Transition-Metal-Free Aerobic Oxidative Cross-Coupling of Indoles with Arylidenemalononitriles

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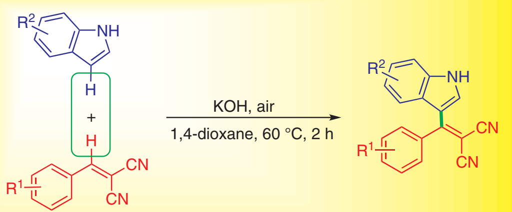

- No transition-metal catalyst
- Air as an oxidant
- Mild condition
- High atom economy
- 22 examples
- Up to 82% yield

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Abstract An efficient method for the direct construction of C(sp^2)–C(sp^2) bonds by aerobic oxidative cross-coupling of indoles with arylidenemalononitriles is described. Various [aryl(1*H*-indol-3-yl)methylene]malononitriles were efficiently synthesized by using air as an oxidant under mild conditions. The salient features for this protocol are no transition-metal catalysts, no organometallic reagents, high atom economy, high yield, mild conditions, and simple workup procedures.

Key words cross-coupling, indoles, arylidenemalononitriles, metal-free synthesis

In oxidative cross-coupling reactions, C–H bonds in two substrates form a new C–C bond under oxidative conditions. This is one of the most atom-economical methods for constructing a new chemical bond, and it eliminates the need for the substrate prefunctionalization steps required in conventional cross-coupling reactions.[1]

Reported methods for the formation of C(sp^2)–C(sp^2) bonds through oxidative cross-coupling generally involve two aromatic C–H nucleophiles.[2] However, the method is far from satisfactory in that transition-metal catalysts are required for the reactions and, because of possible homocoupling of C(sp^2)–H bonds, direct oxidative cross-coupling between two C(sp^2)–H bonds is challenging. In addition, no examples of oxidative cross-couplings between alkene C(sp^2)–H and heteroarene C(sp^2)–H bonds have been reported.

The indole ring system is the most widely distributed heterocycle found in nature. Functionalized indoles have a wide range of physiological activities.[3] In many synthetic methods, cross-coupling of indoles at their C3-position is an important route to functionalized indoles.[4] Although reactions of indoles with arylidenemalononitriles have been previously investigated, only Michael addition products were obtained, and no oxidative cross-coupling reactions were reported.[5]

Here, we report an aerobic oxidative cross-coupling between the C(sp^2)–H bond of arylidenemalononitriles and the C(sp^2)–H of indoles at the C3-position under transition-metal-free conditions using air as an oxidant to give indole-functionalized arylidenemalononitriles.

Initially, we selected the reaction of benzylidenemalononitrile (**1a**) with unsubstituted indole under open-air conditions as a model reaction to determine the optimal conditions. Various bases and solvents were examined for the reaction (Table 1). The reaction was first tested in MeCN at room temperature in the absence of a base, but no product was detected (Table 1, entry 1). When one equivalent of KOH was used as a base and the mixture was stirred at room temperature for two hours, [1*H*-indol-3-yl(phenyl)methylene]malononitrile (**2a**) was isolated in 34% yield (entry 2). This result implied that a cross-dehydrogenation coupling reaction between **1a** and indole had taken place smoothly. Other inorganic bases (NaOH, Cs_2CO_3, K_2CO_3, and NaOAc) were also tested, but no improvement in the yield was achieved (entries 3–6). The organic bases Et_3N, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane (DABCO), and 4-(dimethylamino)pyridine (DMAP) had no effect on the reaction (entries 7–10). However, we found that increasing the amount of KOH significantly enhanced the yield of **2a** (entry 11). In an attempt to improve the yield of **2a**, we also tested various solvents for the reaction. Product **2a** was obtained in trace or low yields in THF, DCE, toluene, EtOH, DMSO, and DMF (entries 12–17). However, in 1,4-dioxane the reaction gave **2a** in a moderate yield (entry 18). Raising the temperature improved the yield of **2a** markedly (entries 19 and 20), the best yield of **2a** (82%) being obtained at 60 °C (entry 20).

