JOC Article

Scope of Ru(II)-Catalyzed Synthesis of Pyridines from Alkynes and Nitriles

Jesús A. Varela, Luis Castedo, and Carlos Saá*

Departamento de Química Orgánica y Unidad Asociada al CSIC, Facultad de Química, Universidad de Santiago de Compostela, 15782 Santiago de Compostela, Spain

qocsaa@usc.es

Received July 22, 2003

Pyridines can be efficiently synthesized by Ru(II)-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes to α,ω-dinitriles or electron-deficient nitriles or by Ru(II)-catalyzed [2 + 2 + 2] cocyclization of electron-deficient alkynes and electron-deficient nitriles. The reactions with dinitriles seem likely to proceed via ruthenacyclopentadiene intermediates and the reactions with electron-poor nitriles via azaruthenacyclopentadienes. The reaction with asymmetric electron-deficient alkynes affords 2,3,6-trisubstituted pyridines in good yield.

Introduction

The synthesis of pyridines by metal-mediated [2 + 2 + 2] cycloaddition of two alkynes to nitriles is a powerful and straightforward methodology.[1] The first metal used was Co(I), which was employed to catalyze the cocyclization of two alkynes with electron-rich nitriles[2] and which since the pioneering work of Bönneman,[3] Wakatsuki,[4] and Vollhardt[2a] has also been employed in developments allowing the use of environmentally friendly solvents[5] and the synthesis of biological targets[2a,6] and oligopyridines.[7] Stoichiometric amounts of Ti[8] and Zr[9] have also been found to promote this type of [2 + 2 + 2] cycloaddition, allowing the assembly of two different asymmetric acetylenes and a nitrile, and recently, it has been reported by Itoh that Cp*Ru(COD)Cl is complementary to Co(I) in that it efficiently catalyzes the [2 + 2 + 2] cycloaddition of 1,6-diynes to electron-deficient nitriles[10,11] and dinitriles.[12] It was suggested that this Ru(II)-catalyzed cycloaddition proceeds via a ruthenacyclopentadiene intermediate analogous to the well-established cobaltacyle intermediates of the Co(I)-catalyzed reactions.[2] However, intriguing questions concerning mechanism and scope remained unanswered. Here we report the results of a comprehensive survey of the reactions of electron-poor alkynes and 1,6-diynes with substituted nitriles and dinitriles (Figure 1) in the presence of the cationic complex $[Cp^*Ru(CH_3CN)_3]PF_6$ (**1a**).

Results and Discussion

To decide between $[Cp^*Ru(CH_3CN)_3]PF_6$ (**1a**) and the less electron-rich catalyst $[CpRu(CH_3CN)_3]PF_6$ (**1b**), we reacted 1 equiv of 1,6-diyne **2a** with 1.5 equiv of the nitrile with which Itoh and co-workers had obtained their best results (malononitrile **3r**) in DMF at room temperature in the presence of 10% of **1a** or **1b** and 10% of Et_4NCl.[10−12] With **1b**, only a 20% yield of pyridine **4r** was obtained, the major isolated product being the dimer of **2a**[10] (33%).[13] By contrast, with **1a** GC−MS showed the total consumption of starting materials in just 10 min and pyridine **4r**[12] was isolated in 84% yield (Scheme 1,

(1) (a) For an excellent account of [2 + 2 + 2] cyclotrimerization, see: Grotjahn, D. B. Transition Metal Alkyne Complexes: Transition-Metal-Catalyzed Cyclotrimerization. In *Comprehensive Organometallic Chemistry II*; Abel, E. W., Stone, F. G. A., Wilkinson, G., Eds.; Hegedus, L. S., Vol. Ed.; Pergamon: Oxford, 1995; Vol. 12, p 741. (b) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (c) Shore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (d) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (e) Fletcher, A. J.; Christie, S. D. R. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1657. (f) Varela, J. A.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787.

(2) For excellent reviews on cobalt-catalyzed synthesis of pyridines, see: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (b) Bönnemann, H.; Brijoux, W. *Adv. Heterocycl. Chem.* **1990**, *48*, 177.

(3) Bönnemann, H.; Brijoux, W. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim 1998; Vol. 1, pp 114−135.

(4) Wakatsuki, Y.; Yamazaki, H. *J. Chem. Soc., Dalton Trans.* **1978**, 1278.

(5) (a) Fatland, A. W.; Eaton, B. E. *Org. Lett.* **2000**, *2*, 3131. (b) Heller, B.; Sundermann, B.; Buschmann, H.; Drexler, H.; You, J.; Holzgrabe, U.; Heller, E.; Oehme, G. *J. Org. Chem.* **2002**, *67*, 4414.

