

Palladium-catalyzed carbonylative coupling of iodobenzene and 2-methyl-3-butyn-2-ol under biphasic conditions: Formation of furanones

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Abstract

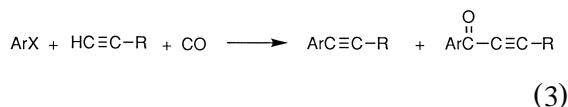
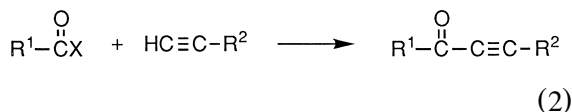
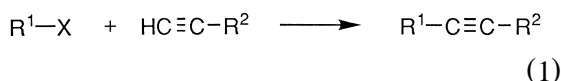
Carbonylative coupling of iodobenzene and 2-methyl-3-butyn-2-ol (**4**) in aqueous NaOH/benzene was carried out by using Pd(OAc)₂/Ph₃P/Bu₄PBr (**A**) and Pd(OAc)₂/Ph₂P(m-C₆H₄SO₃Na) (**B**) as catalyst. In sharp contrast with a homogeneous Et₃N solution, this biphasic solvent system gives 3-isopropylidene-5-phenyl-2(2H)-furanone (**1**) in a moderate yield. The other carbonylated products are 2,2-dimethyl-5-phenyl-3(2H)-furanone (**2**) and benzoic acid. The formation of **1** is explained by the following sequential reactions; carbonylative coupling of iodobenzene with **4** to form 4-hydroxy-4-methyl-1-phenyl-2-pentyn-1-one (**6**), hydrogenolysis of **6** to 4-methyl-1-phenyl-2,3-pentadien-1-one (**8**) and its cyclocarbonylation to **1**. Catalyst **A** gives **1** in a higher yield than **B**. © 1998 Elsevier Science B.V.

1. Introduction

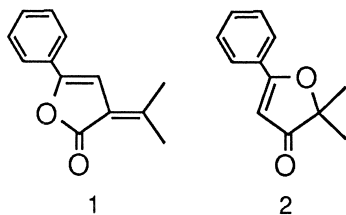
The coupling of aryl and alkenyl halides with 1-alkynes is catalyzed by palladium catalysts in the presence of amines [1,2]. It has been shown that the addition of CuI as a co-catalyst gives better results [3]. This catalytic reaction has found synthetic applications for a variety of disubstituted alkynes and alkynyl ketones (Eqs.

(1) and (2)) [4]. Alkynyl ketones are also prepared by the palladium-catalyzed carbonylative coupling of aryl halides with 1-alkynes (Eq. (3)) and this reaction was studied in detail [5]. In comparison to this reaction, however, the carbonylative coupling of iodobenzene with substituted propargyl alcohols such as 2-methyl-3-butyn-2-ol (**4**) gives 2,2-dimethyl-5-phenyl-3(2H)-furanone (**2**) under the influence of carbon dioxide [6,7]. The formation of the furanone is explained by the addition of carbon dioxide to the alkynyl ketone, followed by its decarboxylative rearrangement.

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In connection with our studies directed toward transition metal catalysis under aqueous/organic biphasic conditions [8], it has now been found that alkynyl ketone **6** formed by the reaction in Eq. (3) is further carbonylated under biphasic conditions to afford 3-isopropylidene-5-phenyl-2(2H)-furanone (**1**), accompanied with **2** (Scheme 1). We now describe a double carbonylation process of iodobenzene and 2-methyl-3-butyn-2-ol under aqueous, basic conditions.

