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Transition-Metal-Free Multicomponent Benzannulation Reactions for the Construction of Polysubstituted Benzene Derivatives

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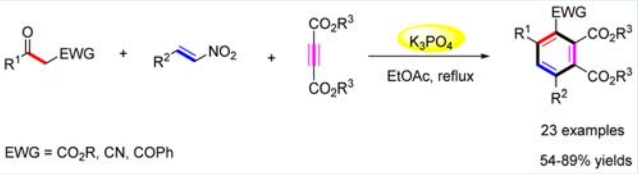
Supporting Information

ABSTRACT: A transition-metal-free multicomponent benzannulation reaction was developed from readily available ketones, nitro-olefins, and diester acetylenedicarboxylate. This approach provides a straightforward and efficient way to construct polysubstituted benzene derivatives under mild conditions in high yields.

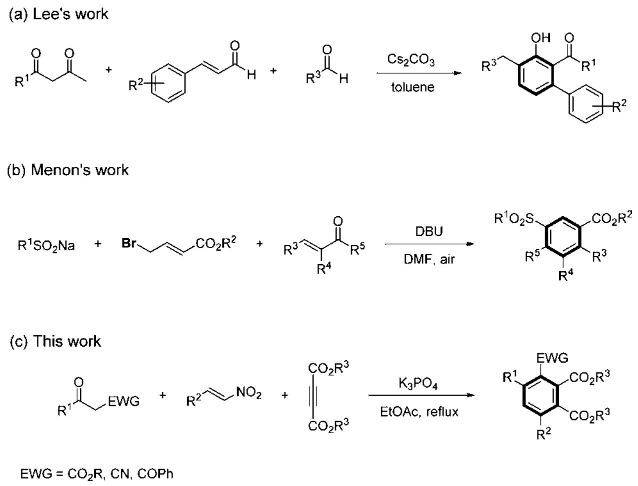


Polysubstituted benzenes and related systems are highly important structural units in natural products, active pharmaceuticals, and agrochemicals.[1] They are also widely used as important scaffolds and building blocks for the construction of optical and functional materials.[2]

In general, classical synthetic methods for polysubstituted benzenes have been dominated by electrophilic and nucleophilic aromatic substitution processes.[3] However, due to the electronic properties and substituent effects, certain groups can be difficult to incorporate into benzene rings by these methods.[10b] In comparison, benzannulation has more advantages in the control of the substitution pattern on the arene ring and has received substantial attention.[4] Benzannulation, the construction of benzene rings from acyclic building blocks, is one of the most important reactions for the construction of functionalized benzene derivatives.[5] Over the past few decades, various benzannulation reactions have been developed for diversely substituted benzene and fused benzene derivatives.[6−9] In particular, increasing attention has been paid to transition-metal-free multicomponent benzannulations in recent years.[10] For example, Lee and co-workers reported a novel transition-metal-free benzannulation reaction for the efficient synthesis of diverse polyfunctionalized biaryl derivatives (Scheme 1a).[10a] In addition, Menon and co-workers developed a base-mediated air-oxidative benzannulation reaction for the regioselective synthesis of substituted arenes via a one-pot three-component process (Scheme 1b).[10b] Therefore, the development of transition-metal-free multicomponent benzannulation reactions with selective control of substitution patterns continues to be actively pursued.[4]

Dimethyl acetylenedicarboxylate (DMAD) is an extremely versatile tool for organic synthesis, is a powerful Michael acceptor, and can take up various nucleophiles.[11] Using it in an initial reaction as a Michael acceptor and then carrying out a cyclization reaction to activated alkenes could construct complex molecules.[12] Herein, we report a novel base-promoted multicomponent benzannulation reaction involving DMAD for the direct construction of polysubstituted benzenes under mild conditions (Scheme 1c).

Scheme 1. Examples of Transition-Metal-Free Multicomponent Benzannulation Reactions



Initially, the three-component reaction of ethyl benzoylacetate (**1a**) and *trans*-*β*-nitrostyrene (**2a**) with DMAD (**3a**) was attempted in CH_3CN in the presence of K_2CO_3 at 80 °C (Table 1, entry 1). To our delight, the multisubstituted benzene compound **4a** was furnished in 45% yield. Considering the importance of polysubstituted benzenes, we sought to optimize the reaction conditions. Several bases, solvents, and temperatures were examined, and the results are summarized in Table 1. Remarkably, the yield of **4a** increased to 81% when the reaction was carried out in the presence of K_3PO_4 (entry 11). Other bases, such as Cs_2CO_3, Na_2CO_3, $NaHCO_3$, CsF, KOH, NaOH, NaOEt, KOAc, and $K_4P_2O_7$, were found to give lower yields (entries 2−10). However, we cannot detect the desired product in the case of using organic base (DABCO, DBU, and DMAP) (entries 12−14). Next, examination of different solvents (DMSO, DMF,

