Article

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A New Cleavage Strategy for Ester Linked Polymer Supports: Generation of a Tertiary Alcohol Library

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The addition of different Grignard reagents to polymer bound esters resulting in the generation of a tertiary alcohol library with concomitant cleavage is described.

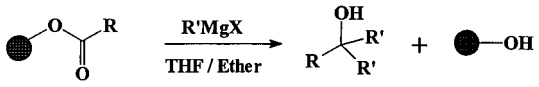
Introduction

Cleavable linkers play an important role in solid phase organic synthesis (SPOS) of combinatorial libraries,[1] and various linkers have been reported.[2] The versatility of the generated library[3] is to some extent dependent on the linker in the same way as a protecting group in solution phase needs to be stable under the reaction conditions used during the synthesis of the small molecule but can be cleaved selectively at the end of the synthesis to release the end product. Carboxylic ester groups are most widely used as linkers, owing to the availability of good methods for coupling carboxylic acids with polymer supported -OH and -Cl resins.[4] Traditionally, the ester linker is cleaved either by solvolysis to afford the corresponding acids or ammonolysis to afford the corresponding amides.[5] Here we report a new protocol, wherein the ester bound polymer can be cleaved by addition of a Grignard reagent to give tertiary alcohols in excellent yields and high purity (see Scheme 1 and Table 1). In this reaction the use of different Grignard cleaving agents can contribute to diversity.

Results and Discussion

Among the few methods available for the generation of tertiary alcohols in solution, addition of nucleophiles to esters is the most straightforward. We reasoned this approach would be equally suitable for solid phase reactions. Accordingly, four polymer supported esters were prepared from 10-undecenoic, 3,4,5-trimethoxybenzoic, pyridine-2-chloro-3-carboxylic, and 3,4-dichlorobenzoic acids. Each acid was neutralized with $NaHCO_3$ and azeotroped with benzene to give a solid Na salt, which was dissolved in DMF and treated with Merrifield resin that had been presoaked in DMF for 30 min. The mixture was stirred for 16 h at 80 °C, allowed to cool to room temperature, then filtered, washed with DMF, water, THF, methanol, CH_2Cl_2, and ether, and then dried under vacuum to yield the resin bound ester. The loading of the resin was confirmed by cleaving (20% TFA in CH_2Cl_2) a known weight of the resin and determining the weight of the recovered acid. The acid loaded resins also showed a strong carbonyl stretch near 1735 cm^{-1}, corresponding to the ester carbonyl frequency. The polymer bound undecenoic acid (P1) was exposed to different Grignard reagents, e.g., PhMgBr, EtMgBr, MeMgI, allylmagnesium bromide, and

Scheme 1



2-thienylmagnesium bromide in 3-fold molar excess equivalents to get the corresponding tertiary alcohol in good yield by simple filtration through a pad of silica gel-ammonium chloride (1:1) mixture. The same was repeated with polymer bound 3,4,5-trimethoxybenzoic acid (P2), pyridine-2-chloro-4-carboxylic acid (P3), and 3,4-dichlorobenzoic acid (P4) to give the corresponding tertiary alcohols, in good yield.

Conclusion

In conclusion, a new cleavage strategy is described involving addition of carbon nucleophiles to ester bound polymers. This allows generation of diversity even during the cleavage step, which is not very common. Addition of more complex heterocyclic nucleophiles is under investigation for the generation of bioactive compounds.

Experimental Section

Commercially available starting materials and reagents were purchased from Aldrich Chemical Co., Inc. All solvents were dried over 4 Å molecular sieves before use; DMF was distilled from calcium hydride. Ether and THF were distilled over sodium and benzophenone. ^1H NMR spectra were obtained in $CDCl_3$ at 200 MHz. Chemical shifts are given in ppm with respect to internal TMS. IR spectra of polymer bound substrates were obtained in the form of KBr pellets, and the units are in cm^{-1}.

