J. Org. Chem. **1996,** *61,* 8765−8770

Real-Time Monitoring of the Catalytic Oxidation of Alcohols to Aldehydes and Ketones on Resin Support by Single-Bead Fourier Transform Infrared Microspectroscopy

Bing Yan,*,† Qun Sun,‡ James R. Wareing,‡ and Charles F. Jewell‡

Department of Central Technologies and Combinatorial Chemistry Group, Sandoz Research Institute, Sandoz Pharmaceuticals Corporation, 59 Route 10, East Hanover, New Jersey 07936-1080

Received July 22, 1996⊗

Catalytic oxidations of primary, benzylic, and secondary alcohols to aldehydes and ketone using tetra-*n*-propylammonium perruthenate (TPAP) were carried out on resin supports for the first time. The reaction time course, percent conversion, and influence of catalyst amount have been determined by analyzing IR spectra taken directly on a single resin bead in real time. Using 0.2 equiv of TPAP, a 92−97% conversion of alcohol to aldehyde or ketone has been achieved in 0.7−4 h based on the rates (rate constants $(1.9 \times 10^{-4})-(2.5 \times 10^{-3})\ s^{-1}$) of disappearance and appearance of IR bands characteristic for alcohol, aldehyde, and ketone. The rapid adaptation of this oxidation method for solid-phase synthesis demonstrates that single-bead FTIR microspectroscopy is a powerful method for facilitating the time-consuming reaction optimization stage of combinatorial chemistry.

Introduction

Combinatorial chemistry has recently become an area of high interest in organic chemistry.[1] The majority of the compound libraries that have been assembled to date have been synthesized on solid supports, mostly on polystyrene resin cross-linked with 1−2% divinylbenzene. Solid-phase organic synthesis (SPOS) is different from solid-phase polypeptide and polynucleotide synthesis in that reactions to be carried out are extremely diverse. Before any combinatorial library can be produced, substantial effort is often required to develop the necessary solid-phase reactions. Since the introduction of solid-phase peptide synthesis,[2] the number of solution-phase organic reactions adapted to solid-phase conditions[3] has amply demonstrated that many organic reactions can be conducted on solid supports. However, optimization and reaction development are usually required. Analytical methods such as single-bead FTIR microspectroscopy[4] (single-bead IR) are potential analytical tools to facilitate both the transformation of known solution-phase reactions and the development of new solid-phase chemistry that does not have a current solution-phase counterpart. Rapid on-bead determination of both percent conversion and the time required for reaction completion would obviate the tedious cleavage of intermediates for each analysis. Accurate knowledge of the time required for a reaction step to reach completion is also important during the production of compound libraries on solid-phase supports as well as during reaction optimization.

Reactions of aldehydes and ketones lead to a wide range of molecules of interest for combinatorial libraries. Oxidation of alcohols is one of the most useful synthetic procedures to obtain aldehydes and ketones for solid-phase chemistry. Limited examples of the solid-phase oxidation of alcohols to aldehydes and ketones have been reported.[5] These reactions can require a large excess of reagent and still have a slow reaction rate. Solution-phase studies have demonstrated that tetra-*n*-propylammonium perruthenate (TPAP) is a mild catalytic oxidant for the high-yield conversion of alcohols to aldehydes and ketones at room temperature. Most functional groups, protecting groups, and chiral centers are inert to these oxidation conditions.[6] Although the oxidation of alcohols to aldehydes or ketones with TPAP has been very successful in solution,[6b] it has not been demonstrated whether this synthetic procedure can be adapted on a solid support, especially considering the sterically demanding aspect of the reagent.[6b] We have evaluated this solution-phase catalytic oxidation reaction for use on alcohols attached to a solid support. We use the single-bead IR as a tool for real-time monitoring of the progression of oxidation reactions on solid supports. Here we report the time courses and yields for all synthetic steps determined directly on a single bead and the effect of the amount of catalyst on the reaction rate.

Results and Discussion

Oxidation of a Primary Alcohol to an Aldehyde. The IR spectrum of the starting material Wang resin is shown in the bottom of Figure 1. One interesting feature

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* Corresponding author: tel, 201-503-8224; fax, 201-503-6008.

† Department of Central Technologies.

‡ Combinatorial Chemistry Group.

⊗ Abstract published in *Advance ACS Abstracts*, December 1, 1996.

