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Synthesis of (*Z*)-1-benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarbonitriles via three-component reaction of 2-alkynylbenzaldehyde, malononitrile, and indole

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ABSTRACT

Three-component reaction of 2-alkynylbenzaldehyde, malononitrile, and indole under mild conditions is described, which generates the desired (*Z*)-1-benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarbonitriles in moderate to good yields. This reaction proceeds smoothly with high selectivity. The tandem condensation, nucleophilic addition, and 5-*exo*-cyclization may be involved in the process.

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As we know, the indene core is regarded as a privileged scaffold which can be found in many natural products and drug candidates with remarkable biological activities.[1] Furthermore, in the filed of materials science many applications have been demonstrated concerning about the function of indene-related compounds.[2] Therefore, new approaches continue to be appearing for the synthesis of indene-related compounds.[3–6] With an expectation for the construction of diverse indene-related compounds for our specific biological assays, the development of novel method for efficient assembly of indenes is of high demand. Recently, we reported an unprecedented route for the generation of (*Z*)-1-benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarboxylates via *t*-BuOK-promoted tandem addition–cyclization reaction of 2-(2-(alkynyl)benzylidene)malonate with indole (Scheme 1, Eq. 1).[7] This reaction worked efficiently with high selectivity. Since cyano is an important group for further functionalization, reaction of 2-benzylidenemalononitrile was tested (Scheme 1, Eq. 2). However, the reaction was complicated under the standard conditions, and only 20% isolated yield of the corresponding product was obtained. In order to find a more efficient way to generate this kind of molecules, we thus started to re-explore the possibility of this transformation.

It is well recognized that multi-component reaction is an attractive process since the strategy pushes the limits of synthetic efficiency by using more than two reactants to create novel products with an optimal number of new bonds and functionalities.[8] Since 2-benzylidenemalononitrile could be traced back to 2-alkynylbenzaldehyde and malononitrile, we considered that three-component reaction of 2-alkynylbenzaldehyde **1**, malononitrile, and indole **2** might be occurring under suitable conditions (Scheme 1, Eq. 3). Recently, 2-alkynylbenzaldehyde was discovered as a useful building block for the construction of carbo- and heterocycles.[9] We also demonstrate its utility in tandem reactions for heterocycles construction.[10] Encouraged by these results, we conceived that after condensation of 2-alkynylbenzaldehyde **1** with malononitrile, the subsequent nucleophilic addition of indole and intramolecular 5-*exo*-cyclization would occur to afford the desired product **3**.

With these considerations in mind, the initial studies were performed for the reaction of 2-alkynylbenzaldehyde **1a** (Scheme 1, Eq. 3: R^1 = H, R^2 = Ph), malononitrile, and indole **2a** (R^3 = H) in the presence of different bases and solvents. No desired product **3a** was detected when *t*-BuOK was utilized as a base in MeCN. To our delight, compound **3a** was afforded in 18% yield when Cs_2CO_3 (1.0 equiv) was used as a base replacement in the reaction. Inferior results were observed when other bases were screened. Further investigation revealed that lower yield of compound **3a** was furnished when the reaction occurred in THF, EtOH, DCE, or toluene in the presence of Cs_2CO_3. Fortunately, the yield could be increased to 49% when the solvent was changed to pyridine. The presence of Cs_2CO_3 was essential since blank experiment indicated that no reaction took place in pyridine without the addition of Cs_2CO_3. Reactions with additives (Na_2SO_4, $PdCl_2$, CuI, AgOTf, etc.) were

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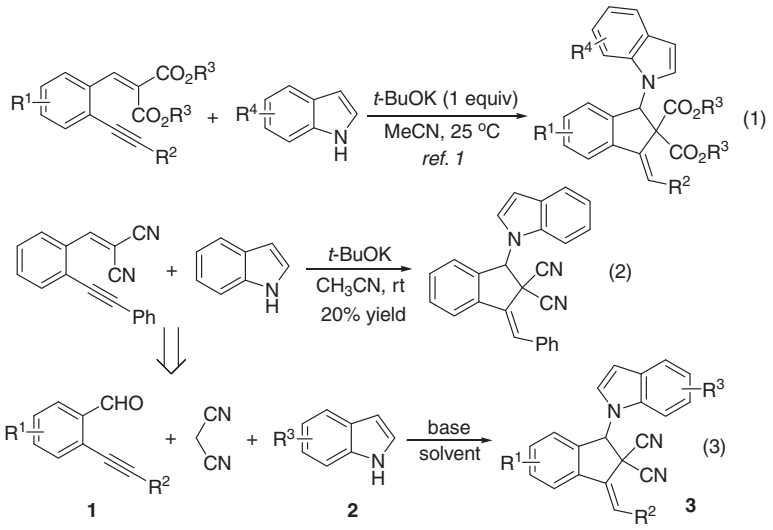
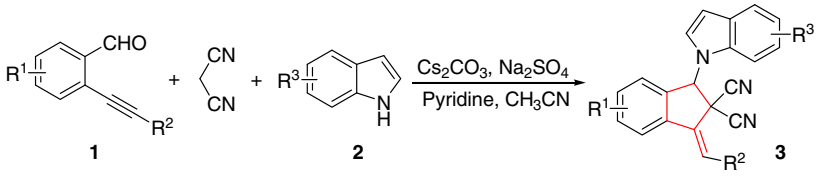


Scheme 1.

examined as well. Finally, we realized that the reaction worked most efficiently in the presence of Cs_2CO_3 and Na_2SO_4 in pyridine/MeCN (v/v 1:2) at room temperature, which generated the desired product **3a** in 66% yield.

