Reaction of arynes, *N*-heteroaromatics and nitriles†

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Various *N*-heteroaromatic compounds, including pyridines, quinolines and isoquinoline, react with arynes and nitrile-containing solvents to give *N*-arylated 1,2-dihydro-2-pyridinyl, -2-quinolinyl and -1-isoquinolinyl nitriles in excellent yields.

The addition of nucleophiles to benzynes, generating the corresponding zwitterionic species as intemediates, has played a crucial role in the development of benzyne chemistry.[1] With its low-lying LUMO, benzyne can readily accept an electron lone pair from neutral nucleophiles such as pyridines,[2] pyrroles,[3] aziridines,[4] imidazoles,[5] amides,[1c] amines,[6] urea,[7] isocyanides,[1a,b] alcohols[8] and carboxylic acids.[8] Trapping of the resulting zwitterionic species with various electrophiles such as proton sources,[1c,6,8] imines or aldehydes[1a,b] gave the final products.

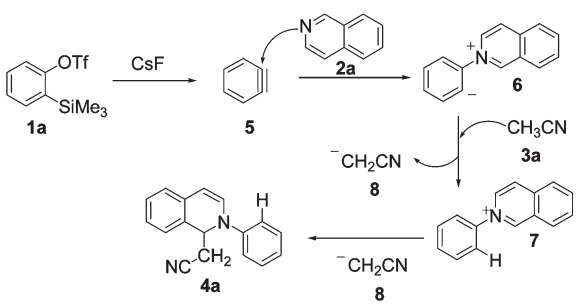
Although a vast number of reactions involving the addition of nucleophiles to arynes are known, there is no report of the trapping of the nucleophile–aryne zwitterions by nitrile-containing solvents. Our continuous interest in new aryne chemistry[9] has led us to the observation that alkyl nitriles with an α-hydrogen, acting as both a proton donor and a nucleophile, react with pyridine–benzyne zwitterions at both the benzyne and the pyridine moieties. Herein, we report the reaction of arynes, *N*-heteroaromatics and nitrile-containing solvents. The observation of the reaction of CH_3CN with aryne-based zwitterionic species is particularly important to benzyne chemistry in view of the fact that the generation of arynes from 2-trimethylsilylaryl triflates and CsF are often carried out in CH_3CN.

When 2-trimethylsilylphenyl triflate (**1a**) was treated with isoquinoline (**2a**) in CH_3CN (**3a**) in the presence of CsF at 50 °C for 8 h, a three-component assembled product from a molecule of isoquinoline, benzyne and CH_3CN, **4a**, was obtained in 85% isolated yield (Table 1, entry 1). It is noteworthy that CH_3CN was a reagent as well as a solvent in the reaction. The reaction is completely regioselective, with the cyanomethyl group adding only to the C-1 position of the isoquinoline ring. Product **4a** was thoroughly characterized by its ^1H and ^{13}C NMR, and mass data. In the reaction, benzyne was generated *in situ* from **1a** and CsF.[10]

The formation of product **4a** can be understood based on the mechanism shown in Scheme 1. Isoquinoline **2a** undergoes nucleophilic addition to benzyne **5** to give zwitterionic species **6**. The negative charge of the zwitterionic species abstracts a proton from CH_3CN (**3a**) to give intermediate **7** and acetonitrile anion **8**. The latter undergoes nucleophilic addition to the C=N double bond of isoquinolinium cation **7** to give product **4a**. This proposed mechanism is related to that of the Reissert reaction,[11] used for the selective addition of various electrophiles and nucleophiles to the C=N double bond of pyridine derivatives. Strong support for the mechanism in Scheme 1 comes from the results of a deuterium-labelling study of the reaction of **1a** and **2a** with CD_3CN **3b**. The observed product, **4b**, contains a CD_2CN group and a deuterium atom at one of the *ortho*-carbons of the phenyl ring (Table 1, entry 2). Product **4b** was characterized by the absence of ^1H NMR signals for the methylene proton, and the absence of ^{13}C NMR signals for the methylene carbon and one of the *ortho*-carbons of the phenyl ring. In addition, the two ^{13}C NMR signals of the two *meta*-carbons of the phenyl group can be clearly distinguished. The parent peak in the mass spectrum of **4b** also showed the presence of three deuterium atoms.

