$CuCl_2$-Induced Regiospecifical Synthesis of Benzene Derivatives in the Palladium-Catalyzed Cyclotrimerization of Alkynes

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Received December 13, 2000

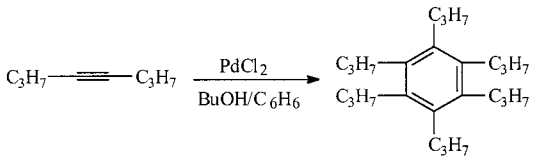
Introduction

Many metals or their complexes can catalyze the cyclotrimerization of alkynes to give benzene derivatives.[1−9] Among these catalysts, palladium chloride[10] and its bis(benzonitrile) complex[11] are the most convenient. In these reactions, the yields of benzene derivatives generally depend on the substituents of alkynes. In the past 50 years, the regio- and chemoselectivity for the cyclotrimerization of alkynes are the major challenge of synthetic chemists.[12] In this paper, we wish to report a regioselective and highly chemoselective method for preparing benzene derivatives via palladium chloride-catalyzed cyclotrimerization of alkynes in the presence of $CuCl_2$.

Results and Discussion

In our study of palladium-catalyzed carbonylation of alkynes,[13] we found that 4-octyne, a symmetrically internal alkyne, was cyclotrimerized in high yield (98%) in the presence of $PdCl_2$−$CuCl_2$−NaOAc in alcohol/benzene at room temperature (entry 1, Table 1). Preliminary results showed that the reaction can also take place even in the absence of NaOAc (entries 1 and 2, Table 1). Then, we studied the influence of the oxidant and the solvent on the yield of the reaction.

Table 1. Palladium-Catalyzed Cyclotrimerization of 4-Octyne[a]



1a **2a**

run	time (h)	conversion (%)[b]	yield (%)[c]
1[d]	4	100	98
2	4	100	98
3[e]	4	100	99
4[f]	5	100	98
5[g]	6	100	71
6[h]	6	77	77
7[i]	6	53	21
8[j]	6	100	75
9[k]	4	100	77
10[l]	4	84	70
11[m]	4	100	98
12[n]	4	100	99
13[o]	4	100	98
14[p]	4	100	98
15[q]	6	72	66

[a] Reaction conditions: 4-octyne (1 mmol), $PdCl_2$ (10 mg, 0.056 mmol), $CuCl_2$ (2 mmol), and BuOH/benzene (0.6/10, 10.6 mL) at 40 °C. [b] Detected by GC analyses. [c] Isolated yields. [d] NaOAc (2 mmol) was added. [e] $CuCl_2$ (3 mmol) was added. [f] $CuCl_2$ (1 mmol) was added. [g] No $CuCl_2$ was added. [h] Add $FeCl_3$ (2 mmol) instead of $CuCl_2$. [i] Add LiCl (4 mmol) instead of $CuCl_2$. [j] Add $Ce(SO_4)_2$ (2 mmol) instead of $CuCl_2$. [k] Add $PdCl_2(PhCN)_2$ instead of $PdCl_2$. [l] Only BuOH (10 mL) was used as solvent. [m] Only CH_2Cl_2 (10 mL) was used as solvent. [n] Add *s*-BuOH (0.6 mL) instead of BuOH. [o] Add EtOH (0.6 mL) instead of BuOH. [p] BuOH/C_6H_6 (1.0/10, 11 mL). [q] No BuOH was added.

Influence of Catalyst System. 4-Octyne could be cyclotrimerized even without the addition of $CuCl_2$, but the rate of the reaction is slower. In the absence of $CuCl_2$ after 5 h (entry 5), the reaction reached a conversion of 100% and a yield of 70%. The amount of $CuCl_2$ was examined, and we found that $CuCl_2$/4-octyne (2/1) gave the highest yield (entries 2−5). The results showed that the rate of the reaction decreased sharply using $FeCl_3$ or LiCl instead of $CuCl_2$ (entries 6 and 7). The addition of $Ce(SO_4)_2$ has no effect (entry 8). Using $PdCl_2(PhCN)_2$−$CuCl_2$ as the catalyst, the reaction was less effective (entry 9).