Table 1
Three-component reaction of 2-alkynylbenzaldehyde **1**, malononitrile, and indole **2**[11]



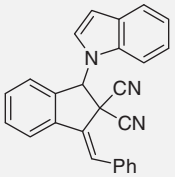
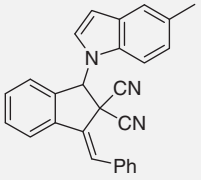
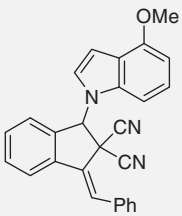
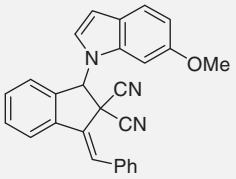
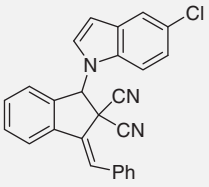
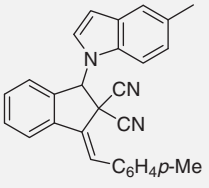
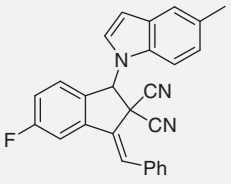
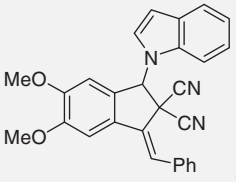
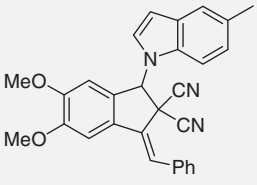
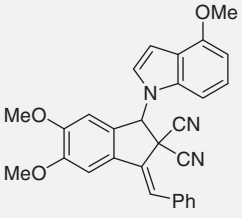
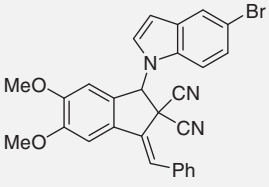
Entry	R^1, R^2	R^3	Product/yield[a]
1	H, C_6H_5 (**1a**)	H (**2a**)	 **3a**: 66%
2	H, C_6H_5 (**1a**)	5-Me (**2b**)	 **3b**: 77%
3	H, C_6H_5 (**1a**)	4-OMe (**2c**)	 **3c**: 70%
4	H, C_6H_5 (**1a**)	6-OMe (**2d**)	 **3d**: 74%

Table 1 (*continued*)

Entry	R^1, R^2	R^3	Product/yield[a]
5	H, C_6H_5 (**1a**)	5-Cl (**2e**)	 **3e**: 35%
6	H, *p*-MeC_6H_4 (**1b**)	5-Me (**2b**)	 **3f**: 40%
7	H, *n*-Bu (**1c**)	5-Me (**2b**)	—
8	H, cyclopropyl (**1d**)	5-Me (**2b**)	—
9	4-F, C_6H_5 (**1e**)	5-Me (**2b**)	 **3g**: 52%
10	4,5-$(OMe)_2$, C_6H_5 (**1f**)	H (**2a**)	 **3h**: 50%
11	4,5-$(OMe)_2$, C_6H_5 (**1f**)	5-Me (**2b**)	 **3i**: 70%
12	4,5-$(OMe)_2$, C_6H_5 (**1f**)	4-OMe (**2c**)	 **3j**: 60%
13	4,5-$(OMe)_2$, C_6H_5 (**1f**)	5-Br (**2f**)	 **3k**: 41%

[a] Isolated yield based on 2-alkynylbenzaldehyde **1**.

Based on the above results, we started to explore the scope of this three-component reaction under the preliminary optimized conditions [Cs_2CO_3 (1.0 equiv), Na_2SO_4 (2.0 equiv), pyridine/MeCN (v/v 1:2)], and the results are summarized in Table 1. From Table 1, we noticed that, for most cases, the base-promoted three-component reaction of 2-alkynylbenzaldehyde **1**, malononitrile, and indole **2** proceeded smoothly leading to the corresponding products **3** in moderate to good yields. Usually, 24–30 h were needed for completion of the reaction. As expected, the reaction of 2-alkynylbenzaldehyde **1a**, malononitrile, and 5-methylindole **2b** gave rise to the desired product **3b** in 77% yield (entry 2). Similar yield was generated when 4-methoxyindole **2c** or 6-methoxyindole **2d** was used as a partner in the reaction (entries 3 and 4). However, the yield decreased dramatically when 5-chloroindole **2e** was employed as a substrate (35% yield, entry 5). With respect to the R^2 group attached on the triple bond in substrate **1**, it seemed that the alkyl group was not suitable in this transformation. For example, compound **3f** was afforded in 40% yield when

