Tetrahedron Letters 49 (2008) 6137–6140

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

1,4-Cyclohexadiene with Pd/C as a rapid, safe transfer hydrogenation system with microwave heating

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ARTICLE INFO

Article history:
Received 21 May 2008
Revised 31 July 2008
Accepted 6 August 2008
Available online 23 August 2008

Keywords:
Transfer hydrogenation
Palladium on carbon
1,4-Cyclohexadiene
Microwave

ABSTRACT

A method for the rapid, safe hydrogenation of alkenes and deprotection of benzyl ethers and carboxybenzyl amides is described using catalytic transfer hydrogenation under microwave heating conditions. Commonly available Pd/C catalyst is extremely effective with 1,4-cyclohexadiene as the hydrogen transfer source. In general, the reactions are complete within five minutes at 100 °C.

Catalytic hydrogenation is a mainstay in the synthetic chemist's armamentarium.[1] It has a long list of advantages, including operational simplicity, chemoselectivity, and high chemical yields. Oftentimes all that is required in the way of reaction work-up and purification is a simple filtration to remove the spent catalyst and removal of the solvent. In spite of these advantages there remain a number of drawbacks, including the inconvenience of monitoring reaction progress, the need for specialized apparatus, safety issues involved with pressurized reaction vessels and using highly flammable hydrogen gas in the laboratory. While hydrogenation reactions are commonly carried out at high pressures and temperatures in an industrial setting, this is seldom the case in the small-scale discovery laboratory. The most common reaction set-up in the small-scale discovery lab is either 'a balloon' of hydrogen at essentially atmospheric pressure and ambient temperature, or a commercial hydrogenator,[2] operating at 40–60 psig H_2, also at ambient temperature. In either case it is inconvenient to monitor reaction progress by standard methods such as TLC or LC–MS. Removal of an aliquot for analysis involves disrupting the hydrogen atmosphere, which must then be re-established if the reaction is to continue. It is also inconvenient to run laboratory scale hydrogenation reactions at elevated temperatures when the reaction does not proceed at ambient temperature.

We report herein an operationally simple, safe, and fast procedure for the catalytic hydrogenation of alkenes to alkanes as well as removal of the common protecting groups benzyl (Bz) and carboxybenzyl (Cbz). Our goal was to develop a robust hydrogenation protocol that minimized or eliminated the disadvantages enumerated above, while maintaining the ease of work-up and purification that are hallmarks of the traditional hydrogenation procedure.

Microwave heating technology has revolutionized many synthetic procedures in the laboratory, enabling access to high temperatures and pressures that can dramatically shorten reaction times.[3] Additionally, microwave reactors are designed to work at high pressures and engineered to contain debris in the event of a failure. We felt that microwave technology was ideally suited for the development of an improved hydrogenation procedure.

A long standing interest in parallel, high-throughput synthesis guided our initial choices of reaction protocols, where excess starting materials and reaction byproducts would be easily separated from the compounds of interest. Our initial experiments focused on the replacement of hydrogen gas with a hydrogen transfer source.[4] Ammonium formate is a commonly used hydrogen donor that fulfils these requirements.[5] When cinnamic acid, **1**, was heated in a microwave reactor[6] at 100 °C with Pd/C and ammonium formate, quantitative conversion to 3-phenyl propionic acid, **2**, was observed in the crude HPLC. The use of ammonium formate, however, had a number of drawbacks. Although ammonium formate is a very active hydrogen donor source, its reaction byproducts are gaseous (carbon dioxide and ammonia) and its use resulted in considerable pressure build-up by the end of the reaction. This required a manual venting of the reaction vessel for safety purposes before the microwave cavity could be opened. Additionally, the excess ammonium formate required an aqueous extraction as a part of the reaction work-up.

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doi:10.1016/j.tetlet.2008.08.023

In an effort to reduce the final pressure in the reaction vessel as well as simplify the reaction work-up and purification, the alternative hydrogen transfer source, 1,4-cyclohexadiene, was examined.[7] Using this hydrogen source also resulted in the quantitative formation of 3-phenyl-propionic acid, **2**, from cinnamic acid **1**. Upon completion of the reaction, the microwave reaction tube was under no observable pressure. The use of cyclohexadiene has an additional benefit in that both it and its reaction byproduct, benzene, are volatile liquids, easily removed by standard evaporation techniques.

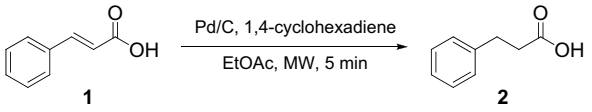
Having found that 1,4-cyclohexadiene was an effective hydrogen transfer source for catalytic hydrogenations, we then set out to optimize several reaction parameters, including the reaction time, temperature, equivalents of cyclohexadiene, and solvent.

