

Tandem thia-Fries rearrangement – cyclisation of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate benzyne precursors†‡

Cite this: *Chem. Commun.*, 2013, **49**, 7602

Received 17th June 2013,
Accepted 9th July 2013

DOI: 10.1039/c3cc44529a

www.rsc.org/chemcomm

Catherine Hall, Jaclyn L. Henderson, Guillaume Ernouf and Michael F. Greaney*

A novel transformation of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate arylene precursors is described.

The introduction of 2-(trimethylsilyl)phenyl trifluoromethanesulfonate as a precursor to *ortho*-benzyne has fueled a renaissance in arylene chemistry.¹ Discovered in 1983 by Kobayashi,² the precursor generates benzyne under the notably mild conditions of simple fluoride treatment at room temperature. The initial conditions of CsF in MeCN have been expanded to include a variety of fluoride sources and solvent combinations, conferring a degree of control on the rate of benzyne generation and thus opening up new areas of chemistry that were previously inaccessible using classical arylene precursors.

In the course of developing new transformations of *ortho*-benzyne,³ we observed that fluoride treatment of bromo-substituted precursor **1a** led to the unexpected formation of phenoxathiin-dioxide **2a** in 51% yield (Scheme 1). The heterocycle was isolated as a single regio-isomer and characterised by single crystal X-ray diffraction⁴ (Fig. 1). This intriguing reaction is without precedent in arylene chemistry, prompting us to conduct further investigations to try and understand the mechanistic pathway leading to **2a**. In addition, phenoxathiin-dioxides are a scarcely studied class of heterocycle, and novel methods for their synthesis could prove useful.⁵

We began our study by repeating the reaction at room temperature, observing the formation of **2a** in slightly lower

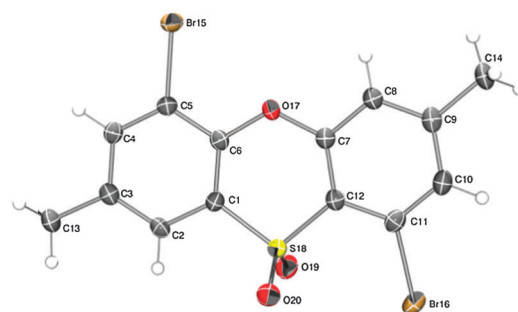
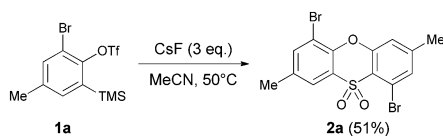


Fig. 1 X-ray structure of **2a**. Thermal ellipsoids at 50% probability.



Scheme 1 Phenoxathiin-dioxide synthesis.

School of Chemistry, University of Manchester, Oxford Rd, Manchester M13 9PL, UK. E-mail: michael.greaney@manchester.ac.uk

† Celebrating 300 years of Chemistry at Edinburgh.

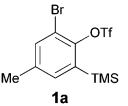
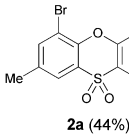
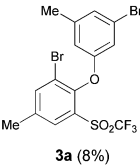
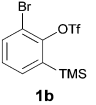
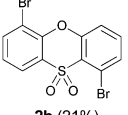
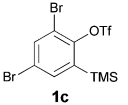
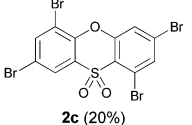
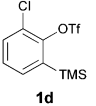
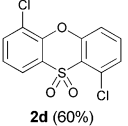
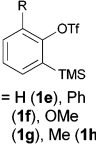
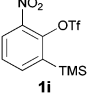
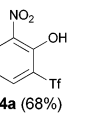
‡ Electronic supplementary information (ESI) available: Data for new compounds and experimental procedures. CCDC 945230. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc44529a

yield along with a small amount of the triflone **3a** (Table 1, entry 1). Isolation of **3a** is significant as it suggests that it, or a related species, may be a precursor to the final phenoxathiin-dioxide product **2a**. The methyl group in **1a** was not a requirement for reaction (entry 2), with the bromo-compound **1b** providing **2b** in 21% yield at room temperature along with small amounts of uncyclised triflone. The yield of the process could be improved by raising the temperature to 60 °C (47% yield, entry 3), or by adding toluene to the solvent system, with a 3 : 1 MeCN:toluene mix providing **2b** in 60% yield at room temperature (entry 4). Addition of a less polar solvent would be expected to slow the rate of reaction of CsF with the silane starting material **1a**. Adding an additional bromine atom to the substrate reduced the reaction efficiency (entry 5), but the chloro derivative **1c** proved successful in the reaction, providing **2d** in 60% yield (entry 6).

