Pergamon

Tetrahedron Letters 40 (1999) 5035–5038

TETRAHEDRON LETTERS

Pd(0)-Catalyzed Selective [2 + 2 + 2] Cycloaddition of Dimethyl Nona-2,7-diyne-1,9-dioate Derivatives with Dimethyl Acetylenedicarboxylate

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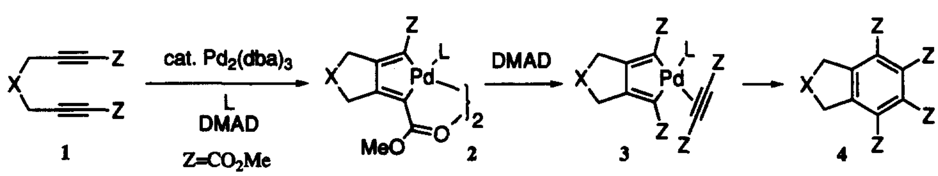
Received 15 March 1999; revised 23 April 1999; accepted 30 April 1999

Abstract

In the presence of 2.5 mol % of $Pd_2(dba)_3$ and 5 mol % of PPh_3, nearly equimolar amounts of dimethyl nona-2,7-diyne-1,9-dioate derivatives and dimethyl acetylenedicarboxylate (DMAD) were reacted in toluene at 110 °C to give indan, phthalin, and isoindoline derivatives selectively in moderate to good yields. The competing homo-couplings of both the diynediesters and DMAD were completely suppressed. The ester groups on the alkyne terminus plays an important role; the corresponding diynediketone and diynemonoester gave unsatisfactory results. The present Pd(0)-catalyzed cyclotrimerization was further extended to the intramolecular [2 + 2 + 2] cycloaddition of a triynediester.

Keywords: Palladium catalyst; Cycloadditions; Alkynes; Bicyclic aromatic compounds

Transition-metal catalyzed [2 + 2 + 2] cycloaddition of alkynes is a viable tool to synthesize highly substituted benzene derivatives [1]. The control of both the chemo- and regiochemistry in the cyclotrimerization of two or three different alkyne components, however, has so far been a cumbersome problem. The intermolecular coupling between a diyne and a monoyne is an effective strategy to control the substitution pattern on an arene ring [2]. The use of *excess* amount of the monoyne is, however, essential to suppress the competing dimerization of the diyne. In this context, we developed the Pd(0)-catalyzed intermolecular coupling of dimethyl nona-2,7-diyn-1,9-dioate derivatives **1** with dimethyl acetylenedicarboxylate (DMAD). Using our method, nearly equimolar amounts of the diyne and DMAD selectively gave highly substituted bicyclic benzenes **4** in moderate to good yields (Scheme 1).



Scheme 1

Several decades ago, Ishii and Maitlis independently reported that an oligomeric palladacyclopentadiene was obtained from the reaction of $Pd(dba)_2$ (dba: dibenzalacetone)

PII: S0040-4039(99)00927-2

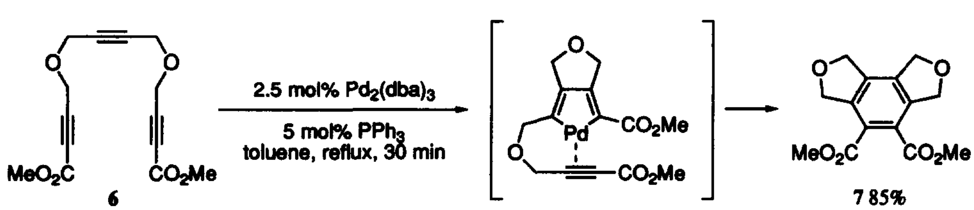
and DMAD [3a-d], and the palladacycle reacted with DMAD or tolane to give hexasubstituted benzene rings. Under catalytic conditions, however, the cross-coupling product was not obtained from DMAD with electronically neutral monoalkynes, because DMAD was readily trimerized to hexamethyl mellitate [3b,e]. This shows that electron-deficient DMAD is selectively coordinated by electron-rich Pd(0) to form the palladacycle intermediate, and DMAD is more easily incorporated into this intermediate than neutral alkynes. This selectivity is in sharp contrast to that in the reported selective co-cyclotrimerization of DMAD with a cycloalkene [4]. This fact suggested that cycloalkenes bind more strongly to the highly electron-deficient palladacycle than does electron-deficient DMAD. Taking these results into account, we envisaged that the selective coupling of dimethyl nona-2,7-diyn-1,9-dioate **1** and DMAD could be achieved because the bicyclopalladacycle formation from the diyne **1** might be more entropically favorable than that from DMAD (**2**, Scheme 1) and, in turn, DMAD would bind more strongly to the bicyclopalladacycle than would the less electron-deficient diyne (**3**, Scheme 1).

