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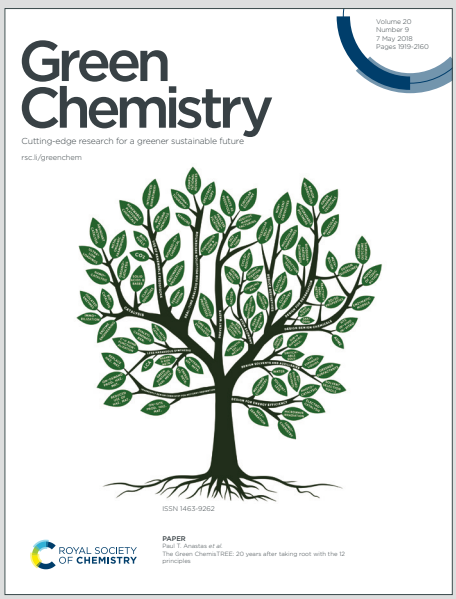

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COMMUNICATION

Base Mediated Benzannulation of α-Cyano Crotonates with Ynones: Facile Synthesis of Benzonitriles and Fluorenes

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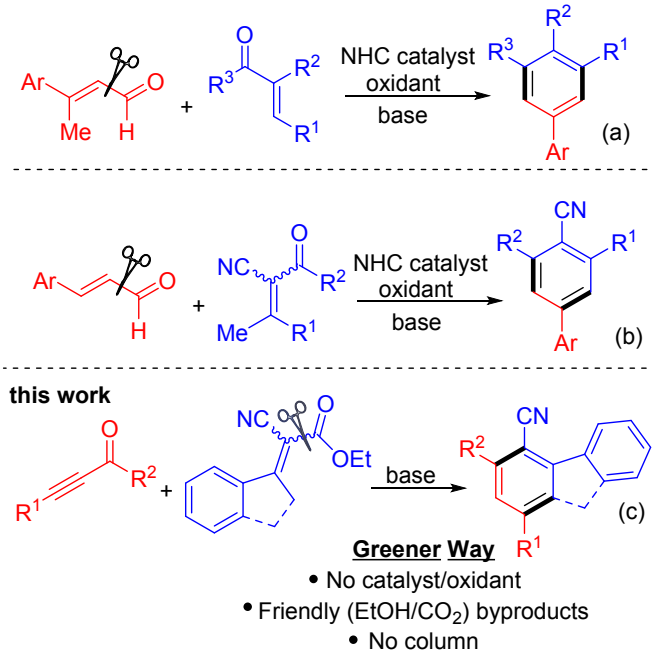
We demonstrate here in a strategic rapid approach for benzonitriles and cyanofluorenes via [3 + 3] benzannulation of readily available alkynones and α-cyanocrotonates, a protocol par excellence for aryl nitriles. This decarboxylative annulation is assisted solely by a base without the need of any catalyst. The only by-product is EtOH (and CO_2) and the product is cleanly filtered off the contents after reaction at ambient temperature.

Benzannulation is a powerful strategy to rapidly construct the benzene derivatives from acyclic precursors. Appropriately functionalized acyclic precursors give highly and selectively substituted adducts avoiding the linear tedious processes.[1] While reducing the chemical wastage, it imparts high convergence in the approach. Conjugated carbonyls are often the feedstock in these annulations where Michael addition usually triggers the annulation and thus renders it a high regioselectivity.

Within the realm of organic chemistry, aryl nitriles are fascinating molecules to synthesis due to their perpetual utility as key structural motifs in a wide array of medicinal agents, natural products and functional materials.[2] The highness of nitrile in aryl nitriles is further explored by the transformations to comprehensive range of functional groups such as amides, amines, aldehydes and carboxylic acids.[3] For structural diversification standpoint aryl nitriles are highly sought by chemical community. Indeed, over the decades there has been meteoric development in synthesis of aryl nitriles. Canonical methods were devoted to TM catalyzed synthesis which in general requires metal (metalloid) CN source and led to heavy metal wastage. Even though some nonmetallic CN sources have been developed, such sources are in its infancy stage.[6] In this regard, most recently, the groups of Wang *et al*. and Ye *et al*. (Scheme 1b) simultaneously came up with an NHC catalyzed synthesis of aryl nitriles following a protocol developed by Chi *et al*. for substituted benzenes (Scheme 1a).[4] The success of these transformations eventually depends on NHC catalytic system. Not surprisingly, these findings have created a void to prosper protocol which is environmentally more conscious and economically further viable.

