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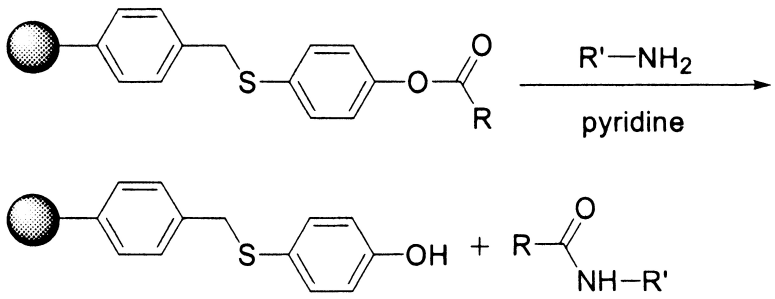

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Kinetics Study of Amine Cleavage Reactions of Various Resin-Bound Thiophenol Esters from Marshall Linker

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The kinetics of cleavage reactions of seven resin-bound thiophenol esters with three amines has been studied by single-bead FTIR. The reactivity of these seven thiophenol esters was dependent on their structures and could be summarized as follows: 5-benzimidazolecarboxylic thiophenol ester > alkyl thiophenol ester > aromatic thiophenol ester. The reactivity of three amines was summarized as follows: *n*-butylamine > 3,4-dimethoxyphenethylamine > 1-piperonylpiperazine. The rate of the cleavage reaction increased 2-fold per 10 °C rise in reaction temperature. Oxidation of the thiophenol linker increased the rate of the cleavage reaction by 580-fold.

Introduction

A recent survey[1] has confirmed that solid-phase synthesis[2] continues to hold a dominant position (82% in 2000) in combinatorial synthesis as more and more chemistries are redeveloped on this medium. To be successful, reaction conditions for each step have to be thoroughly optimized. As the final step toward a high-quality library, the desired products must be released from the solid support by a chemical or photochemical reaction. Mild cleavage conditions may result in the partial release of products, leading to a poor yield. On the other hand, harsh cleavage conditions could cause product degradation and resin breakdown, leading to a low purity. Therefore, cleavage condition optimization is a key step for generating a high-quality library and keeping the integrity of the products.

The Marshall linker[3] has been widely used to synthesize compounds that can be cleaved by primary and secondary amines to afford the corresponding amides. The Marshall linker has been used in the synthesis of three or more diversity-site libraries because it allows the addition of one more diversity element at the cleavage step. While the original report[3] on the Marshall linker involved the oxidation of the linker before cleavage, the efficient release of the resin-bound compounds using nucleophiles from the unoxidized linker has been reported.[4−7] We employ parallel solid-phase synthesis methods to make lead discovery libraries containing ∼5000 compounds in each library. Marshall resin has been used widely in our combinatorial syntheses.[4,5]

We have reported a cleavage kinetics study using trifluoroacetic acid (TFA) for a range of acid-labile linkers.[6] In this paper, we report our study on the kinetics of amine cleavage reactions of various thiophenol esters from the Marshal linker.

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Results and Discussion

Synthesis of Resin-Bound Thiophenol Esters. Resin-bound thiophenol esters were synthesized according to the first step in Scheme 1. Resins **3a**−**c** were made from aromatic acids, while resins **3e**−**g** were made from alkyl acids and resin **3d** was made from benzimidazolecarboxylic acid (Chart 1). All seven resin-bound thiophenol esters showed a characteristic phenol ester carbonyl band at 1740−1760 cm^{-1} in the FTIR spectra (Table 1), which confirmed the formation of thiophenol esters on the beads. This phenol ester carbonyl band serves as an indicator for the study of cleavage reactions (second step) with three amines (Chart 2). These resins have a loading of ∼1.03 mmol/g based on the loading of the initial resin (by sulfur elemental analysis) and the evidence of the completion of the coupling reaction (by negative phenol test; see Experimental Section). No decomposition of these resins was found after 4 months as determined by single-bead FTIR.

Cleavage of Resin-Bound Thiophenol Esters with *n*-Butylamine. The reactivity of seven resin-bound thiophenol esters toward *n*-butylamine varied depending on their structures. The reaction of aromatic thiophenol esters (resins **3a**−**c**) took about 24 h to complete, as indicated by the complete disappearance of the carbonyl band in single-bead FTIR spectra. On the other hand, the same reaction with alkyl thiophenol esters (resins **3e**−**g**) went to completion in less than 8 h. The reaction with benzimidazolecarboxylic thiophenol ester (resin **3d**) was the fastest, finishing in 3 h.