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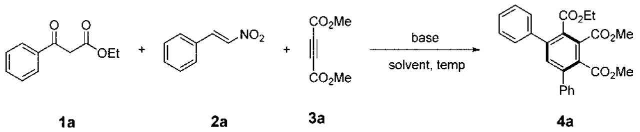
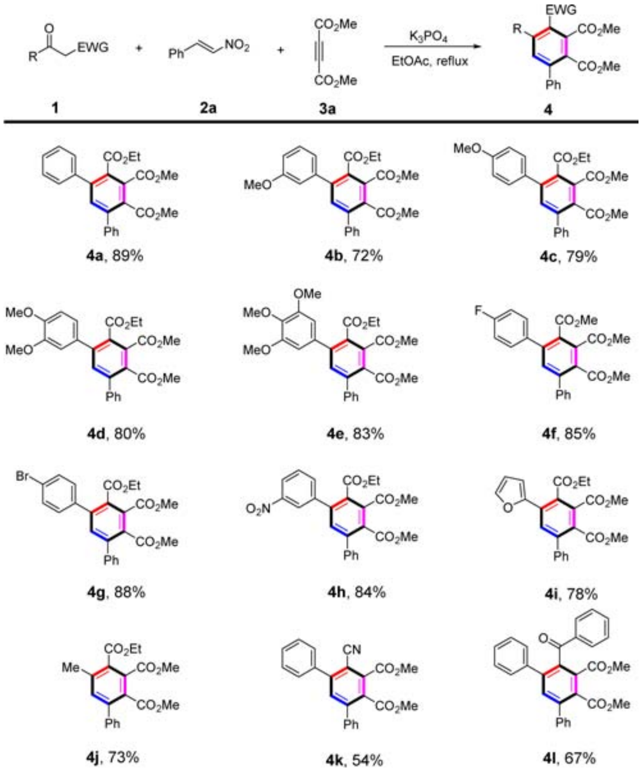
Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	base	temp (°C)	yield (%)[b]
1	CH_3CN	K_2CO_3	80	45
2	CH_3CN	Cs_2CO_3	80	10
3	CH_3CN	Na_2CO_3	80	67
4	CH_3CN	$NaHCO_3$	80	73
5	CH_3CN	CsF	80	76
6	CH_3CN	KOH	80	
7	CH_3CN	NaOH	80	
8	CH_3CN	NaOEt	80	64
9	CH_3CN	KOAc	80	35
10	CH_3CN	$K_4P_2O_7$	80	32
11	CH_3CN	K_3PO_4	80	81
12	CH_3CN	DABCO	80	
13	CH_3CN	DBU	80	
14	CH_3CN	DMAP	80	
15	DMSO	K_3PO_4	80	
16	DMF	K_3PO_4	80	48
17	DCE	K_3PO_4	80	59
18	dioxane	K_3PO_4	80	78
19	toluene	K_3PO_4	80	71
20	**EtOAc**	$\mathbf{K_3PO_4}$	**reflux**	**89**
21	EtOAc	K_3PO_4	rt	75
22	EtOAc	K_3PO_4	40	79
23	EtOAc	K_3PO_4	60	80

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), **3a** (0.1 mmol, 1.0 equiv), base (0.3 mmol, 3.0 equiv), and solvent (2 mL) for 2 h. [b] Isolated yields.

Scheme 2. Scope of Ketones[a]



[a] Reactions were carried out with **1** (1.0 mmol, 1.0 equiv), **2a** (1.0 mmol, 1.0 equiv), **3a** (1.0 mmol, 1.0 equiv), and K_3PO_4 (3.0 equiv) in EtOAc (5 mL) at 77 °C for 2 h. Isolated yields are shown.

DCE, dioxane, toluene, and EtOAc) revealed that EtOAc was the best choice for the reaction, and the corresponding yield increased to 89% (entries 15–20). However, none of the desired product **4a** was afforded in DMSO (entry 15). Variation of the reaction temperature proved that reflux temperature was the optimal result for this protocol (entries 20–23).

