PAPER

Ammonium Formate/Palladium on Carbon: A Versatile System for Catalytic Hydrogen Transfer Reductions of Carbon–Carbon Double Bonds

Zdzisław Paryzek,* Hanna Koenig, Bartłomiej Tabaczka

Faculty of Chemistry, A. Mickiewicz University, Pozna, Poland Fax +48(61)8291233; E-mail: zparyzek@amu.edu.pl *Received 18 March 2003; revised 11 June 2003*

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Catalytic hydrogen transfer reduction is an alternative method to the classical hydrogenation reactions.¹ According to literature data, a considerable variety of olefinic compounds can be hydrogenated in good to excellent yield by catalytic transfer hydrogenations (CTH) under homogenous or heterogeneous conditions.² Homogenous reductions require catalysts of various complexity, salts and complexes of Pd, Pt, Ru, Rh, Ir, Fe, Co, Ni and others.² In heterogeneous catalytic transfer hydrogenations, palladium on carbon or palladium black catalysts are by far the most frequently used.^{1,2} Less versatile catalysts are derived from Ni, Rh, Ru, Pt, Ir, Os and Co. These catalysts are used as finely divided metals or metals dispersed on various carriers.³ The list of hydrogen donor compounds is diverse and includes simple olefins, unsaturated terpenes, alcohols, hydrazine, formic acid and formates, and others.² Cyclohexene, due to its high reactivity and availability appears to be the most frequently used hydrogen donor.² In some cases, however, higher temperatures are required to complete the reduction¹ and/or solubility problems may arise.

Application of ammonium formate in organic synthesis has been reviewed by Ram and Ehrenhaufer.⁴ This versatile and cheap reagent has been used as a source of hydrogen in catalytic transfer hydrogenations and has been frequently applied in reduction of the following functional groups: azido,⁵ nitro,^{6–8} cyano,⁹ and carbonyl in aldehydes or ketones.¹⁰ Ammonium formate has also served as hydrogen donor in dehalogenation reaction,¹¹ reductive amination,¹² and for deprotection of functional groups, in particular in peptide^{4,13,14} and carbohydrate¹⁵ chemistry. In reductions with ammonium formate, chemoselectivity has been frequently observed.⁴ A recent paper on reduction of pyridine *N*-oxides to piperidines provides another

Synthesis 2003, No. 13, Print: 18 09 2003. Web: 19 08 2003. Art Id.1437-210X,E;2003,0,13,2023,2026,ftx,en;T02803SS.pdf. DOI: 10.1055/s-2003-41024 © Georg Thieme Verlag Stuttgart · New York example of the use of ammonium formate in reduction reactions. $^{\rm 16}$

Olefins are generally reduced by CTH and a considerable variety of olefinic compounds have been hydrogenated in good to excellent yield by this method, using several catalytic systems in cooperation with a variety of donors like cyclohexene, formic acid, isopropyl alcohol and many more.¹ Surprisingly, a literature search revealed that ammonium formate has not been frequently used as an active hydrogen donor in CTH reactions of compounds with carbon–carbon double bonds and only few hydrogenations with the use of trialkylammonium formates have been reported.² In a recent communication, hydrogenation of alkenes by the CTH method using expensive decaborane has been described.¹⁷

In this report we wish to describe a simple and convenient method for the catalytic hydrogen-transfer reduction of carbon–carbon double bonds in olefins and α , β -unsaturated carbonyl compounds using readily available and inexpensive ammonium formate, as a hydrogen donor, under mild conditions (Equation 1). In the study of reductive removal of benzyl group from 1,3-dibenzyluracil 1 under CTH conditions we found that debenzylation was accompanied by reduction of the 5,6-double bond in uracil.¹⁸ Thus, reaction of 1 gave 2 and 3 (Figure 1) in an approximate ratio of 1:2. It has been reported, that reduction of the substituted uracil derivatives required L-selectride as a reducing agent.¹⁹ These results prompted us to examine CTH reactions of other unsaturated compounds with carbon-carbon double bonds. Our previous interest in steroids allowed access to a series of steroidal olefins with the double bonds of different type of substitution pattern and steric hindrance.