Single-bead FTIR spectra of resin **3g** at various times during the *n*-butylamine cleavage reaction are shown in Figure 1A. The HPLC/UV_{214nm} chromatograms of the cleaved product in solution at various times are shown in Figure 1B. The cleaved product was identified by LC/UV/MS based on its mass. The peak area of the carbonyl band at 1750 cm^{-1} and the peak area of the product in the UV chromatogram at various times were integrated and plotted against time

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Scheme 1. Thiophenol Ester Formation and Amine Cleavage Reaction Scheme

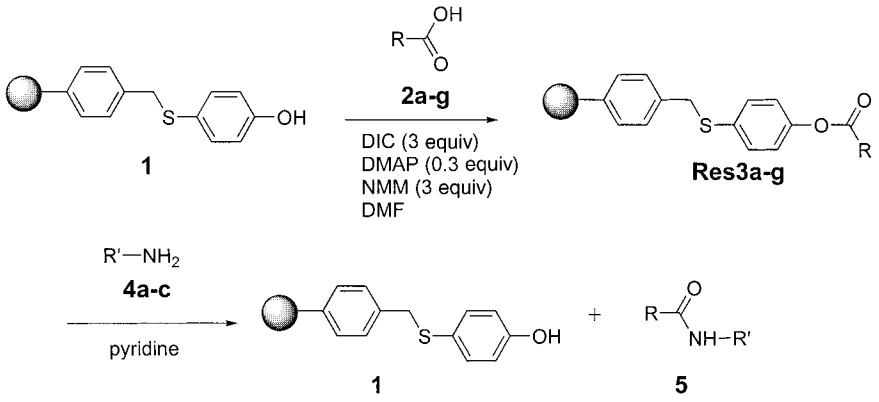


Chart 1. Structures of Seven Resin-bound Thiophenol Esters

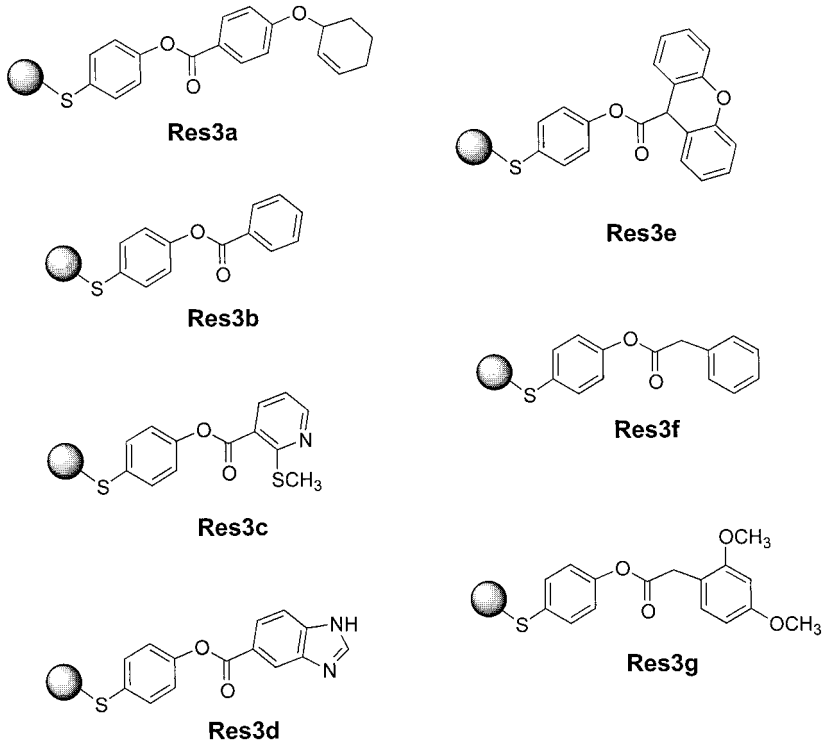
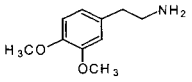
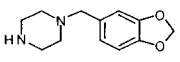


Table 1. Summary of IR Characteristics and Rate Constants

			Rate constant ($x10^{-6}$)		
		O=C str. (1/cm)			
Aryl esters	res3a	1740	10.4	4.1	1.9
	res3b	1744	30.9	17.9	4
	res3b 20oC	1744	30.9		
	res3b 40oC	1744	65.7		
	res3b 60oC	1744	126.1		
	res3b Ox	1744	17900		
	res3c	1735	47.8	29.7	1.2
Alkyl esters	res3e	1757	269.9	102.3	4.9
	res3f	1757	356.8	156.6	6
	res3g	1760	541.3	230.8	15.5
Benzimidazole ester	res3d	1757	1341.3	438.9	11.8

