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# Efficient Method for the Synthesis of Polysubstituted Benzenes by One-Pot Tandem Reaction of Vinyl Malononitriles with Nitroolefins

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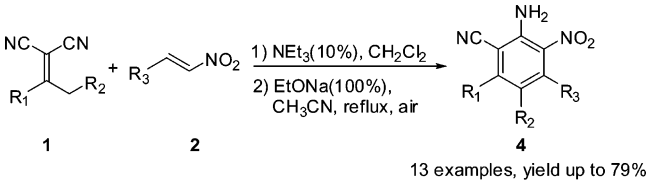


The one-pot synthesis of polysubstituted benzene derivatives was achieved via vinylogous Michael addition of vinyl malononitriles and nitroolefins as the key step and a sequential tandem reaction. A series of complex aryl compounds such as biphenyls and terphenyls can be obtained with satisfactory yields.

Polysubstituted benzenes are highly useful compounds in organic chemistry, natural product chemistry, and materials science. The regioselective preparation of polysubstituted aromatic compounds is one of the challenging problems in organic synthesis.[1] Classical approaches are based on aromatic substitution, which introduces a substituent to the given arene. A variety of synthetic methodologies based on this route has been developed including electrophilic[2] or nucleophilic substitutions,[3] coupling reactions[4] catalyzed by transition metals, and metalation−functionalization reactions.[5] However, these approaches have some drawbacks from the viewpoint of atom economy[6] or environmental concern. Conceptually different approaches that construct the aromatic backbone from acyclic precursors have received growing interest due to their short synthetic steps and the avoidance of regioisomeric problems.[7] These general features are common in the most useful benzannulation reactions such as the [3 + 2 + 1] Dotz reaction of Fisher carbene complexes,[8] alkyne-cyclobutenone [4 + 2] cyclization,[9] [4 + 2] cycloaddition of metalacyclopentadienes and alkynes,[10] transition metal catalyzed [2 + 2 + 2] and [4 + 2] cycloadditions,[11] [4 + 2] benzannulation of *o*-alkynyl benzaldehyde and alkyne,[12] [3 + 3] cyclocondensation between bielectrophiles and binucleophiles,[13] 1,6-electrocyclization reaction,[14] [5 + 1] benzannulation strategy between alkenoyl keteneacetals and nitroalkane,[15] synthesis of acetophenones and methyl benzoates via the reaction of 1,3-dinitroalkanes with 2-ene-1,4-dione or 2-ene-4-oxo ester derivatives,[16] and [4 + 2] annulation strategy from the Baylis−Hillman reaction.[17] Recently, we reported that the electron-deficient dicyanoalkenes could behave as good hydride acceptors in conjugate reduction reactions[18] and also act as versatile direct vinylogous donors in asymmetric Michael addition reactions with excellent chemo- and stereoselectivity.[19] The concept of $\gamma$-position activation according to strong electron-withdrawing groups was expressed adequately.

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**SCHEME 1. Strategy for Synthesis of Polyfunctionalized Aromatic Compounds from Ketones**

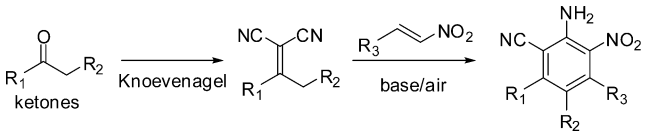
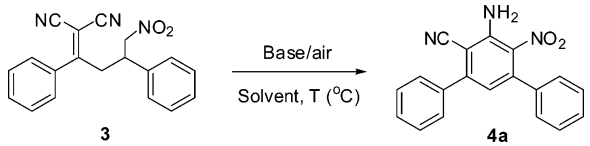



