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Tetrahedron 62 (2006) 2231–2234
Tetrahedron

Iridium complex-catalyzed addition of water and alcohols to non-activated terminal alkynes

Tomotaka Hirabayashi, Yoshio Okimoto, Akiyo Saito, Masao Morita, Satoshi Sakaguchi and Yasutaka Ishii*

Department of Applied Chemistry and High Technology Research Center, Faculty of Engineering, Kansai University, Suita, Osaka 564-8680, Japan

Received 15 November 2005; revised 3 December 2005; accepted 6 December 2005

Available online 10 January 2006

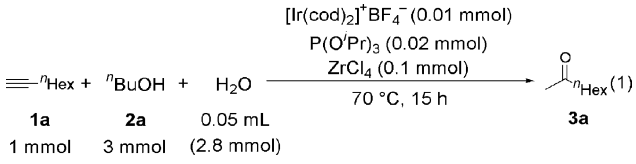
Abstract—The addition of water and alcohols to non-activated terminal alkynes was found to be promoted by an iridium complex combined with Lewis acid and phosphite. Thus, terminal alkynes reacted with water or alcohols to give ketones or ketals, respectively, in good to excellent yields. α,ω-Diyne like 1,7-octadiyne was converted into 1-(2-methyl-cyclopent-1-enyl)ethanone through the intramoleculer aldol condensation of the resulting 2,7-octanedione induced by Lewis acid.

1. Introduction

Addition of oxygen nucleophile to non-activated alkynes is an important tool to construct a carbon–oxygen bond.[1] In particular, metal-catalyzed hydration of alkynes is the most straightforward and environmentally-benign method to prepare ketones and aldehydes. There has been considerable works done on the addition of water to non-activated alkynes using transition metals. Conventionally, the hydration was carried out using toxic Hg(II) salts[2] to enhance the reaction. Several works on the addition of alcohols to alkynes have been reported by the use of various transition metals such as silver(I),[3] osmium(II),[4] palladium(II),[5] platinum(II),[6] rhodium(III)[7] and so on.[8] Recently, Wakatsuki et al. developed the addition of water to alkynes catalyzed by Ru(II) complexes to form predominantly anti-Markovnikov hydration products such as aldehydes.[9] Hayashi et al. showed that the hydration of alkynes was achieved by Au(I) with high turnover frequency (TOF) ($\sim$15,600 h^{-1}).[10] However, there has been only limited study so far on the addition of water and alcohols to alkynes by iridium catalysts.[11] Previously, we reported that the addition of carboxylic acids to non-activated alkynes leading to vinyl esters was efficiently catalyzed by iridium complexes.[12] In continuation of our studies to develop a new catalytic reaction using iridium complexes, we now found that the addition of water and alcohols to non-activated alkynes was enhanced by $[IrCl(cod)]_2$ or $[Ir(cod)_2]^+BF_4^-$ combined with a Lewis acid such as $ZrCl_4$, $GdCl_3$ and $AlCl_3$. In this paper, we wish to report the iridium-catalyzed reaction of alkynes with oxygen nucleophiles like water or alcohols.

2. Results and discussion

In the first place, we examined the reaction of 1-octyne (**1a**) with 1-butanol (**2a**) in the presence of water catalyzed by several Ir-complexes under various conditions (Eq. 1 and Table 1).



The reaction of **1a** (1 mmol) with **2a** (3 mmol) and water (0.05 mL, ca. 2.8 mmol) under the influence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and $ZrCl_4$ (0.1 mmol) at 70 °C for 15 h (standard reaction conditions) led to 2-octanone (**3a**) in high yield (96%), but not 2-octanone dibutylketal (**4aa**) (entry 1). The reaction in the absence of alcohol **2a** resulted in low yield of **3a** (45%) at 60% conversion (entry 2). When water was removed from the reaction system, the reaction proceeded somewhat slowly to form **4aa** in 56% yield (entry 3). This may suggest that the reaction proceeds successively through the formation of ketal **4aa** followed by hydrolysis of the resulting ketal with water. It was found that the yield of **3a** was markedly decreased in the absence of