After establishing the optimal reaction conditions, we next explored the substrate scope of the ketones (**1**), as shown in Scheme 2. It is noteworthy that the electronic properties of the substituents on the aromatic ring system were shown to have little influence on the efficiency of this reaction. The ketones bearing electron-neutral (H), electron-donating (3-OMe, 4-OMe, 3,4-2OMe, 3,4,5-3OMe), and halogen-substituted (4-F, 4-Br) groups attached to the benzene ring were smoothly transformed into their corresponding products in good to excellent yields (72–89%; **4a**–**4g**). Furthermore, good yields were also obtained with electron-withdrawing (3-NO_2) and heteroaromatic (2-furyl) substrates (84 and 78%, respectively; **4h** and **4i**). Much to our satisfaction, with R = Me, the reaction proceeded well to afford the expected product in good yield (73%; **4j**). In addition, with the cyano and benzoyl groups at the α position of the ketones, products **4k** and **4l** were afforded in 54 and 67%, respectively. The structure of **4a** was identified by single-crystal X-ray diffraction (Figure 1).

A variety of *trans-β*-nitrostyrenes were then used to explore the effect of substituents on the nitro-olefin (Scheme 3). The *trans-β*-nitrostyrenes containing electron-rich/deficient functional groups attached to the benzene ring reacted smoothly to give the corresponding products in good to excellent yields (72–83%; **5a**, **5b**, and **5g**). In addition, the halogen-substituted (4-F, 4-Cl, 2,4-2Cl, 2-Br) groups were also suitable in this reaction, affording the corresponding products in high yields (80–87%; **5c**–**5f**). The heteroaromatic (2-furyl, 2-thienyl) nitro-olefins were also compatible, giving the expected products **5i** and **5j** in 76 and 79% yield, respectively. Notably, the sterically hindered 1-naphthyl group was well-tolerated, leading to product **5h** in 81% yield. Diethyl acetylenedicarboxylate also participated in the annulation reaction to afford the benzene ring product **5k** in 88% yield. Furthermore, other alkynes such as 1,2-diphenylacetylene, phenylacetylene, methyl propiolate, and methyl 2-butynoate were also checked in this reaction system, but the corresponding products were not afforded (these results have not been listed in Scheme 3).

To gain insight into the mechanism of this benzannulation reaction, several control experiments were performed (Scheme 4). When the model reaction of **1a**, **2a**, and **3a** was carried out in the presence of 2.0 equiv of K_3PO_4 in EtOAc at room temperature for 2 h, compound **6** was afforded in 29% yield (Scheme 4, eq 1). Under the standard conditions, **6** could transform into the desired product **4a** in excellent yield (Scheme 4, eq 2). These results indicate that compound **6** is probably an intermediate in the annulation reaction. Furthermore, the structure of compound **6** was determined by X-ray crystallographic analysis (Figure 1).

On the basis of the above-mentioned experimental results, a possible reaction mechanism for this reaction is proposed in Scheme 5 (**4a** as an example). Initially, ethyl benzoylacetate **1a** transforms into **1a′** in the presence of K_3PO_4, which subsequently reacts with DMAD **3a**, affording vinyl anion **A**.[13]

