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Cycloaddition of 1,4-Diaryl-1,3-butadiynes with Nitriles: An Atom-economic One-pot Approach to Benzo[*f*]quinazolines

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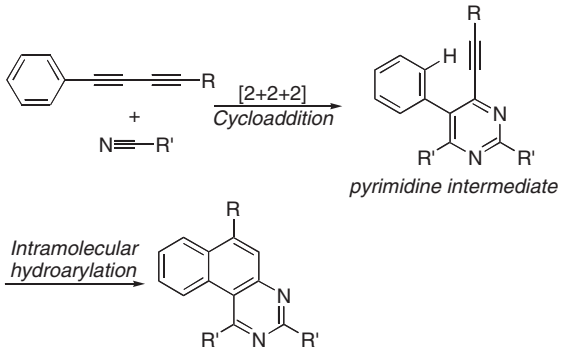
A one-pot synthesis of benzo[*f*]quinazoline by a novel cycloaddition of 1,4-diaryl-1,3-butadiynes with nitriles in the presence of trifluoromethanesulfonic acid at 120 °C is developed.

Quinazoline derivatives are an important class of *N*-heterocyclic compounds, which have been found as the core structure in many natural and synthetic products showing biological and physiological activities,[1] or optoelectronic properties.[2] Therefore, many methods have been developed for the synthesis of such compounds.[3] Recently, various domino reactions based on substituted phenyl halides have also been developed as powerful methods to construct quinazoline skeletons.[4]

On the other hand, benzoquinazolines also exhibit interesting biologic activities such as antifolate[5a] and antimalarial activities[5a] and show inhibiting effects on many enzymes such as thymidylate synthase[5b,5c] and topoisomerase.[5d] However, only a few methods for the syntheses of benzoquinazolines have been reported, including the use of naphthylamine derivatives[5a,6a] or tetralone derivatives,[6b] which are not easily accessible, as the starting materials or those employing simple starting compounds but involve multiple steps and give a low total yield.[7]

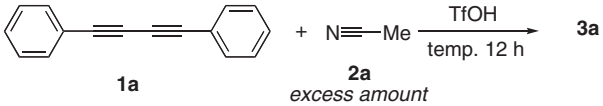
In recent years, 1,4-disubstituted-1,3-butadiynes, which are easily obtained from alkynes by several efficient synthetic methods,[8] have become an important class of starting materials for the synthesis of cyclic compounds such as furans,[9] pyrroles,[9,10] naphthalenes,[11] thiophenes,[9b,12] and others.[13] Inspired by our previous work on naphthalene synthesis from 1,4-diaryl-1,3-butadiyne,[11] we design a domino route for the formation of the benzoquinazoline ring, via the [2 + 2 + 2] cycloaddition of aryl-substituted 1,3-butadiyne with two molecules of nitrile to form pyrimidine derivatives and subsequent intramolecular hydroarylation of the other C–C triple bond to achieve a novel cycloaddition reaction, as shown in Scheme 1.

It is well known that strong protonic acids can promote the [2 + 2 + 2] cycloaddition of alkynes with nitriles to afford pyrimidine derivatives[14] and the intramolecular hydroarylation of alkynes.[15] Thus, we examined the reaction of 1,4-diphenyl-1,3-butadiyne (**1a**) with acetonitrile (**2a**) in 1,2-dichloroethane (DCE) in the presence of different acidic reagents. Lewis acids such as $CuCl_2$, $Cu(OTf)_2$, $AuCl_3$, and protonic acids such as AcOH, TFA, methanesulfonic acid, and sulfuric acid failed to promote the cycloaddition reaction. Fortunately, trifluoromethanesulfonic acid (TfOH) (2.5 equiv) could promote the expected cycloaddition reaction at 80 °C to afford 1,3-dimethyl-6-phenylbenzo[*f*]quinazoline (**3a**) in low yield (Table 1, Entry 1).



Scheme 1. Strategy for the formation of benzoquinazolines.

Table 1. The cycloaddition of 1,4-diphenyl-1,3-butadiyne (**1a**) with acetonitrile (**2a**) under different conditions[a]



Entry	TfOH/equiv	**2a**/mL	Temp/°C	Yield of **3a**/%
1[b]	2.5	1	80	5
2	2.5	1	80	11
3	2.5	4	80	25
4	2.5	10	80	26
5	2.5	4	100	33
6	2.5	4	120	45
7	2.5	4	150	39
8	4.0	4	120	44
9	0.5	4	120	0

[a]The reactions were carried out with 0.5 mmol of **1a**, acetonitrile (**2a**) in the presence of TfOH. [b]The reaction is conducted in DCE (4.0 mL).

The structure of **3a** was confirmed from spectroscopic data and X-ray crystallography (Figure 1).[16] The other possible structure of the cycloadduct 2,4-dimethyl-6-phenylbenzo[*h*]quinazoline (**3a′**) could not be determined at all in the reaction mixture, indicating that **3a** was formed with high selectivity (Scheme 2).

