Tetrahedron Letters 53 (2012) 2202–2205

Contents lists available at SciVerse ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of 9-substituted xanthenes by the condensation of arynes with *ortho*-hydroxychalcones

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ARTICLE INFO

Article history:
Received 12 July 2010
Revised 13 February 2012
Accepted 15 February 2012
Available online 25 February 2012

Keywords:
Arynes
ortho-Hydroxychalcones
Nucleophilic
Michael addition
Cesium carbonate

ABSTRACT

The reaction of *o*-(trimethylsilyl)aryl triflates, CsF, and *o*-hydroxychalcones affords a general and efficient way to prepare biologically interesting 9-substituted xanthenes. This chemistry presumably proceeds by the tandem intermolecular nucleophilic attack of the phenoxide of the chalcone on the aryne and subsequent intramolecular Michael addition. The introduction of an external base, Cs_2CO_3, has proven beneficial in this reaction.

Herein, we wish to present a novel route to 9-substituted xanthenes in a simple one step process under mild reaction conditions starting from readily available *o*-hydroxychalcones.[1] During the course of our work, related chemistry has been reported by Huang et al.[2] While the Huang protocol allows one to efficiently obtain xanthenes and acridine derivatives, our work has focused on the scope and limitations of this process. Also, our procedure allows one to obtain the desired products in an operationally simpler way using shorter reaction times.

From some of the oldest known dyes[3] to newly developed agriculturally- and pharmaceutically-interesting intermediates,[4] xanthenes have attracted attention for decades and continue to be the focus of biological and material science studies today.

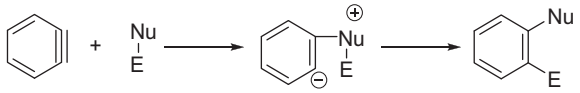
Many naturally-occurring and man-made xanthene derivatives have been reported to exhibit extraordinary biological activities, including anti-malarial,[5] anti-trypanosomal,[6] anti-leishmanial,[6] and anti-tumor[7] activities. More recently, the notable fluorescent properties of xanthenes have received attention. For example, xanthene derivatives have been prepared as fluorescent probes,[8] and electrostatic sensors.[9]

The synthesis of xanthene derivatives has also been widely studied. There are several well established approaches to xanthene derivatives,[10] which typically feature the formation of the central heterocyclic ring, often by the combinations of Friedel–Crafts methodology and C–O bond formation. Xanthenes can also be obtained by reduction of the corresponding xanthones.[11] However, most of these synthetic approaches involve either multistep procedures or fairly harsh reaction conditions.

Since a convenient approach to aryne generation by the fluoride-induced 1,2-elimination of *o*-(trimethylsilyl)aryl triflates was first reported in 1983,[12] the reactivity of arynes, especially their electrophilicity, has been explored extensively. For example, in our group, in situ generated benzyne has been coupled with simple nucleophiles, such as amines, sulfonamides, phenols, and arenecarboxylic acids,[13] to generate monosubstituted arenes. Besides those simple coupling reactions, insertion processes (Scheme 1) have been reported for nucleophiles bearing neighboring electrophiles, such as ureas,[14] keto esters,[15] amides,[15] sulfonamides,[16] and acid halides.[17]

We have been particularly interested in annulation processes, which rapidly construct the biologically-interesting ring systems by simple tandem processes. For example, we have reported that salicylates and in situ generated arynes readily react to form heteroatom ring systems, such as xanthones, thioxanthones, and acridones (Scheme 2).[18]

Herein, we present a novel coupling reaction between *o*-hydroxychalcones and *o*-(trimethylsilyl)aryl triflates, which provides a new method for the synthesis of 9-substituted xanthenes in a simple one step process under very mild reaction conditions.



Scheme 1. Aryne insertion reactions.