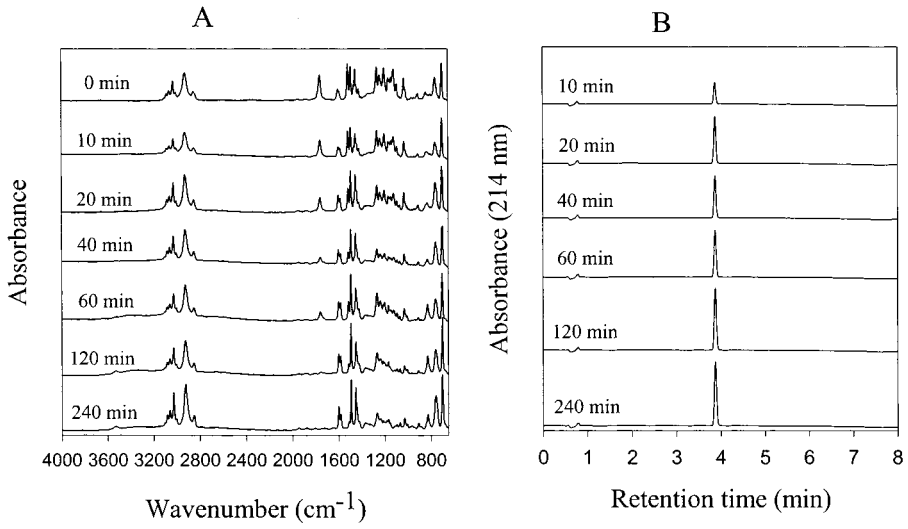


Figure 1. Single-bead FTIR spectra (A) and HPLC/UV chromatograms (B) of resin **3g** at various times during the *n*-butylamine cleavage reaction.

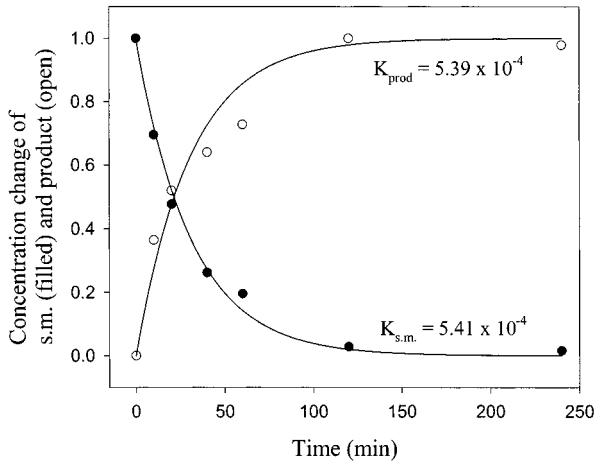
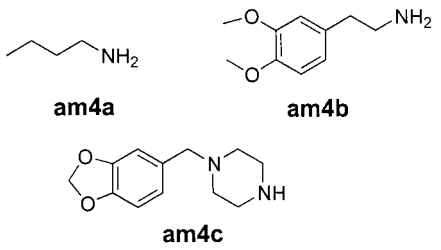


Figure 2. Cleavage time courses and pseudo-first-order best fit for single-bead FTIR (●) and HPLC/UV analysis (○).

Chart 2. Structures of Three Cleavage Amines



(Figure 2). Both time courses were analyzed by curve-fitting statistics and were found to fit well to a pseudo-first-order rate equation. The calculated rate constant, 5.41×10^{-4}, was obtained from single-bead FTIR analysis by direct on-bead monitoring of the disappearance of starting material. The calculated rate constant, 5.39×10^{-4}, was obtained from HPLC analysis by monitoring the formation of product in solution. Even though this reaction could be monitored by both methods, the single-bead FTIR method had the advantage of speed and convenience over HPLC/UV or LC/UV/MS for the study of reaction kinetics.

Peak area integration and kinetics analysis procedures were applied to all resins that underwent cleavage reactions. All data sets fit a pseudo-first-order kinetics. The calculated rate constants are 1.04×10^{-5}, 3.09×10^{-5}, 4.78×10^{-5}, 134.1×10^{-5}, 26.99×10^{-5}, 35.68×10^{-5}, and 54.1×10^{-5} (Table 1) for resins **3a**−**3g**. The *n*-butylamine cleavage time courses of all esters from single-bead FTIR analysis and the best fit with pseudo-first-order rate constants are shown in the first column of Figure 3.

When *n*-butylamine was used for cleavage, the rates of the alkyl thiophenol esters were approximately 13 times faster than the rates of the aromatic thiophenol esters. The rates of benzimidazolecarboxylic thiophenol esters were 45 times faster than the rates of aromatic thiophenol esters and 3 times faster than the rates of the alkyl thiophenol esters.

