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N-Heterocyclic Carbene Catalyzed 1,6-Conjugate Addition of Me_3Si-CN to *para*-Quinone Methides and Fuchsones: Access to α-Arylated Nitriles

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Supporting Information

ABSTRACT: An organocatalytic approach toward α-arylated nitriles using *N*-heterocyclic carbene (NHC) as a catalyst is described. This protocol comprises an NHC catalyzed activation of Me_3Si-CN followed by 1,6-conjugate addition of cyanide to *para*-quinone methides (*p*-QMs) and fuchsones leading to α-diaryl- and α-triaryl nitriles in good to excellent yields.

α-Aryl nitriles have emerged as an essential architectural motif, often found in many pharmaceuticals and biologically active natural molecules.[1] Specifically, many of the α-diaryl and α-triaryl nitriles possess interesting biological and therapeutic properties (Figure 1). For example, darotropium bromide (**1**) has been

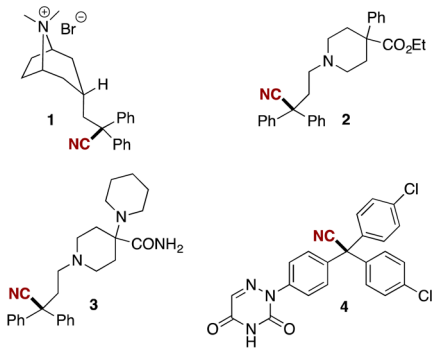

Figure 1. Some biologically significant α-arylated nitriles.

recognized as a very potent mAchR antagonist.[2a] Other α-diaryl nitrile based drugs such as diphenoxylate (**2**)[2b] and piritramide (**3**)[2c] are being used for the treatment of diarrhea and postoperative pain, respectively. α-Triaryl nitrile derivative **4** shows remarkable inhibition activity toward the growth of protozoa.[2d] Besides the therapeutic importance, the nitrile moiety has also been utilized as an important building block for the synthesis of aldehydes, carboxylic acids, amides, amines, and *N*-containing heterocycles.[3] Furthermore, nitriles are extensively employed as a key precursor for the synthesis of valuable drugs.[4] Owing to the significance of α-aryl nitriles, considerable effort has been made for their syntheses through different approaches.

The conventional method for the synthesis of α-aryl nitriles involves a nucleophilic substitution of benzyl halides with alkali metal or ammonium cyanides[5] and dehydration of aldoximes/amides.[6] Alternatively, α-aryl nitriles could be accessed through a Lewis acid catalyzed addition of trimethylsilyl cyanide (Me_3Si-CN) to diarylcarbinols and their derivatives.[7] In the recent past, another fascinating strategy entailing a transition metal catalyzed coupling of benzyl cyanides with an appropriate aryl coupling partner has been realized.[8] Besides, some metal-free approaches have been recognized for the synthesis of α-aryl nitriles.[9] In general, most of the hitherto known methods involve either the use of expensive metal catalysts or harsh reaction conditions. Therefore, developing a mild and efficient strategy for the synthesis of α-arylated nitriles, especially, under metal-free organocatalytic conditions is highly desired.

Over the past two decades, *N*-heterocyclic carbene (NHC) catalysis has emerged as a unique tool for C−C and C−heteroatom bond forming reactions.[10] Apart from the Umpolung reactivity toward carbonyl compounds, NHCs have been demonstrated to activate silicon nucleophiles through the formation of a hypervalent silicon−NHC complex.[11] In line with this concept, many C−C bond forming transformations and polymerization reactions have been reconnoitered.[12] In fact, NHC catalyzed cyanation of aldehydes and imines using Me_3Si-CN as a nucleophile has been reported.[13] However, surprisingly, NHC catalyzed conjugate addition of Me_3Si-CN to enone or dienone systems has not been reported to date, although there are a few reports available for metal catalyzed 1,4-conjugate cyanation to enone systems.[14] In fact, only one example is reported for the 1,6-conjugate addition HCN to puupehenone, which is a dienone system.[15] In our continuing program on the development of NHC catalyzed transformations,[16] we sought to employ the NHC catalyzed silicon activation concept for the synthesis of α-arylated nitriles through 1,6-conjugate addition of Me_3Si-CN to *para*-quinone methides (*p*-QMs) [Figure 2]. While