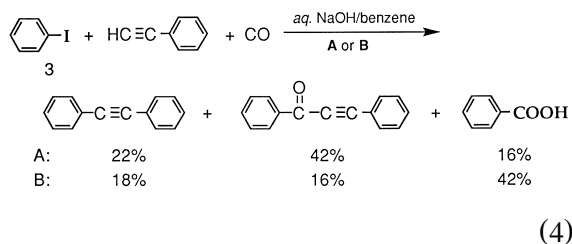


2. Results and discussion

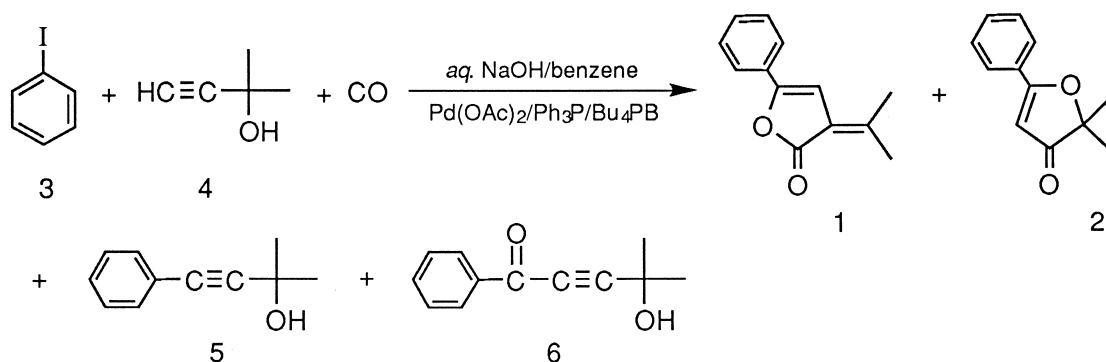
Extensive studies have been carried out in organometallic phase transfer catalyst (PTC) applications [9,10]. Among them many studies are on the catalysis of combinations of transition metals (M) and phase transfer agents. In organometallic PTC applications, however, we have pointed out that there are two possibilities

with respect to the catalytic system of biphasic reactions. One is a M/water-soluble phosphine system, where the transition metal catalyst itself functions as a PTC and the other is a combination of a M/hydrophobic phosphine/PTC system. In the former system, organic reactants are transferred by the transition metal catalyst into the aqueous phase, where the catalytic reaction occurs [11]. In comparison, in the latter catalysis, organic reactants locate in the organic phase and anions such as hydroxide ion are transferred into the organic phase. Both catalytic systems were investigated in the present study.

The first step of the present carbonylative coupling is the oxidative addition of iodobenzene to palladium in the organic phase, followed by carbonylation to afford a benzoylpalladium intermediate. In order to see the reactivity of the benzoylpalladium intermediate, the reaction of iodobenzene with phenylacetylene was first carried out under 2 M aqueous/benzene two-phase conditions. The reaction was performed at 100°C and 20 atm. In both catalytic systems, however, benzoic acid was formed in considerable amounts as shown in Eq. (4). This fact shows that the benzoylpalladium intermediate readily liberates benzoic acid before it reacts with phenylacetylene. The formation of benzoic acid seems to be unavoidable in the present case.



Next, 2-methyl-3-butyn-2-ol (**4**) was substituted for phenylacetylene. The reaction in the homogeneous solutions has been studied extensively by Inoue et al. [6,7] in the presence or absence of carbon dioxide. When iodobenzene (**3**) and **4** were treated with carbon monoxide



(20 atm) in Et_3N and a catalytic system consisting of $\text{Pd}(\text{OAc})_2$ ($3/\text{Pd} = 100/1$) and Ph_3P ($\text{P}/\text{Pd} = 2/1$) for 8 h at 100°C , ketone **6** was isolated by distillation in a 51% yield. The carbonylative coupling product **6** is easily converted into furanone **2** *in situ*, if carbon dioxide is present [7]. The biphasic reaction (in 2 M aqueous $\text{NaOH}/\text{benzene}$) was conducted under similar conditions to those of the homogeneous reaction described above, using **A** at first. Benzoic acid was isolated from the aqueous phase. In benzene-soluble products we noticed the presence of a carbonyl compound, of which the IR spectrum had a higher carbonyl stretching frequency than those of alkynyl ketone **6** and furanone **2**. The IR spectrum showed a strong carbonyl absorption at 1753 cm^{-1} . Column chromatography of the benzene-soluble products gave needles, whose chemical formula was revealed to be $\text{C}_{13}\text{H}_{12}\text{O}_2$ by high resolution mass spectrometry. The ^1H -NMR showed three singlets at 2.15, 2.42, and 6.46δ (3:3:1) and peaks due to aromatic protons at $7.2\text{--}7.7\delta$. The ^1H and ^{13}C -NMR spectra were consistent with furanone **1**, which has already been reported [12]¹. The other products detected were **2**, **5** and **6** as shown in Scheme 1 and benzoic acid. It should be noted that two molecules of carbon monoxide were incorporated into the product (**1**). Its formation was promoted by water, while

