An Expedient Route to 3-Chlorothioxanthen-9-one-10,10-dioxide and Derivation by Palladium-Catalyzed Coupling

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Received 23 February 2006

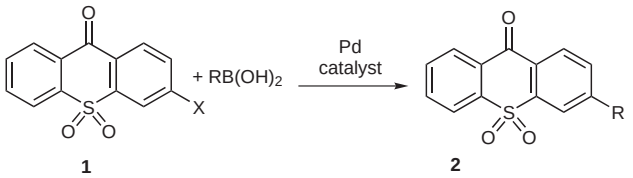
This paper is dedicated to Professor Richard Heck, a pioneer in palladium-catalyzed carbon–carbon bond formation.

Abstract: Chemistry has been developed that allows for the synthesis of a series of novel tricyclic thioxanthen-9-one-10,10-dioxides. A regioselective synthesis of the novel core substrate 3-chlorothioxanthen-9-one-10,10-dioxide was achieved in 85% yield over three steps without the need for chromatographic purification. Subsequent microwave-assisted coupling methodology afforded the desired novel 3-substituted tricyclic compounds in good to excellent yield.

Key words: catalysis, heterocycles, palladium, Suzuki reaction, thioxanthenone dioxide

The facile assembly of therapeutically valuable molecular entities such as thioxanthen-9-one-10,10-dioxides is an important goal. Thioxanthenones as well as thioxanthen-9-one-10,10-dioxides have been shown to possess potent antitumor,[1] antiallergic[2] and monoamine oxidase[3] (MAO) inhibitory activity. A facile approach to this class of molecules is essential for the development of better drug candidates based on this motif. Herein we report a versatile, expedient and efficient route to this class of molecules and demonstrate its utility with a small library of novel thioxanthen-9-one-10,10-dioxides derivatives **2**.

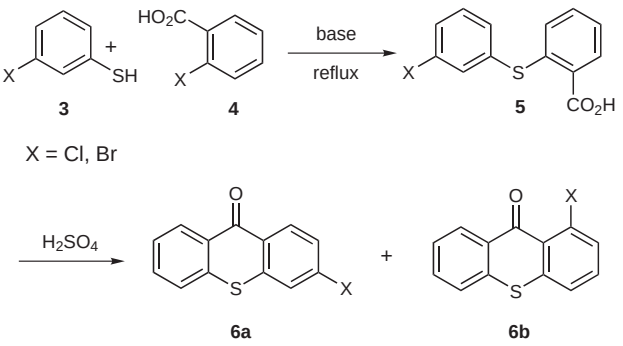
The approach that has been developed relies on the use of the Suzuki reaction on a 3-halo-thioxanthen-9-one-10,10-dioxide (**1**, Scheme 1). The Suzuki reaction was chosen in part for the large number of commercial boronic acids and esters available. For this to be a viable approach to this class of molecule, a reasonable quantity of the halide was required. Consequently, the initial goal became the development of a practical, efficient and expedient route to the core halo substrate **1**.



1 **2**

Scheme 1

The reported syntheses of similar 3-halo-thioxanthenone ring systems utilize as their first step the reaction of the corresponding *m*-halo-benzenethiol substrate **3** with 2-halo-benzoic acid **4**. Subsequent treatment with mineral acid, affords the desired Friedel–Crafts product 3-halo-thioxanthenone ring system **6** (Scheme 2).[2b,d,4] While effective, this methodology invariably yields a mixture of 3- and 5-regioisomeric products (**6a** and **6b**) that require tedious chromatographic and/or recrystallization in order to obtain the products in pure form. Alternative protocols, although efficient, make use of both reagents and reaction conditions (e.g. low temperatures, pyrophoric bases such as *t*-BuLi, longer reaction times),[5] which can be incompatible with both scale-up and parallel synthesis.



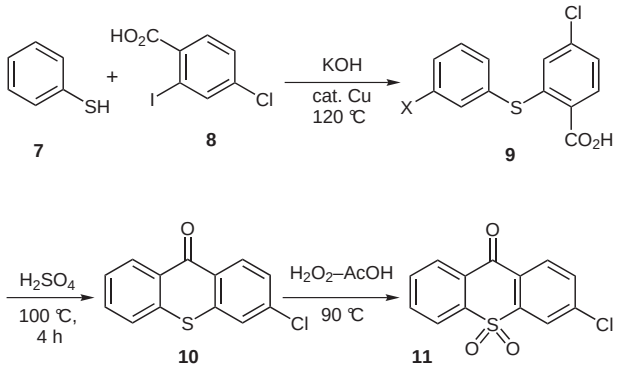
Scheme 2

Because of these problems a route starting from thiophenol and 2-iodo-3-chlorobenzoic acid was developed. Under basic conditions the nucleophilic substitution of thiophenol **7** with the suitably substituted 2-iodo-3-chlorobenzoic acid building block **8** in the presence of a catalytic amount of copper[6a–c] for eight hours affords the desired coupled sulfide **9**[6b] in virtually quantitative yield (Scheme 3).

