Palladium-catalyzed hydrogenations in dichloromethane

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ABSTRACT
Dichloromethane is shown to be a useful solvent in catalytic hydrogenation reactions of easily reduced functional groups (alkenes, alkynes, imines, and nitroarenes) using palladium on carbon as the catalyst under mild conditions (ambient pressure and temperature).

GRAPHICAL ABSTRACT

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Catalytic hydrogenation; dichloromethane; ease of removal; lack of flammability; palladium on carbon

Introduction
The most commonly used solvents for reductions of alkenes via catalytic hydrogenation using palladium on carbon as the catalyst include ethanol, methanol, isopropyl alcohol, and ethyl acetate.[1,2] Less commonly employed solvents include tetrahydrofuran, 2-methyltetrahydrofuran, isopropyl acetate, toluene, N,N-dimethylformamide, N,N-dimethylacetamide, and acetone. All the above-mentioned solvents are flammable. A recent publication compared the pyrophoricity of palladium on carbon catalysts filtered from these 11 solvents.[3] Self-ignition was observed with methanol, ethanol, and isopropyl alcohol.

Compounds being used in conjunction with another of our research projects had limited solubility in the above-mentioned hydrogenation solvents but were readily soluble in dichloromethane (DCM). DCM has previously been used in hydrogenation reactions with palladium on carbon catalysts, most often in mixed solvent systems and at high temperatures. However, the use of DCM as a sole solvent has not been widely reported. This study explores the suitability of DCM as a solvent for palladium-catalyzed hydrogenations.

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pressures and/or temperatures.\textsuperscript{[4–13]} It has been reported that DCM is dehydrohalogenated at sufficiently high pressures and temperatures (6 bar, 80 °C), liberating hydrogen chloride.\textsuperscript{[14]} The possibility of this decomposition may be one reason DCM has been infrequently used as a single solvent for hydrogenation reactions at low pressures and ambient temperatures.\textsuperscript{[15–19]} Other factors, including the toxicity of DCM and restrictions on its commercial use, may also play a part. Nevertheless, DCM seemed to us underutilized as a hydrogenation solvent given the factors in its favor: high solvent ability, ease of removal, and lack of flammability.\textsuperscript{[20]} We carried out a survey of hydrogenation reactions in DCM with commercial palladium on carbon catalysts at ambient pressure and temperature and present the results in Table 1.

\section*{Results and discussion}

All but one of the substrates tested were soluble in DCM at the concentrations and under the conditions employed (see Table 1). Mono-, di-, tri-, and tetrasubstituted alkenes were all rapidly reduced to the corresponding saturated compounds in high yields. Both electron-rich and electron-poor alkenes were easily reduced. Remote ketonic carbonyls (entries 3, 4, and 21), as well as conjugated ketonic carbonyls (entries 5–9 and 21), remained intact. Reduction of trans-cinnamaldehyde (entry 10) produced, in 95% yield, a 3:1:1 mixture of 3-phenylpropanol, 3-phenylpropanal, and propylbenzene. Attempted reduction of 3-phenylpropanal under the same reaction conditions (entry 11) returned 86% of the starting aldehyde and produced small amounts of 3-phenylpropanol (8%) and propylbenzene (2%). Conjugated and isolated carboxylic acid and ester functionalities (entries 12–17) were unaffected. 1-Cyclopentene carboxylic acid (entry 12) was not completely soluble in DCM, but the product 1-cyclopentanecarboxylic acid was soluble. Nitroarenes were efficiently reduced to the corresponding anilines, while ester, nitrile, and primary alkyl bromide functionalities also present in the molecules remained largely intact under the conditions employed (entries 16–19). Hydrogenation of cholesterol produced a 99:1 mixture of 5α- and 5β-cholestanols as determined by \textsuperscript{1}H NMR analysis (entry 20). Hydrogenation of 4-androstene-3,17-dione produced a 24:76 mixture of 5α- and 5β-androstane-3,17-diones as determined by \textsuperscript{1}H NMR analysis (entry 21). N-Methylbenzylidimine was reduced to N-methylbenzylamine in high yield (entry 22).

Many of the substrates examined in this study have previously been reduced via catalytic hydrogenation using palladium on carbon catalysts in one or more of the traditionally employed solvents listed in the introduction. We observed comparable or higher isolated yields employing DCM as solvent vs. published methods that used flammable solvents (e.g., see the literature references cited in Table 1). We observed no loss of solvent volume over the course of our experiments. We assume the product mixtures that arose from attempted reductions of trans-cinnamaldehyde and 3-phenylpropanal were due to the intermediacy of tautomeric intermediates. In molecules with two or more reducible functional groups, easily reduced functional groups (carbon-carbon double and triple bonds, carbon-nitrogen double bonds, nitroarenes) were rapidly reduced, while functional groups that are more resistant to reduction (carbon-oxygen double bonds, carbon-nitrogen triple bonds, carbon-halogen bonds) were either not reduced or
**Table 1.** Hydrogenations in dichloromethane using 10% palladium on carbon catalysts.\(^a\)