Moving away from halogens at the *ortho*-position to the trifluoromethanesulfonate, however, immediately shut down the reaction. Phenyl, methoxy, methyl and simple hydrogen-substitution all gave intractable mixtures from which no phenoxathiin dioxide could be isolated (entry 7). The *ortho*-nitro substrate **1i**, however, reacted to give the rearranged phenol **4a** in 68% yield (entry 8).

Collectively, these results point to a mechanism involving an anionic thia-Fries rearrangement. Fluoride treatment of **1** results in C–Si bond cleavage as the first step in the mechanism,

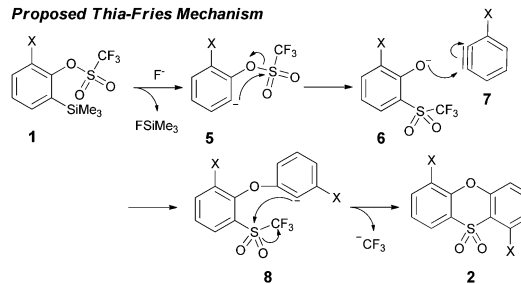
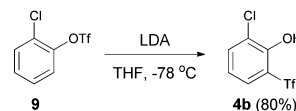
Table 1 Phenoxathiin-dioxide synthesis

Entry	Substrate	Conditions	Products ^a
1		MeCN, CsF, rt, 4 h	 2a (44%)  3a (8%)
2		MeCN, CsF, rt, 4 h	 2b (21%)
3	1b	MeCN, CsF, 60 °C, 4 h	2b (47%)
4	1b	MeCN:toluene (3:1), CsF, rt, 24 h	2b (60%)
5		MeCN, CsF, rt, 6 h	 2c (20%)
6		MeCN:toluene (3:1), CsF, rt, 24 h	 2d (60%)
7	 R = H (1e), Ph (1f), OMe (1g), Me (1h)	MeCN, CsF, rt, 24 h	Complex mixtures
8		MeCN, CsF, rt, 24 h	 4a (68%)

^a Isolated yields.

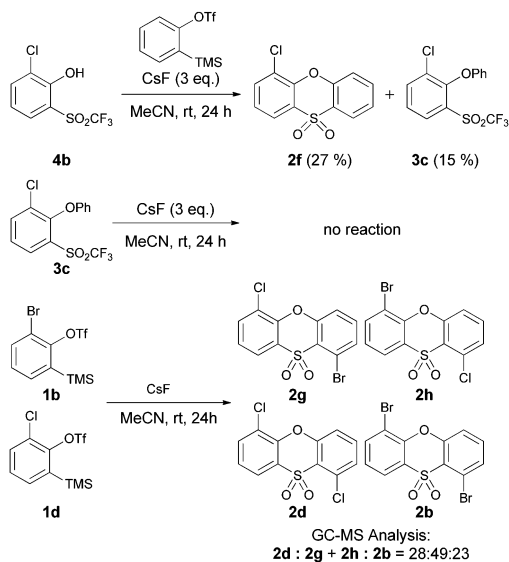
followed by thia-Fries reaction of the resulting anion.⁶ The phenolate **6** can then react with an aryne molecule **7**, formed from **5** *via* trifluoromethanesulfonate elimination in the established aryne generation pathway. Cyclisation of the resultant phenyl anion **8** onto the trifluoromethanesulfonate group gives the heterocyclic phenoxathiin-dioxide products (Scheme 2).