Keywords: Iridium complex; Alkynes; Lewis acid.
* Corresponding author. Tel.: +81 6 6368 0793; fax: +81 6 6339 4026; e-mail: ishii@ipcku.kansai-u.ac.jp

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doi:10.1016/j.tet.2005.12.010

Table 1. Addition of water to **1a** catalyzed by iridium complex under various reaction conditions

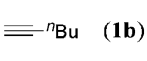
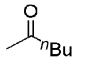
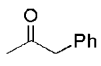
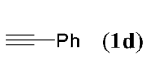
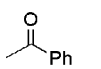
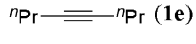
Entry	Ir-complex	Conditions	Conv. (%)	Yield (%)
1	$[Ir(cod)_2]^+BF_4^-$	Standard[a]	99	96
2[b]	$[Ir(cod)_2]^+BF_4^-$	Without **2a**	60	45
3[c]	$[Ir(cod)_2]^+BF_4^-$	Without H_2O	59	56 (**4aa**)
4	$[Ir(cod)_2]^+BF_4^-$	Without $ZrCl_4$	22	2
5	$[Ir(cod)_2]^+BF_4^-$	Without $P(O^iPr)_3$	27	15
6	None	Standard	No reaction	
7	$[IrCl(cod)]_2$	Standard	99	93
8[d]	$[Ir(cod)_2]^+BF_4^-$	Standard	99	71
9[e]	$[Ir(cod)_2]^+BF_4^-$	Without $ZrCl_4$	No reaction	

[a] Compound **1a** (1 mmol) was allowed to react with **2a** (3 mmol) and H_2O (0.05 mL, ca. 2.8 mmol) in the presence of Ir-complex (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and $ZrCl_4$ (0.1 mmol) at 70 °C for 15 h.
[b] Toluene (1 mL) was used as a solvent.
[c] 2-Octanone dibutylketal (**4aa**) was formed.
[d] MeOH (**2b**) (3 mmol) was used instead of **2a**.
[e] $Gd(OTf)_3$ was used instead of $ZrCl_4$.

either $P(O^iPr)_3$ or $ZrCl_4$ (entries 4 and 5). Needless to say, the reaction did not take place at all without the Ir-complex (entry 6). The reaction using $[IrCl(cod)]_2$ in place of $[Ir(cod)_2]^+BF_4^-$ under standard conditions afforded **3a** in good yield (93%) (entry 7). When methanol (**2b**) was employed instead of **2a** under these conditions, **3a** was obtained in slightly lower yield (71%) (entry 8). In addition, the present Ir-catalyzed reaction with $Gd(OTf)_3$ in place of $ZrCl_4$ did not occur at all.

Table 2 shows the representative results of the reaction of several alkynes with **2a** and water catalyzed by $[Ir(cod)_2]^+BF_4^-$ under standard conditions. The reaction of 1-hexyne (**1b**) and 3-phenyl-1-propyne (**1c**) led to almost the same results as that of **1a** (entries 1 and 2), while phenyl acetylene (**1d**) was less reactive than **1a** to give acetophenone (**3d**) in 70% yield (entry 3). Unfortunately, internal alkyne like 4-octyne (**1e**) did not react at all under these conditions (entry 4).

Table 2. Addition of water to various alkynes catalyzed by $[Ir(cod)_2]^+BF_4^-$ [a]

Entry	Alkyne	Product	Conv, (%)	Yield (%)
1	 (**1b**)	 (**3b**)	99	77
2	 (**1c**)	 (**3c**)	99	82
3	 (**1d**)	 (**3d**)	73	70
4	 (**1e**)	No reaction		

[a] Compound **1** (1 mmol) was allowed to react with **2a** (3 mmol) and H_2O (0.05 mL, ca. 2.8 mmol) in the presence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and $ZrCl_4$ (0.1 mmol) at 70 °C for 15 h (standard conditions).

