DOI: 10.1002/ejoc.200900676

A New Synthetic Route to Unsymmetrical 9-Arylxanthenes[‡]

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Keywords: Fused-ring systems / Oxygen heterocycles / Arenes / Synthetic methods

A facile and general three-step synthetic route towards unsymmetrical 9-arylxanthenes was developed. The reaction sequence involves nucleophilic substitution of commercially available 2-fluorobenzaldehydes with arenoxides, Grignard reaction of the resulting 2-arenoxybenzaldehydes with arylmagnesium bromides, followed by $FeCl_3$-catalyzed intramolecular diarylmethylation of the resulting carbinols. This strategy was extended to access symmetrical as well as unsymmetrical 9-arylthioxanthenes.

Introduction

Xanthenes and dibenzo[*a*,*j*]xanthenes have attracted considerable attention over the years as a result of their wide range of biological properties such as antiviral,[1] anti-inflammatory,[2] and antibacterial activities.[3] These compounds have also been utilized as antagonists for paralyzing action of zoxazolamine[4] and in photodynamic therapy (PDT).[5] The flat, rigid structure of xanthenes has been used to advantage as a linker for peptide synthesis and in unnatural amino acids and related pharmaceutical precursors.[6] More importantly, xanthenes and the related condensed ring system variants have also been used as dyes, fluorescent materials for visualization of biomolecules, and in laser technologies as a result of their useful spectroscopic properties.[7] Oxidation of these compounds produce xanthylium salts, which are also useful as dyes and fluorescent materials.[8] For example, fluorescein and fluorone are structurally related xanthene dyes (Figure 1). Fluorone derivatives have found numerous applications such as in the detection of a variety of metal ions,[9] sugars,[10] phosphorylated molecules,[11] HIV-1 nucleocapsid protein,[12] reactive oxygen species,[13] in screening assays for mitochondrial permeability,[14] acetylcholinesterase inhibition,[15] and telomerase inhibition.[16]

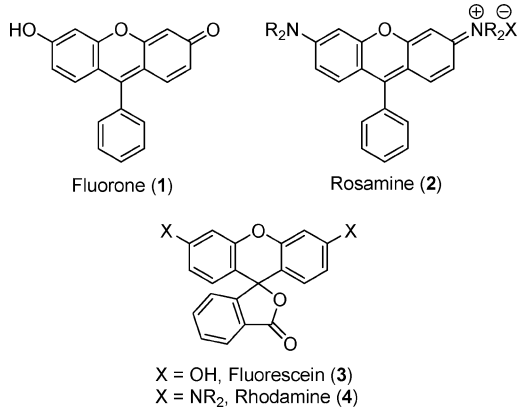

Figure 1. Structures of some common xanthene dyes.

Results and Discussion

Over the past several years we have been involved in the design, synthesis, and antitubercular and anticancer activities of various triarylmethanes (TRAMs).[17] In continuation of our research program in this direction, we became interested in synthesizing 9-arylxanthenes as conformationally constrained analogues of TRAMs.

However, a literature survey revealed that the synthesis of 9-arylxanthenes are known by three routes: (a) reaction of xanthones with arylmagnesium halides (ArMgX) or aryllithiums (ArLi) followed by subsequent conversion of the resulting carbinols;[18] (b) condensation of β-naphthol with aromatic aldehydes;[19] (c) coupling of arynes with aromatic aldehydes.[20] However, only route (a) can permit the synthesis unsymmetrical 9-arylxanthenes. Because substituted xanthones are not commercially available, this method of synthesizing unsymmetrical 9-arylxanthenes also requires the synthesis of the starting xanthones, which, in turn, may be a multistep process. Therefore, access to symmetrical as well as unsymmetrical 9-arylxanthenes by a short and efficient method incorporating a wide range of substituent patterns would further expand the scope of their applications in our ongoing research program.