Under standard conditions, the substrate (Figure 1) was hydrogenated in refluxing methanol in the presence of 10% Pd/C catalyst and an excess of ammonium formate. Refluxing methanol is the solvent of choice because reductions are generally fast and the solubility problems are avoided in this solvent. The optimum catalyst:substrate ratio for effective hydrogenation was estimated as 10% of

Abstract: Various carbon–carbon double bonds in olefins and α , β -unsaturated ketones were effectively reduced to the corresponding alkanes and saturated ketones, using ammonium formate as a hydrogen transfer agent in the presence of Pd/C as catalyst in refluxing methanol.





Figure 1 Structures of substrates and products used in this study

the weight of olefin. When 2% or 5% of the catalyst was used for the reduction of the standard olefin, 5α -cholest-2-ene (**15**), the substrate was still present after 12 hours of reaction and the hydrogenation could not be completed. In the presence of 10% of the catalyst this reduction required 2 hours. The results of the hydrogenations are summarized in Table 1.

The unhindered endocyclic Δ^2 -double bond in 5 α -cholest-2-ene (**15**)²⁰ was easily reduced to **16**, while the more hindered Δ^2 -double bond in compound **26**²¹ having a lanostane skeleton required 20 hours reaction time to give dihydrolanosterol (**27**).²² In accord with previous data,²³ the trisubstituted Δ^5 -double bond in compounds **19**²⁴ and **25** was found unreactive, as was the highly hindered Δ^8 double bond in lanosterol (**28**). The Δ^{24} -double bond in the side chain of lanosterol (**28**) was completely reduced to give dihydrolanosterol (**29**)²⁵ in the prolonged reaction. Reduction of the Δ^{24} -double bond, quite common in triter-

 Table 1
 Catalytic Transfer Hydrogenation of Unsaturated Compounds^a

Entry	Substrate ^b	Product ^b	Yield (%)	Reaction Time (h)
1	4	5 + 6 (2:9)	99	3.5
2	7	8	94	1.5
3	9	10	94	0.5
4	11	12	97	0.5
5	13	14	90	2
6	15	16	99	2
7	17	18	99	1.5
8	19	20	91	2
9	21	22 + 23 (2:1)	98	5
10	24	25	98	0.6
11	26	27	92	20
12	28	29	99	7
13	30	31	71	3
14	32	33	95	1
15	34	35	98	1

^a Reaction conditions: HCO₂NH₄, Pd/C, MeOH, reflux.

^b For the structures of substrates and products, see Figure 1.

penoids, often required a substantial proportion of Adam's catalyst, prolonged reaction times, high temperature and/or elevated pressures.²⁶ Exocyclic double bond in 3-methylene-5 α -cholestane (21)²⁷ has been reduced in a fast reaction to give 3 β - and 3 α -methyl-5 α -cholestane (22²⁸ and 23) in the ratio 2:1, respectively. Reduction of 21 with Adam's catalyst was reported to give 22 and 23 in the ratio 1:4.²⁹

The reduction of vinyl- and allyl-substituted steroids, 17^{30} and 19, gave the respective saturated compounds 18^{31} and 20,³² with excellent, practically quantitative yield. Also other compounds having allyl residues attached to an oxygen or nitrogen atom were easily hydrogenated, as proved by the hydrogenation of benzylallyl ether (13)³³ to 14^{33} and *N*-allylpyrrolidinone (7)³⁴ to compound 8.³⁵ The 1-allyl-3-benzoyluracil (4)¹⁸ gave 1-propyluracil derivatives **5** and 6^{36} in a 2:9 ratio, respectively. In the reaction of allyl phenyl ether, a hydrogenolysis of C(aliphatic)–oxygen bond was observed, however.³⁷ In this case phenol was isolated as the only product in 88% yield.

