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Cobalt-Catalyzed Intramolecular [2 + 2 + 2] Cocyclotrimerization of Nitrilediynes: An Efficient Route to Tetra- and Pentacyclic Pyridine Derivatives

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ABSTRACT

In this paper, we wish to report the intramolecular [2 + 2 + 2] cocyclotrimerization of nitrilediynes catalyzed by the CoI_2(dppe)/Zn system at 80 °C in CH_3CN. Under these reaction conditions, various highly substituted nitrilediynes having steric conjunction at the α and β positions to a nitrile group and a bulkier substitution at the terminal carbon of alkyne undergo [2 + 2 + 2] cocylotrimerization to afford tetra- and pentacyclic pyridine derivatives in good to excellent yields.

The preparation of complex polycyclic pyridine derivatives is an important synthetic goal because of the utility of these molecules as potential pharmaceuticals.[1] In addition, these derivatives are versatile building bocks in the synthesis of natural products[2a−c] and useful ligands in phosphorescent emitters for organic light-emitting diodes.[2d−g] Transition-metal-catalyzed [2 + 2 + 2] cocyclotrimerization of two alkynes with a nitrile is an exceedingly attractive method for the construction of pyridine derivatives in highly atom-economical manner.[3−9] Wakatsuki and Yamazaki reported[4a] the first example of intermolecular cobalt-catalyzed cocy-

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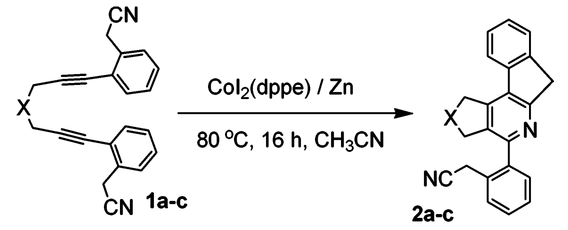
clotrimerization of two alkynes with a nitrile affording pyridine derivatives, while Naiman and Vollhardt observed[4b] the first cobalt-catalyzed partially intermolecular cocyclotrimerization of diynes with a nitrile providing bicyclic pyridines. There are now numerous examples of [2 + 2 + 2] cocyclotrimerization of alkynes or diynes with a nitrile using various metal complexes such as Co,[4−5] Ru,[6] Ni,[7] and Rh[8a] as catalysts.[9] However, to the best of our knowledge, only one report of the intramolecular version appeared very recently.[6e] This report discussed only three examples of cyanodiynes, which having less hindered substituents (H or Me) at the terminal carbon underwent the intramolecular cocyclotrimerization via slow-addition technique in order to aviod the bimolecular side reactions.

Our continuous interest in metal-catalyzed cocyclotrimerization reactions[10] prompted us to explore the possibility of using cobalt phosphine complexes as catalysts for the [2 + 2 + 2] cocyclotrimerization of nitrilediynes. In this paper, we wish to report the intramolecular [2 + 2 + 2] cocyclotrimerization of nitrilediynes catalyzed by a cobalt phosphine complex under relatively mild conditions. The cobalt complex shows excellent catalytic activity toward nitrilediynes having steric conjunction at α and β positions to a nitrile group and a bulkier substitution at the terminal carbon of alkyne. Although many synthetic routes to pyridines exist, most methods are scarcely used due to the lack of generality or selectivity and the requirement of harsh reaction conditions.[11] The present catalytic reaction provides an efficient method for the synthesis of tetra- and pentacyclic pyridine derivatives in excellent yields under mild conditions in one pot.

The intramolecular [2 + 2 + 2] cocyclotrimerization of 1,7-bis(2-cyanomethylbenzene)hepta-1,6-diyne **1a** proceeded smoothly in the presence of CoI_2(dppe) (5 mol %) and Zn (2.75 mmol) in CH_3CN at 80 °C for 16 h yielding tetracyclic pyridine derivative **2a** in 85% yield (Scheme 1). The other competitive cycloaddition products were not observed in the ^1H NMR of the crude reaction mixture. Product **2a** was thoroughly characterized by its ^1H and ^{13}C NMR and mass spectral data. Control experiments revealed that in the absence of the cobalt catalyst or Zn powder, no **2a** was obtained.

