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A FACILE SYNTHESIS OF BENZOFURAN DERIVATIVES: A USEFUL SYNTHON FOR PREPARATION OF TRYPSIN INHIBITOR[#]

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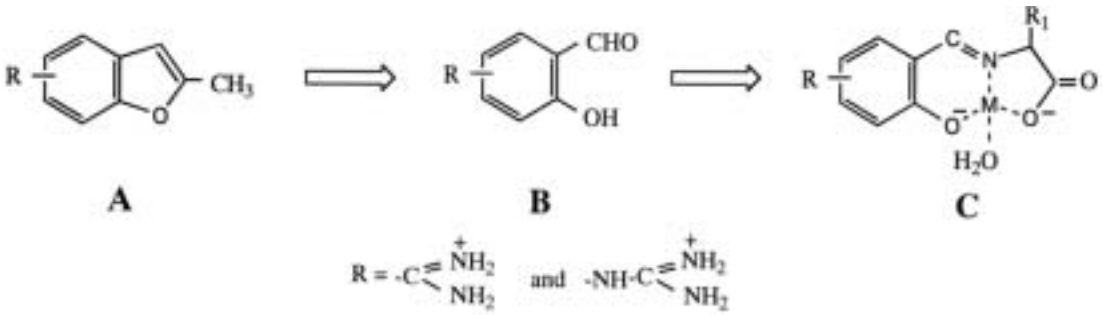
Abstract—Mono-substituted 2-methylbenzo[*b*]furans were prepared by Claisen rearrangement of corresponding allyl phenyl ethers and subsequent bis(benzonitrile)palladium(II) chloride-mediated cyclization of *o*-allylphenols.

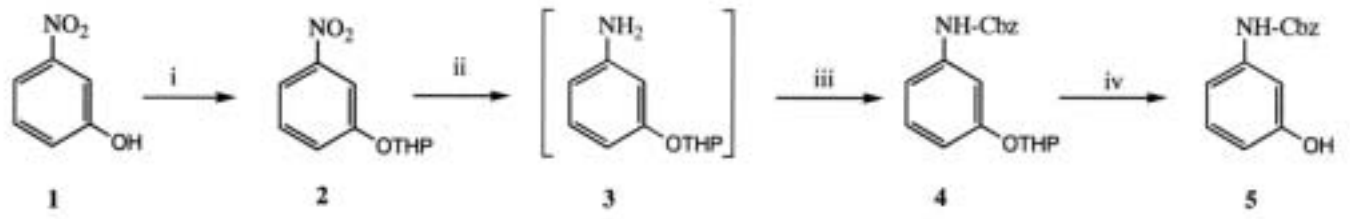
Protection of functional groups [1] is one of the most important synthetic technique in the preparative organic chemistry. In the synthesis of multifunctional molecules the problem often arises that a given functional group has to be protected from a certain reactions. Of the many functional groups requiring synthetic manipulation involving protection, one frequently encounter *ortho*-formylphenol, i.e., salicylaldehyde residue. The most strategic approach for protection of salicylaldehyde residue seems to be the formation of benzofuran ring. This benzofuran linkage may be taken as very stable protection for the salicylaldehyde,[2] and it was easily converted to salicylaldehyde residue by cleavage of furan ring as shown in the previous paper.[3] Previously, we reported that formation of a very stable chelate composed of salicylaldehyde, α-amino acid, and metal ion (structure **C**, Scheme 1).[4] The series of Schiff bases chelates were applied to the design of bio-specific compound, and they were found to be very useful trypsin-inhibitor.[5] We are interested in these trypsin-inhibitors, therefore, we examined the utility of benzofuran derivatives for the synthesis of various position isomers of salicylaldehyde possessing amidine and guanidine function at the benzene ring.