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S0022-3263(96)01389-8 CCC: $12.00

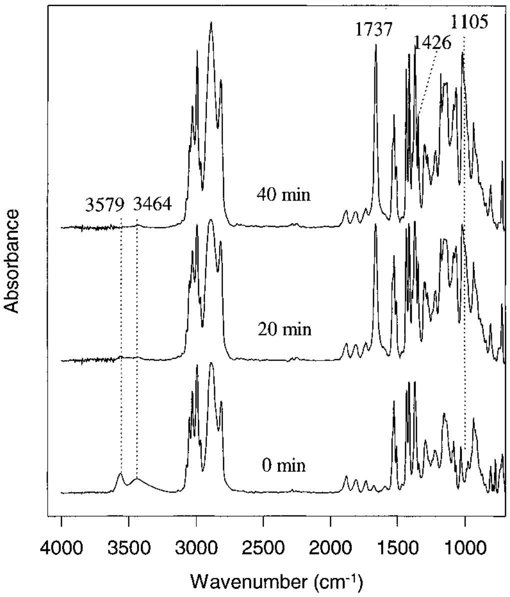
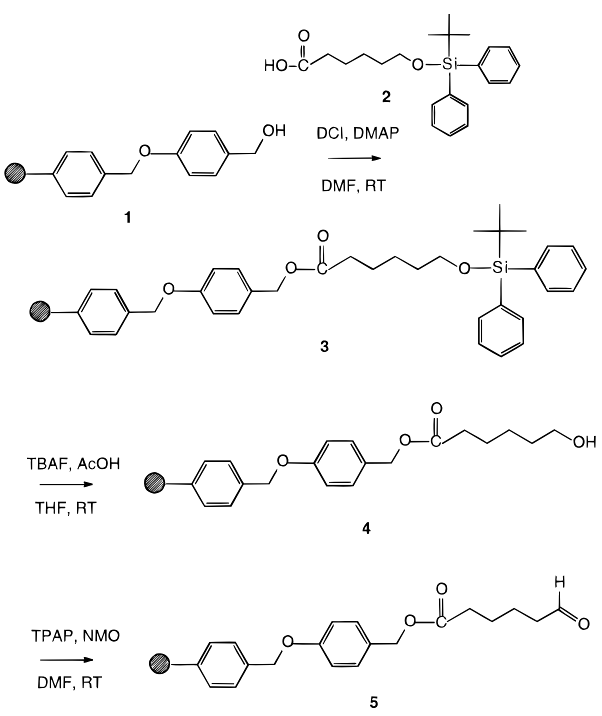


Figure 1. IR spectra taken from a single bead at various times in the course of the first step in Scheme 1. Spectra were taken from a single flattened bead at 0, 20, and 40 min after the initiation of the reaction. All spectra were taken using the transmission mode at room temperature. The hydrogen-bonded and unbonded hydroxyl stretches at 3464 and 3579 cm^{-1} disappear as the ester band (1737 cm^{-1}) and the Si−Ph and Si−O (1426 and 1105 cm^{-1}) stretching signals increase.

is that the spectrum exhibits two prominent bands in the hydroxyl stretching region: a broad band at 3420 cm^{-1} and a sharp band at 3578 cm^{-1}. The latter is from the free hydroxyl groups, while the former is from hydrogen-bonded hydroxyl groups. Rink acid resin and the compound **4** synthesized in this work all exhibit this property. This result confirms previous findings for alcohol[7] and carboxyl[8] resins. It is not clear if the hydrogen bonding occurs between hydroxyl groups inside the bead or between the hydroxyl groups and water molecules in the resin. Heating the bead at 115 °C for 3 h or lyophilizing (0.1 mmHg) the bead at −71 °C for 20 h did not eliminate the broad hydrogen-bonded peak. This may suggest that internal hydrogen bonding between hydroxyl groups may be responsible for this IR band. Site interactions have been detected previously in the low-cross-linked (1−2%) polystyrene resins.[9] However, a large extent of "site separation"[10] does occur in this polystyrene resin cross-linked with 1% divinylbenzene, as demonstrated by the existence of the band indicating free hydroxyl groups.

