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Expeditious Synthesis of Natural Benzofuran, Eupomatenoid-6 by Umpolung of α-Aminophosphonates

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Simple and practical synthesis of natural benzofuran derivative eupomatenoid-6 *via* Horner-Emmons type condensation as the key step is described. The *umpolung* property of aldehyde derivative, α-aminophosphonate was efficiently employed in this reaction. α-Aminophosphonate of anisaldehyde subjected to Horner-Emmons type condensation with 5-bromo-2-methoxybenzaldehyde to yield the deoxybenzoin, which was further methylated and then underwent tandem demethylation-cyclodehydration to afford the benzofuran scaffold in excellent yield. Finally Suzuki coupling with propenyl boronic acid afforded eupomatenoid-6 with an overall yield of 56.8%.

Key Words : α-Aminophosphonate, Kebachnik-Fields reaction, Horner-Emmons type condensation, Suzuki coupling, Eupomatenoid-6

Introduction

Substituted benzofurans are attractive targets of organic synthesis because of their physiological, pharmacological and therapeutic properties.[1] For example, a variety of benzofuran derivatives have been investigated as antifungal agents,[2] estrogen receptor (ER) ligands,[3] selective ligands for the dopamine D_3 receptor subtype,[4] H_3 receptor antagonists[5] and metalloproteinase-13 inhibitors.[6] 2-Arylbenzo[*b*]furan nucleus is widely exists in natural products such as phytoalexins and neolignans.[7] Their broad range of biological and pharmacological properties have generated extensive and enduring efforts toward the synthesis of these important heterocyclic compounds. Synthetic methods to construct 2-arylbenzo[*b*]furans include the palladium-catalyzed cross coupling cyclization of alkynes and *o*-halophenols,[8] cyclization of vinylic phenols through McMurry coupling,[9] [3,3]-sigmatropic rearrangement of oxime-ethers[10] and palladium-catalyzed enolate arylation.[11] Recently, Dong *et al.* reported the rhodium-catalyzed coupling of vinylphenols and nonchelating aldehydes.[12] Another approach from 2-methoxychalcone epoxides has also been reported.[13]

Eupomatenoids are distinct class of neolignans, isolated originally from two plant species which belong to the angiosperm family Eupomatiaceae.[14] Structurally, the eupomatenoids (**1**) (Fig. 1) are characterized by a 2,3,5-substitution pattern with an aryl substituent in the 2-position, a methyl substituent in the 3-position and a C_3-substituent R in the 5-position. They exhibit antitumor, insecticidal, antimicrobial and antioxidant properties.[15] Thus much efforts have been directed for the synthesis of this important scaffold.[11-13,16] Few groups reported the synthesis of eupomatenoid-6.[10,11,13,16] Although many synthetic methods have been reported in the literature, procedures for the construction of benzofuran motif *via* the formation of 2-alkoxydeoxybenzoin are highly desirable.

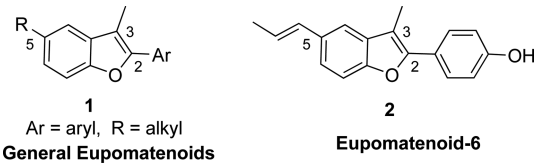


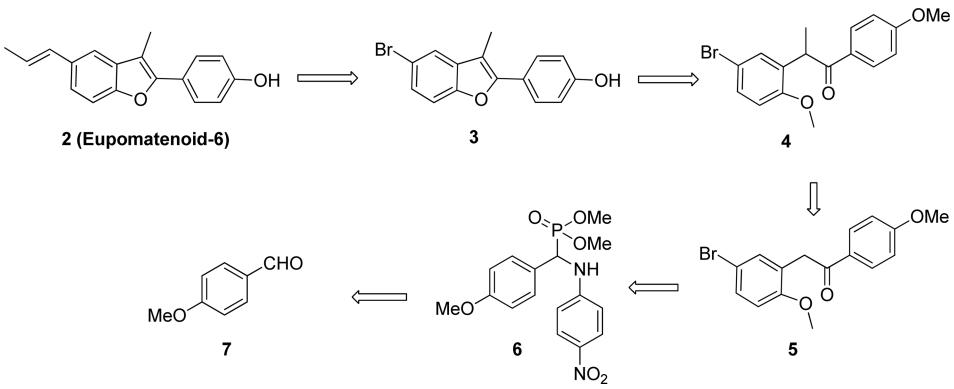
Figure 1. General structure of eupomatenoids (**1**) and eupomatenoid-6 (**2**).