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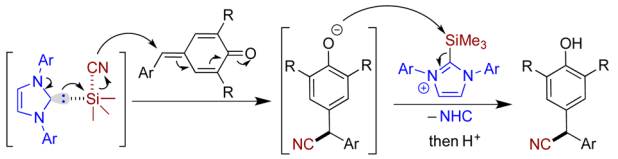
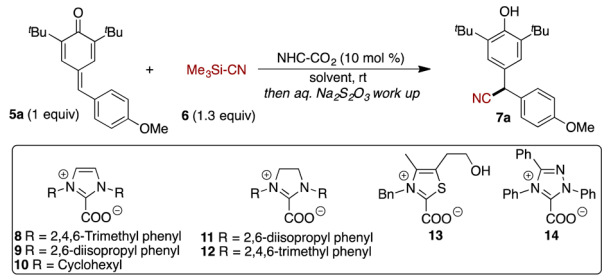


Figure 2. Our hypothesis for the synthesis of α-arylated nitriles.

the chemistry of *p*-QMs has been investigated by many research groups[17] including our group,[18] this particular NHC catalyzed vinylogous conjugate cyanation reaction of *p*-QMs using Me_3Si-CN as a cyanide source has not been examined to date, which prompted us to investigate this transformation in a detailed manner.

The preliminary optimization studies were conducted on **5a**[17a] using Me_3Si-CN (**6**) as a cyanide source and a wide range of NHC−CO_2 adducts (**8**−**14**) as precatalysts (Table 1). It is well

Table 1. Catalyst Screen and Optimization[a]



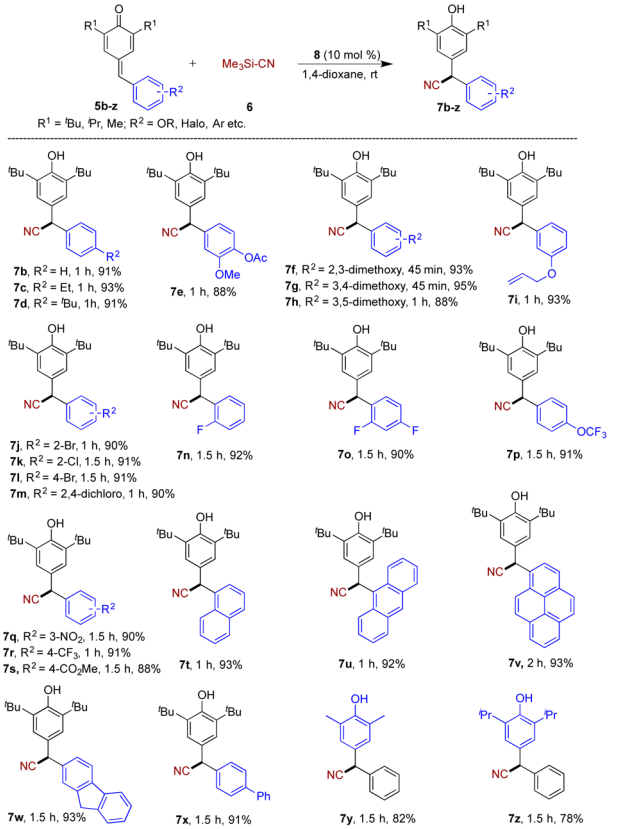
entry	precatalyst	solvent	time [h]	yield of **7a** [%]
1	**8**	DCM	24	N.D.
2	**8**	THF	24	trace
3	**8**	Et_2O	24	27
4	**8**	DCE	24	33
5	**8**	PhMe	24	50
6	**8**	DMSO	3	80
7	**8**	MeCN	24	45
8	**8**	DMF	3	85
9	**8**	^{t}BuOH	24	60
10	**8**	**1,4-dioxane**	**1**	**97**
11	**9**	1,4-dioxane	4	85
12	**10**	1,4-dioxane	6	88
13	**11**	1,4-dioxane	6	90
14	**12**	1,4-dioxane	4	91
15	**13**	1,4-dioxane	24	trace
16	**14**	1,4-dioxane	24	trace
17	-	1,4-dioxane	24	0