The presence of catalytic copper powder is crucial to the efficiency of this synthetic step, presumably via the in situ formation of the corresponding cupric benzoate.[2c,7]

Treatment of **9** with concentrated sulfuric acid at 100 °C over four hours affords the Friedel–Crafts adduct, thioxanthenone **10**. Upon pouring the reaction mixture onto ice, the product precipitates out as an off-white solid. No further purification is required, although copious amounts of water were vital to remove adventitious sulfuric acid.

SYNLETT 2006, No. 18, pp 3045–3048
Advanced online publication: 25.10.2006
DOI: 10.1055/s-2006-951520; Art ID: S02206ST



Scheme 3

Oxidation of **10** to the desired key sulfone substrate **11** required fine-tuning of the oxidative protocols reported for similar deactivated aromatic ring systems (Table 1).[8] The majority of the probed systems led to mixtures of sulfoxide and sulfone derivatives ranging from 45:10% to 80:5%. The effects of reaction time, temperature, solvent and oxidant stoichiometry were monitored for each oxidation method but no significant improvement on the sulfone:sulfoxide adduct ratio was evident. Ultimately, the H_2O_2–AcOH (1:2 v/v) oxidative system (Table 1, entry 5) by means of slow addition as well as an optimal reaction temperature of 90 °C was selected to be the method of choice. Worth noting is the fact that, previously reported oxidations of similar thioxanthenone tricyclic systems,[8d] a 30% H_2O_2 (v/v) solution, does not effect the oxidation of this system as efficiently as the 50% H_2O_2 herein reported. In addition to being inexpensive and practical this method afforded 80% of isolated **11** and only a small amount (5%) of sulfoxide by-product. Sulfone **11** could be purified by recrystallization from ethyl acetate–hexane, providing compound **11** in pure form as yellow needles in 70% yield.

With **11** in hand, conditions for the microwave-assisted Suzuki coupling to give novel 3-substituted thioxanthen-9-one-10,10-dioxides were screened.[9] This effort utilized the model reaction of sulfone **11** with commercially available phenyl boronic acid (Table 2).

In-house or readily available catalytic palladium sources were used under several conditions. When using catalysts such as $Pd_2(dba)_3$, $Pd(OAc)_2$, $Pd(dppf)Cl_2$, Pd/C and Fibrecat® (encapsulated palladium; Johnson Matthey Inc.) isolated yields of coupled product were modest, ranging from 40–60%. These results were not significantly affected by variation of solvent, temperature, base used or reaction times. In all cases a substantial amount of unreacted sulfone **11** was observed and recovered.

The best results were obtained using a combination of $Pd(PPh_3)_4$ as catalyst, EtOH as solvent, Cs_2CO_3 as base (1.0 M solution in H_2O) and a reaction temperature of 110 °C for a period of 10 minutes (Table 2, entry 6). The use of Cs_2CO_3 as a solution rather than a solid reagent proved to be a significant improvement in the overall methodology with the yield increasing from 65% to 87%.

The use of a polymer-supported (PS) surrogate of this catalyst system, PS–Ph_3–Pd (Argonaut Technologies; Table 2, entry 9) resulted in an isolated yield of 78% of coupled product. In general, the use of PS–Pd catalyst systems is well known to provide cleaner reaction mixtures in coupling reactions, such as the Suzuki coupling, due to higher stability of the former to potential decomposition.[10] However, in this case simple $Pd(PPh_3)_4$ provided products of equivalent purity.

In our hands, the use of simultaneous cooling (air stream at 40 psi) while running this microwave-assisted Suzuki coupling reaction led to a yield increase of **13** by 10% when compared to standard reaction conditions.[11]

Given the efficiency of the reaction, it was decided that screening of additional catalytic systems known to enhance coupling of less reactive chloro Suzuki substrates[12] was not necessary. For the same reason, and although it is known to often play a crucial role in the efficiency of palladium-catalyzed reactions, it was deemed superfluous to proceed with the degassing of solvent used for this reaction.

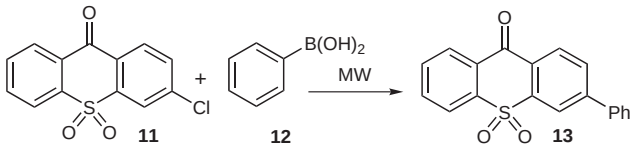
The optimized conditions for the synthesis of **13** (Table 2, entry 6) were utilized in the synthesis of novel analogues, which were obtained in isolated yields varying from 20–87% (Table 3). We believe that both the inherent lack reactivity of **11** and the boronic acid were the chief reason

Table 1 Selected Oxidation Screening Conditions of **10**

Entry	Oxidant	Conditions	Yield of **11** (%)[a,b]	Yield of sulfoxide (%)
1	PIFA	$CHCl_3$, r.t.	45	10
2	Oxone	DMF, 80 °C	60	10
3	MCPBA	CH_2Cl_2, r.t.	42	15
4	$RuCl_3$–$NaIO_4$	CCl_4–MeCN–H_2O (1:1:2 v/v), r.t.	66	5
5	**H_2O_2–AcOH**	**H_2O_2–AcOH (1:2 v/v), 90 °C**	**80**	**5**

[a] Reactions were carried out at 0.81 mmol of 10 and using 2.2 equiv of oxidant as starting point whilst screening for optimal stoichiometric values.
[b] Isolated yields after reverse-phase preparative HPLC.

