Pergamon

Tetrahedron Letters, Vol. 38, No. 27, pp. 4831-4834, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01047-2

A Convenient Synthesis of 3-Iodohomoallylic Alcohols and the Further Transformation to α,β-Unsaturated γ-Lactones

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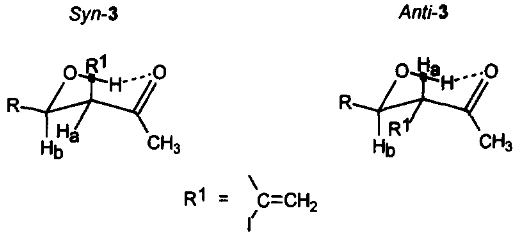
Abstract: The tandem nucleophilic addition-aldol reaction of 3,4-pentadien-2-one, iodide ion, and aldehydes in the presence of $ZrCl_4$ as the catalyst gave the 3-iodohomoallylic alcohols in good yields, which could be further transformed to α,β-unsaturated γ-lactones by palladium-catalysed cyclocarbonylation. © 1997 Elsevier Science Ltd.

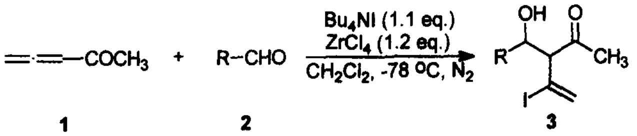
Nucleophilic addition to electron-deficient allenes is a well known reaction but examples in which the electrophilic component of the nucleophile-electrophile partnership is other than a proton are rare.[1,2] Recently, we have successfully trapped the carbanions generated by the addition of the nucleophilic phosphines to electron-deficient allenes with electron-deficient olefins as the electrophiles, leading to a novel phosphine-catalysed [3+2] cycloaddition reaction.[3] To extend our study, trapping the carbanions formed by the addition of another type of nucleophile, iodide ion, to electron-deficient allenes with aldehydes as the electrophile was investigated. We describe herein a tandem nucleophilic addition-aldol reaction of 3,4-pentadien-2-one, iodide ion, and aldehydes in the presence of Lewis acid $ZrCl_4$. The reaction gave the 3-iodohomoallylic alcohols in good yields, which could be further transformed to α,β-unsaturated γ-lactones by palladium-catalysed cyclocarbonylation.

A mixture of 3,4-pentadien-2-one, an aldehyde and Bu_4NI in dry CH_2Cl_2 was reacted at -78 °C in the presence of $ZrCl_4$. After the reaction was complete, aqueous work-up followed by extraction with CH_2Cl_2 and chromatography afforded adducts **3** (Table 1).[4,5] The use of aliphatic aldehydes resulted in the formation of a pair of *syn* and *anti* isomers of **3** in a ratio of about 1 : 1, which could be separated by chromatrography. When aromatic aldehydes were used, the distribution of *syn*-**3** and *anti*-**3** was affected evidently by the substituent on the benzene ring of the aldehyde. If the substituent was an electron-withdrawing group, the reaction gave the *syn*-**3** as the major isomer, while the electron-donating substituent resulted in the formation of the *anti*-**3** as the sole product. The *syn* and *anti* stereochemistry was assigned according to the magnitude of the vicinal coupling constants between H_a and H_b protons. It has been observed in similar systems that the H_a-H_b coupling constant of *anti*-isomer is usually larger than that of the corresponding *syn*-isomer (Scheme 1).[6]



Scheme 1

Table 1. Preparation of 3-iodohomoallylic alcohol 3[a]

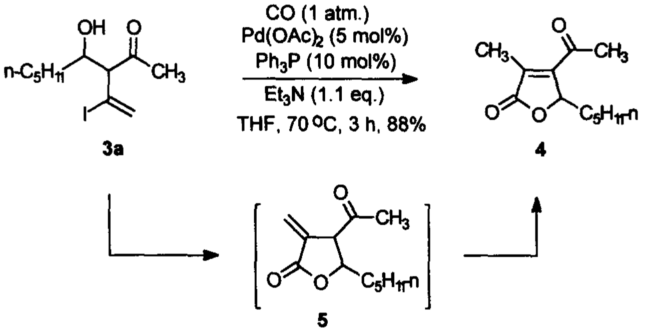


Entry	Aldehyde		Product		
	2	R	**3**	Yield (%)[b]	*syn/anti*
1	**2a**	n-C_5H_{11}	**3a**	71	50 : 50[c]
2	**2b**	n-Pr	**3b**	64	50 : 50[c]
3	**2c**	i-Pr	**3c**	75	40 : 60[d]
4	**2d**	p-$NO_2C_6H_4$-	**3d**	68	93 : 7[d]
5	**2e**	p-ClC_6H_4-	**3e**	51	80 : 20[d]
6	**2f**	Ph	**3f**	71	29 : 71[c]
7	**2g**	p-MeC_6H_4-	**3g**	67	0 : 100
8	**2h**	p-$MeOC_6H_4$-	**3h**	72	0 : 100

[a] **1** (1.0 mmol), **2** (1.2 mmol), Bu_4NI (1.1 mmol), and $ZrCl_4$ (1.2 mmol) in CH_2Cl_2 (5 ml) at -78 °C under N_2. [b] Yield of isolated products. [c] Calculated based on the isolated products. [d] Determined by ^1H NMR spectra.

