Article

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J. Comb. Chem., **2000**, 2 (1), 66-74• DOI: 10.1021/cc990051w • Publication Date (Web): 30 November 1999

Kinetic Comparison of Trifluoroacetic Acid Cleavage Reactions of Resin-Bound Carbamates, Ureas, Secondary Amides, and Sulfonamides from Benzyl-, Benzhydryl-, and Indole-Based Linkers

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Received September 2, 1999

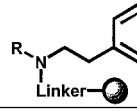
The kinetics of cleavage reactions of 16 resin-bound carbamates, ureas, secondary amides, and sulfonamides from four different acid labile linkers including benzyl, benzhydryl, and indole linkers has been investigated. The optimized cleavage conditions are generally milder than those commonly used and reported (e.g., 0.5% TFA as opposed to 5%). Among various linkers studied in this work, the indole linker has been found to be the most acid labile followed by the Rink linker. The rate of cleavage of compounds linked to the resin via various functional groups can be summarized as follows: sulfonamide >carbamate ∼ urea > amide. This study shows that cleavages of 16 compounds from four different acid labile linkers have been optimized to much milder conditions in terms of TFA concentration and the reaction time. It also demonstrates that single bead FTIR is an effective tool for optimizing cleavage conditions.

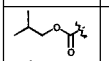
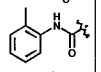
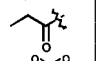
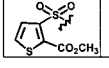
Introduction

Combinatorial chemistry[1] promises to synthesize more well-defined and structurally diverse compounds at an accelerated rate. Solid-phase organic synthesis (SPOS)[2a−d] has become a major methodology for synthesizing small molecule combinatorial libraries, although solution-phase methodologies have also been developed.[2e] However, the time-consuming task in the development of solid-phase methodologies is the optimization of reaction conditions for resin loading, intermediate synthetic steps, and the cleavage of desired compounds from solid support. Compound library synthesis without going through careful optimization procedures tends to give lower yields and higher impurities in the final products. The low-quality libraries will lead to ambiguity and uncertainty in the assay results. Thus, prior reaction optimization of each synthetic step on a chosen solid support becomes imperative.

The successful assembly of organic compounds on a solid support represents only part of the challenge in SPOS. After completion of synthetic sequence, the compounds must be cleaved from a solid support by a chemical or photochemical reaction, for example, treatment of a polymer-bound compound with acids, bases, nucleophiles, redox reagents, and even photons. Too mild of cleavage conditions may lead to incomplete cleavage of the desired compound from a solid support. On the other hand, too harsh of conditions may cause compound degradation and side reactions. Harsh conditions will cause the partial breakdown of resin and the leaching of unidentified impurities into the final products. Harsh cleavage conditions also demand the stability of all compounds under such conditions. This may limit the scope of combinatorial synthesis and the exploration of molecular diversity. Therefore, cleavage strategy[3] is a key element in SPOS, and this necessitates the selection of an optimal linker. In principle, an optimal linker should be stable to a variety of reaction conditions used in a synthesis, should provide an efficient loading of a monomer onto a solid support, and should allow a rapid and efficient cleavage of products under

Table 1[a]



R	Linker (I)	Linker (II)	Linker (III)	Linker (IV)
	**11**, *70*	**12**, *71*	**13**, *67*	**14**, *68*
	**15**, *72*	**16**, *72*	**17**, *77*	**18**, *75*
	**19**, *71*	**20**, *71*	**21**, *75*	**22**, *60*
	**23**, *75*	**24**, *80*	**25**, *83*	**26**, *57*

[a] The numbers in bold represent the organic molecule bound to a polymer through a representative linker. The numbers in italics represent the yield of a compound after the cleavage with 5% TFA at room temperature for 6 h. These cleavages were done before the kinetic analysis of these resins. Products were characterized using NMR and MS. High-resolution ^{1}H NMR (400 MHz) showed that all cleaved crude products were baseline pure.

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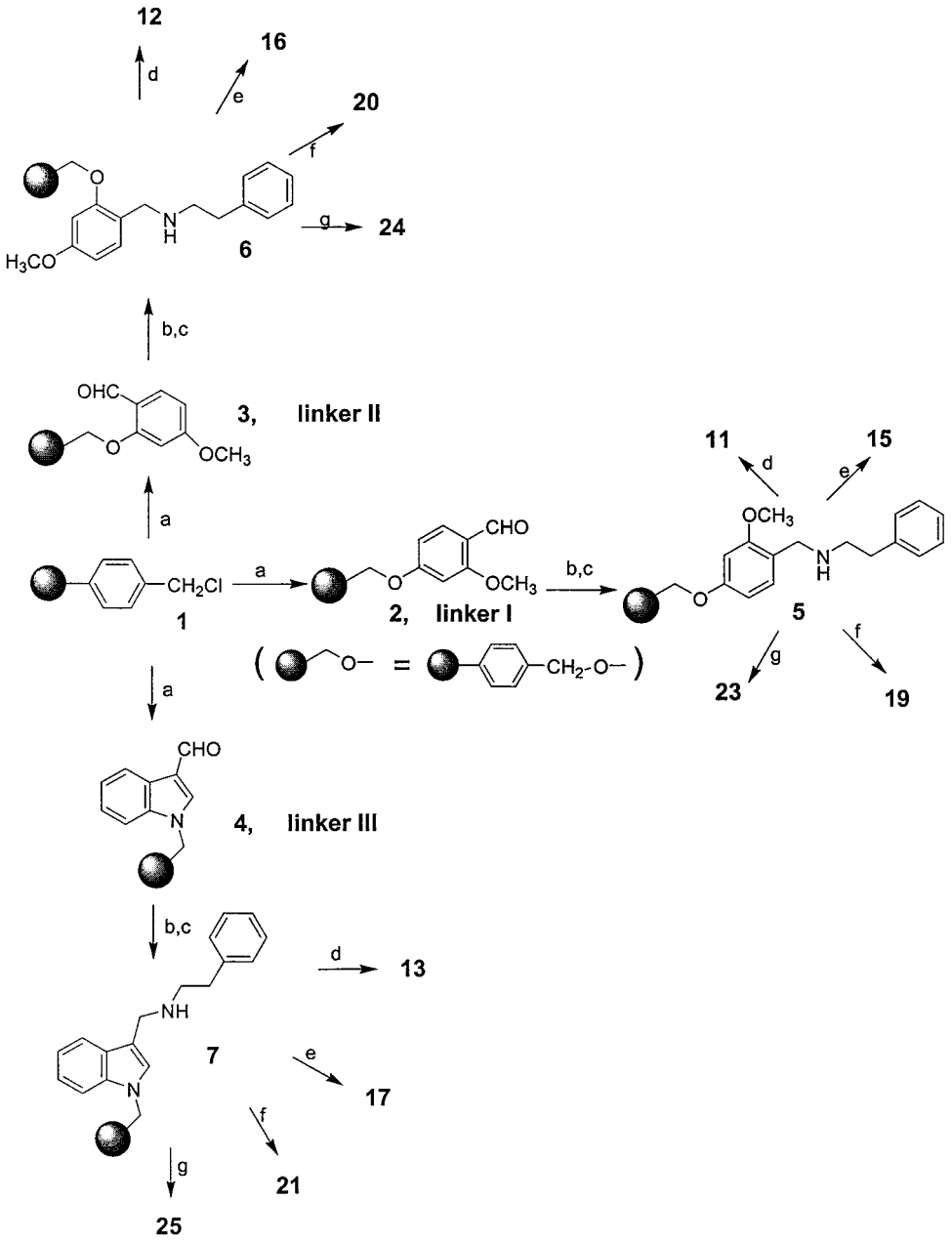
10.1021/cc990051w CCC: $19.00
Published on Web 11/30/1999