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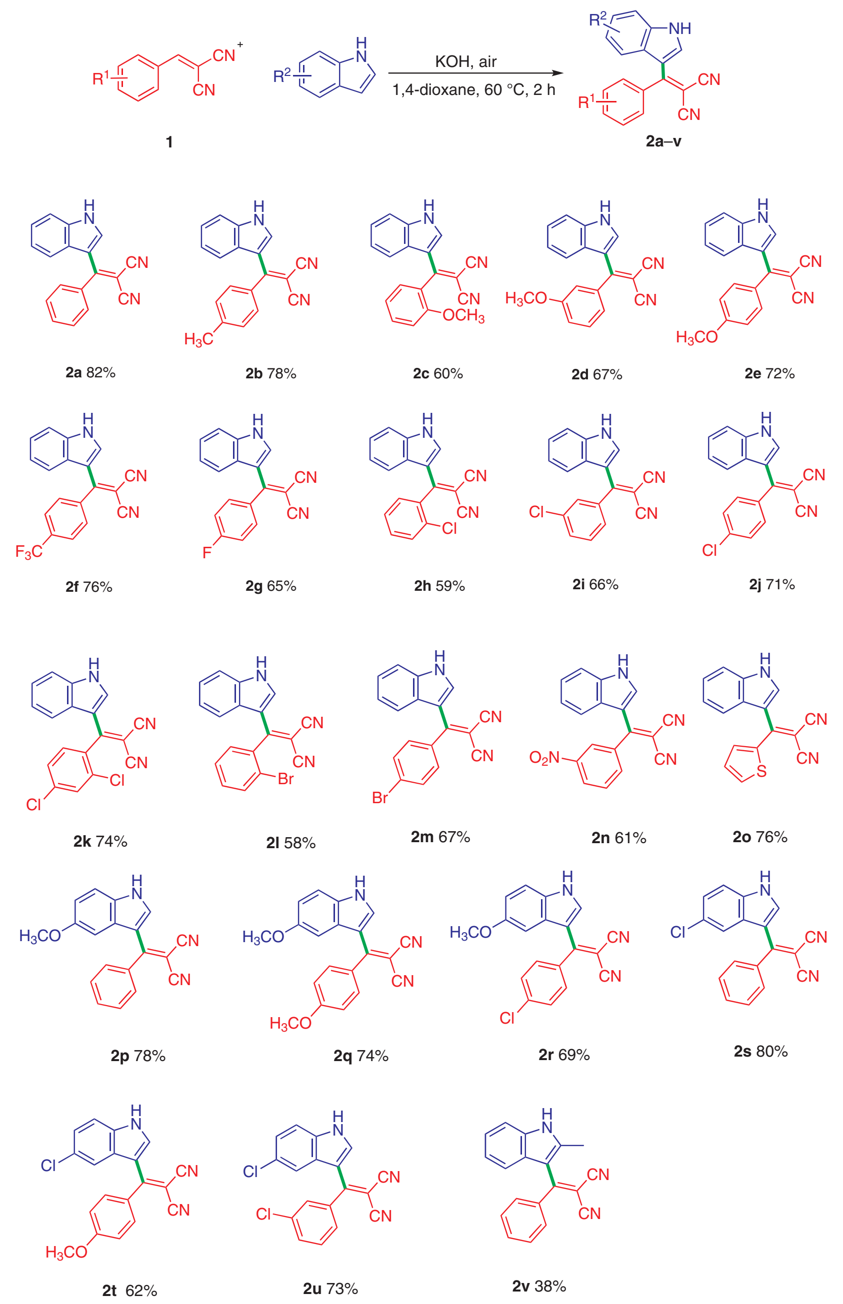
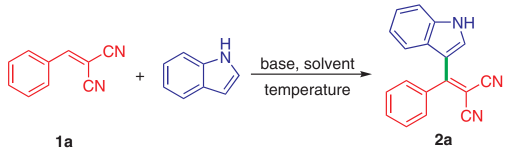
With the optimized reaction conditions in hand, we examined the scope of the formation of C(sp^2)–C(sp^2) bonds through aerobic oxidative cross-coupling of indole or substituted indoles with various arylidenemalononitriles at 60 °C in the presence of two equivalents of KOH as a base (Scheme 1).[6] We found that for typical cases, a wide range of substituents on the arylidenemalononitrile, including H, Me, MeO, CF_3, F, Cl, Br, and NO_2 groups, were tolerated (**2a**–**n**). The yield from the aerobic oxidative cross-coupling was satisfactory for both electron-donating and electron-withdrawing substituents. Due to the lower steric hindrance, the yields from *meta*- and *para*-substituted substrates (**2b**, **2d**–**2g**, **2i**, **2j**, **2m**, and **2n**) were slightly higher than those from *ortho*-substituted substrates (**2c**, **2h**, and **2l**). A substrate containing a hetaryl ring (thiophene) also gave the corresponding product **2o** in good yield. Furthermore, with



Scheme 1 Synthesis of [aryl(1*H*-indol-3-yl)methylene]malononitriles **2a**–**v**. *Reagents and conditions*: **1** (0.5 mmol), indole (0.5 mmol), KOH (1.0 mmol), 1,4-dioxane (4 mL), under air, 60 °C, 2 h.

substituted indoles (R^2 = 5-MeO, 5-Cl), the corresponding aerobic oxidative cross-coupling products **2p–u** were obtained smoothly and in good yields. However, for a methyl-substituted indole (R^2 = 2-Me), the corresponding aerobic oxidative cross-coupling product **2v** was obtained in only 38% yield, possibly because of high steric hindrance. An attempt to react *N*-methylindole was not successful.

