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REGIOSELECTIVE HYDRATION OF ALKYNONES BY PALLADIUM CATALYSIS

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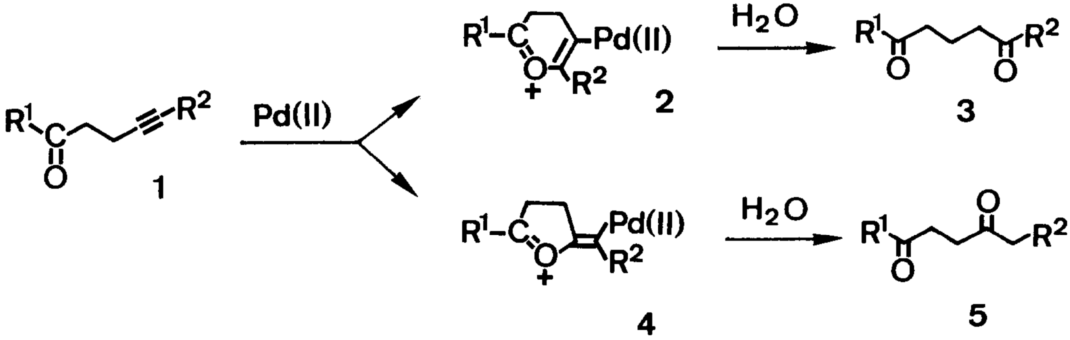
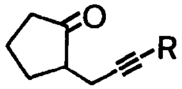
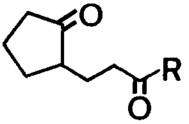
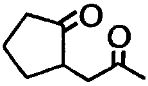
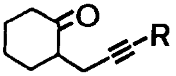
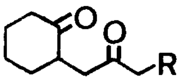
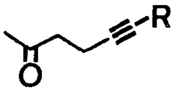
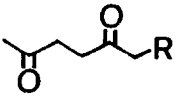
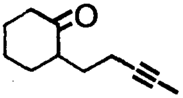
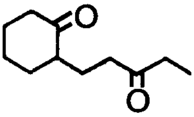
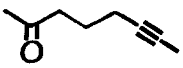
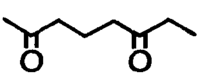
Abstract: Diketones are regioselectively prepared from alkynyl ketones under mild conditions by palladium catalysis; 5-heptyn-2-one and 2-(2-nonynyl)cyclohexanone give 1,4-dikektones whereas 2-(2-heptynyl)cyclopentanone and 5,6-didehydroprostaglandin E_2 methyl ester afford 1,5-diketones.

Methyl ketones are conveniently prepared from easily accessible terminal acetylenes by mercury catalyzed hydration in acidic media.[1] Other ketones, however, are seldom prepared from internal acetylenes because of low regioselectivity.[2] Although the orientation of hydration of internal acetylenes has been controlled by neighboring group participation,[1,3-6] application to acetylenes bearing acid sensitive groups has afforded less satisfactory results. Recently reported intramolecular regioselective oxypalladation[7,8] prompted us the possible use of palladium catalysts for hydration of alkynones. This paper describes regioselective hydration of alkynones in neutral conditions by palladium catalysis.[9]



Hydration of 3-alkynyl ketones 1 was examined first. To an acetonitrile-water (10:1, 2.2 mL) solution of 2-(2-heptynyl)cyclopentanone (**6a**, 170 mg, 0.96 mmol), $PdCl_2(MeCN)_2$ (13 mg, 0.05 mmol, 5 mol%) was added and the mixture was irradiated by ultrasonic wave[10] for 10 h at room temperature. The mixture was diluted with water and extracted with ether. The ethereal solution was dried over Na_2SO_4 and concentrated to give a 1,4-diketone, 2-(3-oxoheptyl)cyclopentanone (**7a**, 180 mg, 96% yield) exclusively.[11] Treatment of 1-octyne with aqueous acetonitrile under the above described palladium catalysis did not give any hydrated product after prolonged ultrasonic irradiation. 5-Decyne was also recovered after analogous treatment with palladium catalyst. These observations indicated the importance of intramolecular assistance of ketone for palladium-catalyzed hydration of acetylenes. In contrast to cyclopentanone derivative, 2-(2-nonynyl)cyclohexanone (**9a**) gave a 1,5-diketone, 2-(2-oxononyl)-

