo)[60]fullerenes[a]

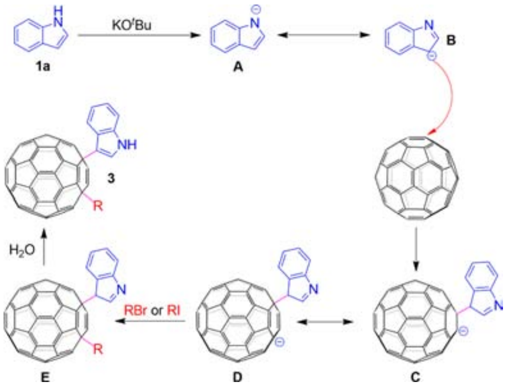
compd	E_1	E_2	LUMO level[b] (eV)
C_{60}	−1.078	−1.463	−3.722
PCBM	−1.158	−1.537	−3.642
3aa	−1.170	−1.615	−3.630
3ab	−1.107	−1.584	−3.693
3ad	−1.135	−1.566	−3.665
3ae	**−1.157**	**−1.609**	**−3.643**
3af	**−1.162**	**−1.556**	**−3.638**
3ag	−1.178	−1.600	−3.622
3ah	**−1.168**	**−1.582**	**-3.632**
3df	−1.165	−1.607	−3.635
3dh	**−1.179**	**−1.589**	**−3.621**
3ea	−1.134	−1.565	−3.666
3eb	−1.100	−1.597	−3.700
3ee	−1.137	−1.580	−3.663
3fa	−1.151	−1.580	−3.649

[a] Versus ferrocene/ferrocenium. Experimental conditions: 1 mM of compound and 0.1 M of *n*-Bu_4NClO_4 in anhydrous *o*-dichlorobenzene; reference electrode: SCE; working electrode: Pt; auxiliary electrode: Pt wire; scanning rate: 50 mV·s^{-1}. [b] Estimated using the following equation:[9] LUMO level = $-(4.8 + E_1)$ eV.

PCBM and may have potential application as acceptors in organic photovoltaic devices.

On the basis of the above observed experimental results and our previous research on KO^{t}Bu-mediated coupling reaction of indoles and C$_{60}$,[8] a proposed mechanism is illustrated in Scheme 3. Initially, the first step, which leads to fulleroindole monoanion **C**, is the same as previously proposed.[8] 1,2-Fulleroindole monoanion **C** can form 1,4-fulleroindole monoanion **D** via resonance. Because of steric hindrance, further nucleophilic attack of **D** to haloalkanes would lead to 1,4-di(organo)-fulleroindole **E**. Compound **E** may easily convert into the desired product **3** by a proton-transfer process from water.

Scheme 3. Proposed Reaction Mechanism



In conclusion, transition-metal-free, three-component coupling reaction of indoles, C$_{60}$, and haloalkanes mediated by inexpensive KO^{t}Bu has been developed as a practical, convenient method for the one-pot effective synthesis of various 1,4-(3-indole)(organo)[60]fullerenes. The reaction exhibits high regioselectivity at the 3-position of the indoles and the 1,4-position on the [60]fullerene core. Furthermore, this methodology features excellent functional group tolerance, such as chloro, ester, cyano, and nitro on indole.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00067.

> Detailed experimental procedures and characterization data, ^{1}H NMR, ^{13}C NMR, and UV−vis spectra of **3aa**−**3hd**, and CV of representative products (PDF)

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Notes

The authors declare no competing financial interest.

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