Three-Step Synthesis of (Thio)xanthene and Dibenzothiepine/Dibenzoxepine by an Intramolecular Mizoroki–Heck Reaction of Diaryl (Thio)Ethers

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Abstract: We present a novel three-step protocol for preparing xanthene/thioxanthene and dibenzothiepine/dibenzoxepine from readily available starting materials. The Mizoroki–Heck cyclization as the final step was optimized to afford full conversion of the corresponding diaryl (thio)ethers and furthermore to achieve reasonably good selectivity between the 6-*exo* and the 7-*endo* products.

Key words: fused-ring systems, Heck reaction, heterocycles, palladium, sulfur

Tricyclic heterocyclic compounds have been of great interest within medicinal chemistry during several decades.[1] Since six- and seven-membered sulfur-containing tricyclics have been extensively applied in Central Nervous System (CNS) drugs,[1,2] it is of interest to develop new methodologies to improve the accessibility of these scaffolds. As an extension of our recent work on sulfur-containing heterocycles,[3] we became interested in developing a new protocol for preparing thioxanthene and dibenzothiepine to complement existing literature methods.[4]

Recently, Buchwald and co-workers[5] reported an elegant method for synthesizing carbazoles, acridines, and dibenzazepines, containing a central five-, six-, and seven-membered nitrogen heterocycle, respectively, by the use of palladium-catalyzed transformations. Their protocol offers excellent regioselectivity, and by slightly varying the reaction conditions it was possible to control formation of the desired compound. In this work, we decided to explore the possibility of extending this method for preparation of the corresponding sulfur and oxygen heterocycles thioxanthene (**1a**), xanthene (**1b**), dibenzothiepine (**2a**), and dibenzoxepine (**2b**; Figure 1).

Our protocol is based on a palladium-catalyzed intramolecular Mizoroki–Heck reaction[6] of diaryl (thio)ethers. The overall route involves only three steps from the readily available starting materials **3** and **4a**,**b** (Scheme 1).

Scheme 2 summarizes the synthesis of the precursors for the fused heterocycles. First, the aldehydes **5a**,**b** were prepared by a nucleophilic aromatic substitution reaction of 2-fluorobenzaldehyde (**3**) and 2-bromo(thio)phenols (**4a**,**b**) in the presence of potassium carbonate in yields of 71% and 84%, respectively. The resulting aldehydes **5a**,**b**

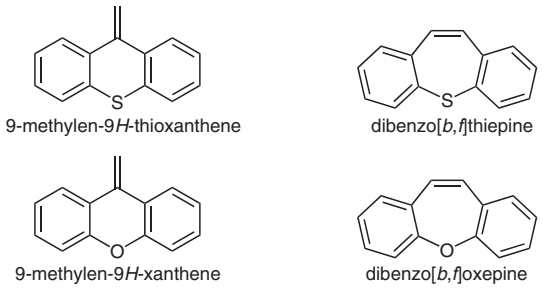
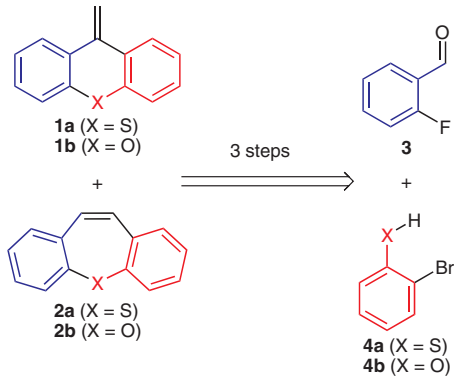


Figure 1 Structures of target molecules



Scheme 1 Retrosynthetic strategy for synthesizing six- and seven-membered oxygen- and sulfur-containing tricyclics from simple starting materials

were then subjected to Wittig olefination with methyltriphenylphosphonium iodide and potassium *tert*-butoxide to afford the alkenes **6a**,**b** in yields of 93% and >95%, respectively.