(6) Saá, C.; Crotts, D. D.; Hsu, G.; Vollhardt, K. P. C. *Synlett* **1994**, 487.

(7) (a) Varela, J. A.; Castedo, L.; Saá, C *J. Org. Chem.* **1997**, *62*, 4189. (b) Varela, J. A.; Castedo, L.; Saá. C. *J. Am. Chem. Soc.* **1998**, *120*, 12147. (c) Varela, J. A.; Castedo, L.; Saá, C *Org. Lett.* **1999**, *1*, 2141. (d) Varela, J. A.; Castedo, L.; Maestro, M.; Mahía, J.; Saá, C. *Chem. Eur. J.* **2001**, *7*, 5203.

(8) Suzuki, D.; Tanaka, R.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **2002**, *124*, 3518.

(9) (a) Takahashi, T.; Tsai, F.; Kotora, M. *J. Am. Chem. Soc.* **2000**, *122*, 4994. (b) Takahashi, T.; Tsai, F.; Li, Y.; Wang, H.; Kondo, Y.; Yamanaka, M.; Nakajima, K.; Kotora, M. *J. Am. Chem. Soc.* **2002**, *124*, 5059.

(10) Yamamoto, Y.; Okuda, S.; Itoh, K. *Chem. Commun.* **2001**, 1102.

(11) For application of this method to the synthesis of pyridones, see: Yamamoto, Y.; Tkagishi, H.; Itoh, K. *Org. Lett.* **2001**, *3*, 2117.

(12) Yamamoto, Y.; Ogawa, R.; Itoh, K. *J. Am. Chem. Soc.* **2001**, *123*, 6189.

(13) When other halogen sources were used (Bu_4NF, Bu_4NBr, Bu_3NI), the reaction was much slower reaction (Br) or failed to take place. In the absence of chloride, only the dimer of **2a** was observed. Reaction of malononitrile (**3r**) with 1,6-heptadiyne (**2b**) afforded the corresponding pyridine derivative, but with 1,7-octadiyne (**2c**) neither pyridine derivatives nor dimers of **2c** were obtained.

10.1021/jo035050b CCC: $25.00 © 2003 American Chemical Society
Published on Web 10/08/2003

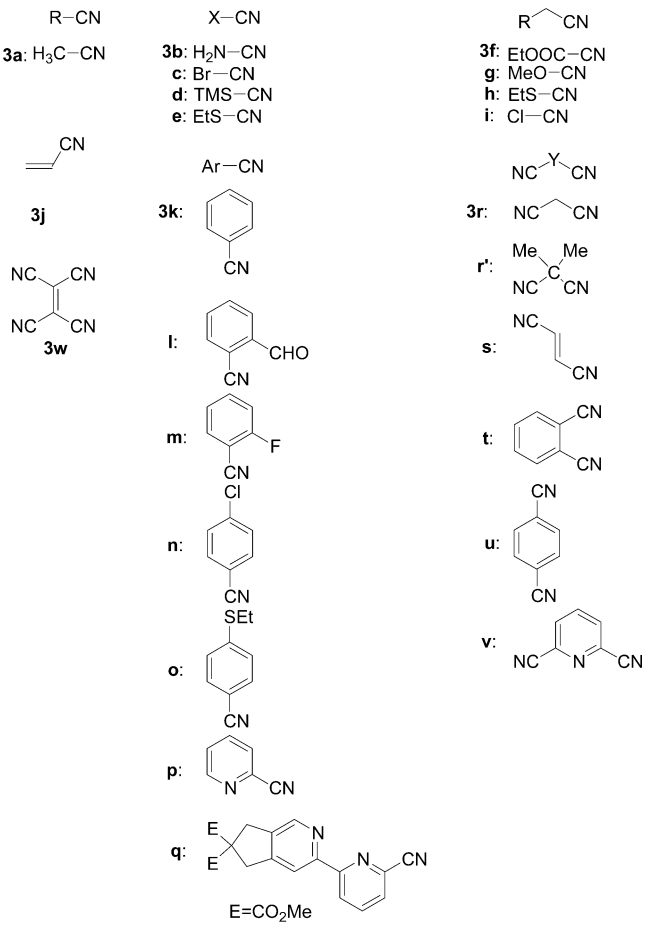


FIGURE 1. Nitriles used for the Ru(II)-catalyzed [2 + 2 + 2] cycloadditions.

