Tetrahedron Letters,Vol.25,No.46,pp 5323-5326,1984 0040-4039/84 $3.00 + .00
Printed in Great Britain

PALLADIUM(II) CATALYZED CYCLIZATION OF ALKYNOIC ACIDS

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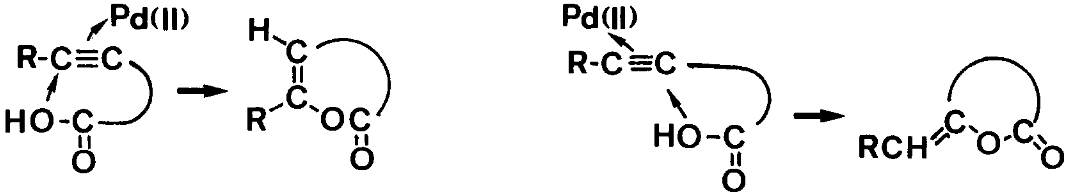
Abstract: Under the catalytic action of palladium(II) in the presence of triethylamine, 3-, 4-, and 5-alkynoic acids afford 3-buten-4-olides, 4-penten-4-olides, and 5-hexen-5-olide, respectively, in good to excellent yields.

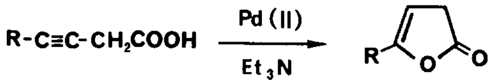
Intramolecular addition of an alcohol or a carboxylic acid to an acetylene becomes an efficient route toward heterocycles.[2-9] Mercuric salts, inspite of their toxicity, have been used as effective catalysts for the above reactions.[10] Recently was reported the use of nontoxic palladium catalysts for intramolecular additions of alcohols or an amine to an acetylene producing oxygen or nitrogen heterocycles.[11,12] This paper describes an additional effective use of palladium(II) catalysts for the intramolecular endo or exo additions of carboxylic acids to acetylenes affording unsaturated lactones.[13]



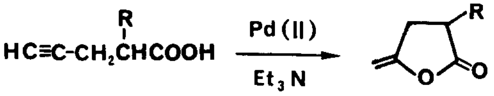
Cyclization of 3-alkynoic acids (I) was examined first. The reaction proceeded regioselectively in 5-Endo-Dig manner affording 3-alken-4-olides (II) in excellent yields.

To a solution of $PdCl_2(PhCN)_2$ (38 mg, 0.1 mmol) and triethylamine (0.4 mL, 30 mg, 0.3 mmol) in 20 mL of THF, 3-decynoic acid (I, R = n-C_6H_{13}, 1.68 g, 10 mmol) was added and the reaction mixture was stirred under reflux for 1 h. The whole was concentrated and chromatographed on silica gel [hexane-ethyl acetate (7:3) as eluent] affording 1.41 g (84% yield) of 3-decen-4-olide (II, R = n-C_6H_{13}).[14] Other 3-alkynoic acids were treated analogously except 3-pentynoic acid (I, R = CH_3) which was treated with $PdCl_2(MeCN)_2$, in place of $PdCl_2(PhCN)_2$, affording 3-penten-4-olide (II, R = CH_3) by direct distillation of the reaction mixture.[15] Yields of lactones II are shown in Table 1.[16]

Under the above described conditions, cyclization of 4-pentynoic acids (III) bearing alkyl group on C-2 afforded 4-penten-4-olide (IV) exclusively by 5-Exo-Dig manner. Isomerization of double bond from exo to endo cyclic position could not be observed under the reaction conditions. When acid III (R = Me_3Si) was treated analogously, the protodesilylated product IV (R = H) was isolated. Results are summarized in Table 2.[17]



I II



III IV

Table 1. 3-Buten-4-olides (II)

Entry	R	Yield (%)	Ref.
1	CH_3	95[a]	18
2	$n\text{-}C_6H_{13}$	84	19
3	$n\text{-}C_8H_{17}$	88	19
4	Ph	38	20

a) $PdCl_2(MeCN)_2$ was used as catalyst.

Table 2. 4-Penten-4-olides (IV)

Entry	R	Yield (%)	Ref.
1	H	quant.[a]	5
2	$n\text{-}C_4H_9$	81	19
3	$n\text{-}C_6H_{13}$	84	19
4	Ph	96	5
5	$PhCH_2$	85	19
6	Me_3Si	63[b]	5

a) $PdCl_2(MeCN)_2$ was used as catalyst.
b) Product was IV (R = H).