Next, the ring closure of compounds **6a**,**b** to furnish the 6-*exo* (**1a**) and 7-*endo* (**2a**) products by the Mizoroki–Heck reaction was investigated under different conditions. Table 1 summarizes the yields as a function of reaction conditions, which involved application of different phosphine ligands (Figure 2), temperature, and solvents. The palladium source $Pd_2(dba)_3$ and the base sodium *tert*-butoxide were kept constant. Gratifyingly, all the examined reaction conditions afforded quantitative conversion of the diaryl thioether **6a** into **1a** and **2a**. Entry 1 shows the outcome of using DavePhos as phosphine ligand in dioxane at 180 °C for 30 minutes under microwave heating. A ratio of 7:3 *endo*/*exo* was observed according to GC–MS

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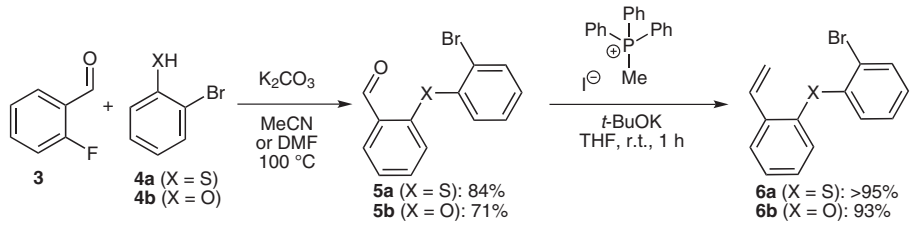


Scheme 2 Synthesis of diaryl (thio)ethers

and LC–MS, which corresponds to a moderate selectivity for the dibenzothiepine (**2a**). Dibenzothiepine and 9-methylenethioxanthene were isolated in yields of 59% and 28%, respectively. Using the same ligand, Buchwald and co-workers[5] obtained solely the 7-*endo* cyclized product dibenzazepine from a corresponding nitrogen analogue (using, however, a chloroaryl precursor rather than a bromoaryl). Moreover, Buchwald achieved regioselective 6-*exo* cyclization to form 9-methylacridine by using P(*t*-Bu)$_3$ as ligand in toluene. Using this ligand, as well as several others, approximate 1:1 *endo*/*exo* product ratios were observed by cyclization of **6a**. Although the two products were difficult to separate by GC resulting in some uncertainty in the estimated product ratios provided in Table 1, the lack of selectivity in the ring closure is striking in comparison to the excellent selectivities obtained for the nitrogen analogues.[5] Table 2 summarizes the screening of reaction conditions for synthesis of 9-methylenexanthene (**1b**) and dibenzoxepine (**2b**) from the diaryl ether **6b**. Here much better separation of products was achieved by GC–MS. Again, all the attempted ligands (except dpe-phos, entry 13) afforded quantitative conversion of the diaryl ether. DavePhos was employed in entries 1–4 with either dioxane or toluene as solvent, and a modest selectivity for the 6-*exo* product was achieved in entries 2–4. In addition we observed formation of the dehalogenated starting material as a minor by-product.

By using [HP(*t*-Bu)$_3$]BF$_4$ as ligand, it was possible to even further favor the formation of the 6-*exo* product **1b** over the 7-*endo* **2b**, however, at the expense of increased formation of the dehalogenated by-product. In entries 9–13, PCy$_3$, S-Phos and dpe-phos were employed as phosphine ligands. S-Phos was observed to give a modest selectivity for the 7-*endo* compound. Classical Heck-type conditions were examined (entry 14) by using Pd(PPh$_3$)$_2$Cl$_2$ and triethylamine in acetonitrile. With no apparent formation of the dehalogenated by-product, an improved selectivity for the 7-*endo* product (7-*endo*/6-*exo* = 65:35) was observed.