General Procedure for the Preparation of Resin Bound Substrates. To a solution of sodium salt of undecenoic acid (1.751 g, 8.5 mmol) in DMF (20 mL) was added preswollen Merrifield resin (1 g, 1.7 mmol) in DMF (10 mL), and the mixture was warmed to 80 °C for 16 h. The resin was filtered and washed with DMF (2 × 20 mL), water (2 × 20 mL), dioxane (2 × 20 mL), methanol (2 × 20 mL), methylene chloride (2 × 20 mL), and ether (2 × 20 mL). The resin was dried in a vacuum to yield 1.326 g of polymer bound undecenoic acid **P1**. IR: 1735 cm^{-1}.

General Procedure for the Preparation of Grignard Reagents. Magnesium turnings were placed in a well-dried

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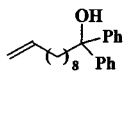
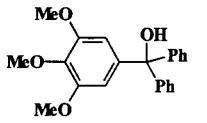
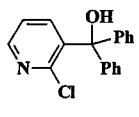
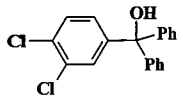
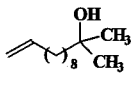
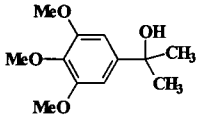
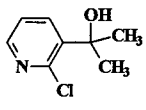
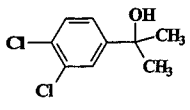
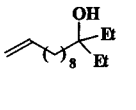
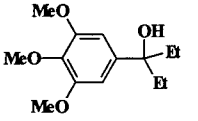
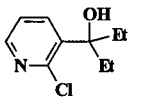
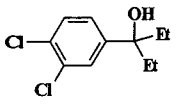
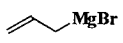
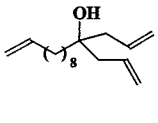
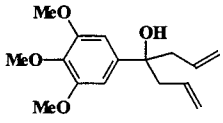
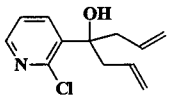
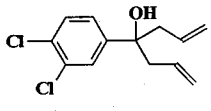
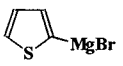
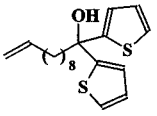
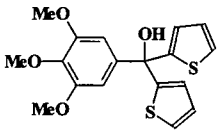
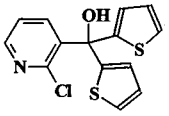
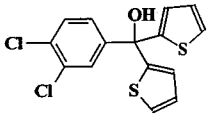
Table 1. Addition of Grignard Reagents to Polymer Supported Esters[a]

	P1	P2	P3	P4
PhMgBr a	 1a (85)	 2a (77)	 3a (80)	 4a (75)
MeMgI b	 1b (88)	 2b (78)	 3b (85)	 4b (70)
EtMgBr c	 1c (84)	 2c (90)	 3c (69)	 4c (82)
 d	 1d (75)	 2d (73)	 3d (68)	 4d (74)
 e	 1e (78)	 2e (65)	 3e (71)	 4e (75)

[a] ● = Chloromethyl polystyrene (2% divinyl benzene cross-linked). The percent yields of cleavage are mentioned in parentheses.

two-necked 100 mL round-bottomed flask. One neck was protected with a rubber septum while a double surfaced condenser was placed in the other neck. The whole system was flushed with nitrogen and maintained as such throughout the course of the reaction. To this was added dry THF (10 mL) through syringe, and the mixture was stirred for 15 min. Bromobenzene (0.18 mL, 1.68 mmol) was added slowly through syringe, and the mixture was stirred gently for 1 h to give phenylmagnesium bromide.

General Procedure for the Addition of Grignard Reagents to Resin Bound Substrates. To preswollen resin **P1** (0.250 g, 0.42 mmol) in dry THF (10 mL) under nitrogen atmosphere was added 4 equiv of preformed phenylmagnesium bromide, and the mixture was gently stirred for 4 h. The reaction mixture was filtered through a pad of silica gel and ammonium chloride (1:1) mixture and washed with ether (2 × 20 mL). The combined filtrates were evaporated under vacuum to afford 1,1-diphenyl-10-undecen-1-ol, **1a** (0.114 g, 85%). NMR ($CDCl_3$): δ 7.1−7.4 (m, 10H), 5.65−5.58 (m, 1H), 4.8−5 (m, 2H) 1.9−2.35 (m, 4H), 1.2−1.52 (m, 12H). Mass: 322. Anal. Calcd for $C_{23}H_{30}O$: C, 85.66; H, 9.38. Found: C, 85.37; H, 9.16.