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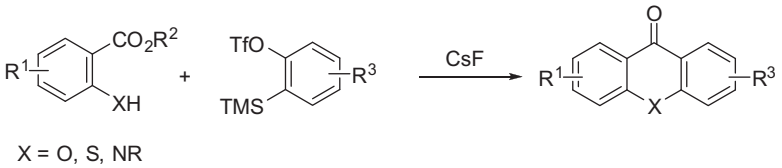
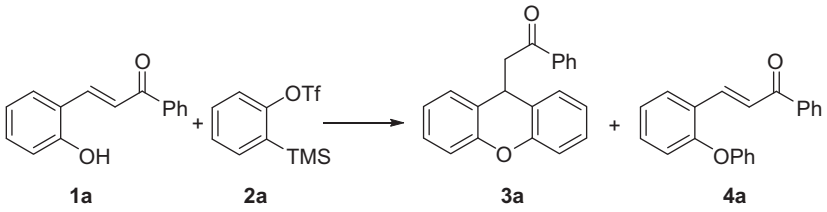
doi:10.1016/j.tetlet.2012.02.072



Scheme 2. Synthesis of xanthones and analogues using arynes.

Table 1
Optimization studies[a]



Entry	CsF (equiv)	Solvent	Temp (°C)	Additive (equiv)	% Yield[b] **3a** (**4a**)
1	2.0	MeCN	rt	—	32 (68)
2	2.0 TBAF[c]	THF	rt	—	17 (65)
3	2.0	THF	rt	—	Trace[d]
4	2.0	THF	65	—	60 (17)
5	3.0	THF	65	—	67
6	5.0	THF	65	—	74
7	3.0	THF	65	1.0 Cs_2CO_3	80

[a] Reactions were conducted on a 0.25 mmol scale with 1.2 equiv of **2a** in 10 ml of solvent for 24 h.
[b] Yields of products isolated by column chromatography.
[c] TBAF (1 M in THF).
[d] Very low conversion.

Our optimization work was carried out using commercially available *o*-hydroxychalcone **1a** and *o*-(trimethylsilyl)phenyl triflate (**2a**) under a variety of different reaction conditions (Table 1). We first examined some commonly used benzyne reaction conditions, namely MeCN with added CsF (entry 1), and THF with TBAF[19] (entry 2). Not surprisingly, our initial studies indicated that significant amounts of the corresponding phenyl ether **4a** were generated alongside **3a**, which was produced in only a low yield. When employing CsF in THF (entry 3), although the reaction proceeded in very low conversion, the desired product **3a** was generated as the major product, which suggested that THF was able to suppress proton abstraction.[16] By raising the temperature to 65 °C (entry 4), the reaction could be completed in 24 h and 60% yield was produced. Interestingly, we observed that as the amount of the base CsF added to the system was increased (entries 5 and 6), the yield improved. Finally, with the addition of 1 equiv of Cs_2CO_3 (entry 7), the yield was improved to 80%. Other bases, such as Li_2CO_3 and K_2CO_3, were also tested, but none of them was as effective as Cs_2CO_3. Thus, the reaction conditions reported in entry 7 (3 equiv of CsF, 1 equiv of Cs_2CO_3 in THF solvent at 65 °C) were chosen as our optimal conditions for further study.

We next examined a wide range of *o*-hydroxychalcones bearing various functional groups (Table 2). Chalcones with electron-donating methoxy (entry 2) and methyl (entry 3) substituents provided decent yields, 74% and 64%, respectively. A fluoro-substituted chalcone (entry 4) also afforded good results. Substrates with other electron-withdrawing groups, such as I (entry 5), Br (entry 6), and NO_2 (entry 7) groups, resulted in much lower yields under our 'optimal' conditions. However, by simply removing the Cs_2CO_3 base (1.2 equiv of **2a**, 3.0 equiv of CsF, THF, 65 °C), the yields can be improved significantly. This is probably because phenoxide anions bearing electron-withdrawing groups can be generated in substantial amounts when Cs_2CO_3 is present, which favors the formation of the side product (see the mechanistic discussion).

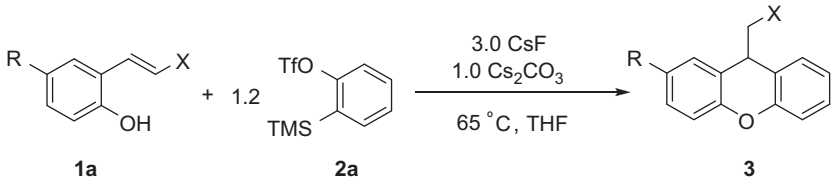
The effect of the group X on the carbon–carbon double bond has also been examined. Decent yields were provided by substrates with different acyl groups (entries 8–12). Aldehyde (entry 13) and cyano (entry 14) groups are also tolerated. For the substrate with an ester group (entry 15), an inseparable mixture of the desired product and arylation side product was generated. For reasons that are not obvious, a sulfonyl group does not activate the Michael acceptor sufficiently in this chemistry to produce a good yield. The use of additional benzyne precursor, a lower temperature, and a longer reaction time was necessary to get a decent yield (entry 16).