A number of observations were made during the optimization of this reaction.[8] The reaction is sensitive to both the temperature and the number of equivalents of 1,4-cyclohexadiene (Table 1). When 2 equiv of cyclohexadiene were used, only 2% conversion to product was observed (Table 1, entry 1). With 3 or more equivalents, the reaction goes to >95% completion (Table 1, entries 2–4). To ensure complete conversion of starting materials, subsequent reactions were typically run with 5 or 6 equiv of cyclohexadiene. Reducing the reaction temperature below 80 °C resulted in no reaction (Table 1, entries 6–7). The use of the less active hydrogen donor cyclohexene resulted in no reaction under our conditions, (Table 1, entry 9). The reaction worked equally well with 10% Pd/C (dry) (all entries in Tables 1 and 2), or 5% Pd/C (50 wt % H_2O) (Table 3). The presence of water in the catalyst had no effect on the reaction. Switching from Pd to Pt on carbon as a catalyst resulted in no reaction (Table 1, entry 10). For activated alkenes, such as cinnamic acid, the reaction was remarkably fast. A reaction time of 2 min resulted in quantitative conversion by HPLC.

The reaction was found to be insensitive to the nature of solvent (Table 2). Both protic and non-protic solvents worked well. Of the solvents investigated, only water gave a poor conversion (24%) under our standard conditions which was likely due to the poor solubility of the reactants.

The scope of this hydrogenation protocol was examined as shown in Table 3.[9] The reaction worked equally well for electron-rich (Table 3, entries 1, 6, 7, and 9) and electron-poor (Table 3, entries 3, 4, and 8) systems. It is notable that 4-chlorocinnamic acid, **17**, (Table 3, entry 8) did not undergo dehydrohalogenation. In general, the reactions are complete within 5 min at 100 °C. In several cases (Table 3, entries 8 and 9), additional heating was required for complete conversion.

Table 1
Effect of cyclohexadiene equivalents and temperature on the hydrogenation reaction

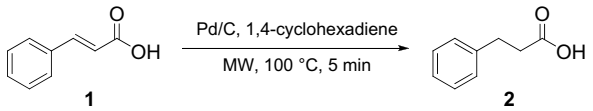


1 2

Entry	Cyclohexadiene (equiv)	Temperature (°C)	Conversion[a] (isolated yield) (%)
1	2	100	2
2	3	100	95
3	4	100	94
4	5	100	>99 (95[b])
5	5	100	98.7[c]
6	5	60	0
7	5	70	0
8	5	80	96
9	5[d]	100	0
10	5	100	0[e]

[a] From HPLC of crude reaction.
[b] Isolated yield.
[c] Reaction heated by oil bath.
[d] Cyclohexene used.
[e] Pt/C used.

Table 2
Effect of solvent on the hydrogenation reaction



1 2

Entry	Solvent	Conversion (%)
1	Acetonitrile	>99
2	Ethanol	>99
3	THF	>99
4	Acetone	>99
5	Water	24.4
6	DMF	>99
7	Ethyl acetate	>99

The transfer hydrogenation occurred smoothly with conventional heating, using an oil bath pre-heated to 100 °C (Table 1, entry 5). This, however, required the use of a sealed tube apparatus and the accompanying safety shield. The microwave reactor offers significant advantages in terms of safety and convenience. Additionally, the microwave synthesizer can be equipped with sample automation that allows multiple reactions to be carried out in a serial fashion.

