ORGANIC LETTERS

2006
Vol. 8, No. 17
3725−3727

Microwaves Make Hydroformylation a Rapid and Easy Process

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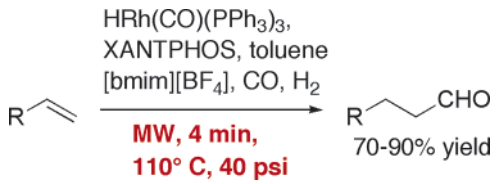
Received May 30, 2006

ABSTRACT



Hydroformylation of alkenes can be carried out in a few minutes under microwave activation at a relatively low pressure (40 psi) using commercially available catalysts and ligands. The 80 mL vial of a Discover microwave oven was connected to a cylinder of CO and H_2, and after filling the reactor at 40 psi, a mixture of an alkene, the Wilkinson catalyst, and XANTPHOS was submitted to microwave irradiation giving, after 4 min, high conversion into the corresponding aldehyde without formation of the isomerized alkene.

Among the methods available for the preparation of aldehydes, the hydroformylation reaction (oxo process) is one of the most versatile. The reaction is based on the simultaneous addition of CO and H_2 to an alkene mediated by transition-metal catalysts, thus providing the formation of two new C−C and C−H bonds.[1] Tons of aldehydes are produced every year via hydroformylation making it the largest applied process that uses homogeneous catalysis.[2] Recently, the design of new ligands has rendered the reaction chemoselective toward the double bond (excellent n/iso ratios) and compatible with the presence of functional groups on the alkene substrate. The choice of the ligands (phosphines or phosphites) and the reaction conditions (CO and H_2 pressure, temperature) allow us in many cases to achieve the desired regio- and chemocontrol.[3] Moreover, if the substrates contain suitable nucleophilic residues or if nucleophilic reagents are present during the hydroformylation step, tandem or cascade reactions take place.[4]

However, despite outstanding applications in industrial processes, the hydroformylation reaction is still under utilized in the design of chemical sequences by the organic community. Examining the experimental conditions generally required for performing standard hydroformylation, several difficulties are apparent in the use of gaseous CO and H_2 at high pressure (50−80 bar) and long reaction times (1−3 days).[5] The reaction must be carried out inside stainless steel autoclaves located in dedicated rooms not always available, especially in academic laboratories. Moreover, the absence of control in the contemporary migration of the double bond may occur in some cases during the hydroformylation.[6]

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(1) Wender, I.; Pino, P. *Organic Synthesis via Metal Carbonyls*; Wiley: New York, 1977; Vol. 2. *Rhodium Catalyzed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C., Eds.; Kluwer Academic Publishing: London, U.K., 2000. Siegel, H.; Himmele, W. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 178. Cornils, B.; Herrmann, W. A.; Kohlpaintner, C. W. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2144. Cornils, B.; Herrmann, W. A. *Applied Homogeneous Catalysis with Organometallic Compounds*; VCH: Weinheim, Germany, 1996. Kovacs, I.; Ungva'ry, F. *Coord. Chem. Rev.* **1997**, *161*.

(2) Bizzarri, S. N.; Fenelon, S.; Ishikawa-Yamaki, M. *Chemical Economics Handbook*; SRI International: Menlo Park, 1999; pp 682.7000A.

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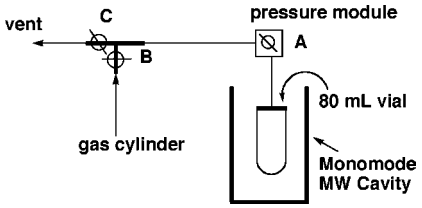
10.1021/ol061312v CCC: $33.50
Published on Web 07/29/2006

Recently, Breit and co-workers reported the first example of hydroformylation at 1 atm of CO/H_2, using standard laboratory glassware.[7] The use of a new catalyst Rh(I) 6-(diphenylphosphino)pyridin-2(1*H*)-on [6-DPPon)/Rh(I)] operative in a chelation system gave excellent regioselectivity in the formation of linear aldehydes from terminal alkenes.[8] This work represents a real breakthrough rendering the hydroformylation reaction practical to use in fine organic synthesis.

Following our interest in the use of microwaves[9] and application of hydroformylation in organic synthesis,[10] we were intrigued by the possibility to carry out this reaction under microwave irradiation. Thus, we adapted a Discover microwave oven equipped with the 80 mL vial for reaction under pressure.[11] This glass vial, tested for resisting up to 250 psi (17 bar, 1723 KPa), is provided with a tube connection to an external pressure controlling system equipped with a valve and an exit tube for venting the vial at the end of the reaction. When the valve of the pressure controlling system is closed, the reactor vial is under pressure (registered by the system), whereas when the valve is open, the vial is connected with the exit tube.

