Palladium-Catalyzed Regioselective Cyclotrimerization of Acetylenes in Supercritical Carbon Dioxide

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Keywords: Alkynes / Cyclotrimerization / Palladium / Regioselectivity / Supercritical fluids

The cyclotrimerization process of different substituted alkynes occurred smoothly in supercritical carbon dioxide for the first time. The reactions are catalyzed by palladium chloride. High yields and regioselectivities were observed when 2 equiv. of $CuCl_2$ and 5 mL of MeOH were added.

Introduction

Considerable attention has been focused recently on using supercritical carbon dioxide ($scCO_2$) as a medium for organic reactions,[1] owing to its low viscosity and high solubility as well as nontoxic properties. In addition, CO_2 is inexpensive and nonflammable, separation of CO_2 from a reaction mixture is energy-efficient and the product can be obtained by simple treatment. All these properties of $scCO_2$ have made it superior to conventional organic solvents with regard to environmental and health considerations.

The cyclotrimerization of alkynes to give benzene derivatives was already a vast field three decades ago[2−6] as polysubstituted benzene derivatives are central to many biological and polymer molecules.[3] A large number of transition-metal-based systems can be used for this reaction, which is a powerful synthetic method for the construction of cyclic compounds. Among these catalysts, palladium chloride and its bis(benzonitrile) complex are the simplest and the most convenient to use, and the yields of benzene derivatives generally depend on the substituents of the alkyne. Despite this huge body of work, the regio- and chemoselectivity for the cyclotrimerization of alkynes are still the focus of much attention.

In our previous work, we reported several examples of the cyclotrimerization of acetylenes under normal conditions. However, little attention has been paid to cyclotrimerization of acetylenes in the "environmentally friendly" supercritical carbon dioxide ($scCO_2$). We now report some interesting results obtained from our studies on palladium-catalyzed cyclotrimerization of alkynes in $scCO_2$.

Results and Discussion

Our investigation began with 1-phenyl-1-propyne, an unsymmetrical internal alkyne, which was cyclotrimerized in high yield (92%) in $scCO_2$ in the presence of $PdCl_2/CuCl_2$ in MeOH (Scheme 1; Entry 1, Table 1). Encouraged by these results, we attempted to cyclotrimerize other acetylenes in $scCO_2$. We first chose 1-heptyne and diphenylacetylene. Unfortunately, the cyclotrimerization of these two acetylenes did not give any benzene derivatives, and only unidentified red oils were isolated (Entries 2 and 3, Table 1).

We then carried out the reaction of the internal alkyne 4-octyne in $scCO_2$. It was found to react readily with good yields and regioselectivity (Entry 4, Table 1). 3,3′-Dimethyl-1-butyne (**1c**) and ethyl propiolate (EP, **1d**) also react smoothly with excellent yields and regioselectivities. The reaction of 3,3′-dimethyl-1-butyne gave only 1,3,5-tri-*tert*-butylbenzene (Entry 10, Table 1), while ethyl propiolate gave triethyl 1,2,4-benzenetricarboxylate as the main product (Entry 11, Table 1).

We also tried to carry out the cyclotrimerization of the simplest alkyne, acetylene (HC≡CH), in $scCO_2$; the cyclotrimerization product benzene was detected in this reaction (Entry 13, Table 1). Phenylacetylene (PhC≡CH) gave the Glaser coupling product diphenyldiyne instead of the cyclotrimerization product (Entry 12, Table 1, Scheme 2).

When the cyclotrimerization reactions of methyl propargyl ether (**1f**) and dimethyl acetylenedicarboxylate (DMAD, **1g**) were carried out in $scCO_2$, only low yields or traces of products were detected (Entries 14 and 15, Table 1).

4-Octyne was chosen as a model substrate for the optimization process (Entries 4−9, Table 1). The final optimized

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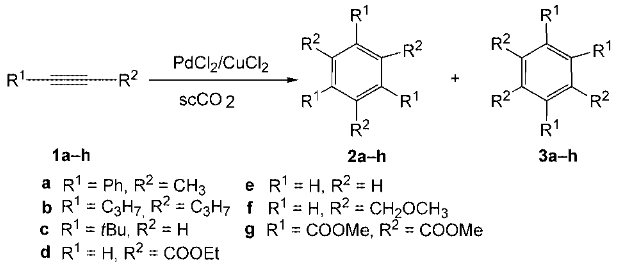
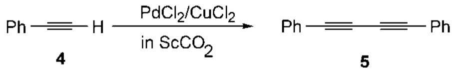
Table 1. Palladium-catalyzed cyclotrimerization of acetylenes in $scCO_2$

