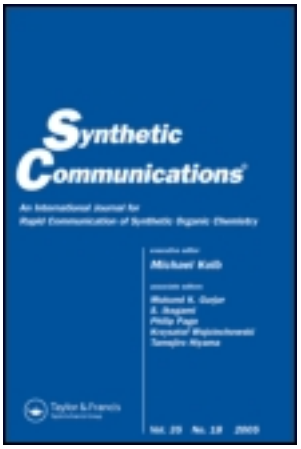

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One-Pot Synthesis of Hydroxybenzo[d]-oxazole-2-aliphatic Acid Derivatives by Meerwein's Reagent

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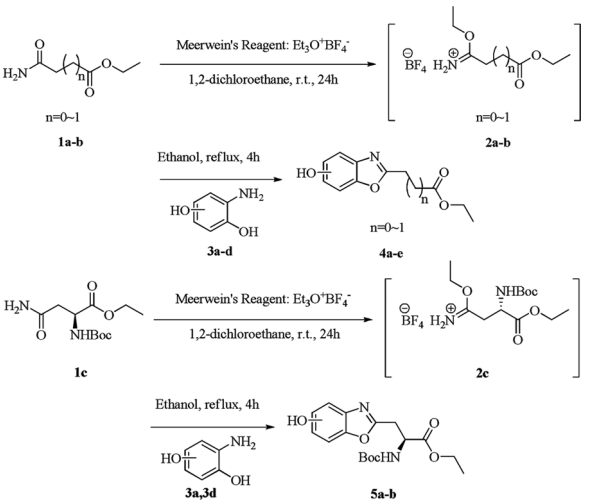
ONE-POT SYNTHESIS OF HYDROXYBENZO[d]-OXAZOLE-2-ALIPHATIC ACID DERIVATIVES BY MEERWEIN'S REAGENT

Wei Zhang, Wenlu Liu, Xizhen Jiang, Faqin Jiang, and Lei Fu
School of Pharmacy, Shanghai Jiao Tong University, Shanghai, China

GRAPHICAL ABSTRACT



Abstract *A general one-pot synthesis of hydroxylbenzo[d]oxazole-2-aliphatic acid esters and hydroxylbenzo[d]oxazole-2-amino acid esters was successfully achieved in good yield by using Meerwein's reagent.*

Keywords 2-Aminophenol; benzo[d]oxazole; Meerwein's reagent; triethyloxonium tetrafluoroborate

INTRODUCTION

Benzoxazole derivatives were found to have biological activities. In cancer research, benzoxazoles have been explored as VEGFR-2 inhibitors,[1] CSF-1 R inhibitors,[2] LPAAT-β inhibitors,[3] EDGR inhibitors,[4] Janus kinases inhibitors[5], and GnRH receptor inhibitors.[6] In the mean time, benzoxoazole fragments have drawn

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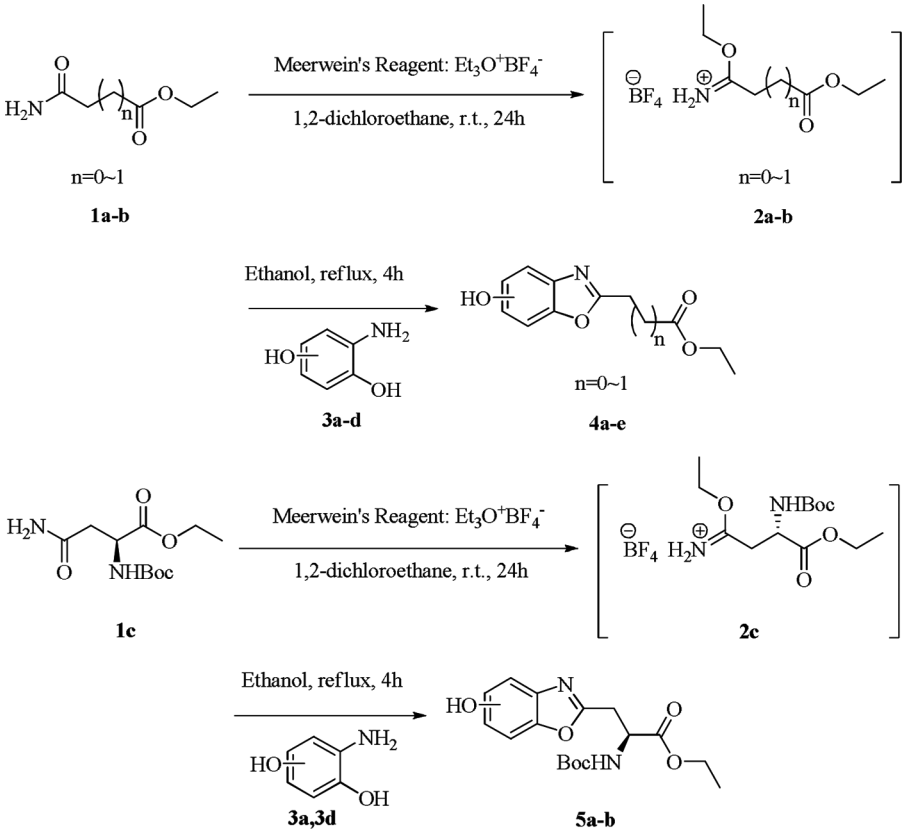
considerable attention over the past few years for their antimicrobial activities, and antibiotics containing benzoxoazole modules have been developed.[7,8]

