Pergamon

Tetrahedron Letters 40 (1999) 9085–9089

TETRAHEDRON LETTERS

Synthesis of acetoxyamides and acetates by zinc bromide assisted cleavage of Merrifield resin-bound ethers

Wen-Ren Li * and Ying-Chih Yo

Department of Chemistry, National Central University, Chung-Li, Taiwan 32054, ROC

Received 10 August 1999; revised 1 October 1999; accepted 8 October 1999

Abstract

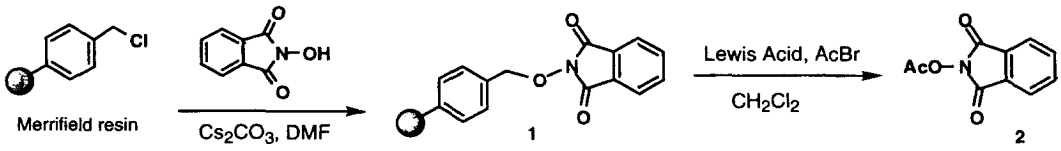
A new method for the synthesis of acetoxyamides and acetates using Merrifield resin is described. The method uses zinc bromide to promote the conversion of Merrifield resin-bound ethers to acetates under ambient conditions. The cleavage products obtained are of high yields and chemical purity. © 1999 Elsevier Science Ltd. All rights reserved.

Combinatorial chemistry has been recognized as one of the most powerful tools for the discovery of pharmaceutically interesting compounds. Most recent research in this area has utilized the solid phase organic synthesis to construct large libraries of small molecules.[1] A key aspect of any solid phase synthesis strategy is the linkage element which acts as a tether to the polymeric support material and should be stable through a given synthesis sequence. Therefore, the generation of combinatorial libraries and the development of new organic reactions on solid phase support are dependent on the properties of the linker.[2] Merrifield resin has been used for more than 20 years for the production of a range of peptides. Cleavage of the finished substrates from this resin typically requires a strong acid such as HF or trifluoromethanesulfonic acid. Due to the drastic conditions employed for the final cleavage, the utility of Merrifield resin is limited in the organic solid phase synthesis. In most cases acid labile linkers such as Wang,[3] Sasrin[4,5] and THP[6] anchors are required to avoid side reactions. Note that the reactions cannot be carried out under mild acidic conditions because these linkers are cleaved by treatment with trifluoroacetic acid in methylene chloride. In order to add another dimension to the strategy of solid phase synthesis, we sought to develop a mild method which would allow direct cleavage of Merrifield resin-bound ethers and broaden the application of this resin. Our approach to the development of a new direct cleavage protocol for Merrifield resin was inspired by the Lewis acid catalyzed conversion of benzyl ethers to acetates in solution. These methods ($FeCl_3/Ac_2O$[7] and ZnI_2/Ac_2O[8]), however, required drastic reaction conditions using a large excess of Ac_2O at high temperature (80°C). Therefore, our initial efforts were directed at selecting the most suitable catalyst and reaction conditions for the cleavage of Merrifield resin. As shown in Table 1, to convert Merrifield resin-bound ethers into the corresponding acetates in

* Corresponding author.

PII: S0040-4039(99)01927-9

Table 1
Synthesis of acetoxyamide **2** by Lewis acids assisted cleavage of Merrifield resin-bound ether



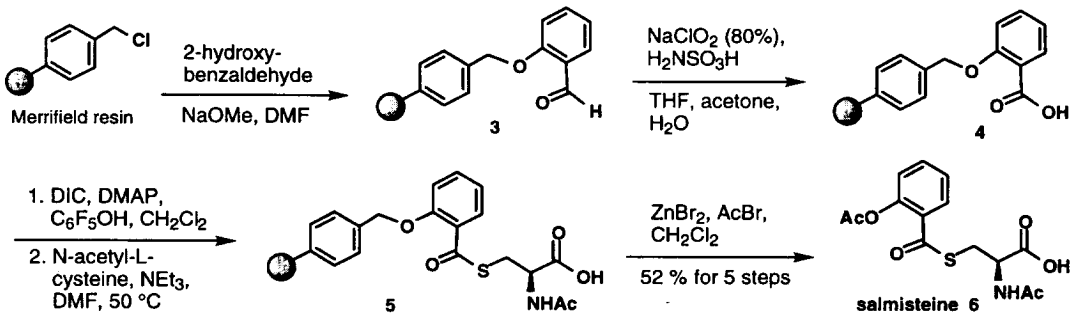
Entry	Lewis Acid	Time (h)	Yields[a] (%)	Purity[b] (%)
1	$ZnBr_2$	24	91	> 99
2	ZnI_2	24	31	75
3	$SnBr_2$	24	15	92
4	TMSOTf	24	36	93
5	$FeCl_3$	5	67	90
6	$FeCl_3$	24	51	80
7	$AlCl_3$	24	88	95
8	$SnCl_2$	24	62	80
9	BBr_3	24	21	< 20
10	BF_3•OEt_2	24	25	77

