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Synthesis of tribromobenzofuran and tribromobenzopyran derivatives from methyl 2-allyl-4,5,6-tribromo-3-hydroxybenzoate

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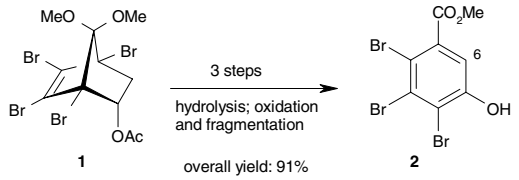
Abstract—Palladium(II)-catalyzed oxidative cyclization of methyl 2-allyl-4,5,6-tribromo-3-hydroxybenzoate **4** gave a mixture of methyl 5,6,7-tribromo-2-methyl-benzofuran-4-carboxylate **5** and methyl 6,7,8-tribromo-2*H*-1-benzopyran-5-carboxylate **6**; the ratio of the two products varied between 71:29 and 24:76 depending on the reaction conditions. On the other hand, NBS or NIS mediated cyclization of **4** followed by treatment with NaOMe or DBU furnished benzofuran derivative **5** in good overall yield.

Benzofuran and benzopyran derivatives are ubiquitous in nature and show a wide range of biological activities.[1] Numerous methods are available for the synthesis of these heterocycles.[2] Palladium(II)-catalyzed reactions of 2-allylphenols is particularly attractive for this purpose.[3] The pioneering work of Hosokawa and Murahashi not only demonstrated the feasibility of this useful reaction but also studied the influence of various factors such as additives and ligands on the Pd(II) salt on the regioselectivity.[4] Recently, Bumagin and co-workers reported the formation of benzofurans from *o*-allylic phenols possessing substituents such as methyl, methoxy, acetamido, bromo, and ethoxycarbonyl on the benzene ring while a nitro group predominantly furnished a six-membered ring.[5] Larock and co-workers demonstrated that a catalytic amount of $Pd(dba)_2$ in the presence of oxygen and DMSO furnished exclusively, benzopyrans from *o*-allylic phenols.[6]

We have reported a highly efficient three-step protocol for the synthesis of tribromophenol derivative **2** from the readily available Diels–Alder adduct **1** prepared from tetrabromo-5,5-dimethoxycyclopentadiene and vinyl acetate (Eq. 1).[7] Recently, this methodology was extended for the preparation of substituted tribromophenol derivatives with alkyl or aryl substituents (at position 6) starting with the corresponding β-substituted vinyl acetates.[8] It occurred to us that the *o*-allylic phenol derivative of **2** would be an interesting substrate to study palladium(II)-catalyzed oxidative cyclization. The tribromo heterocyclic products thus formed should be of interest as convenient building blocks. The ever growing number of bioactive organohalogen compounds from marine sources provided further impetus.[9]



1 2 (1)

The required *o*-allylic phenol derivative was prepared as depicted in Scheme 1. Treatment of **2** with allyl bromide in the presence of K_2CO_3 in refluxing acetone furnished the aryl allyl ether **3**. Claisen rearrangement of **3** in refluxing xylene gave *o*-allylic phenol derivative **4** in high overall yield.

The *o*-allylic phenol derivative **4** was subjected to a variety of palladium(II)-catalyzed oxidative cyclization conditions as shown in Table 1. Reaction of **4** in the presence of a catalytic amount of $Pd(OAc)_2$ (2 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.5 equiv), and oxygen in MeOH–H_2O at 65 °C furnished a separable mixture of methyl 5,6,7-tribromo-2-methyl-benzofuran-4-carboxylate **5** and methyl 6,7,8-tribromo-2*H*-1-benzopyran-5-carboxylate **6** in a ratio of 71:29 in 68% overall yield (Table 1, entry 1).[10] Changing the palladium and copper sources to the corresponding chloride salts improved the yield to 81% while **5** remained the predominant product (Table 1, entry 2). No improvement in yield or regioselectivity was

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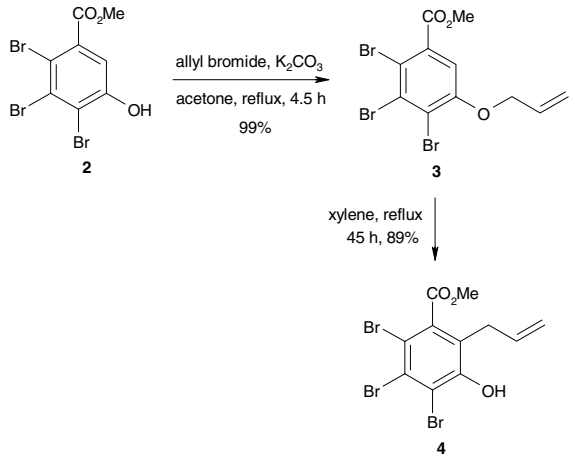
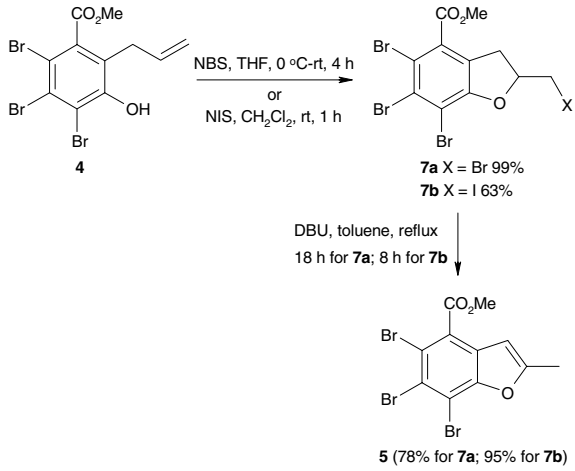