The anionic thia-Fries rearrangement was first reported by Lloyd-Jones and co-workers (also working in the context of aryne generation).⁷ Treatment of 2-(chloro)phenyl trifluoromethanesulfonate **9** with LDA at -78 °C led to either thia-Fries rearrangement (to compound **4b**) or aryne generation, a dichotomy that could be controlled by the amount of DIPA present in the reaction. Subsequent elucidation of the reaction mechanism revealed the degree of metalation to be the critical factor in partitioning the reaction between thia-Fries and aryne generation.⁶ The reaction has also been demonstrated to occur for 2-(trimethylsilyl)phenyl trifluoromethanesulfonates, with Butenschön and co-workers reporting examples using

Proposed Thia-Fries Mechanism**Anionic Thia-Fries (Lloyd-Jones)****Scheme 2** Proposed mechanism for phenoxathiin-dioxide formation.

aryltricarboxylchromium complexes as substrates.^{8,9} Our substrate scope in Table 1 is in line with literature reports on the thia-Fries rearrangement of trifluoromethanesulfonates. Electron withdrawing groups *ortho* to the trifluoromethanesulfonate, halogens in particular, activate this pathway and subsequent phenoxathiin-dioxide formation. Moving away from this substitution pattern results in the reaction shutting down, in line with literature precedent. The nitro-containing substrate **1i** clearly demonstrates the thia-Fries pathway in operation, providing the rearranged phenol **4a** as the only product.^{9a} It appears that the strongly electron withdrawing nitro group deactivates **1i** to benzyne formation, providing no aryne **7** for further reaction to the heterocyclic products **2**. Indeed, we were unable to find any reports of 6-nitro-2-(trimethylsilyl)phenyl trifluoromethanesulfonates being successfully used as aryne precursors in the literature. Halo-substituted compounds, however, can generate arynes and undergo further reaction to give the adduct **8**. Protonation of this anion affords the triflones **3** isolated as side-products. In contrast to Lloyd-Jones' reaction system in the cryogenic regime, where thia-Fries rearrangement was orthogonal to aryne generation depending on reaction conditions, here we require the substrate **1** to bifurcate between both thia-Fries and aryne generation in the same reaction. The final cyclisation of anion **8** involves displacement of CF_3 anion from the triflone, a process preceded for Grignard addition in sulfone synthesis.^{9b,10}

Further experiments were carried out to test this mechanistic conjecture. We prepared the halo-phenol **4b** separately and reacted it with benzyne under the reaction conditions. Successful cyclisation to the phenoxathiin-dioxide product **2f** was observed, (along with formation of **3c**), establishing phenol-aryne addition as a viable step in the mechanism (Scheme 3). Re-subjection of triflones such as **3c** to the reaction conditions did not result in cyclisation to the heterocyclic products **2**. This indicates that the neutral molecule is insufficiently nucleophilic to undergo intramolecular attack at the triflone group, and reaction through the anionic intermediate **8** is necessary to displace CF_3 at the sulfur centre. The formation of small amounts of **3** in the reaction is likely due to competitive protonation from the MeCN solvent, a common side-product



Scheme 3 Mechanistic studies.

in aryne couplings involving silyl-trifluoromethanesulfonate precursors **1**.^{3e}

Finally, we conducted cross-over experiments with two different aryne precursors in the same pot, **1b** and **1d**. A statistical mixture of hetero- and homo-coupled phenoxathiin-dioxides were observed on GC-MS analysis, supporting the dual reaction mode of the trifluoromethanesulfonate starting materials with respect to thia-Fries rearrangement and free benzyne formation in the same pot.

In conclusion, we have discovered a new reaction of 2-(trimethylsilyl)aryl trifluoromethanesulfonate benzyne precursors, where they bifurcate between thia-Fries rearrangement and aryne generation on simple fluoride treatment. Subsequent union and cyclisation affords novel phenoxathiin-dioxides. This pathway will be relevant to the design of new aryne reaction systems in general, where it may manifest when halogen or nitro-containing aryne precursors are used to explore substrate scope.¹¹ Finally, the reaction affords phenoxathiin-dioxides by a new route that does not require the preparation of a phenoxathiin and subsequent oxidation.

We thank the University of Manchester and the EPSRC for funding (Leadership fellowship to M.F.G.). Dr Anna Collins (University of Edinburgh) is thanked for X-ray crystallography

and we thank the EPSRC mass spectrometry service at the University of Swansea.