[‡] CDRI communication number 7732

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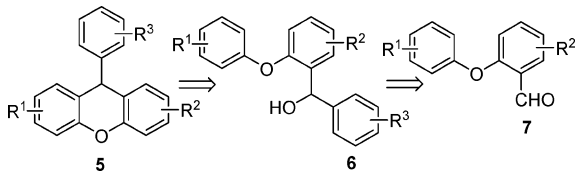
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900676.

In 2005, we reported the synthesis of unsymmetrical trisubstituted methanes (TRSMs) by intermolecular diarylmethylation of electron-rich arenes by using diaryl carbinols as alkylating agents.[21] Accordingly, it was envisaged that utilization of this diarylmethylation of electron-rich arene reaction could be applied to the synthesis of various symmetrical as well as unsymmetrical 9-arylxanthenes **5** by an intramolecular fashion in a diarylcarbinol **6** containing a tethered arenoxy group (Scheme 1). Carbinol **6** could be obtained by the Grignard reaction of aromatic halides with 2-arenoxybenzaldehydes **7**.

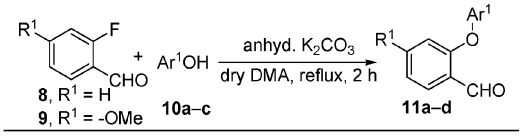


Scheme 1. Retrosynthetic analysis of 9-arylxanthenes.

Our study began with the synthesis of a series of four 2-arenoxybenzaldehydes **11a**–**d** by following a literature procedure that involved heating a solution of 2-fluorobenzaldehydes **8** or **9**)[29] and aromatic hydroxy compounds **10a**–**c** in dry DMA at reflux in the presence of anhydrous K_2CO_3 as a base (Table 1).[22] With 2-arenoxybenzaldehydes **11a**–**d** in hand, we turned our attention for the next steps. Thus, initially 2-phenoxybenzaldehyde **11a** was treated with freshly prepared phenylmagnesium bromide to get carbinol **12a** in very high yield (see the scheme for Table 3). It was subsequently chosen as a model substrate for the investigation of the intramolecular diarylmethylation reaction leading to 9-phenylxanthene. In view of the use of a catalytic amount of concentrated H_2SO_4 in our previous work on the synthesis of unsymmetrical TRSMs,[21] we first examined the cyclization of alcohol **12a** in the presence of concentrated H_2SO_4 (Table 2, Entry 1). Thus, a solution of **12a** in dry benzene was heated at reflux for 30 min to afford 9-arylxanthene **13a** (75% yield). Similarly, the use of some other well-known Friedel–Crafts protic and Lewis acid catalysts such as anhydrous $AlCl_3$, $Sc(OTf)_3$, and TfOH in the above reaction was also effective under suitable reaction conditions. Also, it was found that **12a** could be transformed into **13a** in high yield by treating a solution of **12a** in dry CH_2Cl_2 at room temperature with the use of $FeCl_3$ (10 mol-%).

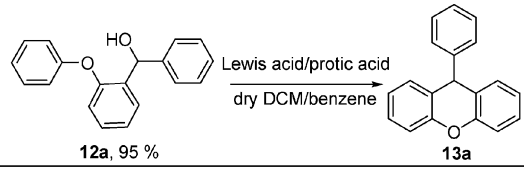
It appeared that the high stabilization of the diarylmethyl carbocation made the cyclization reaction very effective. However, although the above intramolecular diarylmethylation of electron-rich arenes could be done by using a wide range of Lewis and Brønsted acid catalysts, we were interested to do the reaction using less-expensive anhydrous $FeCl_3$, which has already been used in alkylation of electron-rich arenes with aromatic aldehydes,[23] arylation of benzyl alcohols and benzyl carboxylates,[24] hydroarylation of styrenes,[25] benzylation of 1,3-dicarbonyl compounds,[26] and intramolecular hydroamination and hydroalkoxylation of alkenes.[27] Also owing to the toxic nature of benzene,[28] we chose dichloromethane (DCM) as the reaction medium.

Table 1. Synthesis of 2-arenoxybenzaldehydes **11a**–**d**.