Scheme 1.



Scheme 2.

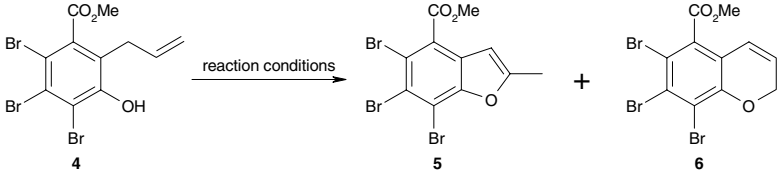
recorded when reaction of the sodium salt of **4** in the presence of stoichiometric amounts of $PdCl_2(PhCN)_2$ in benzene (conditions originally employed by Hosokawa[4b]) was carried out (Table 1, entry 3).

We next turned our attention to DMSO–H_2O, which is an efficient solvent system for Pd(II) catalysis.[6] Employing 5 mol % of Pd(II) catalyst [$Pd(OAc)_2$ or $PdCl_2$] in the presence of $KHCO_3$ (0.5 equiv) and atmospheric air in DMSO–H_2O (9:1) furnished good isolated overall yields (69% and 71%) of **5** and **6** but with a reversal in regioselectivity (32:68 and 31:69) leading predominantly to the six-membered derivative **6** (Table 1, entries 4 and 5). Finally, a DMF–H_2O solvent system was employed in the presence of $PdCl_2$ (4 mol %), $Cu(OAc)_2{\cdot}H_2O$ (3.0 equiv), and LiCl (3.0 equiv) at 55–60 °C.[5] Under these conditions an 83% isolated yield of **5** and **6** in a ratio of 24:76 was obtained (Table 1, entry 6).

Although *o*-allylic phenols could in principle undergo either 5-*exo*-trig or 6-*endo*-trig cyclizations leading to benzofuran or benzopyran derivatives, the former appears to be more common in the literature especially for phenols having both electron donating and withdrawing substituents on the aromatic ring but with an unsubstituted *o*-allylic group.[3b,5] However, the presence of a *para*–NO_2 group was reported to give predominantly the benzopyran derivative.[5] The precise mechanistic reasons for these observations is not clear. It is reasonable to assume the intermediacy of either a Pd π-olefin or a π-allylpalladium complex. While the former could lead to both five- or six-membered rings, the latter could only furnish a six-membered derivative.

We next turned our attention to electrophilic cyclization mediated by NBS or NIS as delineated in Scheme 2. The reaction of phenol **4** with NBS in THF furnished a near quantitative yield of 2-bromomethyl dihydrobenzofuran derivative **7a** while a similar reaction with NIS gave **7b** in 63% yield.[10] We first subjected **7a** to NaOMe in MeOH–THF at room temperature, which furnished the benzofuran derivative **5** in 67% yield. When DBU was employed as a base in refluxing toluene,[2f] the yield of **5** improved to 78% from **7a**. Under these conditions **7b** gave a 95% yield of **5**. In order to avoid decomposition of the sensitive 2-iodomethyl derivative **7b** during

Table 1. Palladium(II)-catalyzed oxidative cyclization of methyl 2-allyl-4,5,6-tribromo-3-hydroxybenzoate **4**[10]



Entry	Reaction conditions	Time (h)	Overall yield **5** + **6**[a] (%)	Ratio **5**:**6**[a]
1	$Pd(OAc)_2$ (2 mol %), $Cu(OAc)_2{\cdot}H_2O$ (0.5 equiv), O_2 (bubbling), MeOH–H_2O, 65 °C	2	68	71:29
2	$PdCl_2$ (2 mol %), $CuCl_2$ (0.5 equiv), O_2 (bubbling), MeOH–H_2O, 65 °C	4	81	60:40
3	$PdCl_2(PhCN)_2$ (1.0 equiv), NaOMe (1.0 equiv), benzene, 55–60 °C	1	68	44:56
4	$Pd(OAc)_2$ (5 mol %), $KHCO_3$ (0.5 equiv), air, DMSO–H_2O, 60 °C	16	69	32:68
5	$PdCl_2$ (5 mol %), $KHCO_3$ (0.5 equiv), air, DMSO–H_2O, 60 °C	20	71	31:69
6	$PdCl_2$ (4 mol %), $Cu(OAc)_2{\cdot}H_2O$ (3.0 equiv), LiCl (3.0 equiv), DMF–H_2O, 55–60 °C	2.5	83	24:76[b]

[a] Based on the isolated yield of analytically pure **5** and **6**.
[b] Ratio was also confirmed from ^1H NMR of the mixture prior to purification.

column purification, the crude product was directly carried forward in the next step in a separate experiment to obtain an 86% overall yield of **5**.