Notes and references

- (a) P. M. Tadross and B. M. Stoltz, *Chem. Rev.*, 2012, **112**, 3550–3577; (b) C. M. Gampe and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2012, **51**, 3766–3778; (c) A. Bhunia, S. R. Yetra and A. T. Biju, *Chem. Soc. Rev.*, 2012, **41**, 3140–3152; (d) A. V. Dubrovskiy, N. A. Markina and R. C. Larock, *Org. Biomol. Chem.*, 2013, **11**, 191–218.
- Y. Himeshima, T. Sonoda and H. Kobayashi, *Chem. Lett.*, 1983, 1211–1214.
- (a) T. Pirali, F. Z. Zhang, A. H. Miller, J. L. Head, D. McAusland and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2012, **51**, 1006–1009; (b) D. McAusland, S. Seo, D. G. Pintori, J. Finlayson and M. F. Greaney, *Org. Lett.*, 2011, **13**, 3667–3669; (c) K. Biswas and M. F. Greaney, *Org. Lett.*, 2011, **13**, 4946–4949; (d) A. A. Cant, L. Roberts and M. F. Greaney, *Chem. Commun.*, 2010, **46**, 8671–8673; (e) A. A. Cant, G. H. V. Bertrand, J. L. Henderson, L. Roberts and M. F. Greaney, *Angew. Chem., Int. Ed.*, 2009, **48**, 5199–5202.
- CCDC 945230 contains the crystallographic data for **2a**. ORTEP-3 was used to produce the thermal ellipsoid plots: L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.
- For the development of phenoxathiin-dioxides as monoamine oxidase inhibitors, see: M. Harfenist, D. P. C. Mcgee and H. L. White, *J. Med. Chem.*, 1991, **34**, 2931–2933.
- Intramolecular O_{Ar} → C_{Ar} sulfone transfer has been established in the anionic thia-Fries rearrangement by Lloyd-Jones and co-workers, using a crossover experiment with labelled substrates: A. M. Dyke, D. M. Gill, J. N. Harvey, A. J. Hester, G. C. Lloyd-Jones, M. P. Munoz and I. R. Shepperson, *Angew. Chem., Int. Ed.*, 2008, **47**, 5067–5070.
- J. P. H. Charmant, A. M. Dyke and G. C. Lloyd-Jones, *Chem. Commun.*, 2003, 380–381.
- (a) Z. Zhao, J. Messinger, U. Schön, W. Rudolf and H. Butenschön, *Chem. Commun.*, 2006, 3007–3009; (b) G. Werner, C. W. Lehmann and H. Butenschön, *Adv. Synth. Catal.*, 2010, **352**, 1345–1355; (c) G. Werner and H. Butenschön, *Eur. J. Org. Chem.*, 2012, 3132–3141.
- Other examples of the anionic thia-Fries rearrangement: (a) I. R. Hardcastle, PhD thesis, University of Manchester, 1990; (b) R. Kargbo, Y. Takahashi, S. Bhor, G. R. Cook, G. C. Lloyd-Jones and I. R. Shepperson, *J. Am. Chem. Soc.*, 2007, **129**, 3846–3847; (c) X. H. Xu, X. Wang, G. K. Liu, E. Tokunaga and N. Shibata, *Org. Lett.*, 2012, **14**, 2544–2547; (d) E. Yoshioka and H. Miyabe, *Tetrahedron*, 2012, **68**, 179–189; (e) X. H. Xu, M. Taniguchi, A. Azuma, G. K. Liu, E. Tokunaga and N. Shibata, *Org. Lett.*, 2013, **15**, 686–689.
- R. W. Steensma, S. Galabi, J. R. Tagat and S. W. McCombie, *Tetrahedron Lett.*, 2001, **42**, 2281–2283.
- For examples of 6-halo-2-trimethylsilyl(phenyl) trifluoromethanesulfonates used with fluoride to generate arynes, see: (a) J. D. Kirkham, P. M. Delaney, G. J. Ellames, E. C. Row and J. P. A. Harrity, *Chem. Commun.*, 2010, **46**, 5154–5156; (b) B. Lakshmi, U. K. Wefelscheid and U. Kazmaier, *Synlett*, 2011, 345–348; (c) D. Rodriguez, A. Cobas, D. Peña, D. Perez and E. Guitian, *Org. Lett.*, 2012, **14**, 1363–1365; (d) Y. Zeng, L. Zhang, Y. Zhao, C. Ni, J. Zhao and J. Hu, *J. Am. Chem. Soc.*, 2013, **135**, 2955–2958.