Entry	Aldehyde	Ar^1	Product, yield
1	**8**	Ph, **10a**	R^1 = H Ar^1 = Ph **11a**, 90%
2	**8**	4-$OMeC_6H_4$, **10b**	R^1 = H Ar^1 = 4-$OMeC_6H_4$ **11b**, 93%
3	**8**	2-naphthyl, **10c**	R^1 = H Ar^1 = 2-naphthyl **11c**, 91%
4	**9**	Ph, **10a**	R^1 = OMe Ar^1 = Ph **11d**, 85%

Table 2. Optimization studies for the synthesis 9-phenylxanthene.

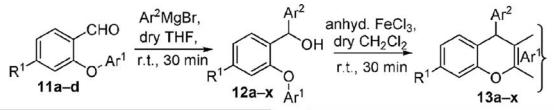


Entry	Lewis or protic acid	Conditions	Yield [%][a]
1	conc. H_2SO_4	benzene, 80°C, 30 min	75
2	anhyd. $AlCl_3$ (1 equiv.)	benzene, r.t., 30 min	85
3	TfOH (10 mol-%)	CH_2Cl_2, r.t., 20 min	90
4	$Sc(OTf)_3$ (10 mol-%)	CH_2Cl_2, r.t., 20 min	88
5	anhyd. $FeCl_3$ (10 mol-%)	CH_2Cl_2, r.t., 20 min	91

[a] Isolated yield of **13a** after silica gel column chromatography.

On the basis of these facts and the above optimization results, we then turned our attention to explore the scope of $FeCl_3$-catalyzed diarylmethylation of electron-rich arenes with various diarylcarbinols containing tethered arenoxy groups. Towards that objective, a series of carbinols **12b**–**x** was first synthesized by the addition of various freshly prepared arylmagnesium bromides on **11a**–**d** (Table 3). All the reactions were very high yielding (90–96%). Next, treatment of the resulting carbinols with $FeCl_3$ (10 mol-%) in dry CH_2Cl_2 at room temperature furnished the corresponding 9-arylxanthenes **13b**–**x** in high yields (Table 3). The reaction was amenable to a variety of aromatic rings for the synthesis of unsymmetrical 9-arylxanthenes. The reaction sequence shown in Table 3 involves several salient features: (a) the diverse collection of 9-arylxanthenes demonstrates

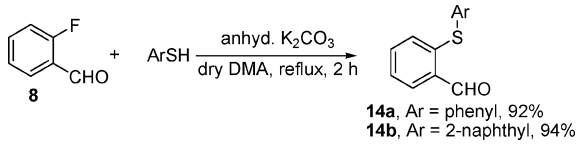
Table 3. Synthesis of 9-arylxanthenes **13b**–**x**.