Scheme 1[a]



[a] Reaction conditions: (a) 4-hydroxy-2-methoxybenzaldehyde, or 2-hydroxy-4-methoxybenzaldehyde, or indole-3-carboxaldehyde, NaH, DMF; (b) $CH(OMe)_3$, phenethylamine; (c) $NaBH_4$, THF, EtOH; then MeOH reflux; (d) isobutylchloroformate, DIEA, DCM; (e) *o*-tolyl isocyanate, DMF, 60 °C; (f) propionyl chloride, DIEA, NMM, DCM; (g) carbomethoxythiophene-3-sulfonyl chloride, NMM, DCM.

mild conditions with no trace of the linkage. Acid labile linkers which attach a building block through a nitrogen atom have been commonly used in the synthesis of a variety of libraries by using the vast source of reactive building blocks including acid chlorides, sulfonyl chlorides, carboxylic acids, isocynates, and chloroformates.

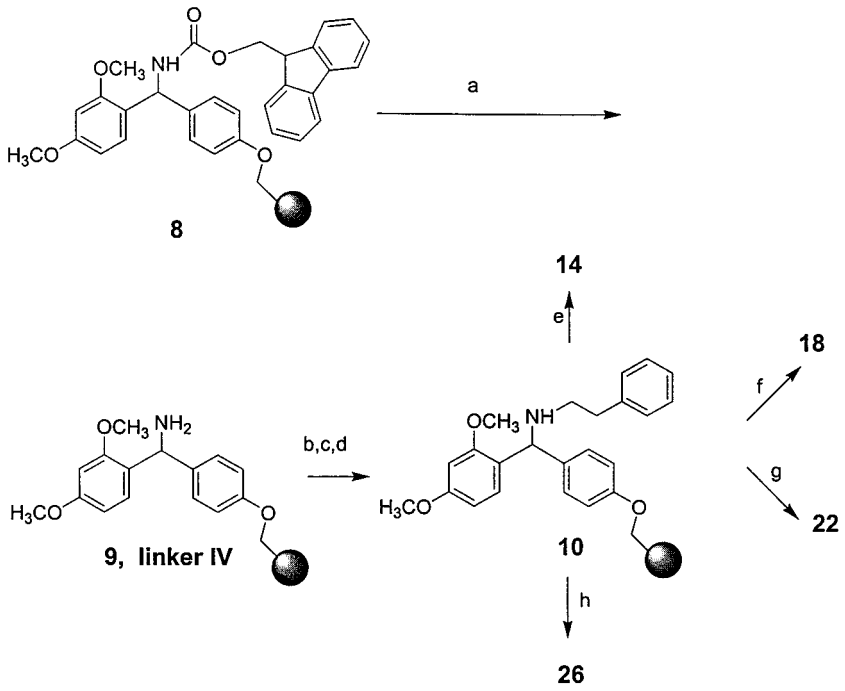
As part of our efforts to optimize SPOS, we recently focused our attention on the investigation of the kinetics of TFA cleavage reactions. A set of carbamates, ureas, secondary amides, and sulfonamides (Table 1) were synthesized, and their cleavage from four different acid labile linkers including benzyl, benzhydryl, and indole linkers was investigated. The kinetics of cleavage reactions of these resin-bound products at various TFA concentrations is described herein.

Results and Discussion

Benzyl-, benzhydryl-, and indole-based linkers have been used in SPOS with a nitrogen atom as an anchoring point. In this work, the assembly of four classes of compounds carbamates, ureas, amides, and sulfonamides on four different linkers and a thorough investigation of the cleavage kinetics of these compounds from polymeric support under various concentration of TFA are reported below.

Synthesis of Resin-Bound Compounds and Reaction Monitoring. The resin-bound aldehydes **2**−**4** (linkers I, II, and III, see Scheme 1) were prepared by reacting Merrifield resin **1** with various aldehydes through the formation of an O− or N−alkyl bond. Rink amide was used to prepare linker IV (Scheme 2). The reductive amination of these resin-bound aldehydes or the amidation and reduction of the Rink amine

Scheme 2[a]



[a] Reaction conditions: (a) 20% piperidine in DMF, rt; (b) phenylacetic acid, DIC, CH_2Cl_2, rt; (c) BH_3 in THF, rt; (d) MeOH, reflux; (e) *o*-tolyl isocyanate, DMF, 60 °C; (f) isobutylchloroformate, DIEA, DCM; (g) propionyl chloride, DIEA, NMM, DCM; (h) carbomethoxythiophene-3-sulfonyl chloride, NMM, DCM.

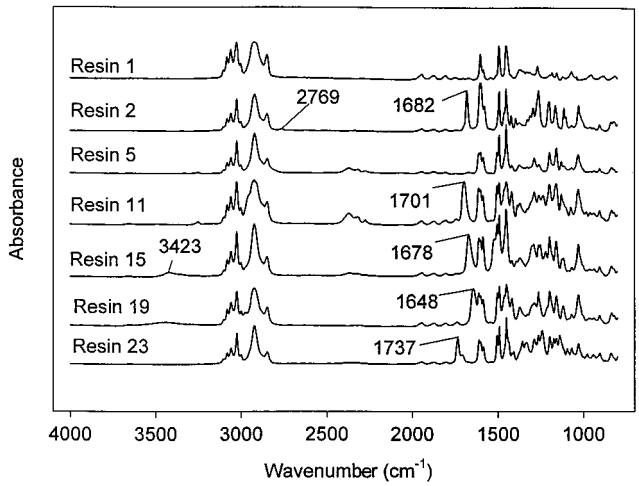


Figure 1. IR spectra of the reaction intermediate and products on linker I (Scheme 1) leading to the formation of **11**, **15**, **19**, and **23**.

