J|A|C|S
COMMUNICATIONS

Published on Web 11/07/2006

Efficient Intermolecular [2 + 2 + 2] Alkyne Cyclotrimerization in Aqueous Medium Using a Ruthenium(IV) Precatalyst

Victorio Cadierno,* Sergio E. García-Garrido, and José Gimeno*

Departamento de Química Orgánica e Inorgánica, Instituto Universitario de Química Organometálica "Enrique Moles" (Unidad Asociada al CSIC), Universidad de Oviedo, Julián Claveria 8, E-33006 Oviedo, Spain

Received September 11, 2006; E-mail: vcm@uniovi.es; jgh@uniovi.es

For reasons of cost, safety, and environmental concerns, the development of organic transformations in aqueous media has become one of the major cornerstones in modern chemistry.[1] Following this general trend, the design of novel transition-metal catalysts for organic reactions in water has arisen a growing interest in recent years,[2] disclosing up to date a wide variety of highly efficient and selective synthetic approaches.[1,2]

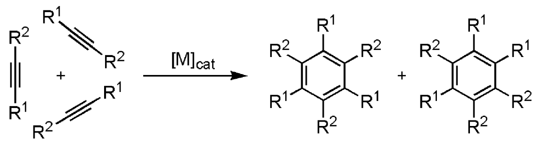
Transition-metal-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes can be considered as one of the most powerful and general methodologies used to assemble arene rings (Chart 1). After the pioneering work of Reppe,[3] a large number of transition-metal catalysts have been developed for alkyne-cyclotrimerization in organic media.[4] Nevertheless, despite the great interest of this atom-economical transformation in synthesis,[5] efforts devoted to develop alternative methods in water have been scarce, probably owing to the competitive hydration of the alkynes in water to give carbonyl derivatives.[6,7] In particular, to the best of our knowledge, only a few examples of efficient catalysts for the chemoselective intermolecular cyclotrimerization of alkynes in aqueous media have been described to date, namely the cyclopentadienyl−cobalt complexes $[\mathrm{CoCp(CO)_2}]$,[8] $[\mathrm{Co}(\eta^5\text{-}\mathrm{C_5H_4R})(\mathrm{COD})]$ (R = $\mathrm{CO_2Me}$, $\mathrm{CO(CH_2)_3OH}$; COD = 1,5-cyclooctadiene),[9] and $[\mathrm{Co}\{\eta^5{:}\kappa^1(P)\text{-}\mathrm{C_5H_4(CH_2)_2P^tBu_2}\}(\eta^2\text{-}\mathrm{CH_2{=}CH_2})]$.[10,11]

Herein we report a novel catalyst for the intermolecular [2 + 2 + 2] cyclotrimerization of alkynes in aqueous medium, that is, the commercially available bis(allyl)-ruthenium(IV) dimer $[\{\mathrm{Ru}(\eta^3{:}\eta^3\text{-}\mathrm{C_{10}H_{16}})(\mu\text{-Cl})\mathrm{Cl}\}_2]$ ($\mathrm{C_{10}H_{16}}$ = 2,7-dimethylocta-2,6-diene-1,8-diyl) (**1**; see Figure 1).[12] This compound, previously used by us in catalytic isomerizations of allylic alcohols and amines in water,[13] represents the first example of a ruthenium catalyst for this process in aqueous media, which in addition shows a remarkable activity and tolerance to functional groups.

The catalytic performance of complex **1** (2.5 mol %) for the [2 + 2 + 2] cyclization of terminal alkynes **2** in a mixture water/methanol (90:10) at 75 °C is shown in Table 1. Under these conditions almost all the alkynes tested were chemoselectively transformed, through head-to-tail and head-to-head coupling reactions, into the corresponding arenes **3**/**4** in excellent yields (72−99%) after 0.5−24 h.[14,15] As expected on the basis of steric grounds, the symmetric 1,3,5-substituted arenes **3** prevails in all cases over their 1,2,4-substituted counterparts **4**.