Cyclization of 4-alkynoic acids (V) proceeded slowly under the same reaction conditions as described above. Yields of lactones (VI and VII) , however, were good to excellent after prolonged heating in acetonitrile. Reaction of 4-hexynoic acid (V, R = CH_3, R' = H) is illustrative. To a solution of $PdCl_2(PhCN)_2$ (38 mg, 0.1 mmol) and triethylamine (0.3 mmol) in 20 mL of acetonitrile, 4-hexynoic acid (V, R = CH_3, R' = H, 1.12 g, 10 mmol) was added and the reaction mixture was refluxed for 3 h. The whole was concentrated and chromatographed affording a mixture of 4-hexen-4-olides (VI:VII = 84:16, R = CH_3, R' = H). Combinations of the yields, R, R', and the product ratios (VI:VII) are shown in Table 3.

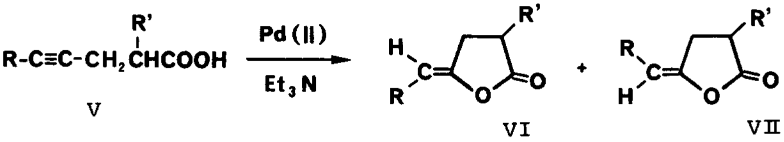
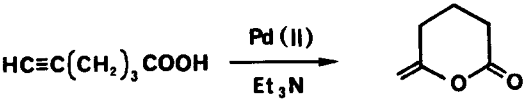


Table 3. 4-Alken-4-olides (VI and VII)

Entry	R	R'	Yield (%)	Ratio (VI/VII)	Reaction Time (h)	Ref.
1	CH_3	H	87	84/16	3	4
2	Ph	H	85	100/0	2	6
3	n-C_6H_{13}	Ph	66	87/13	4	21

Cyclization of 5-hexynoic acid (VIII) under the catalytic action of $PdCl_2$ in acetonitrile in the presence of triethylamine (3 mol%) proceeded selectively in 6-Exo-Dig manner affording 5-hexen-5-olide (IX) in 43% yield after heating at reflux for 8 h.



VIII IX

The above described results indicate the utilities of palladium(II) catalyst for the cyclization of alkynoic acids under mild conditions. This highly regioselective reaction will be a useful method for the preparation of butenolides and specially for the application to the synthesis of natural products.

Acknowledgements: The authors wish to thank the Ministry of Education, Science, and Culture for Grant-in-Aid (59470081). The travelling grant for C.L. from this Ministry is also acknowledged.

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13. Palladium(II) mediated cyclization of alkenoic acids was reported: A. Kasahara, T. Izumi, K. Sato, M. Maemura, and T. Hayasaka, *Bull. Chem. Soc. Jpn.*, **50**, 1899 (1977). Stoichiometric amount of Na_2PdCl_4 was used and 2-butenolides were obtained in 30-40% yields.

14. Cyclization reactions were observed only in the presence of palladium(II) and triethylamine. Without triethylamine, the palladium(II) catalyst was almost inactive even in long refluxing time.

15. In order to avoid the contamination of benzonitrile in the isolated product, acetonitrile complex was used.

16. The yields indicated in this paper are isolated yields. Except for the case of II-4, the starting material was consumed completely at the end of the reaction time (checked by TLC).

17. In the case of III-1 (R = H), the reaction proceeded at room temperature.

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19. New compounds.
    II-2: ^{1}H-nmr (CCl_4), δ ppm, 0.88 (3H, t, J = 6 Hz), 1.2-1.7 (8H, m), 2.22 (2H, m), 3.06 (2H, d-d), 5.03 (1H, m), IR (neat, cm^{-1}), 1780, 1650.
    II-3: ^{1}H-nmr, 0.83 (3H, t, J = 6 Hz), 1.16-1.73 (12H, m), 2.2 (2H, m), 3.0 (2H, d-d), 5.03 (1H, m). IR, 1780, 1660.
    IV-2: ^{1}H-nmr, 0.9 (3H, t, J = 6 Hz), 1.2-1.9 (6H, m), 2.3-3.1 (3H, m), 4.22 (1H, m), 4.57 (1H, m). IR, 1780, 1650.
    IV-3: ^{1}H-nmr, 0.87 (3H, t, J = 6 Hz), 1.13-1.67 (10H, m), 2.4-3.1 (3H, m), 4.23 (1H, m), 4.61 (1H, m). IR, 1780, 1650.
    IV-5: ^{1}H-nmr, 2.4-3.2 (5H, m), 4.05 (1H, m), 4.51 (1H, m), 7.1 (5H, m). IR, 1780, 1660, 1570.

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21. Two isomers were not separated. A mixture of VI and VII (R = n-C_6H_{13}, R' = Ph): ^{1}H-nmr (CCl_4), δ ppm, 0.9 (3H, m), 1.2-1.5 (8H, m), 2.12 (2H, m), 2.96 (2H, m), 3.77 (1H, d-d), 4.46 (1H, m, VI), 4.96 (1H, m, VII). IR (neat, cm^{-1}), 1780, 1660, 1600.

(Received in Japan 6 August 1984)