RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2020, **10**, 29171

Received 15th June 2020
Accepted 28th July 2020

DOI: 10.1039/d0ra05251e

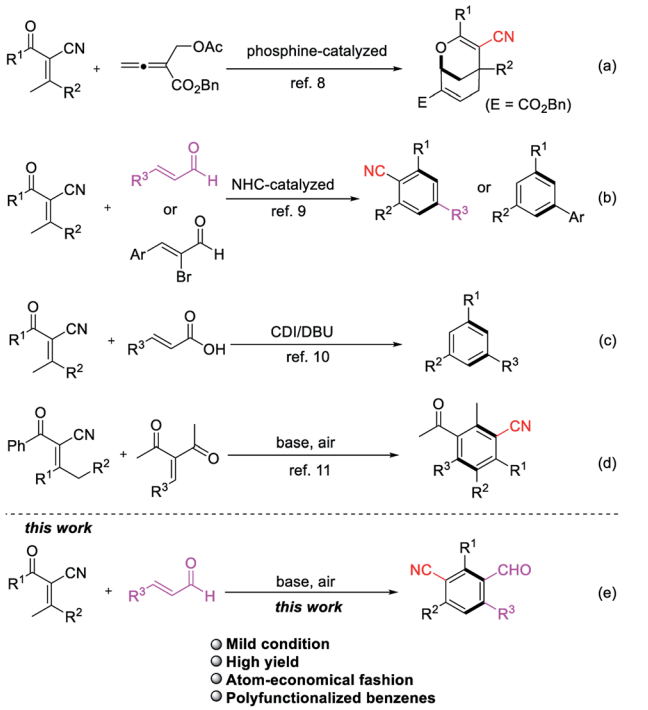
rsc.li/rsc-advances

Direct access to multi-functionalized benzenes *via* [4 + 2] annulation of α-cyano-β-methylenones and α,β-unsaturated aldehydes†

Qianfa Jia,[a] Yunfei Lan,[b] Xin Ye,[b] Yinhe Lin*[a] and Qiao Ren*[b]

An efficient [4 + 2] benzannulation of α-cyano-β-methylenones and α,β-unsaturated aldehydes was achieved under metal-free reaction conditions selectively delivering a wide range of polyfunctional benzenes in high yields respectively (up to 94% yield).

Multi-substituted benzenes are privileged structural units ubiquitous in pharmaceuticals,[1] natural products[2] and advanced functional materials.[3] Various excellent methodologies have been investigated for the construction of functionalized aromatics including nucleophilic or electrophilic substitution,[4] transition metal-catalyzed coupling reactions[5] and directed metalation.[6] However, the widespread application of these strategies established thus far suffer from the limitations of functional groups introduced on the pre-existing benzene and regioselectivity issues. Among various synthetic methods, tandem benzannulation reactions arguably represent an attractive alternative to classical methods for rapid construction of polysubstituted benzenes in an atom-economical fashion.[7] This protocol featuring an efficient transformation of acyclic building blocks into structurally valuable benzene skeletons. In this context, α-cyano-β-methylenones has been employed as substrates to format six-membered ring in tandem cyclization reactions due to the activation of the pronucleophile methyl group. In 2015, Tong and co-workers developed a phosphine-catalyzed addition/cycloaddition domino reactions of β′-acetoxy allenoate with 2-acyl-3-methyl-acrylonitriles to give 2-oxabicyclo[3.3.1]nonanes (Scheme 1a).[8] Soon after that, the construction of benzonitrile derivatives and 1,3,5-trisubstituted benzenes *via* N-heterocyclic carbene catalysis has been reported by the groups of Wang and Ye independently (Scheme 1b).[9] Then the synthesis of 1,3,5-trisubstituted benzenes by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)-mediated annulation of α-cyano-β-methylenones and α,β-unsaturated carboxylic acids was also developed by Ye and co-workers (Scheme 1c).[10] Shi *et al.* reported a base-promoted tandem cyclization reaction of α-cyano-β-methylenones and α,β-unsaturated enones, which have electron-withdrawing group (EWG), accessing to a wide range of benzonitriles in a different C–C bond formation process (Scheme 1d).[11] As part of our ongoing interest in harnessing enones for developing new methodologies for the construction of functionalized benzenes, we have recently demonstrated NHC-catalyzed convenient benzonitrile assembly in the presence of oxidant.[9a] While the same reaction of enals and α-cyano-β-methylenones