The rate of this cyclization process is strongly dependent on the electronic properties of the terminal alkyne. Thus, while the cyclotrimerization of phenylacetylene (**2a**), *p*-tolylacetylene (**2b**), and the methoxy-susbtituted derivatives **2c**,**d** requires 19−24 h (entries 1−4), aryl-alkynes **2e**−**h** containing electron-withdrawing halide substituents are readily cyclotrimerizated in almost quantitative yields after only 0.75−1.25 h (entries 5−8). The activated keto-alkyne **2i** and acetylenic esters **2j**−**l** also undergo a rapid (0.5−1.25 h) and clean transformation leading to the corresponding functionalized arenes in >92% yield (entries 9−12). Remarkably, this cyclotrimerization reaction also works efficiently for aliphatic alkynes lacking hydrophilic functional groups, such as 1-hexyne (**2m**) and 1-octyne (**2n**), although a longer time is required (24 h; entries 13−14).[16] It is also worthy to note that complex **1** is also able to catalyze the [2 + 2 + 2] cyclotrimerization of terminal 1,3-enynes. Thus, commercially available 1-ethynylcyclohexene (**2o**) can be transformed into a mixture of **3o**/**4o** (ca. 69:31 ratio) in 72% yield after 24 h (entry 15). As far as we know, this is the first example reported to date of a 1,3-enyne cyclotrimerization performed in aqueous media.

Chart 1



To evaluate the scope of this catalytic process, some experiments using internal instead of terminal alkynes have been performed (see

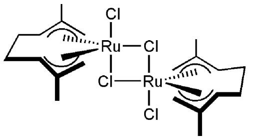
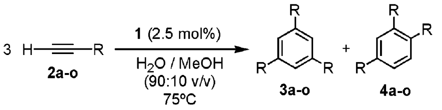


Figure 1. Structure of the bis(allyl)-ruthenium(IV) complex **1**.

Table 1. Cyclotrimerization of Terminal Alkynes Catalyzed by **1**[a]

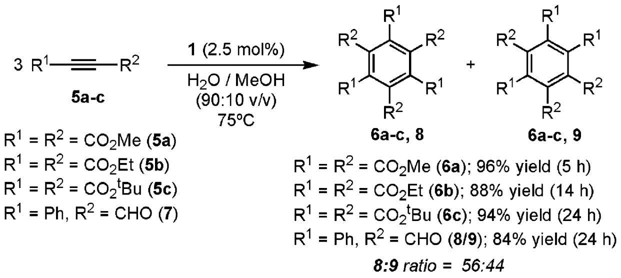


entry	substrate	time	yield (%)[b]	**3/4** ratio[c]
1	R = Ph (**2a**)	19 h	91 (81)	63:37
2	R = 4-$\mathrm{C_6H_4Me}$ (**2b**)	24 h	93 (78)	56:44
3	R = 4-$\mathrm{C_6H_4OMe}$ (**2c**)	24 h	90 (78)	58:42
4	R = 3,4,5-$\mathrm{C_6H_4(OMe)_3}$ (**2d**)	24 h	89 (80)	54:46
5	R = 4-$\mathrm{C_6H_4F}$ (**2e**)	1 h	97 (86)	52:48
6	R = 4-$\mathrm{C_6H_4Cl}$ (**2f**)	1 h	97 (83)	51:49
7	R = 4-$\mathrm{C_6H_4Br}$ (**2g**)	1.25 h	96 (86)	56:44
8	R = 4-$\mathrm{C_6H_4I}$ (**2h**)	0.75 h	97 (83)	57:43
9	R = C(=O)Me (**2i**)	0.5 h	92 (79)	88:12
10	R = $\mathrm{CO_2Me}$ (**2j**)	0.5 h	99 (85)	63:37
11	R = $\mathrm{CO_2Et}$ (**2k**)	0.75 h	99 (85)	57:43
12	R = $\mathrm{CO_2{}^tBu}$ (**2l**)	1.25 h	99 (88)	53:47
13	R = ^{n}Bu (**2m**)	24 h	89 (74)	54:46
14	R = ^{n}Hex (**2n**)	24 h	97 (84)	60:40
15[d]	R = 1-cyclohexenyl (**2o**)	24 h	72 (57)	69:31

[a] Reactions performed under N_2 atmosphere at 75 °C using 4 mmol of the alkyne (0.2 M solution in a mixture H_2O/MeOH (90:10 v/v)) and 0.1 mmol of complex **1** (5 mol % of Ru). [b] Yields determined by GC (isolated yields). [c] GC determined. [d] ca. 25% of unreacted 1-ethynylcyclohexene is recovered.

