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Improved Method for the Diimide Reduction of Multiple Bonds on Solid-Supported Substrates

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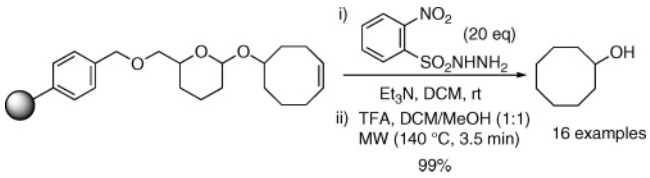
Received October 25, 2006



A mild and improved method for reducing multiple bonds on various resins with diimide is described. The simple procedure readily generates diimide from 2-nitrobenzenesulfonohydrazide and triethylamine at room temperature. A number of representative multiple bonds in various steric and electronic environments were examined, including polar double bonds such as carbonyl and azo, for ease and selectivity of reduction. A general trend of reactivity was identified which revealed, *inter alia*, that terminal olefins, 1,2-disubstituted olefins, electron-poor olefins, and terminal alkynes were the most easily reduced.

The range of useful reactions available for solid-phase organic synthesis has expanded significantly in the past decade.[1] However, one area that has received comparatively little attention is the reduction of multiple bonds on solid supported substrates. Carbon−carbon multiple bonds have rarely been reduced on the solid-phase, largely due to the inherent incompatibility with traditional heterogeneous catalytic hydrogenation conditions, as a consequence of the unfavorable kinetics of solid-on-solid reactions.[2] Even with non-cross-linked polymers, catalytic hydrogenation, though successful, is rare.[3a,b] There is one recent report of successful homogeneous hydrogenation with Wilkinson's catalyst at 60 psi in a polypeptide substrate on a modified Rink amide resin.[3c] Diimide reduction, on the other hand, would appear to offer an attractive solution to this important problem.[4] The reasons are manifold: diimide can be generated from numerous precursors; it is compatible with most functional groups; reaction yields are typically excellent; and the reduction is operationally simple.

TABLE 1. Methods of Diimide Generation in the Presence of a Solid-Support (PS-DES)

entry	conditions	solvent	conversion (**5** to **7**)
1	H_2NNH_2, $CuSO_4$, air, rt	EtOH	13%
2	H_2NNH_2, $CuSO_4$, H_2O_2, rt	*i*-PrOH/THF	40%
3	H_2NNH_2, $NaIO_4$, AcOH, rt	*i*-PrOH/THF	none
4	H_2NNH_2, $CuSO_4$, O_2, rt	*i*-PrOH/THF	50%
5	PTS, Et_3N, reflux	glyme	none
6	2,4,6-TIBS, Et_3N, rt	*i*-PrOH	5%
7	2-NBSH, Et_3N	DCM	100%

In connection with a program of research designed to create compound libraries inspired by medium-ring natural products, including the powerful antitumor agent octalactin A,[5] we required the synthesis and subsequent reduction of several THP-linked[6] unsaturated primary and secondary alcohols, such as those depicted in Scheme 1. Cognizant of the inherent difficulties with hetereogenous catalytic hydrogenation, we initially looked to homogeneous hydrogenation using the Wilkinson, Crabtree, and similar catalysts. Unfortunately, after repeated attempts with Wilkinson's catalyst, no detectable reduction products could be isolated, and it was further found that metallic rhodium was precipitated over the course of the reaction, indicating slow decomposition of the catalyst. After several additional failed hydrogenation attempts with the other catalysts, we turned our attention to diimide reduction. The only previous report concerning the use of diimide with solid supported systems examined cinnamic or styryl derivatives with a stable ester linked Merrifield-type resin.[7] The relatively harsh reaction conditions required for complete reductions (e.g., 100 °C in DMF) were unlikely to be compatible with our more labile linkers. Accordingly, we decided to investigate other diimide-forming reaction protocols that would be suitable for use with our supports. Additionally, we were interested in examining the scope of diimide reduction with a more representative range of substrates in various steric and electronic environments. Herein we describe an improved method for the reduction of double and triple carbon−carbon bonds in several solid supported substrates, including natural products. We also present the first

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(1) Dolle, R. E. *J. Comb. Chem.* **2005**, *7*, 739.