Cleavage with 3,4-Dimethoxyphenethylamine. The reactivity of seven resin-bound thiophenol esters toward 3,4-dimethoxyphenethylamine is consistent with the trend seen in *n*-butylamine cleavage reactions, i.e., benzimidazole > alkyl > aromatic. However, it is clear that the cleavage reaction with 3,4-dimethoxyphenethylamine was slower than that with *n*-butylamine for the same esters.

Samples were analyzed by single-bead FTIR as described above. Data sets were fitted well to a pseudo-first-order kinetics. The calculated rate constants are 4.11×10^{-6}, 17.91×10^{-6}, 29.67×10^{-6}, 438.9×10^{-6}, 102.3×10^{-6}, 156.59×10^{-6}, and 230.8×10^{-6} (Table 1) for resins **3a**−**g**. The cleavage time courses for all seven esters and the their pseudo-first-order kinetics fit are shown in the second column of Figure 3.

The rate constant for the same resin-bound thiophenol esters with 3,4-dimethoxyphenethylamine was decreased by 2- to 3-fold compared to that with *n*-butylamine. The rate constant of benzimidazolecarboxylic thiophenol ester was 25 times higher than that of aromatic thiophenol esters and 3 times higher than that of the alkyl thiophenol esters.

Cleavage with 1-Piperonylpiperazine. The reactivity of seven resin-bound thiophenol esters toward 1-piperonylpiperazine was much lower than that seen with *n*-butylamine but still had the same trend. The reaction of aromatic thiophenol esters (resins **3a**−**c**) did not go to completion after 48 h, as indicated by the substantial amount of carbonyl band in FTIR spectra (only 20−50% completion). The same

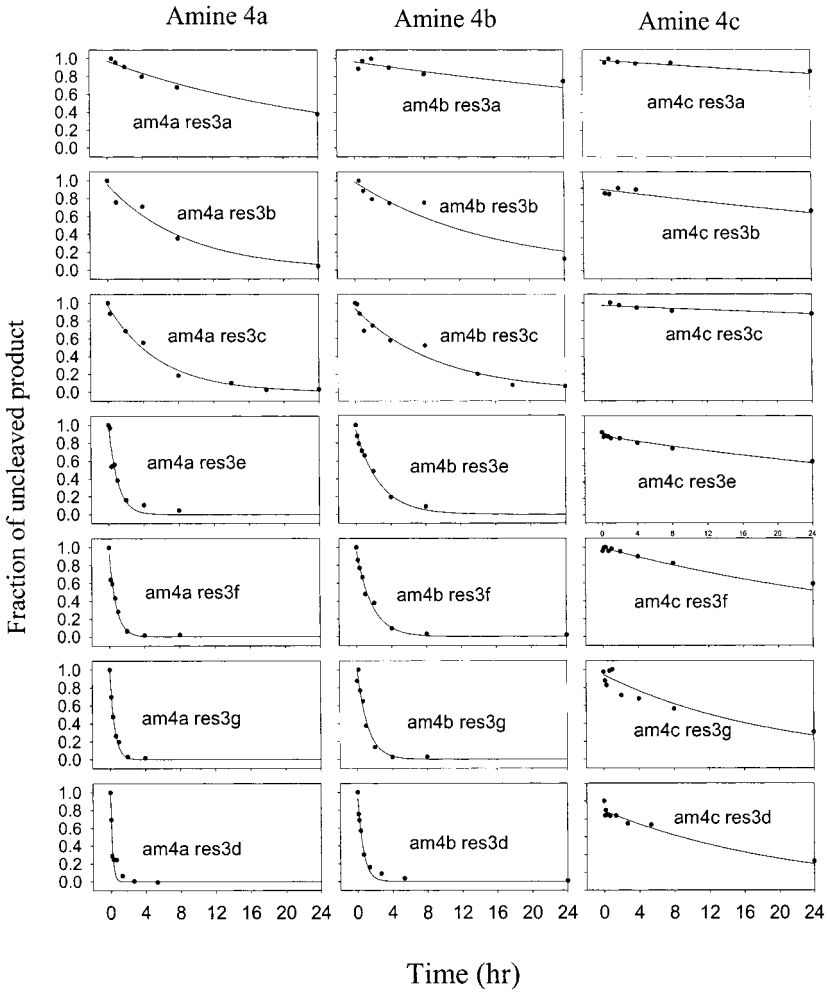


Figure 3. Cleavage time courses of all 21 cleavage reactions during a 24 h period and their pseudo-first-order best fit (lines).

reaction for alkyl thiophenol esters (resins **3e**−**g**) went to 70−90% completion during the same time period. The reaction of benzimidazolecarboxylic thiophenol ester (resin **3d**) went to 90% completion in 48 h.