Encouraged by the initial results, we studied the reaction of **1a** with **2a** under different conditions in detail to optimize the reaction conditions for the formation of **3a**. Screening of solvents revealed that when the reaction was carried out in organic solvents such as DCE, DCM, DMF, toluene, THF, and *n*-hexane at 80 or 120 °C in a sealed tube, **3a** was formed in low yield (<10%), while under solvent-free conditions, the forma-

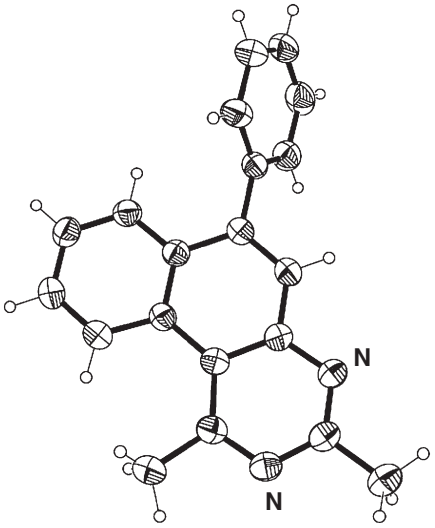
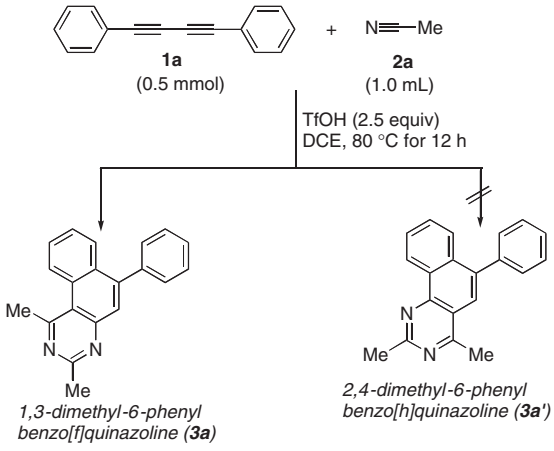


Figure 1. Molecular structure of **3a**.

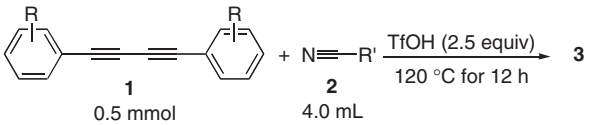


Scheme 2. TfOH-promoted cycloaddition of 1,4-diphenyl-1,3-butadiyne (**1a**) with acetonitrile (**2a**).

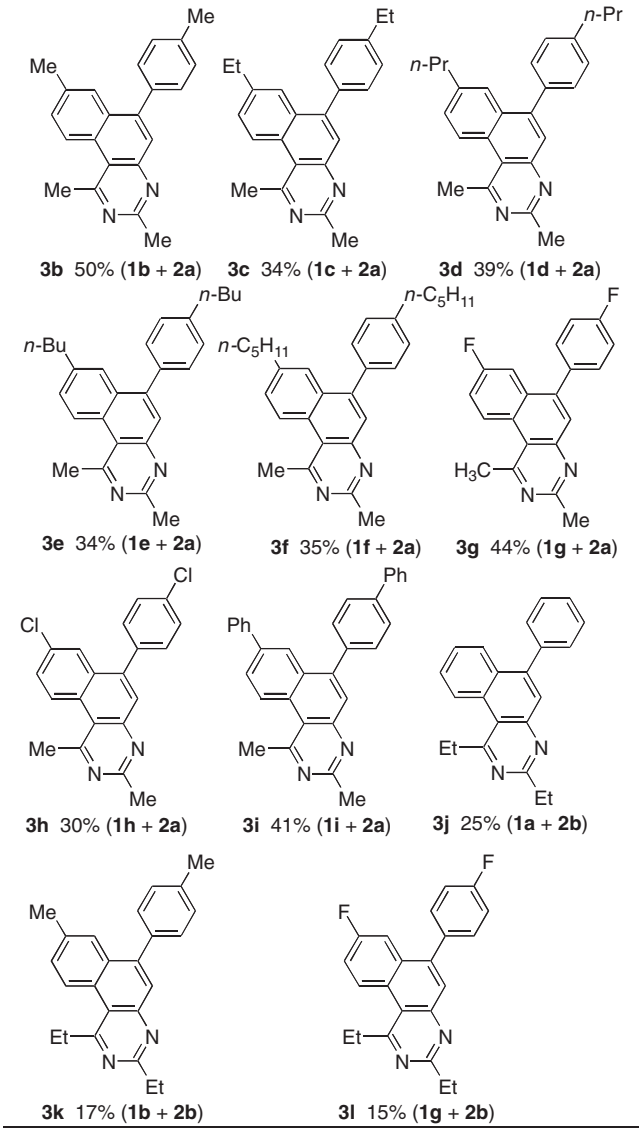
tion of **3a** improved considerably (Entry 2 vs. Entry 1 in Table 1). An increase in the amount of **2a** (Entries 3 and 4) or the reaction temperature (Entries 5 and 6) could also improve the yield of **3a**. When the reaction was performed in 120 °C with ca. 153 equiv (4.0 mL) of **2a**, **3a** was obtained in 45% isolated yield (Entry 6). However, the yield of **3a** could not be further improved by increasing the reaction temperature to 150 °C (Entry 7) or by increasing the number of equivalents of TfOH (Entry 8). It should be noted that the use of excess amounts of TfOH is crucial to realize the present transformation, since the use of 0.5 equiv of TfOH resulted in no formation of **3a**, probably because **3a** is a weakly basic compound (Entry 9).

