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$Cu(OTf)_2/Et_3N$-promoted cyclocondensation of activated α-methylene alkenes and nitroolefins: a novel one-pot synthesis of polysubstituted benzenes

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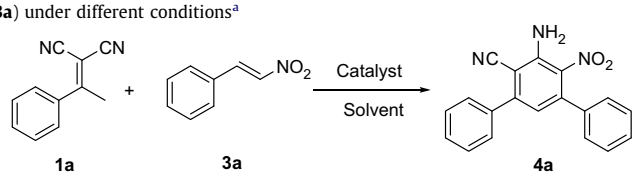
ABSTRACT

A simple and efficient one-pot synthesis of polyfunctionalized benzenes has been developed via cyclocondensation of activated α-methylene alkenes such as vinyl malononitriles and ethyl vinyl cyanoacetates with nitroolefins using $Cu(OTf)_2/Et_3N$ as a novel catalytic system.

As useful compounds in organic chemistry and natural product chemistry, polysubstituted benzenes also play important roles in medicinal chemistry for the fact that they have common structural features in various bioactive molecules and are frequently employed as precursors for the synthesis of many bioactive heterocyclic compounds.[1] Consequently, enormous number of procedures have been developed for the construction of polysubstituted benzenes. Aromatic substitutions, including Friedel–Crafts acylations and alkylations,[2] nucleophilic substitutions,[3] and coupling reactions[4] based on the given aromatics are interpreted as traditional approaches. On the other hand, the approach to construct aromatic backbone from catenulate precursors has received growing interest not only due to the short sequence and regioselectivity, but also due to the advancement from the viewpoint of atom economy[5] and environmental concern. Herein, [3+2+1]Dotz reaction,[6] [4+2]benzannulation,[7] [3+3]cyclocondensation[8], and Vilsmeier reagent assisted arylation[9] have been discovered and developed in recent years.

In general, it is difficult to introduce amino, nitrile, and/or ester group to the given aromatics. Some methods were developed to synthesize these functionalized benzenes from acyclic compounds as follows: (i) base-promoted cyclocondensation of arylethylidene- and arylidenemalono- nitriles and the elimination of nitrile group in succession, which provides polysubstituted 2-amino isophthalonitriles,[10] (ii) one-pot two-step tandem reaction of vinylmalononitriles and nitroolefins promoted by two different kinds of bases

Table 1
Reaction of 2-(1phenylethylidene)malononitrile (**1a**) and (*E*)-(2-nitrovinyl)benzene (**3a**) under different conditions[a]



1a **3a** **4a**

Entry	Solvent	Catalyst	Loading (mol %)	Yields[b] (%)
1	CH_3CN	$Cu(OTf)_2$	5	0
2	CH_3CN	$Cu(OTf)_2/Et_3N$	5/10	79
3	CH_3CN	$Cu(OTf)_2/Et_3N$	5/5	82
4	CH_3CN	$Cu(OTf)_2/Et_3N$	10/5	82
5	CH_3CN	$Zn(OTf)_2/Et_3N$	5/5	64
6	CH_3CN	$Mg(OTf)_2/Et_3N$	5/5	56
7	CH_3CN	$Sc(OTf)_2/Et_3N$	5/5	81
8	CH_3CN	$CuCl_2$/ Et_3N	5/5	39 (52[c])
9	CH_3CN	Et_3N	5	35 (36[d])
10	CH_3CN	Piperidine	10	29
11	CH_3CN	KOH	100	0
12	CH_3CN	EtONa	100	Trace
13	CH_2Cl_2	$Cu(OTf)_2/Et_3N$	5/5	0
14	$CHCl_3$	$Cu(OTf)_2/Et_3N$	5/5	62
15	DMF	$Cu(OTf)_2/Et_3N$	5/5	71
16	EtOH	$Cu(OTf)_2/Et_3N$	5/5	79
17	Dioxane	$Cu(OTf)_2/Et_3N$	5/5	55
18	Toluene	$Cu(OTf)_2/Et_3N$	5/5	40

[a] The reaction was carried out at 80 °C reflux for 5 h.
[b] Yield of isolated product.
[c] In the presence of 40 mol % of $CuCl_2$ and 5 mol % of Et_3N .
[d] In the presence of 10 mol % of Et_3N.