All seven reactions fitted well to a pseudo-first-order kinetics from single-bead FTIR analysis of the carbonyl band disappearance. The calculated rate constants are 1.89×10^{-6}, 3.95×10^{-6}, 1.17×10^{-6}, 11.79×10^{-6}, 4.87×10^{-6}, 6.04×10^{-6}, and 15.53×10^{-6} (Table 1) for resins **3a**−**g**. Their cleavage time courses and the pseudo-first-order kinetics fit are shown in the third column of Figure 3.

From examination of the data in Table 1, it is evident that the cleavage reaction with amine **4c**, 1-piperonylpiperazine, was the slowest among all three amines for the same ester. The calculated rate constants of the alkyl, aromatic, and benzimidazole esters with amine **4c** were decreased by 10-, 50-, and 100-fold compared to those with *n*-butylamine. The relative rate constants of three ester groups with amine **4c** are 1, 4, and 5 for aromatic, alkyl, and benzimidazole esters, respectively. However, these relative rate constants with amine **4a** are 1, 13, and 45. This difference might be attributed to a leveling effect when the reaction rate was substantially decreased in the case of 1-piperonylpiperamine.

Effect of Temperature on Cleavage Reaction. The rate of a chemical reaction depends on temperature. A useful rule of thumb for many organic reactions in solution is that a 10 °C change in temperature causes a 2- to 3-fold change in the rate of reaction.[8] To study the temperature dependence of solid-phase reactions, the cleavage reaction of resin **3b** with *n*-butylamine at 40 and 60 °C was carried out in an oven with a rotating plate. Single-bead FTIR spectra of resin **3b** at various times during *n*-butylamine cleavage at 20, 40, and 60 °C are shown in parts A, B, and C of Figure 4, respectively. The cleavage time courses and pseudo-first-order rate fits at these three temperatures are shown in Figure 5.

The rate constants from single-bead FTIR analysis are 3.09×10^{-5}, 6.57×10^{-5}, and 12.6×10^{-5} (Table 1) at 20, 40, and 60 °C, respectively. Therefore, compared to the reaction at 20 °C, the solid-phase cleavage reaction of resin **3b** is 2 times faster at 40 °C and 4 times faster at 60 °C.

Cleavage Rate Dependence on the Oxidation State. According to Marshall[3] and Beech,[7] the oxidation of the thiophenol linker will increase the reaction rate. To study this effect, the sulfide group of resin **3b** was oxidized using *m*-CPBA. The single-bead FTIR of oxidized resin **3b** (resin **3b-OX**) shows many new bands in the fingerprint region of the spectrum (Figure 6). One band at 1084 cm^{-1} corresponds to the S═O stretch for sulfoxide, and bands at 1127, 1157, 1295, and 1323 cm^{-1} can be assigned to asymmetric and symmetric stretches of S═O in sulfone. We conclude that the oxidation reaction resulted in a mixture of sulfoxide and

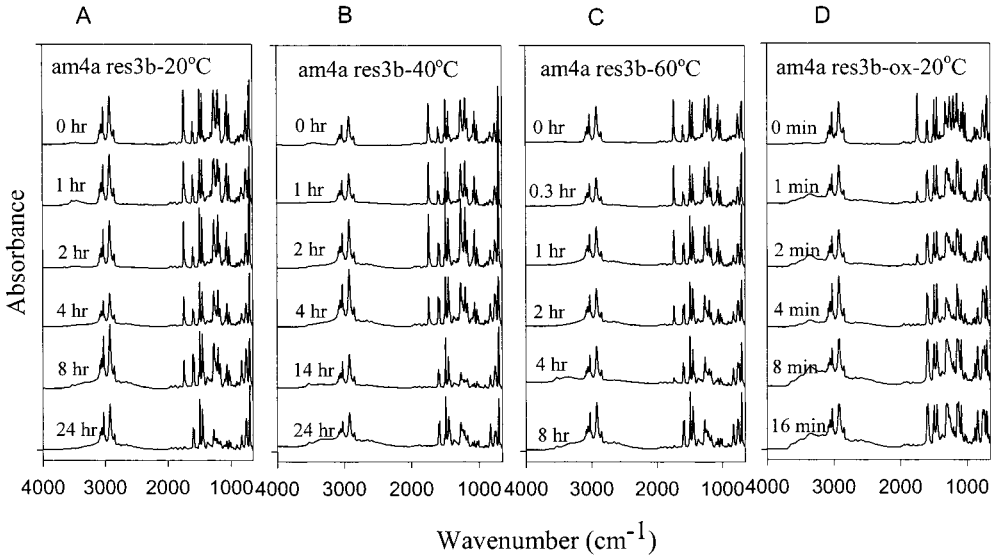


Figure 4. Single-bead FTIR spectra of resin **3b** at 20 °C (A), 40 °C (B), and 60 °C (C) and resin **3b-OX** (D) at various times during the *n*-butylamine cleavage reactions.