Scheme 1

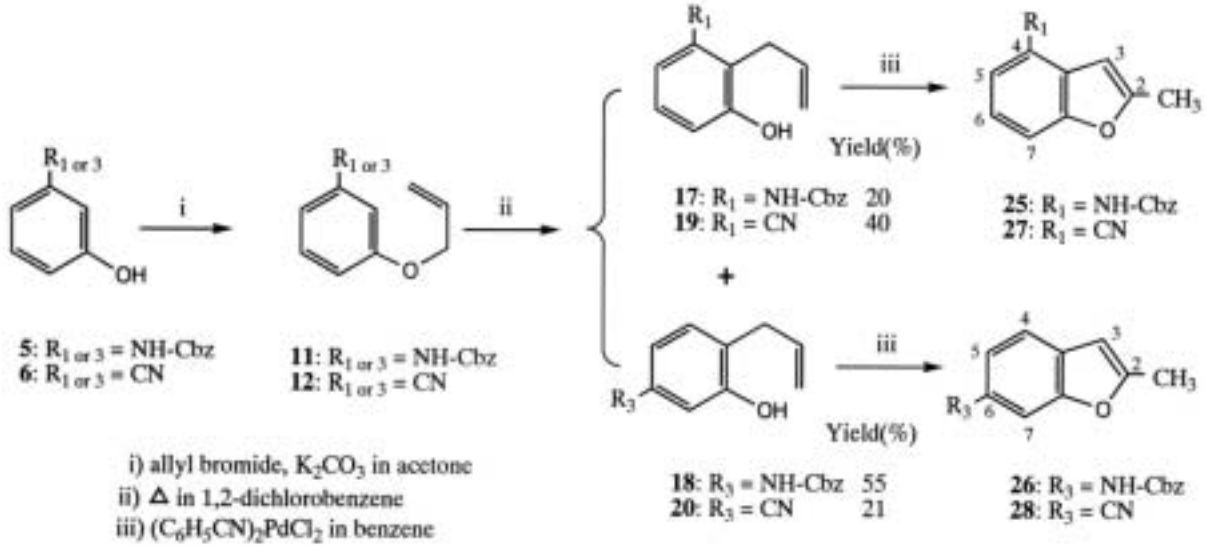
[#] This paper is dedicated to Emeritus Professor Yuichi Kanaoka, Hokkaido University, on the occasion of his 75th birthday.

In this paper, we report a facile synthesis of benzofuran derivatives (**25-32**) (Schemes 3 and 4). These compounds possess the nitrogen-containing groups at various position of benzene ring, and these functional groups can be converted into the site-specific groups for trypsin such as amidino and guanidino groups. Our strategy for the preparation of benzofuran derivative by means of palladium(II)-mediated cyclization is shown in Schemes 3 and 4. The starting material, *p*-*N*-Cbz-aminophenol (**7**), was prepared as previously reported.[6] The isomer, *m*-*N*-Cbz-aminophenol (**5**), was also prepared according to our previous paper [6] as shown in Scheme 2. Tertrahydropyranylation of *m*-nitrophenol (**1**) gave the *m*-tetrahydropyran-2-yloxy-



Scheme 2.

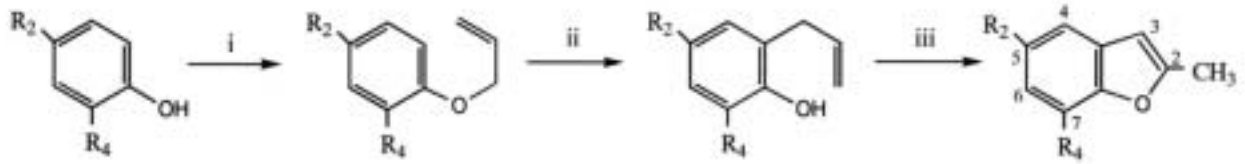
nitrobenzene (**2**). Compound (**2**) was converted to the *m*-aminophenol derivative (**3**), then, the amino group of **3** was protected with *N*-(benzyloxycarbonyloxy)succinimide (Cbz-ONSu) to give *m*-tetrahydro-pyran-2-yloxy-*N*-Cbz-aminobenzene (**4**). Deprotection of **4** gave *m*-*N*-Cbz-aminophenol (**5**) in 54% yield from **1**. The other starting materials, 3-cyanophenol (**6**), 4-cyanophenol (**8**), 4-cyanomethylphenol (**9**), and 2-cyanophenol (**10**), are commercially available.



