Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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To cite this article: Giuliana Righi & Leucio Rossi (1996) Mild Regioselective Catalytic Hydrogenation of α,β-Unsaturated Carbonyl Compounds with Lindlar Catalyst, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 26:7, 1321-1327, DOI: 10.1080/00397919608003491

To link to this article: http://dx.doi.org/10.1080/00397919608003491

SYNTHETIC COMMUNICATIONS, 26(7), 1321-1327 (1996)

MILD REGIOSELECTIVE CATALYTIC HYDROGENATION OF α,β-UNSATURATED CARBONYL COMPOUNDS WITH LINDLAR CATALYST

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Abstract: *The hydrogen-Lindlar catalyst system is effective for the highly regioselective reduction of α,β-unsaturated carbonyl compounds to the corresponding α,β-saturated compounds.*

Regioselective reduction of α,β-unsaturated carbonyl compounds is an important transformation in organic synthesis[1]; the selective reduction of highly functionalized molecules is a recent subject of considerable interest, especially in the synthesis of natural products. The hydrogenation of these carbonyl compounds, over any of a miriad of catalysts, gives a wide variety of products depending on the reaction conditions employed.

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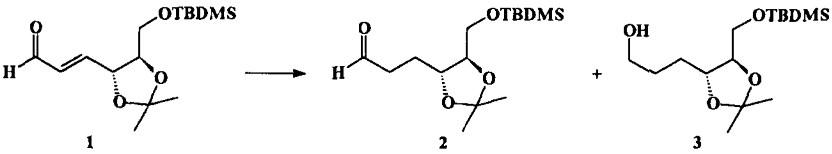
Table 1: Reduction of aldehyde **1** with different catalytic systems.



Reducing Agent	Catalyst[a]	Solvent[b]	Conditions	Ratio 2:3[c]	Yield(%)[c]
HCO_2H-Et_3N	Pd/C (10%)	---	100°C, 8 h	---	—[d]
H_2	Pd/C (10%)	MeOH	r.t., 3 h	8:92	88
H_2	Pd/C (10%)	MeOH-Et_3N (5%)	r.t., 1 h	70:30	65
H_2	Pd/C (10%)	MeOH-Et_3N (10%)	r.t., 1 h	81:19	70
H_2	Pd/$CaCO_3$-Pb (5%)	MeOH	r.t., 3 h	> 98:2	98

a: Value in parentheses is referred to Palladium.
b: Value in parentheses is the amount of triethilamine in the solvent.
c: Yields and product ratio was determinated by GC.
d: Only degradation products.

These include the method of catalyst preparation, source of metal used, solvents used in catalyst preparation and catalyst use, catalyst support, additives (both known and impurities) and amount of catalyst used.

During our study concerning the synthesis of natural products, we needed to reduce regiospecifically the α,β-unsaturated aldehyde 1 to the corresponding saturated aldehyde 2 (Table 1). Since previously reported methods[1] were not completely satisfactory[2,3] or suffered from serious economic or operational drawbacks[4], we tried to use a hydrogenation catalyst with reduced catalytic activity.

As shown in Table 1, the addition of small amount of triethylamine to the hydrogen-palladium on charcoal system afforded the desired compound with quite good regioselectivity and chemical yield. Better results were obtained employing Lindlar catalyst (palladium 5% on calcium carbonate, poisoned with lead); we obtained only compound **2** in nearly quantitative yields. The method was successfully applied to other α,β-unsaturated carbonyl compounds. As shown in Table 2, a large number of carbonyl compounds were treated with hydrogen-Lindlar Catalyst in methanol at room temperature affording the corresponding saturated compounds.

The reaction proceeds regiospecifically and in high yield with a variety of acyclic unsaturated carbonyl compounds like aldehydes, ketones and esters; only in the case of cynnamaldehyde **11** the reduction was very slow and resulted in a mixture of saturated compounds (Run 6).

Selective reduction of unsaturated aldehydes and ketones occurs without detectable reduction of the carbonyl function and α,β-double bonds can be cleanly reduced in the presence of nonconjugated double bonds (Run 2). This is a synthetically valuable characteristic of the present reduction system. The conjugated dienone, β-ionone **14**, produced only the α,β-saturated dihydro ionone **15** in quantitative yields (Run 7); while the acyclic conjugated dienale, 2,4-decadienal **9** gave the saturated aldehyde (Run 5). Quite unexpectedly phorone **16** gave only the monoreduction product even using long reaction times (Run 8).

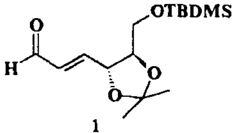
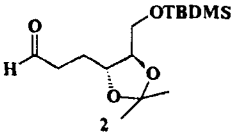
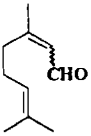
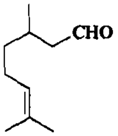
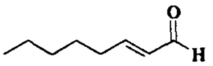
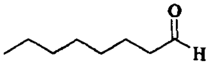
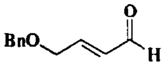
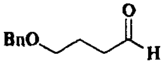
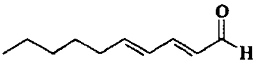
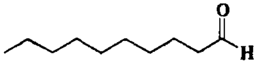
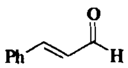
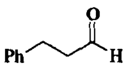
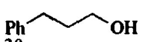
Furthermore the method was highly chemoselective towards other functional groups present in the molecule; protective groups like acetonide, tert-butyldimethylsilyl (TBDMS) and even benzyl groups are neither removed nor hydrogenolyzed in the reaction conditions used (Runs 1 and 4).