The following compounds were synthesized using the above protocol.

1,1-Dimethyl-10-undecene-1-ol (1b). NMR ($CDCl_3$): δ 5.7−5.9 (m, 1H), 4.9−5.1 (m, 2H), 2−2.15 (q, J = 8.6 Hz, 2H), 1.25−2.00 (m, 14H), 1.2 (s, 6H). Mass (M^+): 198. Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.51; H, 12.61. HRMS Calcd: 198.3478, Found: 198.3481.

1,1-Diethyl-10-undecene-1-ol (1c). NMR ($CDCl_3$): δ 5.6−5.8 (m, 1H), 4.8−5 (m, 2H), 1.3−2 (m, 16H), 1.9−2.1 (q, J = 4.5 Hz, 4H), 0.7−0.9 (t, J = 6.9 Hz, 6H). Mass (M^+): 226. Anal. Calcd for $C_{15}H_{30}O$: C, 79.58; H, 13.36. Found: C, 79.43; H, 13.26.

1,1-Diallyl-10-undecene-1-ol (1d). NMR ($CDCl_3$): δ 5.1−5.47 (m, 6H), 5.6−5.7 (m, 3H), 2.3−2.4 (d, J = 4.5 Hz, 4H), 2.1−2.2 (t, J = 6.9 Hz, 2H), 1.1−1.4 (m, 14H). Mass (M^+): 250. Anal. Calcd for $C_{17}H_{30}O$: C, 81.54; H, 12.07. Found: C, 81.32; H, 11.64.

1,1-Di(2-thienyl)-10-undecen-1-ol (1e). NMR ($CDCl_3$): δ 6.80−7.40 (m, 6H), 5.75−5.90 (m, 1H), 4.92−5.10 (m, 2H), 2.00−2.39 (m, 4H), 1.20−1.64 (m, 12 H). Mass (M^+): 334. Anal. Calcd for $C_{19}H_{26}O$: C, 68.22; H, 7.83; S, 19.17. Found: C, 68.14; H, 7.81.

Diphenyl-3,4,5-trimethoxyphenylmethanol (2a). NMR ($CDCl_3$): δ 7.2−7.4 (m, 10H), 6.5 (s, 2H,), 3.65−3.75 (s, 6H), 3.8−3.9 (s, 3H). Mass (M^+): 350. Anal. Calcd for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.26; H, 6.12.

2-(3,4,5-Trimethoxyphenyl)-2-propanol (2b). NMR ($CDCl_3$): δ 1.5−1.6 (s, 6H), 3.8−3.85 (s, 3H), 3.85−3.9 (s, 6H), 6.65 (s, 2H). Mass (M^+): 226. Anal. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02. Found: C, 63.42; H, 7.84. HRMS Calcd: 226.2718, Found: 226.2719.

3-(3,4,5-Trimethoxyphenyl)-3-pentanol (2c). NMR ($CDCl_3$): δ 0.6−0.75 (t, J = 6.9 Hz, 6H), 1.6−1.8 (q, J = 4.5 Hz, 4H), 3.65−3.7 (s, 3H), 3.7−3.75 (s, 6H), 6.45 (s, 2H). Mass (M^+): 254. Anal. Calcd for $C_{14}H_{22}O_4$: C, 66.14; H, 9.44. Found: C, 66.13; H, 9.44.

4-(3,4,5-Trimethoxyphenyl)-1,6-heptadiene-4-ol (2d). NMR ($CDCl_3$): δ 3.8 (s, 3H), 3.85 (s, 6H), 4.9−5.1 (m, 4H), 5.7−5.9 (m, 2H), 2.5−2.6 (m, 4H). Mass (M^+): 278. Anal. Calcd for $C_{16}H_{22}O_4$: C, 69.04; H, 7.97. Found: C, 68.76; H, 7.65.