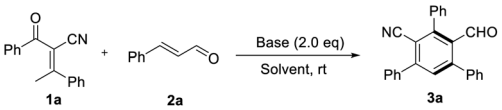
Scheme 1 α-Cyano-β-methylenones in cycloaddition domino reactions.

[a]*Chongqing Key Laboratory of Inorganic Special Functional Materials, College of Chemistry and Chemical Engineering, Yangtze Normal University, Fuling, Chongqing 408100, P. R. China*

[b]*College of Pharmaceutical Science, Southwest University, Chongqing 400715, P. R. China*

† Electronic supplementary information (ESI) available. CCDC 1957055. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d0ra05251e

Table 1 Optimization of the reaction conditions[a]



Entry	Base	Solvent	Time (h)	Yield[b] (%)
1	Cs_2CO_3	Toluene	24	70
2	Na_2CO_3	Toluene	24	42
3	K_2CO_3	Toluene	24	38
4	NaOH	Toluene	12	78
5	NaOAc	Toluene	24	52
6	KOH	Toluene	12	74
7	K_3PO_4	Toluene	24	58
8	DBU	Toluene	24	33
9	Et_3N	Toluene	48	46
10	NaOH	DCM	12	88
11	**NaOH**	**$CHCl_3$**	**12**	**94**
12	NaOH	DCE	12	84
13	NaOH	H_2O	48	0
14[c]	NaOH	$CHCl_3$	12	85
15[d]	NaOH	$CHCl_3$	12	84
16[e]	NaOH	$CHCl_3$	12	80

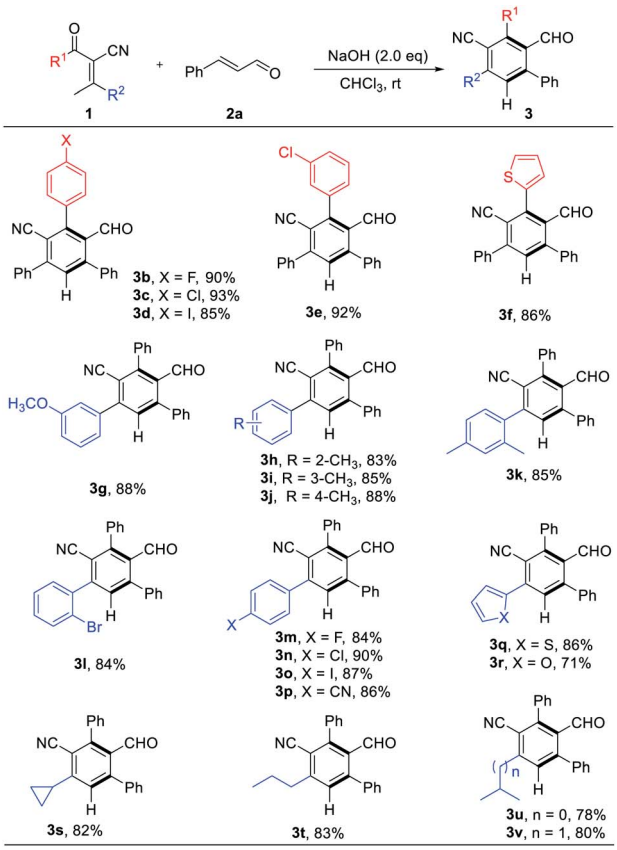
[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), base (0.2 mmol, 2.0 equiv.), and solvent (1 mL) for 12 h. [b] Isolated yields. [c] **1a** : **2a** = 1 : 1.2. [d] NaOH used 1.2 equiv. [e] 50 °C.

was conducted in the basic condition without NHC, a novel polyfunctionalized benzene product was obtained (Scheme 1e). The result inspired us to extend the synthetic potential of benzannulation strategy to access diverse benzonitriles, particularly from simpler, abundantly available starting materials.