We connected this exit tube to a cylinder containing the mixture CO/H_2 1:1 (syngas) through a three-way connector equipped with two taps (Scheme 1). Then, we ran the following preliminary experiment. A solution of 1-octene in toluene was mixed together with $HRh(CO)(PPh)_3$ and XANTPHOS[12] as the catalyst (4 mol % of a 1:4 mixture) in the 80 mL vial. The solution contained also ionic liquid [bmim][BF_4] (butylmethylimidazolium tetrafluoroborate), an additive recommended to enhance heat transfer from the microwaves toward the reaction mixture.[13] Then, while tap C was closed, taps A and B were opened to fill the vial with syngas (CO/H_2 1:1) until the internal pressure reached 40 psi (the pressure was registered in real time by the computer connected to the Discover device).

Scheme 1. Connections Required to Carry Out MW-Assisted Hydroformylation in a Discover Microwave Oven[12]



Finally, tap A was closed, and the vial was inserted in the MW cavity and irradiated at 150 W of power for 4 min (two cycles of 2 min each). The internal temperature reached 110 °C, and the power was automatically modified to maintain this temperature. We observed a decrease of the internal pressure indicating that the gas was adsorbed by the reaction (see Supporting Information). The vial was cooled to room temperature, and the taps A and C were opened to release the gas contained in the vial inside a fume cupboard. After GC/MS analysis of the crude reaction mixture, we were pleased to find that the peak at *m*/*z* 112 (1-octene or an isomer) had disappeared, and instead a single peak at *m*/*z* 142 was present, indicating that the hydroformylation was operating. The formation of 1-nonanal was confirmed by NMR after purification of the mixture by column chromatograhy. To check the influence of the parameters involved in the reaction, different experiments on 1-octene were performed. Thus, we found that the reaction worked similarly with 1 mol % loading of catalyst and ligand and in a scale-up to 1 g of substrate.[14]

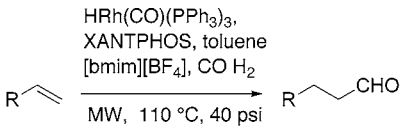
The presence of the ionic liquid was crucial for the reaction. Although the presence of the Rh(I) catalyst allowed the temperature of the reaction mixture to rise to 60 °C, in the absence of [bmim][BF_4] the conversion of 1-octene was not complete even after 15 cycles of 2 min each.

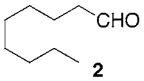
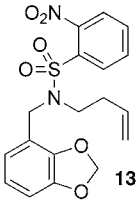
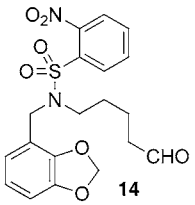
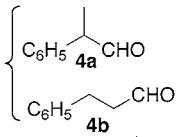
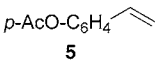
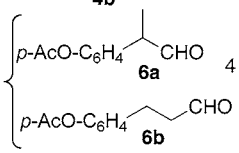
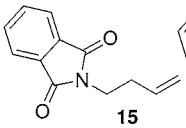
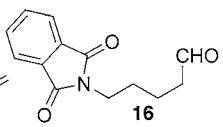
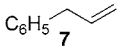
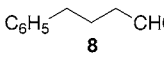
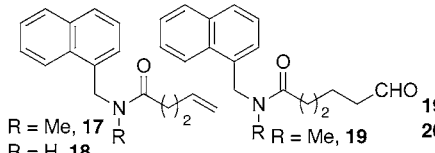
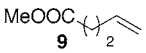
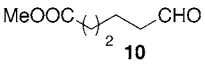
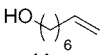
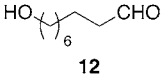
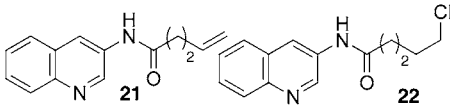
Several terminal alkenes (**3**, **5**, **7**, **9**, **11**, **13**, **15**, **17**, **18**, **21**) were submitted to the above reaction conditions and all gave high conversion into the linear aldehydes (**2**, **8**, **10**, **12**, **14**, **16**, **19**, **20**, **22**) without notable formation of the branched isomers (Table 1) with the exception of the two styrenes **3** and **5** which gave a mixture of products, respectively, **4a**/**4b** (iso/n 9:1) and **6a**/**6b** (iso/n 15:1). Similar results were observed under standard hydroformylation conditions using the Wilkinson catalyst and XANTPHOS.[15] These results suggest that for the hydroformylation reaction no special effects can be ascribed to the microwaves except for a tremendous increase of the reaction rate. The compatibility of the process with different functional groups is demonstrated by the high-yielding transformations carried out successfully on alkenes **9**, **11**, **13**, **15**, **17**, **18**, and **21** (see Table 1). The impact of the microwave effect on the hydroformylation reaction is impressive in terms of practicability and efficiency.