Di-(2-thienyl)-3,4,5-trimethoxyphenylmethanol (2e). NMR ($CDCl_3$) δ 6.65−7.40 (m, 8H), 3.95 (s, 3H), 3.8 (s, 6H). Mass (M^+): 362. Anal. Calcd for $C_{18}H_{18}O_4S_2$: C, 59.65; H, 5.01; S, 17.69. Found: C, 59.58; H, 4.99.

2-Chloro-3-pyridyl-diphenylmethanol (3a). NMR ($CDCl_3$): δ 8.35−8.45 (m, 1H), 8.1−8.2 (m, 1H), 7.5 (d, J = 5 Hz, 1H), 7.25−7.35 (m, 10H). Mass (M^+): 295. Anal. Calcd for $C_{18}H_{14}ClNO$: C, 73.10; H, 4.77. Found: C, 72.75; H, 4.48.

2-(2-Chloro-3-pyridyl)-2-propanol (3b). NMR ($CDCl_3$): δ 8.15−8.45 (d, J = 5 Hz, 1H), 8.1−8.15 (d, J = 5 Hz, 1H), 7.5−7.6 (d, J = 5 Hz, 1H), 1.4 (s, 6H). Mass (M^+): 171. Anal. Calcd for $C_8H_{10}ClNO$: C, 55.99; H, 5.87 Found: C, 55.56; H, 5.62.

3-(2-Chloro-3-pyridyl)-3-pentanol (3c). NMR ($CDCl_3$): δ 8.1−8.2 (d, 5 Hz, 1H), 7.8−7.9 (m, 1H), 7.5−7.6 (m, 1H), 1.8−1.9 (q, J = 4.5 Hz, 4H), 0.65−0.75 (t, J = 6.9 Hz, 6H). Mass (M^+): 199. Anal. Calcd for $C_{10}H_{14}ClNO$: C, 60.15; H, 7.07. Found: C, 60.01; H, 7.07.

4-(2-Chloro-3-pyridyl)-1,6-heptadiene-4-ol (3d). NMR ($CDCl_3$): δ 8.3−8.35 (m, 1H), 8.1−8.2 (m, 1H), 7.5−7.6 (m, 1H), 5.6−5.8 (m, 2H), 4.9−5.1 (m, 4H), 2.45−2.55 (m, 4H). Mass (M^+): 223. Anal. Calcd for $C_{12}H_{14}ClNO$: C, 64.42; H, 6.31. Found: C, 64.31; H, 6.15.

2-Chloro-3-pyridyl-di(2-thienyl)-methanol (3e). NMR ($CDCl_3$): δ 6.80−8.43 (m, 9H). Mass (M^+): 307. Anal. Calcd for $C_{14}H_{10}ClNOS_2$: C, 54.63; H, 3.27. Found: C, 54.52; H, 3.26.

3,4-Dichlorophenyl-diphenylmethanol (4a). NMR ($CDCl_3$): d 8.0−8.1 (d, J = 5 Hz, 1H), 7.85−7.95 (d, J = 5 Hz, 1H), 7.55−7.65 (s, 1H), 7.3−7.45 (m, 10H). Mass (M^+): 329. Anal. Calcd for $C_{19}H_{14}Cl_2O$: C, 69.32; H, 4.29. Found: C, 69.09; H, 4.11.

2-(3,4-Dichlorophenyl)-2-propanol (4b). NMR ($CDCl_3$): δ 8.15−8.2 (d, J = 5 Hz, 1H), 7.9−7.95 (d, J = 5 Hz, 1H), 7.5−7.6 (s, 1H), 1.5 (s, 6H). Mass (M^+): 205. Anal. Calcd for $C_9H_{10}Cl_2O$: C, 52.71; H, 4.91. Found: C, 52.54; H, 4.75.

3-(3,4-Dichlorophenyl)-3-pentanol (4c). NMR ($CDCl_3$): δ 8.1−8.2 (d, 5 Hz, 1H), 7.8−7.9 (d, J = 5 Hz, 1H), 7.5−7.6 (s, 1H), 1.8−1.9 (q, J = 4.5, 4 H), 0.65−0.75 (t, J = 6.9 Hz, 6H). Mass (M^+): 233. Anal. Calcd for $C_{11}H_{14}Cl_2O$: C, 56.67; H, 6.05. Found: C, 56.54; H, 5.73.