To expand the utility of the present synthetic method for benzo[*f*]quinazoline derivatives, reactions of a variety of 1,4-diaryl-1,3-butadiynes with excess amounts of nitriles under the conditions indicated in Entry 6 of Table 1 were investigated (Table 2).[17] The results concluded in Table 2 revealed several features of the present cyclocondensation: (1) there was no notable effect of the electron-donating group (**1b**–**1f**) or electron-withdrawing group (**1g**–**1i**) on the aromatic ring of the diynes,

Table 2. Synthesis of benzo[*f*]quinazoline derivatives



R = H (**1a**), R = *p*-Me (**1b**), R = *p*-Et (**1c**), R = *p*-*n*-Pr (**1d**), R = *p*-*n*-Bu (**1e**), R = *p*-*n*-C_5H_{11} (**1f**), R = *p*-F (**1g**), R = *p*-Cl (**1h**), R = *p*-Ph (**1i**); R' = Me (**2a**), R' = Et (**2b**)



3b 50% (**1b** + **2a**) **3c** 34% (**1c** + **2a**) **3d** 39% (**1d** + **2a**)

3e 34% (**1e** + **2a**) **3f** 35% (**1f** + **2a**) **3g** 44% (**1g** + **2a**)

3h 30% (**1h** + **2a**) **3i** 41% (**1i** + **2a**) **3j** 25% (**1a** + **2b**)

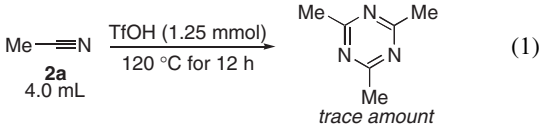
3k 17% (**1b** + **2b**) **3l** 15% (**1g** + **2b**)

and the reactions afforded the desired products in 30–50% yield; (2) the cyclocondensation of **1a**, **1b** (electron-rich alkyne), and **1g** (electron-deficient alkyne) with propionitrile **2b** also occurred under the reaction conditions to afford the expected benzo[*f*]-quinazoline derivatives **3j**–**3l** in relatively low yields. Note that when benzonitrile was used, the desired product was not obtained at all.

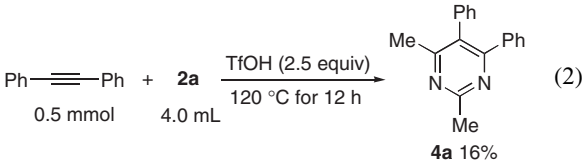
In addition, we examined the reaction of monoalkyl-substituted 1,3-butadiyne with **2a**, but the desired benzoquinazoline derivatives could not be isolated from the reaction mixtures since these reactions afforded a complex mixture of products,

possibly because of the shift of the C–C triple bond and/or isomerization of the C–C triple bond to allenes or dienes under the reaction conditions.

As shown in eq 1, the behavior of **2a** under the same reaction conditions in the absence of the diyne was studied, and the formation of trace amounts of 2,4,6-trimethyl-1,3,5-triazine was detected by GC-MS analysis of the reaction mixture. Moreover, since there seems to be no general report on the synthesis of pyrimidines via [2 + 2 + 2] cycloaddition of alkynes with two molecules of nitriles,[14,18] the reaction of diphenylacetylene with **2a** was also examined, and a low yield of 2,4-dimethyl-5,6-diphenylpyrimidine (**4a**) was isolated from the reaction mixture. In addition, the formation of some unidentified products (eq 2) was noted. These results support the designed route for the formation of benzoquinazolines through a pyrimidine intermediate, as shown in Scheme 1.



(1)



(2)

In conclusion, we have established a one-pot strategy for the synthesis of benzo[*f*]quinazoline derivatives via a novel cycloaddition of aryl-substituted 1,3-butadiynes with acetonitrile or propionitrile in the presence of trifluoromethanesulfonic acid. Although the yields of the products were modest, the present protocol is an attractive synthetic route to benzo[*f*]quinazolines, with notable advantages of high atom efficiency, one-pot operation, and easy availability of the starting materials.

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