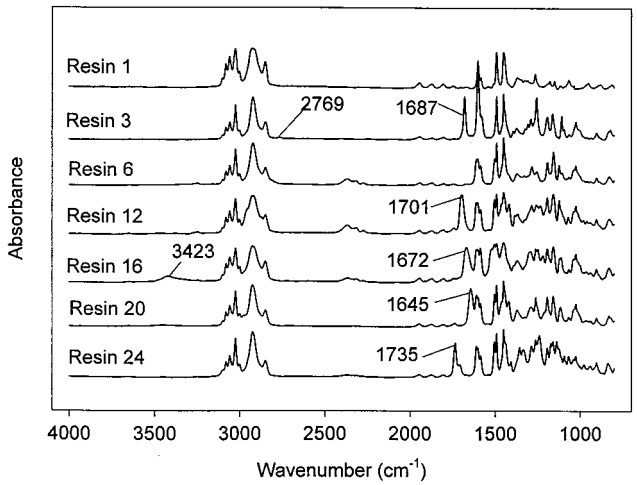


Figure 2. IR spectra of the reaction intermediate and products on linker II (Scheme 1) leading to the formation of **12**, **16**, **20**, and **24**.

produced secondary amines **5**, **6**, **7**, and **10**. They reacted with electrophiles to produce desired products. The monitoring of these synthesis processes is described below.

Synthesis of 11, 15, 19, and 23 on Linker I. Immobilization of 4-hydroxy-2-methoxybenzaldehyde onto Merrifield resin **1** gave **2** (Scheme 1) which was confirmed by the new IR bands at 2769 and 1682 cm^{-1} (Figure 1) attributable to the aldehyde functionality. The quantitative transformation in this step was also determined by combustion elemental analysis of chlorine. The chlorine content of Merrifield resin **1** was 0.97 mmol/g which was diminished to <0.01 mmol/g for the product. The conversion of **2** to **5** was analyzed on resin by single bead FTIR, and quantitative transformation was assessed on the basis of the area integration of the aldehyde IR band at 1682 cm^{-1}. The IR signals at 2273−2373 cm^{-1} in resins **5** and **11** and other resins shown in various figures are from borohydride complexed with resin-bound amine. Finally, the presence of characteristic IR bands of resin-bound products **11**, **15**, **19**, **23** (Table 1) at 1701, 1678, 1648, and 1737 cm^{-1}, respectively, confirmed the formation of desired products (Figure 1).

Synthesis of 12, 16, 20, and 24 on Linker II. On bead FTIR analysis of resin **3** showed characteristic bands pertaining to aldehyde functionality at 2769 and 1687 cm^{-1} which indicates the successful O-alkylation reaction of 2-hydroxy-4-methoxybenzaldehyde with Merrifield resin **1** (Figure 2). Further, as mentioned above, a near-quantitative conversion of chlorine functionality in this step was confirmed by combustion elemental analysis of residual chlorine content in resin **3** (chlorine content 0.01 mmol/g compared to 0.97 mmol/g in resin **1**). The conversion of **3** to **6** was

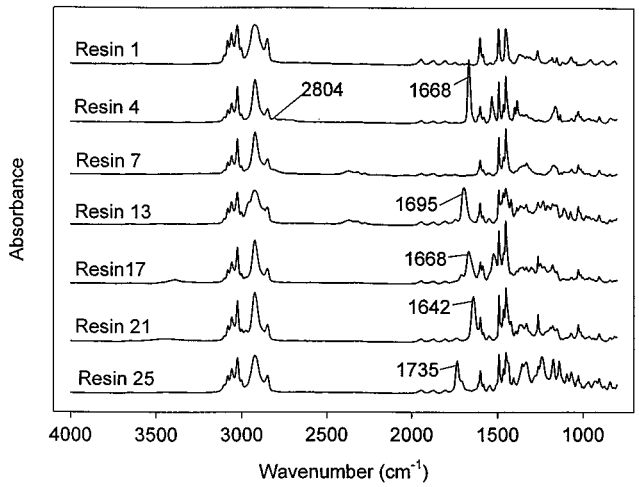


Figure 3. IR spectra of the reaction intermediate and products on linker III (Scheme 1) leading to the formation of **13**, **17**, **21**, and **25**.

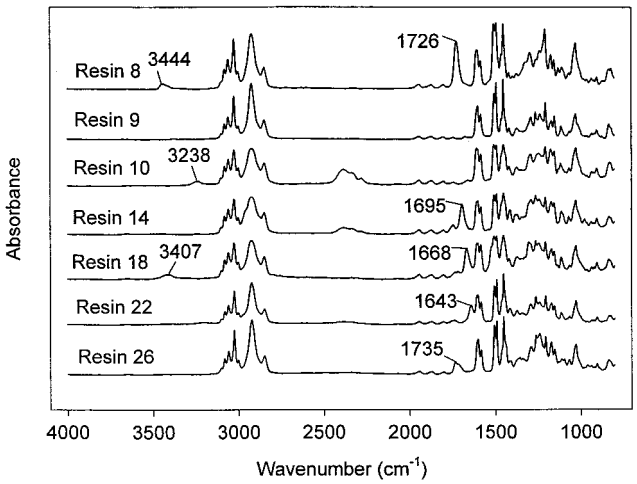


Figure 4. IR spectra of the reaction intermediate and products on linker IV (Scheme 2) leading to the formation of **14**, **18**, **22**, and **26**.

confirmed on resin by single bead FTIR as indicated by complete disappearance of the aldehyde carbonyl band at 1687 cm^{-1}. The synthesis of **12**, **16**, **20**, and **24** was confirmed by observing IR bands of products at 1701, 1672, 1645, and 1735 cm^{-1}, respectively.

Synthesis of 13, 17, 21, and 25 on Linker III. N-Alkylation of indole-3-carboxaldehyde with Merrifield resin **1** (Scheme 1) gave **4** which was confirmed by the new IR bands at 2804 and 1668 cm^{-1}, both bands attributable to aldehyde functionality (Figure 3). Determination of residual chlorine content in resin **4** indicated the nearly quantitative transformation of the chlorine functionality (chlorine content in **4** is 0.04 mmol/g compared to 0.97 mmol/g for resin **1**, 96% of alkylation). The conversion of **4** to **7** was analyzed on resin by single bead FTIR on the basis of the area integration of the aldehyde IR band at 1668 cm^{-1}. Finally, the synthesis of **13**, **17**, **21**, and **25** was confirmed by single bead FTIR by observing characteristic IR bands for products at 1695, 1668, 1642, and 1735 cm^{-1}, respectively.