4-(3,4-Dichlorophenyl)-1,6-heptadiene-4-ol (4d). NMR ($CDCl_3$): δ 8.15−8.25 (m, 1H), 7.85−7.95 (m, 1H), 7.5−7.6 (s, 1H), 5.7−5.9 (m, 2H), 5.1−5.3 (m, 4H), 2.3−2.45 (m, 2H). Mass (M^+): 257. Anal. Calcd for $C_{13}H_{14}Cl_2O$: C, 60.72; H, 5.44. Found: C, 60.51; H, 5.23.

3,4-Dichlorophenyl-di(2-thienyl)-methanol (4e). NMR ($CDCl_3$): δ 6.75−7.60 (m, 9H). Mass (M^+): 341. Anal. Calcd for $C_{15}H_{10}Cl_2OS_2$: C, 52.79; H, 2.95. Found: C, 52.68; H, 2.95.

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References and Notes

(1) (a) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor , S. P. A.; Gallop, M. A. *J. Med. Chem.* **1994**, *37*, 1385. (b) Ellmann, J. A. *Acc. Chem. Res*. **1996**, *29*, 132. (c) Liskamp, R. M. *Angew. Chem., Int. Ed. Engl*. **1994**, *33*, 633. (d) Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron*. **1998**, *54*, 15385.

(2) (a) Merrifield, R. B. *J. Am. Chem. Soc*. **1963**, *85*, 2149. (b) Wang, S. S. *J. Am. Chem. Soc*. **1973**, *95*, 1328. (c) Mergler, M.; Tanner, R.; Gostli, J.; Grogg, P. *Tetrahedron Lett*. **1988**, *22*, 4005. (d) Kurth, M. J.; Evarts, J.; Halm, C. *Tetrahedron Lett*. **1997**, *38*, 7709. (e) Hauske, J. R.; Dorff, P. *Tetrahedron Lett*. **1995**, *36*, 1589. (f) Whitehouse, D. L.; Savinov, S. N.; Austin, D. J. *Tetrahedron Lett*. **1997**, *38*, 7851. (g) Artherton, E.; Logon, C. J.; Sheppard, R. C. *J. Chem. Soc. Perkin Trans. 1*, **1981**, *1*, 538. (h) Mitchell, A. R.; Erickson, B. W.; Ryabtsev, M. N.; Hidges, R. S.; Merrifield. R. B. *J. Am. Chem. Soc*. **1976**, *98*, 7357. (i) Akai, K.; Kiso, Y.; Carpino, L. A. *J. Chem. Commun*. **1990**, 584. (j) For a detailed review, see: James, W. I. *Tetrahedron* **1999**, *55*, 4855.

(3) (a) Gordon, D. W.; Steele, J. *Biorg. Med. Chem. Lett*. **1995**, *5*, 47. (b) Burbaum, J. J.; Ohlmeyer, M. H.; Reader, J. C.; Henderson, I.; Dillard, L. W.; Li, G.; Randle, J. L.; Sigel, N. H.; Chelsky, D.; Baldwin, J. *J. Proc. Natl. Acad. Sci.* U.S.A. **1995**, *92*, 6027.

(4) (a) Mioskowski, C.; Wagner,, A.; Sylvain, C. *Tetrahedron Lett.* **1999**, *40*, 875. (b) Frenette, R.; Friesen, R. W. *Tetrahedron Lett.* **1994**, *35*, 9177. (c) Fields, G. B.; Noble, R. L. *Int. J. Protein Res.* **1990**, *35*, 161. (d) Hannesian, S.; Yang, R. Y. *Tetrahedron Lett.* **1996**, *37*, 5835. (e) Kurth, M. J.; Ahlberg Randall, L. A.; Chen, C.; Melander, C.; Miller, C.; Miller, R. B.; McAlister, K.; Reitz, G.; Kang, R.; Nakatsu, T.; Green, C. *J. Org. Chem*. **1994**, *59*, 5862.

(5) (a) Ley, S. V.; Mynett, D. M.; Koot, W. J. *Synlett* **1995**, 1017. (b) Gisin, B. F. *Helv. Chim. Acta* **1973**, *56*, 1476.

(6) IICT Communication No. 4292.

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