Entry	Carbinol, yield	9-Arylxanthene, yield
1	R^1 = H Ar^1 = Ph Ar^2 = 2-OMeC$_6$H$_4$ **12b**, 96%	R^1 = H Ar^1 = Ar^2 = 2-OMeC$_6$H$_4$ **13b**, 88%
2	R^1 = H Ar^1 = Ph Ar^2 = 3-OMeC$_6$H$_4$ **12c**, 93%	R^1 = H Ar^1 = Ar^2 = 3-OMeC$_6$H$_4$ **13c**, 91%
3	R^1 = H Ar^1 = Ph Ar^2 = 4-OMeC$_6$H$_4$ **12d**, 95%	R1 = H Ar^1 = Ar^2 = 4-OMeC$_6$H$_4$ **13d**, 92%
4	R^1 = H Ar^1 = Ph Ar^2 = 2-SMeC$_6$H$_4$ **12e**, 97%	R^1 = H Ar^1 = Ar^2 = 2-SMeC$_6$H$_4$ **13e**, 92%
5	R^1 = H Ar^1 = Ph Ar^2 = 2-thienyl **12f**, 90%	R^1 = H Ar^1 = Ar^2 = 2-thienyl **13f**, 85%
6	R^1 = H Ar^1 = Ph Ar^2 = 9-phenanthryl **12g**, 96%	R^1 = H Ar^1 = Ar^2 = 9-phenanthryl **13g**, 93%
7	R^1 = H Ar^1 = 4-OMeC$_6$H$_4$ Ar^2 = Ph **12h**, 97%	R^1 = H Ar^1 = Ar^2 = Ph **13h**, 92%
8	R1 = H Ar^1 = 4-OMeC$_6$H$_4$ Ar^2 = 2-OMeC$_6$H$_4$ **12i**, 94%	R^1 = H Ar^1 = Ar^2 = 2-OMeC$_6$H$_4$ **13i**, 90%
9	R^1 = H Ar^1 = 4-OMeC$_6$H$_4$ Ar^2 = 3-OMeC$_6$H$_4$ **12j**, 95%	R^1 = H Ar^1 = Ar^2 = 3-OMeC$_6$H$_4$ **13j**, 93%
10	R^1 = H Ar^1 = 4-OMeC$_6$H$_4$ Ar^2 = 4-OMeC$_6$H$_4$ **12k**, 95%	R^1 = H Ar^1 = Ar^2 = 4-OMe$_6$H$_4$ **13k**, 92%
11	R^1 = H Ar^1 = 4-OMeC$_6$H$_4$ Ar^2 = 4-*t*BuC$_6$H$_4$ **12l**, 93%	R^1 = H Ar^1 = Ar^2 = 4-*t*BuC$_6$H$_4$ **13l**, 90%
12	R^1 = H Ar^1 = 4-OMeC$_6$H$_4$ Ar^2 = 2-thienyl **12m**, 90%	R^1 = H Ar^1 = Ar^2 = 2-thienyl **13m**, 88%
13	R^1 = H Ar^1 = 4-OMeC$_6$H$_4$ Ar^2 = 9-phenanthryl **12n**, 96%	R^1 = H Ar^1 = Ar^2 = 9-phenanthryl **13n**, 91%
14	R^1 = H Ar^1 = 2-naphthyl Ar^2 = Ph **12o**, 96%	R^1 = H Ar^1 = Ar^2 = Ph **13o**, 94%
15	R^1 = H Ar^1 = 2-naphthyl Ar^2 = 2-OMeC$_6$H$_4$ **12p**, 95%	R^1 = H Ar^1 = Ar^2 = 2-OMeC$_6$H$_4$ **13p**, 94%
16	R^1 = H Ar^1 = 2-naphthyl Ar^2 = 3-OMeC$_6$H$_4$ **12q**, 93%	R^1 = H Ar^1 = Ar^2 = 3-OMeC$_6$H$_4$ **13q**, 91%
17	R^1 = H Ar^1 = 2-naphthyl Ar^2 = 4-OMeC$_6$H$_4$ **12r**, 95%	R^1 = H Ar^1 = Ar^2 = 4-OMeC$_6$H$_4$ **13r**, 91%
18	R^1 = H Ar^1 = 2-naphthyl Ar^2 = 2-SMeC$_6$H$_4$ **12s**, 94%	R^1 = H Ar^1 = Ar^2 = 2-SMeC$_6$H$_4$ **13s**, 90%
19	R1 = H Ar^1 = 2-naphthyl Ar^2 = 2-thienyl **12t**, 92%	R^1 = H Ar^1 = Ar^2 = 2-thienyl **13t**, 89%
20	R^1 = H Ar^1 = 2-naphthyl Ar^2 = 9-phenanthryl **12u**, 96%	R^1 = H Ar^1 = Ar^2 = 9-phenanthryl **13u**, 90%
21	R^1 = OMe Ar^1 = Ph Ar^2 = Ph **12v**, 96%	R^1 = OMe Ar^1 = Ar^2 = Ph **13v**, 90%
22	R^1 = OMe Ar^1 = Ph Ar^2 = 3-OMeC$_6$H$_4$ **12x**, 94%	R^1 = OMe Ar^1 = Ar^2 = 3-OMeC$_6$H$_4$ **13x**, 91%

