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Report

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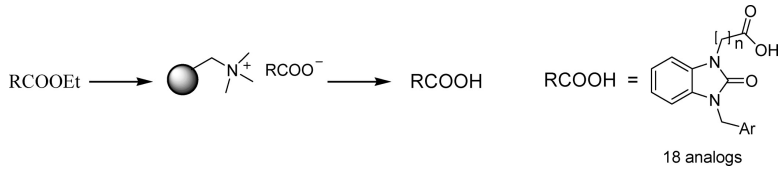

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Report

Tandem Alkylation/Ester Hydrolysis Using Polymer-Supported Hydroxide for Catch and Release Isolation of a Series of Benzoimidazolonecarboxylic Acids

Morgan Welzel† and Tina M. Morwick*

Boehringer Ingelheim Pharmaceuticals, Inc., 900 Ridgebury Road, Ridgefield, Connecticut 06801-0368

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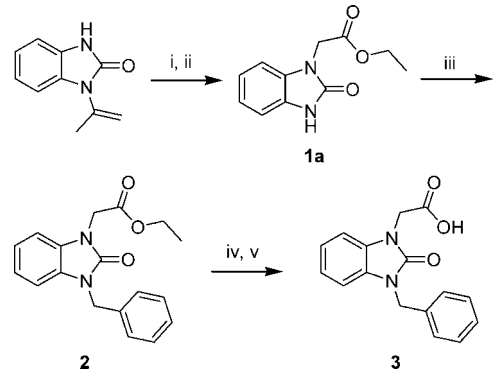
The use of polymer-supported reagents in organic synthesis has afforded a toolbox of methods to support rapid and efficient parallel procedures.[1] Resin-bound reactive species that can act as both reactant and scavenger offer distinct advantages in overall utility. Such reagents are particularly useful when applied to the removal of common protecting groups because these are ubiquitously deployed, and deprotection is frequently the final step of a synthetic protocol.[2] Tandem applications offer added efficiency and convenience.

We have recently described a process for ester hydrolysis with catch and release isolation of the product acids using the ion-exchange resin Amberlyst A26 (OH^-).[3] This method was found to be quite efficient, producing products in good yield and high purity. Considering the pervasive appearance of carboxylic acids in biologically active molecules, including endogenous regulators, natural products, and medicinal agents, we have explored opportunities to apply this protocol for the parallel synthesis of biologically relevant compounds. The benzoimidazolone template is a commonly used scaffold in medicinal chemistry, likely due to the procurement of good physicochemical properties as well as ease of synthetic manipulation. Herein, we report a tandem alkylation/ester hydrolysis procedure generating a series of benzoimidazolone-substituted acetic and propionic acids, previously described as inhibitors of aldose reductase.[4] The optimized method is outlined in Scheme 1. With few exceptions, products are conveniently acquired in good yield and high purity, demonstrating the potential for this methodology in the synthesis of more complex species.

Initially, intermediate **2** was prepared in DMF using a standard isolation and purification procedure, and this purified intermediate was used to independently optimize the second step of the tandem process (resin hydrolysis and product capture). Using the protocol and equivalencies we had previously found to be effective,[3a] we evaluated the suitability of different solvents. The Amberlyst polymer is a macroreticular resin with a permanent pore structure,[5] and therefore solvent-assisted swelling is not critical for functional group accessibility. Several solvents were previously found to be compatible; however it was noted that water-miscible solvents gave better results. Methanol had been used

Scheme 1[a]



[a] Reaction conditions: (i) ethyl bromoacetate, potassium carbonate, DMF; (ii) 37% HCl, ethanol, water; (iii) benzyl bromide, potassium carbonate, acetonitrile; (iv) Amberlyst A26 (OH^-), acetonitrile; (v) formic acid, acetonitrile.

for method development. We therefore decided to compare an alcohol with two additional solvents of potential utility in the alkylation step, DMF, which had been used for the initial synthesis of **2,** and acetonitrile. Ethanol was chosen as the alcohol because our intermediates were generated as ethyl esters. Compound **2** was treated with the resin and agitated overnight independently in each of the three solvents. The resin-captured product (**3**) was isolated by filtration and washed with additional solvent. It was then eluted from the resin in each case with formic acid in the reaction solvent. Both ethanol and acetonitrile provided good yields of pure carboxylic acids (86% and 91% yield, respectively). DMF also gave clean product, but the yield was lower (54%). It was expected that the lower yield was the result of incomplete release from the resin, because concentration of the solvent recovered from the filtration and wash yielded minimal (<1 mg) material. Recovery of the acid could be improved to 75% for the DMF hydrolysis if the solvent was washed from the resin with methanol prior to elution, which was done with a methanolic solution of formic acid.