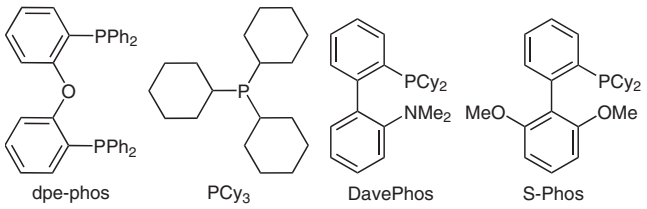
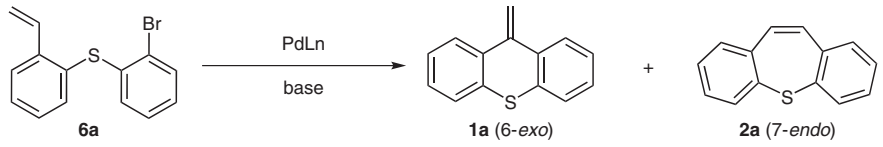


Figure 2 Selected phosphine ligands

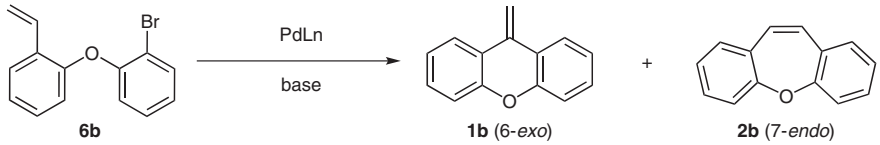
Table 1 Optimization Study for Synthesizing Thioxanthene/Dibenzothiepine[a]



Entry	Ligand	Solvent	Temperature (time)	Conversion (%)	Yield (%)	
					6-*exo*	7-*endo*
1	DavePhos	dioxane	180 °C (0.5 h)[b]	100	30 (28)[c]	70 (59)[c]
2	P(*t*-Bu)$_3$	toluene	180 °C (0.5 h)[b]	100	50	50
3	[HP(*t*-Bu)$_3$]BF$_4$	toluene	110 °C (6 h)	100	50	50
4	PCy$_3$	toluene	180 °C (0.5 h)[b]	100	50	50
5	S-Phos	toluene	180 °C (0.5 h)[b]	100	50	50
6	dpe-phos	toluene	180 °C (0.5 h)[b]	100	50	50

[a] Reaction conditions: diaryl thioether (1.0 equiv), *t*-BuONa (1.5 equiv), Pd$_2$(dba)$_3$ (2.5 mol%), monodentate ligand (7.5 mol%) or bidentate ligand (5.0 mol%). Yields are based on GC–MS (estimates) if not otherwise stated.
[b] Microwave conditions.
[c] Isolated yield.

Table 2 Optimization Study for Synthesizing Xanthene/Dibenzoxepine[a]



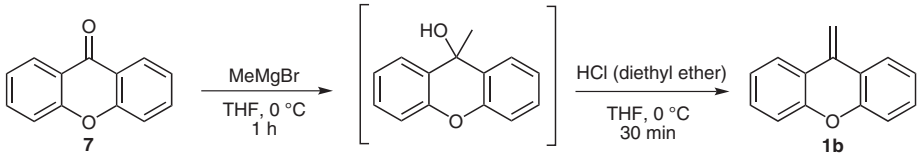
6b **1b** (6-*exo*) **2b** (7-*endo*)

Entry	Ligand	Solvent	Temperature (time)	Conversion (%)	Yield (%)		
					6-*exo*	7-*endo*	Dehalogenated
1	DavePhos	toluene	180 °C (0.5 h)[b]	100	50	50 (44)[c]	–
2	DavePhos	dioxane	180 °C (0.5 h)[b]	100	62	38	–
3	DavePhos	dioxane	110 °C (2.5 h)	100	54	30	16
4	DavePhos	toluene	110 °C (2.5 h)	100	60	40	–
5	$[HP(t\text{-}Bu)_3]BF_4$	toluene	110 °C (2.5 h)	100	60	28	12
6	$[HP(t\text{-}Bu)_3]BF_4$	dioxane	110 °C (2.5 h)	100	61	16	22
7	$[HP(t\text{-}Bu)_3]BF_4$	dioxane	80 °C (48 h)	<10	–	–	–
8	$[HP(t\text{-}Bu)_3]BF_4$	dioxane	60 °C (48 h)	<10	–	–	–
9	PCy_3	toluene	180 °C (0.5 h)[b]	100	55	45	–
10	S-Phos	toluene	180 °C (0.5 h)[b]	100	42	58	–
11	S-Phos	toluene	110 °C (3 h)	100	46	54	–
12	S-Phos	dioxane	110 °C (3 h)	100	39	61	–
13	dpe-phos	toluene	180 °C (0.5 h)[b]	86	38	30	18
14[d]	$Pd(PPh_3)_2Cl_2$[d]	MeCN	110 °C (6 h)	100	65	35	–