[a]Percentage yields are calculated over two steps based on the initial loading level of the resin. Products were synthesized using the described procedure and characterized by NMR, IR and mass spectroscopy. [b]Crude product, detection at 254 nm.

highest yield and chemical purity was obtained by treatment with acetyl bromide and catalytic amount of zinc(II) bromide.

It was decided to concentrate initially on the synthesis of *N*-hydroxyphthalimide derivative **1**, a common intermediate to prepare hydroxamic acid derivatives, in order to compare the propensity of different Lewis acids to effect cleavage from the solid support. After *N*-hydroxyphthalimide was attached to Merrifield resin, the resin was then divided into eight equal batches. Each was suspended in methylene chloride containing 0.5 equivalent of the Lewis acid (relative to the initial loading of the resin) and 2 equivalents of the acetyl bromide. Each suspension was agitated for 5 to 24 h at room temperature. It was found that $ZnBr_2$ and $AlCl_3$ gave superior results compared to the other Lewis acids. The isolated yield of *N*-acetoxyphthalimide **2** following chromatography purification was 91% and 88%, respectively. In contrast, $SnBr_2$, TMSOTf (trimethylsilyl triflate), $SnCl_2$, BBr_3 and $BF_3 \cdot OEt_2$ produced little of the desired acetate. The $FeCl_3$ reagent gave a fair yield (67%) after 5 h, however, a decrease in the purity and yield of the desired crude product was observed by prolonging the cleavage time. Although benzyl ethers could be easily deprotected in the solution phase, our attempts to cleave the Merrifield resin-bound ether **1** to give the corresponding alcohol using catalytic amounts of various Lewis acids in the absence of acetyl bromide were unsatisfactory. Zinc bromide/acetyl bromide was selected as the reagent system of choice for the cleavage of the Merrifield resin-bound ether because the removal of $ZnBr_2$ was easily accomplished by aqueous work-up. Hydroxamic acids, their derivatives, and often their ion complexes have long been known to exert a wide spectrum of biological activities, and hence are legitimate targets as potential therapeutic agents. The solid phase synthesis of hydroxamic acids, based on Wang,[9,10] Sasrin[11], Tentagel–THP[12] or the trityl *O*-hydroxylamine[13–15] bound resin has recently been described in the literature. However, these methods either require an acid labile linker group or are not applicable for the synthesis of *N*-acetoxyamides to provide a further dimension in chemical diversity. Our above strategy would allow us to adapt their synthetic methods to prepare *N*-acetoxyamides using inexpensive Merrifield resin under Boc and Fmoc protecting groups cleavage conditions.