In continuation of our work[17] on the synthesis of bioactive natural products, herein we wish to describe a simple and practical synthesis of eupomatenoid-6 (**2**) *via* Horner-Emmons type condensation as the key step.

Results and Discussion

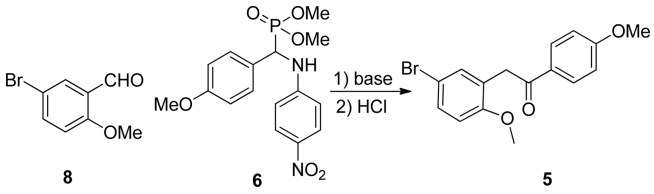
Our retrosynthetic approach to eupomatenoid-6 (**2**) is outlined in Scheme 1. The natural product would be envisioned to arise from benzofuran **3**. Compound **3** would be generated by the BBr_3 mediated demethylation-cyclodehydration of the corresponding intermediate **4** which in turn can be obtained from the key intermediate, 2-methoxydeoxybenzoin **5** by methylation. 2-Methoxydeoxybenzoin **5** would be resulted by the Horner-Emmons type condensation between α-aminophosphonate **6** of commercial 4-methoxybenzaldehyde (**7**) and 5-bromo-2-methoxybenzaldehyde (**8**).

The synthesis of eupomatenoid-6 (**2**) was initiated by the Kebachnik-Fields reaction of 4-methoxybenzaldehyde (**7**), 4-nitroaniline (**9**) and dimethylphosphite (Scheme 2). By using a slight modification to the literature procedure,[18] the α-aminophosphonate **6** was obtained in 93% yield. Utilization of α-aminophosphonates as carbanion precursors for the construction of carbon-carbon bond formation are highly appreciated.[19] Construction of benzofuran motif by employing *umpolung* property of α-aminophosphonate (aldehyde



Scheme 1. Retrosynthesis of eupomatenoid-6.

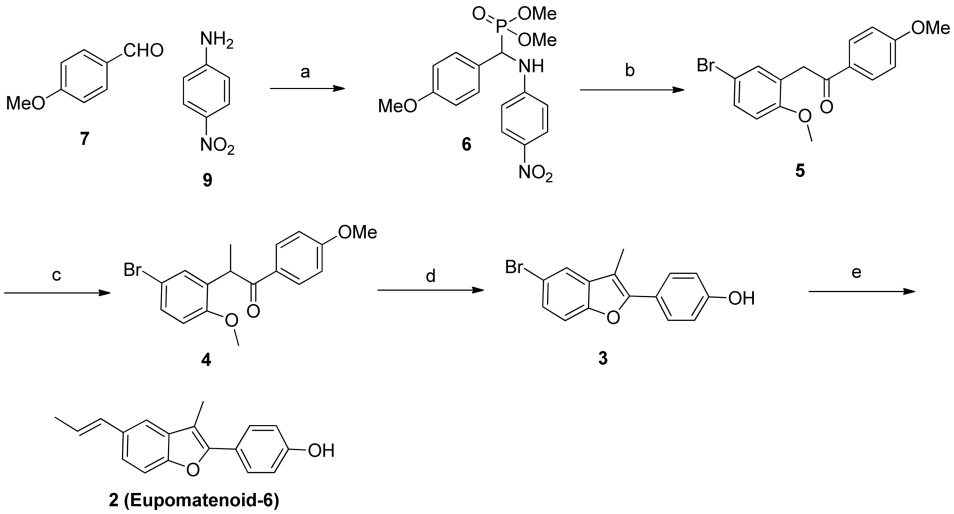
Table 1. Optimization of Horner-Emmons type condensation[a]



Entry	Condition	Yield[b] (%)
1	Cs_2CO_3 (1.2 eq), THF/IPA (4:1), rt, overnight	53
2	NaH (1.4 eq), THF, 0 °C ~ rt, overnight	31
3	^{t}BuOK (1.5 eq), THF, 0 °C ~ rt, 6.5 h	39
4	Cs_2CO_3 (1.3 eq), THF/IPA (4:1), rt, overnight	44
5	Cs_2CO_3 (1.4 eq), THF/IPA (4:1), rt, 48 h	71
6[c]	Cs_2CO_3 (1.4 eq), THF/IPA (4:1), rt, 48 h	18
7[d]	Cs_2CO_3 (1.4 eq), THF/IPA (4:1), rt, 48 h	29