Table 2 Selected Examples of Protocols Screened for Microwave-Assisted Suzuki Coupling Reaction[a,b]



Entry	Catalyst	Catalyst (mol%)	Solvent	Temp (°C)	Base	Yield of **13** (%)
1	$Pd(dba)_3$	3	DMF	155	K_2CO_3	40
2	$Pd(dba)_3$	3	DMA	177	Cs_2CO_3	55
3	$Pd(dba)_3$	3	EtOH	110	Cs_2CO_3	52
4	$Pd(dppf)Cl_2$	10	DMF	155	Cs_2CO_3	56
5	$Pd(PPh_3)_4$	3	EtOH	110	Cs_2CO_3	65
6	**$Pd(PPh_3)_4$**	**3**	**EtOH**	**110**	**1.0 M soln of Cs_2CO_3**	**87**
7	Pd/C	10	DMF	155	Cs_2CO_3	50
8	Fibrecat®	5	DMF	155	Cs_2CO_3	48
9	PS-Ph_3-Pd	10	EtOH	110	Cs_2CO_3	78
10	$Pd(OAc)_2$	3	EtOH	110	Cs_2CO_3	60

[a] Reactions were carried out at 0.81 mmol of **10** and using 2.2 equiv of oxidant as starting point whilst screening for optimal stoichiometric values.
[b] Isolated yields after reverse-phase preparative HPLC.

for the lower yield observed for compound **27**. Additionally, reported low yields such as with **16** (Table 3) are commonly associated with electron-rich boron reagents.

In summary, utilizing our strategy, intermediate **11** can be easily and expediently obtained as a single regioisomer and in multigram quantities. This key intermediate can then be used in the synthesis of a wide variety of derivatives of novel tricyclic thioxanthen-9-one-10,10-dioxides by means of microwave-assisted Suzuki coupling methodology. This methodology makes literally hundreds of novel thioxanthen-9-one-10,10-dioxides available from a single precursor. The development of other alternative analogues of **11** such as its 3-boronic acid congener is under way. Given the wider commercial availability of halides (vs. boronic acids), the 3-boronic acid substrate will allow for the introduction of a more diverse set of functionality.

Table 3 Synthesis of Novel 3-Substituted Thioxanthen-9-one-10,10-dioxide Analogues[a]

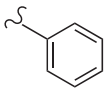
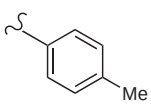
Product	R	Yield (%)[b,c]
13		87
14		59

Table 3 Synthesis of Novel 3-Substituted Thioxanthen-9-one-10,10-dioxide Analogues[a] (continued)

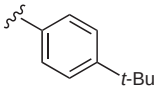
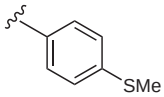
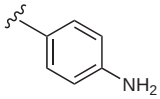
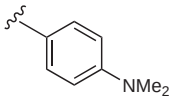
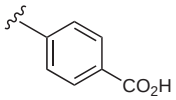
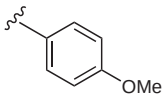
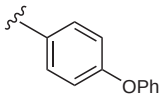
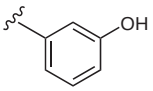
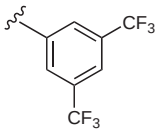
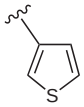
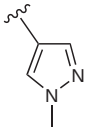
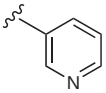
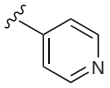
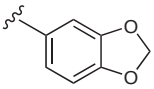
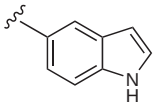
Product	R	Yield (%)[b,c]
15		55
16		30
17		56
18		44
19		61
20		80
21		40

Table 3 Synthesis of Novel 3-Substituted Thioxanthen-9-one-10,10-dioxide Analogues[a] (continued)

Product	R	Yield (%)[b,c]
22		75
23		42
24		43
25		54
26		87
27		20
28		53
29		71

[a] Reactions were run using 0.089 mmol of chlorosulfone **11**, 0.089 mmol of corresponding boronic acid or boronic ester, 3 mol% $Pd(PPh_3)_4$, 0.107 mmol of Cs_2CO_3 (1.0 M solution) and 1.5 mL of EtOH. A microwave irradiation of 200 W was used the temperature being ramped from r.t. to 110 °C in 1 min where it was then held for a total reaction time of 10 min. Simultaneous cooling was used (power-max option on CEM discover microwave unit) for all reactions.
[b] Isolated yields after chromatography.
[c] Unoptimized yields except for the case of **13**.

Acknowledgment

Financial assistance provided by the Robert A. Welch foundation is gratefully acknowledged.

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