The behavior of the aryne precursors **2b**, **2c**, and **2d** (Table 3) has also been examined in this reaction. All of these substrates generated lower yields than benzyne itself, perhaps due to slower aryne generation. We have observed that aryne precursor **2d** affords a single isomeric product **3s**. This regioselectivity for 3-methoxybenzyne has been seen previously in our group and by others.[11a,20]

Based on the experimental results and previous studies,[11,16] we postulate that this coupling reaction proceeds in the following manner (Scheme 3). The intermediate **C** generated from nucleophilic coupling of the aryne and the aryl oxide undergoes intramolecular Michael addition to afford the desired xanthene **B** after protonation.

However, well known proton abstraction by **C** could lead to diaryl ether **A**, which has been observed by us as the major side product for most of the substrates examined in this reaction. Since the

Table 2
Reaction scope with different chalcone derivatives[a]

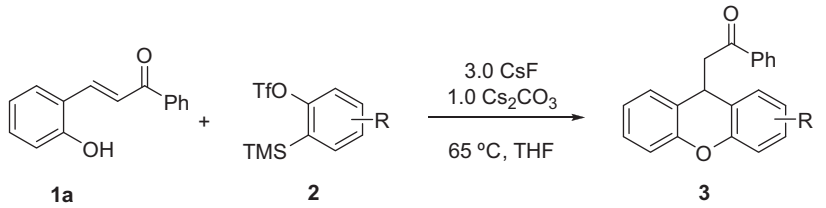


1a 2a 3

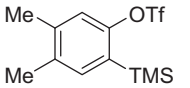
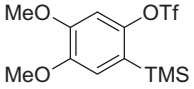
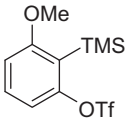
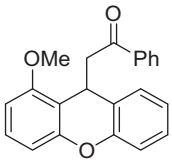
Entry	Chalcone	R	X	Product/yield (%)[b]
1	**1a**	H	C(O)Ph	**3a**/80
2	**1b**	OMe	C(O)Ph	**3b**/74
3	**1c**	Me	C(O)Ph	**3c**/64
4	**1d**	F	C(O)Ph	**3d**/84
5	**1e**	I	C(O)Ph	**3e**/60 (78)[c]
6	**1f**	Br	C(O)Ph	**3f**/58 (75)[c]
7	**1g**	NO_2	C(O)Ph	**3g**/41 (70)[c]
8	**1h**	H	C(O)C_6H_4(OMe)-*p*	**3h**/61
9	**1i**	H	C(O)C_6H_4I-*p*	**3i**/73
10	**1j**	H	C(O)Me	**3j**/71
11	**1k**	H	C(O)*t*-Bu	**3k**/65
12	**1l**	H	C(O)C_6H_{11}	**3l**/64
13	**1m**	H	CHO	**3m**/60
14	**1n**	H	CN	**3n**/70
15	**1o**	H	CO_2*t*-Bu	**3o**/60[d]
16	**1p**	H	SO_2Ph	**3p**/15 (51)[e]

[a] Reactions were conducted on a 0.25 mmol scale for 24 h.
[b] Yields of products isolated by column chromatography.
[c] Reactions were conducted with 1.2 equiv of **2a**, 3.0 equiv of CsF and THF (10 ml) at 65 °C.
[d] ^{1}H NMR spectroscopic yield.
[e] This reaction was conducted with 2.0 equiv of **2a**, 3.0 equiv of CsF and THF (10 ml) at 45 °C for 30 h.