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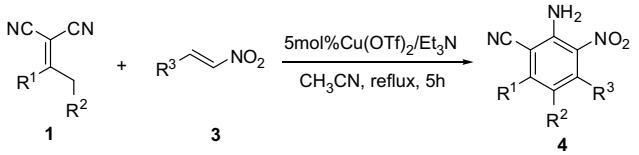
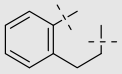
Table 2
$Cu(OTf)_2/Et_3N$ promoted synthesis of 2-amino-3-nitro benzonitriles in refluxing CH_3CN[13]



Entry	R^1	R^2	R^3	Product	Yield[a] (%)
1	Ph	H	Ph	**4a**	82
2	4-MeC_6H_4	H	Ph	**4b**	85
3	4-$MeOC_6H_4$	H	Ph	**4c**	86
4	4-FC_6H_4	H	Ph	**4d**	79
5	4-ClC_6H_4	H	Ph	**4e**	84
6	3-ClC_6H_4	H	Ph	**4f**	76
7		H	Ph	**4g**	85
8			Ph	**4h**	80
9			Ph	**4i**	79
10			Ph	**4j**	78
11		H	Ph	**4k**	81
12	Ph	Me	Ph	**4l**	70
13	4-ClC_6H_4	Me	Ph	**4m**	67
14	4-MeC_6H_4	Ph	Ph	/	0
14	Ph	H		**4n**	83
15	Ph	H		**4o**	82
16	Ph	H	4-$MeOC_6H_4$	**4p**	83
17	Ph	H	3-$NO_2C_6H_4$	**4q**	81

[a] Yield of isolated product.

Table 3
$Cu(OTf)_2$/ Et_3N promoted synthesis of ethyl 2-amino-3-nitro-benzoates in CH_3CN at reflux[14]

Entry	R^1	R^2	R^3	Product	Yield[a] (%)
1	Ph	H	Ph	**5a**	66[b]
2			Ph	**5b**	66
3				**5c**	64
5			Ph	**5d**	62
6	3-ClC_6H_4		Me	**5e**	59[b]

[a] Yield of isolated product based on **2**
[b] Geometrical isomers of **2** were used.

for each step, which obtains a series of substituted 2-amino-3-nitro benzonitriles.[11] Unfortunately, these methods often suffer from certain drawbacks such as long-playing procedures, hazardous by-products and use of stoichiometric or even excess amount of base. Therefore, how to synthesize polysubstituted benzenes efficiently and catalytically is an important question to be answered in organic synthesis.

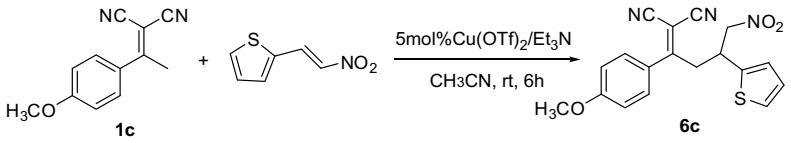
Our group has reported metal triflates as excellent catalysts that are widely used in organic synthesis.[12] As part of our ongoing interest in green chemistry and metal triflates-catalyzed organic reactions, in this Letter, we will introduce a novel and efficient one-pot synthesis of polyfunctionalized benzenes via the reactions of activated α-methylene alkenes and nitroolefins promoted by catalytic amount of copper triflate and triethylamine. The products, a series of 2-amino-3-nitro-benzonitriles and ethyl 2-amino-3-nitro-benzoates, are obtained in good yields.

In our initial research, 5 mol % of $Cu(OTf)_2$ was tested to promote the reaction of 2-(1-phenylethylidene)malononitrile (**1a**) and (*E*)-(2-nitrovinyl) benzene (**3a**). Acetonitrile was selected as solvent due to the solubility of the two starting materials. Disappointedly, no product was observed after refluxing for 10 h. However, the reaction was kept at reflux for 5 h after Et_3N was added, and compound **4a** was obtained in good yield. It i seems that a base is indispensable. Then, the model reaction was investigated with a variety of conditions. The results are summarized in Table 1.

