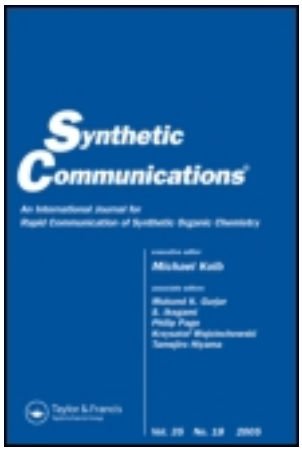

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ACID-CATALYZED ADDITION OF *N*-HYDROXYUREA TO 1-ARYL ALCOHOL DERIVATIVES: A NEW SYNTHESIS OF ZILEUTON

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ABSTRACT

A highly efficient synthesis of Zileuton is described in which the key step involves a site-specific alkylation of hydroxyurea under acid catalysis. Various aryl alcohol electrophiles were tested and the reaction was found to be highly substrate-specific, favoring benzothiophene and benzofuran-based alcohols.

Key Words: Alkylation; Hydroxamic Acids and Derivatives; Regioselection

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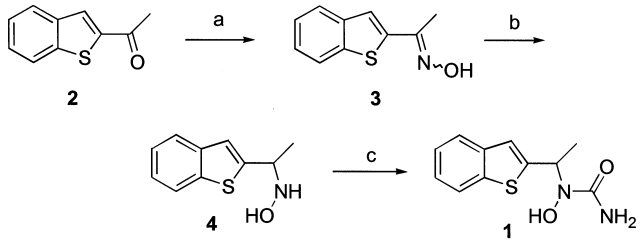
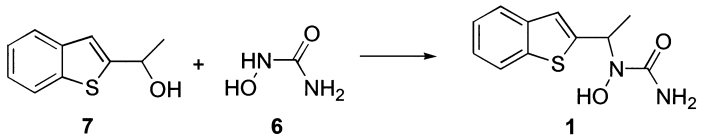
ABT-077 (1), Zileuton, is a 5-lipoxygenase enzyme inhibitor[1] developed by Abbott for the treatment of leukotriene-mediated diseases such as asthma,[2] psoriasis[3] and ulcerative colitis.[4] Several syntheses of Zileuton have been reported, including racemic[5,6] and chiral[7–9] protocols. The first chemically efficient and scaleable process[10] for **1** is outlined in Scheme 1.



Scheme 1. a) H_2NOH, HCl; b) BH_3-Pyridine, HCl; c) KOCN, HCl.

The two major drawbacks of this process are: 1) The oxime isomer mixture requires a large excess of pyridine borane for complete reduction. 2) Pyridine borane is comparatively expensive and is a handling and storage hazard. Due to cost and safety concerns, we found it necessary to develop a more economical process using less hazardous raw materials. Since the discovery of Zileuton, a number of hydroxamic acid derivatives[8,11] have been reported with similar biological activity. Despite the numerous synthetic approaches available, a search of the literature did not reveal any obvious alternative methodologies for the preparation of *N*-alkylated, *N*-hydroxyureas that would suit our manufacturing criteria. The common literature methods for constructing *N*-1 substituted hydroxyureas **8**, involve the assembly of the urea moiety from *N*-substituted hydroxylamines or aminolysis of carbamate precursors. An appealing strategy that would provide a more rapid entry to **1** appeared to be the coupling of *N*-hydroxyurea **6**, with alcohol **7** (Scheme 2).



Scheme 2.

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Acid catalysis[12] proved successful for effecting the alkylation. The high regioselectivity and efficiency for reaction at $N-1$ of urea **6** prompted us to study the utility of the reaction with various aryl alcohols (Table 1).

To compare the reactivity of various aryl alcohol substrates, we chose a standard solvent (THF) and acid (HCl) catalyst. For most of the entries in Table 1, the reaction was conducted at 50°C for 6 hours. With the exception of entry 1, yields were not optimized. In general, products were isolated by cooling the reaction mixture and collecting the solid product by filtration. Some of the isolated yields were low due to high solubility of the product in the reaction solvent. Prolonged exposure to the acidic medium following completion of the reaction may also result in product decomposition.[13] With entry 5, higher temperature and longer reaction time resulted in a lower yield.

General Procedure for Hydroxyurea Additions: (Entry 1, Zileuton)

Substrate alcohol (25 mmol) was stirred in THF (15 mL) and water (5 mL) at room temperature and treated with hydroxyurea (37.5 mmol, 1.5 equiv.), followed by conc. HCl (7.59 g, 75 mmol, 3 equiv.). The reaction was warmed to 50°C for 4 hours then cooled to room temperature and partitioned between EtOAc (25 mL) and water (20 mL). The aqueous layer was extracted with EtOAc (25 mL) and the combined organic layers washed with water (20 mL) and brine (20 mL). Solvents were removed *in vacuo* and the residue was slurried for 10 minutes in a mixture of EtOAc (10 mL), toluene (20 mL) and water (10 mL). The slurry was filtered and the solids washed with 10 mL of water and 15 mL of toluene. Drying *in vacuo* for 18 hours at 60°C afforded 3.52 g (59.7%) white solid, spectroscopically identical to authentic material.