Entry[a]	Alkyne	t [h]	MeOH [mL]	Conv. [%][b]	Isolated yield [%]	Product
1	$PhC\equiv CMe$	8	5	100	92	**2a**
2	$C_5H_{11}C\equiv CH$	18	5	–	–[c]	–
3	$PhC\equiv CPh$	18	5	–	–[c]	–
4	$C_3H_7C\equiv CC_3H_7$	8	5	100	100	**2b** (**3b**)
5[d]	$C_3H_7C\equiv CC_3H_7$	8	0	78	65	**2b** (**3b**)
6	$C_3H_7C\equiv CC_3H_7$	8	1	90	82	**2b** (**3b**)
7[e]	$C_3H_7C\equiv CC_3H_7$	8	5	96	92	**2b** (**3b**)
8[f]	$C_3H_7C\equiv CC_3H_7$	8	10	52	30	**2b** (**3b**)
9[g]	$C_3H_7C\equiv CC_3H_7$	8	5	85	74	**2b** (**3b**)
10	tBuC≡CH	8	5	100	97	**2c**
11[h]	$HC\equiv COOEt$	12	5	99	96	**3d**
12[i]	$PhC\equiv CH$	8	5	100	99	–
13	$HC\equiv CH$	8	5	100	97	**2e** (**3e**)
14	$HC\equiv CCH_2OMe$	8	5	–	trace	–
15	$MeOOCC\equiv CCOOMe$	8	5	25	11	–
16[j]	$ClCH_2C\equiv CCH_2Cl$	8	5	100	98	–
17[k]	$C_3H_7C\equiv CC_3H_7$	8	5	68	56	**2a**
18[k]	$PhC\equiv CMe$	8	5	62	51	**2a**

[a] Reaction conditions: alkyne **1** (1 mmol), $PdCl_2$ (10 mg, 0.056 mmol), $CuCl_2$ (2 mmol), MeOH (5 mL), 40 °C, p_{CO2} = 16 MPa. [b] Determined by GC analysis. [c] The products are red oils and were not identified. [d] No MeOH was added. [e] p_{CO2} = 8 MPa. [f] Only used MeOH (10 mL) as solvent. [g] 1 mmol of $CuCl_2$ added. [h] In the presence of NEt_3. $[PdCl_2(PhCN)_2]$ was used instead of $PdCl_2$. [i] The Glaser coupling product diyne was isolated instead of benzene derivatives (see text, Scheme 2). [j] See text. [k] In the absence of $CuCl_2$.



Scheme 1



Scheme 2

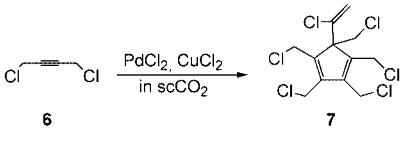
reaction conditions for cyclotrimerization in $scCO_2$ were found to be $PdCl_2$ (10 mg, 0.056 mmol), $CuCl_2$ (0.264 g, 2 mmol), MeOH (5 mL) and CO_2 (16 MPa) at 40 °C.

When carrying out the reaction in either pure MeOH or only $scCO_2$, lower conversions and yields were obtained (Entries 5 and 8, Table 1). Our results show that the presence of MeOH, which serves as co-solvent, increases the solubility of $PdCl_2$ and $CuCl_2$ in $scCO_2$, which leads to a large rate enhancement of the reaction. Decreasing the amount of MeOH to 1 mL (Entry 6, Table 1) decreases the yield to some extent.

The co-catalyst, $CuCl_2$, plays an important role in this reaction. With the assistance of $CuCl_2$, the reaction gives the regioselective benzene derivatives, and regenerates the active $PdCl_2$.[7] Our previous work has shown that acetylene can be cyclotrimerized without adding $CuCl_2$, but with a lower reaction rate.[8] In $scCO_2$, the rate decreases further (Entries 1, 9, 17, 18).

The pressure of CO_2 also affects the reaction rate to some extent. Our results indicate that a higher CO_2 pressure is preferable (Entries 4 and 7, Table 1).

We have also found that in benzene/nBuOH (10:6), 1,4-dichloro-2-butyne undergoes a [2+2+1] cyclotrimerization process to give an interesting five-membered ring product, 1,2,3,4,5-pentakis(chloromethyl)-5-(1′-chlorovinyl)cyclopentadiene (**7**).[5] When the reaction is run in $scCO_2$, the reaction gives the same product instead of benzene derivatives (Entry 16, Table 1, Scheme 3). The structure of this compound was confirmed by X-ray crystallography (Figure 1), mass spectrometry, and ^1H and ^{13}C NMR spectroscopy.