In summary, tribromobenzofuran derivative **5** and tribromobenzopyran derivative **6** were obtained in good yields via palladium(II)-catalyzed oxidative cyclization of methyl 2-allyl-4,5,6-tribromo-3-hydroxybenzoate **4**. A complete reversal in the regioselectivity (71:29 to 24:76) was observed by changing the catalyst cocktail. On the other hand, electrophilic cyclization mediated by NBS or NIS followed by base treatment led exclusively to benzofuran derivative **5**.

Acknowledgements

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10. Illustrative procedure for the palladium(II)-catalyzed oxidative cyclization of **4** (Table 1, entry 6): *o*-allylic phenol derivative **4** (100 mg, 0.23 mmol), LiCl (30 mg, 0.70 mmol), and $PdCl_2$ (1.6 mg, 4 mol %) were added to a solution of $Cu(OAc)_2{\cdot}H_2O$ (140 mg, 0.70 mmol) in DMF–H_2O (4 mL:0.1 mL). The suspension was stirred under atmospheric air at 55–60 °C for 2.5 h. The reaction mixture was diluted with 20 mL of water containing 5 mL of aq 25% ammonia solution and then extracted with diethyl ether (3×15 mL). The combined organic layers were sequentially washed with aq 25% NaOH solution (10 mL), water (15 mL), and brine (15 mL), dried over anhydrous Na_2SO_4 and evaporated. The residue was purified by column chromatography (silica gel pretreated with 7% $AgNO_3$) to afford **5** (19.7 mg, 20%) and **6** (63 mg, 63%). Overall yield: 83% (ratio **5**:**6** = 24:76). Compound **5**: colorless crystalline solid; mp 119–121 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.46 (d, 1H, $J = 1.0$ Hz), 3.92 (s, 3H, OMe), 2.43 (s, 3H, Me); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.0, 159.3, 151.7, 128.8, 125.6 123.2, 117.6, 110.4, 103.6, 52.7, 14.1; IR (KBr): 1730, 1600, 1240, 1150, 810 cm^{-1}; Anal. Calcd for $C_{11}H_7Br_3O_3$: C, 30.95; H, 1.65. Found: C, 31.25; H, 1.76. Compound **6**: white solid; mp 94–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.21–6.18 (td, 1H, $J = 10.0$, 1.9 Hz), 5.89–5.85 (td, 1H, $J = 10.0$, 3.4 Hz), 4.91–4.90 (dd, 2H, $J = 3.4$, 1.9 Hz), 3.88 (s, 3H, OMe); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.4, 151.0, 132.8, 128.3, 125.1, 120.6, 120.0, 115.7, 113.4, 66.5, 53.0; IR (KBr): 1720, 1410, 1250, 1190, 1160, 1050, 980 cm^{-1}; Anal. Calcd for $C_{11}H_7Br_3O_3$: C, 30.95; H, 1.65. Found: C, 30.56; H, 1.71. Compound **7a**: white solid; mp 56–57 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.13–5.06 (m, 1H), 3.88 (s, 3H, OMe), 3.59–3.56 (dd, 1H, $J = 10.7$, 4.2 Hz), 3.52–3.43 (m, 2H), 3.25–3.19 (dd, 1H, $J = 17.0$, 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 157.2, 131.3, 128.4, 125.9,

113.6, 108.8, 82.2, 52.8, 35.3, 33.5; IR (KBr): 2950, 1720, 1560, 1400, 1240, 1120, 820 cm^{-1}; Anal. Calcd for $C_{11}H_8Br_4O_3$: C, 26.02; H, 1.59. Found: C, 26.00; H, 1.61. Compound **7b**: white solid; mp 99–100 °C; ^1H NMR (400 MHz, $CDCl_3$): δ 4.98–4.91 (m, 1H), 3.88 (s, 3H, OMe), 3.52–3.40 (m, 2H), 3.33–3.28 (dd, 1H, $J = 10.4$, 7.8 Hz), 3.13–3.07 (dd, 1H, $J = 17.1$, 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.9, 157.2, 131.3, 128.4, 125.9, 113.5, 108.9, 82.8, 52.9, 37.0, 7.5; IR (KBr): 1720, 1550, 1390, 1230, 1120, 840, 750, 690 cm^{-1}; Anal. Calcd for $C_{11}H_8Br_3IO_3$: C, 23.81; H, 1.45. Found: C, 24.00; H, 1.51.