the carbonylative coupling in a Et_3N solution gave **6** as the carbonylated product.

Since the yield of **1** was low, attempts were made to find reaction conditions favoring the predominant formation of **1** by catalysts **A** and **B** in a long and narrow (23 mm in diameter and 160 mm long) stainless steel autoclave with magnetic stirring. In general, mass transfer between the two phases is crucial for the product distribution under heterogeneous conditions, where competitive reactions occur. Therefore, the contents of the autoclave were stirred vigorously so as to be homogenized. The results are summarized in Table 1. The yields of the products except for benzoic acid were determined by HPLC using naphthalene as an internal standard. In all cases alkyne **5** and ketone **6** were also detected in small amounts (combined yields, $< 10\%$).

Inspection of Table 1 reveals that the yields of **1** do not exceed 40%. Since the arylpalladium intermediate readily affords benzoic acid described above, its formation at the expense of iodobenzene was unavoidable in all cases. Consequently, the yields of **1** based on iodobenzene is moderate. It is likely that the mass transfer between two phases is also affected by changing the scales of reaction in such an autoclave. The fact that the yields of **1** are prone to variation is probably attributable to this mass transfer. The highest yield (38%) was attained by catalyst **A**, when **4** was used in an excess amount (entry 6). Catalyst **B** was not as effective for the forma-

¹ We thank these authors for the spectral data.

Table 1

Carbonylative coupling of iodobenzene (**3**) with 2-methyl-3-butyn-2-ol (**4**) under biphasic conditions

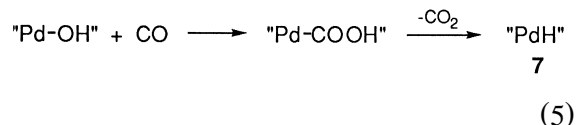
Entry	Catalyst ^b	P(CO) (atm)	4 / 3 (mol/mol)	Product yield (%)		
				1	2	PhCOOH
1	Pd(OAc) ₂ /2tppms (B)	20	1	4	11	42
2	Pd(OAc) ₂ /2Ph ₃ P/3PTC (A)	20	1	11	16	37
3	A	65	1	15	1	42
4	A	65	4	21	2	40
5 ^a	A	65	1	17	11	36
6 ^a	A	65	10	38	18	31

Pd(OAc)₂, 0.05 mmol; PTC (Bu₄PBr), 0.15 mmol; PhI, 5 mmol; benzene, 10 ml; 2M aqueous NaOH, 5 ml, 100°C; 8 h.^aPhI, 2.5 mmol; benzene, 5 ml; 2 M aqueous NaOH, 2.5 ml.^btppms, Ph₂P(m-C₆H₄SO₃Na).