[a]Reaction conditions: All reactions were carried out with **5a** (0.062 mmol), **6** (0.081 mmol) in solvent (0.5 mL). Yields reported are isolated yields.

documented in the literature that generation of the NHC−CO_2 adduct is reversible in solution at ambient conditions; thus, it could be effectively used as an NHC precursor.[19] Moreover, one can perform the reaction under neutral conditions, as no external base is required to generate the free NHC. The results of the optimization studies are shown in Table 1. Our initial attempt in the presence of precatalyst **8** was disappointing, as no product was observed when we conducted the experiment in CH_2Cl_2 at room temperature (entry 1). Changing the solvent from CH_2Cl_2 to THF did not help, as **7a** was observed only in trace amounts (entry 2). To our delight, when Et_2O was used as a solvent, **7a** could be isolated in 27% yield (entry 3). Further screening was performed in a variety of solvents (entries 4−10), and 1,4-dioxane was found to be the best solvent, as the expected product **7a** was isolated in 97% yield in just 1 h under these conditions (entry 10).[20] The optimization studies were then extended using other imidazolium based NHC precatalysts (**9**−**12**) in 1,4-dioxane (entries 11−14). However, the yield of **7a** was found to be lower in all those cases when compared to that of entry 10. Surprisingly, thiazolium (**13**) and triazolium (**14**) based NHC precatalysts were found to be ineffective to drive this transformation (entries 15 and 16). No product formation was observed in the absence of the NHC precatalyst, which clearly indicates that NHC is actually acting as a catalyst for this transformation (entry 17).

Having optimized the reaction conditions successfully, the scope and limitation of the reaction were investigated using a wide range of *p*-QMs (**5b**−**z**), and the results can be found in Scheme 1. It is noteworthy to mention that most of the *p*-QMs

Scheme 1. Substrate Scope with Different *p*-Quinone Methides[a]



[a]Reaction conditions: All reactions were carried out with 20 mg scale of **5**(**b**−**z**) in 0.5 mL of solvent. Yields reported are isolated yields.

utilized for this transformation underwent smooth conversion to their respective α-diaryl nitriles in excellent yields, irrespective of the electronic nature of the substituents present in the aryl moiety of *p*-QMs. For example, *p*-QMs **5b**−**p** (bearing electron-rich and halo substituted aryls) as well as **5q**−**s** (bearing electron-poor aryls) afforded the products **5b**−**s** in 88−95% yields within a short period of time (45 min−1.5 h). Sterically hindered *p*-QMs (**5t**−**v**) also reacted efficiently to afford the successive products in excellent yields (**7t**−**v**). In the cases of *p*-QMs derived from fluorene-2-carboxaldehyde (**5w**) and biphenyl-4-

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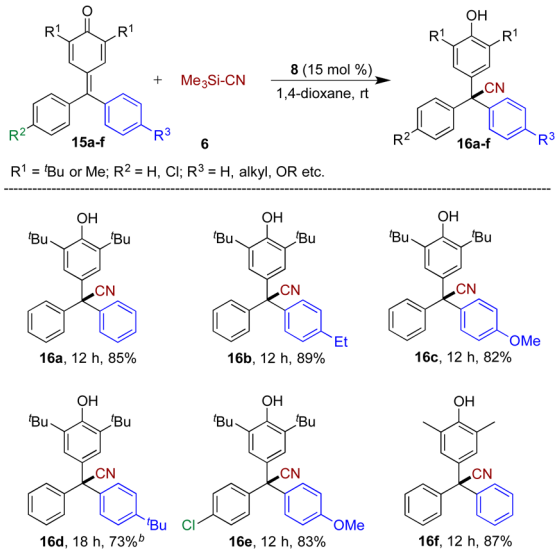
carboxaldehyde (**5x**), the desired products **7w** and **7x** were obtained in 93% and 91% isolated yields, respectively. *p*-QMs (**5y** and **5z**), derived from 2,6-dimethylphenol and 2,6-diisopropylphenol, respectively, were also found to be well suited for this transformation and gave the products **7y** and **7z** in good yields (82% and 78% correspondingly).