2-alkynylbenzaldehyde **1b** was utilized as a replacement (entry 6). However, no reactions occurred when 2-alkynylbenzaldehyde **1c** or **1d** was used in the reaction of malononitrile with 5-methylindole **2b** (entries 7 and 8). Fluoro- or methoxy-substituted 2-alkynylbenzaldehydes **1e** and **1f** were examined meanwhile. It seemed that the electron effect on the aromatic backbone of the substrates was invisible, and all reactions worked well to afford the desired products in moderate to good yields (entries 9–13).

In summary, we have described a three-component reaction of 2-alkynylbenzaldehyde, malononitrile, and indole promoted by Cs_2CO_3. The reaction might proceed through tandem condensation, nucleophilic addition, and intramolecular 5-*exo*-cyclization, giving rise to the corresponding (*Z*)-1-benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarbonitriles in moderate to good yields.

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11. *General experimental procedure for the three-component reaction of 2-alkynylbenzaldehyde **1**, malononitrile, and indole **2***: malononitrile (0.4 mmol) and Na_2SO_4 (0.8 mmol, 2.0 equiv) were added to a solution of 2-alkynylbenzaldehyde (0.4 mmol, 1.0 equiv) in pyridine:CH_3CN (v/v 1:2). The mixture was then stirred at 60 °C for 4 h. Subsequently, indole (0.4 mmol, 1.0 equiv) and Cs_2CO_3 (0.4 mmol, 1.0 equiv) were added, then the reaction mixture was stirred at room temperature for 24–30 h. After the completion of reaction as indicated by TLC, the reaction was quenched with aqueous HCl (1.0 M), extracted with EtOAc (2 × 10 mL), and dried by anhydrous Na_2SO_4. Evaporation of the solvent followed by purification on silica gel provided the product **3**. Data of selected examples: (*Z*)-1-benzylidene-3-(1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarbonitrile (**3a**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.64 (d, *J* = 3.2 Hz, 1H), 6.87 (s, 1H), 6.95 (d, *J* = 3.2 Hz, 1H), 7.22–7.28 (m, 2H), 7.33–7.37 (m, 1H), 7.41 (d, *J* = 7.2 Hz, 1H), 7.45–7.49 (m, 3H), 7.54 (s, 1H), 7.60–7.61 (m, 3H), 7.68–7.72 (m, 2H), 7.77 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.1, 69.0, 104.3, 109.7, 111.7, 113.9, 121.2, 121.4, 121.5, 122.8, 124.8, 125.9, 128.8, 129.1, 129.2, 129.3, 129.4, 130.1, 131.1, 131.4, 133.2, 136.0, 137.0, 138.2; HRMS (ESI) calcd for $C_{26}H_{17}N_3Na$ (M+Na$^+$) 394.1320, found 394.1323. (*Z*)-1-Benzylidene-3-(5-methyl-1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarbonitrile (**3b**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.46 (s, 3H), 6.51 (d, *J* = 3.6 Hz, 1H), 6.80 (s, 1H), 6.87 (d, *J* = 3.2 Hz, 1H), 7.13 (d, *J* = 8.4 Hz, 1H), 7.23 (s, 1H), 7.35–7.39 (m, 1H), 7.42–7.45 (m, 4H), 7.50 (s, 1H), 7.54–7.58 (m, 4H), 7.73 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 44.3, 69.1, 104.1, 109.0, 111.7, 113.9, 121.1, 121.5, 124.3, 124.8, 126.0, 128.7, 128.9, 129.1, 129.3, 129.4, 130.5, 130.7, 131.0, 131.2, 133.1, 135.3, 136.0, 138.1; HRMS (ESI) calcd for $C_{27}H_{19}N_3Na$ (M+Na$^+$) 408.1477, found 408.1498. (*Z*)-1-Benzylidene-3-(4-methoxy-1*H*-indol-1-yl)-1*H*-indene-2,2(3*H*)-dicarbonitrile (**3c**). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3H), 6.63 (d, *J* = 7.6 Hz, 1H), 6.72 (d, *J* = 3.6 Hz, 1H), 6.81–6.82 (m, 2H), 7.24–7.32 (m, 3H), 7.37–7.40 (m, 1H), 7.44–7.50 (m, 3H), 7.53 (s, 1H), 7.58–7.60 (m, 3H), 7.75 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 44.1, 55.3, 69.2, 101.1, 101.9, 102.6, 111.6, 113.9, 119.6, 121.5, 123.3, 123.8, 126.0, 128.7, 128.8, 129.3, 129.4, 130.8, 131.1, 131.5, 133.2, 136.0, 138.1, 138.4, 153.6; HRMS (ESI) calcd for $C_{27}H_{19}N_3NaO$ (M+Na$^+$) 424.1426, found 426.1428.