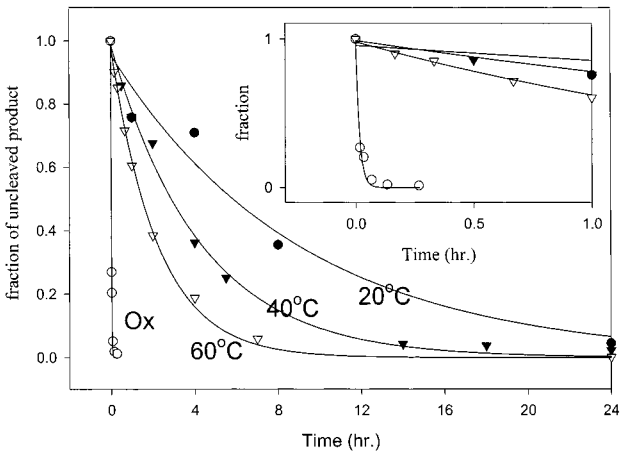


Figure 5. Cleavage time courses of resin **3b** at 20 °C (●), 40 °C (▼), and 60 °C (▽) and resin **3b-OX** (○) during a 24 h period and their pseudo-first-order best fit (lines).

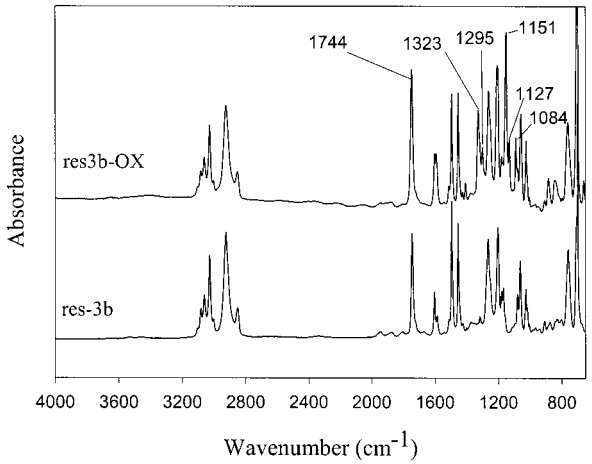


Figure 6. Single-bead FTIR spectra of resin **3b** and resin **3b-OX**.

sulfone on the resin. The ester compound on the resin was not affected by the oxidation reaction, as shown by the relative carbonyl intensity in both resins. The product on the oxidized resin was not decomposed after a period of 4 months, as characterized by single-bead FTIR study.

Cleavage reaction of resin **3b-OX** with *n*-butylamine went to completion in less than 4 min (Figure 4D) compared with 24 h needed for resin **3b** under the same conditions (Figure 4A). The rate constant was determined to be 0.0179, which was a 580-fold increase compared to that of the unoxidized form.

The significant increase in reactivity of resin **3b-OX** toward nucleophilic cleavage could be attributed to the strong electron-withdrawing property of the sulfone/sulfoxide group in the linker.

Stability of Resin-Bound Products. To understand the stability of resin-bound products during the study period (1 month), we carried out an FTIR study of all resins. Resins **3a**−**g** and oxidized **3b** were stored at room temperature for 4 months. Their single-bead FTIR spectra were taken and analyzed for the product peak intensity relative to the polystyrene internal reference peak at 1947 cm^{-1}. Data showed that no product decomposition was detected and that all resins were stable at room temperature.

Conclusions

The kinetics of cleavage reactions of seven resin-bound thiophenol esters with three amines has been studied. The reaction rate of these esters with various amines varied and could be divided into three groups based on their chemical structures: alkyl thiophenol esters (resins **3e**−**g**), aromatic thiophenol esters (resins **3a**−**c**), and 5-benzimidazolecarboxylic thiophenol ester. The calculated rate constants of alkyl thiophenol esters were almost 13 times higher than those of aromatic thiophenol esters. The 5-benzimidazolecarboxylic thiophenol ester was even more reactive than alkyl thiophenol esters. The cleavage rate could be summarized as follows: 5-benzimidazolecarboxylic thiophenol ester > alkyl thiophenol esters > aromatic thiophenol esters. The reactivity of the same resin-bound thiophenol esters with three amines varied as follows: *n*-butylamine > 3,4-dimethoxyphenethylamine > 1-piperonylpiperamine.