SCHEME 1

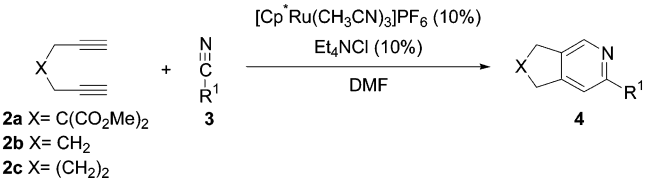
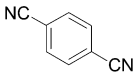
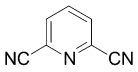


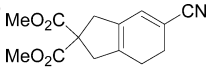
Table 1). Accordingly, [Cp*Ru(CH_3CN)$_3$]PF_6 (**1a**) was used in all subsequent work.[14]

We began by investigating the reactions of 1,6-diynes **2** with nitriles (Scheme 1). As was already observed by Itoh and co-workers,[12] reaction of acetonitrile (**3a**, Figure 1) with 1,6-diyne **2a** gave no pyridine; both at room temperature and at 80 °C, the final reaction mixture containing only unreacted nitrile together with dimers and trimers of the diyne. Nor did acetonitrile derivatives **3f**−**h** react, although nitrile **3i** afforded the corresponding pyridine **4i** in 56% yield (entry 3 in Table 1).[15]

(14) **Typical Procedure.** Nitrile **3** (1 mmol, 2 equiv) was added to a dry and degassed solution of [Cp*Ru(CH_3CN)$_3$]PF_6 (25 mg, 10%) and Et_4NCl (8 mg, 10%) in DMF (3 mL) at room temperature. After being stirred for 10 min, the diyne **2** (0.5 mmol, 1 equiv) was added. After consumption of starting materials (GC monitoring), the reaction was quenched with saturated aqueous solution of NH_4Cl (10 mL) and extracted with ethyl ether (3 × 10 mL). The organic layers were collected, dried over anhydrous Na_2SO_4, and evaporated to dryness under vacuum. Column chromatography of the residue on silica gel using ethyl acetate/hexane as eluent afforded the corresponding pyridine **4**.

TABLE 1. [Cp*Ru(CH_3CN)$_3$]PF_6/Et_4NCl-Catalyzed [2 + 2 + 2] Cycloaddition of 1,6-Diyne 2a to Nitriles 3[a]

Entry	R^1—C≡N	Temp (°C) / time (h)	Yield **4** (%)
1		r.t./0.16	84
2		r.t./0.16	95
3		r.t./1.5	56
4		80/4	53
5		r.t./5	14 (**5**)[b]
6		80/2	56
7		r.t./1.5	61
8		80/4	72
9		r.t/12, 80/2	50

[a] Typical procedure: To a DMF solution (0.33 M) of 2 equiv of nitrile **3** was successively added the ruthenium catalyst (10% of [Cp*Ru(CH_3CN)$_3$]PF_6 and 10% of Et_4NCl) and the diyne **2a** (0.5 mmol). Reaction time and temperature were optimized in each case. [b]  **5**

Similarly, when the series of heteronitriles **3b**−**e** were reacted with **2a**, only **3e** afforded the corresponding pyridine, **4e** (in 53% yield; entry 4 in Table 1). Interestingly, when acrylonitrile (**3j**) was used, cycloaddition occurred in low yield but chemoselectively with respect to the olefin giving the cyclohexadiene **5** (14%; entry 4 in Table 1) and the dimer of **2a** as the major isolated product (41%).[16]

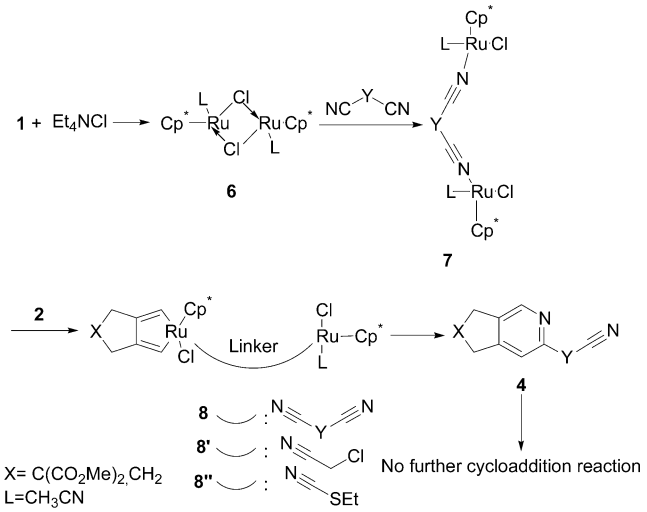
We next tried the arylcyanides **3k**−**o** and heteroaylcyanides **3p** and **3q** but none of them underwent cycloaddition with **2a** either at room temperature or at 80 °C, despite the electron-richness (and coordinating atoms) of the aryl or heteroaryl rings. However, the presence of a second nitrile on the ring resulted in smooth reaction by the first:[17] 1,2- and 1,4-dicyanobenzene (**3t**, **3u**) gave pyridines **4t**[12] and **4u** in 56% and 61% yield, respectively (entries 6 and 7 in Table 1), and 2,5-dicyanopyridine (**3v**) afforded the bipyridine **4v** in a good 72% yield (entry 8). Note that these last two results, with 1,4- and 1,3-

(15) Methylcyanoformate and trichloroacetonitrile are also able to participate in [2 + 2 + 2] cycloadditions to afford pyridines, see ref 10.