Table I. Diketones from Alkynones by Regioselective Hydration

Alkynone		Diketone		Reaction Time (h)	Yield (%)
	6a (R = Bu)		7a	10	96
				[5.5	91][f]
	6b (Me)		7b	2	92
	6c (H)		8	19.5	81[a]
				[2	67][g]
	9a (R = Hex)		10a	40	84
	9b (Me)		10b	3.5	98[b]
				[21	99][h]
	9c (H)		10c	24	99
				[1	92]
	11a (R = Me)		12a	1.5	55[c]
				[50	27][i]
	11b (Ph)		12b	24	79[d]
	13		14	2	67[e]
	15		16	9	67

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[a] Ketoaldehyde **7** (R = H) could not be detected.

[b] Less than 1% of the corresponding delta-diketone was detected by GLC.

[c] Containing 5% of the corresponding delta-diketone.

[d] Containing 4% of the corresponding delta-diketone.

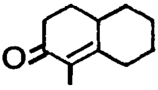
[e] Enone **17** was obtained in 17% yield.

[f] Results obtained by Au catalysis are shown in brackets.

[g] Containing 3% the corresponding ketoaldehyde **7** (R = H).

[h] Containing 10% of delta-diketone.

[i] Obtained a mixture containing 27% of **12a**, 21% of 2,6-heptanedione, and 53% of unchanged starting material **11a**.



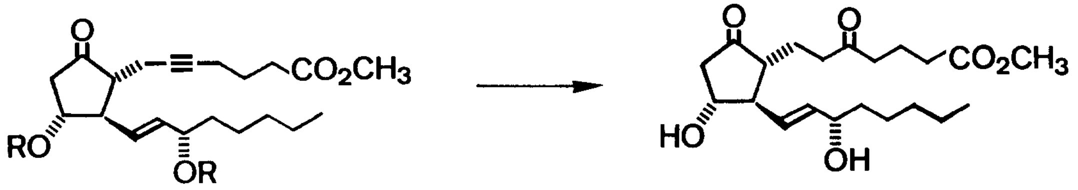
17

cyclohexanone (**10a**)[11] as a sole product in 84% isolated yield. Treatment of 5-heptyn-2-one (**11a**), an example of acyclic alkynone, with palladium catalyst in aqueous acetonitrile gives 2,5-heptanedione (**12a**) exclusively. Analogously 6-phenyl-5-hexyn-2-one (**11b**) gave 6-phenyl-2,5-hexanedione (**12b**). The regioselectivity is determined by the spatial distance between oxygen and any of acetylenic carbon, i.e. oxypalladation followed by hydrolysis through **2** gives a 1,5-diketone **3** and reactions though **4** provides a 1,4-diketone **5**.

Examples of selective hydration of alkynones under the above described conditions are summarized in Table I.

In contrast to 1,5-diketone formation from **6a**, a 1,4-diketone **8** was selectively formed from terminal acetylene **6c**, namely, formation of more stable intermediate **4** takes precedence of the formation of sterically controlled intermediate **2**.

Regioselective hydration of 5,6-didehydroprostaglandin E_2 methyl ester (**18**) illustrates the synthetic utility of the above reaction. Ultrasonic irradiation of a mixture of **18** (50.0 mg, 0.137 mmol) and $PdCl_2(MeCN)_2$ (1 mg, 3 mol%) in 0.5 mL of acetonitrile-H_2O (25:1) at room temperature gave 5-oxo-prostaglandin E_1 methyl ester[12] (**19**, 40.6 mg, 77 % yield). Protected derivative **20** gave the same product **19** in good yield. Removal of the protective group during ultrasonic irradiation was clarified by NMR measurement of the reaction mixture.

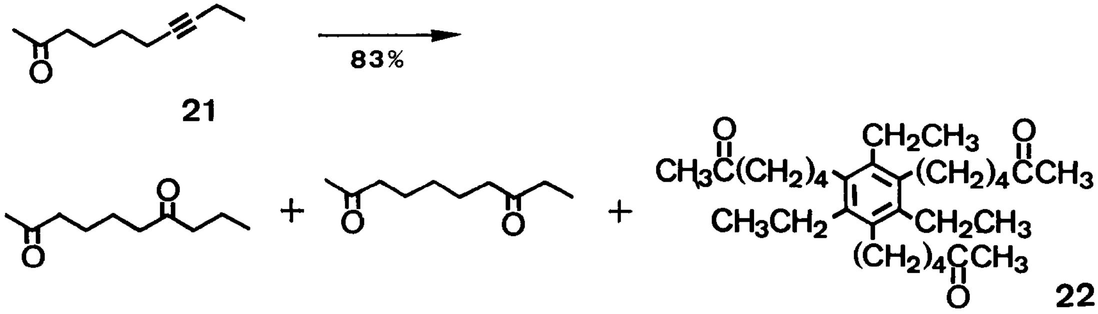


18 R = H

20 R = ${}^tBuMe_2Si$

19

When 7-decyn-2-one (**21**) was subjected to the above hydration, benzene derivative **22**[13] was obtained as the major product with contamination of two possible diketones.