Synthesis of 14, 18, 22, and 26 on Linker IV. The complete removal of Fmoc group in **8** gave **9**. The reaction was monitored using the single bead FTIR by observing the total disappearance of the Fmoc carbonyl band at 1726 cm^{-1} (Figure 4). The complete conversion of **9** to **10** was monitored by Kaiser test and the formation of a N−H vibration band. The synthesis of **14**, **18**, **22**, and **26** was confirmed by single bead FTIR by observing IR bands of products at 1695, 1668, 1643, and 1735 cm^{-1}, respectively.

The high-resolution (400 MHz) NMR showed that all cleaved crude products were baseline pure in ^1H NMR and the yields of the 16 cleaved products were determined to be ∼70 wt %. Since the TFA cleavage step was quantitative as monitored by the single bead FTIR method, these yields may suggest that the lower reactivity of resin-bound secondary amines **5**, **6**, **7**, and **10** may have prevented reactions from completion. Another possibility points to the reductive amination step in which, although the imine formation is quantitative as indicated by IR (Figure 1−3), the reduction efficiency could not be quantitatively monitored.

TFA Cleavage of Resin-Bound Products for IR Analysis. Resins were briefly swollen by suspending in DCM for 15 min. After the solvent was drained, 1% TFA (or other concentration of TFA) in DCM was added to the resin and the mixture was mixed on a rotator. In nearly all cases, the cleavage was visualized by observing the color change on resin. Depending on the compound on resin, the color ranged from light pink to deep purple or dark brown when the cleavage occurred.

Cleavage of Carbamates 11−14 from Various Linkers. Resins **11**−**14** (∼30 mg each) reacted with 1% TFA in DCM. A droplet of suspension was taken at various time intervals for single bead FTIR analysis after washing. Resin **12** underwent about 50% cleavage after 3 h while resin **13** underwent 95% cleavage in 1 min. Conditions were further refined by using 5% TFA for resin **12** and 0.5% TFA for resin **13** (Figure 5). The area of the carbonyl bands for **11**−**14** at various times was integrated after a peak deconvolution procedure using a PeakFit program (Jandel Scientific, San Rafael, CA). The integration data were plotted against time (Figure 9 A−D). The data were also fitted to a first-order reaction rate equation, and rate constants were determined to be 1.2×10^{-4} (1% TFA), 4.8×10^{-3} (5% TFA), 6.5×10^{-3} (0.5% TFA), and 3.4×10^{-2} s^{-1} (1% TFA) for resins **11**−**14**, respectively.

Since the first-order reaction model was established for cleavage reactions by curve-fitting analysis, two advantages for data analysis are evident. First, an experiment with less data points can now be analyzed by simply examining the match between data points and the theoretical time course based on the first-order reaction model, although more data points will improve the accuracy. Second, it is no longer necessary to take data points all the way until the reaction completes. The curve fitting based on available data points will predict completion time of the reaction.

Cleavage of Ureas 15−18 from Various Linkers. Resins **15** and **16** (∼30 mg each) were treated with 1% TFA in DCM, and the more acid labile resins **17** and **18** (∼30 mg each) were treated with 0.5% TFA (Figure 6). The cleavage of **17** and **18** in 1% TFA took less than 2 min. The IR peak area for urea carbonyl was integrated and plotted against time (Figure 9E−H). The time course was fitted to a first-order reaction rate equation, and rate constants were determined

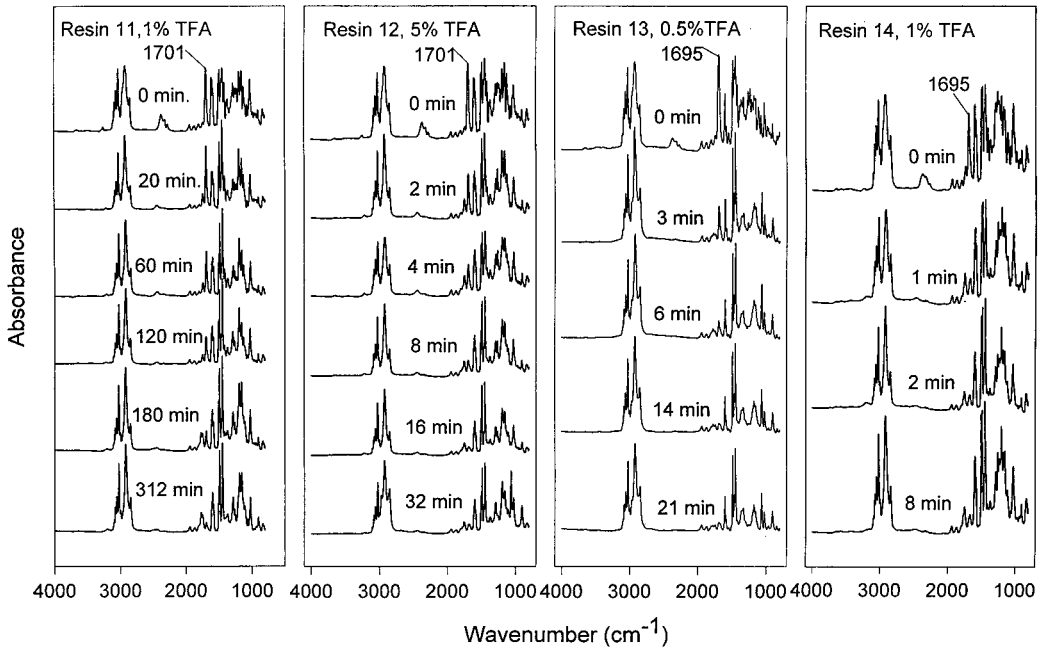


Figure 5. Single bead IR spectra of resins **11**, **12**, **13**, and **14** at various times during the TFA cleavage reaction.