Influence of Solvent. The reactions can also proceed smoothly in CH_2Cl_2 (entry 11). When the solvent was benzene or BuOH, the reactions were not very clean and the yields of hexapropylbenzene were lower (entries 10 and 15). The results in Table 1 also indicated that BuOH (0.6 mL), EtOH, *s*-BuOH, and 1 mL of BuOH were equally effective (entries 2 and 12−14). On the basis of the above results, we concluded that the optimum reaction conditions were *$PdCl_2$ (0.056 mmol), $CuCl_2$ (2 mmol), and at 40 °C in BuOH−benzene (10.6 mL, 0.6/10) or in CH_2Cl_2.*

Cyclotrimerization of Other Alkynes. Other alkynes were tried under the optimum reaction conditions. Unfortunately, the cyclotrimerization of diphenylacetylene did not obtain benzene derivative, and the addition of

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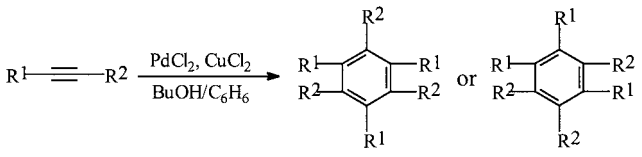
10.1021/jo0017382 CCC: $20.00
Published on Web 04/19/2001

Table 2. Palladium Chloride-Catalyzed Cyclotrimerization of Alkynes[a]



1 **2** **3**

run	R^1	R^2	time (h)	temp (°C)	product	yield (%)[b]
1	Ph	Ph	34	60		*c*
2[d]	Ph	Ph	34	60		*c*
3[d]	C_5H_{11}	H	12	40	**2b**	0
4	C_5H_{11}	H	12	40	**2b**	78
5[e]	C_5H_{11}	H	12	40	**2b**	41
6[f]	C_5H_{11}	H	12	40	**2b**	35
7	C_6C_{13}	H	12	40	**2c**	70
8	*t*-Bu	H	12	40	**2d**	100
9[d]	Ph	H	12	40		*c*
10	Ph	H	12	40		*c*
11	*p*-MePh	H	15	40	**2e**	95
12	*p*-MePh	H	15	40	**2f**	90
13	Ph	Me	12	40	**3**	80

[a] Reaction conditions: **1** (1 mmol), $PdCl_2$ (10 mg), $CuCl_2$ (2 mmol), and BuOH/benzene (0.6/10, 10.6 mL). [b] Isolated yields. [c] The products are red oils and unidentified. [d] No $CuCl_2$ was added. [e] No BuOH was added. [f] Only BuOH was used as solvent.

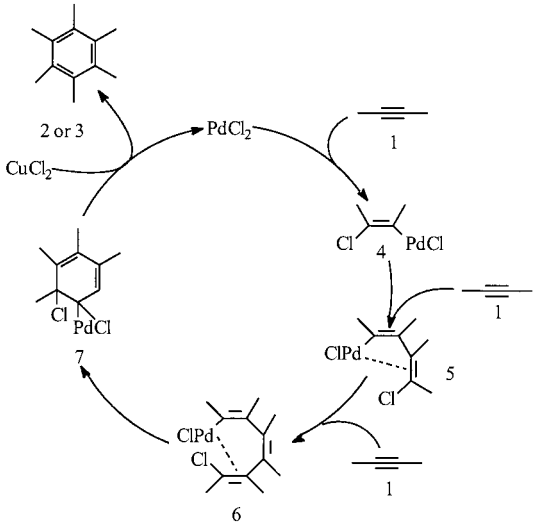
$CuCl_2$ did not affect the results under the optimum reaction conditions (entries 1 and 2, Table 2).

The cyclotrimerization of unsymmetrical alkynes could be carried out smoothly under the optimum reaction conditions (entries 3−13, Table 2). *Cyclotrimerization of unsymmetrical alkynes did not yield benzene derivatives without adding $CuCl_2$ as the oxidant* (entries 3−4). When $CuCl_2$ was added, benzene derivatives were obtained regioselectively in good yields. The solvent did not influence the regioselectivity but did affect the yields to some extent (entries 4−6). It is surprising that the cyclotrimerization of phenylacetylene did not give benzene derivative with or without the addition of $CuCl_2$ (entries 9 and 10), but the cyclotrimerization of *p*-methylphenylacetylene or *p*-chlorophenylacetylene proceeded smoothly (entries 11 and 12) and the reaction of 1-phenyl-1-propyne yielded the more highly sterically strained product **3** (80%, entry 13). No benzene derivatives were obtained in the reaction of alkynols[14] or methyl 2-butynoate.