(2) For an example of a multipolymer solution-phase reaction: Harned, A. M.; He, H. S.; Toy, P. H.; Flynn, D. L.; Hanson, P. R. *J. Am. Chem. Soc.* **2005**, *127*, 52.

(3) An example of a Lindlar reduction on a non-cross-linked polystyrene support has been reported: (a) Chen, S.; Janda, K. D. *J. Am. Chem. Soc.* **1997**, *119*, 8724. (b) Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 3943. For catalytic homogeneous hydrogenation with Wilkinson's catalyst on a Rink resin, see: (c) Whelan, A. N.; Elaridi, J.; Harte, M.; Smith, S. V.; Jackson, W. R.; Robinson, A. J. *Tetrahedron Lett.* **2004**, *45*, 9545.

(4) For a review of methods for generating diimide and its use in the reduction of multiple bonds in homogeneous environments, see: (a) Pasto, D. J.; Taylor, R. T. *Org. React.* **1991**, *40*, 91. (b) Miller, C. E. *J. Chem. Ed.* **1965**, *42*, 254.

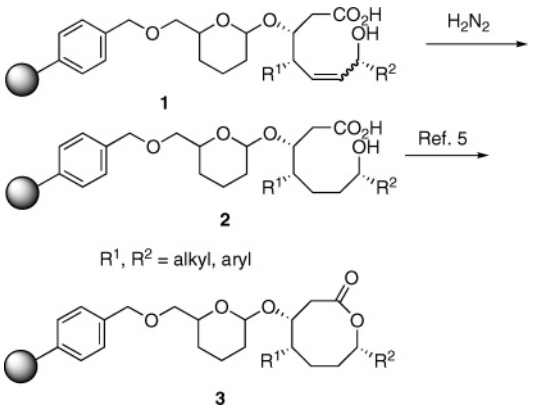
(5) (a) Buszek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511. (b) Buszek, K. R.; Jeong. Y. *Tetrahedron Lett.* **1995**, *36*, 5677. (c) Perchellet, J.-P.; Perchellet, E. M.; Newell, S. W.; Freeman, J. A.; Ladesich, J. B.; Jeong, Y.; Sato, N.; Buszek, K. R. *Anticancer Res.* **1998**, *18*, 97. (d) Buszek, K. R.; Sato, N.; Jeong, Y.; Sill, P. C.; Muino, P. L.; Ghosh, I. *Synth. Commun.* **2001**, *31*, 1781. (e) Buszek, K. R.; Sato, N.; Jeong, Y. *Tetrahedron Lett.* **2002**, *43*, 181.

(6) Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333.

(7) Lacombe, P.; Castagner, B.; Gareau, Y.; Ruel, R. *Tetrahedron Lett.* **1998**, *39*, 6785.

10.1021/jo0622173 CCC: $37.00
Published on Web 03/17/2007

SCHEME 1



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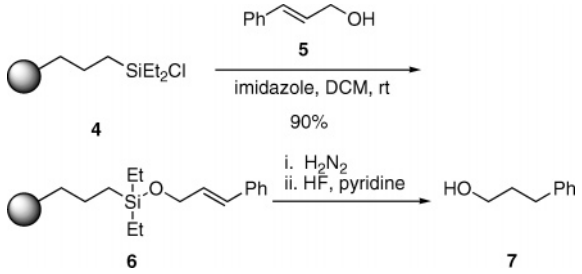

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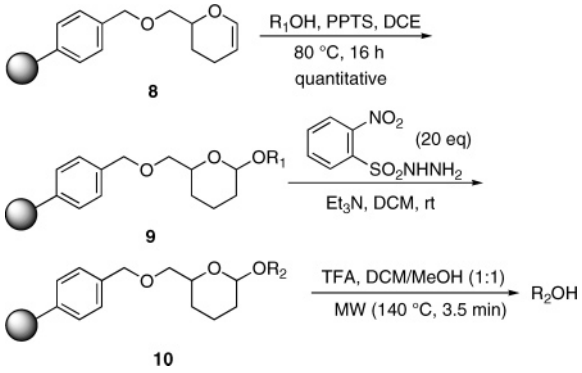