Thus, the addition of water to terminal alkynes was successfully achieved by the $[Ir(cod)_2]^+BF_4^-/P(O^iPr)_3/ZrCl_4$ system in alcohols and water to afford the corresponding ketones in good yields, whereas the addition of alcohols of alkynes without water gave ketals in low yields (Table 1, entries 1 and 3).

In order to improve the yield of the ketal, the addition of **2b** to **1a** by $[Ir(cod)_2]^+BF_4^-$ was examined in the presence of phosphine or phosphite ligands and Lewis acids under several conditions (Eq. 2 and Table 3).

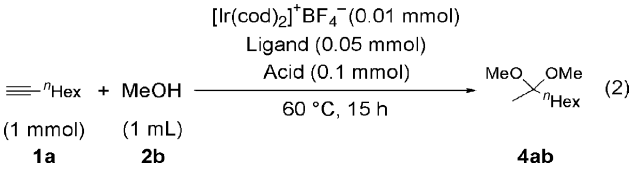


Table 3. Addition of methanol (**2b**) to **1a** catalyzed by $[Ir(cod)_2]^+BF_4^-$ combinated with ligand and acid[a]

Entry	Ligand	Acid	Conv. (%)	Yield (%)
1	$P(OEt)_3$	$AlCl_3$	98	93
2	None	$AlCl_3$	26	9
3	PPh_3	$AlCl_3$	34	<1
4	Dppe	$AlCl_3$	12	nd
5	$P(OMe)_3$	$AlCl_3$	99	90
6	$P(OEt)_3$	None	9	1
7	$P(OEt)_3$	$ZrCl_4$	89	86
8	$P(OEt)_3$	concd HCl	99	76
9	$P(OEt)_3$	TsOH	2	1

[a] Compound **1a** (1 mmol) was allowed to react in the presence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), ligand (0.05 mmol) and acid (0.1 mmol) in methanol (**2b**) (1 mL) at 60 °C for 15 h.

It was found that the reaction took place smoothly when $[Ir(cod)_2]^+BF_4^-$ together with $P(OEt)_3$ and Lewis acid like $AlCl_3$ or $ZrCl_4$ was used. For instance, **1a** reacted with **2b** in the presence of $[Ir(cod)_2]^+BF_4^-$, $P(OEt)_3$ and $AlCl_3$ at 60 °C for 15 h to afford **4ab** in good yield (93%) (entry 1). Removing either the ligand or Lewis acid from the catalytic system resulted in low yield of **4ab** (entries 2 and 6). PPh_3 and bidentate ligand like dppe were inert for the present reaction (entries 3 and 4). It was found that concd HCl served as a good additive, but *p*-toluenesulfuric acid did not induce the reaction (entries 8 and 9). From these results and the result as shown in Table 1 entry 9, Cl^- seems to be essential in the present reaction.

On the basis of these results, the reaction of terminal alkynes with various alcohols was examined (Eq. 3 and Table 4).

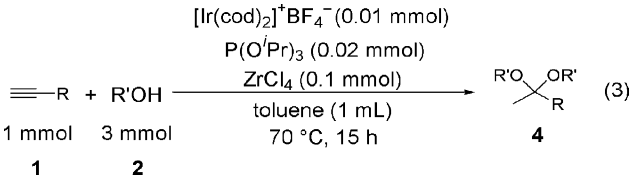


Table 4. Addition of various alcohols to alkynes catalyzed by $[Ir(cod)_2]^+BF_4^-$ [a]

Entry	Alkyne	Alcohol	Conv. (%)	Yield (%)
1	**1a**	**2a**	92	80 (**4aa**)
2	**1a**	**2c**	90	56 (**4ac**)
3	**1a**	**2d**	88	52 (**4ad**)
4[b]	**1a**	**2e**	99	70 (**4ae**)
5[b]	**1a**	**2f**	99	86 (**4af**)
6[b]	**1a**	**2g**	95	46 (**4ag**)
7	**1d**	**2b**	48	35 (**4bb**)

[a] Compound **1** (1 mmol) was allowed to react with **2** (3 mmol) in the presence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and $ZrCl_4$ (0.1 mmol) in toluene (1 mL) at 70 °C for 15 h.
[b] In 1,4-dioxane (1 mL) at 100 °C.

