Tetrahedron Letters, Vol. 34, No. 37, pp. 5963-5966, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .00
Pergamon Press Ltd

A CONVENIENT SYNTHESIS OF γ-(Z)-ALKYLIDENE BUTENOLIDES

Xiyan Lu*, Xiaoling Huang and Shengming Ma

Shanghai Institute of Organic Chemistry, Academia Sinica
345 Lingling Lu, Shanghai 200032, China

ABSTRACT: A convenient synthesis of γ-(Z)-alkylidene butenolides starting from (Z)-3-bromopropenoic acid was described.

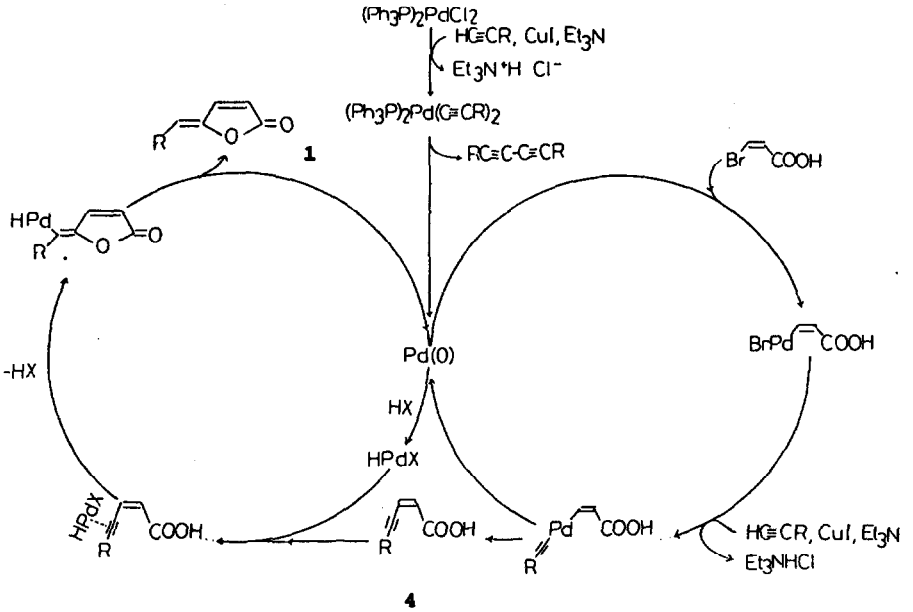
Selectivity provides a formidable challenge for chemists. Thus new synthesis of pure geometrical isomers at a double bond, especially those in the thermodynamically unfavorable (Z)-configuration, would be a significant advance. Protonanemonin (**1**, R=H) and its analogs possess antiviral and antibiotic activity which have been extensively investigated.[1] Marine metabolites such as fibrolides[2] and dihydroxerulin[3] also have the γ-alkylidene butenolide skeleton. Although some synthetic methods are available [4,5], more convenient methods are still desired.

Recently, we reported a one-pot stereoselective synthesis of ynenoic acid derivatives via Pd(0) catalyzed reaction from propiolic acid derivatives.[6] It occurred to us that it might be possible to obtain the precursor of alkylidene butenolide, 4-yn-(2Z)-enoic acid, using propiolic acid as the starting material. When we tried this one-pot reaction, it was unsuccessful because of the poor solubility of lithium (Z)-3-bromopropenoate in acetonitrile. Then we isolated (Z)-3-bromopropenoic acid and tried its reaction with phenylacetylene under the catalysis of $PdCl_2(PPh_3)_2$. To our surprise, we obtained (Z)-benzylidene butenolide (**1a**)[7] instead of the expected product ynenoic acid. Table 1 shows that this is a general reaction with good yields and high stereoselectivity.

The stereochemistry of products (**1a-h**) was assigned on the basis of ^{1}H-NMR chemical shift of exocyclic olefinic protons. A mixture of Z- and E-isomer could be obtained on prolonged reaction time. Chemical shifts at lower fields were assigned to the E-isomers due to the deshielding effect of the lactone oxygen for the E-isomers.[8]

It was reported that phenyl propargylaldehyde and phenyl acetic acid could give butenolide under acid condition by heating at 150°C through an

intermediate of ynenoic acid.[9] Also, a conjugated ynenoic acid could cyclize by the catalysis of $AgNO_3$.[10] In our case, the reaction was carried out at rt implying that palladium must take part in the cyclization of ynenoic acid. Moreover, Utimoto reported the Pd(II) catalyzed cyclization of 4-alkynoic acids through an alkenyl palladium intermediate.[11] So the mechanism of this reaction might be speculated as follows:

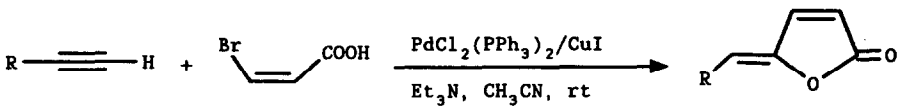


4

[HPdX] represents the active species of Pd(II), which is still not certain whether X represents Cl^-,Br^- or $BrCH{=}CCOO^-$.