Scheme 3.

The key compounds, *o*-allylphenols (**17-24**), were prepared from allyl phenyl ethers (**11-16**) which were obtained from the corresponding phenols (**5-10**) and allyl bromide in satisfactory yields. Claisen rearrangement of allyl *m*-substituted phenyl ethers (**11** and **12**) by refluxing with 1,2-dichlorobenzene for 24-48 h resulted to give a mixture of position isomers as shown in Scheme 3. Claisen rearrangement of allyl phenyl ethers bearing substituent at *para*- (**13-15**) or *ortho*-position (**16**), afforded *o*-allylphenols (**21-24**) in reasonable yields. *o*-Allylphenols (**17-24**) were cyclized to give corresponding derivatives

(**25-32**) by equimolar amount of bis(benzonitrile)palladium(II) chloride, $(C_6H_5CN)_2PdCl_2$, in boiling benzene. The yields are generally moderate (44-78%).



7: R_2 = NH-Cbz, R_4 = H; **8**: R_2 = CN, R_4 = H; **9**: R_2 = CH_2CN, R_4 = H; **10**: R_2 = H, R_4 = CN

13: R_2 = NH-Cbz, R_4 = H; **14**: R_2 = CN, R_4 = H; **15**: R_2 = CH_2CN, R_4 = H; **16**: R_2 = H, R_4 = CN

21: R_2 = NH-Cbz, R_4 = H; **22**: R_2 = CN, R_4 = H; **23**: R_2 = CH_2CN, R_4 = H; **24**: R_2 = H, R_4 = CN

29: R_2 = NH-Cbz, R_4 = H; **30**: R_2 = CN, R_4 = H; **31**: R_2 = CH_2CN, R_4 = H; **32**: R_2 = H, R_4 = CN

i) allyl bromide, K_2CO_3 in acetone; ii) Δ in 1,2-dichlorobenzene; iii) $(C_6H_5CN)_2PdCl_2$ in benzene

Scheme 4.

Finding of the present study will provide a facile mean for the synthesis of benzofuran derivatives from appropriate *o*-allylphenols.

EXPERIMENTAL

Melting points were determined on a Yanagimoto melting point apparatus and are uncorrected. IR spectra were taken on a JASCO FT/IR-460Plus. ^{1}H NMR spectra were recorded on a JEOL JNM-EX 400 (400 MHz) and JEOL LA-300 (300 MHz) spectrometers. Chemical shifts are quoted in parts per million (ppm) with tetramethyl silane (TMS) as an internal standard. HRMS spectra were recorded using a JEOL JMS-DX 303 spectrometer. TLC was performed on Merck Silica gel 60F-254. Column chromatography was carried out on Kieselgel 60 (Merck).

***m*-Tetrahydropyran-2-yloxynitrobenzene (2)** $TsOH\cdot H_2O$ (20 mg) was added to a solution of *m*-nitrophenol (**1**) (13.9 g, 0.1 mol) and 3,4-dihydro-2H-pyran (12.6 g, 0.15 mol) in anhydrous benzene (50 mL). An exothermic reaction occurred immediately after the addition. After the exothermic reaction stopped, the reaction mixture was warmed at 50 ℃ for 1 h. It was diluted with AcOEt (50 mL), washed successively with 1 M aqueous NaOH, water and saturated brine, dried over anhydrous Na_2SO_4 and evaporated *in vacuo*. The residual oil was passed through a short column of silica gel with benzene. Compound (**2**) (18.31 g, 82%) was obtained as a yellow syrup. IR (neat) ν = 2946, 1530, 1351, 1239 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 1.58-1.75 (3H, m), 1.87-2.01 (3H, m), 3.62-3.68 (2H, m), 3.81-3.89 (2H, m), 5.51 (1H, dd, *J* = 3.1, 3.1 Hz), 7.36 (1H, dd, *J* = 7.8, 7.8 Hz), 7.84 (1H, dd, *J* = 7.8, 2.2 Hz), 7.91 (1H, dd, *J* = 2.2, 2.0 Hz). HRMS: Calcd for $C_{11}H_{13}NO_4$: 223.0844. Found: 223.0853.

