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Highly efficient synthesis of 9-aminoxanthenes *via* the tandem reaction of arynes with salicyl *N*-tosylimines

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Abstract

A cascade insertion–nucleophilic annulation reaction of salicyl *N*-tosylimines with aryne generated *in situ* from 2-(trimethylsilyl) aryl triflate and KF-18-crown-6 has been developed, providing 9-aminoxanthenes efficiently in one step.

Keywords: Salicyl *N*-tosylimines; Aryne; 9-Aminoxanthene

Arynes are highly reactive intermediate those have been applied widely in organic chemistry [1]. About 30 years ago, the group of Kobayashi demonstrated that arynes can be generated *in situ* through the fluoride induced 1,2-elimination of 2-(trimethylsilyl) aryl triflates under mild conditions [2]. These findings led to a dramatic growth in aryne chemistry and a variety of important transformations have been developed, such as pericyclic reactions, insertion reactions, multicomponent reactions and others [3]. On the other hand, owing to the biological and pharmaceutical activity, xanthenes and their derivatives have attracted considerable attention over the past decade [4]. Several methods for the preparation of xanthenes have been established and usually involve the Friedel–Crafts reaction to construct the central heterocyclic ring [5]. However, the multistep reaction, complicated manipulation and hash reaction conditions restrain their potential application. Therefore, it is still meaningful to develop more simple and efficient method for the synthesis of this type of compounds.

Recently, Okuma [6], Larock [7] and Huang [8] developed a tandem insertion–nucleophilic cyclization strategy to access xanthenes independently. Through this strategy, arynes coupled with different intramolecular bifunctional (Nu-E) substrates such as 2-substituted benzoates, salicylaldehydes and *ortho*-hydroxychalcones smoothly to give xanthones, 9-hydroxyxanthenes and 9-alkylxanthenes respectively (Scheme 1). In line with our continuing interest of the reaction of organosilicon reagents [9], we envisioned that under the promotion of fluoride, 2-(trimethylsilyl)aryl triflates may proceed a cascade insertion–cyclization reaction with *ortho*-substituted imines to give 9-aminoxanthenes. To the best of our knowledge, no straightforward methodology for the synthesis of this type of xanthene derivatives has been reported. Herein, we would like to disclose our preliminary results on the coupling of arynes with salicyl *N*-tosylimines to give 9-aminoxanthenes under very mild conditions.

At the outset, the tandem reaction of salicyl *N*-tosylimine **2a** with aryne precursor **1a** was selected as the model reaction. To our delight, we found that in the presence of 3.0 equiv. CsF, the cascade reaction proceeded smoothly

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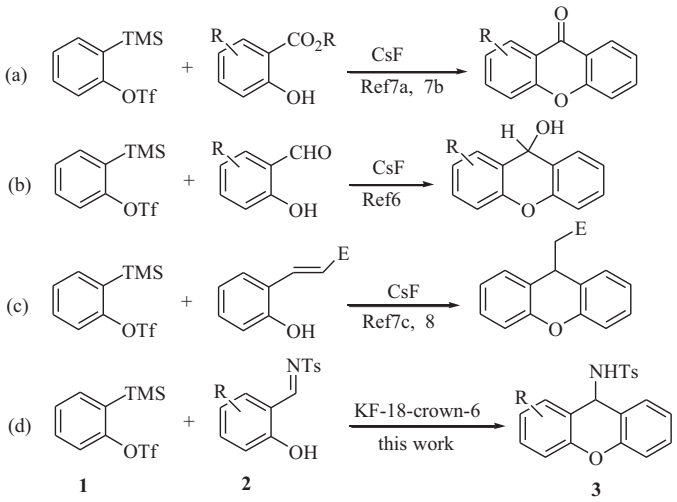


Scheme 1. Fluoride promoted nucleophilic cyclization of arynes to xanthenes.