Primary alcohol **4** was first synthesized in two steps (Scheme 1). Wang resin **1** was reacted with 6-[(*tert*-butyldiphenylsilyl)oxy]hexanoic acid (**2**) using diisopropylcarbodiimide (DIC) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) as coupling reagent in DMF to give the ester **3** on resin. IR spectra taken from a single bead at various times during this reaction are shown in Figure 1. At 40 min, a 98% conversion was achieved based on the analysis of the decreasing area under the IR band at ~3500 cm^{-1} for the hydroxyl group in the starting material. The product **3** is characterized by the prominent ester carbonyl band at 1737 cm^{-1} and two bands from silicon−phenyl and silicon−oxygen bond stretches at 1426 and 1105 cm^{-1}. These two bands also provide probes for the quantitative determination of the percent conversion for the next reaction step. The deprotection of the *tert*-butyldiphenylsilyl group using tetrabutylammonium fluoride in THF and glacial acetic acid gave the hydroxyl derivative **4** on resin. Very mild conditions were chosen for this deprotection so that the ester linkage remained intact (see the band at 1737 cm^{-1} in Figure 2). These conditions allowed the formation of the product **4** slowly (Figure 2). After 30 h, bands at 1426 and 1105 cm^{-1} disappeared, while IR bands for free and hydrogen-bonded hydroxyl stretching at 3579 and 3420 were formed. Note that polystyrene resin-based starting materials may exhibit small IR bands in both ~1426 and ~1105 cm^{-1} (for example, see IR spectrum of Wang resin in the bottom spectrum in Figure 1). Since a standard resin containing pure compound **4** is not available, an estimate was done using Wang resin as a base-line standard (i.e., assuming 0% Si−Ph and Si−O functionalities). Estimation based on the 1105 cm^{-1} band suggested that the reaction is at least 90−95% complete. These results demonstrate that the spectral changes in the fingerprint region are sufficiently distinct and suitable for qualitative and quantitative analysis of some solid-supported reactions.

Scheme 1



Primary alcohol **4** was then oxidized to aldehyde by 0.2 equiv of TPAP and 10 equiv of *N*-methylmorpholine *N*-oxide (NMO) in DMF. The stretching vibration of the primary aldehyde carbonyl is expected to be at ~1730 cm^{-1} which is overlapped completely with the vibration of the ester carbonyl in the starting material (Figures 2 and Figure 3). However, the reaction time course was monitored by the gradually disappearing hydroxyl band

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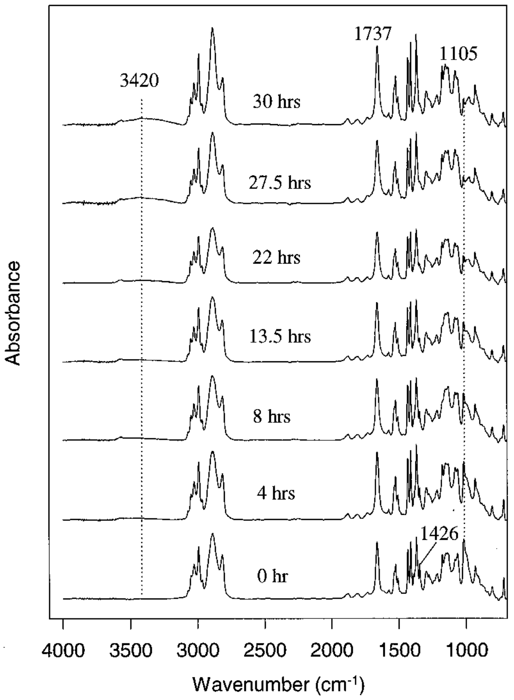


Figure 2. IR spectra taken from a single bead at various times in the course of the second step in Scheme 1. Spectra were taken from a single flattened bead at 0, 4, 8, 13.5, 22, 27.5, and 30 h after the initiation of the deprotection reaction. The hydrogen-bonded and unbonded hydroxyl stretchings near 3420 cm^{-1} are formed gradually as the band at 1105 cm^{-1} for Si−O stretch decreases. The band for the ester bond remains unaltered.