Scheme 1. Cobalt-Catalyzed Intramolecular [2 + 2 + 2] Cocyclotrimerization of Symmetrical Nitrilediynes



1a-c

2a-c

1a: X = CH_2
1b: X = O
1c: X = NTs

2a: 85%
2b: 74%
2c: 61%

To understand the nature of the present catalytic reaction, various cobalt phosphine complexes were tested for the activities using **1a** as the substrate. Monodentate phosphine complexes $CoCl_2(PPh_3)_2$ and $CoI_2(PPh_3)_2$ were active but gave **2a** in only 15 and 20% yields, respectively. Bidentate phosphine complexes are much more active. CoI_2(dppm) and CoI_2(dppp) afforded **2a** in 55 and 49% yields, respectively, while CoI_2(dppe) provided the highest 85% yield of **2a**. For comparison, $CpCo(CO)_2$, which is the most widely used catalyst for the [2 + 2 + 2] cycloaddition of alkynes with a nitrile,[4−5,9] did not show any catalytic activity for the cocyclotrimerization of **1a** in CH_3CN at 80 °C for 16 h. It should be noted that most of the $CpCo(CO)_2$-catalyzed reactions require higher temperature or photoactivation. The present CoI_2(dppe)/Zn catalyst system requires only 80 °C without photoinduction. Of the solvents tested, CH_3CN was most effective, affording the highest yield of **2a**. The other solvents, THF, toluene, and NMP, were totally ineffective.

The scope of the present [2 + 2 + 2] cocyclotrimerization using substituted nitrilediynes was investigated under the optimized reaction conditions (Scheme 1 and Table 1). Similar to **1a**, symmetrical nitrilediynes **1b**,**c** having an oxygen or nitrogen at the central position afforded polycyclic pyridine derivatives **2b** and **2c** in 74 and 61% yields, respectively (Scheme 1). The cocyclotrimerization of unsymmetrical nitrilediynes **1d** and **1e** having a phenyl group at one of the terminal position and 2-cyanomethylbenzene at the other terminal position proceeded smoothly to give tetracyclic pyridine derivatives **2d** and **2e** in excellent yields (Table 1, entries 1 and 2). Similarly, thienyl-, silyl-, and methyl-substituted nitrilediynes **1f**−**i** gave the desired pyridine derivative **2f**−**i** in 74, 79, 84, and 58% yields, respectively (entries 4−6).

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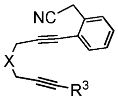
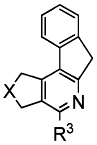
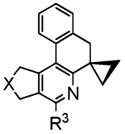
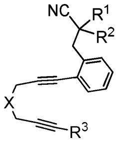
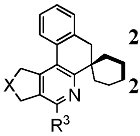
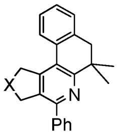
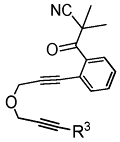
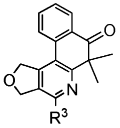
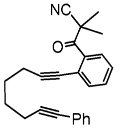
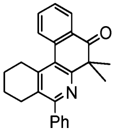
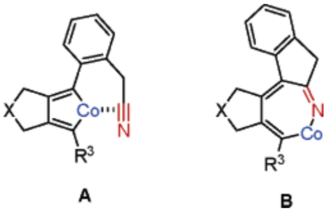
Table 1. Cobalt-Catalyzed Intramolecular [2 + 2 + 2] Cocyclotrimerization of Unsymmetrical Nitrilediynes[a]

entry	1		product 2		yield (%)[b]
1		**1d**: X = CH$_2$, R^3 = Ph		**2d**	91
2		**1e**: X = O, R^3 = Ph		**2e**	94
3		**1f**: X = CH$_2$, R^3 = 2-thienyl		**2f**	74
4		**1g**: X = CH$_2$, R^3 = SiMe$_3$		**2g**	79
5		**1h**: X = O, R^3 = SiMe$_3$		**2h**	84
6		**1i**: X = O, R^3 = CH$_3$		**2i**	58
7		**1j**: X = C(CO$_2$Me)$_2$, R^3 = H		**2j**	52
8		**1k**: X = CH$_2$, R^1+R^2 = -(CH$_2$)$_2$-, R^3 = Ph		**2k**	87
9		**1l**: X = NTs, R^1+R^2 = -(CH$_2$)$_2$-, R^3 = SiMe$_3$		**2l**	65
10		**1m**: X = O, R^1+R^2 = -(CH$_2$)$_5$- , R^3 = Ph		**2m**	92
11		**1n**: X = NTs, R^1+R^2 = -(CH$_2$)$_5$-, R^3 = SiMe$_3$		**2n**	71
12		**1o**: X = CH$_2$, R^1+R^2 = -(CH$_2$)$_5$-, R^3 = 2-thienyl		**2o**	83
13		**1p**: X = NTs, R^1 = R^2 = CH$_3$, R^3 = Ph		**2p**	81
14		**1q**: R^3 = Ph		**2q**	87
15		**1r**: R^3 = 1-napthyl		**2r**	77
16		**1s**		**2s**	46[c]

[a] All reactions were carried out using substituted nitrilediynes **1d**−**s** (1.00 mmol), CoI$_2$(dppe) (5 mol %), and Zn (2.75 mmol) in CH$_3$CN (3.0 mL) at 80 °C for 16 h. [b] Isolated yields. [c] The reaction time was 60 h.