[a]Compound **8** (1.0 eq), compound **6** (1.1 eq) was used. [b]Yields of pure compound after column chromatography. [c]α-Aminophosphonate obtained from diphenylphosphite, 4-methoxybenzaldehyde (**7**) and aniline was used. [d]α-Aminophosphonate obtained from diphenylphosphite, 4-methoxybenzaldehyde (**7**) and 4-nitroaniline was used.

derivative) is very limited in the literature. Previously, only one method was reported in the literature by Seemuth and Zimmer in which they utilized diphenyl 1-(4-nitroanilino)-1-arylmethanephosphonates as carbanion precursors for the synthesis of 2-methoxydeoxybenzoins by employing LDA as base at −78 °C.[20] Umpolung chemistry has been a focus of research in organic synthesis because of its usefulness and unusual reactivity. Modification to the reported method which will allow the reaction at ambient temperature with improved yields is highly desirable. Herein, the *umpolung* property of the aldehyde **7** in the α-aminophosphonate **6** was efficiently employed in reaction with 5-bromo-2-methoxybenzaldehyde to yield the key intermediate, 2-methoxydeoxybenzoin **5**. Horner-Emmons type condensation between compound **6** and compound **8** gave enamine intermediate which was then directly converted to compound **5** by addition of hydrochloric acid. We checked various conditions to afford the compound **5** and finally obtained 71% yield using cesium carbonate as base (Table 1, entry 5). α-Aminophosphonate of 4-methoxybenzaldehyde (**7**), aniline and diphenyl phosphite yielded the product **5** only 18% (Table 1, entry 6) whereas with the α-aminophosphonate of 4-methoxybenzaldehyde (**7**), 4-nitroaniline and diphenyl phosphite the product **5** was formed in 29% yield (Table 1, entry 7).



Scheme 2. Reagents and conditions: (a) dimethylphosphite, $InCl_3$ (10 mol %), THF, reflux, 4 h, 93% (b) (i) 5-bromo-2-methoxybenzaldehyde (**8**), Cs_2CO_3, THF/IPA (4:1), rt, 48 h (ii) con. HCl, MeOH, 60 °C, 3 h, 71% (c) MeI, ^{t}BuOK, THF, 0 °C ~ rt, 2 h , 98% (d) (i) 1.0 M BBr_3 in CH_2Cl_2, rt, 36 h. (ii) H_2O, reflux, 2 h, 91.5% (e) *trans*-propenyl boronic acid, CsF, $Pd(PPh_3)_4$ (3 mol %), DME, 85 °C, 6 h, 96%.

From these experiment we can come to know that replacement of diphenyl phosphite (entry 6) with dimethyl phosphite (entry 5) offered the minimal steric hindrance and the product was obtained in good yield. Increased acidity of benzylic proton using 4-nitroaniline (entry 5) facilitated the reaction more ease than with aniline (entry 7).

The compound **5** was then treated with methyl iodide in the presence of potassium *tert*-butoxide (^{t}BuOK) to give the compound **4** in 98% yield. When *O*-demethylation of compound **4** was carried out using excess of BBr_3 (10.0 eq.) in CH_2Cl_2 at room temperature for 36 h a spontaneous tandem intramolecular cyclization took place as envisaged to furnish compound **3** in 91.5% yield. We checked the same reaction for 24 h and 48 h to achieve quantitative yield but we got the compound **3** only in 76% and 71% yields respectively. Compound **3** was then subjected to Suzuki coupling with propenyl boronic acid in sealed tube to give eupomatenoid-6 in 96% yield. The product gave identical spectral data to that in the literature.[10,14,21]

In conclusion, we have established a practical and improved method for the synthesis of eupomatenoid-6 with an overall yield of 56.8% from commercially available starting materials. We feel that the present synthetic route is readily accessible for the construction of different benzofuran natural products and their analogues.