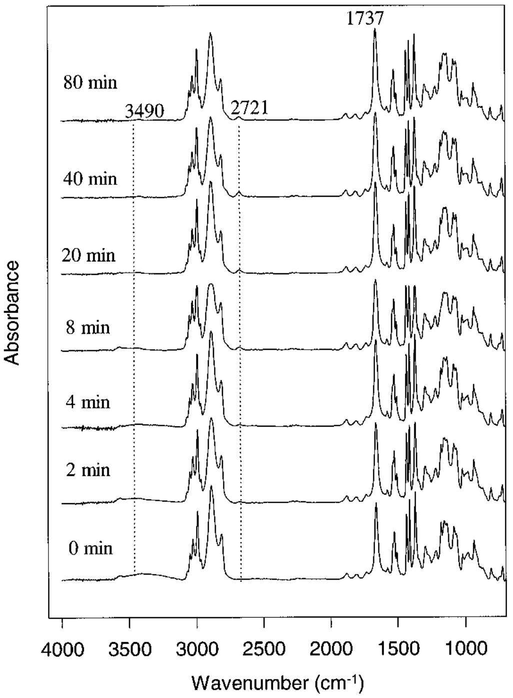


Figure 3. IR spectra taken from a single bead at various times in the course of the third step in Scheme 1. Spectra were taken from a single flattened bead at 0, 2, 4, 8, 20, 40, and 80 min after the initiation of the oxidation reaction. The hydrogen-bonded and unbonded hydroxyl stretches near 3490 cm^{-1} disappear as the band for the aldehyde C−H (2721 cm^{-1}) stretching increases.

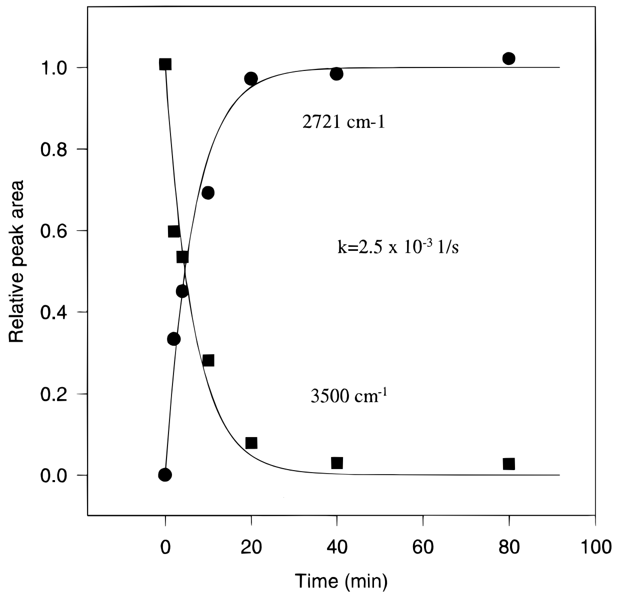
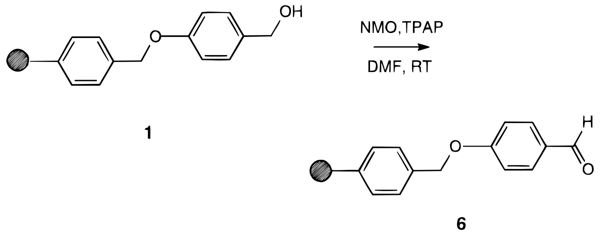


Figure 4. Time course of the oxidation step in Scheme 1. All spectra were normalized to make the intensity of polystyrene peaks at 1947 cm^{-1} the same. The area integrations for the hydroxyl band from 3141 to 3658 cm^{-1} (■) and the aldehyde C−H band from 2658 to 2762 cm^{-1} (●) for spectra at various times were plotted against time. Lines were calculated from the best fit to a first-order reaction equation with the rate constant shown.

Scheme 2



and the concurrent formation of the aldehyde hydrogen stretch at 2721 cm^{-1} (Figure 3). Integrated areas for these two bands taken at various time intervals are plotted in Figure 4. The depletion of the alcohol and the formation of the aldehyde fit well with a first-order reaction rate constant[12a] of 2.5 × 10^{-3} s^{-1}. The lack of nonexpected IR signals, the same rate for the disappearance of the 3490 cm^{-1} band and the appearance of 2721 cm^{-1} bands, and the single rate constant fit for both data sets strongly indicate that there is no side reaction during the 80 min reaction period and no rate-limiting intermediate/product conversion step. Although the absorptivity of the product is unknown, the extent of the depletion of the starting material provided a quantitative measure of the reaction yield when no side reaction or side product was detected. The yield of this conversion was estimated to be ∼97% based on the area integration analysis of the 3490 cm^{-1} band.