10.1021/ja066552k CCC: $33.50 © 2006 American Chemical Society

Scheme 1



Scheme 1). Thus, we have found that both symmetrical (**5a**−**c**) and unsymmetrical (**7**) activated internal alkynes also undergo cyclotrimerization in the presence of complex **1**, affording the fully substituted arenes **6a**−**c** and **8**/**9**, respectively, in excellent yields (84−96%; GC). Apparently, the catalytic activity of dimer **1** is not strongly affected by the presence of an internal C≡C triple bond, the reactions requiring a similar time than for terminal akynes **2a**−**d** and **2m**−**o** (≤24 h).[17a]

As shown in Table 1 and Scheme 1, different functionalities such as ether (alkynes **2c**−**d**), halide (alkynes **2e**−**h**), ketone (alkyne **2i**), aldehyde (alkyne **7**), ester (**2j**−**l** and **5a**−**c**), and olefin (enyne **2o**) groups are tolerated, assessing the generality of this catalytic [2 + 2 + 2] cyclization process.[17b] Such functional groups tolerance has not previously been demonstrated in aqueous media.[8−11]

Although no mechanistic studies have been performed, monitoring our catalytic reactions by GC/MS the formation of free 1,6-dimethyl-1,5-cyclooctadiene is observed, resulting from the reductive coupling of the 2,7-dimethylocta-2,6-diene-1,8-diyl ligand "$C_{10}H_{16}$". This fact seems to indicate that in situ formed Ru(II) complexes are the real catalytically active species.[18,19] Experimental and theoretical mechanistic studies on [2 + 2 + 2] alkyne cyclotrimerizations in organic media are well documented.[19] The classical mechanism involves the oxidative coupling of two η^2-coordinated alkyne ligands to form a ruthenacyclopentatriene intermediate which adds a third alkyne molecule.[19] Several examples of chelate bisalkylidene ruthenium complexes (ruthenacyclopentatrienes) have been isolated and, as expected, some of them have shown to be catalytically active.[20]

In summary, a novel highly efficient and selective catalytic system for the [2 + 2 + 2] cyclotrimerization of alkynes in aqueous media, that is, the Ru(IV) dimer $[\{Ru(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(\mu\text{-}Cl)Cl\}_2]$ (**1**), has been discovered. Complex **1** represents, not only the first ruthenium species able to perform alkyne-cyclotrimerizations in water with a wide tolerance to functional groups, but also a rare example for the efficient intermolecular cyclization of activated internal alkynes in aqueous media. Taking into account the limited applicability of the catalysts known to date in water,[8−11] some of them being even difficult to prepare,[9,10] the excellent performance shown by the commercially available precatalyst **1** deserves a more detailed study. Efforts to assess the scope, limitations, and synthetic applications of this aqueous transformation, as well as a complete mechanistic study, are now in progress.

Acknowledgment. This work was supported by the MCyT of Spain (Grant BQU2003−00255) and FICYT of Asturias (Grant IB05−035). S.E.G.-G. and V.C. thank the MCyT and the ESF for the award of a Ph.D. grant and a Ramón y Cajal contract, respectively.