On the other hand, fluorenes, as the methylene-bridged arenes, are considered as privileged structures in materials because of their easily modifiable nature which help in tuning the physical & chemical properties and thereby the optical and electrical features.[9] Consequently, enormous efforts have been made to find manufacturing approaches for the construction of this interesting structure.[10]



Scheme 1. Benzannulation of conjugated carbonyls with crotonates.

The emergence of ynone as operable cycloaddition and annulation partner is frequently witnessed in the recent literature. The ynones are arguably the most reactive substrates which can be conveniently used as 2, 3 or 4 component partner to access diversified molecular structures.[5] In continuation of our interest in finding new reactivities of functionalized alkyes,[7] we recently reported various novel annulations of ynones.[5i, 7i-j] We envisioned a more promising and generic approach for aryl nitriles by further exploring ynone. We thus report herein a decarboxylative annulation of ynones with α-cyano conjugated esters[8] for the direct access to multisubstituted aryl nitriles and fluorenes (Scheme 1c). This methodology not only avoids requirement of special catalysts and oxidants (to be the greener approach) but also produces

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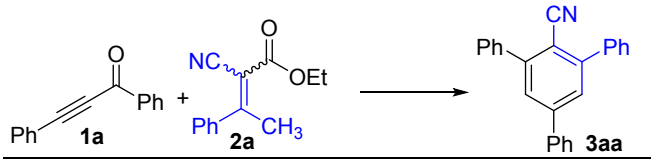
complementary substitution patterns in products compared to earlier protocols (Schemes 1a-b). An interesting mechanism involving an adjacent hydroxyl assisted decarboxylation is suggested.

We began our investigation with ynone **1a** and α-cyanocrotonate **2a** to optimize the conditions (Table 1). No product was observed when the organic bases like DBU or DABCO and Brønsted base NaOH were used in MeCN (entries 1-3). Pleasingly, the desired product was isolated in 20% yield with Cs_2CO_3. Other bases like NaO^{t}Bu and NaOEt produced **3a** but in low yields (entries 5-7) whereas KO^{t}Bu gave it in decent yield of 50% (entry 8). A thorough screening of solvents with this base revealed that the best yield (90%) was obtained in *n*-BuOH. The product was cleanly isolated by filtering the contents through a small silica bed. No workup and additional purification was required.

Table 1. Optimization studies

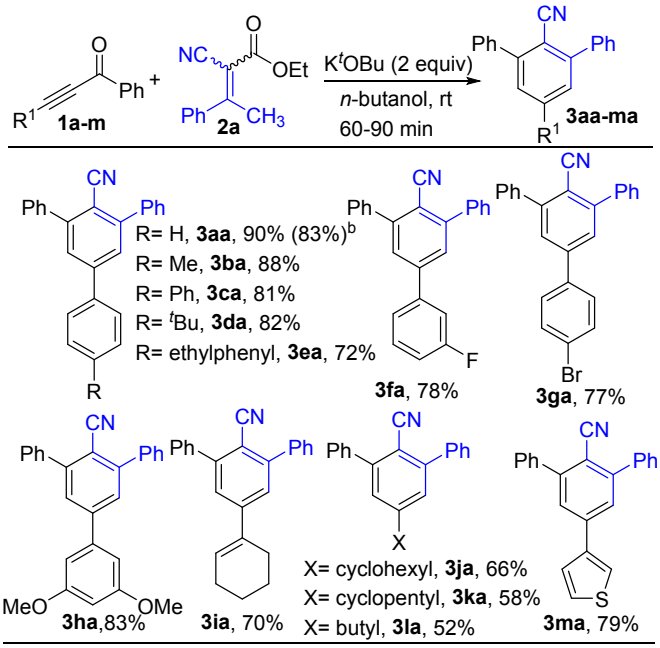


entry	base	solvent	temp	yield(3aa)[b]
1	DBU	MeCN	rt	--
2	DABCO	MeCN	rt	--
3	NaOH	MeCN	rt	--
4	Cs_2CO_3	MeCN	rt	20
5	NaO^{t}Bu	MeCN	rt	35
6	NaOEt	MeCN	rt	40
7	KO^{t}Bu	MeCN	rt	60
8	KO^{t}Bu	DMF	rt	35
9	KO^{t}Bu	EtOH	rt	55
10	KO^{t}Bu	*i*PrOH	rt	68
11	KO^{t}Bu	^{t}BuOH	rt	70
12	**KO^{t}Bu**	***n*-BuOH**	**rt**	**90**
13	KO^{t}Bu	THF	rt	50

Reaction conditions: [a](0.5 mmol) of **1a**, (0.6 mmol) of **2a** using 1mmol of base in 3 mL solvent. [b]Isolated yields.