The similar reaction time for solution-[6b] and solid-phase oxidation of primary alcohols suggests that TPAP is a useful catalytic oxidant for SPOS. To further explore this reagent, we investigated the catalytic oxidations of benzylic and secondary alcohols with TPAP.

Oxidation of a Benzylic Alcohol to an Aldehyde and the Effect of Catalyst Amount. The oxidation of a benzylic alcohol to an aldehyde (Scheme 2) was done in the presence of 0.2 equiv of TPAP. The spectrum of the starting material **1** shows strong hydroxyl bands at 3420 and 3578 cm^{-1} and no bands at 2736 and 1695 cm^{-1}

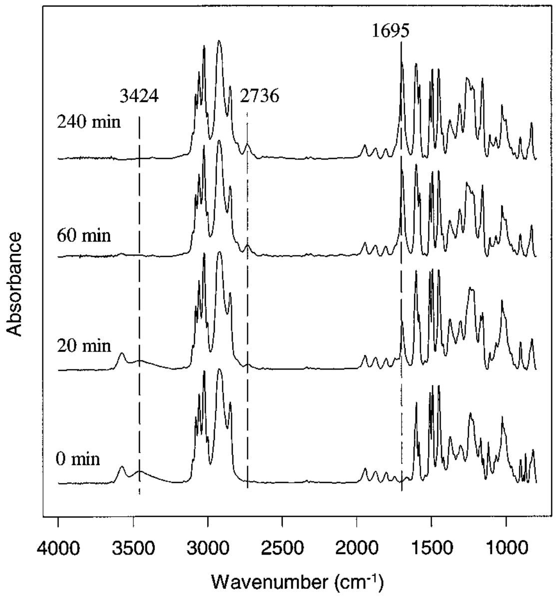


Figure 5. IR spectra taken from a single bead at various times in the course of Scheme 2. Spectra were taken from a single flattened bead at 0, 20, 60, and 240 min after the initiation of the oxidation reaction. The hydrogen-bonded and unbonded hydroxyl stretches near 3424 cm^{-1} disappear as the bands for the aldehyde C−H (2736 cm^{-1}) and the aldehyde carbonyl (1695 cm^{-1}) stretching increase.

(Figure 5). During the progress of the oxidation, the intensity of IR bands attributed to the free and hydrogen-bonded hydroxyl groups decreases. At the same time, two bands are emerging, one at 2736 cm^{-1} assignable to aldehyde C−H stretching and one at 1695 cm^{-1} for aldehyde carbonyl stretching (Figure 5). All spectra were normalized by making the intensity of a polystyrene band at 1947 cm^{-1} equal. Areas under the disappearing band and the emerging bands for all spectra were calculated. Values for these areas are plotted against time in Figure 6A. These data were fit with a first-order rate equation, and the average rate constant is 4.6×10^{-4} s^{-1}. A time course calculated with this average rate constant results in the lines plotted in Figure 6A. These plots suggest that 92% (based on the area under the hydroxyl band at ~3424 cm^{-1}) of benzylic alcohol is oxidized to the aldehyde within 90 min. The lack of nonexpected IR signals, the disappearance of the 3424 cm^{-1} band occurring at the same rate as the appearance of 2736 and 1695 cm^{-1} bands, and the good fit with a single rate constant for all the data sets again strongly suggest that there is no side reaction or a rate-limiting intermediate/product conversion.

In order to determine the effect of the amount of catalyst on the reaction rate in the solid-phase version of this reaction, we also studied the reaction using 0.1 and 0.05 equiv of TPAP. The reaction was slowed down by 2.8- and 3.9-fold, respectively, when 0.1 and 0.05 equiv of catalyst were used. Under the conditions with a reduced amount of catalyst, a 90−92% (based on the area under the hydroxyl band at ~3424 cm^{-1}) oxidation of the alcohol to the aldehyde took about 4−6 h. It is interesting to note that the appearance of the aldehyde bands is relatively slower than the disappearance of the hydroxyl group band when the amount of catalyst is reduced (Figure 6B,C). These findings suggest that the conversion of an intermediate to the product may become rate-limiting under these conditions. The speculated intermediate may have a similar structure as the slowly decomposing chromate ester intermediate in chromic acid-mediated oxidation reactions.[11]