under mild conditions, to give 9-aminoxanthene **3a** in 70% isolated yield (Table 1, entry 1). With these fruitful result in hand, other fluorides such as KF, Bu_4NF and KF/Al_2O_3 [10] were also tested for the reaction, but only obtained the desired product in very low yield (Table 1, entries 2–4). Conducted the reaction in CH_3CN/Et_2O mixed solvent or added 2.0 equiv. carbonate to the reaction, no improvement of the yield was observed (Table 1, entries 5–7). Fortunately, when 2.0 equiv. 18-crown-6 was added as co-additive with 3.0 equiv. KF, the reaction could be converted quantitatively within 1 h (Table 1, entry 8). To our surprise, either increased the amount of 18-crown-6 to 3.0 equiv. or reduced to 1.0 equiv., the reaction yield decreased obviously (Table 1, entries 9 and 10).

Other reaction media such as THF, toluene, ether and dichloromethane were also evaluated briefly, the experiments indicated that acetonitrile was the best choice with respect to yield (Table 1, entries 11–14). Lowered the amount of KF to 2.0 equiv. and 1.0 equiv., respectively, the yield of the reaction also decreased steply (Table 1, entries 15 and 16). Finally, control experiment showed that the reaction cannot occur in the absence of fluoride (Table 1, entry 17).

With the optimal reaction conditions in hand (3.0 equiv. KF, 2.0 equiv. 18-crown-6, CH_3CN, room temperature), the generality of the cascade reaction was evaluated and the results were summarized in Table 2 [11]. For salicyl

Table 1
Evaluation of conditions for the tandem reaction.[a]

Entry	Additives	Solvent	Time (h)	Yield (%)[b]
1	CsF 3.0 equiv.	CH_3CN	12	70
2	KF 3.0 equiv.	CH_3CN	12	<10
3	Bu_4NF 3.0 equiv.	CH_3CN	12	22
4	KF/Al_2O_3 3.0 equiv.	CH_3CN	12	<10
5	KF 3.0 equiv.	CH_3CN/Et_2O	12	<10
6	KF(3.0 equiv.) + Cs_2CO_3(2.0 equiv.)	CH_3CN	12	18
7	KF(3.0 equiv.) + K_2CO_3(2.0 equiv.)	CH_3CN	12	<10
8	KF(3.0 equiv.) + 18-crown-6(2.0 equiv.)	CH_3CN	1	99
9	KF(3.0 equiv.) + 18-crown-6(3.0 equiv.)	CH_3CN	1	71
10	KF(3.0 equiv.) + 18-crown-6(1.0 equiv.)	CH_3CN	1	69
11	KF(3.0 equiv.) + 18-crown-6(2.0 equiv.)	THF	1	8
12	KF(3.0 equiv.) + 18-crown-6(2.0 equiv.)	Et_2O	1	6
13	KF(3.0 equiv.) + 18-crown-6(2.0 equiv.)	Toluene	1	9
14	KF(3.0 equiv.) + 18-crown-6(2.0 equiv.)	CH_2Cl_2	1	57
15	KF(2.0 equiv.) + 18-crown-6(1.3 equiv.)	CH_3CN	6	85
16	KF(1.0 equiv.) + 18-crown-6(0.6 equiv.)	CH_3CN	6	39
17	No additives	CH_3CN	6	0

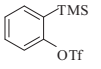
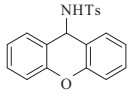
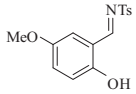
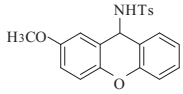
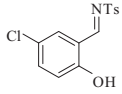
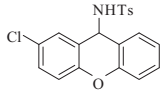
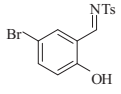
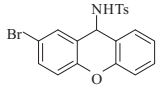
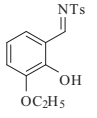
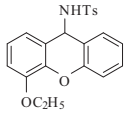
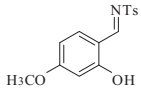
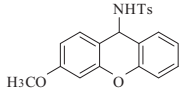
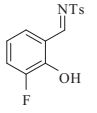
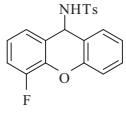
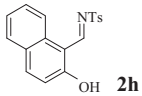
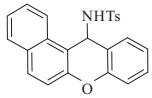
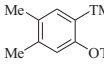
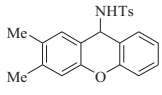
[a] Reaction conditions: **1** (1.5 equiv.) and **2a** (0.1 mol/L, 1.0 equiv.), room temperature.
[b] Isolated yield.