To understand the effect of substituents on the benzyne moiety in the present reaction, various substituted benzyne precursors **1b–g** were tested (Table 1, entries 3–8). Under similar reaction conditions, compound **1b**, containing 4,5-dimethyl groups, reacted smoothly with **2a** and **3a** to give the three-component product **4c** in 89% yield (Table 1, entry 3). Likewise, electron-rich benzyne precursors **1c** and **1d** reacted with **2a** and **3a** to afford **4d** and **4e** in excellent yields (Table 1, entries 4 and 5). Nevertheless, benzyne precursor **1e**, with two electron-deficient fluoride groups attached, gave product **4f** in moderate 51% yield (Table 1, entry 6). Thus, the presence of electron-withdrawing substituents on the benzyne ring appears less favorable for the present reaction, but the reason for this is not yet clear.

We next studied the regioselectivity of unsymmetrical benzynes **1f** and **1g** in the present reaction. When 1-(trimethylsilyl)-2-naphthyl triflate (**1f**) was treated with isoquinoline (**2a**) and CH_3CN (**3a**), two regioisomeric products, **4g** and **4g′**, were isolated in an 85 : 15 ratio in 73% combined yield (Table 1, entry 7). Clearly, **4g** is a steric-controlled product. The regiochemistry of **4g** was further confirmed by NOE experiments. On the other hand, 3-methoxybenzyne (**1g**) afforded **4h**, with the methoxy substituent *meta* to the amino group, exclusively in 75% yield (Table 1, entry 8). In this reaction, both steric and electronic effects favor **4h**.



Scheme 1

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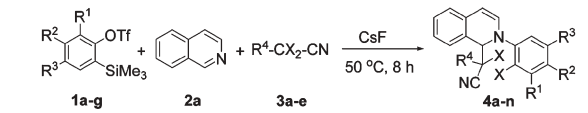
Table 1 Results of the reaction of arynes, *N*-heteroaromatics and nitriles[a]

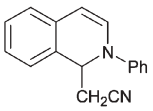
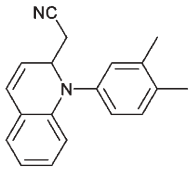
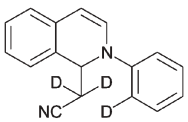
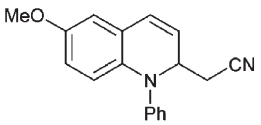
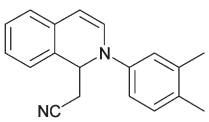
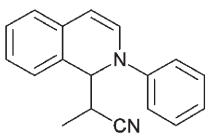
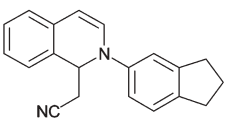
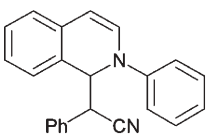
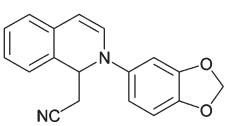
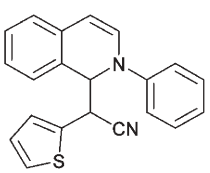
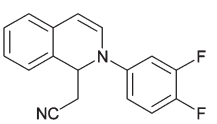
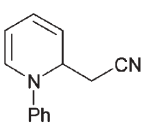
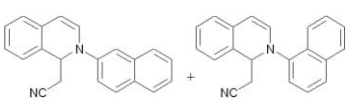
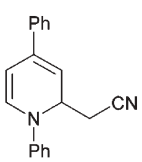
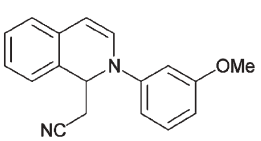
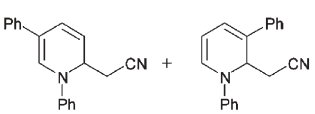
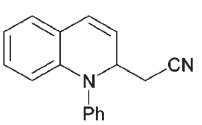
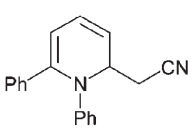