[a] Reaction conditions: diaryl ether (1.0 equiv), *t*-BuONa (1.5 equiv), $Pd_2(dba)_3$ (2.0 mol%), monodentate ligand (6.0 mol%) or bidentate ligand (4.0 mol%). Yields are based on GC–MS if not otherwise stated.
[b] Microwave conditions.
[c] Isolated yield.
[d] Classical Heck-type conditions were used in entry 14, diaryl ether (1.0 equiv), $Pd(PPh_3)_2Cl_2$ (10 mol%), and Et_3N (10 equiv).

Dibenzoxepine was isolated in a yield of 44% using conditions from entry 1, while it was not possible to isolate 9-methylenexanthene, albeit its formation was evident according to GC–MS. Instead, we isolated xanthone (**7**) in a yield of 41%, indicating that **1b** had been transformed quantitatively during the workup. We further elucidated that the xanthene was still present after aqueous workup and that the oxidative cleavage of the exocyclic double bond took place during column chromatography. It is known in the literature[7] that 9-methylenexanthene (**1b**) converts into xanthone during workup. However, there is one report in the literature of an actual isolation of **1b**,[8] but in our hands the compound could not be isolated. To investigate whether palladium residues had an effect on this conversion, we synthesized 9-methylenexanthene by a Grignard addition and subsequent elimination from xanthone (Scheme 3). However, **1b** was still converted into **7** during chromatographic workup.

In conclusion, we have developed a new three-step protocol for preparing (thio)xanthene and dibenzothiepine/dibenzoxepine from readily available starting materials.[9] The Mizoroki–Heck cyclization as the final step was optimized to afford full conversion of the corresponding (thio)ethers. While reasonable selectivity in the formation of 6-*exo* and 7-*endo* products could be obtained by changing the ligand and solvent, it was still strikingly reduced relative to that previously achieved for the corresponding N-containing heterocycles obtained under similar ring-



7 **1b**

Scheme 3 Synthesis of **1b** from xanthone **7**

closure conditions. Despite this modest selectivity, the method provides a convenient synthesis of these fused heterocycles, and the sulfur analogues could easily be separated and isolated by column chromatography. A future prospect is to use the protocol for synthesis of substituted derivatives from suitably functionalized aromatic precursors.

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(9) **Synthesis of 2-(2-Bromophenylsulfanyl)benzaldehyde (5a)**: 2-Fluorobenzaldehyde (**3**; 2.0 g, 16 mmol), 2-bromothiophenol (**4a**; 3.0 g, 16 mmol) and anhyd K_2CO_3 (3.29 g, 23.8 mmol) were dissolved in MeCN (10 mL) and stirred at 100 °C for 30 min under MW conditions. The crude reaction mixture was evaporated onto Celite and purified using column chromatography on silica gel (eluent: heptane → 30% EtOAc in heptane). The title compound was obtained as a colorless solid (3.97 g, 84%); R_f 0.61 (EtOAc–heptane, 1:2); mp 49–50 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.39 (s, 1 H), 7.95 (dd, *J* = 7.6, 1.7 Hz, 1 H), 7.66 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.48–7.51 (m, 1 H), 7.43 (m, 1 H), 7.24–7.28 (m, 1 H), 7.14–7.21 (m, 3 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 191.8, 138.8, 135.7, 134.6, 134.4, 133.6, 133.3, 131.8, 131.6, 129.3, 128.4, 127.5, 126.4. GC–MS: *m/z* = 392 [M$^+$]. Anal. Calcd for $C_{13}H_9BrOS$: C, 53.26; H, 3.09. Found: C, 53.22; H, 3.05.