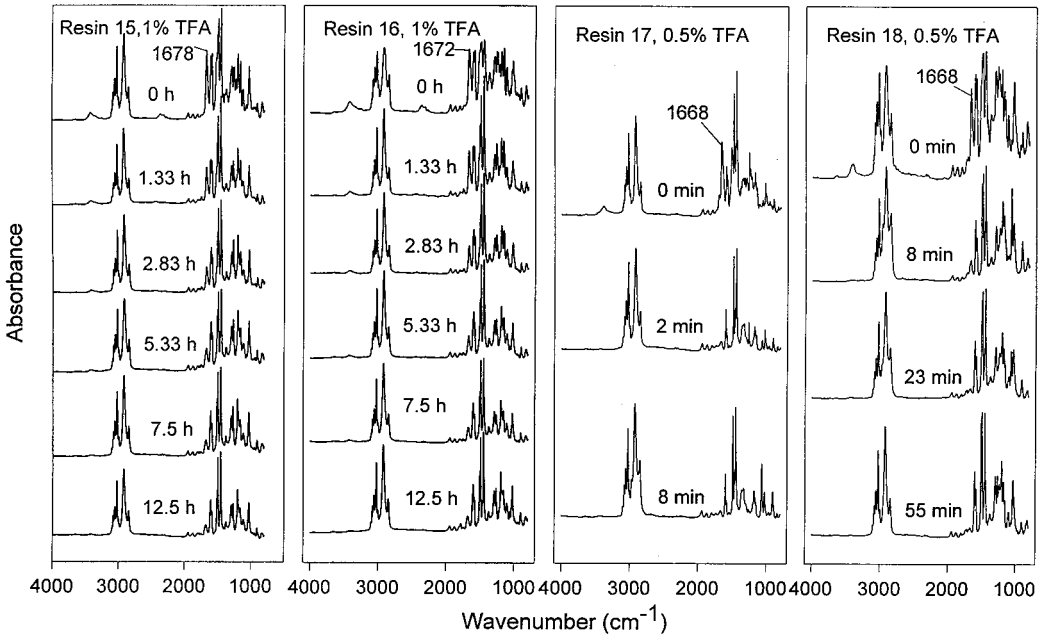


Figure 6. Single bead IR spectra of resins **15**, **16**, **17**, and **18** at various times during the TFA cleavage reaction.

to be 1.2×10^{-4} (1% TFA), 9.5×10^{-5} (1% TFA), 3.0×10^{-2} (0.5% TFA), and 2.5×10^{-3} s^{-1} (0.5% TFA) for resins **15**−**18**, respectively.

Cleavage of Secondary Amides 19−**22 from Various Linkers.** When resins **19**−**22** (∼30 mg each) were reacted with 1% TFA in DCM, the resins **19** and **20** were not cleaved after 24 h while resins **21** and **22** underwent complete cleavage in 8 and 2 h. On the basis of this observation, the resins **19**−**22** were treated with 5% TFA in DCM. Resins **19** and **20** were cleaved in 6−10 h, and resins **21** and **22** were completely cleaved in 8 and 4 min. IR spectra of resins **19** and **20** in 5% TFA and resins **21** and **22** in 1% TFA are shown in Figure 7. The IR peak area for amide carbonyl was integrated and plotted against time (Figure 9I−L). The time course was fitted to a first-order reaction rate equation, and rate constants were determined to be 6.2×10^{-5} (5% TFA), 1.0×10^{-4} (5% TFA), 7.9×10^{-5} (1% TFA), and 3.9×10^{-4} s^{-1} (1% TFA) for resins **19**−**22**, respectively.

Cleavage of Sulfonamides 23−**26 from Various Linkers.** When resins **23**−**26** (∼30 mg each) reacted with 1% TFA in DCM, they were all completely cleaved in 3 min (not shown). These resin-bound compounds were then treated with 0.5% TFA (Figure 8). The IR peak area for sulfonamide carbonyl was integrated and plotted against time (Figure 9M−P). The time course was fitted to a first-order reaction rate equation, and rate constants were determined (at 0.5% TFA for all) to be 4.9×10^{-4}, 2.4×10^{-4}, 4.7×10^{-3}, and 1.4×10^{-4} s^{-1} for resins **23**−**26**, respectively.

Comparison of TFA Cleavage Reactions. To compare the cleavage kinetics of various resin-bound compounds, the

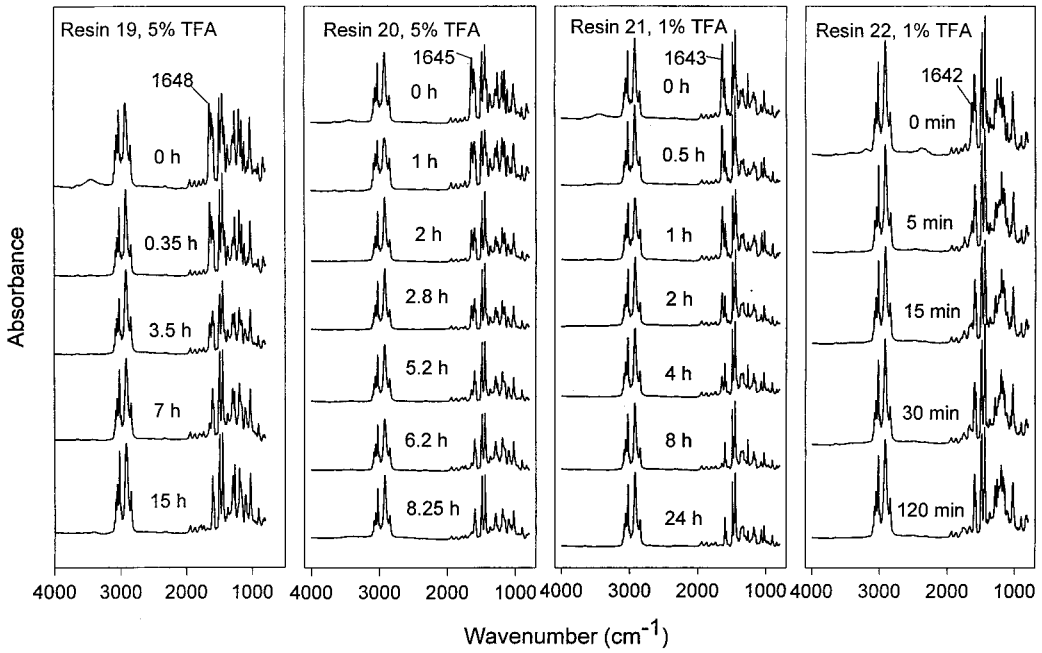


Figure 7. Single bead IR spectra of resins **19**, **20**, **21**, and **22** at various times during the TFA cleavage reaction.