Moreover, when compounds **23** and **24** were submitted to the microwave hydroformylation under our standard conditions, we observed the formation of the dehydropiperidines **25** and **26**, respectively (in relatively low yields), via a cyclohydrocarbonylation reaction. Most of the starting material remained unreacted. In the case of the product protected as Cbz (**24**), it was possible to monitor the presence

(6) Breit, B. *Acc. Chem. Res.* **2003**, *36*, 264.
(7) Seiche, W.; Schuschkowski, A.; Breit, B. *Adv. Synth. Catal.* **2005**, *347*, 1488.
(8) Breit, B.; Seiche, W. *J. Am. Chem. Soc.* **2003**, *125*, 6608. To our knowledge, this ligand is not commercially available: search done on Chmoogle web site (www.chmoogle.com). Moreover, the process required from 20 to 90 h to go to completion.
(9) Minetto, G.; Raveglia, L. F.; Taddei, M. *Org. Lett.* **2004**, *6*, 389.
(10) Dessole, G.; Marchetti, M.; Taddei, M. *J. Comb. Chem.* **2003**, *5*, 198.
(11) Discover microwave ovens for organic synthesis are produced by the CEM Corporation. A photograph of the equipment is enclosed in the Supporting Information.
(12) XANTPHOS: 9,9-dimethyl-4,5-bis(diphenylphosphine)xanthene. Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M. *Organometallics* **1995**, *14*, 3081. The ligand is commercially available from Sigma-Aldrich, Stream, and other chemical suppliers.
(13) Leadbeater, N. E.; Torenius, H. M. *J. Org. Chem.* **2002**, *67*, 3145.
(14) Scale applied to alkene **9**. For security reasons, we did not fill the vial. However, the speed of the reaction allowed us to repeat the process 4 times, producing 4.8 g of aldehyde **10** in 30 min.
(15) Marchetti, M.; Botteghi, C.; Paganelli, S.; Taddei, M. *Adv. Synth. Catal.* **2003**, *345*, 1229.

Table 1. Aldehydes Obtained by Hydroformylation of Differently Functionalized Alkenes

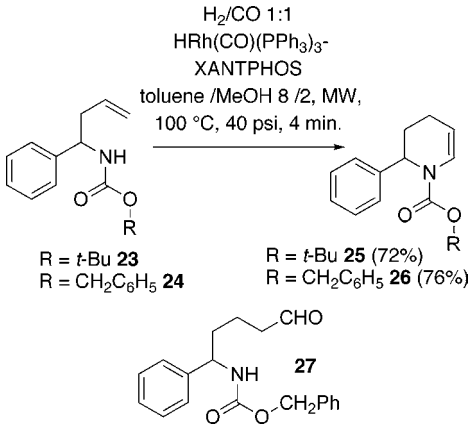


alkene	aldehyde	time, yield (%)[a]	alkene	aldehyde	time, yield (%)[a]
 **1**	 **2**	4 min, 80	 **13**	 **14**	4 min, 95
 **3**	 **4a** **4b**	4 min, 80[b]			
 **5**	 **6a** **6b**	4 min, 72[c]	 **15**	 **16**	4 min, 95
 **7**	 **8**	4 min, 82	 R = Me, **17** R = H, **18** R = Me, **19** R = H, **20**		**19:** 4 min, 80 **20:** 6 min, 65
 **9**	 **10**	4 min, 95			
 **11**	 **12**	4 min, 75	 **21** **22**		6 min, 70

[a] Yield of isolated product. [b] **4a**/**4b** = 9:1. [c] **6a**/**6b** = 15:1.

of the aldehyde **27** in the crude mixture. After 12 h of standing at room temperature, all the aldehyde cyclized to **26**. However, increasing the amount of the couple catalyst ligand to 8%, as well as the addition of 20% of MeOH as cosolvent, allowed the formation of the cyclic enamides **25** and **26** in good yields (Scheme 2).[16]

Scheme 2



In summary, a microwave oven, a nowadays common device for organic synthesis, adapted for gas transfer, allowed for the first time a very rapid access to linear aldehydes from alkenes using the hydroformylation reaction with the classical commercially available catalysts.

It is expected that the present work, together with the report on the hydroformylation at atmospheric pressure,[7] will increase the interest of organic and medicinal chemists to incorporate in their synthetic plans more readily a hydroformylation step. Furthermore, as many chiral ligands are now available for asymmetric hydroformylation of prochiral alkenes, many developments can be anticipated in the near future.

Acknowledgment. This work was partially supported by the University of Siena (PAR-Project 2005). We thank also Prof. B. Breit (University of Freiburg, Germany) for helpful discussions.

Supporting Information Available: General procedure for hydroformylation, characterization or spectra of aldehydes **2**, **4a**, **6a**, **8**, **10**, **12**, **14**, **16**, **19**, **20**, **22**, **25**, and **26**, and images of the equipment for microwave-assisted hydroformylation. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) A similar behavior has already been observed under standard hydroformylation conditions. Ojima, I.; Tzamarioudaki, M.; Eguchi, M. *J. Org. Chem.* **1995**, *60*, 7078.