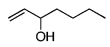
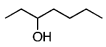
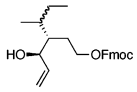
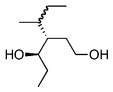
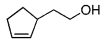
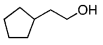
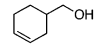
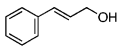
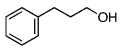
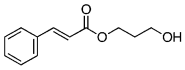
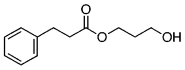
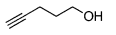
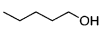
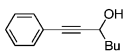
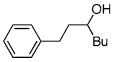
expanded study involving the ease of reduction of many different multiple bonds, including polar bonds, in various steric and electronic environments.

For our initial attempts to find milder diimide reduction conditions, we employed cross-linked polystyrene diethyl silyl ethers (PS-DES)[8] since we found them to be highly susceptible to both hydrolysis and decomposition at elevated temperatures. It was anticipated that any successful diimide reduction conditions would then likely be compatible with more stable linkers. Cinnamyl alcohol was selected as the model substrate for screening various methods of diimide generation. With this substrate attached to the resin (Scheme 2), several methods of diimide generation were examined (Table 1).

These methods include copper-catalyzed oxidation of hydrazine as well as decomposition of arylsofonylhydrazides with various bases and solvents.[4a] After surveying several methods of diimide generation in the presence of the resin-bound substrate, it was found decomposition of 2-nitrobenzene-

(8) Hu, Y.; Porco, J. A., Jr.; Labadie, J. W.; Gooding, O. W.; Trost, B. M. *J. Org. Chem.* **1998**, *63*, 4518.

TABLE 2. Reduction of Unsaturated Compounds on PS-DHP

Entry	R_1OH	R_2OH	% Conversion (Yield)[a]
1			100 (93)
2			100[b] (85)
3			100 (100)
4			100 (93)
5			100 (100)
6			100 (99)
7			100 (96)
8			100 (100)
9			100[c] (100)
10			100[c] (86)

[a] Isolated yields. [b] The Fmoc group was removed on the resin (20% piperidine in CH_3CN) prior to diimide reduction. [c] Two reaction cycles were required.

sulfonohydrazide[9,10] (NBSH, 10 equiv) with an excess of triethylamine in DCM at rt for 24 h gave superior results (Table 1, entry 7), and afforded quantitatively 3-phenylpropanol after cleavage from the resin and analysis by ^{1}H NMR.

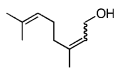
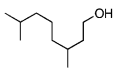
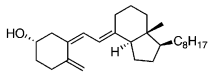
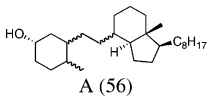
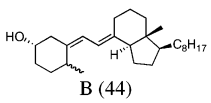
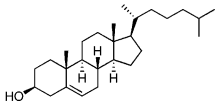
With the preferred diimide generation conditions identified for the PS-DES resin, several representative unsaturated alcohol primary and secondary substrates were selected. The compounds to be reduced were loaded onto Ellman's cross-linked polystrene dihydropyran[6] (PS-DHP) support (Scheme 3). The results are summarized in Table 2.[11] In all cases the extent of reduction and product yields were determined by first cleaving the substrates from the resin with catalytic TFA in 1:1 dichloromethane/methanol in a microwave reactor, followed by analysis of the products by ^{1}H NMR. The yields in all cases were based on purification (chromatography or distillation) of the isolated materials. Mono- and disubstituted primary and secondary allylic alcohols (entries 1, 2, and 7) were cleanly reduced, with the reaction of the more hindered substrate (entry 2) giving a somewhat lower yield. Cyclic olefins of five to eight members are completely and in most cases quantitatively reduced (entries 3−6), while the secondary propargylic alcohol (entry 10) gave the saturated compound in 86% yield. Simple terminal acetylenes also gave complete and quantitative conver-

(9) Synthesis of 2-nitrobenzeneslfonohydrazide (NBSH): Myers, A. G.; Zheng, B.; Movassaghi, M. *J. Org. Chem.* **1997**, *62*, 7507.