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22

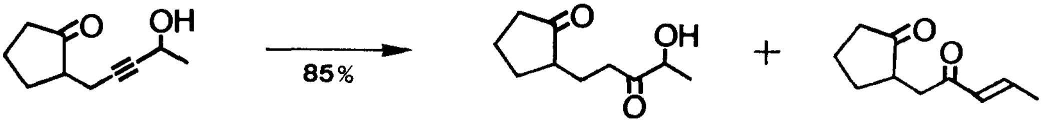
20 : 16 : 64

Recently reported catalytic action of sodium aurate to the intramolecular addition of amine to acetylene moiety prompted the probable application of the catalyst for regioselective hydration alkynones.[14]

Although sodium aurate ($NaAuCl_4$) is effective for hydration of acetylene under neutral condition, lower regioselectivity is observed for the hydration of alkynones. Typical procedures:

a mixture of **6a** (180 mg, 1.01 mmol), $NaAuCl_4 \cdot 2H_2O$ (14 mg, 0.03 mmol, 3 mol%) in 4 Ml of $MeOH-H_2O$ (10:1) was irradiated by ultrasound at room temperature for 5.5 h. Aqueous work-up gave **7a** in 91% yield.[15] Results are added in Table I.

Exceptionally **23** gave diketone **24** (85% yield) selectively by Au(III) catalysis, although a complex mixture was obtained by Pd(II) catalyzed hydration.



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24

> 99 : 1 >

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References and Notes

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6. Although group VIII metals, such as Pd(II) and Ru(III), have been reported as catalysts for the hydration of acetylenes, synthetic applications have little reported.
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9. Palladium-catalyzed transformation of 2-alkynyl ketones into furans via oxypalladation has been observed; H. Shiragami, and K. Utimoto, to be published.
10. Commercial ultrasonic cleaner (Branson B1200J-1) was used.
11. Structure was determined by ^1H NMR, ^{13}C NMR as well as MS.
12. IR 3372 (OH), 1738 (C=O) cm^{-1}; ^1H NMR ($CDCl_3$), 0.89 (3H, br-t, J = 6.4 Hz), 1.20-1.50 (8H, m), 1.50-1.70 (2H, m), 1.76 (2H, dt, J = 7.0, 7.0 Hz), 1.89 (2H, dt, J = 7.1, 7.1 Hz), 2.08 (1H, m), 2.15-2.40 (2H, m), 2.33 (2H, t, J = 7.2 Hz), 2.46 (2H, t, J = 7.3 Hz), 2.60 (2H, dt, J = 3.8, 7.3 Hz), 2.73 (1H, dd, J = 7.5, 18.3 Hz), 3.67 (3H, s), 3.95-4.20 (2H, m), 5.55 (1H, dd, J = 8.2, 15.3 Hz), 5.69 (1H, dd, J = 6.7, 15.3 Hz); ^{13}C NMR ($CDCl_3$), 214.6, 209.6, 173.6, 137.3, 131.2, 72.9, 71.7, 55.1, 53.0, 51.6, 45.8, 41.5, 39.7, 37.3, 33.0, 31.7, 25.2, 22.6, 21.9, 18.8, 14.0.
13. IR 1712 cm^{-1}; ^1H NMR ($CDCl_3$), 1.16 (9H, t, J = 7.5 Hz), 1.4-1.6 (6H, m), 1.73 (6H, quint. J = 7.5 Hz), 2.16 (9H, s), 2.4-2.6 (18H, m); ^{13}C NMR, 208.8, 137.9, 136.2, 43.44, 31.19, 29.98, 29.50, 24.75, 22.33, 15.73; MS m/z 456 (M^+).
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15. Both terminal and internal acetylenes gave ketones in good yields by Au catalysis.

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