***m*-Tetrahydropyran-2-yloxyaminobenzene (3)** A suspension of **2** (11.15 g, 50 mmol) in EtOH (250 mL) containing 10% Pd-C was vigorously stirred in an atmosphere of hydrogen at rt for 4 h. The catalyst was removed by passing the solution through a bed of celite, and the catalyst and celite were washed with EtOH. The combined solution was concentrated *in vacuo*, and the residue (crude **3**) was used for the next reaction without purification.

***m*-Tetrahydropyran-2-yloxy-*N*-(benzyloxycarbonyl)aminobenzene (4)** A solution of crude **3** (from **2**, 50 mmol) in $CHCl_3$ (100 mL) was treated with Cbz-ONSu (12.45 g, 50 mmol). The reaction mixture was stirred at rt for 2 h, then the solution was concentrated to dryness *in vacuo*. The residual oil was passed through a short column of silica gel with a mixture of benzene : AcOEt (6 : 1). Compound (**4**)

(14.39 g, 88%) was obtained as a yellow syrup. IR (neat) ν = 3318, 2946, 1734, 1604, 1221 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 1.54-1.71 (3H, m), 1.79-1.84 (2H, m), 1.92-2.00 (1H, m), 5.17 (2H, s), 5.39 (1H, dd, *J* = 3.1, 3.1 Hz), 6.74 (1H, dd, *J* = 8.1, 2.2 Hz), 6.83 (1H, s), 6.96 (1H, dd, *J* = 8.1, 8.1 Hz), 7.31-7.38 (5H, m). HRMS: Calcd for $C_{11}H_{13}NO_4$: 327.1466. Found: 327.1470.

***m*-*N*-(Benzyloxycarbonyl)aminophenol (5)** A solution of **4** (13.28 g, 40.6 mmol) in MeOH (120 mL) was treated with $TsOH \cdot H_2O$ (771 mg, 40.6 mmol). The reaction mixture was refluxed for 1 h, then evaporated to dryness *in vacuo*. The residual oil was passed through a short column of silica gel with a mixture of benzene : AcOEt (6 : 1), and pure **5** (7.40 g, 75%) was obtained by recrystallization from benzene-AcOEt as colorless needles. mp 129-130 ℃. IR (neat) ν = 3373, 1670, 1608, 1548, 1291, 1246 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.93 (2H, s), 6.39 (1H, br s), 6.60 (1H, dd, *J* = 7.4, 1.2 Hz), 6.68 (1H, dd, *J* = 4.4, 1.2 Hz), 7.11 (1H, *J* = 8.1 Hz), 7.13 (1H, d, *J* = 8.1 Hz), 7.33-7.39 (5H, m). *Anal*. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.38; H, 5.41; N, 5.69.

General procedure for the synthesis of allyl ethers (11-16)----Allyl bromide (2.764 g, 20 mmol) was added to a suspension of phenol derivatives (**5-10**, 10 mmol) and K_2CO_3 (4.14g, 30 mmol) in acetone (100 mL) at rt. The reaction mixture was stirred at rt for 24 h, then the precipitate was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residual oil was passed through a short column of silica gel with benzene : AcOEt (15 : 1 - 1 : 5) to give allyl ether.

Allyl 3-*N*-(benzyloxycarbonyl)aminophenyl ether (11): This was obtained in 98% yield (2.773 g) as a slightly yellow syrup. IR (neat) ν = 3327, 1734, 1708, 1606, 1221 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.51 (2H, d, *J* = 5.3 Hz), 5.19 (2H, s), 5.27 (1H, dd, *J* = 10.3, 1.3 Hz), 5.40 (1H, dd, *J* = 17.3, 1.3 Hz), 6.05 (1H, m), 6.62 (1H, dd, *J* = 8.3, 2.5 Hz), 6.70 (1H, br s), 6.85 (1H, d, *J* = 8.3 Hz), 7.15 (2H, *J* = 8.3 Hz), 7.35-7.39 (5H, m) . HRMS: Calcd for $C_{17}H_{17}NO_3$: 283.1198. Found: 283.1205.