N-tosylimines, substitution of an electron-donating or electron-withdrawing group on the aromatic ring resulted in no obvious effect on the yield (Table 2, entries 1–4). Additionally, different positions of the substituted groups on the aromatic ring were all tolerated and the desired products were obtained in excellent yield (Table 2, entries 5–7). More interestingly, *N*-tosylimine derived from 2-hydroxy-1-naphthaldehyde was also proved to be good reactant for the tandem reaction, afforded compound 3 h in 98% yield (Table 2, entry 8). On the other hand, the substituted aryne precursor **1b** can also react with salicyl *N*-tosylimine to provide 9-aminoxanthene in high yield (Table 2, entry 9).

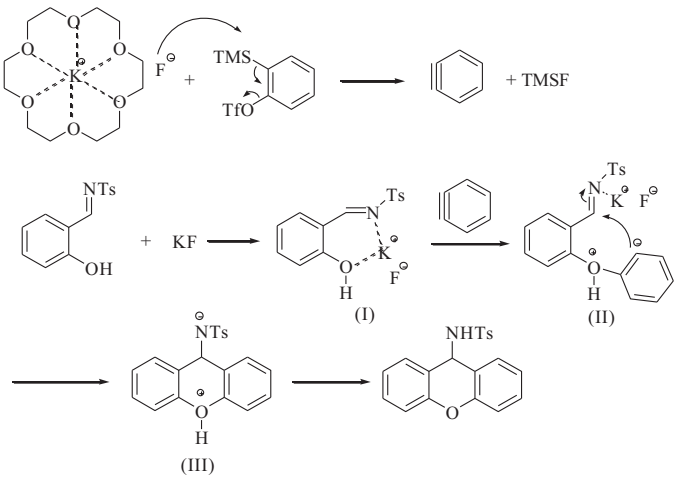
Based on the experiments results and the pioneering work on fluoride promoted insertion–cyclization reactions of arynes, a plausible mechanism was proposed and depicted in Scheme 2. Fluoride ion attacks 2-(trimethylsilyl)aryl triflate **1** to afford aryne, while the free KF complexed with salicyl imine to form intermediate I, which undergo insertion reaction with aryne to give intermediate II, and after nucleophilic cyclization to provide 9-aminoxanthene.

In summary, we have demonstrated a fluoride promoted insertion–nucleophilic annulation of aryne and salicyl tosylimine. The very mild conditions, simple procedure provides a highly efficient approach for the construction of 9-aminoxanthenes. Further exploration and application of this protocol are ongoing in our laboratory.

Table 2
Preliminary scope of the insertion–nucleophilic cyclization reaction.

Entry	Aryne precursor	Salicyl tosylimine	Product	Yield (%)[b]
1	 **1a**	 **2a**	 **3a**	99
2	**1a**	 **2b**	 **3b**	96
3	**1a**	 **2c**	 **3c**	93
4	**1a**	 **2d**	 **3d**	92
5	**1a**	 **2e**	 **3e**	95
6	**1a**	 **2f**	 **3f**	95
7	**1a**	 **2g**	 **3g**	95
8	**1a**	 **2h**	 **3h**	98
9	 **1b**		 **3i**	84

[a] Reaction conditions: **1** (0.45 mmol), **2** (0.3 mmol), KF (0.9 mmol), 18-crown-6 (0.6 mmol), anhydrous acetonitrile 3.0 mL, room temperature.
[b] Isolated yield.



Scheme 2. Proposed reaction mechanism.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2012.11.008.

