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The anionic thia-Fries rearrangement of aryl triflates

Jonathan P. H. Charmant,[a] Alan M. Dyke[b] and Guy C. Lloyd-Jones*[b]
[a] *Structural Chemistry Laboratory, School of Chemistry, Cantock's Close, Bristol, UK*
[b] *Bristol Centre for Organometallic Catalysis, Cantock's Close, Bristol, UK.*
E-mail: guy.lloyd-jones@bris.ac.uk; Fax: 44 117 929 861; Tel: 44 117 928 8165

Received (in Cambridge, UK) 30th October 2002, Accepted 17th December 2002
First published as an Advance Article on the web 14th January 2003

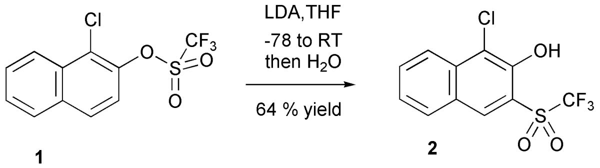
Aryl triflates undergo LDA-mediated rearrangement to generate *o*-hydroxyaryl trifluoromethylsulfones. In some cases, partitioning between rearrangement and aryne generation can be controlled.

In contrast to double defunctionalisation methods to arynes from *o*-Z-Ar-X,[1] the base-mediated elimination of 'HX' from haloarenes (Ar-X) requires only a single functional group and has been explored extensively.[2] The use of pseudohalides was pioneered by Fleming who generated benzynes from aryl benzenesulfonates with the sterically hindered base Li-TMP.[3] However, the yields in these reactions were compromised by *ortho*-metallation of the benzene sulfonyl chloride derived ring.† Subsequently, Scott and Wickham[4] introduced the use of aryl triflates[5] which cannot undergo such side reactions. Employing LDA, generated *in situ* by reaction of BuLi (2 equiv.) with an excess of *N*,*N*-diisopropylamine (DIPA) in THF or DME as solvent, aryl triflates underwent elimination and gave anilines in good yield by trapping, *in situ*,[6] with DIPA.[4,7] Herein, we report that aryl triflates also undergo a competing *anionic* thia-Fries rearrangement. To the best of our knowledge this is unprecedented,[8] however, it may have been overlooked since such reactions are normally quenched with water and the base-soluble phenolic components not extracted or analysed.[4,7]

Table 1 Elimination *versus* anionic thia-Fries rearrangement of aryl triflates

Entry	ArOTf Ar =	Yield[a] (%)	ArN(*i*-Pr)$_2$	Mole fraction[b] *o*-Ar(OH)Tf	ArOH	ArH
1	1-Cl-2-naphthyl (**1**)	64	—[c]	1.00 (**2**)	—[c]	—[c]
2	1-Br-2-naphthyl	49	—[c]	1.00	—[c]	—[c]
3	2-Cl-phenyl (**5**)	80	—[c]	1.00 (**6**)	—[c]	—[c]
4	2-Cl-phenyl (**5**)	65[d]	1.00 (**7**)[d]	—[c]	—[c]	—[c]
5	2-Cl-phenyl (**5**)	59[e]	—[c]	—[c]	1.00	—[c]
6	3-Cl-phenyl	85	0.69[f]	—[c]	0.31	—[c]
7	4-Cl-phenyl	72	0.64[g]	0.36	—[c]	—[c]
8	2-naphthyl (**8**)	67	1.00[h] (**9**)	—[c]	—[c]	—[c]
9	2-naphthyl (**8**)	74[i]	0.59[i] (**9**)	0.41[e] (**10**)	—[c]	—[c]
10	1-naphthyl	46	1.00[j]	—[c]	—[c]	—[c]
11	phenyl	68	1.00	—[c]	—[c]	—[c]
12	4-biphenyl	56	0.71[k]	—[c]	—[c]	0.29
13	4-tolyl	59	1.00[l]	—[c]	—[c]	—[c]
14	2-anisyl	95	1.00[m]	—[c]	—[c]	—[c]
15	3-anisyl	60	1.00[n]	—[c]	—[c]	—[c]
16	4-anisyl	99	1.00[n]	—[c]	—[c]	—[c]

[a] Reaction conditions (except for entries 4, 5 and 9): 1.04 DIPA + 1.00 BuLi in THF at −78 °C to RT (1h) then cooled to −78 °C, ArOTf added, reaction warmed to RT over 10 mins. then stirred o/n and quenched with water. Combined yield of pure materials separated by column chromatography on silica-gel. [b] Based on isolated yields. In no case, except entry 5, was substrate (ArOTf) recovered unreacted. Material balance: polymers. [c] $\leq 3\%$ (not detected by tlc analysis). [d] DIPA as solvent (125 equiv.) with 2.0 LDA; product *m*-chloro aniline/1,3-bis-aniline (7/3). [e] Triflate **5** heated to 240 °C (microwave) in DMF for 10 min. Material balance unreacted **5**. [f] *m*-Chloro aniline/1,3-bis-aniline (3/1). [g] *m/p* 28/72. [h] α/β 16/84. [i] 1.10 equiv. BuLi employed. [j] α/β 28/72. [k] *m/p* 55/45. [l] *m/p* 37/63. [m] >98% *m* isomer. [n] *m/p* 27/73.