The successful implementation of *p*-QMs as electrophiles prompted us to explore fuchsones as an 1,6-acceptor (Scheme 2).

Scheme 2. Substrate Scope with Different Fuchsones[a,b]

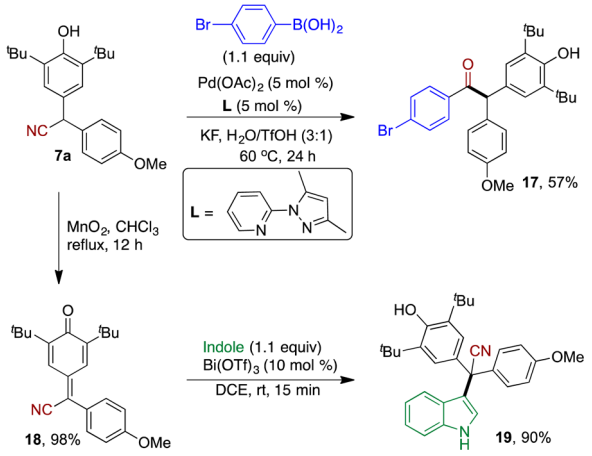


[a]Reaction conditions: All reactions were carried out with 20 mg of **15(a–f)** in 0.5 mL of solvent. [b]Reaction was carried out at 80 °C. Yields reported are isolated yields.

Potentially, this method will allow us to prepare α-triaryl nitriles, which otherwise are very difficult to access through the reported general methods. When a model reaction was performed with fuchsone **15a**[21] under optimized conditions (i.e., with 10 mol % of **8**), the reaction was found to be sluggish and the product **16a** was obtained only in 48% yield. This observation is obvious, as the sixth position of fuchsones is sterically more hindered when compared to that of *p*-QMs, which apparently makes **15a** less reactive toward Me_3Si-CN. However, increasing the catalyst loading to 15 mol % and also increasing the reaction time (12 h) helped in improving the yield of **16a** to 85%. So, further substrate scope studies were performed with 15 mol % of **8**, and the results are shown in Scheme 2. Most of the fuchsones (**15b–e**), derived from corresponding aryl ketones and 2,6-di(*tert*-butyl)phenol, were reacted with Me_3Si-CN under the modified reaction conditions and provided the subsequent products (**16b–e**) in good yields (73–89%). In the case of fuchsone **15f**, derived from 2,6-dimethylphenol and benzophenone, the corresponding product **16f** was isolated in 87% yield after 12 h.

To further show the significance of the developed protocol, derivatization reactions of one of the α-diaryl nitriles were investigated. In an experiment, **7a** was treated with 4-bromophenyl boronic acid under Pd-catalyzed oxidative conditions to give α,α'-diaryl ketone **17** in 57% yield (Scheme 3). α,α'-Diarylated carbonyl compounds are important building blocks for the synthesis of many biologically important molecules.[22] In another experiment, **7a** was oxidized with activated MnO_2 to afford 6-cyano-*p*-quinone methide **18** in almost quantitative yield. Similar types of cyanated *p*-QMs are

Scheme 3. Synthetic Elaborations of α-Diaryl Nitrile 7a



used as a chemical tool for assessing hemolytic anemia induced by naphthoquinones.[23] Besides, 6-cyano-*p*-quinone methide **18** was subjected to a nucleophilic addition reaction with indole to provide a leuconitrile[24] dye analogue **19** in 90% yield (Scheme 3).

In summary, we have demonstrated an efficient organocatalytic protocol for the synthesis of α-diaryl- and α-triarylnitriles. To the best of our knowledge, this is the first example of NHC catalyzed 1,6-conjugate addition of Me_3Si-CN to a dienone system. This transformation occurs under mild conditions and is tolerant to a variety of functional groups. Further, this protocol provides an easy and straightforward access to a set of new compounds in good to excellent yields.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00508.

Experimental details, ^1H, ^{13}C, and ^{19}F spectra of all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(20) Interestingly, in all the optimization experiments, the silylated phenol was not observed. Instead, only the desilylated product **7a** was detected even before the workup. The aqueous $Na_2S_2O_3$ workup was adopted to decompose the excess Me_3Si-CN.

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