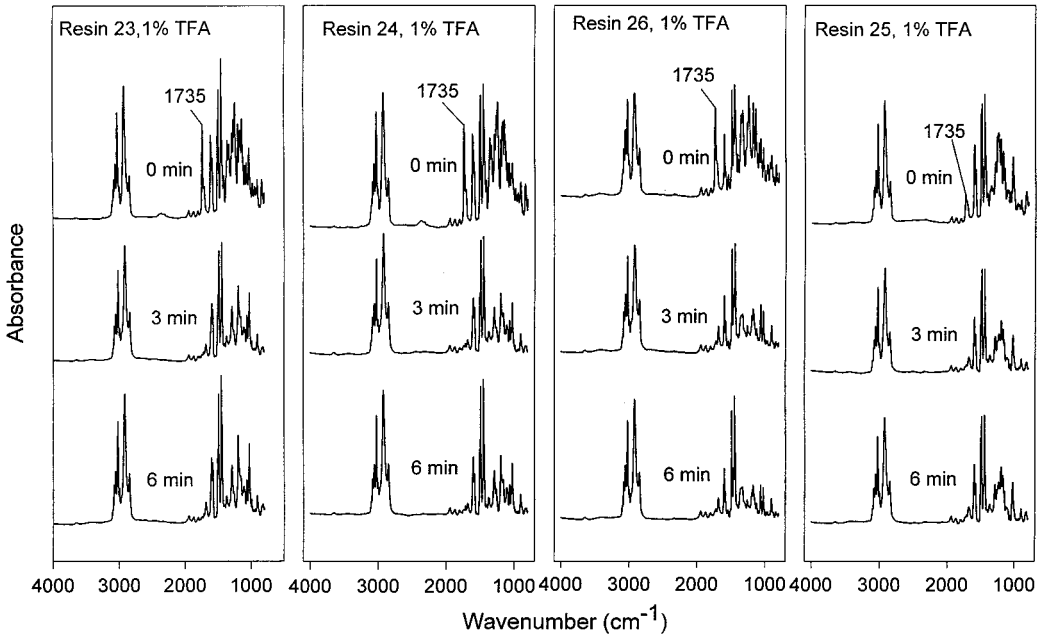


Figure 8. Single bead IR spectra of resins **23**, **24**, **25**, and **26** at various times during the TFA cleavage reaction.

time course curves representing the best fit (for errors from curve fitting, see Figure 9) are plotted in Figures 10 and 11.

Cleavage of Resin-Bound Carbamates 11−14. Indole linker is the most acid labile linker (see resin **13**) for this class of compounds. Rink linker ranks the second. Resin **13** was cleaved with 0.5% TFA in 20 min (Figure 10A). Resin **14** was cleaved with 1% TFA in 2 min. Resins **11** and **12** required higher concentration of TFA. Resin **11** was cleaved with 1% TFA in 5 h. Alternatively, resin **12** was cleaved with 1% TFA in 12 h (Figure 10A) and with 5% TFA in only 16 min (not shown).

Cleavage of Resin-Bound Ureas 15−18. Indole and Rink linkers, generally ranked 1 and 2 in cleavage kinetics, are still the most acid labile linker for this class of compounds. Resins **17** and **18** were cleaved with 0.5% TFA in 2 and 23 min, respectively (Figure 10B). Resins **15** and **16** were cleaved with 1% TFA in more than 10 h. The order of cleavage rates is similar to that of carbamates compounds.

Cleavage of Resin-Bound Secondary Amides 19−22. Amides are the most difficult to cleave among compounds studied. Resin **22** was cleaved with 1% TFA in 2 h (Figure 10C). Resin **21** was cleaved also with 1% TFA in 8 h. Resins **19** and **20** required 5% TFA and 8−15 h. This is the only occasion that linker III was not the most labile bond. Rink linker, the second best in all other series, became the most labile bond.

Cleavage of Resin-Bound Sulfonamides 23−26. All compounds in this class are easily cleaved by 1% TFA in 3 min or by 0.5% TFA in 2−7 h (Figure 10D). Indole linker is still the most labile linker in this class of compounds.

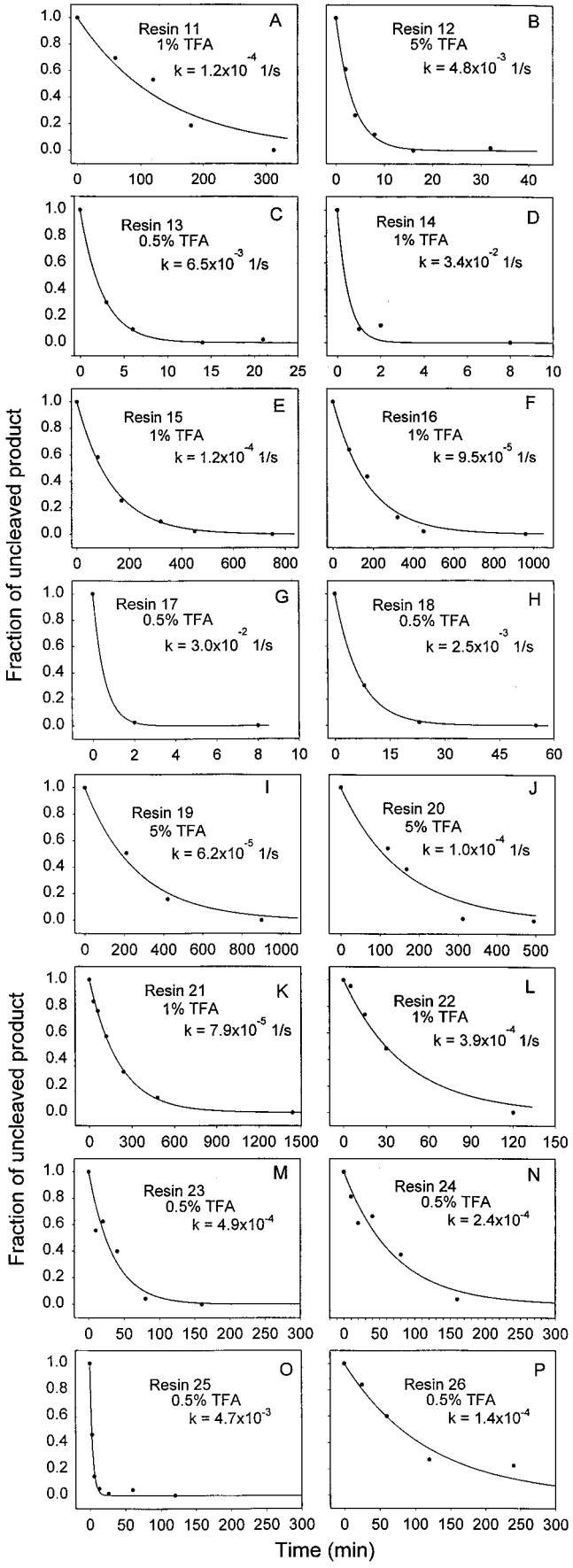


Figure 9. Time courses of TFA cleavage reactions for all 16 resins obtained by integrations of the carbonyl bands. Lines represent the best fit obtained by PeakFit (Jandel Scientific, San Rafael, CA) analysis on a personal computer.