Higher yields of ABT-077 were realized when THF co-solvent was replaced with ethyl acetate. On a multi kilogram scale in the pilot plant,[14] isolated yields averaged 80–90%.

All isolated products from Table 1 were fully characterized by spectroscopic techniques. Analytical data for new compounds are shown below.

***N*-(Diphenylmethyl)-*N*-hydroxyurea (entry 8):** Yield: 26%. Mp 156–57; ^{1}H NMR (300 MHz, DMSO-D_6/TMS) 6.44 (2H, s), 6.49 (1H, s), 7.22–7.35 (10H, m), 9.24 (1H, s); ^{13}C NMR (75.5 MHz, DMSO-D_6/TMS) 63.5, 126.8, 127.9, 128.8, 140.4, 161.7; IR (MIC, cm^{-1}) 1420, 1655, 3260, 3450; MS (CI) m/z 243 $(M+1)^+$; Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82; N, 11.56. Found: C, 69.34; H, 5.89; N, 11.53.

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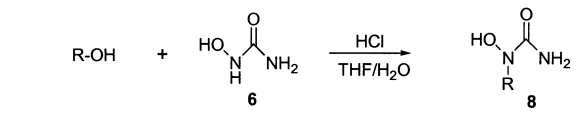
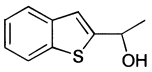
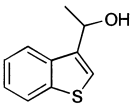
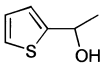
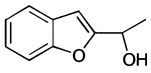
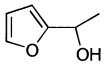
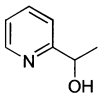
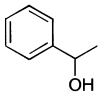
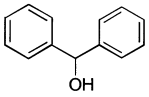
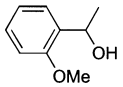
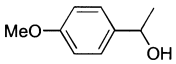
Table 1. Acid-Catalyzed Reaction of Hydroxyurea with Aryl Alcohols



Entry	Aryl Alcohol	Temp (°C)	Time (hrs)	Conversion[a]	Yield (isolated)	Mp (°C) (Lit)
1		50	4	91.3	59.7	147-148.5 (149-151)[16]
2		50	6	30	18.8	177.2-177.6 (180)[15]
3		50	6	59	40	132-133 (131)[15]
4		50	2	89	57.3	143-145.5 (147-150)[15]
5		25	0.75	52	37	147.5-149 (143-144)[15]
6		50	6	0	0	
7		50	6	4.5	0	
8		50	6	85	26	156-157
9		50	6	50	37.2	144-145
10		50	6	58	30	138-139

[a] Determined by peak area % in HPLC of crude product mixtures.

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***N*-Hydroxy-*N*-[1-(2-methoxyphenyl)ethyl]urea (entry 9):** Yield: 37.2%. Mp 144–45; ^{1}H NMR (300 MHz, DMSO-D_6/TMS) 1.31 (3H, d), 3.77 (3H, s), 5.54 (1H, q), 6.28 (2H, bs), 6.84–6.94 (2H, m), 7.15–7.23 (1H, m), 7.40–7.45 (1H, dd), 9.14 (1H, s); ^{13}C NMR (75.5 MHz, DMSO-D_6/TMS) 17.2, 49.7, 55.4, 110.5, 120.0, 127.1 127.6, 131.6, 156.0, 161.1. MS (CI) *m*/*z* 211 $(M+1)^+$; Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.26; H, 6.68; N, 13.20.

***N*-Hydroxy-*N*-[1-(4-methoxyphenyl)ethyl]urea (entry 10):** Yield: 30.0%. Mp 138–139; ^{1}H NMR (300 MHz, DMSO-D_6/TMS) 1.37 (3H, d), 3.72 (3H, s), 5.25 (1H, q), 6.27 (2H, s), 6.85 (2H, d), 7.25 (2H, d), 8.99 (1H, s); ^{13}C NMR (75.5 MHz, DMSO-D_6/TMS) 17.3, 54.4, 55.0, 90.0, 113.2, 128.6, 134.0, 158.1, 161.6; MS (CI) *m*/*z* 243 $(M+1)^+$; Anal. Calcd. for $C_{10}H_{14}N_2O_3$: C, 57.13; H, 6.71; N, 13.32. Found: C, 57.04; H, 6.75; N, 13.28.

In summary, we have shown that acid-catalyzed addition of hydroxyurea to benzo[b]thiophen-2-yl-ethanol provides a simple, safe and highly efficient route to Zileuton. This alkylation methodology is efficient with only a small class of electron-rich heteroaromatic substrates and isolated yields may depend on product solubility and stability in the reaction medium.

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