The synthesis of benzo[d]oxazole has been reported and promoted in many articles. Generally, benzo[d]oxazole has been formed from various 2-aminophenols with acid anhydride,[9] carboxylic acid,[10] acylchloride,[11] amide,[12] or carboxylic ether.[13] These common methods were usually applied to synthesize simple and stable benzo[d]oxazole derivatives, as they require high temperature (100–300 °C)[12,14] and/or stong acidic catalysts (e.g., *p*-TsOH[11], P_2O_5,[15] PPTS[16] and $POCl_3$[17]). A gentle method was therefore developed, in which 2-aminophenols was condensed with imidate esters under reflux conditions in methanol or ethanol to complete cyclization, giving benzo[d]oxazole in good yields.[18,19] However, the imidate esters generally existed in hydrochloride salt form and were presynthesized from nitriles and alcohols in ether or hexane solution by bubbling with dry hydrogen chloride gas.[20,21] Furthermore, the imidate esters are usually water sensitive and unstable, and hence difficult to handle.[22]

Meyers et al.[23] and Hall et al.[24] utilized aromatic imidate esters from aromatic amide by Meerwein's reagent, triethyloxonium tetrafluoroborate ($Et_3O^+BF_4^-$), to

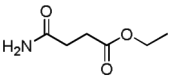
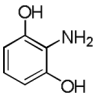
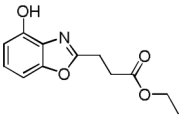
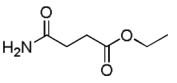
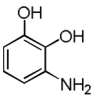
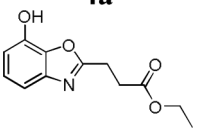
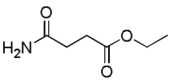
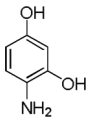
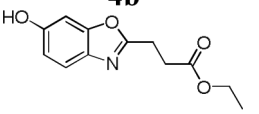
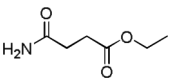
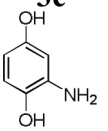
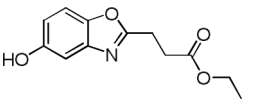
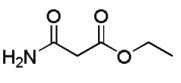
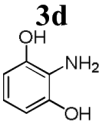
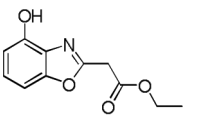
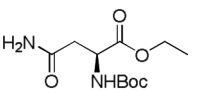
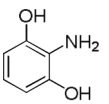
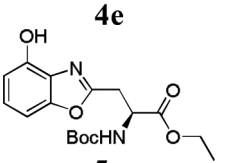
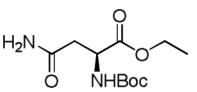
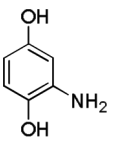
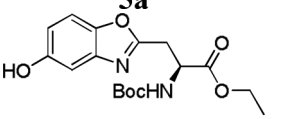


Scheme 1. Synthesis of hydroxybenzo[d]oxazol-2-aliphatic acid esters **4a–e** and **5a** and **b**.

synthesize aryl-substituted oxazoline cycles. Their successful application had prompted us to explore the synthesis of benzo[d]oxazole by Meerwein's reagent.