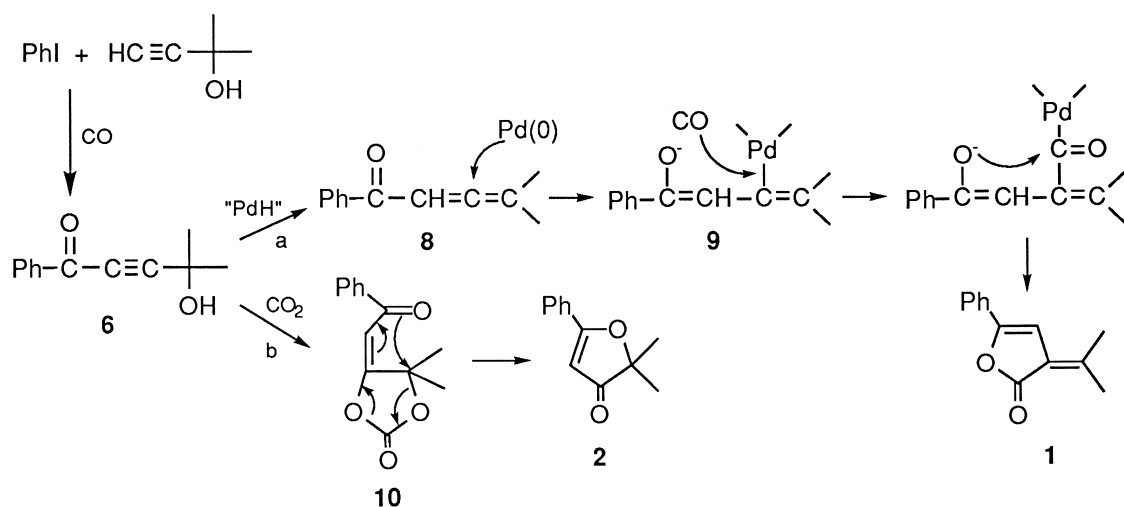
tion of **1** as **A**, since the intermediates such as the benzoylpalladium can locate in both aqueous and benzene phases and tend to form benzoic acid.

A possible mechanism for the formation of **1** is outlined in Scheme 2. The first carbonylative coupling product is ketone **6**, which is the same product as the homogeneous carbonylation. However, the carbonylation under heterogeneous biphasic conditions does not stop at this stage. It has been reported that propargyl compounds undergo palladium-catalyzed hydrogenolysis in the presence of a hydride source to afford allenic compounds [13]. Hydride can

be generated in a number of ways in palladium catalyzed reactions [14]. In the present case it appears likely that a palladium



hydride is formed in situ, as described in Eq. (5). In this manner, the alkynyl ketone **6** undergoes hydrogenolysis (path a), with liberation of carbon dioxide, to give allenyl ketone **8**, which is susceptible to a Michael-type addition of a

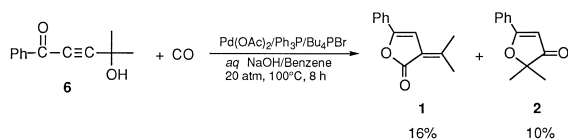


Scheme 2.

Pd(0) species to its allenyl sp carbon atom to form a vinylpalladium complex **9** [15]. A similar intermediate of this type was proposed in the palladium-catalyzed cyclocarbonylation of 3-aryl-1-propynes and iodoarene [16]. Finally, insertion of carbon monoxide into the vinylpalladium, followed by cyclization affords **1**. In this way, the present sequential carbonylation is characteristic of a reaction of tertiary propargyl alcohols under aqueous conditions, since the OH group of the tertiary alcohol is a good leaving group. In a separate experiment it has been confirmed that 2-propyn-1-ol or 2-butyne-1,4-diol do not undergo the addition–elimination of this type (**6** → **9**) to form allenic compounds on palladium-catalyzed carbonylation [17]. Recently, it has been reported that allenyl ketones (derivatives of **8**) cyclize to furanones such as **1** in the presence of carbon monoxide and a catalytic amount of $\text{Fe}(\text{CO})_5$ under UV irradiation [18].

The pathway from **6** to **2** (path b) under the influence of carbon dioxide has been clarified by Inoue et al. [6,7]. Pathway b in Scheme 2 is based on their explanation. In the present reaction carbon dioxide is formed as shown in Eq. (5). In this manner, **1** and **2** are formed concurrently.