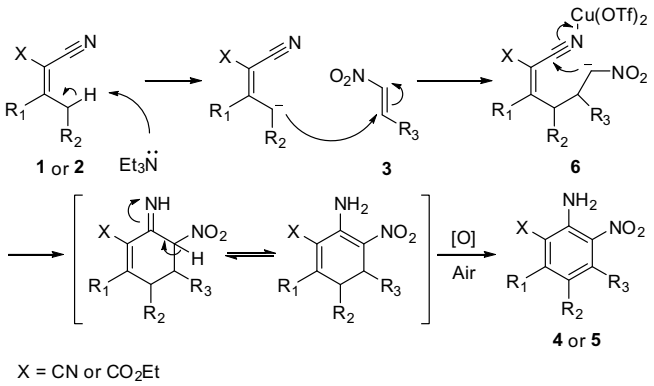
As shown in Table 1, $Cu(OTf)_2$ and Et_3N, each of 0.05 equiv, gave the best yield. The reaction gave low yield when 0.05 or 0.1 equiv of Et_3N alone was used (Table 1, entry 9). Furthermore, any sole organic or inorganic base gave a low yield or even no reaction (Table 1, entries 10–12). $CuCl_2/Et_3N$ system also gave lower yield in 39% (52% with increased amount of the catalyst) (Table 1, entry 8). Other metal triflate/Et_3N catalyst systems, such as $Zn(OTf)_2$/Et_3N, $Sc(OTf)_3/Et_3N$, and $Mg(OTf)_2/Et_3N$, were studied, and only $Sc(OTf)_3/Et_3N$ showed good activity (Table 1, entries 5–7). We also examined different solvents such as CH_2Cl_2, $CHCl_3$, DMF, EtOH, dioxane, and toluene. Among them, CH_3CN was the best one.

With these preliminary results in hand, we paid our attention to a wide scope of vinyl malononitriles **1**. Subsequent studies were carried out under the optimized conditions: with 5 mol % of $Cu(OTf)_2$ and 5 mol % of Et_3N in CH_3CN at reflux for 5 h. Satisfactorily, most vinyl malononitriles reacted with nitroolefins completely and afforded the corresponding products **4a–q** in moderate to good yields, as shown in Table 2.

First, a series of substituted phenylethylidene malononitriles (Table 1, entries 1–6) were used to react with **3a**. Both electron-donating and electron-withdrawing substituents on phenyl were tolerated. When phenyl was replaced with furanyl, the corresponding product was obtained in high yields (Table 2, entry 7, 85% yield). Furthermore, some vinyl malononitriles with aliphatic R^1 and R^2 were also subjected to the reactions with **3a**, which similarly gave the corresponding products in satisfactory yields (Table 2, entries 8–11). Furthermore, we successfully constructed a cyclopropyl benzene framework which was difficult to prepare via traditional approaches. Subsequently, when R^2 = Me (Table 2, entries 12 and 13), a considerable decrease in yields took place. Indeed, no reaction of 2-(2-phenyl-1-*p*-tolylethylidene)malononitrile with **3a** was observed under the same conditions (Table 2, entry 14). This observation might be a result of steric hindrance. Finally, a wide range of nitroolefins with different R^3 were reacted with **1a**. Similar yields were obtained irrespective of R^3 alternating from substituted phenyl to heterocycles (Table 2, entries 14–17).



Scheme 1. Reaction to obtain the intermediate **6c**.



Scheme 2. Plausible reaction mechanism of **1** or **2** with nitroolefins.

To extend the scope of this reaction, other activated α-methylene alkenes, such as Knoveangal products **2** of ketones with ethyl cyanoacetate, were made to react with nitroolefins **3** using the present protocol. The formation of **5** from **2** required longer time (8 h). In general, probably due to the comparatively weaker electron-withdrawing ability of COOEt than CN, these reactions gave significantly lower yields than that of vinyl malononitriles with nitroolefins. The products, a series of ethyl 2-amino-3-nitro benzoates derivatives **5**, were obtained in moderate yields. The results are summarized in Table 3.