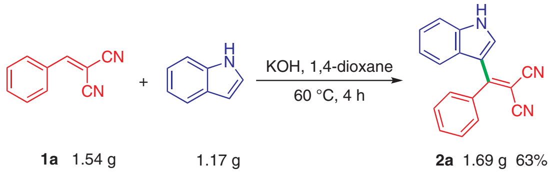
Table 1 Optimization of the Reaction Conditions[a]



Entry	Base (equiv)	Temp (°C)	Solvent	Yield[b] (%)
1	–	r.t.	MeCN	0
2	KOH (1.0)	r.t.	MeCN	34
3	NaOH (1.0)	r.t.	MeCN	25
4	Cs_2CO_3 (1.0)	r.t.	MeCN	21
5	K_2CO_3 (1.0)	r.t.	MeCN	27
6	NaOAc (1.0)	r.t.	MeCN	trace
7	Et_3N (1.0)	r.t.	MeCN	0
8	DBU (1.0)	r.t.	MeCN	0
9	DABCO (1.0)	r.t.	MeCN	0
10	DMAP (1.0)	r.t.	MeCN	0
11	KOH (2.0)	r.t.	MeCN	48
12	KOH (2.0)	r.t.	THF	0
13	KOH (2.0)	r.t.	DCE	trace
14	KOH (2.0)	r.t.	PhMe	trace
15	KOH (2.0)	r.t.	EtOH	trace
16	KOH (2.0)	r.t.	DMSO	trace
17	KOH (2.0)	r.t.	DMF	15
18	KOH (2.0)	r.t.	1,4-dioxane	59
19	KOH (2.0)	40	1,4-dioxane	65
20	KOH (2.0)	60	1,4-dioxane	82

[a] Reaction conditions: **1a** (0.5 mmol), indole (0.5 mmol), base, solvent (4 mL), open to air, 2 h.
[b] Isolated yield.

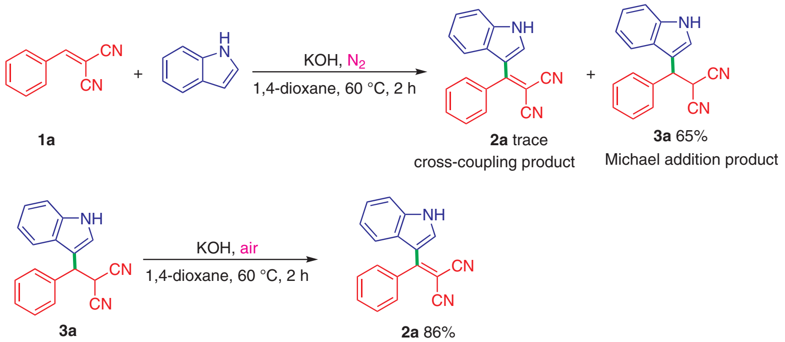
Having successfully demonstrated the generality of our protocol, we next examined the reaction of **1a** with indole on a gram scale. The reaction of 1.54 g of **1a** with 1.17 g of indole in the presence of 1.20 g of KOH in 1,4-dioxane (25 mL) under the optimized condition gave 1.69 g of **2a** in 63% isolated yield. The gram-scale reaction showed that the optimized conditions are suitable for a bulk process to a certain extent (Scheme 2).