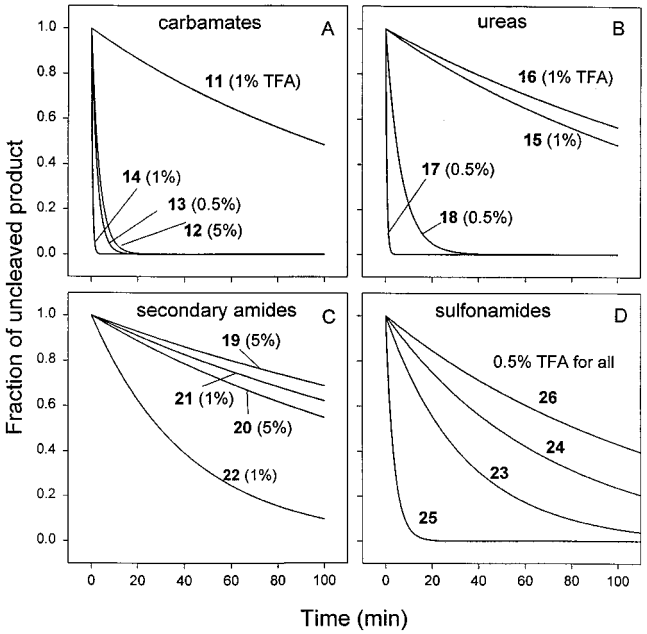


Figure 10. Kinetic comparison of TFA cleavage reactions of 16 resin-bound compounds by resin-bound functional groups. The kinetics of cleavage reaction was analyzed as in Figure 9. The curves represent the best fit and are displayed for each reaction. The first-order reaction rate constants (s^{-1}) determined for these reactions are the following: resins **11** (1%), 1.2×10^{-4}; **12** (5%), 4.8×10^{-3}; **13** (0.5%), 6.5×10^{-3}; **14** (1%), 3.4×10^{-2}; **15** (1%), 1.2×10^{-4}; **16** (1%), 9.5×10^{-5}; **17** (0.5%), 3.0×10^{-2}; **18** (0.5%), 2.5×10^{-3}; **19** (5%), 6.2×10^{-5}; **20** (5%), 1.0×10^{-4}; **21** (1%), 7.9×10^{-5}; **22** (1%), 3.9×10^{-4}; **23** (0.5%), 4.9×10^{-4}; **24** (0.5%), 2.4×10^{-4}; **25** (0.5%), 4.7×10^{-3}; **26** (0.5%), 1.4×10^{-4}. Panels are organized as (A) carbamates; (B) ureas; (C) secondary amides; and (D) sulfonamides.

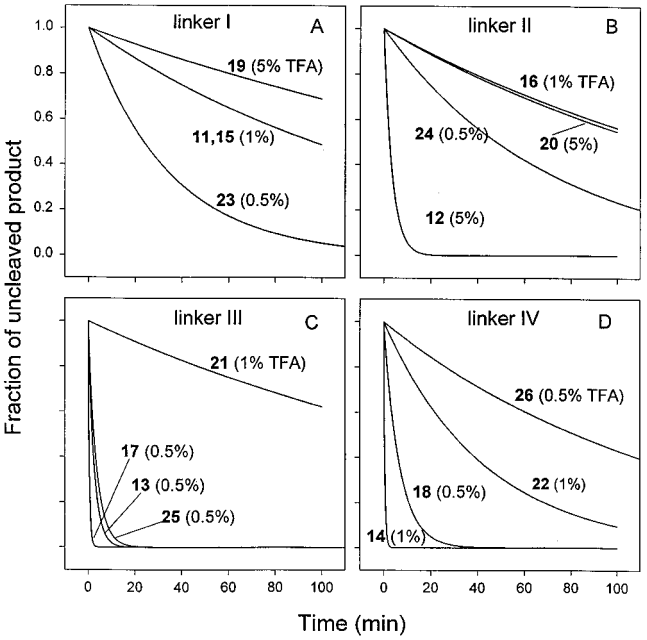


Figure 11. Kinetic comparison of TFA cleavage reactions of 16 resin-bound compounds by linker types. The curves represent the best fit and are displayed for each reaction. Panels are organized as (A) linker I; (B) linker II; (C) linker III; and (D) linker IV.

A general trend was observed when comparing of the cleavage kinetics of these 16 compounds in various TFA concentrations. Despite some small variations when labile

compounds are encountered, the general trend is that linker III and IV, ranked 1 and 2, are more labile compared with linkers I and II.

Cleavage Kinetics from Various Linkers. As seen in Figure 11, sulfonamides generally tend to be cleaved easily (lower TFA concentration and less time). The exceptions occurred with labile linkers III and IV. In these cases, ureas became more labile. On the contrary, secondary amides are the most difficult to cleave. Carbamate compounds are intermediate in term of cleavability.

Based on kinetics data, the order of cleavability for most compounds is clearly linker III > IV > II and I. Occasional exceptions can be seen among two extreme groups, the most labile ones and the most stable ones, i.e., the sulfonamides and the secondary amides. A comparison of the cleavage kinetics of various classes of compounds on the same linker indicates the ease of cleavage: sulfonamide > carbamate ∼ urea > amide. Two factors seem to affect the kinetics of a cleavage reaction. The first factor is the stability of the cation formed during the cleavage reaction. The stability of the cation after cleavage is III > IV > I and II. The second factor is the leaving capability of the leaving group. The order sulfonamide > carbamate ∼ urea > amide, in general, agrees with the order of an increased electron-withdrawing capability of atoms adjacent to the bond to be cleaved. The more electron-withdrawing fragment makes a better leaving anion during the cleavage reaction.

The cost of linkers III, II, and I is $0.7/g, $4/g, and $20/g, respectively, according to the prices of corresponding aldehydes from Lancaster Synthesis, Inc. (Windham, NH). The cost for IV is much higher. Considering the cleavage kinetics from this study and the actual cost, indole linker can be considered as the most attractive choice for the synthesis of carbamates-, ureas-, secondary amides-, and sulfonamides-based libraries, particularly when the compounds have acid labile functionalities. In fact, indole linker has been shown to be a robust linker for a wide range of reactions.[6]

Conclusion

The cleavage strategy is crucial for a successful combinatorial synthesis on solid support. However, the selection of cleavage conditions is seldom based on experimental determination of the yield and kinetics of cleavage reactions. This work presents a thorough kinetics study of cleavage reactions of 16 resin-bound compounds including carbamates, ureas, secondary amides, and sulfonamides from four acid labile linkers in order to establish the optimal cleavage conditions. Our results show that cleavage conditions are generally milder than those commonly used and reported in the literature (e.g., from 5% to 0.5% TFA). Among various linkers studied in this work, the indole linker has been found to be the most suitable linker in terms of cleavage kinetics and actual cost. Rink linker is the second best in term of kinetics. However, the cost of the starting material resin is high. The rate of cleavage of various functional groups linked to the above-mentioned resins can be summarized as follows: sulfonamide > carbamate ∼ urea > amide. Results from this study have demonstrated that optimization of cleavage conditions often leads to a much milder condition and a safer release of precious compounds synthesized on solid support. The single bead FTIR method has proven to be a very powerful method for the optimization of cleavage conditions.

Experimental Section

Materials. Merrifield and Rink resins were purchased from Advanced ChemTech (Louisville, KY). All other solvents and reagents were from Aldrich if not specified.