The reaction conditions of the cycloaddition of **1a** with DMAD were optimized as summarized in Table 1. In the presence of 2.5 mol% $Pd_2(dba)_3$ and 5 mol% PPh_3, **1a** and DMAD (1.1 equiv.) were heated in toluene at 110 °C for 1 h to afford the desired phthalan derivative **4a** [5] in 61% yield (entry 1). As an extra ligand, an electron-withdrawing arylphosphite $P(OPh)_3$ and an electron-donating, bulky alkylphosphine $P(Cy)_3$ (Cy = cyclohexyl) were less effective for the present cycloaddition (entries 2 and 3). Higher dilution of the reaction mixture raised the yield up to 78% (entry 4 vs. 1) [6].

Under the optimized conditions, a variety of diyne esters **1b-f** were reacted with DMAD. The substituents at the alkyne terminus plays an important role. A diethyl ester **1b** selectively gave the corresponding coupling product **4b**, but the yield was slightly lower compared to that of **4a** (entry 5). More electron-withdrawing acetyl groups on a diyne **1c** considerably decreased the yield of the desired cycloadduct **4c** (18%; entry 6). The substitution of one of the two methoxycarbonyl groups in **1a** with a methyl group retarded the desired coupling (entry 7). After the reaction with DMAD for 15 h, diynemonoester **1d** gave an unsymmetrical product **4d** in 23% yield together with hexamethyl mellitate (31%). In contrast, the parent dipropargyl ether gave only a complex product mixture.

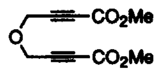
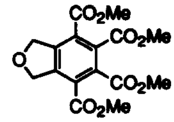
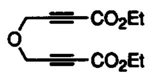
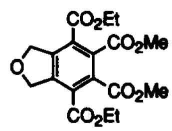
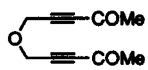
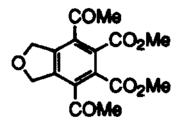
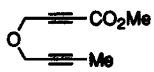
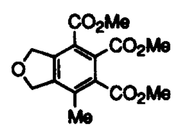
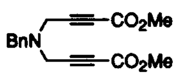
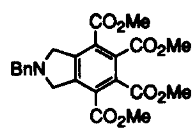
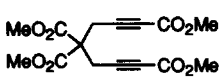
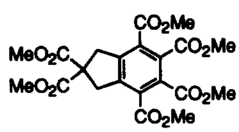
An *N*-benzyl isoindoline **4e** was obtained by the reaction of a dipropargylamine **1e** in 62% yield (entry 8). In addition to the above heterocycles, an indan derivative was also synthesized. A malonate derivative **1f** was reacted with DMAD for 5 h to give **4f** in 67% yield (entry 9). In sharp contrast to the above 1,6-diynes, a 1,7-octadiyne **5** did not give the corresponding coupling product under the same reaction conditions.