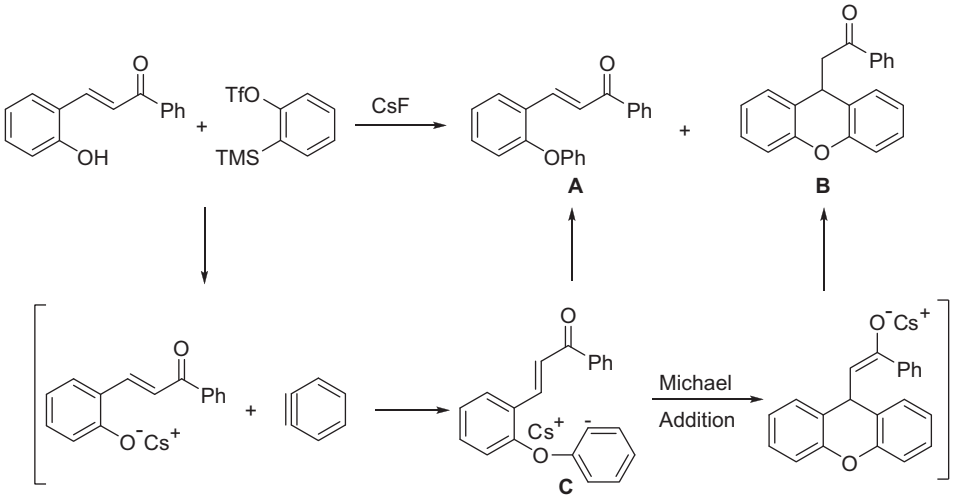
Table 3
Reaction with different benzyne precursors[a]



1a 2 3

Entry	Aryne precursor		Product/yield (%)[b]
1		**2b**	**3q**/51
2		**2c**	**3r**/46[c]
3		**2d**	 **3s**/57

[a] Reactions were conducted on a 0.25 mmol scale for 24 h in 10 ml of THF.
[b] Yields of products isolated by column chromatography.
[c] The reaction time was 48 h.



Scheme 3. Possible mechanism.

proton abstraction of **C** is quite fast, a competition is present between intramolecular cyclization and intermolecular proton abstraction. In order to suppress this side reaction, dry reaction conditions and the addition of an extra base are necessary. This helps to remove the acidic protons present before intermediate **C** is able to react with the proton and generate the side product **A**.

In conclusion, we have demonstrated that *o*-hydroxychalcones and related compounds undergo annulation reactions with *o*-(trimethylsilyl)aryl triflates through tandem nucleophilic coupling and subsequent Michael addition. This reaction affords a general one-pot approach to 9-substituted xanthenes from readily prepared starting materials. Mild reaction conditions allow a variety of functional groups to be tolerated in this reaction. With carbonyl and other functionalities in the products, further elaboration can easily be achieved.

Acknowledgments

We gratefully acknowledge the financial support of this work by the Kansas University NIH Center of Excellence in Chemical Methodology and Library Development (P50 GM069663).

Supplementary data

Supplementary data (experimental procedure and characterization data) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2012.02.072.