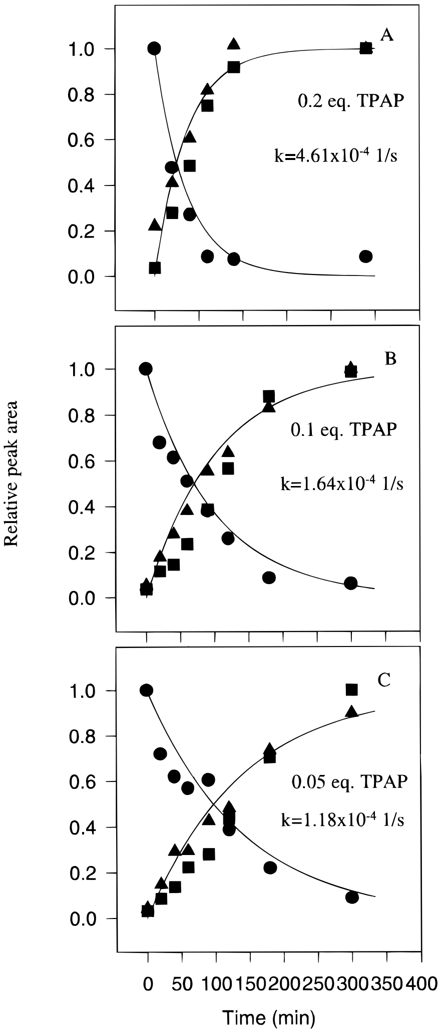


Figure 6. Time course of Scheme 2. All spectra were normalized as described in Figure 4. The area integrations for the hydroxyl band from 3181 to 3637 cm^{-1} (●), aldehyde C−H band from 2664 to 2766 cm^{-1} (■), and aldehyde carbonyl band from 1641 to 1765 cm^{-1} (▲) for spectra at various times were plotted against time. Lines were calculated from the best fit to a first order-reaction equation with the rate constant shown. The amount of catalyst TPAP was 0.2 equiv in A, 0.1 equiv in B, and 0.05 equiv in C.

Oxidation of a Secondary Alcohol to a Ketone. In solution, the oxidation of a secondary alcohol to a ketone by TPAP is generally slower than the oxidation of a primary alcohol suggesting the catalyst is sterically demanding.[6b] The sterically hindered secondary alcohol **7** in Scheme 3 would be expected to be further hindered by attachment to the polystyrene resin. We expect that the rate of this reaction will provide a lower limit estimate for the oxidation rate of a secondary alcohol by TPAP on solid support. The starting material Rink Acid was treated with 0.2 equiv of TPAP in the presence of NMO. IR spectra taken on a single bead from the reaction mixture at various time intervals after the

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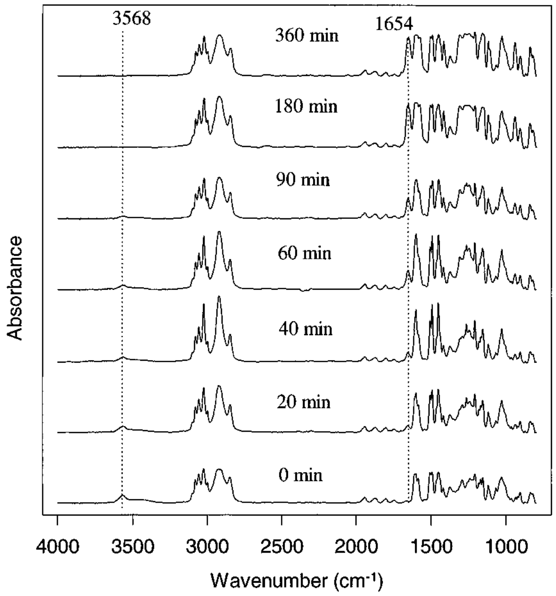


Figure 7. IR spectra taken from a single bead at various times in the course of Scheme 3. Spectra were taken from a single flattened bead at 0, 20, 40, 60, 90, 180, and 360 min after the initiation of the oxidation reaction. The hydrogen-bonded and unbonded hydroxyl stretches at 3420 and 3578 cm^{-1} disappear as the ketone carbonyl group at 1654 cm^{-1} increases.