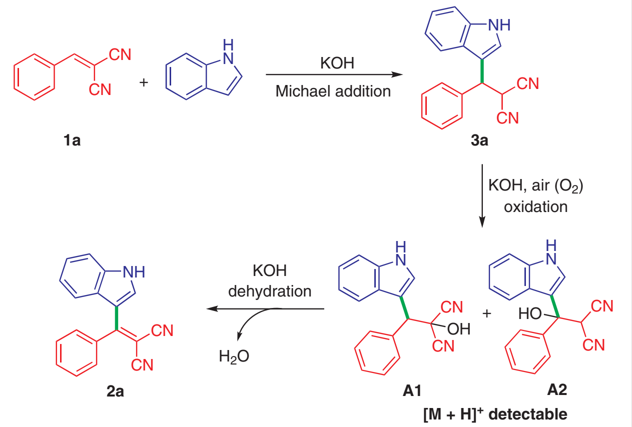
Scheme 2 Gram-scale experiment for **2a**

To investigate the reaction mechanism, we performed two control experiments (Scheme 3). When the reaction of **1a** with indole was carried out under standard conditions under an atmosphere of nitrogen instead of air, the Michael addition product **3a** was obtained in 65% yield, and only traces of the oxidative cross-coupling product **2a** were detected. Moreover, **3a** was readily converted into **2a** in high yield under the standard conditions. This implied that the Michael addition product **3a** is a possible intermediate for the reaction of **1a** with indole to produce **2a**, and that air is indispensable for the formation of **2a**.

Based on the above experiments, a plausible mechanism is proposed for the synthesis of **2a** (Scheme 4). Benzylidenemalononitrile (**1a**) reacts with indole in the presence of potassium hydroxide to give the Michael addition product **3a** initially, as isolated and characterized in the control experiments. **3a** is subsequently oxidized by oxygen in the air to give the hydroxylated intermediates **A1** and **A2**. These intermediates then undergo dehydration in the presence of potassium hydroxide to give **2a** as the final product.



Scheme 3 Control experiments



Scheme 4 Proposed mechanism for the formation of **2a**

In conclusion, we have developed a simple method for the direct construction of C(sp^2)–C(sp^2) bonds between indoles and 2-arylidenemalononitriles by using air as an oxidant under transition-metal-free conditions. This method provides an efficient and high-yielding route for the synthesis of useful 2-[aryl(1*H*-indol-3-yl)methylene]malononitriles. This new processes is characterized by a high efficiency, a short reaction time, and excellent functional-group tolerance, and it provides a practical and versatile strategy for obtaining various (indol-3-yl)methylene-functionalized malononitriles.

Funding Information

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1691532.

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(6) **[Aryl(1*H*-indol-3-yl)methylene]malononitriles 2a–v; General Procedure**
A mixture of the appropriate arylidenemalononitrile **1** (0.5 mmol), indole (0.5 mmol), and KOH (1.0 mmol) in 1,4-dioxane (4 mL) was stirred at 60 °C for 2 h. When the reaction was complete (TLC), the mixture was extracted with EtOAc (3 × 10 mL), and the extracts were washed with sat. brine (3 × 10 mL). The organic phase was dried (Na_2SO_4) and concentrated under reduced pressure, and the residue was purified by column chromatography [silica gel, PE–EtOAc (2:1)].
[1*H*-Indol-3-yl(phenyl)methylene]malononitrile (2a)
Yellow solid; yield: 110 mg (82%); mp 166–170 °C. ^{1}H NMR (600 MHz, DMSO-d_6): δ = 12.60 (s, 1 H), 8.34 (s, 1 H), 7.65 (t, *J* = 7.2 Hz, 1 H), 7.57–7.51 (m, 5 H), 7.19–7.15 (m, 1 H), 6.96–6.93 (m, 1 H), 6.38 (d, *J* = 8.1 Hz, 1 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 168.46, 137.58, 136.78, 134.99, 132.38, 130.30, 129.31, 126.13, 123.64, 122.15, 120.80, 116.75, 116.03, 113.52, 112.65, 72.09. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{18}H_{12}N_3$: 270.1026; found: 270.1023.
[(5-Methoxy-1*H*-indol-3-yl)(phenyl)methylene]malononitrile (2p)
Yellow solid; yield: 117 mg (78%); mp 231–233 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 12.56 (s, 1 H), 8.28 (s, 1 H), 7.69–7.64 (m, 1 H), 7.58 (t, *J* = 7.6 Hz, 2 H), 7.52 (dd, *J* = 8.4, 1.4 Hz, 2 H), 7.43 (d, *J* = 8.8 Hz, 1 H), 6.82 (dd, *J* = 8.9, 2.4 Hz, 1 H), 5.79 (d, *J* = 2.4 Hz, 1 H), 3.43 (s, 3 H). ^{13}C NMR (150 MHz, DMSO-d_6): δ = 168.32, 155.38, 136.90, 135.12, 132.35, 132.10, 130.17, 129.36, 126.98, 116.88, 116.18, 114.24, 113.28, 112.58, 103.37, 71.00, 55.27. HRMS (ESI): *m/z* [M + H]$^+$ calcd for $C_{19}H_{14}N_3O$: 300.1131; found: 300.1132.