Allyl 3-cyanophenyl ether (12): This was obtained in 96% yield (1.526 g) as a colorless liquid. IR (neat) ν = 2230, 1596, 1578, 1290, 1263 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.55 (1H, dd, *J* = 1.4, 1.4 Hz), 4.57 (1H, dd, *J* = 1.4, 1.4 Hz), 5.32 (1H, dd, *J* = 10.3, 1.5 Hz), 5.42 (1H, ddd, *J* = 17.0, 2.9, 1.5 Hz), 6.03 (2H, br s, overlap), 7.25 (1H, d, *J* = 7.3 Hz), 7.36 (1H, dd, *J* = 7.8, 7.3 Hz). HRMS: Calcd for $C_{11}H_{13}NO_4$: 159.0684. Found: 159.0703.

Allyl 4-*N*-(benzyloxycarbonyl)aminophenyl ether (13): This was obtained in 90% yield (2.547 g) as colorless needles. mp 98-99 ℃ (recrystallized from benzene-hexane). IR (KBr) ν = 3310, 1702, 1537, 1236 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.50 (1H, dd, *J* = 1.4, 1.4 Hz), 4.52 (1H, dd, *J* = 1.4, 1.4 Hz), 5.19 (2H, s), 5.28 (1H, dd, *J* = 10.3, 1.4 Hz), 5.39 (1H, dd, *J* = 15.6, 1.4 Hz), 6.04 (1H, m), 6.56 (1H, br s), 6.85 (2H, d, *J* = 9.0 Hz), 7.27 (2H, d, *J* = 9.0 Hz), 7.35 (5H, m)*Anal*. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.01; H, 6.07; N, 4.86.

Allyl 4-cyanophenyl ether (14): This was obtained in 99% yield (1.583 g) as colorless needles. mp 41 ℃ (recrystallized from hexane). IR (KBr) ν = 2220, 1605, 1507, 1256 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.58 (1H, dd, *J* = 1.4, 1.4 Hz), 4.60 (1H, dd, *J* = 1.4, 1.4 Hz), 5.32 (1H, dd, *J* = 10.3, 1.4 Hz), 5.43 (1H, dd, *J* = 15.6, 1.4 Hz), 6.04 (1H, m), 6.96 (2H, d, *J* = 8.8 Hz), 7.58 (2H, d, *J* = 8.8 Hz). *Anal*. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.54; H, 5.77; N, 8.73.

Allyl 4-cyanomethylphenyl ether (15): This was obtained in 85% yield (1.470 g) as a yellow syrup. IR (neat) ν = 2250, 1613, 1512, 1247 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 3.68 (2H, s), 4.53 (1H, dd, *J* = 1.5, 1.5 Hz), 4.55 (1H, dd, *J* = 1.5, 1.5 Hz), 5.29 (1H, dd, *J* = 10.3, 1.4 Hz), 5.41 (1H, dd, *J* = 15.6, 1.4 Hz), 6.04 (1H, m), 6.91 (2H, d, *J* = 8.6 Hz), 7.23 (2H, d, *J* = 8.6 Hz). HRMS: Calcd for $C_{11}H_{13}NO_4$:

173.0841. Found: 173.0856 .

Allyl 2-cyanophenyl ether (16): This was obtained in 89% yield (1.408 g) as a colorless liquid. IR (neat) ν = 2227, 1599, 1491, 1450, 1290 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.65 (1H, dd, *J* = 1.4, 1.4 Hz), 4.66 (1H, dd, *J* = 1.4, 1.4 Hz), 5.32 (1H, dd, *J* = 10.8, 1.4 Hz), 5.48 (1H, dd, *J* = 17.6, 1.5 Hz), 6.03 (1H, m), 6.96 (1H, d, *J* = 8.8 Hz), 7.01 (1H, d, *J* = 7.3 Hz), 7.51 (1H, dd, *J* = 7.8, 1.5 Hz), 7.54 (1H, dd, *J* = 7.8, 1.5 Hz). HRMS: Calcd for $C_{11}H_{13}NO_4$: 159.0684. Found: 159.0689 .