Experimental

All chemicals were purchased from Sigma-Aldrich Chemicals and were used without further purification unless noted otherwise. ^{1}H NMR spectra were recorded at Varian Mercury-300 MHz FT-NMR and 75 MHz for ^{13}C, with the chemical shift (δ) reported in parts per million (ppm) relative to TMS and the coupling constants (*J*) quoted in Hz. $CDCl_3$ was used as a solvent and an internal standard. Mass spectra were recorded using a EI-5977E (Agilent) spectrometer for EIMS and JMS-700 (JEOL) for HRMS. Melting points were measured on a MEL-TEMP II apparatus and were uncorrected. Thin-layer chromatography (TLC) was performed on DC-Plastikfolien 60, F_{254} (Merck, layer thickness 0.2 mm) plastic-backed *silica* gel plates and visualized by UV light (254 nm) or staining with *p*-anisaldehyde.

Dimethyl ((4-Methoxyphenyl)((4-nitrophenyl)amino)-methyl)phosphonate (6). To a mixture of 4-methoxybenzaldehyde (0.24 mL, 2.0 mmol), 4-nitroaniline (276.0 mg, 2.0 mmol) and dimethylphosphite (0.24 mL, 2.0 mmol) in THF (8 mL), was added indium(III) chloride (44 mg, 0.2 mmol) under nitrogen atmosphere and the mixture was refluxed for 4 h. The reaction mixture was then cooled to room temperature, diluted with water and extracted with EtOAc (3 × 30 mL). The combined organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude product was purified by column chromatography ($MeOH/CH_2Cl_2$ = 1/100 to 1/50) to afford the product as pale yellow solid. Yield : 681 mg (93%); R_f 0.45 ($MeOH/CH_2Cl_2$ = 1/20); mp 153-155 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.00 (2H, d, *J* = 9.3 Hz), 7.35 (2H, dd, *J* = 8.1, 1.8 Hz), 6.90 (2H, d, *J* = 9.0 Hz), 6.56 (2H, d, *J* = 9.0 Hz), 5.58 (1H, t, *J* = 8.1 Hz), 4.77 (1H, dd, *J* = 23.7, 7.5 Hz), 3.78 (3H, s), 3.76 (3H, *J* = 11.1 Hz), 3.46 (3H, d, *J* = 10.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6 (d, *J* = 11.4 Hz), 151.6 (d, *J* = 54.6 Hz), 138.8, 128.8 (d, *J* = 21.6 Hz), 125.9 (d, *J* = 26.1 Hz), 125.8, 114.4 (d, *J* = 9.0 Hz), 112.3, 55.4 (d, *J* = 62.7 Hz), 54.2 (d, *J* = 27.3 Hz), 53.6 (d, *J* = 28.5 Hz), 53.4. EIMS *m/z* 366 (M^+), 257 (Base), 211.

2-(5-Bromo-2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)ethanone (5). To a stirred solution of **6** (562 mg, 1.5 mmol) and 5-bromo-2-methoxybenzaldehyde (300 mg, 1.40 mmol) in THF/IPA (4/1; 15 mL) was added cesium carbonate (636 mg, 1.95 mmol) and the reaction mixture was stirred at 25 °C for 48 h. MeOH (3 mL) and conc. HCl (1.5 mL) were added and stirred the mixture at 60 °C for 3 h. H_2O (25 mL) was added to the mixture and extracted with CH_2Cl_2 (3 × 75 mL). The combined organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/10 to 3/20) to afford the product as white solid. Yield: 332 mg (71%); R_f 0.53 (EtOAc/hexane = 1/3); mp 118-120 °C (lit.[13] mp 117-118 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (2H, d, *J* = 8.7 Hz), 7.32 (1H, dd, *J* = 8.1, 2.4 Hz), 7.26 (1H, d, *J* = 8.7 Hz), 6.92 (2H, d, *J* = 8.7 Hz), 6.74 (1H, d, *J* = 8.7 Hz), 4.18 (2H, s), 3.86 (3H, s), 3.75 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.4, 163.3, 156.2, 133.6, 130.8, 130.6, 129.7, 126.2, 113.6, 112.7, 112.1, 55.7, 55.5, 39.3. EIMS *m/z* 334 (M^+), 336 (M+2), 135 (Base).