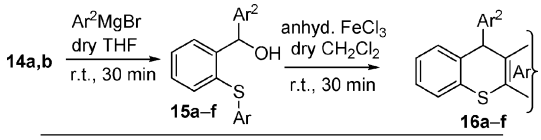
the potential to utilize any 2-arenoxybenzaldehyde as a common precursor to a library of 9-arylxanthenes; (b) many of the products obtained would not be readily accessible by conventional routes; (c) reaction of 2-arenoxy heteroarene-1-aldehydes with heteroarylmagenesium halides or heteroaryllithiums (other than 2-thienylmagnesium bromide) remains unexplored; thus one or more heterocycles should be easily incorporated into the 9-arylxanthene system if so desired; (d) high-yielding access to these compounds is only made possible by the mild reaction conditions employed; (e) symmetrical, as well as unsymmetrical, 9-arylxanthenes could be synthesized.

Next, with the goal of accessing the 9-arylthioxanthenes products, the propensity of $FeCl_3$-catalyzed diarylmethylation of electron-rich arenes with various diarylcarbinols containing a tethered arylsulfanyl group was investigated.



Scheme 2. Synthesis of 2-arylsulfanylbenzaldehydes **14a**,**b**.

Table 4. Synthesis of 9-arylthioxanthenes **16a**–**f**.



Entry	Carbinol, yield	9-Arylxanthene, yield
1	Ar = Ph Ar^2 = Ph **15a**, 96%	Ar = Ar^2 = Ph **16a**, 94%
2	Ar = Ph Ar^2 = 4-$OMeC_6H_4$ **15b**, 95%	Ar = Ar^2 = 4-$OMeC_6H_4$ **16b**, 94%
3	Ar = 2-naphthyl Ar^2 = 4-$OMeC_6H_4$ **15c**, 96%	Ar = Ar^2 = 4-$OMeC_6H_4$ **16c**, 92%
4	Ar = 2-naphthyl Ar^2 = 2-$OMeC_6H_4$ **15d**, 93%	Ar = Ar^2 = 2-$OMeC_6H_4$ **16d**, 90%
5	Ar = 2-naphthyl Ar^2 = 3-$OMeC_6H_4$ **15e**, 95%	Ar = Ar^2 = 3-$OMeC_6H_4$ **16e**, 91%
6	Ar = 2-naphthyl Ar^2 = 4-$OMeC_6H_4$ **15f**, 95%	Ar = Ar^2 = 4-$OMeC_6H_4$ **16f**, 92%

Towards that objective, 2-arylsulfanylbenzaldehydes **14a**,**b** were first synthesized by essentially following the similar strategy as that described for 2-arenoxybenzaldehydes **11a**–**d** (Scheme 2).

Subsequently, treatment of freshly prepared arylmagnesium bromides with **14a**,**b** furnished carbinols **15a**–**f** in high yields. Next, treatment of the resulting carbinols with $FeCl_3$ (10 mol-%) in dry CH_2Cl_2 at room temperature furnished the corresponding 9-arylthioxanthenes **16a**–**f** in high yields (Table 4). In this case, symmetrical, as well as unsymmetrical, 9-arylthioxanthenes could be synthesized depending on the choice of the starting aldehydes and Grignard reagents.

Conclusions

In conclusion, we have demonstrated a new synthetic route of 9-arylxanthenes and 9-arylthioxanthenes by $FeCl_3$-catalyzed diarylmethylation of electron-rich arenes. The reaction was driven by cationic activation of diaryl carbinols by $FeCl_3$ (10 mol-%). Our synthetic strategy could allow significant variation of all aryl rings of symmetrical and unsymmetrical 9-arylxanthenes, which were not easily available.

Supporting Information (see also the footnote on the first page of this article): Experimental procedures and analytical data of selected compounds.

Acknowledgments

This work was supported by the Department of Science and Technology (DST), India. S.K.D and R.S thank the Council of Scientific and Industrial Research (CSIR), India for research fellowships.

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[29] All substituted and unsubstituted 2-fluorobenzaldehydes (**8**, **9**) used were obtained commercially.

Received: June 18, 2009
Published Online: August 20, 2009