**TABLE 1. Optimization of Reaction Conditions of Aromatization Reaction[a]**




3 4a

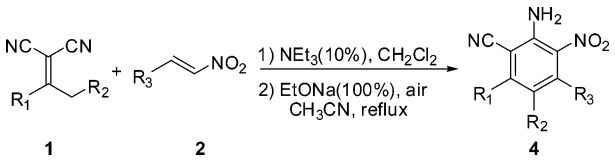
| entry | base (mol %) | solvent | *T* (°C) | *T* (h) | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | $K_2CO_3$ (50) | nitrobenzene | 120 | 20 | 70 |
| 2 | $K_2CO_3$ (100) | nitrobenzene | 120 | 2 | 72 |
| 3 | $K_2CO_3$ (50) | $CH_3CN$ | reflux | 2 | 24 |
| 4 | KOH (100) | $CH_3CN$ | reflux | 4 | 27 |
| 5 | NaH (100) | toluene | 100 | 10 | 56 |
| 6 | NaH (100) | THF | 60 | 30 | 38 |
| 7 | NaOMe (100) | $CH_2Cl_2$ | 30 | 32 | 18 |
| 8 | NaOEt (100) | $CH_2Cl_2$ | rt | 18 | 40 |
| 9 | NaOEt (100) | MeOH | 60 | 13 | 40 |
| 10 | NaOEt (100) | EtOH | 60 | 28 | 38 |
| 11 | NaOEt (100) | THF | 60 | 60 | 56 |
| 12 | NaOEt (100) | nitrobenzene | 120 | 2 | 73 |
| 13 | NaOEt (100) | DMF | 120 | 20 | *c* |
| 14 | NaOEt (100) | DMSO | 120 | 20 | *c* |
| 15 | NaOEt (100) | $CH_3CN$ | 60 | 2 | 70 |
| 16 | NaOEt (50) | $CH_3CN$ | 60 | 4 | 65 |
| 17 | NaOEt (100) | $CH_3CN$ | reflux | 2 | 76 |
| 18 | NaOEt (100) | $CH_3CN$ | reflux | 2 | 65[d] |
| 19 | NaOEt (100) | $CH_3CN$ | reflux | 2 | 0[e] |

[a] All reactions were performed at 0.1 mmol scales and operated under air; for the detailed procedure, see Supporting Information. [b] Isolated yields. [c] No reaction. [d] Reaction was performed under oxygen. [e] Reaction was performed under argon.

In this paper, we found that vinyl malononitriles, obtained from ketones via a Knoevenagel reaction, can react with nitroolefins in the presence of a base and that polysubstituted benzenes are obtained under air via a one-pot tandem addition process (Scheme 1). This introduces a new strategy for the synthesis of polyfunctionalized aromatic compounds using ketones as the starting materials.

In our initial study, we found that the vinylogous Michael addition product **3**[19a] could undergo an intermolecular nucleophilic addition and that polysubstituted benzene **4a** was obtained under air in the presence of a base. The primary inspiring results draw our attention to a new construction method of polysubstituted benzenes. First, we investigated the condition of the aromatization reaction. The aromatization of vinylogous Michael addition product **3** was selected as a model reaction. All reactions were performed under air. The results are shown in Table 1. The base has an obvious effect on this reaction. Among the selected bases, commercially available NaOEt was proven to be the most promising one (Table 1, entries 12 and 15−17). Several solvents have been investigated (Table 1, entries 8−15), and $CH_3CN$ was selected as the best one (Table 1, entries 15−17), although nitrobenzene also showed comparable results (Table 1, entry 12). It is surprising that no reaction was found when DMSO or DMF was used as a solvent (Table 1, entries 13 and 14). Temperature and base loading have an obvious influence on reaction yield. The best result (76% yield) was obtained with 100 mol % NaOEt in refluxing $CH_3CN$ (Table 1, entry17). Oxygen is important for the reaction. When the reaction was run under air or oxygen, compound **4a** was obtained with 76 or 65% yield, respectively, (Table 1, entries 17 and 18). While the reaction was run under argon, a mixture was obtained, and **4a** was not observed (Table 1, entry 19).

**TABLE 2. Synthesis of Polysubstituted Benzenes via One-Pot Tandem Reaction[a]**




1 2 4

| entry | substrate | $R_3$ | product | *T* (h)[b] | yield (%)[c] |
|---|---|---|---|---|---|
| 1 | **1a** | Ph | **4a** | 12 | 68 |
| 2 | **1b** | Ph | **4b** | 62 | 62 |
| 3 | **1c** | Ph | **4c** | 10 | 63 |
| 4 | **1a** | $CH_3CH_2CH_2$ | **4d** | 80 | 62 |
| 5 | **1a** | *p*-$MeOC_6H_4$ | **4e** | 20 | 61 |
| 6 | **1d** | Ph | **4f** | 72 | 63 |
| 7 | **1e** | Ph | **4g** | 72 | 79 |
| 8 | **1a** | naphl | **4h** | 12 | 68 |
| 9 | **1f** | Ph | **4i**[22] | 16 | 71 |
| 10 | **1g** | Ph | **4j** | 12 | 65 |
| 11 | **1h** | Ph | **4k** | 60 | 64 |
| 12 | **1i** | Ph | **4l** | 30 | 67 |
| 13 | **1j** | Ph | **4m** | 40 | 64 |

[a] All reactions were performed under air; vinyl malononitriles **1** (0.1 mmol), nitroolefins **2** (0.1 mmol), and $Et_3N$ (0.01 mmol, 10%) were reacted in 1 mL of $CH_2Cl_2$ and then $CH_3CN$ (5 mL) and EtONa (0.1 mmol) were added. For the detailed procedure, see Supporting Information. [b] Total reaction time for two steps. [c] Isolated yields.