At the outset, model reaction of 2-benzoyl-3-phenylbut-2-enenitrile **1a** and cinnamaldehyde **2a** was used to evaluate reaction parameters. Key results of condition optimization are summarized in Table 1. Several inorganic or organic bases were screened and NaOH turned out to be the most efficient for this transformation to give a novel product **3a**. (33–78% yields, entries 1–9, Table 1). The structure of **3a** was confirmed by X-ray crystallography as an unprecedented functionalized benzene.[12] The configuration of products were assigned unambiguously by X-ray analysis of the product **3a**. A quick solvent screening demonstrated that chloroform is the best choice to produce the benzannulation product **3a** in a desirable yield (entries 10–13, Table 1. For additional details, see the ESI†). Reducing the loading of the cinnamaldehyde or NaOH to 1.2 equivalence led to dramatical loss of the yield (entries 14 &15, Table 1). And raising the reaction temperature to 50 °C resulted in lower yield (80% yield, entries 16, Table 1).

Finally, the standard reaction conditions for the base-promoted synthesis of the multi-functionalized benzene derivatives identified as follows: 1.5 equivalence of NaOH and $CHCl_3$ as the solvent under an atmosphere of air for 12 hours at room temperature.

Table 2 Scope of enones[a]

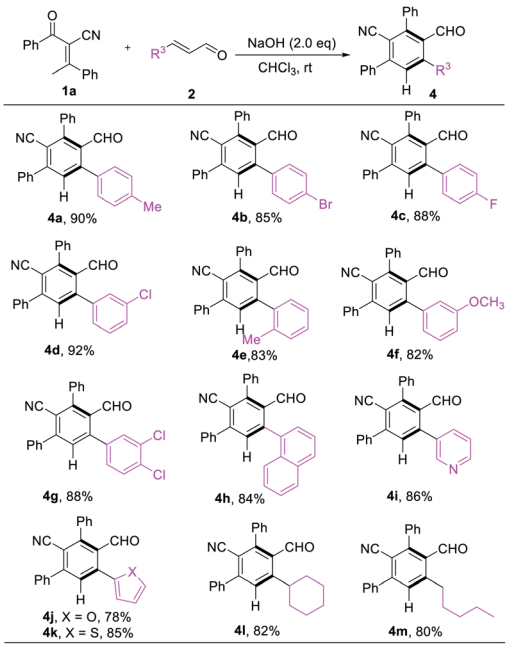


[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), NaOH (0.2 mmol, 2.0 equiv.), and $CHCl_3$ (1 mL) for 12 h.

With the optimized reaction conditions in hand, we explored the scope of the reaction. A series of enones were examined, variation of the electronic nature of the aromatic ring (R^1, including the substituted phenyl or thienyl) has little influence on the reaction efficiency (**3b–f**, 86–93% yields, Table 2). We subsequently examined the effect of R^2 with different substitution patterns and electronic nature, β-arylenones with electron-rich and electron-deficient substituents were worked well to afford the functional benzonitriles in high yields (**3g–r**, 80–90% yields, Table 2). Enones with alkyl group on R^2 position can also be used to afford their corresponding products (**3s–v**, 78–83% yields, Table 2) in good chemical yields.

We next turned our attention to examine the scope of enals. Different substituents on the phenyl ring of cinnamaldehydes were tolerated even disregarding the position and properties, giving **4a–g** in satisfying yields (82–92% yields, Table 3). With respect to heterocycles such as pyridine, furan, thiophene and naphthalenes were also compatible with the reaction conditions (**4h–k**, 82–88% yields, Table 3). Replacement of the β-phenyl substituent with an alkyl unit **4l** & **4m** had limited effect on reaction conversion, the corresponding products were obtained in good yields (82% & 80% yield, Table 3).