In this communication, we reported the synthesis of a family of more complex hydroxybenzo[d]oxazole-2-aliphatic acid derivatives **4a-e** and hydroxybenzo[d]oxazole-2-amino acid derivatives **5a** and **b** as shown in Scheme 1. In general, Meerwein's reagent $(Et_3O^+BF_4^-)$ was prepared according to the modified methods reported by

Table 1. Yields of hydroxylbenzo[d]oxazole-2-aliphatic acid esters (**4a–e**) and hydroxylbenzo[d]oxazole-2-amino acid esters (**5a** and **b**)

Reactant 1	Reactant 2	Products	Yield (%)
 **1a**	 **3a**	 **4a**	80
 **1a**	 **3b**	 **4b**	75
 **1a**	 **3c**	 **4c**	70
 **1a**	 **3d**	 **4d**	60
 **1b**	 **3a**	 **4e**	73
 **1c**	 **3a**	 **5a**	60
 **1c**	 **3d**	 **5b**	55

Hall et al.[24] and Kern.[25] Succinamic acid ethyl ester (**1a**), malonamic acid ethyl ester (**1b**), or *N*′-Boc-*L*-argininate ethyl ester (**1c**) was treated with freshly prepared Meerwein's reagent ($Et_3O^+BF_4^-$) in 1, 2-dichloroethane at room temperature for 24 h. The imidate ethyl esters tetrafluoroborate salts **2a–c** were formed, and they were sequentially reacted in situ with solutions of various hydroxyl-2-aminophenols (**3a–d**) in absolute ethanol at reflux temperature (85 °C). This one-pot reaction yielded hydroxylbenzo[d]oxazole-2-aliphatic acid esters (**4a–d**) and hydroxylbenzo[d]-oxazole-2-amino acid esters (**5a** and **b**) in reasonable yields. All reaction conditions, including the reactants, products, and yields are listed in Table 1, and all compounds **4a–d** and **5a** and **b** were characterized by ^{1}H NMR, electrospray ionization (ESI), and elemental analyses.

Specifically, in this one-pot procedure, solutions of air-sensitive 2-aminophe-nols (**3a–d**) in dry alkyl alcohol prepared from the stable 2-nitrobenzenediol by hydrogenation were introduced directly into the reaction system without further purification of imidate alkyl esters. The alcoholic solvents (e.g., ethanol, methanol) we utilized could quench the excess amount of Meerwein's reagent, thus no alky-lation side products of 2-aminophenols were formed. After addition of aqueous $NaHCO_3$ solution, the excess imidate alkyl esters were transferred into less polar die-sters (e.g., diethyl succinate from **1a**) and conveniently removed by using a flash chromatographic column. The unreacted 2-aminophenols could be removed by washing with diluted mineral acids (e.g., 1 N HCl).

In summary, we have successfully developed an efficient and facile one-pot method to prepare a series of hydroxylbenzo[d] oxazole-2-aliphatic acid derivatives via Meerwein's reagent ($Et_3O^+BF_4^-$). This new procedure avoids the use of vigorous temperature and strong acidic catalysts, and it can be readily utilized to synthesize more complex benzo[d]oxazole derivatives.

EXPERIMENTAL

All commercial chemicals and solvents are analytical grade and were used with-out further purification unless otherwise specified. All reactions except those in aque-ous media were carried out with the use of standard techniques for the exclusion of moisture. Reactions were monitored by thin-layer chromatography (TLC) under 254-nm ultraviolet light. ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Brucker 300 MHz Avance DPX or a Bruker 500-MHz Avance DRX instrument. Chemical shifts are reported in parts per million (δ), and coupling constants (*J*) are in hertz (Hz). Mass spectroscopy was conducted using a Shimadzu QP5000 mass spectrometer. Elemental analyses were performed with a Perkin-Elmer CHNS/O analyzer. Optical rotations were obtained using Jasco polarimeter P-2000.

Meerwein's Reagent: $Et_3O^+BF_4^-$

Under nitrogen protection, at room temperature, epichlorohydrin (30 mL, 0.38 mmol) was added dropwise into a mixture of freshly distilled $Et_2O \cdot BF_3$ (63 mL, 0.5 mmol) in 125 mL ether at a rate sufficient to maintain vigorous boiling. After addition of epichlorohydrin, the resulting mixture was kept refluxing for another 1.0 h. Sequentially, it was cooled to room temperature and left stand for

2 h for the product to crystallize. Ether was cannulated off, and dry ether was added to wash the crystals three times, and then the washing ether was batchwise cannulated off. After drying in vacuum, a white crystal, Meerwein's reagent, was obtained (70 g, yield 97%).