References

[1] Y. Chen, R.C. Larock, in: L. Ackermann (Ed.), Modern Arylation Methods, Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim, Germany, 2009
[2] Y. Himeshima, T. Sonoda, H. Kobayashi, Chem. Lett. (1983) 1211.
[3] A. Bhunia, S.R. Yetra, A.T. Biju, Chem. Soc. Rev. 41 (2012) 3140.
[4] (a) N. Sato, M. Jitsuoka, T. Shibata, J. Med. Chem. 51 (2008) 4765;
(b) M.C. de la Fuente, D. Dominguez, J. Org. Chem. 72 (2007) 8804;
(c) Y.H. Tseng, P.I. Shih, C.H. Chien, Macromolecules 38 (2005) 10055;
(d) T. Kobayashi, Y. Urano, M. Kamiya, J. Am. Chem. Soc. 129 (2007) 6696;
(e) V. Peres, T.J. Nagem, F. Faustido de Oliveira, Phytochemistry 55 (2000) 683.
[5] (a) C. Scala-Valero, D. Doizi, G. Guillaumet, Tetrahedron Lett. 40 (1999) 4803;
(b) M. Ruth, W. Steglich, Synthesis (2000) 677;
(c) M.B. Dinger, M.J. Scott, J. Chem. Soc. Perkin Trans. 1 (2000) 1741;
(d) R.M. Letcher, T.Y. Yue, K.F. Chiu, J. Chem. Soc. Perkin Trans. 1 (1998) 3267;
(e) S. Allameh, A. Davoodnia, A. Khojastehnezhad, Chin. Chem. Lett. 23 (2012) 17.
[6] K. Okuma, A. Nojima, N. Matsunaga, Org. Lett. 11 (2009) 169.
[7] (a) J. Zhao, R.C. Larock, Org. Lett. 7 (2005) 4273;
(b) J. Zhao, R.C. Larock, J. Org. Chem. 72 (2007) 583;
(c) C. Lu, A.V. Dubrovskiy, R.C. Larock, Tetrahedron Lett. 53 (2012) 2202.
[8] X. Huang, T. Zhang, J. Org. Chem. 75 (2010) 506.
[9] (a) G.F. Du, L. He, C.Z. Gu, Synlett (2010) 2513;
(b) Z.H. Cai, G.F. Du, L. He, Synthesis 13 (2011) 2073;
(c) Y.C. Fan, G.F. Du, L. He, Tetrahedron Lett. 53 (2012) 2231;
(d) Z.H. Cai, G.F. Du, L. He, Chin. J. Chem. 30 (2012) 1658.
[10] E.B. David, J.L. James, J. Org. Chem. 52 (1987) 1601.
[11] General procedure: a solution of 2-(trimethylsilyl) aryl triflate (110 μL, 0.45 mmol), salicyl *N*-tosylimine **2a** (83 mg, 0.3 mmol), KF (54 mg, 0.9 mmol), 18-crown-6 (159 mg, 0.6 mmol) in 3.0 mL anhydrous acetonitrile was stirred for 1 h at room temperature, then, the reaction mixture was diluted with 15 mL ethylacetate and filtered through a pad of silica gel. The solvent was concentrated in vacuum and the residue was purified by flash chromatography (silica gel, Pe–EtOAc 5:1–3:1) to give **3a** as pure product. Data for **3a**: White solid, mp 191.2–191.8 °C; Yield: 99%; IR (KBr, cm^{-1}) (3324, 2962, 1599, 1573, 1481, 1454, 1425, 1325, 1263, 1155, 1088, 1022, 884, 817, 744, 662, 557; ^1H NMR (400 MHz, $CDCl_3$): δ 7.72 (d, 2H, J = 8.16 Hz), 7.25 (d, 2H, J = 8.16 Hz), 7.22–7.14 (m, 2H), 7.10–6.86 (m, 6H), 5.68 (d, 1H, J = 8.6 Hz), 4.86 (d, 1H, J = 8.6 Hz), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 150.19, 142.56, 137.52, 128.78, 128.41, 126.09, 122.54 119.32, 115.67, 48.10, 20.57.