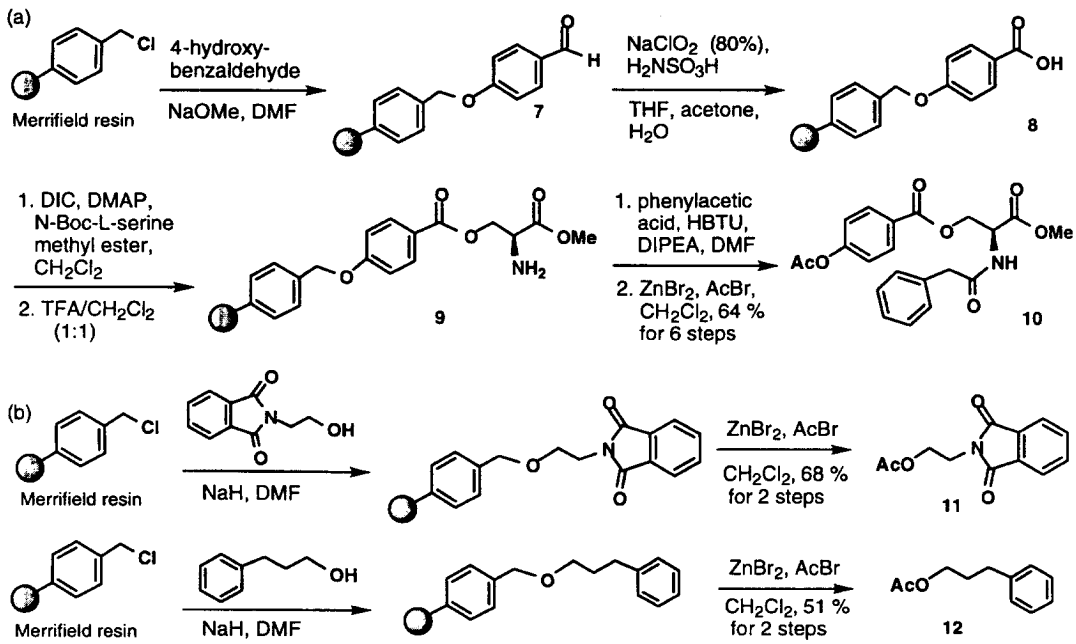
In order to establish the utility of the $ZnBr_2$/AcBr reagent system, the synthesis of salmisteine[16] **6** which has been reported as a potent mucolytic anti-inflammatory and analgesic agent was chosen as a synthetic target (Scheme 1). Treatment of Merrifield resin with 2-hydroxybenzaldehyde in DMF at 80°C for 24 h gave the aldehyde **3**, confirmed by IR spectroscopy (ν_{max} 1684 cm^{-1}). Cleavage of the resulting aldehyde **3** from the resin was readily achieved by the $ZnBr_2$/AcBr reagent system, providing the corresponding acetate in 87% yield and high purity. The polymer-supported aldehyde **3** was oxidized to the corresponding carboxylic acid **4** and then released to afford the acetate in 75% yield. These polymer-supported ethers **3**, **4**, **7** and **8** were stable under basic hydrolytic conditions or TFA treatment (Scheme 2) which gave Merrifield resin an advantage over Wang resin. The literature procedure, which recommended oxidation of the resin-bound aldehyde to the acid using chromic acid was unsatisfactory because it did not go to completion, as evidenced by the incomplete disappearance of the aldehyde carbonyl stretch in the IR spectrum.[17] The common oxidizing reagents such as PDC, ruthenium(IV) oxide and potassium permanganate stained the solid support and also failed to give a clean reaction. We therefore applied a solution approach[18] to our resin-bound carboxylic acid synthesis using 3 equivalents of sodium chlorite (80%) and sulfamic acid in THF:acetone:H_2O (2:1:1) for 2 h. The reaction proceeded very fast at room temperature. The polymer-supported acid **4** from this reaction was bright white and had carbonyl absorbances in the IR spectrum at 1699–1729 cm^{-1} (C=O free and H-bonded) as well as an OH stretch at 3455 cm^{-1}. The carboxylic acid was then converted to the pentafluorophenyl ester under the pentafluorophenol:DIC:DMAP (1:1:0.2) activation conditions. The subsequent coupling reaction with three equivalents of *N*-acetyl-L-cysteine was performed at 50°C in DMF in the presence of triethylamine. Lewis acid assisted cleavage of the resin-bound ether **5** using 0.5 equivalent of $ZnBr_2$ and 2 equivalents of acetyl bromide afforded the pure salmisteine **6** in 52% for five steps from Merrifield resin (0.68 mmol/g loading).



Scheme 1.

Next, we investigated the solid phase synthesis of salmisteine derivative **10** (Scheme 2) by a modification of the above method. A three component compound was chosen in order to take full advantage of the combinatorial strategy. β-Hydroxy-α-amino or β-thio-α-amino ester could be used as a scaffold for the presentation of two fragments in a comformationally controlled way. Salmisteine derivative **10** was cleaved from the polymer support after six chemical steps and could be used directly for solution phase screening without purification (64% yield, chemical purity >90%).[19] In order to further demonstrate that the $ZnBr_2$/AcBr method could be used for the cleavage of alkyl benzyl ethers, compound **11** and **12** were synthesized as shown in Scheme 2. The Lewis acid assisted cleavage of these resin-bound ethers afforded very clean products, therefore the fair yields could be the result of difficult alkylation.