| Entry | Substrate | Product(s) | Reaction time (h) | Yield (%) | Solvent, hydrogen pressure | Yield (%) | References |
|-------|-----------|------------|-------------------|-----------|---------------------------|-----------|------------|
| 1     | Ph\(\equiv\)Ph | Ph\(\equiv\)Ph | 4                 | 96        | Methanol, 1 atm           | 98        | \([21]\)   |
| 2     | \(\equiv\)C\(_{18}\)H\(_{38}\) | C\(_{18}\)H\(_{38}\) | 12                | 96        | Methanol + THF, 1 atm     | 100       | \([22]\)   |
| 3     | ![Cyclic compound](image) | ![Cyclic compound](image) | 1                 | 99        | Acetone, 30 psi           | 100       | \([23]\)   |
| 4     | \(\text{CH}_3\text{CH}==\text{CH}==\text{CH}==\text{CH}==\text{CH}==\text{CH}\text{CH}_3\) | \(\text{CH}_3\text{CH}==\text{CH}==\text{CH}==\text{CH}==\text{CH}\text{CH}_3\) | 3                 | 90        | Methanol, 1 atm           | 81        | \([24]\)   |
| 5     | \(\text{H}_3\text{C}==\text{CH}==\text{CH}==\text{CH}==\text{CH}==\text{CH}_3\) | \(\text{H}_3\text{C}==\text{CH}==\text{CH}==\text{CH}==\text{CH}_3\) | 1.5                | 99        | Methanol, 1 atm           | 68        | \([25]\)   |
| 6     | ![Cyclic compound](image) | ![Cyclic compound](image) | 1.5                | 85        | Ethanol, 1 atm            | 85        | \([26]\)   |
| 7     | ![Cyclic compound](image) | ![Cyclic compound](image) | 1                 | 99        | THF, 2 MPa                | 98        | \([27]\)   |
| 8     | ![Cyclic compound](image) | ![Cyclic compound](image) | 2                 | 99\(^b\) | Ethanol, 1 atm            | 96        | \([28]\)   |

\(^a\) All reactions conducted in dichloromethane using 10% palladium on carbon catalysts. \(^b\) Reaction conducted with hydrogen pressure of 2 MPa.
| Entry | Substrate | Product(s) | Reaction time (h) | Yield (%) | Literature reactions |
|-------|-----------|------------|------------------|-----------|---------------------|
| 9     | H3C (CH2)4CH3 | H3C (CH2)4CH3 | 1                | 98\(^e\)  | Methanol, 2 MPa     |
| 10    | Mixture\(^e\) | Mixture\(^e\) | 3.5              | 95        | Ethanol, 1 atm      |
| 11    | Mixture\(^f\) | Mixture\(^f\) | 3.5              | 10        | NR\(^d\)           |
| 12    | (CH2)4CO2H | (CH2)4CO2H | 1.5              | 91        | NR\(^d\)           |
| 13    | (CH2)4CO2H | (CH2)4CO2H | 4                | 96        | THF, 1 atm          |
| 14    | (CH2)4CO2CH3 | (CH2)4CO2CH3 | 3.5              | 96        | Methanol, 1 atm     |
| 15    | (CH2)3CO2CH3 | CH3(CH2)3CO2CH3 | 2               | 94        | CH2Cl2, 1 atm       |
| 16    | O2N \[CO2CH3 | O2N \[CO2CH3 | 1               | 97        | Methanol, 1 atm     |
| 17    | O2N \[CO2CH3 | O2N \[CO2CH3 | 3.5              | 88        | Ethanol, 1 atm      |
\textsuperscript{a}Reaction conditions: Per mmol of substrate: 50 mg of 10\% palladium on carbon, 10 mL of dichloromethane, hydrogen at ambient (~1 atmosphere) pressure, vigorous magnetic stirring, ambient temperature. Reaction times are given in the Table. Workup: Filtration of the reaction mixture through Celite, washing of the catalyst and Celite with dichloromethane, and removal of volatiles \textit{in vacuo}. Products so obtained were weighed and characterized by \textsuperscript{1}H and \textsuperscript{13}C NMR spectroscopy. Yields were corrected for residual solvent present in the product. 
\textsuperscript{b}A 1:1 ratio of cis to trans isomers as determined by \textsuperscript{1}H NMR analysis.
\textsuperscript{c}An 87:13 ratio of cis to trans isomers as determined by \textsuperscript{1}H NMR analysis.
\textsuperscript{d}Not reported.
\textsuperscript{e}Yield of all products 95\%; ratio of 3-phenylpropanol:3-phenylpropanal:propylbenzene 3:1:1.
\textsuperscript{f}Yield of all products 10\%; ratio of 3-phenylpropanol:3-phenylpropanal:propylbenzene 4:4:3:1.
\textsuperscript{g}Less than 5\% reduction of nitrile observed. Yield of product after purification by column chromatography.
\textsuperscript{h}Yield of all products 99\%; ~7\% dehydrobromination as determined by \textsuperscript{1}H NMR analysis.
\textsuperscript{i}Ratio of 5\textsubscript{\textalpha} to 5\textsubscript{\textbeta} products >99:1 as determined by \textsuperscript{1}H NMR analysis.
\textsuperscript{j}Ratio of 5\textsubscript{\textalpha} to 5\textsubscript{\textbeta} products 24:76 as determined by \textsuperscript{1}H NMR analysis.
minimally affected under the mild reaction conditions (~1 atmosphere, ambient temperature) employed here.