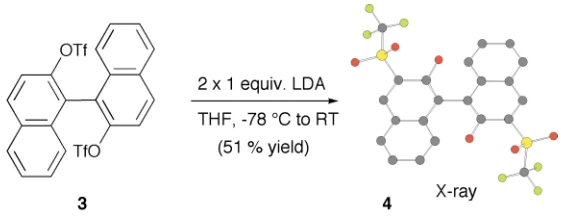


Scheme 1 Anionic thia-Fries rearrangement of triflate **1**.

We recently attempted a Pd-catalysed cross-coupling of 1-chloro-2-naphthalene triflate **1**[9] with a pyridyl zinc halide, generated *in situ* using LDA/ZnCl$_2$.[10] A side product of the reaction was ultimately identified as **2**, the product of a thia-Fries rearrangement of **1**. Further experiments revealed that LDA mediates rearrangement and under simpler conditions (1.0 equiv. LDA, THF, −78 °C to RT) **2** is obtained from **1** in 64% yield after aqueous work-up, Scheme 1, Table entry 1.

LiHMDS gave **2** in lower yield (48%) and other bases such as Li-TMP, *sec*-BuLi/TMEDA or BuLi were not effective. Confirmation that a thia-Fries rearrangement occurs was obtained by single crystal X-ray diffraction of **4**‡ Scheme 2.

In light of the work of Scott and Wickham,[4,7] we were curious that naphthyne derived aniline-type products were not obtained from **1**, as might be expected. We therefore tested other aryl triflates under analogous conditions, Table 1 (except entries 4, 5 and 9).



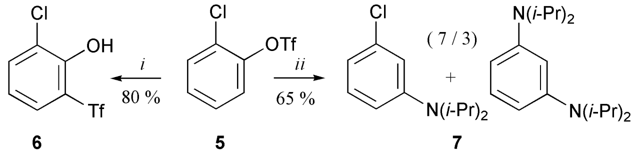
Scheme 2 The single crystal X-ray structure (protons omitted for clarity) of the 2,2′-dihydroxy-3,3′-disulfone **4**, the product of a double anionic thia-Fries rearrangement of 2,2′-bis triflate **3**.

A clear differentiation was found between those substrates bearing an electron withdrawing group *ortho* to the triflate (entries 1–3) which exclusively undergo anionic thia-Fries rearrangement and those with an electron donating group (entries 13–16) which exclusively undergo benzyne generation.

The conditions employed differ substantially from those developed by Scott and Wickham where 2 equiv. LDA was employed in the presence of a large excess of DIPA (10–140 equiv.). The latter was present to ensure rapid capture of the aryne and thereby avoid arene co-products.[4] What emerges from our study is that both DIPA and THF also have a profound influence at an earlier stage of reaction. The effect of THF is evident with substrates that bear electron withdrawing groups and tend to rearrange. For example, *o*-chlorophenyl triflate (**5**) undergoes rearrangement to give sulfone (**6**) as the exclusive non-polymeric product when reacted with LDA in THF (entry 3) but gives the mono and bis-anilines (**7**, 65%), with no trace of **6** when DIPA is employed as solvent. (Table 1, entry 4; Scheme 3).[4] However, when the same reaction is conducted in DIPA

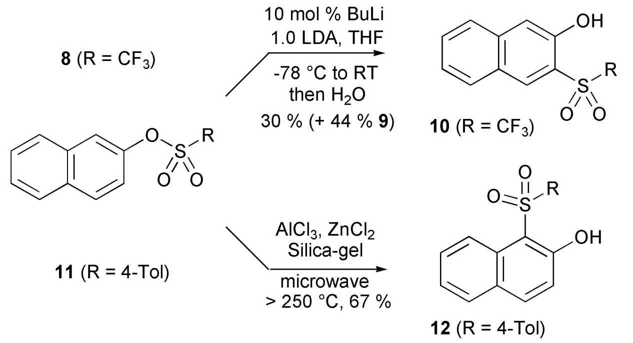
DOI: 10.1039/b210648e

containing as little as 4% THF, rearrangement to **6** competes extensively (40%).