The investigation of reactivity on temperature has shown a 2-fold increase per 10 °C rise in reaction temperature. The

investigation of reactivity on the oxidation state of the thiophenol linker has indicated a 580-fold increase by oxidizing sulfide to sulfone/sulfoxide group. This study has also demonstrated that single-bead FTIR is a very powerful method for the optimization of reaction conditions in combinatorial chemistry.

Experimental Section

1. Materials. All chemicals and solvents were purchased from Aldrich (Milwaukee, WI). Resins were made by solid-phase organic synthesis.

1.a. Synthesis of Resin-Bound Thiophenol Esters 3a−g. A solution of carboxylic acids (18 mmol, 3 equiv) in dimethylformamide (30 mL) was treated with 1,3-diisopropylcarbodiimide (2.27 g, 18 mmol, 3 equiv) and shaken for 15 min. Marshall resin (5.0 g, 1 equiv, 6 mmol) was added, followed by *N*-methylmorpholine (1.82 g, 18 mmol, 3 equiv) and DMAP (0.22 g, 1.8 mmol, 0.3 equiv). The suspensions were shaken on a reciprocal shaker overnight, transferred to a coarse-fritted funnel, and washed according to the following sequence: DMF (×2), methanol (×2), DMF (×2), methanol (×2), dichloromethane (×2), ethanol (×2), and ether (×2). The resins were dried under house vacuum and stored under nitrogen. The loading of the starting resin was 1.03 mmol/g as determined by sulfur elemental analysis. The formation of **3a−g** was complete as shown by a negative phenol test using $FeCl_3$ solution as described in the next section.

1.b. Qualitative Iron Chloride−Pyridine Test for Phenol. An amount of 25−50 mg of resins **3a−g** was transferred to labeled 6 mL Supelco tubes and about the same amount of thiophenol and polystyrene resins to tubes labeled "+Control" and "−Control". A saturated solution of ferric chloride was prepared in chloroform by weighing out 81 mg of ferric chloride into a 15 mL Falcon tube, then adding chloroform to give a final volume of 5 mL. The tubes were replaced on a Supelco vacuum box, then each resin was washed three times with DCM. Enough DCM was added to suspend the resin, then 5 drops of pyridine were added to each tube. Ten drops of the ferric chloride solution were added to each tube and stirred with a clean spatula. The resins were drained and then washed five times with DCM. The resins were examined. A blue or purple color is a positive indication of free phenol. The thiophenol resin should be positive. The polystyrene resin should be negative.

1.c. Oxidation of Resin-Bound Thiophenol Ester (Resin 3b-OX). A 0.5 M solution of *m*-chloroperbenzoic acid (*m*-CPBA is a strong oxidizer and potentially explosive when highly purified) in dichloromethane was prepared using the lowest purity reported on the *m*-CPBA label. This solution was dried over $MgSO_4$ and filtered. To a scintillation vial containing resin **6** (0.5 g, 0.6 mmol) from the procedure in section 1.a was added the above solution (3.5 mL, 17.5 mmol, 3 equiv). (Addition of the *m*-CPBA solution is exothermic.) The vial was capped and allowed to stand for 30 min. The resin was transferred to a coarse-fritted funnel and was immediately washed with the following sequence of solvents: methanol (×2), dichloromethane (×3), pyridine (×3), and ether (×3). The resins were dried under house vacuum and stored under nitrogen.

2. Resin Cleavage Reaction with *n*-Butylamine. The resin beads (10.0 mg, 0.01 mmol) was placed in a fritted reaction syringe (1.5 mL), and anhydrous pyridine (150 μL) was added to swell the resin beads for 30 min. After the removal of solvent, *n*-butylamine in anhydrous pyridine (150 μL, 54 μL of *n*-butylamine in 1.5 mL of anhydrous pyridine, 5 equiv) was added to start the reaction. A total of 6−10 such reaction syringes were prepared to ensure sufficient time points for a reliable kinetics study. These syringes were sealed and placed on a rotator. Individual reactions were stopped at the desired reaction time intervals. The cleavage mixture was collected in a 10 cm × 13 cm test tube, followed by the removal of pyridine under vacuum, and was reconstituted into methanol (300 μL). Since the concentrations of these samples were very high for LC/UV/MS analysis, it was necessary to further dilute them by a factor of 10−30 to keep measurements at all time points within the linear range of UV absorbance. These resin beads were washed with DCM (×3) and dried for single-bead FTIR analysis.

3. Resin Cleavage Reaction with 3,4-Dimethoxyphenethylamine. 3,4-Dimethoxyphenethylamine in anhydrous pyridine (150 μL, 93 μL of 3,4-dimethoxyphenethylamine in 1.5 mL of anhydrous pyridine, 5 equiv) was used in the reaction instead of *n*-butylamine. Everything else was the same as described above.