Pd(0) species is first formed in the presence of an alkyne. The vinyl bromide reacts with an alkyne under the catalysis of Pd(0) to produce the ynenoic acid **4**.[6] Pd(0) species is regenerated and easily converted into Pd(II) species in the solution which contains the acid moiety HX (X represents Br^-, Cl^- or $BrC{=}CCOO^-$). Ynenoic acid is further transformed

Table 1 Synthesis of γ-alkylidene butenolide[a]



2 **3** **1**

2 R		Reaction time (h)	Product **1**	Isolated yield(%)[b]	Z/E[c]
Ph	**(2a)**	10	**1a**	80	>97/3
n-C_5H_{11}	**(2b)**	8	**1b**	60	91/9
n-$C_7H_{15}CH(OH)$	**(2c)**	10	**1c**	74	>97/3
PhCH(OH)	**(2d)**	10	**1d**	56	>97/3
$THPOCH_2$	**(2e)**	12	**1e**	62	93/7
$Me_2C(OH)$	**(2f)**	12	**1f**	86	94/6
HC CCH_2OCH_2	**(2g)**	10	**1g**	54	92/8
$MeOCH_2$	**(2h)**	12	**1h**	62	>97/3

a. Reactions were carried out at room temperature using **1** (1 mmol) in acetonitrile (8 ml) with the molar ratio: **2**:**3**:Et_3N:$PdCl_2(PPh_3)_2$:CuI= 1.5:1:2:0.03:0.03.

b. All compounds were fully characterized by IR, ^{1}H-NMR, MS spectra and elemental analysis.

c. The ratio was determined by ^{1}H-NMR spectra.

into the γ-alkylidene butenolide by the catalysis of Pd(II) through the σ-vinyl-palladium intermediate.[11] The formation of Z-isomer might be explained by the trans-addition of the carboxylate anion across the carbon-carbon triple bond. On reductive elimination, Pd(0) species will be regenerated to yield **1**. It is interesting that the reaction is first catalyzed by Pd(0) species and then by Pd(II) species.

The typical procedure is as follows: A mixture of **2a** (153 mg, 1.5 mmol), **3** (151 mg, 1 mmol), $PdCl_2(PPh_3)_2$(21 mg, 0.03 mmol), CuI(5.7 mg, 0.03 mmol), Et_3N (202 mg, 2 mmol) and acetonitrile (8 ml) was stirred at rt and monitored by TLC. After 10h, the mixture was filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether : ethyl acetate = 15 : 1) to afford the desired product **1a** (137 mg, 80%),mp 85-86°C (Lit.[7] mp 86-87°C).

In conclusion, the regio- and stereoselective reaction described here provides an easy access to γ-(Z)-alkylidene butenolides and holds promise as a useful and versatile method for the preparation of this class of compounds.

Acknowledgement: We thank the National Natural Science Foundation of China and Academia Sinica for financial support.

References:

1. Caltrider, P. G.; Antibiotics, **1967**, *1*, 671.
2. Pettus, J. A.; Wing, R. M.; Sims, J. J.; Tetrahedron Lett. **1977**, 41; Kazlauskas, R. A.; Murphy, P. T.; Wells, R. J.; Tetrahedron Lett. **1977**, 37.
3. Kuhut, D.; Anke, T.; Besl, H.; Bross, M.; Herrmann, R.; Mocek, U.; J. Antibiot. **1990**, *43*, 1413.
4. Rao, Y. S.; Chem. Rev. **1976**, *76*, 625.
5. Auria, M. D.; Piancattelli, G.; Scettri, A.; Tetrahedron, **1980**,*36*, 3071; Kraus, G. A.; Sugimoto, H.; J. Chem. Soc., Chem. Commun. **1978**, 30; Askoka, M.; Yanagida, N.; Ishibashi, K.; Takei, H.; Tetrahedron Lett. **1981**, *22*, 4269.
6. Lu, X.; Huang. X.; Ma, S.; Tetrahedron Lett. **1992**, *33*, 2535.
7. Yamamoto, M.; J. Chem. Soc., Perkin Trans. 1, **1981**, 582.
8. Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli,F.; Pietroni, B. R.; J. Org. Chem. **1992**, *57*, 976.
9. Rao, Y. S.; Filler, R.; Tetrahedron Lett. **1975**, 1457.
10. Belil, C.; Pascual. J.; Serratosa, F.; Tetrahedron, **1964**, *20*, 2701.
11. Yanagihara, N.; Lambert, C.; Iritani, K.; Utimoto, K.; Nozaki, H.; J. Am. Chem. Soc. **1986**, *108*, 2753.

(Received in China 11 May 1993; accepted 14 July 1993)