It was found that the use of toluene as a solvent brought about good results. For example, buthanol (**2a**) added to **1a** to give **4aa** in 80% yield (entry 1). The reaction with hexanol (**2c**) and benzyl alcohol (**2d**) gave the corresponding ketals in moderate yields (entries 2 and 3). Various glycols such as ethylene glycol (**2e**), 1,2-butanediol (**2f**) and 1,2-heptanediol (**2g**) easily added to **1a** (entries 4 to 6).[13] Phenyl acetylene (**1d**) was resistant the addition of **2b**, and acetophenone dibuthyl acetal was formed in low yield (entry 7).

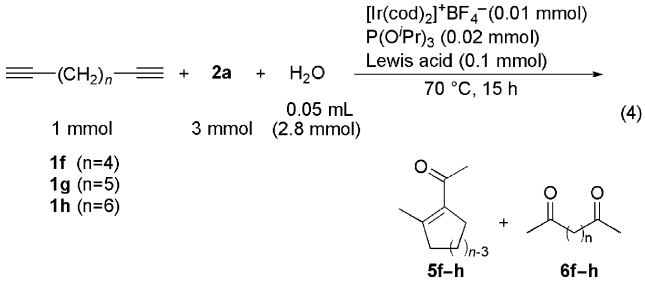
Finally, we tried the addition of water to α,ω-diyne (Eq. 4 and Table 5). There are few reports on the addition of water to α,ω-diynes.[14]

Table 5. Addition of various alcohols to α,ω-diynes catalyzed by $[Ir(cod)_2]^+BF_4^-$ [a]

Entry	Alkyne	Lewis acid	Conv. (%)	Yield (%)	
				5	**6**
1	**1f**	$ZrCl_4$	92	84	5
2	**1f**	$HfCl_4$	94	87	5
3	**1f**	$GdCl_3$	99	34	47
4	**1g**	$ZrCl_4$	78	60	8
5	**1g**	$GdCl_3$	92	2	80
6	**1h**	$ZrCl_3$	99	nd	96
7	**1h**	$GdCl_3$	94	nd	89

[a] α,ω-Diyne (1 mmol) was allowed to react with **2a** (3 mmol) and H_2O (0.05 mL, ca. 2.8 mmol) in the presence of $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), $P(O^iPr)_3$ (0.02 mmol) and Lewis acid (0.1 mmol) at 70 °C for 15 h.

1,7-Octadiyne (**1f**) was found to be converted to 1-(2-methylcyclopent-1-enyl)ethanone (**5f**) in 84% yield by allowing **1f** to react with water catalyzed by an iridium complex combined with Lewis acid in the presence of **2a** (entry 1). The formation of **5f** was rationally explained by assuming the intramolecular aldol condensation of the resulting 2,7-octadione (**6f**) by Lewis acid, $ZrCl_4$, during the reaction. $HfCl_4$ was also an efficient co-catalyst for the condensation to form **5f** in 87% yield (entry 2). However, $GdCl_3$ resulted in **5f** in low yield probably due to its weak basicity (entry 3). 1,8-Nonadiyne (**1g**) produced a mixture of aldol condensation product **5g** and diketone **6g** by the use of $ZrCl_4$ (entry 4), while **6g** was obtained in 80% yield when $GdCl_3$ was used as a Lewis acid (entry 5). 1,9-Decadiyne (**1h**) afforded exclusively diketone **6h** under these reaction conditions because of the difficulty of the formation of the seven-membered ring product corresponding to **5h** (entries 6 and 7).



In summary, we have succeeded in the addition of water and alcohols to non-activated alkynes by an iridium complex combined phosphite ligand and Lewis acid. The reaction of α,ω-diyne with water afforded aldol-condensation products in good yields.