3-Iodohomoallylic alcohols **3** are useful synthetic intermediates, but their preparation was not convenient using literature methods.[7] This reaction offered an easy entry to the synthesis of this kind of compounds.

γ-Lactones constitute an important group of natural products exhibiting wide range of biological activities.[8] With the compound **3** in hand, we investigated their conversion into γ-lactones by means of palladium-catalysed cyclocarbonylation.[7,9] For example, cyclocarbonylation of **3a** was achieved employing the $Pd(OAc)_2/Ph_3P$ catalytic system. A mixture of **3a** (1.0 mmol), $Pd(OAc)_2$ (5 mol%), Ph_3P (10 mol%), and Et_3N (1.1 mmol) in THF was heated at 70 °C under an atmosphere of carbon monoxide, giving the α,β-unsaturated γ-lactone **4** in 88% yield.[10, 11] The expected α-methylene-γ-lactone **5** was not obtained, which might be due to that compound **5** was unstable in the reaction condition and rearranged to the more stable isomer **4** (Scheme 2).



Scheme 2

In conclusion, the tandem nucleophilic addition-aldol reaction of iodide ion, 3,4-pentadien-2-one, and aldehydes in the presence of $ZrCl_4$ as the Lewis acid catalyst provided a facile synthesis of 3-iodohomoallylic alcohols, which could be conveniently converted to α,β-unsaturated γ-lactones.

Acknowledgements: We thank the National Natural Science Foundation of China and Chinese Academy of Sciences for financial support.

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4. Typical procedure for the preparation of 3-iodohomoallylic alcohols **3**: To a mixture of 3,4-pentadien-2-one (**1**, 82 mg, 1.0 mmol), 1-hexanal (**2a**, 120 mg, 1.2 mmol) and Bu_4NI (400 mg, 1.1 mmol) in dry CH_2Cl_2 (5 ml) was added $ZrCl_4$ (280 mg, 1.2 mmol) at -78 °C. After stirring at -78 °C under N_2 for 12 h, the reaction was complete as monitored by TLC. Water (5 ml)

was then added and followed by extraction with CH_2Cl_2 (3 × 5 ml). The combined organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The resulting residue was subjected to silica gel column chromatography (petroleum ether/ethyl acetate = 10 : 1) to give ***syn*-3a** (110 mg) and ***anti*-3a** (110 mg).

5. All new compounds are fully characterized by spectral and elementary analyses. Data for ***syn*-3a**: IR (neat) 3400, 2900, 1700, 1600, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, J = 1.55 Hz, 1H), 6.17 (d, J = 1.58 Hz, 1H), 4.08 (m, 1H), 3.32 (d, J = 6.25 Hz, 1H), 2.24 (s, 3H), 1.50-1.24 (m, 8H), 0.88 (t, J = 6.65 Hz, 3H); MS m/z (%) 311 (M^++1, 12.55), 83 (100.00); Anal. Calcd for $C_{11}H_{19}O_2I$ (310.17): C, 42.60; H, 6.17. Found: C, 42.49; H, 6.12. Data for ***Anti*-3a**: IR (neat) 3400, 2950, 1720, 1610, 1355 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.43 (d, J = 1.61 Hz, 1H), 6.05 (d, J = 1.64 Hz, 1H), 4.06 (d, J = 8.66 Hz, 1H), 3.20 (d, J = 8.66 Hz, 1H), 2.23 (s, 3H), 1.60-1.23 (m, 8H), 0.89 (t, J = 6.8 Hz, 3H); MS m/z (%) 292 (M^+-H_2O, 3.74), 43 (100.00); Anal. Calcd for $C_{11}H_{19}O_2I$ (310.17): C, 42.60; H, 6.17. Found: C, 42.30; H, 5.86.
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10. Cyclocarbonylation of **3a**: A mixture of **3a** (310 mg, 1.0 mmol), palladium acetate (11 mg, 0.05 mmol), triphenylphosphine (26 mg, 0.10 mmol), and triethylamine (110 mg, 1.1 mmol) in THF (5 ml) was heated at 70 °C under an atmosphere of carbon monoxide for 3 h. After the reaction mixture was cooled to room temperature, water (5 ml) was then added and followed by extraction with ethyl acetate (3 × 5 ml). The organic layer was dried ($MgSO_4$), and concentrated. The residue was puried by chromatography on silica gel (petroleum ether/ethyl acetate = 5 : 1) to give the carbonylated product **4** (185 mg, 88%).
11. Data for **4**: IR (neat) 3400, 1940, 1760, 1680, 1370, 800 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.17-5.13 (m, 1H), 2.50 (s, 3H), 1.99-1.27 (m, 8H), 0.89 (t, J = 6.8 Hz, 3H); MS m/z (%) 211 (M^++1, 7.90), 210 (M^+, 10.38), 43 (100.00); Anal. Calcd for $C_{12}H_{18}O_3$ (210.27): C, 68.55; H, 8.62. Found: C, 68.30; H, 8.52.

(*Received in China* 8 *April* 1997; *accepted* 4 *May* 1997)