In addition, reaction of 2-(1-(4-methoxyphenyl)ethylidene) malononitrile (**1c**) with (*E*)-2-(2-nitrovinyl)thiophene was carried out at room temperature and was catalyzed by 5 mol % $Cu(OTf)_2$ and 5 mol % Et_3N for 6 h (Scheme 1). The detection of the Michael intermediate **6c** indicates the ionic path of the whole cyclocondensation.[15]

Based on the experimental results, a plausible mechanism was proposed in Scheme 2, involving the Michael addition of activated α-methylene alkenes and nitroolefins, the cyclation catalyzed by $Cu(OTf)_2$ and Et_3N, and the oxidation in atmosphere.

In summary, we have developed a simple, convenient and efficient synthetic protocol for polysubstituted benzenes using $Cu(OTf)_2/Et_3N$ as a novel catalytic system in CH_3CN. The simplicity, efficiency, easy work-up, short reaction time, and the need for catalytic amount of base make it a preferred procedure for the preparation of polysubstituted benzenes.

Acknowledgments

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13. *General procedure for the synthesis of 2-amino-3-nitro-benzonitriles*. To a mixture of vinyl malononitrile (1 mmol) and nitroolefin (1 mmol) in CH_3CN (3 mL), $Cu(OTf)_2$ (0.05 mmol, 18 mg) and triethylamine (0.05 mmol, 5 mg) were added. The reaction mixture was stirred at reflux for 5 h. After the completion of the reaction, EtOAc (15 mL) was added to dilute the reaction solution. Then, the mixture was washed with water and brine. The combined organic phases were dried and concentrated in vacuo, and the residue was purified by column chromatography (hexane/AcOEt = 8:1) to afford compounds **4**.
14. *General procedure for the synthesis of ethyl 2-amino-3-nitro-benzoates*. To a mixture of **2** (1 mmol) and nitroolefin (1 mmol) in CH_3CN (3 mL), $Cu(OTf)_2$ (0.05 mmol, 18 mg) and triethylamine (0.05 mmol, 5 mg) were added. The reaction mixture was stirred at reflux for 8 h. After the completion of the reaction, EtOAc (15 mL) was added to dilute the reaction solution. Then, the mixture was washed with water and brine. The combined organic phases were dried and concentrated in vacuo, and the residue was purified by column chromatography (hexane/AcOEt = 8:1) to afford compounds **5**.
15. *Procedure for the synthesis of* **6c**. To a mixture of **1c** (1 mmol) and (*E*)-2-(2-nitrovinyl)thiophene (1 mmol) in CH_3CN (3 mL), $Cu(OTf)_2$ (0.05 mmol, 18 mg) and triethylanmine (0.05 mmol, 5 mg) were added. The reaction mixture was stirred at room temperature for 6 h. After the completion of the reaction, EtOAc (15 mL) was added to dilute the reaction solution. Then, the mixture was washed with water and brine. The combined organic phases were dried and concentrated in vacuo, and the residue was purified by column chromatography (hexane/AcOEt = 10:1) to afford the **6c** as a yellow crystalline powder.
Spectral data for selected products:
3-Amino-2-nitro-1-phenyl-9,10-dihydrophenanthrene-4-carbonitrile (**4h**): Yellow crystals, mp 201–202 °C (201.2–203.4 °C[11]), yield: 80%. ^1H NMR (500 MHz, $CDCl_3$): δ 8.24 (t, J = 2.0 Hz, 1H), 7.40–7.47 (m, 5H), 7.28 (dd, J_1 = 6.5 Hz, J_2 = 8.5 Hz, 1H), 7.20–7.22 (m, 2H), 5.66 (s, 2H), 2.63–2.65 (m, 2H), 2.38–2.40 (m, 2H). ^{13}C NMR (125 Hz, $CDCl_3$): δ 143.3, 142.5, 140.4, 139.8, 135.7, 131.1, 130.5, 128.8, 128.6, 128.0, 127.9, 127.4, 127.1, 117.2, 95.4, 29.1, 26.0. IR (KBr) ν_{max}: 3466, 3382, 2214, 1620, 1512, 920, 706 cm^{-1}. MS (EI): m/z (%) = 341 (54, M^+), 305 (100).
3-Amino-5-(furan-2-yl)-4-nitrobiphenyl-2-carbonitrile (**4n**): Yellow crystals, mp 164–165 °C, yield: 83%. ^1H NMR (500 MHz, $CDCl_3$): δ 7.50–7.58 (m, 5H),

