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Reductive One-Carbon Homologation of Aldehydes and Ketones

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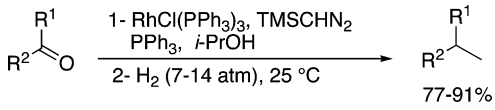
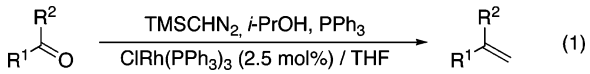
Received August 9, 2005



A rhodium-catalyzed methylenation−hydrogenation cascade process allows the homologation of carbonyl compounds to lead to the corresponding alkanes in high yields.

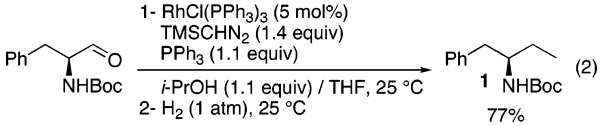
Cascade processes are a very efficient way to produce a variety of compounds while minimizing the number of manipulations, reagents, and solvents, thus decreasing the amount of generated waste and improving the overall efficiency.[1] As a number of transition-metal complexes are known to catalyze more than one chemical transformation, they are very well suited to be included in cascade processes. Furthermore, it is also possible to combine more than one transition-metal complex that catalyzed different chemical transformations in multicatalytic processes.[2] We have recently reported the methylenation of a variety of carbonyl derivatives catalyzed by Wilkinson's complex in the presence of trimethylsilyldiazomethane, triphenylphosphine, and 2-propanol, producing the corresponding terminal alkene in high yields (eq 1).[3,4]



(1)

We have shown that multicatalytic processes including our rhodium-catalyzed methylenation reaction allowed the formation of various substituted alkenes directly from alcohols, without isolation of any intermediate.[5] We can take also advantage of the dual catalytic activity of the Wilkinson complex toward carbonyl and alkene derivatives to functionalize in situ our methylene unit. Indeed, we have recently disclosed a new rhodium-catalyzed cascade process involving a methylenation−hydroboration reaction sequence to produce the corresponding organoborane, which was then oxidized or homologated.[6] In this paper, we present a similar rhodium-catalyzed process in which a hydrogenation reaction is performed in cascade with a methylenation reaction to produce directly alkanes from carbonyl compounds.[7]

Wilkinson's complex, $ClRh(PPh_3)_3$[8] is well-known to catalyze a variety of reactions with alkenes, including hydrogenation.[9,10] It was anticipated that we could switch the atmosphere of argon to hydrogen after the methylenation is completed to directly produce the corresponding alkane. Indeed, it was possible to react in situ with hydrogen the alkene produced by the methylenation of (*S*)-2-(*t*-Boc-amino)-3-phenylpropan-1-al and obtain the corresponding alkane **1** in 77% isolated yield (eq 2).



(2)

However, the basic nitrogen functionality present in the substrate in eq 2 apparently made the resulting methylenation product particularly suitable for hydrogenation, since when this functionality is absent, further conversion to an alkane such as **2** is not observed (Table 1, entry 1). We postulated that the catalytic activity of Wilkinson's catalyst was slowed by byproducts resulting from the methylenation reaction (triphenylphosphine oxide or remaining triphenylphosphine); thus, we tested

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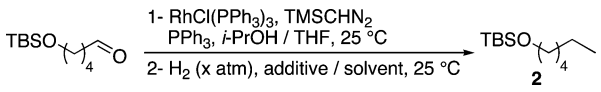
10.1021/jo0516741 CCC: $30.25
Published on Web 10/20/2005

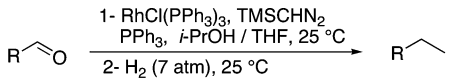
TABLE 1. Optimization of the Rhodium-Catalyzed Methylenation−Hydrogenation Process[a]

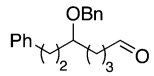
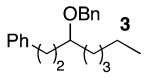
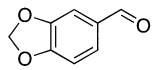
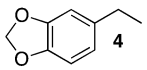
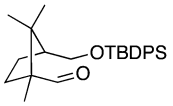
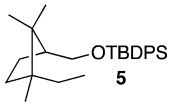
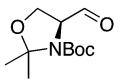
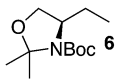
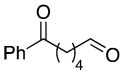
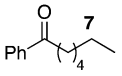


entry	hydrogenation conditions	conv[b,c] (%)
1	1 atm of H_2/THF	≤5
2	1 atm of H_2/dioxane	≤5
3	1 atm of H_2, $AlCl_3$/THF	≤5
4	1 atm of H_2, H_2O_2/THF	≤5
5	1 atm of H_2/hexanes	≤5
6	**7 atm of H_2/THF**	**≥98 (91)**

[a] Reaction Conditions: 5 mol % of $RhCl(PPh_3)_3$, 1.4 equiv of $TMSCHN_2$, 1.1 equiv of PPh_3, 1.1 equiv of *i*-PrOH. [b] Conversion by GC−MS after 12 h of H_2. [c] Isolated yield in parentheses.