In summary, we have established that the zinc bromide/acetyl bromide reagent system can be used to prepare acetates via Merrifield resin based synthesis. Zinc bromide assisted release of Merrifield resin-bound ethers is particularly mild and clean. Therefore, this protocol should alleviate the limitation on the



Scheme 2.

use of Merrifield resin caused by the conventional harsh cleavage conditions. Another characteristic of this strategy is that it requires no linker to the resin other than the functional group constructed during the synthesis and should stimulate the wider application of the Merrifield resin in the combinatorial chemistry. The precise mechanism of action of this reagent system is unknown. However, the ability of zinc bromide to act as Lewis acid is probably an important factor. We have also demonstrated the preparation of salmisteine and its derivative on the Merrifield resin which offers the distinct advantage of being stable to all reagents commonly used in Boc or Fmoc peptide synthesis. Application to the automated synthesis of diverse libraries is in progress.

Acknowledgements

The authors are grateful to the National Science Council, ROC, for the financial support (NSC 88-2113-M-008-005) of this work.

References

1. Booth, S.; Hermkens, P. H. H.; Ottenheijm, H. C. J.; Rees, D. C. *Tetrahedron* **1998**, *54*, 15385.
2. Fruchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17.
3. Wang, R. B. *J. Am. Chem. Soc.* **1972**, *95*, 1328.
4. Katritzky, A. R.; Toader, D.; Watson, K.; Kiely, J. S. *Tetrahedron Lett.* **1997**, *38*, 7849.
5. Mergler, M.; Tanner, R.; Gosteli, J.; Grogg, P. *Tetrahedron Lett.* **1988**, *29*, 4005.
6. Thompson, L. A.; Ellman, J. A. *Tetrahedron Lett.* **1994**, *35*, 9333.
7. Ganem, B.; Small, V. R. J. *J. Org. Chem.* **1974**, *39*, 3728.
8. Benedetti, M. O. V.; Monteagudo, E. S.; Burton, G. *J. Chem. Res. (S)* **1990**, 248.
9. Floyd, C. D.; Lewis, C. N.; Patel, S. R.; Whittaker, M. *Tetrahedron Lett.* **1996**, *37*, 8045.
10. Richter, L. S.; Desai, M. C. *Tetrahedron Lett.* **1997**, *38*, 321.

11. Gordeev, M. F.; Hui, H. C.; Gordon, E. M.; Patel, D. V. *Tetrahedron Lett.* **1997**, 1729.
12. Ngu, K.; Patel, D. V. *J. Org. Chem.* **1997**, *62*, 7088.
13. Mellor, S. L.; McGuire, C.; Chan, W. C. *Tetrahedron Lett.* **1997**, *38*, 3311.
14. Khan, S. I.; Grinstaff, M. W. *Tetrahedron Lett.* **1998**, *39*, 8031.
15. Bauer, U.; Ho, W.-B.; Koskinen, A. M. P. *Tetrahedron Lett.* **1997**, *38*, 7233.
16. Dannan, H.; Khawam, M. N.; Bogardus, J. B.; Hussain, A. A.; Crooks, P. A. *J. Pharm. Sci.* **1986**, 75, 1081; Gobetti, M.; Vandoni, G. BE 0897617;19831216.
17. Ayres, J. T.; Mann, C. K. *J. Polym. Sci., Polym. Lett. Ed.* **1965**, *3*, 505.
18. Hauser, F. M.; Ellenberger, S. R. *Synthesis* **1987**, 723.
19. General procedure for the cleavage of Merrifield resin-bound ethers: Merrifield resin **9** (0.401 mmol, 600 mg) was swelled with CH_2Cl_2 (4 mL) and treated with $ZnBr_2$ (0.081 mmol, 18.3 mg) and acetyl bromide (8.1 mmol, 0.6 mL) under an argon atmosphere. The mixture was agitated for 24 h at room temperature, then the resin was collected by filtration. The filtrate was washed with 5% $NaHCO_3$, 5% HCl and saturated NaCl solutions. The organic layer was dried (Na_2SO_4), filtered and concentrated to afford product **10**: ^1H NMR in $CDCl_3$ (δ, ppm): 2.34 (s, 3H), 3.62 (s, 2H), 3.76 (s, 3H), 4.60 (d, 2H, J=3.66 Hz), 4.93 (m, 1H), 6.26 (d, 1H, J=7.68 Hz), 7.14 (d, 2H, J=6.81 Hz), 7.22–7.30 (m, 5H), 7.87 (d, 2H, J=8.79 Hz); ^{13}C NMR in $CDCl_3$ (δ, ppm): 21.09, 43.44, 51.74, 52.89, 64.06, 121.68, 126.64, 127.40, 128.94, 129.28, 131.17, 134.13, 154.52, 164.96, 168.75, 169.77, 170.77; HRMS calcd for $C_{21}H_{21}NO_7$ (M) 399.1318, found 399.1271.