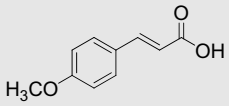
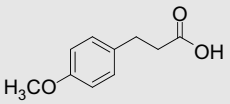
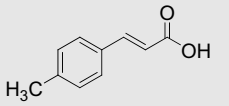
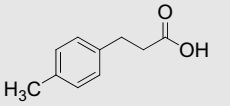
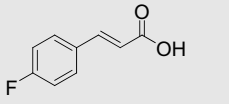
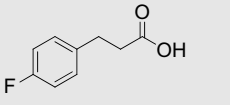
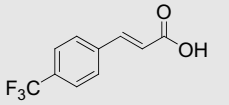
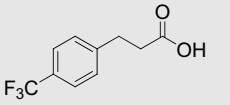
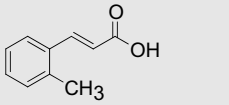
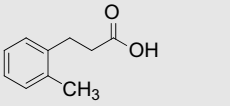
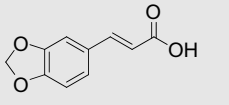
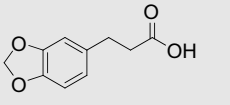
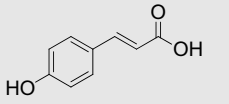
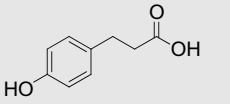
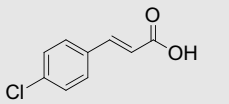
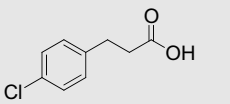
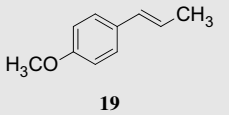
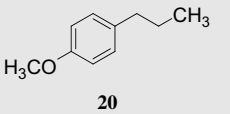
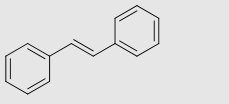
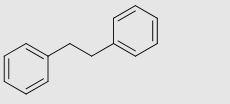
In addition to hydrogenations, the reaction protocol also proved to be useful for the rapid hydrogenolysis of the common protecting groups benzyl (Bz) and carboxybenzyl (Cbz) (Table 4, entries 1–5). The Cbz-protected di-peptide **23** was smoothly deprotected to give the primary amine **24** in 85% isolated yield. Likewise, the secondary amine **25** was cleanly debenzylated to give anisidine **26** in 88% isolated yield. The reported conditions were equally adept at deprotection of benzyl phenol ethers (Table 4, entries 3 and 4). Aniline **27** was converted to aminophenol **28** and benzoic acid **29** was converted to 4-hydroxybenzoic acid **30** in 86% and 99% yields, respectively. The final entry (Table 4, entry 5) demonstrates a convenient, neutral, non-aqueous route for unmasking carboxylic acids that are protected as benzyl esters. Benzyl 4-hydroxybenzoate **31** is converted to 4-hydroxybenzoic acid **30** in 86% isolated yield. Interestingly, in the case of Cbz-protected benzyl phenylalanine, **32**, deprotection under the standard conditions in ethyl acetate as solvent leads to a 75% isolated yield of Cbz-phenylalinine, **33**. The same reaction in methanol leads to a quantitative yield of phenylalaline **34**. All the reaction byproducts were volatile and in each case, purification involved only filtration and concentration.

Hydrogenolysis of *N*-Cbz-*O*-benzyl phenylalanine, **32,** shows an interesting, and potentially useful, selectivity (Scheme 1). Under our standard conditions (MW, 100 °C, 5 min, 6 equiv cyclohexadiene) using ethyl acetate as the solvent, a 64% isolated yield of *N*-Cbz-phenylalanine, **33**, is obtained as the sole product.

Inspection of the HPLC and ^{1}H NMR of the crude reaction shows no evidence for phenylalanine or benzyl phenylalanine. However, when the reaction solvent is switched to methanol, a quantitative yield of completely deprotected phenylalanine **34** is obtained.

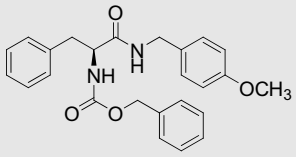
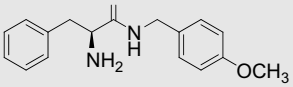
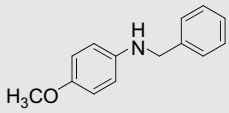
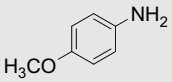
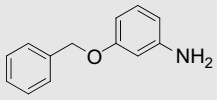
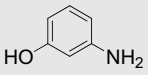
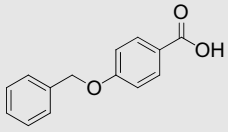
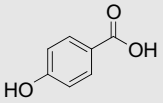
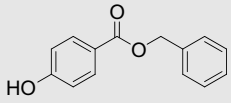
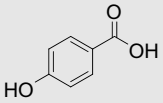
In summary, our reported hydrogenation procedure utilizes widely available Pd/C catalyst under transfer hydrogenation conditions. Reaction monitoring and optimization is straightforward, as a sample may be withdrawn through the septum cap on the microwave process vial for standard TLC or HPLC analysis. In analogy to traditional methods involving hydrogen gas, all that is required in the way of work-up and purification is a filtration to remove the

