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Cobalt-Catalyzed Alkyne–Nitrile Cyclotrimerization To Form Pyridines in Aqueous Solution

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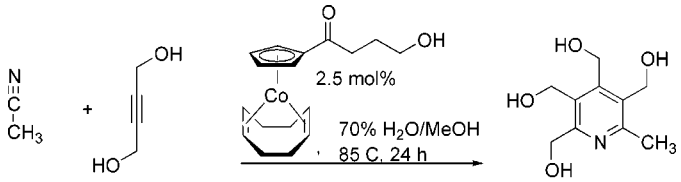
ABSTRACT



A new, water-soluble cobalt(I) catalyst has been used in the aqueous, chemospecific, cyclotrimerization of one nitrile with two alkynes for the synthesis of highly functionalized pyridines. Several different functional groups are well incorporated in this transformation, including unprotected alcohols, ketones, and amines. Double isotopic crossover data, as well as nitrile dependence on the rate of product formation, suggest associative rate-determining coordination of the nitrile.

An increasing number of useful chemical transformations are being conducted in aqueous solution.[1] Environmental concerns around volatile organic solvents have created an impetus to develop these new chemistries.[2] Moreover, water has also been shown to induce rate enhancements,[3] chemoselectivity,[4] and stereoselectivity[5] in various synthetic transformations. Numerous transition-metal-catalyzed transformations employing oxidatively stable metal species are conducted in water.[6] We recently reported on the first examples of benzene formation by cyclotrimerization of alkynes in aqueous solution employing a new cobalt catalyst.[7] Typically, cyclopentadienylcobalt(dicarbonyl) (**1**) catalyzed cyclotrimerizations are photochemical and conducted in refluxing aprotic solvents. The organic substrates commonly used in these cyclizations have protected functional groups presumably because of the sensitivity of low oxidation state cobalt complexes.[8] Transition-metal-catalyzed cyclotrimerization is a powerful synthetic methodology that Vollhardt[9] has elegantly exploited in the synthesis of numerous complex carbo- and heterocyclic aromatic molecules. Herein we report the first example of cobalt-mediated pyridine formation in aqueous solution with a new cobalt catalyst, **2** (eq 1), under

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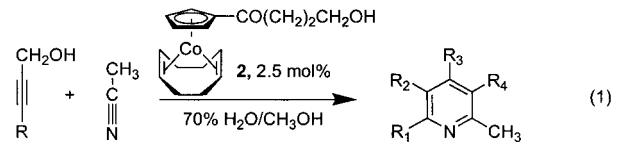
purely thermal conditions without photochemical activation or the need to supply the nitrile reagent in excess.



3, R = CH_2OH
28, R = H

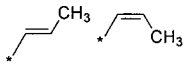
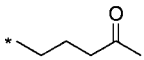
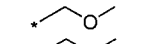
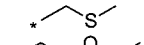
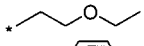
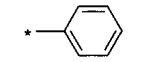
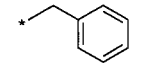
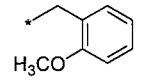
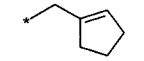
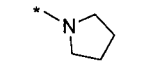
4, $R_1 = R_2 = R_3 = R_4 = CH_2OH$
29, $R_1 = R_3 = H$; $R_2 = R_4 = CH_2OH$
30, $R_1 = R_4 = H$; $R_2 = R_3 = CH_2OH$
31, $R_2 = R_3 = H$; $R_1 = R_4 = CH_2OH$
32, $R_2 = R_4 = H$; $R_1 = R_3 = CH_2OH$

Cobalt-catalyzed cyclotrimerization of alkynes and nitriles to form pyridines was first reported by Wakatsuki and Yamazaki.[10] Recently, exciting work by Heller[11] on cobalt-catalyzed cyclotrimerization to form pyridines under photochemical conditions and with the inclusion of surfactants in the aqueous reaction medium has sparked renewed interest in cobalt-catalyzed formation of pyridines. To date, many transition-metal-catalyzed cyclotrimerizations used in the synthesis of pyridines yield a substantial amount of the corresponding benzene as a side product.[12] This significantly diminishes the utility of this methodology for the synthesis of heterocycles and can lead to the use of excess reagents, which is a serious limitation when expensive nitriles are required.[13] Creative methods have been employed to suppress the competing side reaction to form benzenes in these cyclotrimerizations with varying success.[14]