In conclusion, the results shown that the hydrogen-Lindlar catalyst is a very fast, effective and convenient system for the reduction of α,β-unsaturated carbonyl compounds to the corresponding saturated carbonyl compounds. The observed selectivities and yields, comparable or superior to those reported in literature, indicate that this procedure is an attractive alternative to the reported methods.

EXPERIMENTAL

GENERAL: TLC analyses were performed on Merck kieselgel 60 F254 plates. Flash chromatography was carried out on silica gel (230-400 mesh).

Table 2. Conjugate reduction of α,β-unsaturated aldehydes.

Run	Substrate	Time (h)	Product(s)[a]	Yield (%)[b]
1	 1	4	 2	>98
2	 3	4	 4	95
3	 5	4	 6	>98
4	 7	4	 8	>98
5	 9	5	 10	>98
6	 11	16	 12  13 70:30	54

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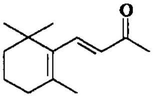
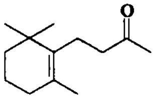
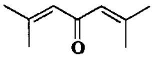
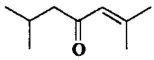
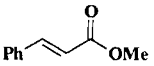
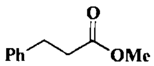
a: Product assignments was determinated by ^{1}H and ^{13}C NMR compared to authentic materials or literature assignments.

b: Yield and product ratio were determinated by GC.

Table 2 Continued Conjugate reduction of α,β-unsaturated ketones and esters.

Run	Substrate	Time (h)	Product(s)[a]	Yield (%)[b]
7	 14	3	 15	98
8	 16	16	 17	>98
9	 18	3	 19	>98

a: Product assignments was determinated by ^{1}H and ^{13}C NMR compared to authentic materials or literature assignments.

b: Yield and product ratio were determinated by GC.

Methanol was used as commercial solvent grade. ^{1}H and ^{13}C-NMR spectra were determinated at 200 and 50.3 MHz respectively in $CDCl_3$. GC analyses were performed with a Supelco SPB-1 id 32, 30 mts lenght column. Lindlar catalyst was supplied by Aldrich.

The α,β-unsaturated compounds 3, 5, 9, 11, 14, 16 and 18 are commercially available and were used as received; compound 7 was prepared from the corresponding *cis*- 4-benzyloxy-2-buten-1-ol (Aldrich) according to ref. 5.

Aldehyde 1: The compound was prepared by Wittig reaction of 4-O-(t-butyldimethylsilyl)-2,3-O-isopropilidene-D-threose[6] with formylmethylenetriphenyl phosphorane according to ref.7. Anal. calc. for $C_{15}H_{28}O_4Si$: C 59.96, H 9.39; found C 59.99, H 9.44.

^{1}H-NMR: 9.54 (d, 1H, J=7.9 Hz); 6.81 (dd, 1H, J=15.7, 4.7 Hz); 6.35 (ddd, 1H,

J=15.7, 8.0, 1.4 Hz); 4.62-3.57 (m, 1H); 3.87-3.67 (m, 3H); 1.41 (s, 3H); 1.39 (s, 3H); 0.87 (s, 9H); 0.04 (s, 6H) ppm. *^{13}C-NMR*: 192.9; 153.2; 131.7; 110.0; 80.5; 78.0; 62.8; 26.8; 26.6; 25.7; 16.1; -5.5; -5.6 ppm.

General procedure for the reduction of α,β-unsaturated carbonyl compounds.

A solution of carbonyl compound (1.0 mmol) and Lindlar Catalyst (0.01 mmol) in methanol (10 mL) was stirred under a hydrogen atmosphere at room temperature. When the reaction was completed (TLC monitoring) the mixture was filtered on Celite and eluted with methanol. The solvent was evaporated in vacuo affording the saturated compound wich was checked by ^{1}H and ^{13}C-NMR and elemental analysis.

Compounds **4**, **6**, **8** **10**, **12**, **13**, **15**, **17** and **19** are well known compounds; product assignment was determined by ^{1}H-NMR, ^{13}C-NMR and elemental analysis compared to authentic materials or literature assignments.

Aldehyde 2: Anal. calc. for $C_{15}H_{30}O_{4}Si$: C 59.56, H 10.00; found C 59.62, H 10.16. *^{1}H-NMR:* 9.70 (s,1H); 3.87-3.54 (m, 4H); 2.52 (t, 2H, J=7.3 Hz); 2.05-1.64 (m, 2H); 1.29 (s, 3H); 1.26 (s, 3H); 0.81 (s, 9H); -0.2 (s, 6H) ppm. *^{13}C-NMR*: 201.3; 108.5; 80.5; 76.4; 63.4; 40.1; 27.1; 26.8; 25.7; 25.5; 18.1; -5.6 ppm.

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(Received in the UK 20th September 1995)