Synthesis of 2-(2-Bromophenoxy)benzaldehyde (5b): 2-Fluorobenzaldehyde (**3**; 2.0 g, 16 mmol), 2-bromophenol (**4b**; 2.8 g, 16 mmol), and anhyd K_2CO_3 (3.29 g, 23.8 mmol) were dissolved in anhyd DMF (20 mL) and the mixture was refluxed for 2 h. The mixture was then diluted with EtOAc (30 mL) and brine (100 mL); the layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with 2 M aq NaOH (2 × 20 mL) and H_2O (20 mL), dried with $MgSO_4$, filtered, concentrated in vacuo onto Celite, and purified using column chromatography on silica gel (eluent: heptane → 30% EtOAc in heptane). Compound **5b** was obtained as a pale-yellow solid (3.19 g, 71%); R_f 0.60 (EtOAc–heptane, 1:2); mp 62–63 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 10.60 (s, 1 H), 7.96 (dd, *J* = 7.8, 1.6 Hz, 1 H), 7.66–7.70 (m, 1 H), 7.50 (m, 1 H), 7.32–7.37 (m, 1 H), 7.19 (td, *J* = 7.7, 0.8 Hz, 1 H), 7.10 (m, 2 H), 6.74 (d, *J* = 8.4 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 189.2, 159.4, 152.5, 135.7, 134.2, 129.0, 128.6, 126.3, 126.1, 123.3, 121.7, 116.9, 115.5. GC–MS: *m/z* = 276 [M$^+$]. Anal. Calcd for $C_{13}H_9BrO_2$: C, 56.34; H, 3.27. Found: C, 56.39; H, 3.25.

Synthesis of 2-Bromophenyl-2-vinylphenylsulfane (6a): Methyltriphenylphosphonium iodide (3.31 g, 8.19 mmol) was dissolved in anhyd THF (50 mL) and the solution was cooled to 0 °C under an argon atmosphere. *t*-BuOK (1.15 g, 10.2 mmol) was added by which the solution turned yellow and after stirring for 10 min, compound **5a** (2.00 g, 6.82 mmol) was added and the mixture was allowed to reach r.t. and stirred for 1.5 h. The crude mixture was concentrated in vacuo directly onto Celite and purified using column chromatography on silica gel (eluent: heptane → 30% EtOAc in heptane). Compound **6a** was obtained as a yellow solid (1.98 g, 100%); R_f 0.77 (EtOAc–heptane, 1:2); mp 58–59 °C. ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.69 (dd, *J* = 7.9, 1.2 Hz, 1 H), 7.53 (dd, *J* = 7.9, 1.3 Hz, 1 H), 7.48 (dd, *J* = 7.7, 1.3 Hz, 1 H), 7.42 (m, 1 H), 7.29 (td, *J* = 7.6, 1.4 Hz, 1 H), 7.18 (dd, *J* = 17.4, 11.0 Hz, 1 H), 7.07–7.10 (m, 1 H), 6.97 (td, *J* = 7.6, 1.5 Hz, 1 H), 6.63 (dd, *J* = 8.0, 1.5 Hz, 1 H), 5.73 (dd, *J* = 17.4, 0.9 Hz, 1 H), 5.29 (dd, *J* = 11.0, 0.9 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 141.3, 138.9, 136.0, 134.4, 132.8, 130.3, 129.7, 128.9, 128.2, 127.7, 126.5, 126.4, 121.6, 116.7. GC–MS: *m/z* = 290 [M$^+$]. Anal. Calcd for $C_{14}H_{11}BrS$: C, 57.74; H, 3.81. Found: C, 53.72; H, 3.85.