We previously reported that a wide range of functional groups were tolerated by **2** in alkyne cyclotrimerizations to form benzenes.[7] To investigate the tolerance of nitrile functional groups in cyclotrimerization with alkynes catalyzed by **2** to form pyridines, 2-butyne-1,4-diol (**3**) was treated with acetonitrile (**4**, 20 equiv) and **2** (2.5 mol % based on alkyne).[15] After less than 2 h at 85 °C, there was an appreciable amount of precipitate in the reaction vessel. After a total reaction time of 20 h, workup of the reaction mixture revealed the precipitate to be the desired pyridine **16**. In a series of experiments, the concentration of **4** was systematically reduced from 20 equiv to 0.5 equiv relative to **3** and still afforded the desired pyridine **16**. To determine if the nitrile substituent would have an impact on the stoichiometry required for successful cyclotrimerization with **3** to form pyridines, the nitriles shown in Table 1 were tested under the standard reaction conditions using a 2:1 alkyne:nitrile ratio.[15]

Table 1 illustrates that most functional groups tested were incorporated with good to excellent yield. The exceptions were the nitriles **8** and **9**, which gave poor yields of the expected pyridine.[16] This negative effect on cyclotrimerization may have its origin in the juxtaposition of the nitrile and ether (or sulfide) functionalities in **8** (or **9**), but future investigation is required to better understand this result. Substrate **10** gave a good yield of **22,** showing that an ether functionality can be included as a nitrile substituent in this cyclotrimerization method.

Table 1. Pyridine Product Yields from Various Nitriles Cyclotrimerized with **3** under the General Reaction Conditions[15]

nitrile:product	R'—C≡N	yield, %[a]
4:16		76
5:17		71
6:18		73
7:19		75
8:20		32
9:21		38
10:22		78
11:23		99
12:24		74
13:25		88
14:26		75
15:27		71

[a] Isolated yields of cyclotrimerization products of listed nitriles and **3**. [b] An asterisk indicates the position of the nitrile carbon. **5** is a 50/50 mixture of cis and trans isomers.

For all the examples reported in Table 1, no benzene side products from competing alkyne cyclotrimerization were isolated or observed by NMR. To detect even trace amounts of benzene side products, reactions were analyzed using LC-MS. As representative examples, nitriles **4** and **11**, which are both sterically and electronically different, were chosen to react with **3** for this LC-MS study (Figure 1). These reactions were monitored by ^1H NMR and LC-MS for greater than 3 half-lives.[15] All samples contained less than 1% of the hexa(hydroxymethyl)benzene side product.

Cyclotrimerizations catalyzed by **1** to form pyridines in organic solvents have not shown any nitrile concentration dependence on the rate of product formation.[17] To better understand catalyst **2**, kinetic studies were performed in

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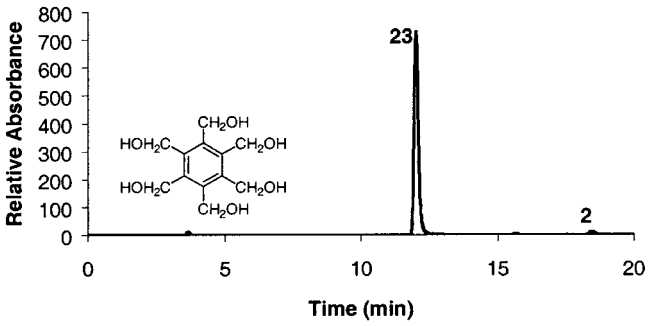

Figure 1. LC trace of the cyclotrimerization between **3** and **11**.