Similar to *N*-allyl derivatives, *N*-vinyl compounds were also efficiently hydrogenated. Thus, *N*-vinyl lactams **9** and **11** were quickly reduced to *N*-ethyl compounds **10**³⁸ and **12**,³⁹ respectively.

In further experiments it was found that the CTH system described is also effective for the reduction of unhindered,

 α ,β-unsaturated steroid ketones, which otherwise require more vigorous conditions and/or platinum catalyst.²³ Thus, the unhindered Δ¹-double bond in 5α-cholest-1-en-3-one (**30**)⁴⁰ was easily reduced to ketone **31**, while the highly hindered 8,9-double bond in 3β-acetoxy-5αlanost-8-en-7-one was unchanged after prolonged reaction.

Interestingly, cholest-4-en-3-one (**32**) was stereoselectively reduced to 5 β -cholestan-3-one (**33**).⁴¹ This stereochemical outcome of the reaction is important since catalytic reduction of steroid Δ^4 -3-ketones usually affords a mixture of 5 α - and 5 β -3-ketones, while reduction with metals in liquid ammonia results in formation of 5 α -steroids.²³ The Δ^5 -double in 3 β -acetoxycholest-5-en-7-one (**34**)⁴² was stereoselectively reduced to 7-ketone **35**⁴³ having the 5 α configuration. The efficient and fast reduction of Δ^{16} -double bond was found in the reaction of 3 β -acetoxypregna-5,16-dien-20-one (**24**). The product **25** was slightly contaminated with the 17 β -H isomer (¹H NMR).

Other examples of effective hydrogenation include reduction of ethyl cinnamate to 2-phenylpropionic acid ethyl ester (96%, 1.5 h) and maleic anhydride, which gave succinic anhydride and succinic acid in the ratio 2:3 (0.6 h).

In summary, these results demonstrate that the reducing system $Pd/C-HCO_2NH_4/MeOH$ is simple, effective, and applicable for reduction of a variety of carbon–carbon double bonds under mild conditions. The reduction may be chemoselective if the double bonds under consideration differ markedly in steric hindrance.

An important benefit is an easy isolation of the products from the reaction mixture. It requires only filtration of the catalyst followed by removal of the solvent. In some cases filtration of the crude product through a short column of silica gel, followed by crystallization is preferable. This hydrogenation procedure offers an attractive alternative to other methods available for reduction of carbon–carbon double bonds.

¹H NMR spectra were recorded with a Varian Gemini 300 VT spectrometer at 300 MHz in CDCl₃ using TMS as an internal standard. Electron-impact mass spectra were recorded with an AMD 402 spectrometer using ionization energy of 70 eV. The substrates were either commercial products and were used as purchased or were prepared according to literature procedures. The progress of the reaction was followed by TLC on silica gel (Merck 60 F₂₅₄) plates impregnated with silver nitrite and/or ¹H NMR analysis. The reduction products were identified by comparison of their ¹H NMR and mass spectra with those of authentic samples.

Catalytic Transfer Hydrogenation of Unsaturated Compounds; General Procedure

To a solution of an olefin or enone (see Figure 1) (1 mmol) in MeOH (5 mL), the catalyst 10% Pd/C (Fluka) (10% of olefin by weight) and ammonium formate (630 mg, 10 mmol) was added. The mixture was refluxed until reduction was complete (TLC monitoring, time given in Table 1). After cooling, the mixture was filtered and the solvent evaporated under reduced pressure. To the residue, $CHCl_3$ (few mL) was added to precipitate the excess of ammonium formate. After filtration, the solvent was evaporated to give crude product of sufficient purity. This was filtered through a short

silica gel (Merck, 70–230 mesh) column and/or crystallized from the appropriate solvent (see Figure 1 for products).

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