(10) Recent use of NBSH as a diimide source: Haukaas, M. H.; O'Doherty, G. A. *Org. Lett.* **2002**, *4*, 1771.

(11) All compounds exhibited satisfactory spectroscopic data consistent with their structure.

TABLE 3. Reduction of Natural Products on PS-DHP

Entry	R_1OH	R_2OH	% Coversion (Yield)[a]
1			100[b] (86)
2		 A (56)  B (44)	(82)[b,c]
3		Recovered SM	0

[a] Isolated yields. [b] Two reaction cycles were required. [c] The saturated and unsaturated alcohols were obtained in 82% combined yield after two reaction cycles in a 56:44 ratio. Separation was achieved after chromatographic separation of their corresponding 4-nitrobenzoate esters.

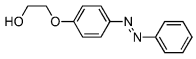
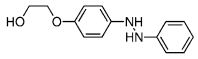
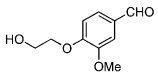
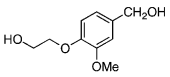
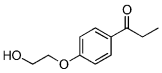
sion to the alkane (entry 9). The cinnamyl ester (entry 8) was completely and quickly reduced, an observation consistent with the fact that electron-deficient alkenes in general are also the most rapid to react with diimide under conventional homogeneous conditions.[12,13]

The results with some complex unsaturated natural products are also shown (Table 3). Geraniol (entry 1) was converted to its corresponding saturated alcohol in 86% yield after two reaction cycles. Resin-bound cholecalciferol (entry 2) revealed some regioselectivity with diimide among the three olefins, and gave the saturated alcohol and the conjugated diene in a 56:44 ratio. After conversion to their 4-nitrobenzoate esters, separation could be achieved via chromatography. The attempted reduction of cholesterol (entry 3) gave only recovered starting material. This result was not surprising given that the very hindered olefin is only reduced up to 20% with conventional solution diimide protocols.[4a] The additional steric demand conferred on the substrate by the resin probably accounts for the small difference.

Finally, the reduction of some azo and carbonyl functional groups with diimide on the same resins was examined for the sake of completeness (Table 4), even though this method is generally considered less useful for inherently polar bonds.[14] The azo benzene (entry 1) gave a 29% isolated yield of the hydrazine. The benzaldehyde (entry 2) afforded a 19% yield of the alcohol, with the remaining material consisting of its hydrazone, which formed as a result of the much faster reaction with the sulfonylhydrazide. Interestingly, the aryl ketone (entry 3) did not give detectable reduction products, nor did it appear to react with the hydrazide.

To illustrate the advantage of our method, a comparison study was undertaken. A sample of PS-THP-bound cholecalciferol was

TABLE 4. Attempted Reduction of Polar Double Bonds on PS-DHP

Entry	R_1OH	R_2OH	% Yield[a]
1			29
2			19[b]
3		Recovered SM	0

[a] Isolated yields. [b] Remainder of material is the 2-nitrobenzenesulfonylhydrazone derivative.

subjected twice to our conditions for diimide reduction (i.e., two reaction cycles were ran) and a separate sample of PS-THP-bound cholecalciferol was subjected to the conditions reported by Lacombe[7] (benzenesulfonohydrazide in DMF at 100 °C). After washing (CH_2Cl_2 twice, Et_2O four times) and cleavage from the resin (CH_2Cl_2, MeOH, cat. TFA, microwave, 140 °C, 4 min) the products were analyzed. Under our reaction conditions, a 82% yield of a 56:44 mixture of two reduced compounds was obtained. Analysis of the wash showed only material resulting from 2-nitrobenznesulfonohydrazide and triethylamine. However, with Lacombe's original procedure, decomposition was observed after only 3 h. From a sample of 109 mg of resin (load = 0.76 mmol/g) subjected to Lacombe's conditions, the isolated mass of resin after reaction was only 91 mg, corresponding to a 58% loss in material originally loaded onto the resin. ^{1}H NMR analysis of the wash from the reaction showed broad signals in the range of δ 2.0 to 0.0 ppm, consistent with decomposition of cholecalciferol. Cleavage of the resin resulted in an isolated yield of only 40% of material in which the ^{1}H NMR did not match either that of cholecalciferol or the reduced product obtained by our method. This experiment clearly demonstrates that under our conditions, thermally unstable resin-bound substrates can be reduced without decomposition.