To confirm this mechanism alkynyl ketone **6**, which was prepared by the reaction of benzoyl chloride with 2-methyl-3-butyne-2-ol, was carbonylated under the same conditions (Eq. (6)). Furanones **1** and **2** were confirmed to be formed in moderate yields.



(6)

3. Experimental

3.1. General procedure

All operations were carried out under an atmosphere of argon. Organic solvents were dehydrated by the conventional methods and stored under an atmosphere of argon. Distilled water was degassed with argon before use. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-500 spectrometer. Mass spectra were obtained on a Hitachi-4100 apparatus. HPLC was performed on a Hitachi L-6000 series liquid chromatography (column, Inertsil SIL 5 μm 4.6 \times 250 mm).

3.2. Carbonylative coupling of iodobenzene with 2-methyl-3-butyne-2-ol under biphasic conditions

A representative procedure (entry 2) was as follows. A benzene solution (10 ml) of $\text{Pd}(\text{OAc})_2$ (11 mg, 0.05 mmol), Ph_3P (27 mg, 0.1 mmol), Bu_4PBr (51 mg, 0.15 mmol), iodobenzene (1.02 g, 5 mmol) and 2-methyl-3-butyne-2-ol (0.42 g, 5 mmol) and 2 M aqueous NaOH (5 ml) were placed in a 50 ml stainless steel autoclave. Carbon monoxide was charged up to 20 atm and the autoclave was heated at 100°C for 8 h with stirring. After the reaction, the organic layer was separated from the aqueous phase and washed with water (30 ml \times 3) and dried over Na_2SO_4 . The evaporation of solvent gave an oily substance (0.87 g), which was subjected to HPLC analysis using naphthalene as an internal standard (mobil phase 95:5, hexane/THF; flow rate, 10 ml/min). The formation of **2** was confirmed by comparing both the CO stretching frequency (1697 cm^{-1}) of the IR spectrum of the benzene-soluble products and the retention time of HPLC with those of the authentic sample [6,7]. The aqueous layer was acidified and extracted with ether. From this ethereal solution benzoic acid was isolated.

3.3. Isolation of furanone **1**

The oil described above (0.30 g) was chromatographed on 30 ml of Wakogel C-200 using

hexane (100 ml); 4:1, hexane/benzene (100 ml); 2:1, hexane/benzene (90 ml); 1:1, hexane/benzene (100 ml); benzene (100 ml); 1:1, benzene/CHCl₃ (100 ml); CHCl₃ (100 ml) and methanol (50 ml) as the eluent in this order. The eluate of 1:1, hexane/benzene gave solids, which were recrystallized from hexane. Needle crystals (42 mg) were obtained with mp. 109°C. HRMS calculated for C₁₃H₁₂O₂, 200.0837; found, 200.0840 (M⁺).

IR (KBr): $\nu(\text{C}=\text{O})$ 1753 cm⁻¹; ¹³C-NMR (CDCl₃): δ 20.98, 24.49, 100.24, 123.54, 124.69, 128.72, 129.43, 151.42, 153.46, 167.14.

3.4. Carbonylation of **6**

Ketone **6** was prepared by the coupling of benzoyl chloride with 2-methyl-3-butyn-2-ol [4]. A benzene solution of **6** (0.94 g, 5 mmol), Pd(OAc)₂ (11 mg, 0.05 mmol), Ph₃P (27 mg, 0.1 mmol), Bu₄PBr (51 mg, 0.15 mmol) and 2 M aqueous NaOH (5 ml) were placed in the autoclave. The carbonylation was performed under CO pressure (20 atm) at 100°C for 8 h. After the usual workup the products were analyzed by HPLC as described above.

4. Conclusion

Homogeneous carbonylative coupling of iodobenzene with 2-methyl-3-butyn-2-ol gives alkynyl ketone. In sharp contrast, however, the aqueous NaOH/benzene biphasic system produces a 2-furanone by successive reactions of carbonylation, reduction and cyclocarbonylation. The use of aqueous NaOH is the key to this double carbonylation.

Acknowledgements

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