To our surprise, nitrilediynes having structures similar to **1d**−**i** but with a terminal alkyne group (R^3 = H) do not undergo the expected [2 + 2 + 2] cocyclotrimerization under the standard reaction conditions. Among the nitrilediynes with a terminal alkyne group tested, only **1j** having a quaternary carbon center afforded the expected product in 52% yield (entry 7). This is probably due to the stronger Thorpe−Ingold effect[12] of **1j** relative to the other nitrilediynes **1d**−**i** (R^3 = H) leading to easier formation of the cobaltacycle intermediate.

The current method can be successfully extended to various nitrilediynes **1k**−**s** in which substituents are present at the α and β carbon of the nitrile group. Thus, nitrilediynes **1k** and **1l** possessing a cyclopropane group underwent the expected cycloaddition to give pentacyclic pyridines **2k** and **2l** in 87 and 65% yields (entries 8 and 9). Nitrilediynes **1m**−**o**, having an oxygen or an amide group at the internal atom X and a cyclohexane substitution at the α carbon to the nitrile group, give the corresponding substituted pentacyclic pyridines **2m**−**o** in 92, 71, and 83% yields (entries 10−12). Likewise, nitrilediyne **1p** with dimethyl substitution at the α carbon also gave a highly functionalized pyridine **2p** in 81% yield (entry 13). In a similar manner, nitrilediynes **1q** and **1r** having a keto group at the β position afford tetracyclic pyridine derivatives **2q** and **2r** in 87 and 77% yields (entries 14 and 15). Compared to **1q** and **1r**, nitrilediyne **1s** is less reactive requiring 60 h at 80 °C to produce **2s** in only 46% yield (entry 16). The construction of a 6-membered ring from the 1,7-octadiyne group in **1s** appears less facile than the formation of the corresponding 5-membered rings from **1q** and **1r**. These above results clearly revealed that nitrilediynes having steric conjunction at the α and β position to the nitrile group and bulkier substitutions at the terminal carbon works smoothly to give the corresponding cocyclotrimerization products in good to excellent yields (entries 8−16).



The catalytic reaction is likely initiated by the reduction of Co(II) species to Co(I) species by zinc powder.[13] Coordination of the diyne groups of nitrilediyne to the cobalt center followed by cyclometalation produces cobaltacyclopentadiene intermediate **A**. Intramolecular coordination of the nitrile group and subsequent insertion into a Co(III)-carbon bond gives cobaltacycloheptadiene intermediate **B**. Final reductive elimination affords product **2** and regenerates the Co(I) catalyst.

It is important to point out that in most of the reported [2 + 2 + 2] cocyclotrimerization reactions of diynes with a nitrile and with other carbon−carbon multiple bonds, the reactions proceeded only with diynes having less hindered substituents (H, Me, or Et) at the terminal carbon(s).[3−9] For diynes having bulkier substituents (Ph or naphthyl), the reaction gave only minor amount of the corresponding cocyclotrimerization product.[3−9] In contrast, in our present system, the [2 + 2 + 2] cocyclotrimerization of nitrilediynes requires a bulkier substituent such as Ph, thienyl, SiMe$_3$, or naphthyl at the terminal carbon to obtain high product yields (Table 1, entries 1−16). This observation is crucial to the success of the present catalytic reaction. While the exact reason is not yet clear, a bulkier group at the terminal alkyne carbon likely prevents intermolecular [2 + 2 + 2] cocyclo-

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trimerization among the alkynyl groups due to the steric hindrance imparted by the substituents (R^3) but allows the less reactive and yet less bulkier CN group to have a greater chance to undergo intramolecular [2 + 2 + 2] cocyclotrimerization with the two alkyne groups.

In conclusion, we have demonstrated the first intramolecular [2 + 2 + 2] cocyclotrimerization of nitrilediynes catalyzed by the $Co(dppe)I_2/Zn$ system to afford polycyclic pyridine derivatives at relatively low temperature in a highly atom-economical manner. The presence of a bulkier substitution at the terminal alkyne carbon of the nitrilediynes is essential for this catalytic intramolecular [2 + 2 + 2] cocyclotrimerization to proceed smoothly. The cobalt system appears to be an alternative to the widely used $CoCp(CO)_2$ as the catalyst for [2 + 2 + 2] cycloaddition.

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Supporting Information Available: Starting material preparations, spectral data, and copies of ^1H and ^{13}C NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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