Safety Considerations. TFA and all chemicals (reagents and solvents) are regarded as hazardous, and skin and eye contact and inhalation should be avoided. Personal protection and mechanical ventilation should be used. Resin beads are considered to be nonhazardous materials, but skin contact or inhalation of powder should be avoided.

Solid-Phase Organic Synthesis. (a) Resin-Bound Aldehyde 2. To a suspension of sodium hydride (2.44 g of 60% dispersion in mineral oil, 61 mmol) in DMF (150 mL) at 0 °C was added a solution of 4-hydroxy-2-methoxybenzaldehyde (10.04 g, 66 mmol) in DMF (50 mL) dropwise. After completion of addition, ice bath was removed and the reaction mixture was stirred at room temperature for 30 min. To this was added Merrifield resin **1** (0.97 mmol/g, 20 g, 20 mmol), and the reaction mixture was kept at 80 °C with slow stirring for 24 h. The reaction mixture was cooled to room temperature, and the resin was filtered. This was sequentially washed with MeOH (100 mL), water (200 mL), MeOH (200 mL), CH_2Cl_2 (200 mL), and finally with MeOH (200 mL). The resin was dried, and IR was taken.

(b) Resin-Bound Aldehyde 3. Procedure and workup is the same as that in **2**.

(c) Resin-Bound Aldehyde 4. Procedure and workup is the same as that in **2**, but the alkylation reaction was conducted at room temperature for 24 h instead of 80 °C.

(d) Resin-Bound Secondary Amine 5. To a suspension of resin **2** (1.0 g, 0.97 mmol) in TMOF (5 mL) was added phenethylamine (1.21 g, 10 mmol), and the resulting mixture was stirred at room temperature for 20 h. The resin was filtered, washed with methylene chloride (20 mL), and dried, and IR was taken. The resin from this step was suspended in a 1:1 mixture of ethanol and tetrahydrofuran (20 mL), and sodium borohydride (0.378 g, 10 mmol) was added in three lots over a 10 min period. This was stirred at room temperature for 14 h. The resin was filtered and washed with MeOH (10 mL), water (20 mL), MeOH (20 mL), CH_2Cl_2 (20 mL), and finally with MeOH (20 mL). The resin was suspended in methanol (10 mL) and refluxed for 8 h. The reaction mixture was cooled to room temperature. The resin was filtered and washed with methanol (20 mL). The resin was dried, and IR was taken. Following the same procedure, resin-bound secondary amines **6** and **7** were prepared.

(e) Resin-Bound Secondary Amine 10. Rink amide resin **8** (3 g, 0.7 mmol/g, 2.1 mmol) was subjected to Fmoc deprotection using 20% piperidine in DMF (30 mL) for 30 min. The resin was filtered, washed with methylene chloride (20 mL) and methanol (20 mL), and dried, and IR was taken. The dried resin was suspended in methylene chloride (30 mL), and phenylacetic acid (2.859 g, 21 mmol) was added

followed by diisopropylcarbodiimide (1.325 g, 10.5 mmol). The reaction mixture was stirred at room temperature for 14 h, and the resin was filtered and washed with MeOH (10 mL), CH_2Cl_2 (10 mL), MeOH (10 mL), CH_2Cl_2 (10 mL), and finally with MeOH (20 mL). The resin was dried, and IR taken. The resin from the previous step was suspended in 2 M borane in THF (20 mL) and was stirred for 20 h at room temperature. The resin was filtered and washed with THF (30 mL) and MeOH (40 mL). The resin was suspended in methanol (40 mL) and refluxed for 8 h. The reaction mixture was cooled to room temperature. The resin was filtered and washed with methanol (40 mL). The resin was dried and IR recorded.

(f) Resin-Bound Carbamate 11−14. To a suspension of resins **5** or **6** or **7** or **10** (200 mg) in methylene chloride (4 mL) were added DIEA (10 equiv) and then isobutylchloroformate (10 equiv). The resulting reaction mixture was mixed for 14 h at room temperature. The resin was filtered and washed with MeOH (5 mL), CH_2Cl_2 (10 mL), and finally with MeOH (10 mL). The resin was dried under high vacuum and IR recorded.

(g) Resin-Bound Ureas 15−18. To a suspension of resins **5** or **6** or **7** or **10** (200 mg) in DMF (4 mL) was added *o*-tolyl isocynate (10 equiv), and the resulting reaction mixture was stirred at room temperature for 5 h and then at 60 °C for a period of 4 h. The reaction mixture was cooled to room temperature and the resin filtered. Resin was washed with MeOH (5 mL), CH_2Cl_2 (10 mL), and finally with MeOH (20 mL). The resin was dried and IR recorded.

(h) Resin-Bound Secondary Amides 19−22. To a suspension of resins **5** or **6** or **7** or **10** (200 mg) in methylene chloride (4 mL) was added DIEA or NMM (10 equiv) followed by dropwise addition of propionyl chloride (10 equiv). The resultant reaction mixture was mixed for 14 h at room temperature. The resin was filtered and washed with MeOH (5 mL), CH_2Cl_2 (10 mL), and finally with MeOH (10 mL). The resin was dried and IR recorded.

(i) Resin-Bound Sulfonamides 23−26. To a suspension of resins **5** or **6** or **7** or **10** (400 mg) in methylene chloride (8 mL) was added NMM (10 equiv) and 2-carbomethoxythiophene-3-sulfonyl chloride (10 equiv). The resulting reaction mixture was mixed at room temperature for 14 h. The resin was filtered and washed with MeOH (5 mL), CH_2Cl_2 (10 mL), and finally with MeOH (20 mL). The resin was dried and IR recorded.

TFA Cleavage Reaction. Resin-bound secondary amides, carbamates, ureas, and sulfonamides (∼30 mg) were cleaved using 5%, 1%, or 0.5% TFA in dichloromethane (1 mL) for various times at room temperature. Resin was thoroughly washed with CH_2Cl_2 (10 times) and analyzed by single bead FTIR.

Single Bead FTIR Microspectroscopy and Data Analysis. (a) The Single Bead FTIR Method. All spectra were collected on a Nicolet Magna 550 FTIR spectrophotometer coupled with a NicPlan microscope. The microscope is equipped with a 36X Cassegrain objective and liquid nitrogen cooled mercury−cadmium-telluride (MCT) detector. The general procedure for IR measurement is as in ref 4. Flattened bead was used throughout experiments.[5]

(b) Data Analysis. IR spectra were normalized by making the intensity of a polystyrene band at 1947 cm^{-1} equal. The areas under the specific band of the starting material or the product were integrated. The values of integration were used for quantifying the percentage of conversion or plotted against time for kinetic analysis. These data points were fitted to a pseudo-first-order rate equation by using a nonlinear regression program—SigmaPlot for windows (Jandel Scientific, San Rafael, CA)—on a personal computer.

References and Notes

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CC990051W