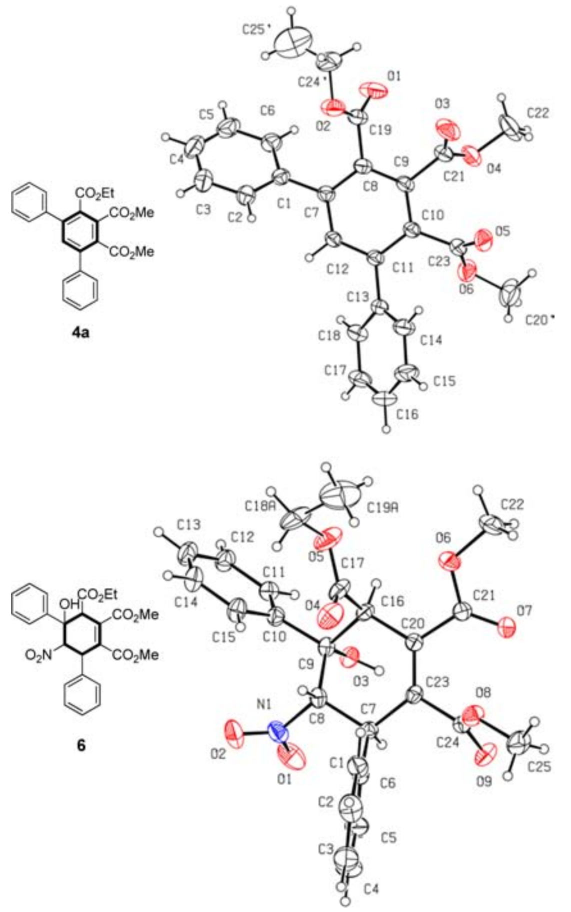
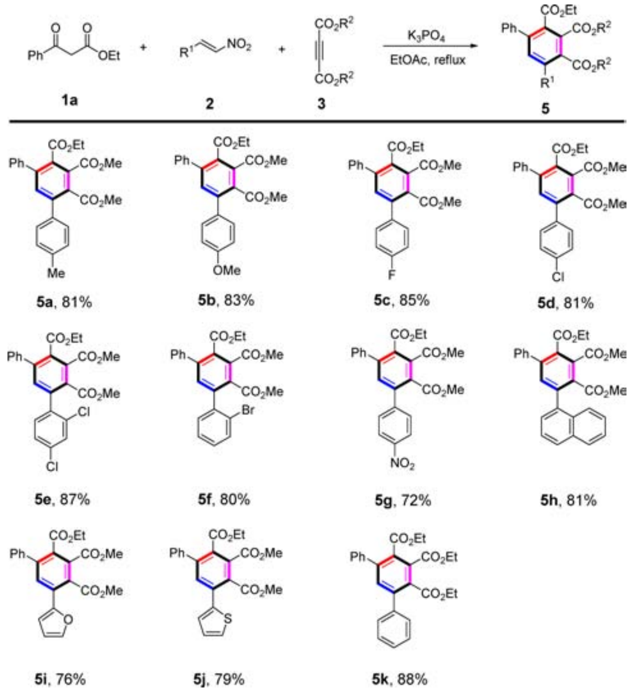


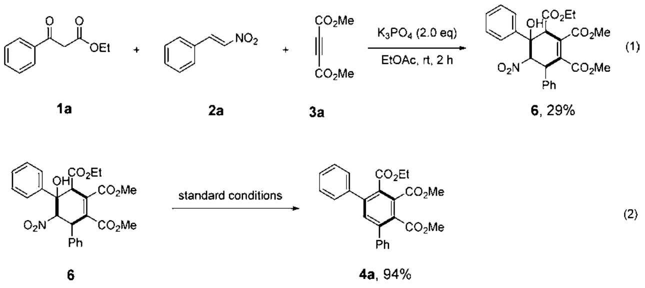
Figure 1. X-ray crystal structures of **4a** and **6**.

Scheme 3. Scope of Nitro-olefins and Diester Acetylenedicarboxylate[a]



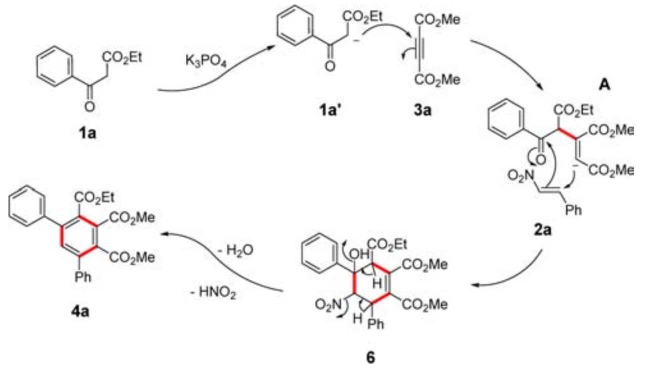
[a] Isolated yields.

Scheme 4. Control Experiments[a]



[a] Isolated products.

Scheme 5. Possible Mechanism



Intermediate **A** then attacks *trans*-*β*-nitrostyrene **2a**, leading to the cyclized compound **6**. Finally, intermediate **6** is converted to the desired product **4a** via an aromatization reaction, with elimination of H_2O and HNO_2.

In conclusion, we have developed a novel and efficient transition-metal-free multicomponent benzannulation reaction for the directed synthesis of polysubstituted phthalic acid derivatives. Available starting materials, simple reaction conditions, and broad substrate scope make this protocol very practical and attractive. Further studies on the applications of this methodology are in progress in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02548.

Experimental procedures, product characterizations, crystallographic data, and copies of the ^{1}H and ^{13}C NMR spectra (PDF)
X-ray data for **6** (CIF)
X-ray data for **4a** (CIF)

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Notes

The authors declare no competing financial interest.

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