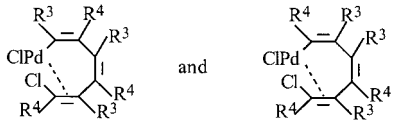
In the catalytic system of Pd(II)/chlorohydroquinone/NPMoV/O_2,[4] Ishii's group has reported that the cyclotrimerization of diphenylacetylene gives hexaphenylbenzene and the cyclotrimerization of 1-octyne yields a complex mixture. Obviously, their results are quite different from ours (entries 1 and 7 in Table 2).

On the basis of the above results, several noteworthy points are summarized. (1) The palladium-catalyzed cyclotrimerizations of alkynes depend not only on the size and the nature of the substituents of alkynes but also on the oxidant and solvent. (2) The effect of $CuCl_2$ on the cyclotrimerization of alkynes is obvious. $CuCl_2$ can accelerate the reaction and increase the yields of the $PdCl_2$-catalyzed cyclotrimerization. Especially, $CuCl_2$ can activate the palladium-catalyzed cyclotrimerization of unsymmetrical alkynes. (3) The effect of solvent (might be the polarity of the solvent) can affect the rate and the yield of the reaction to some extent, but it has no effect on the regioselectivity. In benzene or in BuOH, 4-octyne cannot be reacted completely and the reaction is not clean. In alcohol−benzene, the reaction proceeded smoothly. (4) The excess amount of Cl^- inhibits the reaction.

Scheme 1



Scheme 2



6a **6b**

Mechanism. We proposed a possible mechanism of the palladium chloride-catalyzed cyclotrimerization of alkynes, shown in Scheme 1. Our hypothesis is that the *cis*-addition of alkynes and $PdCl_2$ may form *cis*-chloropalladation intermediate **4**,[13,15] followed by consecutive *cis*-addition of alkynes and the chloropalladation intermediate to give the new chloropalladation intermediate **6** which then cyclizes by closing the ring to generate intermediate **7**. Upon the assistance of $CuCl_2$[16] and alcohol,[17] the reaction gives benzene derivatives and regenerates the active $PdCl_2$ quickly (the step can proceed in the absence of $CuCl_2$ and/or alcohol) (Scheme 1).

Why did the cyclotrimerization of 1-phenylpropyne yield the more highly sterically strained product? We speculate that the addition of intermediate **5** and alkynes results in two choices of intermediates, **6a** and **6b,** in the formation of the intermediate **6** (Scheme 2) during the

(14) For example, the reaction of 2-butyne-1,4-diol gave (*E*)-2,3-dichloro-2-butyne-1,4-diol (100%) under the optimum reaction conditions.

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(17) Our results showed that the addition of alcohol (for example, BuOH) is in favor of the reaction. There is a report describing that the addition of alcohol could facilitate the regeneration of catalyst system, although they used alcohol for the opposite purpose to reduce Pd(II) to Pd(0) species: Quan, L. G.; Lamrani, M.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4827.

cyclotrimerization of unsymmetrical alkynes. When R^3 = alkyl or *p*-ClPh or *p*-MePh, R^4 = H and R^3 = alkyl, R^4 = alkyl in Scheme 2, there is less steric hindrance in **6a** during the ring-closure process, and the products of the cyclotrimerization are symmetrical benzene derivatives. When R^3 = Ph, R^4 = Me, **6a** is more sterically hindered, holding back the ring-closure process more than **6b**, so the more highly sterically strained product was obtained.

The reason why cyclotrimerization of diphenylacetylene and phenylacetylene did not give benzene derivatives is under investigation.[18]

Conclusion

In conclusion, we reported a novel regioselective and highly chemoselective procedure for the synthesis of benzene derivatives. The effect of $CuCl_2$ and the solvent on the Pd(II)-catalyzed cyclotimerization of alkynes was also discussed.

Experimental Section

All ^{1}H NMR and ^{13}C 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.