1a-g **2a** **3a-e** **4a-n**

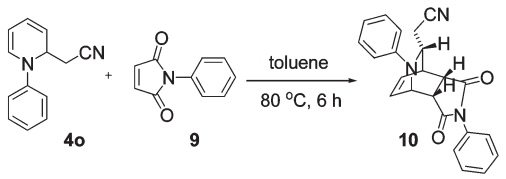
1a: $R^1 = R^2 = R^3 = H$
1b: $R^1 = H$, $R^2 = R^3 = Me$
1c: $R^1 = H$, $R^2 + R^3 = -(CH_2)_3-$
1d: $R^1 = H$, $R^2 + R^3 = -O-CH_2-O$
1e: $R^1 = H$, $R^2 = R^3 = F$
1f: $R^1 + R^2 = -CH=(CH)_2=CH-$, $R^3 = H$
1g: $R^1 = OMe$, $R^2 = R^3 = H$

2b: qunoline
2c: 6-methoxy qunoline
2d: pyridine
2e: 4-phenyl pyridine
2f: 3-phenyl pyridine
2g: 2-phenyl pyridine

3a: $R^4 = H$, X = H
3b: $R^4 = D$, X = D
3c: $R^4 = Me$, X = H
3d: $R^4 = Ph$, X = H
3e: R^4 = thiophene, X = H

Entry	1	2	3	Product	4	Yield (%)[b]	Entry	1	2	3	Product	4	Yield (%)[b]
1	**1a**	**2a**	**3a**		**4a**	85	10	**1b**	**2b**	**3a**		**4j**	80
2	**1a**	**2a**	**3b**		**4b**	84	11	**1a**	**2c**	**3a**		**4k**	79
3	**1b**	**2a**	**3a**		**4c**	89	12	**1a**	**2a**	**3c**[d]		**4l**	45[e]
4	**1c**	**2a**	**3a**		**4d**	85	13	**1a**	**2a**	**3d**[d]		**4m**	75[e]
5	**1d**	**2a**	**3a**		**4e**	83	14	**1a**	**2a**	**3e**[d]		**4n**	68[e]
6	**1e**	**2a**	**3a**		**4f**	51	15	**1a**	**2d**	**3a**		**4o**	70
7	**1f**	**2a**	**3a**		**4g**, **4g′**	73	16	**1a**	**2e**	**3a**		**4p**	85
8	**1g**	**2a**	**3a**		**4h**	75[c]	17	**1a**	**2f**	**3a**		**4q**, **4q′**	82
9	**1a**	**2b**	**3a**		**4i**	82	18	**1a**	**2g**	**3a**		**4r**	80

[a] Reaction conditions: Benzyne precursor **1** (1.0 mmol), pyridines **2** (1.2 mmol), nitrile **3a** or **3b** (3 ml) and CsF (2.0 mmol) at 50 °C for 8 h. [b] Isolated yields. [c] Reaction was carried out at room temperature for 8 h. [d] For nitriles **3c–e**, 1.0 ml was used. [e] 1 : 1 diastereoisomeric ratio.