After establishing an optimized set of reaction conditons, we were keen to explore the generality of this new benzannulation. We initially headed to assess the scope of the alkyne terminal of ynone (Table 2). Substrates containing phenyl group with alkyl (Me, Bu and phenethyl) and phenyl substitution (**1b-e**) cleanly furnished the desired adducts in 72-88% yields. Halo aryl (**1f-g**) and alkoxy (**1h**) ynones also smoothly benzannulated with **2a** to deliver the expected products (**3fa-ha)** in 77-83% yields. Cyclohexenyl benzonitrile **3ia** was obtained in 70% yield from enynone **1i**. Alkyl (cyclohexyl, cyclopentyl and butyl) ynones (**1j-l**) were not discriminated from aryl ynones in this benzannulation although the products were obtained in slightly lower yields (52-66%). Thiophenylated benzonitrile was **3ma** similarly obtained from corresponding ynone **1m** in 79% yield. **3aa** was obtained in 83% yield when the reaction was conducted in a gram scale. We then verified the reaction with substitution variation at carbonyl terminal of ynone (Table 3). Alkyl (Me), alkoxy (OMe), halo (F and Cl) substituted phenyl ynones (**1n-q**) were cleanly transformed to the corresponding adducts (**3na-qa**) in 77-85% yields. *o*-Brominated ynones (**1r-s**) suffered no impact of steric repulsion and produced the desired adducts in 63-67% yields. Terminal alkyne function in **3sa** was successfully survived the reaction. Diynone **1t** cleanly gave the desired benzonitrile **3ta** with ortho alkynyl function for further modifications.

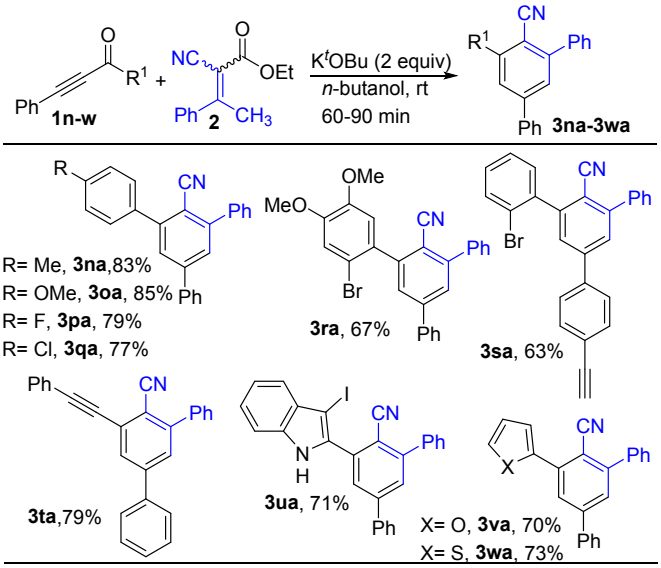
Table 2. Scope of ynones in benzannulation.



[a]Reaction conditions: **1** (0.5mmol), **2** (0.6 mmol), KO^{t}Bu (2 equiv) in *n*-BuOH, at rt, open air. [b] yield in gram scale.

Expanding the scope, ynones with heteroaryls including indole, furan and thiofuran were transformed well under standard conditions to get hetero-arylated benzonitriles (**3ua-wa**) in 70-73% yields.

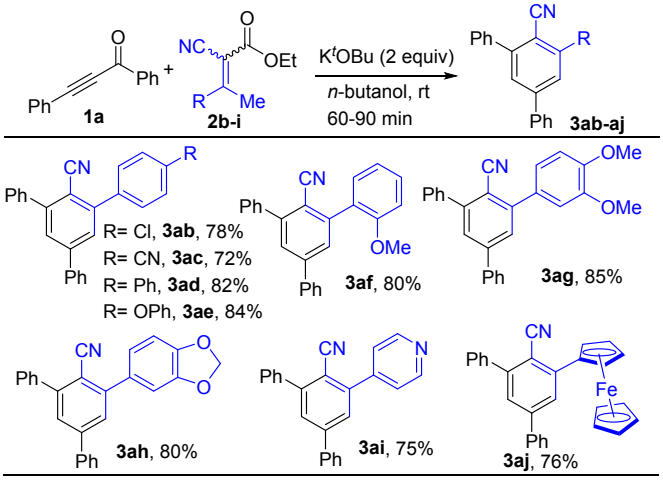
Table 3. Scope of ynones in benzannulation.