Scheme 3

Based on the results shown in Table 1, we can conclude that: (i) addition of MeOH can increase the dissolution of $PdCl_2$ and $CuCl_2$ in $scCO_2$; (ii) in $scCO_2$, the presence of $CuCl_2$ plays an important role in enhancing the reaction rate; and (iii) "environmentally friendly" supercritical carbon dioxide ($scCO_2$) may be a substitute for toxic organic solvents.

In summary, we have observed that cyclotrimerization reactions can proceed smoothly in good yield and regioselectivity in $scCO_2$. This reaction is environmentally more friendly than the traditional reaction in organic solvents and shows potential utility in industry. The mechanism and ap-

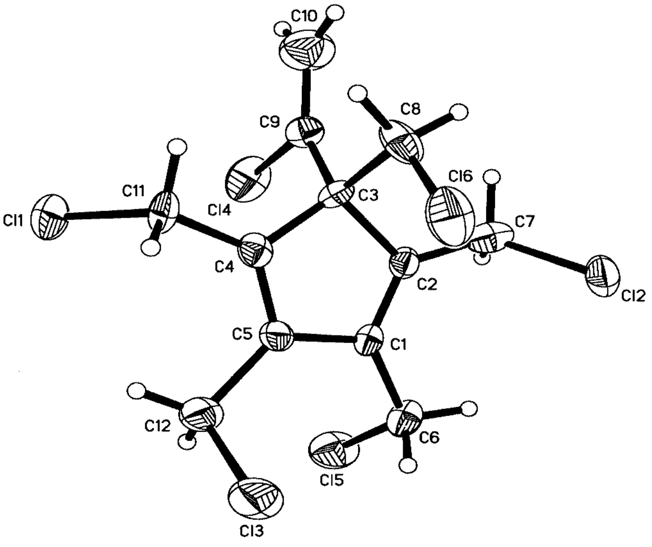


Figure 1. Crystal structure of **7**; selected bond lengths [Å] and angles [°]: Cl(1)−C(11) 1.813(8), Cl(2)−C(7) 1.776(10), Cl(3)−C(12) 1.761(9), Cl(4)−C(9) 1.819(8), Cl(5)−C(6) 1.800(8), Cl(6)−C(8) 1.683(9), C(1)−C(2) 1.298(9), C(1)−C(6) 1.444(10), C(2)−C(7) 1.460(11), C(3)−C(9) 1.444(12), C(4)−C(5) 1.368(9), C(6)−H(6A) 0.9700, C(6)−H(6B), 0.9700, C(7)−H(7A) 0.9700, C(7)−H(7B) 0.9700, Cl(9)−C(10) 1.292(8), C(10)−H(10A) 0.9300, C(10)−H(10B) 0.9300, C(11)−H(11A) 0.9700, C(11)−H(11B) 0.9700, C(2)−C(1)−C(6) 130.0(7), C(2)−C(1)−C(6) 130.0(7), C(2)−C(1)−C(5) 107.2(8), C(9)−C(3)−C(2) 111.7(8), C(4)−C(5)−C(12) 120.1(7), Cl(5)−C(6)−H(6A) 109.1, Cl(5)−C(6)−H(6B) 109.1, C(1)−C(6)−H(6A) 109.1, H(6A)−C(6)−H(6B) 107.8, Cl(2)−C(7)−H(7B) 108.7, C(5)−C(1)−C(2)−C(7) −179.4(8), C(6)−C(1)−C(2)−C(3) −179.2(8), C(6)−C(1)−C(5)−C(4) −179.7(9), C(2)−C(1)−C(5)−C(12) −178.9(10), C(2)−C(3)−C(9)−C(10) −120.5(10), C(4)−C(3)−C(9)−C(10)−124.9(10)

plications of the reaction are currently under investigation in our laboratory.

Experimental Section

General: ^{1}H NMR spectra were recorded at 400 MHz using $CDCl_3$ as solvent. TLC was performed using commercially prepared 100−400 mesh silica gel plates (HF_{254}) and visualization was effected at 254 nm. $CuCl_2$ was dried at 130 °C under HCl gas. All other reagents were used directly as obtained commercially. All melting points are uncorrected.