Ethyl 3-(4-Hydroxybenzo[d]oxazol-2-yl)propanoate (4a)

Succinamic acid ethyl ester (1a) (0.2 g, 1.38 mmol) was dissolved in 10 mL 1, 2-dichloroethane, and then freshly prepared Meerwein's reagent $Et_3O^+BF_4^-$ (0.262 g, 1.38 mmol) was added in portions under nitrogen. The resulting mixture was stirred for 24 h at rt. A newly prepared solution of 2-aminobenzene-1,3-diol (**3a**) (0.19 g, 1.52 mmol, prepared from 2-nitrobenzene-1,3-diol and 10%Pd/C in absolute ethanol under hydrogen at 1 atm) in 20 mL ethanol was transferred into the solution through a syringe. The mixture was heated to reflux for 4 h and cooled to rt. Next, 20 mL saturated aqueous $NaHCO_3$ solution was added, and then the aqueous layer was extracted with 30 mL dichloromethane. The organic layer was washed with brine and dried with anhydrous Na_2SO_4. After filtration and concentration, the crude product was then purified on silica gel, eluting with petroleum ether–EtOAc (2: 1) to give a pure compound **4a**, brown ceraceous solid, 277 mg, 80% yield, mp 44–46 °C. MS (ESI), m/z: 236 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 8.52 (br, 1H, OH), 7.20 (t, $J=8.1$ Hz, 1H, ArH), 7.04 (d, $J=8.1$ Hz, 1H, ArH), 6.86 (d, $J=8.1$ Hz, 1H, ArH), 4.15 (q, $J=7.2$ Hz, 2H, CH_2), 3.30 (t, $J=7.8$ Hz, 2H, CH_2), 2.91 (t, $J=7.2$ Hz, 2H, CH_2), 1.23 (t, $J=7.0$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 171.22, 164.15, 151.46, 147.50, 128.57, 125.45, 110.55, 101.69, 60.49, 30.52, 23.35, 13.64. Anal. calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.30; H, 5.52; N, 6.01.

Ethyl 3-(7-Hydroxybenzo[d]oxazol-2-yl)propanoate (4b)

Brown ceraceous solid, 75% yield, mp 22–25 °C. MS (ESI), m/z: 236 $[M+H]^+$.^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.44 (br, 1H, OH), 7.21 (dd, $J=8.1$ Hz, $J=0.6$ Hz, 1H, ArH), 7.13 (t, $J=8.0$ Hz, 1H, ArH), 6.84 (dd, $J=7.5$ Hz, $J=1.2$ Hz, 1H, ArH), 4.15 (q, $J=7.1$ Hz, 2H, CH_2), 3.25 (t, $J=7.2$ Hz, 2H, CH_2), 2.92 (t, $J=7.3$ Hz, 2H, CH_2), 1.23 (t, $J=7.2$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 171.75, 164.78, 147.42, 142.30, 124.47, 120.21, 111.24, 96.51, 60.56, 30.32, 23.38, 13.66. Anal. calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.32; H, 5.61; N, 5.93.

Ethyl 3-(6-Hydroxybenzo[d]oxazol-2-yl)propanoate (4c)

Yellow solid, 70% yield, mp 39–42 °C. MS (ESI), m/z: 236 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.46 (d, $J=8.8$ Hz, 1H, ArH), 6.96 (d, 1H, $J=2.4$ Hz, ArH), 6.80 (dd, $J=8.4$ Hz, $J=2.0$ Hz, 1H, ArH), 4.17 (q, $J=7.2$ Hz, 2H, CH_2), 3.21 (t, 2H, $J=7.4$ Hz, CH_2), 2.90 (t, $J=7.6$ Hz, 2H, CH_2), 1.25 (t, $J=7.4$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 171.66, 164.01, 154.17, 151.08, 133.51, 118.86, 112.55, 97.23, 60.61, 30.29, 23.32, 13.62. Anal. calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.35; H, 5.59; N, 5.96.