TABLE 2. Rhodium-Catalyzed Methylenation−Hydrogenation Process[a]

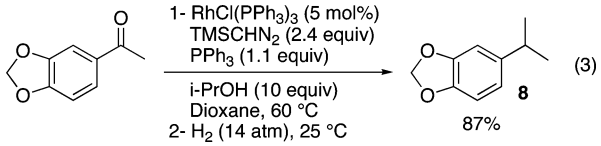


entry	substrate	product	yield (%)[b]
1		 **3**	77
2		 **4**	85
3		 **5**	85
4		 **6**	89
5		 **7**	78

[a] Reaction conditions: 5 mol % of $RhCl(PPh_3)_3$, 1.4 equiv of $TMSCHN_2$, 1.1 equiv of PPh_3, 1.1 equiv of *i*-PrOH. [b] Isolated yield.

more basic solvent (dioxane, entry 2) and a number of additives (entries 3 and 4) which could quench these byproducts. However, no product **2** was observed with these modifications. The use of hexane to precipitate phosphine byproducts did not lead to a good result either (entry 5). Finally, simply increasing the pressure of hydrogen restored the catalytic activity of the rhodium complex, and alkane **2** was isolated in 91% yield.

These reaction conditions were general and were used to produce a variety of alkanes (Table 2). Both aliphatic and aromatic aldehydes produced the corresponding alkane in excellent yields from (entries 1−4). The hydrogenation reaction conditions are mild enough to be compatible with a variety of protecting groups including benzyl ethers (entry 1). Hindered α-substituted aldehydes are also converted to the corresponding alkane with excellent yields (entries 3 and 4).[11] As our methylenation reaction is chemoselective for aldehydes over other carbonyl groups, ketone **7** was also isolated with a very good yield (entry 5). Conversely, if the methylenation reaction is performed in dioxane at 60 °C with excess of trimethylsilyldiazomethane and 2-propanol,[3b] followed by the hydrogenation reaction at 14 atm of hydrogen, alkane **8**[12] was produced in 87% yield from the corresponding ketone without the isolation of the alkene intermediate (eq 3).



In conclusion, we have devised a new rhodium-catalyzed methylenation hydrogenation process to synthesize one-carbon homologated alkanes directly from aldehydes and ketones with high efficiency.

Experimental Section

Typical Experimental Procedure for the Rhodium-Catalyzed Methylenation−Hydrogenation of Aldehydes. To a solution of chlorotris(triphenylphosphine)rhodium (0.046 g, 0.050 mmol) and triphenylphosphine (0.290 g, 1.10 mmol) in THF (10.0 mL) in a hydrogenation pressure vessel was added 2-propanol (0.084 mL, 1.10 mmol) followed by the aldehyde (1.00 mmol). To the resulting red mixture was added trimethylsilyldiazomethane (0.197 mL, 7.10 M, 1.40 mmol). Gas evolution was observed, and the resulting mixture was stirred at room temperature. When the methylenation was completed by TLC analysis, the reaction mixture was purged with hydrogen, pressurized at 100 psi (7 atm) of hydrogen, and then stirred for 12 h. After this time, the solvent was evaporated under reduced pressure and the crude alkane was purifed by flash chromatography using the indicated solvent.

***tert*-Butyl (*R*)-1-Phenylbutan-2-ylcarbamate (1).** The title compound was prepared from *tert*-butyl (*S*)-1-formyl-2-phenylethylcarbamate (0.240 g, 1.00 mmol) according to the typical experimental procedure using 1 atm of hydrogen. The alkane **1** (0.184 g, 77%) was obtained as a white solid after flash chromatography (5% ethyl acetate/hexane): R_f 0.36 (5% ethyl acetate/hexane); $[\alpha]^{25}_D$ +5.00 (*c* 1.80, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32−7.28 (m, 2H), 7.24−7.19 (m, 3H), 4.33 (s (br), 1H), 3.77 (s (br), 1H), 2.83−2.75 (m, 2H), 1.58−1.50 (m, 1H), 1.43 (s, 9H), 1.36−1.28 (m, 1H), 0.94 (t, J = 8 Hz, 3H); ^{13}C NMR (100 MHz, DMSO, 120 °C) δ 156.2, 140.5, 130.0, 128.9, 126.7, 78.6, 54.6, 41.7, 29.3, 28.1, 10.9; IR (neat) 3343, 2926, 1683, 1364, 1167, 698 cm^{-1}; HMRS (ESI) calcd for $C_{15}H_{23}NO_2Na$ $[M + Na]^+$ 272.1630, found 272.1621.

***tert*-Butyl(hexyloxy)dimethylsilane (2).**[13] The title compound was prepared from 5-(*tert*-butyldimethylsilyloxy)-1-hexanal (0.216 g, 1.00 mmol), according to the typical experimental procedure. The alkane **2** (0.196 g, 91%) was obtained as a colorless oil after flash chromatography (2% ethyl acetate/hexane): R_f 0.75 (2% ethyl acetate/hexane); ^1H NMR (400 MHz, $CDCl_3$) δ 3.62 (t, J = 7 Hz, 2H), 1.56−1.49 (m, 2H), 1.37−1.27 (m, 6H), 0.92 (s (br), 12H), 0.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 63.3, 32.8, 31.6, 25.9, 25.4, 22.6, 18.3, 14.0, −5.26.

(11) Surprisingly, the hydrogenation of the alkene derived from Gardner's aldehyde did not take place with 1 atm of hydrogen, although this substrate contains a basic nitrogen group. Presumably, the ring strain precludes the activation of Wilkinson's catalyst.

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Acknowledgment. This research was supported by NSERC (Canada), the Canadian Foundation for Innovation, Boehringer Ingelheim (Canada) Ltée, Merck Frosst Canada, and the Université de Montréal. Acknowledgment is also made to the donors of the American Chemical Society Petroleum Research Fund for partial support of this research.

Supporting Information Available: Characterization data and spectra (^{1}H and ^{13}C NMR) for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0516741