General procedure for the synthesis of Claisen rearrangement products (17-24)----A solution of allyl ethers (**11-16**, 5 mmol) in 1,2-dichlorobenzene (100 mL) was refluxed for 24 - 48 h in an atmosphere of nitrogen. The reaction mixture was evaporated to dryness *in vacuo* and the residual oil was passed through a short column of silica gel with benzene : AcOEt (15 : 1 - 1 : 5) to give allyl phenol.

2-Allyl-3-*N*-(benzyloxycarbonyl)aminophenol (17): This was isolated in 20% yield (283 mg) as a colorless syrup. IR (neat) ν = 3392, 1704, 1598, 1532, 1470, 1227 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 4.51 (2H, d, *J* = 5.3 Hz), 5.19 (2H, s), 5.27 (1H, dd, *J* = 10.3, 1.3 Hz), 5.40 (1H, dd, *J* = 17.3, 1.3 Hz), 6.05 (1H, m), 6.62 (1H, dd, *J* = 8.3, 2.5 Hz), 6.70 (1H, br s), 6.85 (1H, d, *J* = 8.3 Hz), 7.15 (2H, *J* = 8.3 Hz), 7.35-7.39 (5H, m) . HRMS: Calcd for $C_{11}H_{13}NO_4$: 283.1208. Found: 283.1205.

2-Allyl-5-*N*-(benzyloxycarbonyl)aminophenol (18): This was isolated in 55% yield (778.3 mg) as colorless needles. mp 108-109 ℃ (recrystallized from benzene-hexane). IR (KBr) ν = 3349, 1686, 1554, 1247, 1229 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 3.34 (2H, d, *J* = 6.4 Hz), 5.08 (1H, s), 5.11 (1H, d, *J* = 5.4 Hz), 5.19 (2H, s), 5.90 (1H, br s), 5.98 (1H, m), 6.66 (1H, dd, *J* = 8.8, 2.4 Hz), 6.69 (1H, s), 6.99 (1H, d, *J* = 8.3 Hz), 7.22 (1H, br s), 7.33-7.39 (5H, m). *Anal*. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 71.99; H, 6.23; N, 4.77.

2-Allyl-3-cyanophenol (19): This was isolated in 40% yield (318 mg) as colorless needles. mp 119-120 ℃ (recrystallized from benzene). IR (KBr) ν = 3324, 2237, 1583, 1465, 1290 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 3.65 (2H, d, *J* = 6.4 Hz), 5.16 (1H, dd, *J* = 7.8, 0.9 Hz), 5.19 (1H, s), 5.47 (1H, br s), 5.99 (1H, m), 7.05 (1H, dd, *J* = 7.3, 1.5 Hz), 7.19-7.26 (2H, m). *Anal*. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.45; H,5.77; N, 8.75.

2-Allyl-5-cyanophenol (20): This was isolated in 21% yield (167.1 mg) as colorless fine needles. mp 118-119 ℃ (recrystallized from benzene-hexane). IR (KBr) ν = 3328, 2238, 1583, 1465, 1290 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 3.65 (2H, dd, *J* = 6.3, 1.4 Hz), 5.13 (1H, dd, *J* = 1.5, 1.5 Hz), 5.18 (1H, dd, *J* = 1.5, 1.5 Hz), 5.95 (1H m), 6.03 (1H, br s), 7.05 (1H, d, *J* = 7.4 Hz), 7.12 (1H, d, *J* = 7.4 Hz), 7.23 (1H, s). *Anal*. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.45; H, 5.77; N, 8.75.

2-Allyl-4-*N*-(benzyloxycarbonyl)aminophenol (21): This was obtained in 75% yield (1.061 g) as colorless fine needles. mp 84-85℃ (recrystallized from benzene-hexane). IR (KBr) ν = 3369, 3298, 1657, 1542, 1245 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 3.37 (2H, d, *J* = 6.3 Hz), 5.14 (2H, dd, *J* = 13.7, 1.5 Hz), 5.18 (2H, s), 5.98 (1H, m), 652 (1H, br s), 6.73 (2H, d, *J* = 8.8 Hz), 7.09 (2H, d, *J* = 8.0 Hz), 7.26 (1H, br s), 7.38 (5H, m). *Anal*. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.00; H, 6.13; N, 4.74.