Synthesis of 1-Bromo-2-(2-vinylphenoxy)benzene (6b): Methyltriphenylphosphonium iodide (5.51 g, 13.6 mmol) was dissolved in anhyd THF (50 mL) and the solution was cooled to 0 °C under an argon atmosphere. *t*-BuOK (1.64 g, 14.6 mmol) was added by which the solution turned yellow

and after stirring for 10 min, compound **5b** (2.7 g, 9.7 mmol) was added and the mixture was allowed to reach r.t. and subsequently stirred for 1 h. The crude mixture was concentrated in vacuo directly onto Celite and purified using column chromatography on silica gel (eluent: heptane → 30% EtOAc in heptane). Compound **6b** was obtained as a pale-yellow oil (2.49 g, 93%); R_f 0.76 (EtOAc–heptane, 1:2). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 7.62 (m, 2 H), 7.18–7.23 (m, 2 H), 7.14 (t, *J* = 7.4 Hz, 1 H), 6.93–7.04 (m, 2 H), 6.82 (dd, *J* = 8.1, 0.8 Hz, 1 H), 6.76 (dd, *J* = 8.2, 1.4 Hz, 1 H), 5.81 (dd, *J* = 17.7, 1.1 Hz, 1 H), 5.30 (dd, *J* = 11.1, 1.1 Hz, 1 H). ^{13}C NMR (151 MHz, $CDCl_3$): δ = 154.2, 153.2, 133.7, 130.7, 129.3, 129.0, 128.6, 126.8, 124.3, 124.3, 119.2, 118.9, 115.7, 113.7. GC–MS: *m*/*z* = 274 [M$^+$]. Anal. Calcd for $C_{14}H_{11}BrO$: C, 61.11; H, 4.03. Found: C, 61.20; H, 4.02.

Synthesis of Thioxanthene (1a) and Dibenzothiepine (2a; Entry 1, Table 1): A microwave vial was purged with anhyd dioxane (2.0 mL) and then compound **6a** (0.29 g, 1.0 mmol), DavePhos (29.5 mg, 0.075 mmol), $Pd_2(dba)_3$ (22.9 mg, 0.0250 mmol), and *t*-BuONa (144 mg, 1.50 mmol) were added to this vial under a flow of argon and finally the tube was capped. The mixture was heated for 30 min at 180 °C under MW conditions for full conversion of starting material. Judged from LC–MS and GC–MS, the reaction mixture contained a 30:70 ratio of **1a/2a** and it was concentrated in vacuo directly onto Celite and purified using column chromatography on silica gel (eluent: heptane → 30% EtOAc in heptane). Compounds **1a** (59 mg, 28%) and **2a** (124 mg, 59%) were obtained as colorless oils and the characterization data were in accordance with the literature data.[4i,m]

Synthesis of Xanthene (1b)/Xanthone (7) and Dibenzoxepine (2b; Entry 1, Table 2): The procedure described above for preparing compounds **1a** and **2a** was followed using anhyd toluene (2.0 mL), compound **6b** (0.150 g, 0.545 mmol), DavePhos (12.9 mg, 0.0327 mmol), $Pd_2(dba)_3$ (9.98 mg, 0.0109 mmol), and *t*-BuONa (78.6 mg, 0.818 mmol). The mixture was heated for 30 min at 180 °C under MW conditions. Judged from LC–MS and GC–MS, the reaction mixture contained a 1:1 ratio of **1b/2b** and it was concentrated in vacuo directly onto Celite and purified using column chromatography on silica gel (eluent: heptane → 30% EtOAc in heptane). Compound **2b** was isolated as a colorless solid (47 mg, 44%). During workup compound **1b** underwent conversion into xanthone (**7**), which was isolated as a colorless solid (44 mg, 41%). Characterization data of **2b** and **7** were in accordance with the literature data.[10]

(10) (a) Drake, J. A. G.; Jones, D. W. *Spectrochim. Acta, Part A* **1981**, *37*, 77. (b) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117.