With this information in hand, we next looked at the tandem process. Using potassium carbonate as the base, alkylation of a benzoimidazolone acetate or propionate ester was carried out in either acetonitrile or DMF. For example, intermediate **1a** was treated with benzylbromide and base at 60 °C until complete conversion to **2** was achieved.[6] Reactions were then filtered to remove the carbonate base and hydroxide-bound Amberlyst was added.[7] The resulting mixtures were agitated overnight, and product acids were isolated as described above. Additional equivalents of the resin-bound hydroxide were found to be

* To whom correspondence should be addressed. Phone: 203-798-5751. Fax: 203-791-6072. E-mail: tmorwick@rdg.boehringer-ingelheim.com.
† BI Summer Intern.

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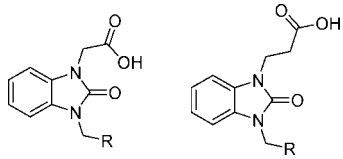
Table 1. Products Prepared According to Scheme 1



A B

entry	A/B	R	time[a]	alkylating agent[b]	yield (%)	purity (%) UV[c]	purity (%) ^{1}H NMR
3	A	Ph	2	1.4	70	96	>95
4	A	2-ClPh	2	1.6	74	95	>95
5	A	3-ClPh	2	1.6	74	94	>95
6	A	4-ClPh	2	1.8	85	96	>95
7	A	2-MePh	3	1.6	71	98	>95
8	A	3-MePh	3	1.6	63	100	>95
9	A	4-MePh	3	1.6	88	99	>95
10	A	4-CF_3Ph	4	2	90	98	>95
11	A	2-naphthyl	5	1.8	78	94	>95
12	A	1-naphthyl	8	3[d]	68	100	>95
13	A	2,4-DiMePh	3	2	80	84	80
14	A	3,4 DiClPh	2	1.4	94	96	>95
15	A	2,4-DiClPh	14	3[d]	82	95	>95
16	B	4-ClPh	2	2	96	96	>95
17	B	4-MePh	2	2	96	95	>95
18	B	4-CF_3Ph	4	2	85	97	>95
19	B	3,4 DiClPh	2	2	91	95	>95
20	B	2,4-DiClPh	14	3[d]	93	95	>95

[a] Reaction time (h) at 60 °C affording complete alkylation. [b] Number of equivalents of the arylalkyl bromide used. [c] Purity by LCMS (UV detection; 254 nm). [d] Arylalkyl chlorides were used.

necessary for the tandem process to achieve yields comparable to the direct hydrolysis of purified **2**. This is believed to be caused by the presence of residual carbonate exchanging available sites on the resin. Acetonitrile again proved to be superior to DMF. While both provided pure product, recovery of the acid was 2-fold greater in acetonitrile than DMF, even when the alcohol wash and elution protocol described above was used. Solvent recovered from the DMF reaction prior to treatment with the eluent appeared to contain a significant amount of the acid, suggesting product exchange with possibly a greater quantity of residual solublized carbonate in the DMF solutions.

We then applied the optimized protocol in acetonitrile to the synthesis of a variety of arylalkyl-substituted benzoimidazolone acetates and propionates. Our results are shown in Table 1. As can be seen from the data, good yields were achieved for the two steps, and in general, no contaminants were observed in the products. One exception was **13**, but in this case, the 2,4-dimethylbenzyl bromide reagent was later found to be contaminated to a similar extent. Varied regiochemistry on the arylalkyl halide was tolerated, and electronics also did not appear to alter the outcome. An exception to this general observation was our unsuccessful attempt to prepare an electron-rich 4-methoxybenzyl analog. However, again the problem seemed to be associated with the arylalkyl bromide, in this case likely a stability issue. The propionate analog of **1a** (**1b**) was prepared via Michael addition of 1-isopropenyl-1,3-dihydro-benzoimidazole-2-one to methyl acrylate, followed by removal of the isopropenyl group. This intermediate was used for the synthesis of **16**−**20**. The results show that the acetates and propionates compare favorably. 2-D NMR analysis of **16** validated the regiochemical assignments regarding N- versus O-alkylation (Supporting Information).

In summary, we have studied the use of Amberlyst A26 (OH^-) for a tandem alkylation/ester hydrolysis with catch and release isolation of the product benzoimidazolone carboxylic acids. The results demonstrate the utility of hydroxide exchange polymers in tandem processes, where ester deprotection is the terminal step, and highlight the convenience offered by polymer-bound reactants in deprotection/capture strategies. The method affords useful options for parallel synthesis of complex carboxylic acids.