3. Experimental

3.1. General procedure

^1H and ^{13}C NMR were measured at 270 and 67.5 MHz, respectively, in $CDCl_3$ with TMS as the internal standard. Infrared (IR) spectra were measured as thin films on NaCl plate or KBr press disk. A GLC analysis was performed with a flame ionization detector using a 0.2 mm×25 m capillary column (OV-17). Mass spectra were determined at an ionizing voltage of 70 eV. All starting materials, catalysts, and initiators were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

3.2. General procedure for the addition of water to alkyne

An apparatus, consisting of a shulenk, inlet tube sealed with a rubber septum, and magnetic stirring bar, is evacuated, then flushed with argon. A buthanol (3 mmol) solution of triisopropyl phosphite (0.02 mmol), $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), and $ZrCl_4$ (0.1 mmol) was placed in the flask. To this solution are added alkyne (1 mmol) and water (0.05 mL, ca. 2.8 mmol) at room temperature. The reaction was carried out at 70 °C for 15 h. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate=9:1) to give the corresponding product. The products were characterized by ^1H and ^{13}C NMR, IR, and GC–MS, respectively.

3.3. General procedure for the addition of alcohol to alkyne

An apparatus, consisting of a shulenk, inlet tube sealed with a rubber septum, and magnetic stirring bar, is evacuated, then flushed with argon. A toluene (1 mL) solution of triisopropyl phosphite (0.02 mmol), $[Ir(cod)_2]^+BF_4^-$ (0.01 mmol), and $ZrCl_4$ (0.1 mmol) was placed in the

flask. To this solution are added alkyne (1 mmol) and alcohol (3 mmol) at room temperature. The reaction was carried out at 70 °C for 15 h. Removal of the solvent under reduced pressure afforded a cloudy solution, which was purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 15:1) to give the corresponding product. The products were characterized by ^{1}H and ^{13}C NMR, IR, and GC–MS, respectively.

3.3.1. 2-Hexyl-2-methyl-1,3-dioxolane (4ae). ^{1}H NMR δ 3.97–3.90 (m, 4H), 1.65–1.61 (t, $J=6.7$ Hz, 2H), 1.38–1.29 (m, 11H), 0.90–0.87 (t, $J=7.2$ Hz, 3H); ^{13}C NMR δ 110.2, 64.5, 39.2, 31.7, 29.4, 24.0, 23.8, 22.5, 14.0; IR (NaCl) 2932, 2873, 1208, 1080 cm^{-1}; HRMS (EI): calcd for $C_{10}H_{20}O_2$ $[M-H]^+$: 172.1463; found: 172.1466.

3.3.2. 4-Ethyl-2-hexyl-2-methyl-1,3-dioxolane (4af). ^{1}H NMR δ 3.96–3.87 (m, 3H), 1.63–1.58 (t, $J=6.7$ Hz, 2H), 1.44–1.28 (m, 13 H), 0.92–0.86 (m, 6H); ^{13}C NMR δ 110.9, 68.8, 62.8, 40.6, 32.1, 29.9, 25.2, 24.6, 23.2, 22.8, 14.8; IR (NaCl) 2944, 2877, 1221, 1099 cm^{-1}; HRMS (EI): calcd for $C_{12}H_{24}O_2$ $[M-H]^+$: 200.1776; found: 200.1772.

3.3.3. 2-Hexyl-2-methyl-4-pentyl-1,3-dioxolane (4ag). ^{1}H NMR δ 3.99–3.89 (m, 3H), 1.68–1.64 (t, $J=6.7$ Hz, 2H), 1.49–1.26 (m, 19 H), 0.92–0.86 (m, 6H); ^{13}C NMR δ 112.6, 69.2, 62.2, 39.6, 33.2, 31.1, 29.4, 24.8, 24.2, 23.2, 22.9, 18.2, 14.1; IR (NaCl) 2932, 2873, 1208, 1080 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{30}O_2$ $[M-H]^+$: 242.2246; found: 242.2250.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Science and Culture, Culture, Japan, and Daicel Chemical Industries Ltd.

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