**Conclusion**

The results reported herein, together with its high solvent ability, ease of removal, and lack of flammability, suggest that DCM should be considered when planning catalytic hydrogenation reactions to reduce alkenes, alkynes, imines, nitroarenes, and other easily reduced functional groups using palladium on carbon as the catalyst, especially when considering large scale reactions.\[38\]

**Experimental**

**General experimental**

Dichloromethane was used as supplied by the commercial source (Fisher, assay 99.5% min, water 0.02% max). 10% Palladium on carbon was used as supplied by the commercial sources (Sigma-Aldrich, Lot MKCQ402; Acros Organics, Lot B0144254). Substrates were commercially obtained and were purified before use as necessary or were prepared by the literature methods indicated. Reactions were carried out at an ambient temperature in flasks equipped with magnetic stir bars under hydrogen gas at ambient atmospheric pressure using doubled balloons. Workup consisted of filtration of reaction mixtures with the aid of Celite, washing of the Celite/catalyst with DCM, and removal of volatiles by rotary evaporation. Analytical thin-layer chromatography (TLC) was carried out on pre-coated silica gel 60 F-254 plates, and plates visualized with UV light, anisaldehyde stain, or 10% phosphomolybdic acid solution in 95% EtOH. In some cases, column chromatography was performed using silica gel 60 (flash 32–63 μm, gravity 70–230 μm). Melting points (uncorrected) were measured on an Electrothermal melting point apparatus. \(^1\)H NMR and \(^{13}\)C NMR spectra were recorded on an Automated NEO-500 NMR spectrometer (500 MHz for \(^1\)H NMR and 126 MHz for \(^{13}\)C NMR). Chemical shifts (δ) are expressed in ppm, and are internally referenced (0.00 ppm for tetramethylsilane for \(^1\)H NMR and 77.16 ppm for CDCl₃ for \(^{13}\)C NMR). NMR spectra of products were consistent with published data (references appear in the Supplementary Information).

**Table entry 3**

**Reduction of 8-cyclohexadecen-1-one to cyclohexadecanone**

A mixture of 8-cyclohexadecen-1-one (709 mg, 3.00 mmol) and 10% palladium on carbon (160 mg) in DCM (30 mL) was vigorously stirred under hydrogen for 1 h. To remove residual DCM from the product, the residue was taken up in Et₂O (25 mL) and the volatiles removed in vacuo three times, giving the product as a white foam, R_f 0.45 (20% EtOAc/heptane), mp 63–64 °C (lit\[^{[39]}\] mp 62.5–63.5 °C); yield 712 mg, 2.98 mmol, 99%; \(^1\)H NMR (500 MHz, CDCl₃) \(\delta\) 1.20–1.39 (m, 22H), 1.64 (apparent p, \(J = 7\) Hz, 4H), 2.41 (t, \(J = 7\) Hz, 4H) ppm; \(^{13}\)C NMR (126 MHz, CDCl₃) \(\delta\) 23.6, 26.6, 26.6, 26.6, 27.1, 27.3, 27.8, 42.2, 212.7 ppm.
Table entry 16

Reduction of methyl 5-nitrosalicylate to methyl 5-aminosalicylate

A mixture of methyl 5-nitrosalicylate (591 mg, 3.0 mmol) and 10% palladium on carbon (160 mg) in DCM (30 mL) was vigorously stirred under hydrogen for 1 h. Product was obtained as a cream-colored solid, Rf 0.26 (40% EtOAc/heptane), mp 94–96°C (lit\[^{[40]}\] mp 96–97°C); yield 490 mg, 2.9 mmol, 97%; \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.45 (br s, 2H), 3.92 (s, 3H), 6.82 (d, \(J = 8.9\) Hz, 1H), 6.87 (dd, \(J = 8.9, 2.8\) Hz, 1H), 7.15 (d, \(J = 2.9\) Hz, 1H), 10.20 (s, 1H) ppm; \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 52.3, 112.3, 114.8, 118.3, 124.4, 138.5, 154.9, 170.5 ppm.

Supplementary Information

Full experimental detail, \(^1\)H and \(^{13}\)C NMR spectra of products, and literature references for characterization data of known compounds can be found via the “Supplementary Information” section of this article’s webpage.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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