7.26 (s, 1H), 7.05 (s, 1H), 6.76 (d, J = 3.2 Hz, 1H), 6.53 (dd, J_1 = 2.0 Hz, J_1 = 3.2 Hz, 1H), 6.58 (s, 2H). ^{13}C NMR (125 Hz, $CDCl_3$): δ 117.0, 110.7, 107.3, 106.7, 99.5, 92.3, 92.1, 90.9, 80.5, 78.2, 74.8, 74.1. MS (EI): m/z (%) = 302 (23, M^+), 232 (100). HRMS calcd for $C_{17}H_{11}N_3O_3$ (M^+): 305.0800; found: 305.0801.

Ethyl 2-amino-3-nitro-4-(thiophen-2-yl)-5,6,7,8-tetrahydronaphthalene-1-carboxylate (**5c**): Yellow crystals, mp 173–174 °C, yield: 64%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41 (dd, J_1 = 0.8 Hz, J_2 = 5.2 Hz, 1H), 7.05 (dd, J_1 = 3.6 Hz, J_2 = 5.2 Hz, 1H), 6.88 (dd, J_1 = 1.2 Hz, J_2 = 3.2 Hz, 1H), 5.03 (d, J = 2.4 Hz, 2H), 4.44 (q, J = 6.8 Hz, 2H), 2.85 (t, J = 6.4 Hz, 2H), 2.45 (t, J = 6.4 Hz, 2H), 1.65–1.74 (m, 4H), 1.41 (t, J = 6.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 141.2, 137.0, 135.3, 130.8, 128.0, 127.8, 127.0, 126.9, 119.7, 64.6, 29.1, 27.7, 22.3, 22.2, 14.2. MS (EI): m/z (%) = 347 (12, M^++1), 346 (42, M^+), 282 (100). HRMS calcd for $C_{17}H_{18}N_2O_4S$ (M^+): 346.0987; found: 346.0988.

Ethyl 5-amino-6-nitro-7-phenyl-2,3-dihydro-1H-indene-4-carboxylate (**5d**): Yellow crystals, mp 94–95 °C, yield: 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34–7.42 (m, 3H), 7.20–7.23 (m, 2H), 6.93 (s, 2H), 4.41 (q, J = 7.2 Hz, 2H), 3.27 (t, J = 7.6 Hz, 2H), 2.57 (t, J = 7.6 Hz, 2H), 1.92–1.99 (m, 2H), 1.42 (t, J = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 152.3, 143.6, 137.6, 137.6, 137.0, 132.3, 128.5, 128.0, 127.5, 110.9, 61.1, 36.8, 31.6, 24.6, 14.3. MS (EI): m/z (%) = 327 (12, M^++1), 326 (100). HRMS calcd for $C_{18}H_{18}N_2O_4$ (M^+): 326.1267; found: 326.1269.

2-(1-(4-Methoxyphenyl)-4-nitro-3-(thiophen-2-yl)butylidene)malononitrile (**6c**): Yellow crystalline powder; mp 84–85 °C; yield: 92%. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.62 (dd, J_1 = 2.4 Hz, J_2 = 6.4 Hz, 2H), 7.54 (d, J = 8.8 Hz, 1H), 6.98–7.04 (m, 3H), 6.89 (s, 1H), 5.68 (s, 1H), 3.87–3.90 (m, 4H), 2.62 (s, 3H). MS (EI): m/z (%) = 353 (10, M^+), 197 (100). HRMS (EI) calcd for $C_{18}H_{15}N_3O_3S$ ([M]$^+$) 353.3950; found: 353.3947.