Table 3 Scope of enals[a]

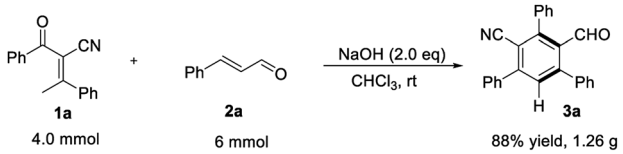


[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv.), **2a** (0.15 mmol, 1.5 equiv.), NaOH (0.2 mmol, 2.0 equiv.), and $CHCl_3$ (1 mL) for 12 h.

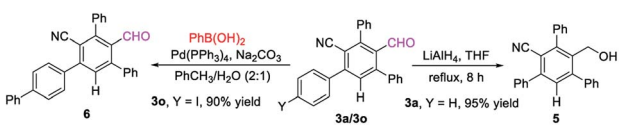
To highlight the practicality of this mild and efficient method, the reaction of 2-benzoyl-3-phenylbut-2-enenitrile **1a** at 4.0 mmol scale proceed well under the standard conditions to generate the desired product in 88% yield (Scheme 2).

The formyl group could be easily reduced by using $LiAlH_4$ in THF at reflux, leading to the formation of the benzyl alcohol product **5** in 95% yield while keeping the CN group intact. Suzuki coupling of **3o** with phenylboronic acid furnished derivative **6** in 90% yield[13] (Scheme 3).

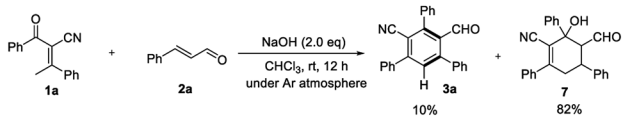
To gain insight into the role of air in this reaction, a control experiment was designed and investigated (Scheme 4). When the reaction of **1a** and **2a** was carried out under an argon atmosphere, the desired product **3a** was obtained in 10% yield



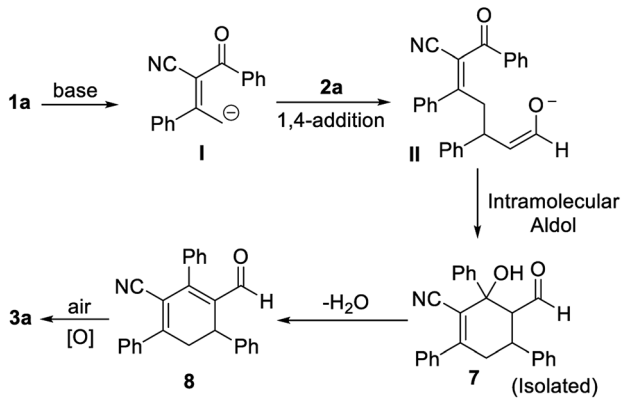
Scheme 2 Gram-Scale Synthesis of **3a**.



Scheme 3 Synthetic transformation.



Scheme 4 Control experiment.



Scheme 5 The proposed mechanism.

and product **7** could be isolated in 82% yield. The results indicate that oxygen is necessary for the oxidation process and played a key role in this reaction.

A postulated reaction course is illustrated in Scheme 5. Briefly, α-deprotonation of enone **1a** in the presence of bases, subsequent 1,4-addition of deprotonated enone **I** to enal **2a** generates intermediate **II**, which undergoes an intramolecular aldol reaction to yield the adduct **7**.[14] Lastly, dehydration of **7** followed by spontaneous oxidative aromatization affords the polysubstituted benzonitrile **3a**.

Conclusions

In summary, we have developed the example of catalyst-free [4 + 2] cycloaddition reaction of α-cyano-β-methylenones and α,β-unsaturated aldehydes. This protocol provides straightforward access to the corresponding highly functionalized benzenes in good to excellent yields under ambient conditions. Such studies are actively underway in our laboratory, and more results will be reported in due course.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work is financially supported by the National Natural Science Foundation of China (No. 21602179) and Science Foundation of Yangtze Normal University (No. 2017KYQD123, 2018QNRC17).

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14 The adduct **7** was isolated from the reaction of **1a** and **2a** under standard conditions for 0.5 h and the structure was determined by NMR, HRMS, for details, see the ESI.†