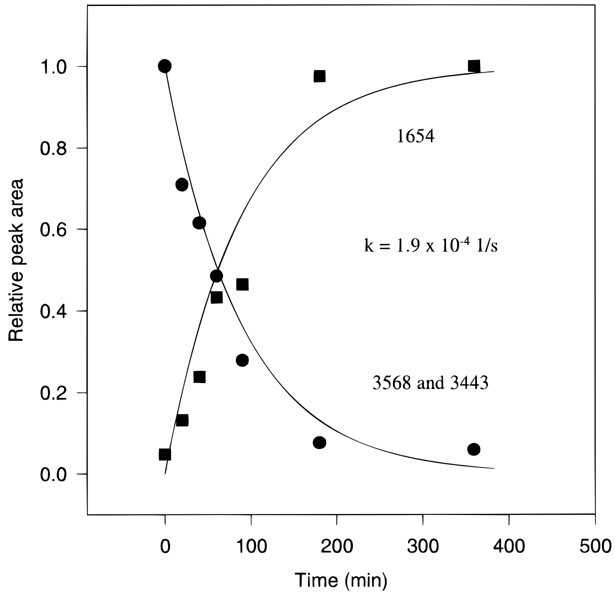
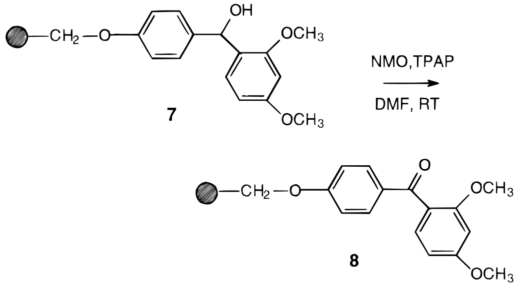


Figure 8. Time course of Scheme 3. All spectra were normalized as described in Figure 4. The integrated areas for the hydroxyl band from 3181 to 3637 cm^{-1} (●) and the ketone carbonyl band from 1625 to 1715 cm^{-1} (■) for spectra at various times were plotted against time. Lines were calculated from the best fit to a first-order reaction equation with the rate constant shown.

Scheme 3



initiation of the reaction are shown in Figure 7. The disappearance of a band at 3568 cm^{-1} due to the hydroxyl group and the increasing band at 1654 cm^{-1} attributed to the ketone carbonyl are evident (see highlighted bands in Figure 7). Areas under these two peaks, when plotted against time, fit well with a first-order reaction equation (Figure 8). The average rate constant is 1.9×10^{-4} s^{-1}. The same rate for the disappearance of the hydroxyl group and the appearance of the ketone carbonyl indicates that only one reaction, i.e., the oxidation of the alcohol **7** to the ketone **8**, is occurring. Based on the area calculations under the 3568 cm^{-1} band, a 97% conversion of **7** to **8** takes about 4 h.

Summary

TPAP-catalyzed oxidations of alcohols have been carried out on solid phase for the first time. A 92–97% oxidation of primary, benzylic, and secondary alcohols to the corresponding aldehydes and ketone on solid supports has been achieved in 0.7–4 h at room temperature using 0.2 equiv of TPAP. All five synthetic steps in three reaction schemes have been monitored in real time to obtain the time course and percent conversion directly on bead by single-bead IR. The information obtained allowed accurate determination of the timing for the next synthetic step without having to stop the reaction and cleave the product for analysis. Single-bead IR is not only valuable for monitoring reactions but also for optimizing SPOS, as demonstrated here by the selection of catalyst amount. Single-bead IR will continue to play an important role in the selection of optimal resin, solvent, and reaction conditions in general. This work demonstrates that single-bead IR is a powerful analytical tool for facilitating the time-consuming solid-phase reaction optimization necessary for combinatorial chemistry. Further experiments to determine the scope and utility of TPAP-catalyzed oxidation of resin-bound alcohols are currently underway.

Experimental Section

Materials. Wang resin (*p*-benzyloxybenzyl alcohol resin) was purchased from Midwest Bio-Tech (Fishers, IN) and Rink acid resin from NovaBiochem (San Diego, CA). Both Wang and Rink acid resins are based on 1% cross-linked divinylbenzene–styrene copolymer. They are 100–200 mesh with a loading of 1.00 and 0.61 mmol/g, respectively. One drop of resin suspension was taken from the reaction vessel at specified times. The resins were filtered and washed four times with DMF (0.5 mL each time), THF (four times), and then dichloromethane (four times). The sample was dried under vacuum for 15 min. All reagents, if not specified, were purchased from Aldrich (Milwaukee, WI).