triplicate under pseudo-first-order conditions by increasing the concentration of **4** while keeping the concentration of **2** and **28** constant. Increasing the concentration of **4** resulted in a corresponding increase in the rate of pyridine formation (Figure 2). A plot of the pseudo-first-order rate constant (k_{obs})

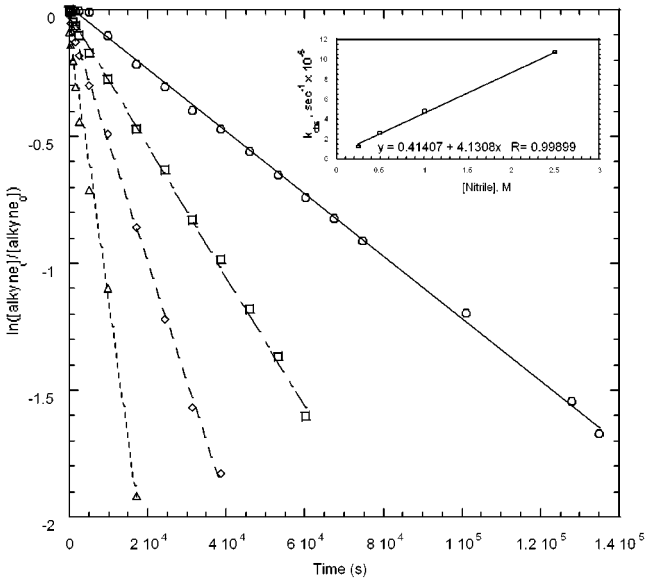

Figure 2. Dependence of concentration of acetonitrile on the rate of pyridine formation: (○) 250 mM acetonitrile, (□) 500 mM, (◊) 1 M, (△) 2.5 M.

vs the concentration of **4** gave good linearity ($r = 0.9989$) and a second-order rate constant of 4.1×10^{-5} M^{-1} s^{-1} (see inset graph in Figure 2). The observed nitrile dependence is unprecedented in alkyne−nitrile cyclotrimerization.

The results presented thus far do not explain the unprecedented chemoselectivity of **2** to form exclusively pyridines, at 2:1 alkyne:nitrile stoichiometry. Pyridines are well know to serve as good ligands in transition metal complexes.[18] It was of interest to determine what effect a pyridine product could have on an *alkyne* cyclotrimerization catalyzed by **2**. We began by conducting a cyclotrimerization using **3** and monitoring the conversion to hexa(hydroxymethyl)benzene by ^{1}H NMR. After 1 half-life, pyridine **16** (50 mol %) was added and the rate of hexa(hydroxymethyl)benzene formation dropped by more than an order of magnitude. After following the cyclotrimerization of **3** for 5 h, a stoichiometric amount of **4** was added and the rate of pyridine **16** formation was followed by ^{1}H NMR. The rate of cyclotrimerization of **3** to give hexa(hydroxymethyl)benzene was found to be approximately 100 times slower under these conditions than the reaction of **3** and **4** to give **16**. Taken together, these results imply the formation of a cobalt−pyridine complex that is too tightly coordinated to be displaced by an alkyne yet weak enough to be substituted by a nitrile in an associative process.

In summary, we have extended the applicability of aqueous cyclotrimerizations to include the formation of highly functionalized pyridines under mild conditions without the need for photochemical activation. The reaction requires only a stoichiometric amount of nitrile and a low catalyst loading, making the use of expensive nitriles more feasible. The reaction conditions are amenable to a wide range of unprotected functional groups with good to excellent yields in most examples. Double isotopic crossover data show there is no dissociation of ligands during the catalytic cycle. The results of the nitrile dependence on the rate of pyridine formation, as well as the product inhibition studies, suggest associative rate-determining coordination of the nitrile. It appears that **2** has some interesting and unforeseen attributes as a cyclotrimerization catalyst. Given the ease in the preparation of **2**, and the mild thermal conditions under which nitrile−alkyne cyclotrimerization occurs, it is anticipated that this catalyst will find significant utility in the synthesis of highly functionalized pyridines.

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Supporting Information Available: Experimental details and chemical characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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