(16) In this case the reaction conditions were not optimized.

(17) α,ω-Dinitriles and 1,2-dicyanobenzene also give good-to-excellent yields of 2-(ω-cyano)alkyl- and 2-[(2-cyano)phenyl]pyridines using Cp*Ru(COD)Cl, see ref 12.

SCHEME 2

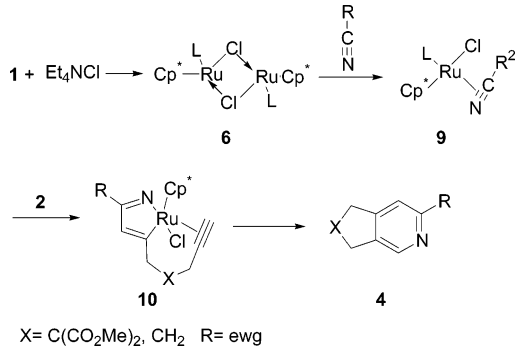


dinitriles, rule out the reaction's involving the mechanism accepted for α,ω-dinitriles, because η^2-coordination of the two cyano groups is geometrically impossible.[12] Finally, the nonaryl dinitrile *trans*-fumaronitrile (**3s**) gave pyridine **4s** in rather good yield (50%; entry 8 in Table 1); and substitution on the central carbon of malononitrile increased the yield from the 84% achieved with **3r** to an excellent 95% with dimethylmalononitrile (**3r′**) (entry 2). Unexpectedly, tetracyanoethylene (**3w**) failed to give either pyridine derivatives or dimers or trimers of the starting diyne, probably due to poisoning or capture of the Ru catalyst.

The above results may be explained by the mechanism depicted in Scheme 2. Changes in the ^{1}H NMR spectrum suggest that mixing the cationic catalyst [Cp*Ru(CH_3-$CN)_3$]$^+$ with Et_4NCl probably leads to the formation of the neutral complex [Cp*Ru(CH_3CN)Cl]$_2$ (**6**).[18] Dinitriles, which have two good coordinating groups, can split this dimer by forming the dinuclear complex **7**,[19] which allows formation of the intermediate ruthenacyclopentadiene **8** by reaction with **2a**. This is followed by the formation of pyridine **4** by insertion of the Ru-bound cyano group into the Ru−C bond, and since pyridine **4** cannot properly coordinate two ruthenium atoms they detach as the reconstituted dimer **6** (Scheme 2).

The ability of electron-deficient nitriles to participate in Ru(II)-catalyzed [2 + 2 + 2] cycloadditions with 1,6-diynes[10] can similarly be attributed to their electron deficiency enabling them to split the dinuclear complex **6** and coordinate to the metal of the resulting mononuclear complex **9**[20] (Scheme 3); in this case, reaction with **2a** probably gives the azaruthenacyclopentadiene **10** as Itoh had already suggested,[10] which evolves to the final pyridine **4**. In the case of nitriles **3i** and **3e**, either mechanism may be operative (for formation of ruthenacyclopentadienes **8′** or **8″**, the coordinating ligand would be chlorine or sulfur, respectively instead of one of the cyano groups).

SCHEME 3



Having delimited the scope of the reaction with 1,6-diynes, we turned our attention to the ability of the Ru(II) complex to catalyze the complete intermolecular [2 + 2 + 2] cocyclization of two asymmetric alkynes and a nitrile. At the outset we anticipate that at least one of the partners must be electron-deficient.[21] However, although cocyclization proceeded smoothly in high yield when methyl propiolate (**11a**) was reacted with a nitrile bearing an electron-withdrawing group, such as **3x**−**z** (Scheme 4),[22] and also occurred when **11b** was reacted with **3x**, reaction of **11a** with malononitrile (**3r**) gave only unreacted **3r** together with a quantitative combined yield of the benzene derivatives **16** and **17**, produced by trimerization of the alkyne. On the other hand, simple alkynes such as *n*-hexyne and (trimethylsilyl)acetylene gave no cocyclized products with electron-poor nitriles **3x** and **3z**, respectively.[23] It therefore seems that both partners must be electron-poor for cocyclization to pyridines **13**.