4. Resin Cleavage Reaction with 1-Piperonylpiperamine. 1-Piperonylpiperamine in anhydrous pyridine (150 μL, 121 mg of 1-piperonylpiperamine in 1.5 mL of anhydrous pyridine, 5 equiv) was used in the reaction instead of *n*-butylamine. Everything else was the same as described above.

5. Resin 3b Cleavage Reaction with *n*-Butylamine at 40 and 60 °C. Resin beads (10.0 mg, 0.01 mmol) were allowed to swell in anhydrous pyridine (150 μL) for 30 min in a rotator oven set at 40 °C for each reaction syringe. After the removal of solvent, *n*-butylamine solution (150 μL, 54 μL of *n*-butylamine in 1.5 mL of anhydrous pyridine, 5 equiv) was added to initiate the reactions. These syringes were sealed and placed on the 40 °C rotator oven for the duration of their reactions. Reactions were stopped at 0.5, 1, 2, 4, 5.5, 14, 18, and 24 h, and resin beads were washed and dried for single-bead FTIR analysis.

For the 60 °C cleavage, the rotator oven was set at 60 °C. Everything else was the same as described above. Reactions were stopped at 10, 20, 40 min and 1, 2, 4, 7, and 24 h.

6. Single-Bead FTIR Microspectroscopy and Data Analysis. 6.1. Single-Bead FTIR Method. FTIR spectra were collected on a Nicolet Nexus 670 with a continuum microscope, using OMNIC software. The microscope is equipped with a 15× Cassegrain objective and a liquid nitrogen-cooled mercury−cadmium−telluride (MCT) detector. The view mode aided in locating a single bead. The transmission mode was used for the whole-bead measurement. Beads flattened with a diamond window (SpectraTech, Shelton, CT) were used for all experiments in transmission mode. A clean diamond window (SpectraTech, Shelton, CT) was used to collect the background spectrum. Data were collected at 4 cm^{-1} resolution, and 32 scans were averaged

for each beads. Ester carbonyl stretch data for all resins were listed in Table 1.

6.2. Data Analysis. IR spectra were normalized by making the intensities of a polystyrene band at 1947 cm^{-1} equal. The areas under the specific band of the starting material were integrated and used for the calculation of the percentage conversion. Average integrated peak areas from three to five beads were plotted against time for kinetics analysis. These data points were fitted to a pseudo-first-order rate equation by using SigmaPlot (Jandel Scientific, San Rafael, CA) on a PC.

6.3. HPLC/UV Analysis. HPLC separation was performed on a HP1100 system (Hewlett-Packard, Palo Alto, CA), which consists of a vacuum degasser, binary pump, autosampler, column compartment, and diode array detector. Data were processed by HP Chemstation software.

Reversed-phase HPLC was carried out on a C18 column (3.0 mm × 100 mm, 5 μm, 100A) from Phenomenex (Phenomenex, Torrance, CA) at 40 °C with a flow rate of 1.0 mL/min. Two mobile phases (mobile phase A, 99% water, 1% acetonitrile, 0.05% TFA; mobile phase B, 1% water, 99% acetonitrile, 0.05% TFA) were employed to run a gradient condition from 0% B to 100% B in 6.0 min followed by running 100% B for 2.0 min and reequilibrating at 0% B for 2.0 min. An injection volume of 10 μL was used.

6.4. LC/UV/MS Analysis. LC/UV/MS was performed using a PE Sciex (Concord, Ontario, Canada) model API 150 EX single-quadrupole mass spectrometer equipped with a turbo ion spray ionization interface. The HPLC system consisted of a Gilson 215 liquid handler equipped with an 819 injection valve (Middleton, WI), a HP1100 vacuum degasser, binary pump, column compartment, and a diode array detector (Hewlett-Packard, Palo Alto, CA)**.** Reversed-phase HPLC was carried out on a Luna C18 column (2.0 mm × 30 mm, 5 μm, 100A) from Phenomenex (Phenomenex, Torrance, CA) at 40 °C with a flow rate of 3.0 mL/min. Two mobile phases (mobile phase A, 99% water, 1% acetonitrile, 0.1% acetic acid; mobile phase B, 1% water, 99% acetonitrile, 0.1% acetic acid) were employed to run a gradient condition from 10% B to 100% B in 3.0 min followed by staying at 100% B for 0.5 min and reequilibrating for an additional 0.5 min.

The signal from UV_{214} was collected through a PE Nelson 900 series interface to a Mac computer using MassChrom 1.1 at a rate of 50 data points per second. All peak areas and their qualitative peak purity were processed in MultiView 1.4.

References and Notes

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