In summary, a practical and improved method for the reduction of solid-supported unsaturated compounds in excellent yields has been achieved. It is clear from the results that very sterically hindered olefins (e.g., cholesterol) are recovered unchanged by these reduction conditions. With some substrates, a second reaction cycle at room temperature was necessary to obtain an acceptable level of reduction. Even so, the mild reaction conditions and simple operation make this an attractive method. The procedure takes place under mild conditions, which should be compatible with many labile linked resins. Furthermore, the procedure is operationally simple, even in those cases where repeated cycles are required. We are now examining additional complex resin-bound substrates to define further the generality of this approach to the reduction of unsaturated systems on solid-supported platforms. These results will be reported as developments warrant.

Experimental Section

Preparation of 2-Nitrophenylsulfonylhydrazide. Following the method of Myers[9] a flame dried 250 mL 3-necked round-bottom

(12) van Tamelen, E. E.; Timmons, R. J. *J. Am. Chem. Soc.* **1962**, *84*, 1067.

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flask was flushed with nitrogen and charged with 22.2 g (100 mmol) of 2-nitrophenylsulfonyl chloride, which was subsequently dissolved in 100 mL of dry THF. The solution was then cooled to −30 °C. To the cooled solution was then added 12.1 mL (250 mmol) of hydrazine hydrate, dropwise over 5 min. The mixture was then stirred for 40 min at −30 °C, after which time thin layer chromatography indicated complete reaction. The reaction mixture was then diluted with 200 mL of ethyl acetate and transferred to a separatory funnel and washed five times with 100 mL of a 10 wt % solution of ice-cold aqueous sodium chloride. The combined organic phase was then dried over sodium sulfate at 0 °C and filtered. This solution was then slowly added to 1200 mL of hexanes and the resulting off-white solid was filtered and washed with 20 mL of hexane. The solid was dried under vacuum at room temperature in the dark for 14 h to yield 19.0 g (87%) of the title compound as an off-white solid.

General Procedure for Loading of Alcohols to PS-DHP Resin. In a dry 25 mL round-bottom flask was added 250 mg (0.35 mmol) of PS-DHP resin pre-swollen in 1,2-dichloroethane. To the resin is added 176 mg (0.7 mmol) of PPTS followed by a solution of the alcohol (1.75 mmol, 5 equiv based on resin substitution) in 5 mL of 1,2-dichloroethane. The slowly stirring suspension is then heated to reflux under nitrogen atmosphere. After stirring for 20 h at reflux, the suspension is cooled to rt and filtered, then washed with dichloromethane, dimethylformamide (four times), and dichloromethane (four times). The resin is then dried under vacuum and stored in a desiccator. Yields vary from 74% to 100% (based upon mass gain of the resin).

PS-DHP-Bound (3*S*,4*R*)-3-*sec*-Butylhex-5-ene-1,4-diol. In a dry 25 mL round-bottom flask 340 mg (0.255 mmol) of PS-DHP-bound (9*H*-fluoren-9-yl)methyl (3*S*, 4*R*)-3-*sec*-butyl-4-hydroxyhex-5-enyl carbonate was suspended in 4 mL of acetonitrile. To this was added 1 mL of piperidine and the contents gently stirred under nitrogen for 1 h. The resin was then filtered off and washed with dichloromethane (twice), dimethylformamide (twice), and dichloromethane (three times). The resin was then dried under vacuum for 20 min to yield 280 mg (100%) of the title compound as pale yellow beads.