[a]Reaction conditions: **1** (0.5mmol), **2** (0.6 mmol), KO^{t}Bu (2 equiv) in *n*-BuOH, at rt, open air.

We next headed to test the reaction with variation of substitution in α-cyanocrotonates (Table 4). Initially the β-aryl was subjected to the change. Substrates with electron deficient cyano phenyl, chloro phenyl and pi extended phenyl-phenyl group showed no resistance to the transformation and produced the expected triaryl benzonitriles (**3ab-ad**) in 72-82% yields. The products (**3ae-ah**) with alkoxy groups (OPh, OMe, di-OMe, and -OCH_2O-) were obtained in excellent yields irrespective of the number or position of the functions. Pyridyl group was successfully installed at C2 of benzonitrile **3ai** using β-pyridocrotonate **2i**. Interestingly, 2-ferrocenyl benzonitrile **3aj** was obtained cleanly in 76% yield from the corresponding starting material **2j**.

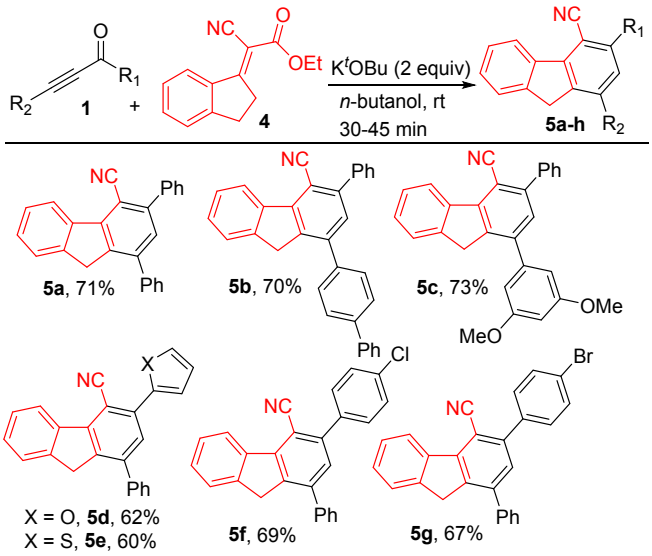
Table 4. Scope of α-CyanoCrotonates in benzannulation.



[a]Reaction conditions: **1** (0.5mmol), **2** (0.6 mmol), KO^{t}Bu (2 equiv) in *n*-BuOH, at rt, open air.

Finally, to further expand the scope of the reaction, impact of substitution at the methyl group of crotonate was studied. We initially chose indanone based

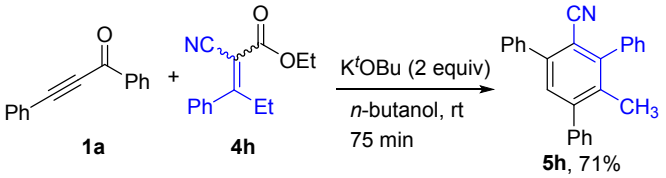
Table 5. Synthesis of Cynofluorenes.



[a]Reaction conditions: **1** (0.5mmol), **2** (0.6 mmol), KO^{t}Bu (2 equiv) in *n*-BuOH, at rt, open air.

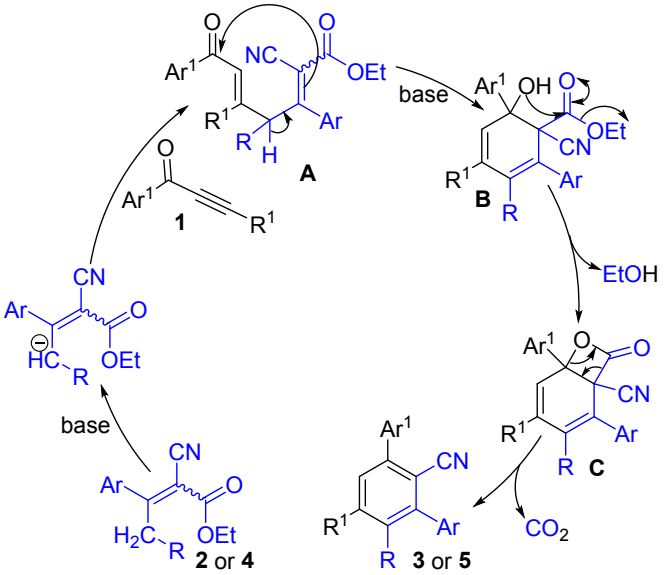
α-cyanocrotonate system **4** so as to obtain highly interesting and useful fluorenes (Table 5). Thus, treating **4a** with ynone **1a** under standard conditions cleanly resulted the cyanofluorene **5a** in 71% yield. Substrate scope for this new tricyclic system was then studied. Different aryl/heteroaryl groups with varied substitution were thus installed at C2 and C4 to get a wide range of cyanofluorenes (**5b-g**) in good to excellent yields. Further, noncyclic methyl crotonate **4h** cleanly gave the tetrasubstituted benzonitrile **5h** in 71% yield (Scheme 2).