From a synthetic point of view, one-pot procedures beginning with simple, readily available substrates provide ideal strategies for the regioselective formation of substituted benzene. We found that the vinylogous Michael addition and aromatization of addition products can be processed in one pot and that polysubstituted benzenes can be obtained with satisfactory yields. In our previous work,[19a] we found that tertiary amine can catalyze the vinylogous Michael reaction between vinyl malononitriles and nitroolefins, and thus, $NEt_3$ was used as the catalyst in the first step.[20] The intermediate was not separated, and the base NaOEt was added with optimized reaction conditions as shown in Table 1. As is shown in Table 2, a wide range of nitroolefins bearing aliphatic, aryl, and heteroaryl groups is reacted with vinyl malononitriles **1a**−**j** (for the structure, see Figure 1) derived from corresponding ketones and malononitrile, and a series of polysubstituted benzenes is obtained in all the one-pot processes. Polysubstituted biphenyl could be obtained when aliphatic vinyl malononitrile **1b** reacts with aryl nitroolefin (Table 2, entry 2) or when aryl vinyl malononitrile **1a** reacts with aliphatic nitroolefin (Table 2, entry 4). Polysubstituted terphenyl could be obtained when aryl vinyl malononitrile **1a** reacts with aryl nitroolefin (Table 2, entries 1, 5, and 8). Polycyclic compounds could be obtained when cyclic vinyl malononitriles **1c**, **1f**, **1g**, and **1h** reacted with nitroolefins, respectively (Table 2, entries 3 and 9−11). Reaction of heteroarylvinyl malononitrile **1i** or **1j** with aryl nitroolefin was found to produce the corresponding adducts **4** with heteroaromatic substituents with good yields (Table 2, entries

(20) When NaOEt was used as a base, a complex mixture was obtained.

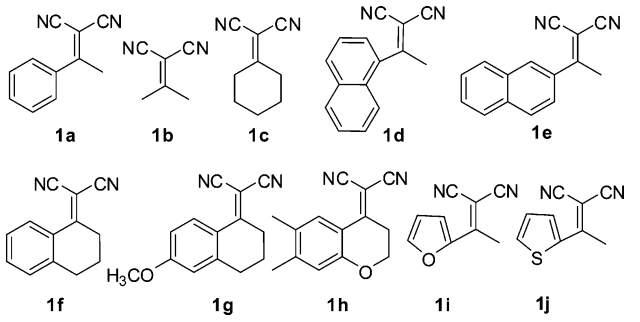
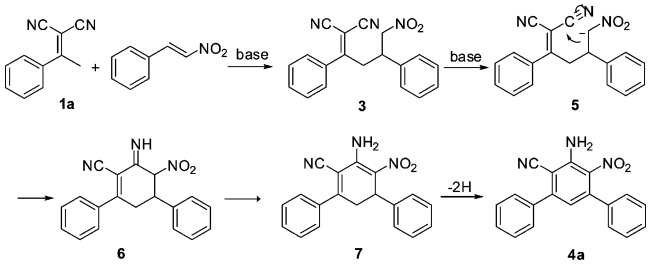



**FIGURE 1.** Structure of vinyl malononitriles.

**SCHEME 2. Postulated Reaction Course**




12 and 13). The possibility of one-pot introduction of aromatic and heteroaromatic substituents avoids the need for the cross-coupling reactions that are usually employed in the preparation of biphenyl systems.[21,22]

To explain the mechanism of the tadem reaction, a postulated reaction course is illustrated in Scheme 2. In the first step, adduct **3** was obtained according to the vinylogous Michael addition of **1a** to nitrolefin under the catalysis of a base.[19a] In the second step, the proton adjacent to the $NO_2$ group of compound **3** was deprived by NaOEt to produce a carbon nucleophilic center. Then, the carbon anion in **5** attacked the carbon center of the triplet bond in CN by an intermolecular nucleophilic addition to produce imine **6**,[23] and then isomeration of **6** gave diene **7**.[24] After one molecule of hydrogen was released via an oxidation process, aromatized compound **4a** was obtained. For the elimination of hydrogen in the process, we supposed that oxygen in air played a key role (Table 1, entries 17−19).