2-(5-Bromo-2,4-dimethoxyphenyl)-1-(4-methoxyphenyl)propan-1-one (4). To a suspension of potassium *tert*-butoxide (128.6 mg, 1.15 mmol) in tetrahydrofuran (THF) (3 mL) was added deoxybenzoin **5** (320 mg, 0.96 mmol) in THF (3 mL) slowly at 0 °C. After stiring for 5 min., iodomethane solution in THF (2 mL) was added gradually. The reaction mixture was then allowed to warm to 25 °C. After stirring for 2 h at 25 °C, the reaction mixture was slowly quenched with 2 N HCl and extracted with EtOAc (2 × 50 mL). Combined organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentraed *in vacuo*. The crude was purified on a short column (EtOAc/hexane = 1/5) to yield the pure compound as colorless liquid. Yield: 327 mg (98%); R_f 0.64 (EtOAc/hexane = 1/3). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (2H, d, *J* = 8.4 Hz), 7.24 (2H, d, *J* = 3.3 Hz), 6.84 (2H, d, *J* = 8.4 Hz), 6.72 (1H, d, *J* = 8.4 Hz), 5.00 (1H, q, *J* = 6.9 Hz), 3.84 (3H, s), 3.82 (3H, s), 1.42 (3H, d, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 162.6, 154.3, 132.1, 130.2, 130.1, 130.0, 113.1, 112.8, 111.9, 55.3, 54.9, 39.1, 17.3. EIMS *m/z* 348 (M^+), 350 (M+2), 135 (Base).

4-(5-Bromo-3-methylbenzofuran-2-yl)phenol (3). To a stirred solution of 2-methoxydeoxybenzoin **4** (166.0 mg, 0.48 mmol) in CH_2Cl_2 (10 mL) was added 1.0 M BBr_3/CH_2Cl_2 (4.75 mL, 4.75 mmol) at room temperature under nitrogen atmosphere. The mixture was stirred for 36 h, then water (15 mL) was added and CH_2Cl_2 was evapoarted at reduced pressure. The mixture was then refluxed for 2 h. After cooling to room temperature extracted with EtOAc (2

× 40 mL). Combined organic layer was washed with brine (2 × 50 mL), dried over anhydrous Na_2SO_4 and concentraed *in vacuo*. The crude product was purified by column chromatography (EtOAc/hexane = 1/2) to afford the product as colorless solid. Yield: 126 mg (91.5%); R_f 0.48 (EtOAc/hexane = 1/3); mp 151-153 °C (lit.[16c] mp 157-159 °C; lit.[13] mp 155-156 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, d, J = 8.7 Hz), 7.60 (1H, s), 7.32 (2H, d, J = 2.7 Hz), 6.93 (2H, d, J = 9.0 Hz), 4.99 (1H, s), 2.39 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.7, 152.4, 152.1, 133.4, 128.6, 126.8, 123.9, 121.9, 115.8, 115.5, 112.4, 109.4, 9.6. EIMS *m/z* 302 (M^+), 304 (M+ 2), 135 (Base).

(*E*)-4-(3-Methyl-5-(prop-1-en-1-yl)benzofuran-2-yl)phenol (eupomatenoid-6) (2). To a stirred mixture of benzofuran **3** (80 mg, 0.28 mmol), powdered CsF (168 mg, 1.11 mmol) and *trans*-propenylboronic acid (71 mg, 0.83 mmol) in DME (1.25 mL) in sealed tude was added $Pd(PPh_3)_4$ (9.6 mg, 0.03 mmol) at room temperature. The reaction mixture was stirred for 6 h at 85 °C. After cooling to room temperature, the reaction mass was concentrated *in vacuo*. The crude was purified by column chromatography (EtOAc/hexane = 1/5) to afford the product as colorless solid. The spectroscopic data were identical with those previously reported.[14,16] Yield: 70 mg (96%); R_f 0.43 (EtOAc/hexane = 1/4); mp 145-147 °C (lit.[16c] mp 147.5-148 °C; lit.[16a] mp 147.5-149 °C; lit.[14a] mp 148-150 °C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, dd, J = 6.9, 2.1 Hz), 7.41 (1H, d, J = 1.5 Hz), 7.34 (1H, d, J = 8.4 Hz), 7.27 (1H, d, 1.5 Hz), 6.92 (2H, d, J = 9.0 Hz), 6.50 (1H, dd, J = 15.6, 1.2 Hz), 6.22 (1H, m), 4.91 (1H, s), 2.42 (3H, s), 1.90 (3H, dd, J = 6.9, 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 153.0, 151.2, 132.7, 131.6, 131.4, 128.4, 124.5, 124.3, 122.3, 116.2, 115.7, 110.8, 110.0, 18.8, 9.7. EIMS *m/z* 264 (M^+), 223 (Base), 165. HRMS (EI) calcd for $C_{18}H_{16}O_2$ M^+ 264.1150, found 264.1150.

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