FTIR Microspectroscopy. All spectra were collected on a BIO-RAD, FTS-40 spectrophotometer coupled with a UMA-300 IR microscope, using a SPC-3200 data station. The microscope is equipped with a 36X Cassegrain objective and a liquid nitrogen-cooled mercury–cadmium–telluride (MCT) detector. General procedure for IR measurement is as in Yan et al.[4] Flattened bead was used throughout experiments.[12b]

Data Treatment and Analysis. IR spectra were normalized by making the intensity of a polystyrene band at 1947 cm^{-1} equal. The areas under the typical bands of the starting material or the product were integrated. The values of integration were then plotted against time. These data points were fitted to a rate equation[12a] by using a nonlinear regression program, SigmaPlot for windows (Jandel Scientific, San Rafael, CA), on a PC computer.

Synthesis and Oxidation of a Primary Alcohol (4). In Scheme 1, Wang resin (300 mg, 1.00 mmol/g) was washed with 8 mL of DMF for 15 min and then drained. Diisopropylcarbodiimide (379 mg, 3.0 mmol) was added to a solution of 6-[(*tert*-butyldiphenylsilyl)oxy]hexanoic acid (1.068 g, 3 mmol) in 8 mL of dry DMF. The mixture was added to the resin and stirred for 5 min. Then 4-(*N*,*N*-dimethylamino)pyridine (DMAP) (37 mg, 0.30 mmol) was added to the resin suspension. One drop of resin suspension was taken out of the reaction mixture at various times, washed with DMF (four times, 0.5 mL each time), THF (four times), and dichloromethane (four times), and dried for 15 min. The reaction was monitored by single-bead IR until it was completed after 40 min. Then the whole reaction mixture was drained, washed with 8 mL of DMF (four times), THF (four times), and dichloromethane (four times), and dried under vacuum for 2 h.

In the second reaction step, 5 mL of 1 M tetrabutylammonium fluoride in THF was added to the dried resin followed by the addition of 322 μL of glacial acetic acid. The reaction was monitored by single-bead IR until it was completed after 30 h. The reaction mixture was drained, washed with 8 mL of DMF (four times), THF (four times), and dichloromethane (four times), and dried under vacuum for 2 h.

In the third reaction step, a solution of *N*-methylmorpholine *N*-oxide (NMO) (352 mg, 3.00 mmol) in 10 mL of dry DMF was added to the dried resin, and then tetrapropylammonium perruthenate (TPAP) (21.1 mg, 0.06 mmol) was added to the resin suspension. The reaction was monitored by single-bead IR until the reaction was completed after 80 min. The reaction mixture was drained, washed with 8 mL of DMF (four times), THF (four times), and dichloromethane (four times), and dried under vacuum for 2 h.

Oxidation of a Benzylic Alcohol (1). In Scheme 2, Wang resin (300 mg, 1.00 mmol/g) was washed with 8 mL of DMF and drained. A solution of NMO (352 mg, 3.00 mmol) in 10 mL of dry DMF was added to the resin, and then TPAP (21.1 mg, 0.06 mmol) was added to the resin suspension. The reaction was monitored by single bead-IR until the reaction was completed after 90 min. Then, the reaction mixture was drained, washed with 8 mL of DMF (four times), THF (four times), and dichloromethane (four times), and dried under vacuum for 2 h.

Oxidation of a Secondary Alcohol 7. In Scheme 3, Rink acid resin (300 mg, 0.61 mmol/g) was washed with 8 mL of DMF and drained. A solution of NMO (215 mg, 1.83 mmol) in 8 mL of dry DMF was added to the resin, and then TPAP (12.9 mg, 0.037 mmol) was added to the resin suspension. The reaction was monitored by single-bead IR until the reaction was completed after 3 h. Then, the reaction mixture was drained, washed with 8 mL of DMF (four times), THF (four times), and dichloromethane (four times), and dried under vacuum for 2 h.

Acknowledgment. We thank Richard W. Versace for providing us with compound **2** and Drs. Emil Fu and Jeffrey Nadelson for critical reading of the manuscript.

JO9613895