Ethyl 3-(5-Hydroxybenzo[d]oxazol-2-yl)propanoate (4d)

Brown ceraceous solid, 60% yield, mp 76–79 °C. MS (ESI), m/z: 236 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.33 (d, $J=9.0$ Hz, 1H, ArH), 7.11 (d, $J=2.1$ Hz, 1H, ArH), 6.83 (dd, $J=8.7$ Hz, $J=2.7$ Hz, 1H, ArH), 5.16 (s, 1H, OH), 4.18 (q, $J=7.2$ Hz, 2H, CH_2), 3.24 (t, $J=7.2$ Hz, 2H, CH_2), 2.93 (t, $J=7.3$ Hz, 2H, CH_2), 1.27 (t, $J=7.2$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 171.45, 166.10, 153.13, 144.72, 140.96, 112.92, 110.07, 104.72, 60.55, 30.23, 23.47, 13.63. Anal. calcd. for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.57; N, 5.95. Found: C, 61.26; H, 5.55; N, 5.93.

Ethyl 2-(4-Hydroxybenzo[d]oxazol-2-yl)acetate (4e)

White solid, 73% yield, mp 102–104 °C. MS (ESI), m/z: 222 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.26 (t, $J=8.1$ Hz, 1H, ArH), 7.08 (dd, $J=8.1$ Hz, $J=0.6$ Hz, 1H, ArH), 6.89 (dd, $J=8.1$ Hz, $J=0.8$ Hz, 1H, ArH), 4.22 (q, $J=7.2$ Hz, Hz, 2H, CH_2), 4.10 (s, 2H, CH_2), 1.26 (t, $J=7.3$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 166.15, 158.53, 151.67, 147.77, 126.25, 110.79, 61.62, 34.33, 13.58. Anal. calcd. for $C_{11}H_{11}NO_4$: C, 59.73; H, 5.01; N, 6.33. Found: C, 59.88; H, 4.97; N, 6.31.

(S)-Ethyl 2-(*tert*-Butoxycarbonylamino)-3-(4-hydroxybenzo[d]oxazol-2-yl)propanoate (5a)

Yellow sticky oil, 60% yield. $[\alpha]_D^{15}$ p= −14 (c = 0.22 in acetone). MS (ESI), m/z: 351 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.23 (t, $J=8.1$ Hz, 1H, ArH), 7.05 (d, $J=8.1$ Hz, 1H, ArH), 6.87 (d, $J=8.1$ Hz, 1H, ArH), 5.66 (d, $J=8.1$ Hz, 1H, NH), 4.86–4.82 (m, 1H, CH), 4.22 (q, $J=7.2$ Hz, 2H, CH_2), 3.50 (d, $J=5.4$ Hz, 2H, CH_2), 1.39 (s, 9H, $3CH_3$), 1.22 (t, $J=7.2$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 170.37, 161.47, 154.74, 151.59, 147.39, 128.44, 125.71, 110.37, 101.85, 79.80, 61.57, 51.04, 31.09, 27.78, 13.54. Anal. calcd. for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.43; H, 6.28; N, 7.99.

(S)-Ethyl 2-(*tert*-Butoxycarbonylamino)-3-(5-hydroxybenzo[d] oxazol-2-yl)propanoate (5b)

Yellow sticky oil, 55% yield. $[\alpha]_D^{15} = -6.6$ (c = 0.30 in acetone). MS (ESI), m/z: 351 $[M+H]^+$. ^{1}H NMR (300 MHz, $CDCl_3$), δ: 7.30 (d, $J=8.4$ Hz, 1H, ArH), 7.10 (s, 1H, ArH), 6.83 (dd, $J=8.4$ Hz, $J=1.5$ Hz, 1H, ArH), 5.68 (m, 1H, NH), 4.82–4.79 (m, 1H, CH), 4.20 (q, $J=7.0$ Hz, 2H, CH_2), 3.43 (dd, dd, $J=-15.9$ Hz, $J=5.1$ Hz, $J=4.5$ Hz, 2H, CH_2), 1.41 (s, 9H, $3CH_3$), 1.19 (t, $J=7.0$ Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$), δ: 170.35, 163.36, 154.90, 152.99, 144.91, 141.19, 112.99, 110.08, 104.98, 79.93, 61.54, 50.81, 31.23, 27.78, 13.51. Anal. calcd. for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.30; H, 6.35; N, 8.02.

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