In summary, we have developed a new and efficient method to obtain polysubstituted benzenes via a one-pot tandem process with vinylogous Michael addition of vinyl malononitriles and nitroolefins as the key step. This provides a new strategy for the synthesis of polyfunctionalized aromatic compounds using ketones as the starting materials because vinyl malononitriles easily can be prepared from the corresponding ketones via a Knoevenagel reaction. According to this methodology, a series of complex aryl compounds such as biphenyls and terphenyls could be obtained with satisfactory yields. Current studies are actively underway to extend this methodology to the synthesis of complex aryl compounds and their function in materials science.

## Experimental Section

**Procedure for Synthesis of Compound 3 ([2-(4-Nitro-1,3-diphenylbutylidene)malononitrile]).** A 25 mL round-bottomed flask was charged with 2-(1-phenylethylidene)malononitrile[25] (168.1 mg, 1 mmol), (*E*)-(2-nitrovinyl)benzene (149 mg, 1 mmol), 10 mL of $CH_2Cl_2$, and 14 $\mu$L of $Et_3N$ (0.01 mmol). The solution was stirred at room temperature and monitored by TLC. After the completion of the reaction, the solvent was removed under reduced pressure. The raw product was purified by silica gel column chromatography (EtOAc/hexanes, 1:10) to yield 307 mg of a white solid; yield: 97%; mp: 88.0−89.1 °C; $^1$HNMR (300 Hz, $CDCl_3$) $\delta$ (ppm): 3.38−3.50 (m, 3H), 4.53−4.70 (m, 2H), 6.98 (s, 2H), 7.29−7.63 (m, 8H); $^{13}$C NMR (75 Hz, $CDCl_3$) $\delta$ (ppm): 175.4, 133.4, 132.6, 129.4, 129.0, 127.6, 127.5, 112.3, 112.1, 79.2, 42.7, 40.1; IR (KBr): 3417, 2947, 2879, 2231, 1636, 1587, 1557, 1496, 1454, 1326, 1052, 767, 702 cm$^{-1}$; HRMS (ESI) $(M + Na)^+$: $C_{19}H_{15}N_3O_2$ + Na, calcd: 340.1056, found: 340.1058.

**Optimization of Reaction Conditions of Aromatization Reaction.** A 5 mL tube was charged with 2-(4-nitro-1,3-diphenylbutylidene)malononitrile **3** (50 mg, 0.159 mmol), a base, and a solvent (1.6 mL). The mixture was stirred with the time and temperature shown in Table 1. After the completion of the reaction, the solvent was removed under reduced pressure. The raw product was purified by silica gel column chromatography (EtOAc/hexanes, 1:8) to give a light yellow solid with the yield shown in Table 1.

**Typical One-Pot Procedure for the Synthesis of 4a.** The following typical procedure has been adopted for the synthesis of all the products. A 5 mL tube was charged with vinyl malononitrile[25] **1a** (0.1 mmol), nitroolefins[25] (0.1 mmol), 1 mL of $CH_2Cl_2$, and 1.4 $\mu$L of $Et_3N$ (0.01 mmol). The solution was stirred at room temperature and monitored by TLC. After the reaction was completed (10 h), $CH_2Cl_2$ was removed under reduced pressure, and 5 mL of $CH_3CN$ and 6.8 mg of EtONa (0.1 mmol) were added. The mixture was refluxed and monitored by TLC. After the reaction was completed (2 h), the solvent was removed under reduced pressure. The product was purified by silica gel column chromatography (EtOAc/hexanes, 1:8) to yield the polysubstituted benzene **4a** as a yellow solid with 76% yield. mp: 204.2−205.8 °C; $^1$HNMR (300 Hz, $CDCl_3$) $\delta$ (ppm) 5.81 (s, 2H), 6.74 (s, 1H), 7.18−7.51 (m, 10H); $^{13}$CNMR (75 Hz, $CDCl_3$) $\delta$ (ppm) 149.5, 144.8, 142.9, 137.3, 137.0, 129.8, 128.9, 128.5, 127.2, 121.2, 115.8, 97.8; IR (KBr): 3469, 3363, 2923, 2214, 1619, 1559, 1497, 1445, 1328, 1277, 1076, 865, 821, 770, 698, 636 cm$^{-1}$; HRMS (ESI) $(M + Na)^+$: $C_{19}H_{13}N_3O_2$+Na, calcd: 338.0900, found: 338.0898.

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**Supporting Information Available:** Experimental procedures for the synthesis of **4a**−**4m** and copies of $^1$H and $^{13}$C NMR and HRMS spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(24) For similar synthesis of chiral diene, see ref 19e.

(25) For the synthesis of vinyl malononitriles **1a**−**j** and nitroolefins in detail, see refs 18b and 19a.