Scheme 2

In addition to **2a**, quinoline (**2b**) underwent the three-component reaction efficiently with acetonitrile and benzyne precursors **1a** and **1b** under similar reaction conditions to provide products **4i** and **4j** in 82 and 80% yields, respectively (Table 1, entries 9 and 10). Similarly, 6-methoxyquinoline (**2c**) reacts with **1a** and **3a** to afford **4k** in 79% yield (Table 1, entry 11). The present protocol can be further applied to substituted acetonitriles **3c–e**. Propionitrile (**3c**) reacted effectively with **1a** and **2a** to give a pair of diastereomers **4l**, albeit in only 45% yield and a 1 : 1 diastereoisomeric ratio (Table 1, entry 12). The low yield relative to CH_3CN is probably due to the lower acidity of the α-protons in propionitrile. Likewise, 2-phenylacetonitrile (**3d**), and 2-(2-thienyl)-acetonitrile (**3e**) furnished the corresponding products **4m** and **4n** in 75 and 68% yields, respectively, both in *ca.* 1 : 1 diastereoisomeric ratios (Table 1, entries 13 and 14), determined by ^{1}H NMR experiments. It is noteworthy that 1,2-dihydroisoquinoline and 1,2-dihydroquinoline skeletons are found in a large number of naturally-occurring and synthetic biologically-active heterocyclic compounds. These substances exhibit psychotropic, anti-allergenic anti-inflammatory, sedative, anti-depressant, anti-tumor, and anti-microbial activities.[12]

The present methodology can be further extended to pyridines **2d–g**. Under the standard reaction conditions, the reaction of pyridine (**2d**) with **1a** and **3a** afforded **4o** in 70% yield (Table 1, entry 15). Similarly, 4-phenylpyridine (**2e**) gave **4p** in 85% yield (Table 1, entry 16). The use of unsymmetrically-substituted pyridine **2f** as a substrate uncovers the regioselectivity of the reaction. Treatment of 3-phenylpyridine (**2f**) with **1a** and **3a** provided two regioisomeric products **4q** and **4q′** with a 55 : 45 ratio in 82% combined yield (Table 1, entry 17). Products **4q** and **4q′** were separated by column chromatography and fully characterized by spectroscopic techniques. In contrast, 2-phenylpyridine (**2g**) reacted with **1a** and **2a** regioselectively to afford **4r** exclusively in 80% yield (Table 1, entry 18). The other regioisomer was not observed in the ^{1}H NMR spectrum of the crude reaction mixture. The result of the three-component reaction of pyridine (**2d**) with **1a** and **3a** is surprising in view of the results reported by Ihara *et al.*, which showed the formation of pyridine–benzyne polymer at a slightly lower temperature.[2d] Therefore, we checked carefully the reaction mixtures and observed some polymerized product, but in a very low yield. For the substituted pyridines **2e–g**, no polymerization product was observed.

To demonstrate the utility of 1,2-dihydropyridine in organic synthesis, we carried out the [4 + 2] Diels–Alder cycloaddition reaction of 1,2-dihydropyridine with *N*-phenyl maleimide (**9**).[13] Treatment of **4o** with **9** in toluene at 80 °C for 6 h afforded 2-azabicyclo[2.2.2]octane (isoquinuclidine) derivative **10** in 80% isolated yield (Scheme 2). The reaction is highly stereospecific and only one diastereomer was isolated. The stereochemistry was determined by NOE experiments.[13b] It is important to point out that isoquinuclidines are widely occurring natural products that show various biological activities.[13c]

In conclusion, we have observed a new reaction of arynes, *N*-heteroaromatic compounds and nitriles. The involvement of CH_3CN in the present reaction, and also the likely role of aryne-based zwitterionic species, is particularly important in the development of benzyne chemistry, due to the fact that benzynes are often generated in this solvent. This method allows the construction of new C–C and C–N bonds in one pot, and allows an efficient synthesis of various *N*-arylated 1,2-dihydro-1-isoquinolinyl, 1,2-dihydro-2-quinolinyl and 1,2-dihydro-2-pyridinyl nitriles in good to excellent yields. Further studies with other pronucleophiles and different *N*-heteroaromatic compounds are in progress.

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