The present Pd(0)-catalyzed co-cyclotrimerization can be extended to the intramolecular cyclization of a triynediester **6** (Scheme 2). In the presence of 2.5 mol % $Pd_2(dba)_3$ and 5 mol % of PPh_3, **6** was heated in toluene at 110 °C for 30 min to afford the expected tricycle **7** [7] in 85% yield.

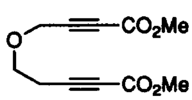


Scheme 2

Table 1. Pd(0)-Catalyzed Co-cyclotrimerization of Diynes 1a-f with DMAD[a]

entry	diyne	additive L	conc. (M)	time (h)	product (yield %)[b]	mellitate (yield %)[b]
1	 1a	PPh_3	0.5	1	 4a (61)	0
2	1a	$P(OPh)_3$	0.5	10	4a (17)	14
3	1a	PCy_3	0.5	18	4a (27)	6
4	1a	PPh_3	0.1	0.5	4a (78)	0
5	 1b	PPh_3	0.1	0.5	 4b (66)	0
6	 1c	PPh_3	0.1	1	 4c (18)	0
7	 1d	PPh_3	0.1	15	 4d (23)	31
8	 1e	PPh_3	0.1	0.5	 4e (62)	0
9	 1f	PPh_3	0.1	5	 4f (67)	0

[a]Conditions: $Pd_2(dba)_3$ (2.5 mol %), DMAD (1.1 equiv.), L (5 mol %), toluene, 110 °C. [b]Isolated yields.



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In conclusion, we developed the Pd(0)-catalyzed intermolecular [2 + 2 + 2] cycloaddition of nona-2,7-diyne-1,9-dioate derivatives and dimethyl acetylenedicarboxylate. In the presence of 2.5 mol % $Pd_2(dba)_3$ and 5 mol % PPh_3, highly substituted phthalans, an isoindolin, and an indan were selectively synthesized in good yields from the diynediesters and *nearly equimolar amounts of* DMAD. This is in striking contrast to other known examples, which requires *excess* amounts of monoynes in order to supress the competing dimerization of diynes. The ester groups on the alkyne terminus plays an important role; the corresponding diynediketone and diynemonoester gave unsatisfactory results. The present Pd(0)-catalyzed cyclotrimerization was further extended to the intramolecular [2 + 2 + 2] cycloaddition of a triynediester. Further application of this method and the mechanistic elucidation are now underway.

Acknowledgment.
We gratefully acknowledge financial support (09305059) from the Ministry of Education, Science Sports and Culture, Japan.

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[5] Analytical data for **4a**: mp 133-134 °C; IR ($CHCl_3$) 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (6 H, s), 3.91 (6 H, s), 5.32 (4 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.1, 53.2, 74.1, 126.3, 133.5, 144.0, 164.6, 166.6; Anal Calcd for $C_{16}H_{16}O_9$: C, 54.55; H, 4.58. Found: C, 54.29; H, 4.56.

[6] Typical procedure for the coupling of the diynediesters 1 and DMAD: the solution of the diyne **1a** (60 mg, 0.29 mmol) and $Pd_2(dba)_3{\cdot}CHCl_3$ (7.4 mg, 0.007 mmol) in toluene (2.8 mL) was stirred under Ar at ambient temperature for 30 min. To the resultant dark green suspension, was added PPh_3 (3.7 mg, 0.014 mmol) and DMAD (45 mg, 0.32 mmol), and the suspension was stirred for 30 min at 110 °C. The resultant brown solution was concentrated in vacuo and the residue was purified by silica gel chromatography (hexane : AcOEt = 4 : 1) to afford the phthalan **4a** (79 mg, 78%) as colorless solids.

[7] Spectral data for **6**: IR ($CHCl_3$) 1724 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.89 (6 H, s), 5.05 (4 H, s), 5.22 (4 H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 52.7, 72.0, 73.5, 124.9, 136.0, 140.5, 166.7; Anal Calcd for $C_{14}H_{14}O_6$: C, 60.43; H, 5.07. Found: C, 60.30; H, 4.99.