The above examples suggest that with electron-poor alkynes electron-poor nitriles behave in the same way as with 1,6-diynes, splitting the dinuclear complex **6** to form a mononuclear complex (**9**) that evolves to the final pyridines via an azaruthenacycle (in this case **12**; Scheme 4).[24] By contrast, it appears that preferential coordination of an electron-poor alkyne such as **11a** excludes malononitrile from the Ru coordination sphere, giving a complex that evolves to benzenes via ruthenacycles **15**.

To sum up, the combination of [Cp*Ru(CH_3CN)$_3$]PF_6 and Et_4NCl efficiently catalyzes [2 + 2 + 2] cocyclization between 1,6-diynes and dinitriles or electron-deficient nitriles, both of which appear able to split the dimer [Cp*Ru(CH_3CN)Cl]$_2$. With electron-deficient nitriles, the reaction seems likely to proceed via an azaruthenacyclopentadiene intermediate, and with dinitriles via a ruthenacyclopentadiene. 2,3,6-Trisubstituted pyridines can be

(18) Koelle, U.; Kang, B.-S.; Englert, U. *J. Organomet. Chem.* **1991**, *420*, 227.

(19) Dinuclear Ru(II) complexes with dicyanamides have in fact been observed, see: Valerga, P.; Puerta, M. C.; Pandey, D. S. *J. Organomet. Chem.* **2002**, *648*, 27.

(20) Strong π-acceptor ligands tend to cleave dinuclear Ru(II) complexes and form Cp*RuL_2X-type complexes; see ref 17.

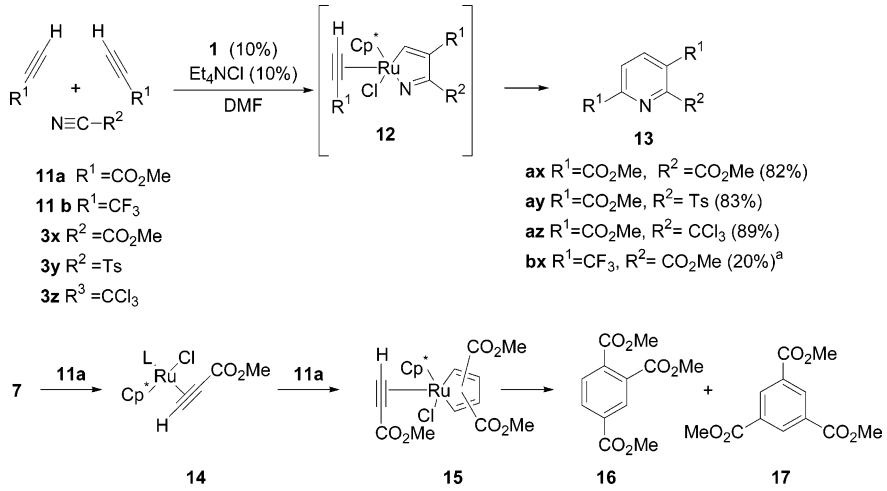
(21) Ru(II)-catalyzed trimerization of *n*-hexyne failed, whereas methyl propiolate gave an almost quantitative yield of a mixture of isomeric 1,2,4- and 1,3,5-benzene derivatives. Moreover, as described above, only electron-poor nitriles and dinitriles have been able to participate in Ru(II)-catalyzed [2 + 2 + 2] cycloadditions with 1,6-diynes.

(22) Traces of the 2,3,5-substituted pyridines (less than 3%) were also dedtected. The two pyridines are easily separated by chromatography. See the Supporting Information.

(23) Starting nitriles were quantitatively recovered.

(24) Methyl cyanoformate (**3x**) also undergoes cocyclization with 1,6-diyne **2a** (giving the corresponding pyridine in quite good yield, see ref 10) but not with 2,2-dibut-2-ynyl malonic acid dimethyl ester, failure in this case probably being due to the location of the methyl α to the ruthenium in the ruthenacyle intermediate corresponding to **10**.

SCHEME 4



synthesized in good-to-excellent yields by Ru(II)-catalyzed [2 + 2 + 2] cocyclization of asymmetric alkynes with nitriles so long as both alkyne and nitrile are electron-deficient.

Acknowledgment. This work was funded by the Xunta de Galicia (Project No. PGIDT00PXI20908) and by the Ministerio de Ciencia y Tecnología (Spain) and the European Regional Development Fund (Project No. BQU2002-02135).

Supporting Information Available: Typical procedures for the Ru-catalyzed reactions and spectral data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO035050B