Supporting Information Available. Experimental methods for the synthesis of **1a**, **1b**, and **2**, the general method for the hydrolysis of purified **2**, the general method for the tandem alkylation/hydrolysis (synthesis of **3**−**20**), ^{1}H and ^{13}C NMR (APT) and LCMS data for **3**−**20,** and summary of 2D NMR analysis of **16** is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) (a) Chighine, A.; Sechi, G.; Bradley, M. *Drug Discovery Today* **2007**, *12*, 459–464. (b) Ley, S. V. ; Baxendale, I. R. ; Myers, R. M. Evolution or Revolution: The Challenge to Today's Medicinal Chemist. In *Proceedings of The Chemical Theater of Biological Systems*; Bozen, Italy, May 24–28, 2004; Beilstein-Institut: Frankfurt, Germany, 2005. (c) Ley, S. V.; Baxendale, I. R.; Le, A-L. Polymer-Supported Hydroxide. In *Reagents for High-Throughput Solid-Phase and Solution-Phase Organic Synthesis*; Wipf, P., Ed.; Handbook of Reagents for Organic Synthesis Series; John Wiley & Sons: Chichester,U.K., 2005. (d) Bhattacharyya, S. *Curr. Opin. Drug Discovery Dev.* **2004**, *7*, 752–764. (e) Baxendale, I. R. ; Storer, R. I. ; Ley, S. V. ; Supported Reagents and Scavengers in Multi-step Organic Synthesis. In *Polymeric Materials in Organic Synthesis and Catalysis*, 1st ed.; Buchmeiser, M. R., Ed.; Wiley-VCH: Weinheim, Germany, 2003. (f) Ley, S. V.; Baxendale, I. R. *Nat. Rev. Drug Discovery* **2002**, *1*, 573–586. (g) Kirschning, A.; Monenschein, H.; Wittenberg, R. *Angew. Chem., Int. Ed.* **2001**, *40*, 650–679. (h) Ley, S. V.; Baxendale, I. R.; Bream, R. N.; Jackson, P. S.; Leach, A. G.; Longbottom, D. A.; Nesi, M.; Scott, J. S.; Storer, R. I.; Taylor, S. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3815–4195. (i) Thompson, L. A. *Curr. Opin. Chem. Biol.* **2000**, *4*, 324–337. (j) Drewry, D. H.; Coe, D. M.; Poon, S. *Med. Res. Rev.* **1999**, *19*, 97–148.

(2) For examples of the use of solid phase sulfonic acids for amine deprotection and capture, see: (a) Mukade, T.; Dragoli, D. R.; Ellman, J. A. *J. Comb. Chem.* **2003**, *5*, 590–596. (b) Liu, Y-S.; Zhao, C.; Bergbreiter, D. E.; Romo, D. *J. Org. Chem.* **1998**, *63*, 3471–3473.

(3) (a) Morwick, T. M. *J. Comb. Chem.* **2006**, *8*, 649–651. (b) For another recent example of the use of Amberlyst A26 (OH^-) for ester hydrolysis, see: Dandapani, S.; Lan, P.; Beeler, A. B.; Beischel, S.; Abbas, A.; Roth, B. L.; Porco, J. A., Jr.; Panek, J. S. *J. Org. Chem.* **2006**, *71*, 8934–8945. For other hydrolysis examples using resin-bound hydroxide, see: (c) Baxendale, I. R.; Ley, S. V.; Nessi, M.; Piutti, C. *Tetrahedron* **2002**, *58*, 6285–6304. (d) Reed, L. A., III; Risbood, P. A.; Goodman, L. *J. Chem. Soc., Chem. Commun.* **1981**, *15*, 760–761. (e) Arcus, C. L.; Gonzalez, C. G.; Linnecar, D. F. C. *J. Chem. Soc., Chem. Commun.* **1969**, *23*, 1377.

(4) Howard, H. R.; Siegel, T. W.; Beyer, T. A. *Eur. J. Med. Chem.* **1992**, *27*, 779–789.

(5) (a) Svec, F.; Fréchet, J. M. J. *Science* **1996**, *273*, 205–211. (b) Svec, F.; Fréchet, J. M. J. *Ind. Eng. Chem. Res.* **1999**, *38*, 34–48.

(6) It is essential that the alkylation reaction goes to completion to avoid product contamination with the hydrolyzed intermediates **1a** and **b**.

(7) Filtration of the mixtures prior to addition of the resin was found to be necessary to achieve good product yields. This was believed to be the result of carbonate exchange with available sites on the resin, because product acids were found to be partially released into the solvent prior to elution when the filtration step was excluded.

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