References and notes

1. Lu, C.; Larock, R. C. *Abstracts of Papers, 235th National Meeting of the American Chemical Society*; New Orleans: LA, Aug, 2008. 6–10.
2. Huang, X.; Zhang, T. *J. Org. Chem.* **2010**, *75*, 506.
3. (a) Sekar, N. *Colourage* **2003**, *50*, 59; (b) Catalina, F.; Santamaria, R.; Bosch, P.; Peinado, C. *Revista de Plasticos Modernos* **2000**, *529*, 38; (c) Sekar, N. *Colourage* **1999**, *46*, 43; (d) Neckars, D. C.; Valdes-Aguilera, O. M. *Adv. Photochem.* **1993**, *18*, 315; (e) Farris, R. E. Kirk-Othmer Encycl. Chem. Technol., 3rd Ed. 1983, 24, 662.
4. (a) Carmen de la Fuente, M.; Domínguez, D. *J. Org. Chem.* **2007**, *72*, 8804; (b) Pellicciari, R.; Costantino, G.; Marinozzi, M.; Macchiarulo, A.; Amori, L.; Flor, P. J.; Gasparini, F.; Kuhn, R.; Urwyler, S. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 3179; (c) Henkel, B.; Zeng, W.; Bayer, E. *Tetrahedron Lett.* **1997**, *38*, 3511; (d) McWilliams, K.; Kelly, J. W. *J. Org. Chem.* **1996**, *61*, 7408; (e) Bennett, G. J.; Lee, H. H. *Phytochemistry* **1989**, *28*, 967.
5. Wu, C. P.; Donelly, A.; Schalkwyk, V.; Taylor, D.; Smith, P. J.; Chibale, K. *Int. J. Antimicrob. Ag.* **2005**, *26*, 170.
6. Chibale, K.; Visser, M.; Schalkwyk, D. V.; Smith, P. J.; Saravanamuthu, A.; Fairlamb, A. H. *Tetrahedron* **2003**, *59*, 2289.
7. (a) Burmester, J. K. U. S. Patent WO 2006102102, 2006.; (b) Xiao, Y.; Ottenbrite, R. U. S. Patent WO 2006083869, 2006.; (c) Greene, M. I.; Murali, R.; Cheng, X.; Ottenbrite, R.; Xiao, Y. U. S. Patent WO 2006083970, 2006.
8. (a) Zhebentyaev, A. I.; Zhernosek, A. K.; Egorava, S. I.; Mchedlov-Petrosyan, N. O. *J. Anal. Chem.* **1997**, *52*, 856; (b) Nagano, T.; Urano, Y.; Kenmoku, S. *J. Am. Chem. Soc.* **2007**, *129*, 10324.
9. Fitchen, N.; O'Shea, P.; Williams, P.; Hardie, K. R. *Mol. Immunol.* **2003**, *40*, 407.
10. (a) Hepworth, J. D.; Gabutt, C. D.; Heron, B. M. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science Ltd.: Oxford, 1996; vol. 5, p 379. For recent contributions, see:; (b) Scala-Valero, C.; Doizi, D.; Guillaumet, G. *Tetrahedron Lett.* **1999**, *40*, 4803; (c) Sirkecioglu, O.; Talinli, N.; Akar, A. *J. Heterocycl. Chem.* **1998**, *35*, 457; (d) Ruth, M.; Steglich, W. *Synthesis* **2000**, 677; (e) Dinger, M. B.; Scott, M. J. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1741; (f) Novak, L.; Kovacs, P.; Pirok, G.; Kolonits, P.; Szabo, E.; Fekete, J.; Weiszfeiler, V.; Szantay, C. *Synthesis* **1995**, 693; (g) Caruso, R. J.; Lee, J. L. *J. Org. Chem.* **1997**, *62*, 1058; (h) Letcher, R. M.; Yue, T. Y.; Chiu, K. F.; Kelkar, A. S.; Cheung, K. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3267.
11. (a) Vázquez, R.; de la Fuente, M. C.; Castedo, L.; Domínguez, D. *Synlett* **1994**, 433; (b) Mustafa, A.; Asker, W.; Sobhy, M. E. E. *J. Am. Chem. Soc.* **1955**, *77*, 5121; (c) Gilman, H.; Diehl, J. *J. Org. Chem.* **1961**, *26*, 4817; (d) Shi, J.; Zhang, X.; Neckers, D. C. *J. Org. Chem.* **1992**, *57*, 4418; (e) Xuong, N. D.; Buu-Hoi, N. P. *J. Chem. Soc.* **1952**, 3741.
12. Himeshina, Y.; Sonoda, T.; Kobayashi, H. *Chem. Lett.* **1983**, 1211.
13. (a) Liu, Z.; Larock, R. C. *J. Org. Chem.* **2006**, *71*, 3198; (b) Liu, Z.; Larock, R. C. *Org. Lett.* **2004**, *1*, 99; (c) Liu, Z.; Larock, R. C. *Org. Lett.* **2003**, *24*, 4673.
14. Yoshida, H.; Shiakawa, E.; Honda, Y.; Hiyama, T. *Angew. Chem., Int. Ed.* **2002**, *41*, 3247.
15. Tambar, U. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 5340.
16. (a) Liu, Z.; Larock, R. C. *J. Am. Chem. Soc.* **2005**, *127*, 13112; (b) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168.
17. Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, *23*, 2405.
18. (a) Zhao, J.; Larock, R. C. *Org. Lett.* **2005**, *19*, 4273; (b) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583.
19. 1 M Tetrabutylammonium fluoride in THF solution with 5% water.
20. (a) Sanz, R. *Org. Prep. Proced. Int.* **2008**, *40*, 215; (b) Cheong, P. H.-Y.; Paton, R. S.; Bronner, S. M.; Im, G.-Y. J.; Garg, N. K.; Houk, K. N. *J. Am. Chem. Soc.* **2010**, *132*, 1267.