General Procedure for Diimide Reduction of Resin-Bound Unsaturated Compounds. To a dry 25 mL round-bottom flask is added 100 mg of the resin. To this is added 1 mL of dichloromethane, followed by 20 equiv (based on resin substitution) of 2-nitrophenylsulfonylhydrazide. Another 8 mL of dichloromethane is added, followed by 1 mL of triethylamine. The suspension is gently stirred for 6 h at rt under nitrogen. The mixture is then filtered and washed with dichloromethane, dimethylformamide (three times), dimethylformamide/water 1:1 (three times), THF (three times), and finally dichloromethane (three times). The resin is then dried under vacuum and stored in a desiccator.

General Procedure for Cleavage of Reduced Compounds from PS-DHP Resin. The cleavage is performed with a microwave synthesis reactor. In a 5.0 mL vial was added 50 mg of the resin. To this was added 0.9 mL of dichloromethane, 0.9 mL of methanol, and 2−3 drops of TFA. The vial was sealed and placed in the reactor. The reaction was run at 140 °C for a total time of 4.0 min (2 min fixed hold time). After cooling to room temperature, the vial was opened and the solution was filtered off from the resin. The solution was then concentrated under reduced pressure and further dried under high vacuum for 20−30 min. The products were then analyzed by ^{1}H NMR spectroscopy to determine the extent of reduction. Isoated yields of products after chromatography or distillation ranged from 85% to 100%. Representative compounds: **(3*R*,4*R*)-3-*sec*-butylhexane-1,4-diol (Table 2, entry 2):** 25 mg of PS-DHP-bound (3*S*,4*R*)-3-*sec*−butylhexane-1,4-diol (as an optically active mixture of diastereomers) was subjected to the above procedure and the crude material obtained was purified via column chromatography to give 3.3 mg (85%) of 3-*sec*-butylhexane-1,4-diol as a colorless oil. ^{1}H NMR (δ, ppm) 3.78 (m, 2 H), 3.58 (m, 2 H), 1.77−1.02 (m, 9 H), 0.98−0.76 (m, 9 H); ^{13}C NMR (δ, ppm) 74.8, 73.9, 62.6, 61.8, 46.2, 45.4, 35.0, 34.7, 29.3, 29.2, 28.5, 27.9, 27.5, 25.1, 16.9, 14.7, 11.9, 11.7, 10.0, 9.5. HRMS calcd for $C_{10}H_{22}O_2$ 174.1620, found 174.1618.

1-phenylheptan-3-ol (Table 2, entry 10): ^{1}H NMR (δ, ppm) 7.31 (m, 5 H), 3.64 (m, 1 H), 2.81 (m, 1 H), 2.70 (m, 1 H), 1.80 (m, 2 H), 1.49−1.30 (series of m, 7 H), 0.91 (t, 3 H, J = 6.8 Hz); ^{13}C NMR (δ, ppm) 142.2, 128.4, 128.37, 125.8, 71.4, 39.1, 37.3, 32.1, 27.8, 22.7, 14.1. HRMS (EI) *m*/*e* calcd for $C_{13}H_{20}O$ 192.1514, found 192.1511.

3,7-Dimethyloctan-1-ol (Table 3, entry 1): ^{1}H NMR (δ, ppm) 3.71 (m, 2 H), 1.62−1.11 (series of m, 10 H), 0.90 (d, 3 H, J = 6.8 Hz), 0.88 (d, 6 H, J = 6.8 Hz); ^{13}C NMR (δ, ppm) 61.2, 40.0, 39.2, 37.3, 29.5, 27.9, 24.7, 22.7, 22.6, 19.6. HRMS (EI) *m*/*e* calcd for $C_{10}H_{22}O$ 158.1671, found 158.1675.

Acknowledgment. We acknowledge support of this work by the National Institutes of Health (The University of Kansas Chemical Methodology and Library Development Center of Excellence), P50 GM069663. We wish to thank Mr. Benjamin Neuenswander from the KU-CMLD Library Design and Analysis Core for performing the LC-MS work.

Supporting Information Available: ^{1}H NMR data for all reduced compounds reported in Tables 2−4. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0622173