General Procedure for the Cyclotrimerization of Terminal Alkynes. To a mixture of $PdCl_2$ (0.056 mmol) and $CuCl_2$ (2 mmol) in C_6H_6 (10 mL)−BuOH (0.6 mL) was added alkyne (1 mmol). The reaction was stirred at the desired temperature. After complete conversion of acetylenes as monitored by GC analyses, the mixture was filtered, and the benzene was removed by rotary evaporation to give crude products. The products were then purified by preparative TLC on silica gel (light petroleum ether−ethyl ether). The conversions were measured by GC analyses using an internal standard.

Hexapropylbenzene (2a). Solid, mp 100−103 °C (lit.[19] mp 102−102.5 °C); ^{1}H NMR δ 1.030−1066 (t, 3H), 1.526 (m, 2H), 2.454−2.495 (t, 2H); ^{13}C NMR δ 15.2, 24.8, 32.2, 136.7; 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-Tripentylbenzene (2b). ^{1}H NMR δ 0.864−0.898 (t, 3H), 1.236−1.322 (m, 4H), 1.552−1.605 (m, 2H), 2.375 (t, 2H), 6.383 (s, 3H); ^{13}C NMR δ 13.9, 22.4, 27.2, 30.8, 39.9, 120.3, 137.7; MS *m*/*z* 266, 262, 241, 227, 205, 192, 171, 149, 135, 113, 99, 91, 77, 55, 41, 29.

1,3,5-Trihexylbenzene (2c). ^{1}H NMR δ 0.851−0.885 (t, 3H), 1.236−1.300 (m, 6H), 1.542−1.577 (m, 2H), 2.356−2.393 (t, 3H), 6.381 (s, 3H); ^{13}C NMR δ 14.0, 22.5, 27.5, 28.3, 31.5, 39.9, 120.3, 137.7; MS *m*/*z* 292, 290, 269, 248, 219, 206, 185, 163, 149, 135, 109, 91, 79, 55, 43, 29.

1,3,5-Tri(*tert*-butyl)benzene (2d). Solid, mp 70−73 °C (lit.[20] mp 73 °C);^{1}H NMR δ 1.207 (s, 27H), 6.523 (s, 3H); ^{13}C NMR δ 28.9, 39.2, 117.9, 148.0; MS *m*/*z* 246 (M^+), 234, 219, 202, 199, 183, 163, 157, 143, 123, 107, 91, 77, 65, 57, 41, 29.

1,2,4-Tri(*p*-methylphenyl)benzene (2e). Solid, mp 173−175 °C (lit.[21] mp 178 °C); ^{1}H NMR δ 2.369 (s, 9H), 7.175−7.196 (d, 6H), 7.271 (s, 3H), 7.592−7.6130 (d, 6H); ^{13}C NMR δ 21.2, 121.2, 126.5, 129.2, 134.9, 135.9, 139.3; MS *m*/*z* 348 (M^+), 333, 317, 302, 267, 252, 232, 215, 189, 163, 151,133, 107, 101, 89, 65, 51, 39, 27.

1,3,5-Tri(*p*-chlorophenyl)benzene (2f). Solid, mp 242−245 °C (lit.[21] mp 246 °C); ^{1}H NMR δ 7.264 (s, 3H), 7.345−7.366 (d, 6H), 7.628−7.650 (d, 6H); ^{13}C NMR δ 122.1, 127.8, 128.7, 135.3, 135.9; MS *m*/*z* 348, 344, 333, 307 (− $^{37}Cl^-$), 272 (− $^{35}Cl^-$), 236 (− $^{37}Cl^-$), 202, 185, 161, 136, 118, 100, 87, 75, 66, 51, 36.

1,2,4-Trimethyl-3,5,6-triphenylbenzene (3). Solid, mp 220−222 °C (lit.[11f] mp 224 °C); ^{1}H NMR δ 1.705 (s, 6H), 2.030 (s, 3H), 6.964−7.438 (m, 15H); ^{13}C NMR δ 1.0, 15.2, 121.8, 128.4, 129.2, 132.5; MS *m*/*z* 348 (M^+), 333, 318, 302, 289, 271, 255, 241, 215, 191, 178, 165, 151, 105, 91, 77, 65, 51, 43.

Acknowledgment. We are grateful to the National Natural Science Foundation of China for financial support (Grants 29772036 and 29872039). We also thank Dr. Fanglü Huang and Professor Xiyan Lu (Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences) for helpful discussion.

Supporting Information Available: Spectral data (^{1}H, ^{13}C, MS) of all the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0017382

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