Typical Procedure: MeOH (5 mL) and alkyne (1 mmol) were added to a mixture of $PdCl_2$ (0.056 mmol) and $CuCl_2$ (2 mmol) in an HF-25 autoclave. Liquid CO_2 was then transferred into the autoclave to the desired pressure. The reaction mixture was stirred at room temp. for 10 h. After completion of the reaction, the CO_2 was vented and the surplus was extracted with Et_2O. The conversion was determined by GC using an internal standard. The product was then purified by preparative TLC on silica gel using light petroleum ether/EtOAc (10:1) as eluent.

1,2,4-Trimethyl-3,5,6-triphenylbenzene (2a): Solid, m.p. 220−222 °C (ref.[9] 224 °C). ^{1}H NMR ($CDCl_3$): δ = 1.71 (s, 6 H), 2.04 (s, 3 H), 6.97−7.43 (m, 15 H) ppm. ^{13}C NMR: δ = 1.0, 15.2, 121.8, 128.5, 129.0, 132.5 ppm. MS: m/z = 348 [M^+], 333, 318, 302, 289, 271, 255, 241, 215, 191, 178, 165, 151, 105, 91, 77, 65, 51, 43.

Hexapropylbenzene (2b): Solid, m.p. 100−104 °C. ^{1}H NMR ($CDCl_3$): δ = 1.03−1.07 (t, 3 H), 1.53 (m, 2 H), 2.45−2.50 (t, 2 H) ppm. ^{13}C NMR: δ = 15.2, 24.8, 32.2, 136.7 ppm. MS: m/z = 330 [M^+], 301, 287, 273, 259, 245, 229, 217, 187, 175, 159, 145, 133, 105, 91, 80, 69, 55, 43, 29.

1,3,5-Tri-*tert*-butylbenzene (2c): Solid, m.p. 70−73 °C[10] (ref. 73 °C). ^{1}H NMR: δ = 1.21 (s, 27 H), 6.52 (s, 3 H) ppm. ^{13}C NMR: δ = 28.9, 39.2, 117.9, 148.0 ppm. MS: m/z = 246 [M^+], 219, 202, 199, 183, 163, 157, 143, 123, 107, 91, 77, 65, 57, 41, 29.

Triethyl 1,2,4-Benzenetricarboxylate (3d): White needles, m.p. 104 °C. ^{1}H NMR ($CDCl_3$): δ = 1.23−1.54 (t, 9 H), 4.20−4.45 (t, 6 H), 7.36 (s, 2 H), 8.83 (s, 1 H) ppm. MS: m/z = 294 [M^+], 250, 249, 222, 221, 194, 193, 176, 165, 148, 137, 120, 103, 91, 75, 65, 45, 29.

Benzene (2e): B.p. 80.1 °C, n_D^{20} = 1.5000. ^{1}H NMR ($CDCl_3$ 400 MHz): δ = 7.35 (s, 6 H) ppm. MS: m/z = 78 [M^+], 77, 63, 52, 51, 50, 39, 38, 37. IR (KBr): $\tilde{\nu}$ = 3614, 3035, 1815, 1479, 1036, 675, 415 cm^{-1}.

1,2,3,4,5-Pentakis(chloromethyl)-5-(1′-chlorovinyl)cyclopentadiene (7): White needles, m.p. 119−124 °C. ^{1}H NMR ($CDCl_3$): δ = 4.06 (s, 2 H), 4.26 (d, 2 H), 4.38 (d, 2 H), 4.50 (s, 4 H), 5.56 (s, 1 H), 5.65 (s, 1 H) ppm. ^{13}C NMR ($CDCl_3$): δ = 29.7, 35.0, 43.2, 117.3, 142.7, 144.1 ppm. MS: m/z = 368 [M^+], 370, 366, 364, 337, 335, 333, 321, 319, 317, 299, 297, 295, 265, 261, 235, 211, 199, 181, 177, 163, 141, 128, 115, 103, 89, 76, 57, 51, 29.

Crystal Data for 7: $C_{12}H_{12}Cl_6$, M_r = 368.92, white crystal, grown from petroleum ether, monoclinic, space group $P2_1/n$, a = 13.1340(19), b = 9.4866(13), c = 13.6005(19) Å, β = 112.771(2)°, V = 1562.5(4) Å^3, Z = 4, D_c = 1.568 mg cm^{-3}, λ = 0.71073 Å, T = 293(2)K, μ = 1.079 mm^{-1}, 4647 reflection measured, 2926 unique (R_{int} = 0.0345) were used in all calculations. Final R = 0.0404 (obsd.), 0.0782 (all); $wR(F^2)$ = 0.0772 (obsd.), 0.0849 (all).

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