2-Allyl-4-cyanophenol (22): This was obtained in 73% yield (580.4 mg) as clorless needles. mp 83-84 ℃ (recrystallized from benzene-hexane). IR (KBr) ν = 3245, 2236, 1601, 1283 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 3.40 (2H, d, *J* = 6.3 Hz), 5.14 (1H, dd, *J* = 17.1, 1.5 Hz), 5.19 (1H, dd, *J* = 10.3, 1.5 Hz), 5.98 (1H, m), 6.80 (1H, br s), 6.90 (1H, d, *J* = 8.0 Hz), 7.42 (1H, d, *J* = 8.0 Hz), 7.43 (1H, s). *Anal*. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.36; H, 5.74; N, 8.70.

2-Allyl-4-cyanomethylphenol (23): This was obtained in 84% yield (726.6 mg) as a slightly yellow syrup. IR (neat) ν = 3389, 2258, 1511, 1439 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 3.40 (2H, d, *J* = 6.3 Hz), 3.66 (2H, s), 5.14 (1H, dd, *J* = 9.8, 1.5 Hz), 5.18 (1H, dd, *J* = 1.5, 1.5 Hz), 5.23 (1H, s), 6.00 (1H, m), 6.80 (1H, dd, *J* =8.8, 2.0 Hz) 7.05 (1H, s), 7.06 (1H, d, *J* = 8.8, 2.4 Hz). HRMS: Calcd for $C_{11}H_{13}NO_4$: 173.0841. Found: 173.0853 .

2-Allyl-6-cyanophenol (24): This was obtained in 83% yield (658.3 mg) as colorless plates. mp 38-39 ℃ (recrystallized from hexane). IR (KBr) ν = 3293, 2239, 1461, 1210 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 3.44 (2H, d, *J* = 6.3 Hz), 5.18 (1H, dd, *J* = 15.4, 1.5 Hz), 5.20 (1H, dd, *J* = 2.0, 1.5 Hz), 5.98 (1H, m), 6.95 (1H, dd, *J* = 7.8, 7.8 Hz) 7.34 (1H, dd, *J* = 7.8, 2.4 Hz), 7.40 (1H, dd, *J* = 7.8, 2.4 Hz). *Anal*. Calcd for $C_{10}H_9NO$: C, 75.45; H, 5.70; N, 8.80. Found: C, 75.49; H, 5.80; N, 8.84.

General procedure for the synthesis of the benzofurans (25-32)----Bis(benzonitrile)-palladium(II) chloride (384 mg, 1 mmol) was added to a solution of 2-allylphenols (**17-24**, 1 mmol) in anhydrous benzene (50 mL), and the mixture was refluxed for 2 h in an atmosphere of nitrogen. The inorganic precipitate was removed by passing the solution through a bed of celite, and the filtrate was evaporated to dryness *in vacuo* and the residual oil was passed through a short column of silica gel with benzene or mixture of benzene : AcOEt (6 : 1) to give benzofuran.

4-*N*-(Benzyloxycarbonyl)amino-2-methylbenzo[*b*]furan (25): This was obtained in 60% yield (168.6 mg) as colorless needles. mp 110-111℃ (recrystallized from hexane). IR (KBr) ν = 3316, 1692, 1533, 1267, 1059 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 2.57 (3H, s), 5.44 (2H, s), 6.41 (1H, d, *J* = 0.9 Hz), 7.05 (1H, dd, *J* = 7.8, 7.8 Hz), 7.35-7.54 (5H, m), 7.69 (1H, dd, *J* = 7.8, 0.6 Hz). *Anal*. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.55; H, 5.46; N, 4.83.