Table 3
Transfer hydrogenations under microwave heating

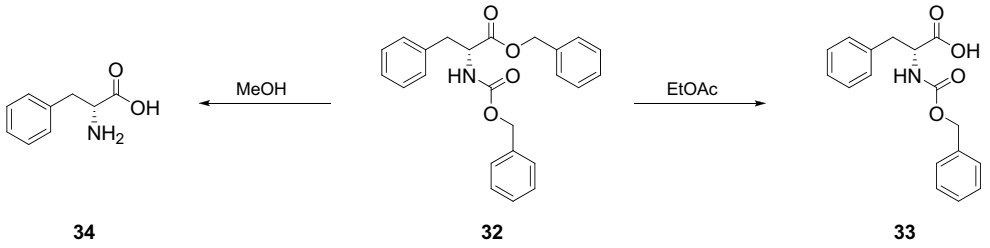
Entry	Substrate	Cyclohexadiene (equiv)	Palladium (equiv)	Product	Isolated yield (%)
1	 **3**	3	0.01	 **4**	94
2	 **5**	6	0.005	 **6**	98
3	 **7**	6	0.005	 **8**	88
4	 **9**	6	0.005	 **10**	96
5	 **11**	6	0.005	 **12**	97
6[a]	 **13**	6	0.005	 **14**	95
7	 **15**	6	0.005	 **16**	93
8[b]	 **17**	6	0.075	 **18**	78
9[c]	 **19**	5	0.05	 **20**	>99[d]
10	 **21**	5	0.06	 **22**	>99[d]

Unless otherwise noted, all reactions performed in ethyl acetate (3 mL), 1 mmol substrate, heated under microwave conditions at 100 °C for 5 min.
[a] Methanol used as solvent.
[b] 30 min reaction time.
[c] 15 min reaction time.
[d] HPLC yield (AUC@254 nM).

Table 4
Transfer hydrogenolysis of common protecting groups under microwave heating

Entry	Substrate	Cyclohexadiene (equiv)	Palladium (equiv)	Product	Isolated yield (%)
1[a]	 **23**	6	0.01	 **24**	85
2	 **25**	6	0.05	 **26**	88
3	 **27**	6	0.05	 **28**	86
4	 **29**	6	0.02	 **30**	99
5[b]	 **31**	6	0.02	 **30**	75

Unless otherwise noted, all reactions performed in ethyl acetate (3 mL), 1 mmol substrate, heated under microwave conditions at 100 °C for 30 min.
[a] 5 min reaction time.
[b] 60 min reaction time.



34 **32** **33**

Scheme 1. Solvent selectivity in hydrogenolysis of *N*-Cbz-*O*-benzyl phenylalanine. Reagents and conditions: reactions were performed in solvent indicated (3 mL), 1 mmol substrate, 6 mmol 1,4-cyclohexadiene, 0.047 mmol Pd/C, heated under microwave conditions at 100 °C for 5 min.

spent Pd catalyst and concentration to remove the solvent, volatile reagents, and byproducts.

Acknowledgement

The authors wish to thank Drs. Michael P. Trova and Bruce Molino for their helpful discussions and suggestions.

References and notes

1. (a) Rylander, P. N. *Hydrogenation Methods*; Academic Press: New York, 1985; (b) Siegel, S. In *Comprehensive Organic Synthesis*; Trost, B. M., Flemming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 8, pp 418–442; (c) Hudlicky, M. *Reductionis in Organic Chemistry*; Ellis Horwood Ltd: Chichester, 1984. pp 1–13.
2. For example, the 3900 series Hydrogenation Apparatus Manufactured by Parr Instrument Company, Moline, IL; www.parrinst.com.
3. *Microwave Methods in Organic Synthesis*; Larhed, M., Olofsson, K., Eds.; Springer-Verlag: Berlin, 2006.
4. For reviews on catalytic transfer hydrogenation see: (a) Brieger, G.; Nestrick, T. J. *Chem. Rev.* **1974**, *74*, 567–580; (b) Johnstone, A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev.* **1985**, *85*, 129–170.
5. Makowski, M.; Rzeszotarska, B.; Smelka, L.; Kubica, Z. *Liebigs Ann. Chem.* **1985**, 1457.
6. All microwave experiments were performed using a Biotage Initiator 2.0 microwave synthesizer.
7. (a) Eberhardt, M. K. *Tetrahedron* **1967**, *23*, 3029; (b) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meyerhofer, J. *J. Org. Chem.* **1978**, *43*, 4194.
8. A representative procedure is as follows: A 5 mL Biotage microwave process tube with stir bar was charged with cinnamic acid (148 mg, 1 mmol), Pd/C (10 wt %, 50 mg, 0.047 mmol), and ethyl acetate (3 mL). 1,4-Cyclohexadiene (0.50 mL, 5.3 mmol) was added and the tube was capped and heated under microwave conditions at 100 °C for 5 min. The reaction mixture was filtered through Celite and evaporated to give hydrocinnamic acid (150 mg, >99%) as white crystals.
9. All compounds had spectral data in agreement with authentic samples.