Scheme 2. Tetrasubstitutedbenzonitrile through benzannulation.



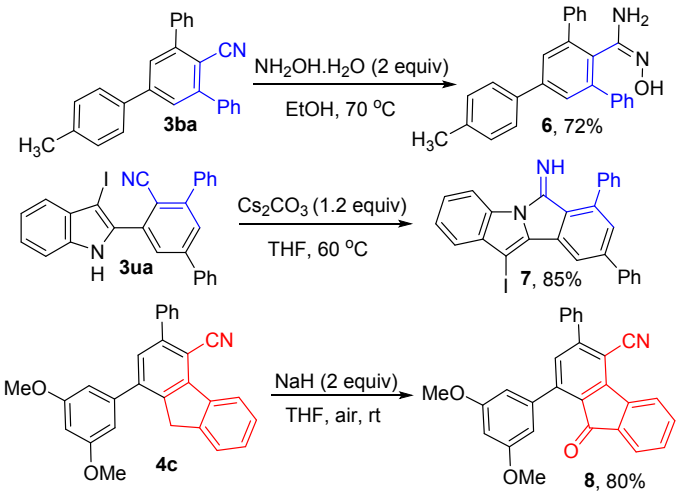
A tentative mechanism for the title benzannulation is depicted in Scheme 3. A base mediated Michael addition of crotonate on ynone triggered the annulation (**A**). The Michael adduct underwent a selective vinylogous addition on ketone than on ester due to high electron deficiency. The resulted cycle **B** underwent a decarboxylation using the assistance of neighboring hydroxy group (**C**) to afford the final product **3**&**5**.

Scheme 3. Mechanistic Proposal.



To demonstrate the utility of this novel benzannulation, some of the obtained products were derivatized to interesting adducts (Scheme 4). Nitrile **3ba** was converted to carboximidamide[2e] **6** in 72% yield using hydroxylamine hydrate in EtOH. Indolylbenzonitrile **3ua** was cyclized to amidine[2f] **7** using Cs_2CO_3. Further, cyanofluorene **4c** was oxidized to fluorenone[9e] **8** using NaH/air.

Scheme 4. Derivatization of title compounds.



In conclusion, we demonstrated a most feasible assembly of highly and selectively substituted benzonitriles and cyanofluorenes from readily available ynones and cyanocrotonates under extremely greener conditions. A four point diversity was successfully shown to get a wide spectrum of the substituted adducts. A plausible mechanism through a neighboring hydroxyl assisted decarboxylation is suggested. Synthetic applicability of the title compounds has been accomplished successfully.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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COMMUNICATION

Base Mediated Benzannulation of α-Cyano Crotonates with Ynones: Facile Synthesis of Benzonitriles and Fluorenes

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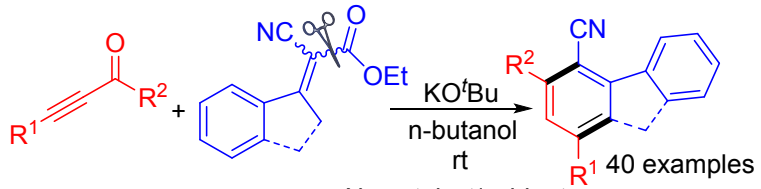

- No catalyst/oxidant
- Friendly (EtOH/CO_2) byproducts
- No column

Benzonitriles and cyanofluorenes are rapidly obtained via [3 + 3] benzannulation of readily available alkynones and α-cyanocrotonates using KOtBu as the only reagent where EtOH (and CO2) is the only by-product.