6-*N*-(Benzyloxycarbonyl)amino-2-methylbenzo[*b*]furan (26): This was obtained in 44% yield (123.7 mg) as colorless fine needles. mp 119-120 ℃ (recrystallized from benzene-hexane). IR (KBr) ν = 3349, 1707, 1580, 1453, 1327, 1286 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 2.43 (3H, s), 5.21 (2H, s), 6.30 (1H, s), 6.72 (1H, br s), 7.00 (1H, dd, *J* = 8.3, 1.8 Hz), 7.32-7.43 (7H, m). HRMS: Calcd for $C_{17}H_{15}NO_3$: 281.1052. Found: 281.1057. *Anal*. Calcd for $C_{17}H_{15}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 73.06; H, 5.50; N, 4.83.

4-Cyano-2-methylbenzo[*b*]furan (27): This was obtained in 58% yield (91.1 mg) as colorless needles. mp 40-41 ℃ (sublimed at room temperature). IR (KBr) ν = 2220, 1603, 1430, 1260 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 2.44 (3H, s), 6.54 (1H, dd, *J* = 1.1, 1.1 Hz), 7.18 (1H, dd, *J* = 8.2, 5.7 Hz), 7.43 (1H, dd, *J* =7.7, 1.1 Hz) 7.53 (1H, d, *J* = 8.2 Hz). HRMS: Calcd for $C_{10}H_7NO$: 157.0528. Found: 157.0514.

6-Cyano-2-methylbenzo[*b*]furan (28): This was obtained in 49% yield (76.9 mg) as colorless needles. mp 66-67 ℃ (recrystallized from benzene-hexane). IR (KBr) ν = 2221, 1602, 1425, 1261, 1195 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 2.42 (3H, s), 6.38 (1H, s), 7.37 (1H, dd, *J* = 7.8, 1.2 Hz), 7.45 (1H, d, *J* =7.8 Hz) 7.60 (1H, d, *J* = 1.2 Hz). HRMS: Calcd for $C_{10}H_7NO$: 157.0528. Found: 157.0515.

5-*N*-(Benzyloxycarbonyl)amino-2-methylbenzo[*b*]furan (29): This was obtained in 45% yield (126.5 mg) as colorless needles. mp 105-106 ℃ (recrystallized from benzene-hexane). IR (KBr) ν = 3313, 1701, 1536, 1240 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ = 2.42 (3H, d, *J* = 1.0 Hz), 6.31 (1H, s), 6.72 (1H, br s), 7.06 (1H, dd, *J* = 8.8, 2.0 Hz), 7.24-7.56 (7H, m). *Anal*. Calcd for $C_{17}H_{25}NO_3$: C, 72.58; H, 5.37; N, 4.98. Found: C, 72.59; H, 5.46; N, 4.78.

5-Cyano-2-methylbenzo[*b*]furan (30): This was obtained in 53% yield (83.2 mg) as colorless

needles. mp 73-74℃ (recrystallized from hexane) (lit.,[7] 76-78 °C).

5-Cyanomethyl-2-methylbenzo[*b*]furan (31): This was obtained in 46% yield (78.7 mg) as a colorless liquid. IR (neat) ν = 2251, 1608, 1493 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 2.46 (3H, s), 6.38 (2H, s), 6.36 (1H, s), 7.10 (1H, dd, *J* = 8.8, 2.8 Hz), 7.37 (1H, d, *J* = 8.6 Hz), 7.43 (1H, d, *J* = 1.8 Hz). HRMS: Calcd for $C_{11}H_{13}NO_4$: 171.0684. Found: 171.0685.

7-Cyano-2-methylbenzo[*b*]furan (32): This was obtained in 78% yield (123.3 mg) as colorless needles. mp 78℃ (recrystallized from hexane). IR (KBr) ν = 2228, 1605, 1423 cm^{-1}. ^1H NMR ($CDCl_3$) δ = 2.53 (3H, s), 6.63 (1H, s), 7.25 (1H, dd, *J* = 7.8, 7.3 Hz), 7.49 (1H, d, *J* = 7.8 Hz), 7.69 (1H, d, *J* =7.3 Hz). HRMS: Calcd for $C_{10}H_7NO$: 157.0528. Found: 157.0538. *Anal.* Calcd for $C_{10}H_7NO$: C, 76.14; H, 4.49; N, 8.91. Found: C, 75.67; H, 4.46; N, 8.64.

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