Supporting Information Available: Experimental procedure and characterization data for **3a**−**o**, **4a**−**o**, **6a**−**c**, **8**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Li, C.-J. *Chem. Rev.* **2005**, *105*, 3095. (b) Li, C.-J.; Chen, L. *Chem. Soc. Rev.* **2006**, *35*, 68.
(2) Joó, F. In *Aqueous Organometallic Catalysis*; Horváth, I. T., Joó, F., Eds.; Kluwer: Dordrecht, The Netherlands, 2001.
(3) Reppe, W.; Sweckendiek, W. J. *Justus Liebigs Ann. Chem.* **1948**, *560*, 104.
(4) (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (b) Saito, S.; Yamamoto, Y. *Chem. Rev.* **2000**, *100*, 2901. (c) Rubin, M.; Sromek, A. W.; Gevorgyan, V. *Synlett* **2003**, 2265.
(5) For atom-economical reactions catalyzed by Ru see Trost, B. M.; Fredericksen, M. U.; Rudd, M. T. *Angew. Chem., Int. Ed.* **2005**, *44*, 6630.
(6) Chen, L.; Li, C.-J. *Adv. Synth. Catal.* **2006**, *348*, 1459.
(7) For a review on transition-metal catalyzed alkyne hydration see Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079.
(8) This catalyst is only active in supercritical water (>374 °C): (a) Jerome, K. S.; Parsons, E. J. *Organometallics* **1993**, *12*, 2991. (b) Borwieck, H.; Walter, O.; Dinjus, E.; Rebizant, J. *J. Organomet. Chem.* **1998**, *570*, 121.
(9) These complexes are only able to catalyze the cyclotrimerization of alkynes containing hydrophilic functional groups: Sigman, M. S.; Fatland, A. W.; Eaton, B. E. *J. Am. Chem. Soc.* **1998**, *120*, 5130.
(10) This is undoubtedly the most efficient and versatile catalyst reported to date, being able to promote the cyclotrimerization of terminal alkynes even at room temperature. Nevertheless, when internal alkynes are used as subtrates the corresponding arenes are formed in low yields (≤51%) requiring also elevated temperature: Yong, L.; Butenschön, H. *Chem. Commun.* **2002**, 2852.
(11) (a) The rhodium complex $[\{RhCl(COD)\}_2]$ associated with the water-soluble phosphine TPPTS is also active albeit only via intramolecular processes: Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* **2003**, *125*, 7784. (b) $[RhCl(CO)_2]$ (supported on an amphiphilic resin) has been reported to catalyze the cyclotrimerization of RC≡CR (R = Ph, CO_2Me) in water. Nevertheless, the product yields were not satisfactory (≤57%): Uozumi, Y.; Nakazono, M. *Adv. Synth. Catal.* **2002**, *344*, 274. (c) $PdCl_2$ is also known to catalyze alkyne cyclotrimerizations, the presence of CO_2 (1.0 MPa) and 2 equiv of $CuCl_2$ per mol of alkyne being required. In addition, this catalytic system was found to be inoperative when alkynes bearing bulky substituents, such as HC≡C^{t}Bu, are used as substrates, leading only to dimerization products: Li, J.-H.; Xie, Y.-X. *Synth. Commun.* **2004**, *34*, 1737.
(12) Available from Strem Chemicals, Inc. (catalog number 44-0203). Synthetic details can be found in Salzer, A.; Bauer, A.; Geyser, S.; Podewils, F.; Turpin, G. C.; Ernst, R. D. *Inorg. Synth.* **2004**, *34*, 59.
(13) (a) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Nebra, N. *Chem. Commun.* **2005**, 4086. (b) Cadierno, V.; García-Garrido, S. E.; Gimeno, J.; Varela-Álvarez, A.; Sordo, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 1360.
(14) The use of lower temperatures and/or catalyst loadings slows down the reaction considerably. Thus, using a catalyst loading of 2.5 mol%, **2a** was cyclotrimerizated in only 60% yield after 24 h at 50 °C. Similarly, using a catalyst loading of 1 mol%, **2a** was cyclotrimerizated in only 49% yield after 24 h at 75 °C. It should be also noted that, although in some cases this transformation can be performed in pure water (alkynes **2i**−**l**), methanol was systematically added to ensure the complete solubilization of the substrates.
(15) Formation of minor amounts of carbonyl compounds, resulting from the hydration of the C≡C bond of the alkynes, takes places if the catalytic reactions are performed at 100 °C. At 75 °C such a competitive process has been only observed in the cyclotrimerization of **2c** (ca. 5% of 4-methoxyacetophenone is formed; GC/MS determined).
(16) Under the same reaction conditions ^{t}BuC≡CH is cyclotrimerizated in only 16% yield (GC) after 24 h. Major amounts of dimerization products (ca. 65%) are formed in this reaction.
(17) (a) Unfortunately, attempts to cyclotrimerize electron-rich internal alkynes, such as EtC≡CEt or ^{n}PrC≡C^{n}Pr, using complex **1** failed. (b) Complex **1** was also found to be ineffective in the cyclotrimerization of alkynes containing OH substituents (i.e., HC≡CCH_2OH and $HOCH_2C$≡CCH_2-OH)
(18) Ru(IV)−Ru(II) reductions starting from $[\{Ru(\eta^3{:}\eta^3\text{-}C_{10}H_{16})(\mu\text{-}Cl)Cl\}_2]$ (**1**) are well-documented: Cadierno, V.; Crochet, P.; García-Garrido, S. E.; Gimeno, J. *Curr. Org. Chem.* **2006**, *10*, 165.
(19) Several Ru(II) complexes are known to catalyze [2 + 2 + 2] alkyne cyclotrimerizations in organic media: (a) Rüba, E.; Schmid, R.; Kirchner, K.; Calhorda, M. J. *J. Organomet. Chem.* **2003**, *682*, 204 and references therein. (b) Kirchner, K.; Calhorda, M. J.; Schmid, R.; Veiros, L. F. *J. Am. Chem. Soc.* **2003**, *125*, 11721.
(20) Cadierno, V.; Gamasa, M. P.; Gimeno, J. *Coord. Chem. Rev.* **2004**, *248*, 1627.

JA066552K