Scheme 3 Conditions: *i*, LDA, THF −78 °C to RT then H_2O; *ii*, LDA, DIPA −78 °C to RT then H_2O.

The effect of DIPA becomes evident with substrates that are more delicately balanced with respect to elimination *versus* rearrangement. It should be noted that in reactions *without* excess DIPA (most entries in Table), there are two complicating factors. Firstly, aniline formation from the aryne consumes DIPA. Secondly, aryl deprotonation by LDA (in principle) generates DIPA. For example, 2-naphthyl triflate (**8**) gives *N*,*N*-diisopropyl-1/2-naphthylamines (**9**) as the exclusive non-polymeric products when reacted with 1.0 equiv. LDA in THF (67% total yield, Table 1, entry 8). However, addition of 10 mol% BuLi (Table, entry 9), which can deprotonate liberated DIPA, results in the anionic thia-Fries rearrangement competing significantly (30% isolated yield of **10**, Scheme 4.).§



Scheme 4 The effect of catalytic BuLi on the anionic thia-Fries rearrangement of triflate **8** and the contrasting regioselectivity of the thermal thia-Fries rearrangement of tosylate **11**.

Conducting the same reaction (10 mol% BuLi) in the presence of the aryne trap diphenylisobenzofuran (which bypasses the depletion of liberated DIPA) results in quantitative aryne generation (99% isolated yield of the 1,2- and 2,3-naphthyne cycloadducts) and no thia-Fries product **10**. BuLi alone is not effective (triflate **8** is recovered together with varying quantities of 2-naphthol) and *catalytic* quantities of DIPA with 1.0 equiv. BuLi do not suffice,¶ perhaps because the DIPA complexes the lithium *o*-sulfonyl phenoxide rearrangement product. Overall the results strongly implicate DIPA in mediating elimination or inhibiting rearrangement.‖

The thermal[11] thia-Fries rearrangement of diaryl sulfonates,[12] which gives both *ortho* and *para* isomers, is promoted by Brønsted and by Lewis acids, *e.g.* HF,[13] $AlCl_3$,[14] acidic clays,[15] and dry supports ($AlCl_3/ZnCl_2$/silica-gel).[16] The anionic thia-Fries rearrangement proceeds under markedly different conditions (low temperature basic medium) and undoubtedly proceeds *via* a different mechanism, giving only the *ortho*-rearranged product. Furthermore, the two processes can be regio-complementary, for example 2-naphthyl triflate (**8**) gives the 3-sulfonyl isomer (**10**) whereas under the microwave/acidic conditions, 2-naphthyl tosylate (**11**) gives the 1-sulfonyl isomer (**12**), Scheme 4.[16] In stark contrast to anionic conditions (Table 1 entry 3), *o*-chlorophenyl triflate (**5**) fails to rearrange on heating (oil bath or microwave) neat, in solution (Table 1, entry 5) or on a Lewis acidic support **

In summary, aryl triflates bearing moderately electron withdrawing substituents, especially at an *ortho*-position, readily undergo an anionic thia-Fries rearrangement on reaction with LDA in the presence of THF to give *o*-hydroxyaryl trifluoromethylsulfones rather than generating arynes. The analogous thermal process does not proceed readily. The ready orthometallation of arylsulfones make the rearrangement products of interest for further elaboration. With substrates that undergo partitioning between both processes, conducting the reaction under conditions in which the concentration of excess DIPA is low favours the anionic thia-Fries rearrangement. The mechanism by which the (formal) elimination of LiOTf and competing anionic thia-Fries rearrangement occur is the subject of an ongoing isotopic labelling, kinetic and computational study which will be reported in full in due course.[17]

AMD thanks the EPSRC for support. GCL-J gratefully acknowledges the RSC for unrestricted funding through the Hickinbottom Fellowship. We thank Dr J. N. Harvey and Professor T. C. Gallagher for valuable discussion.

Notes and references

† Di-and tri-benzothiophen dioxides are generated by single or double insertion of benzyne then cyclisation with loss of PhOLi.

‡ Sequential addition of LDA (2 × 1 equiv., −78 °C to RT) results in stepwise rearrangement, *via* [2-(OLi)-3-(CF_3SO_2)-2′-(OTf)-1,1′-binaphthalene], to give **4** as the only non-polymeric product. Simultaneous twofold addition gives mixtures.

§ Larger excesses of BuLi result in competing reactions. With 100 mol% BuLi, naphthalene (30%) is the sole non-polymeric product.

¶ For example, triflate **1** reacts with 10 mol% LDA and 90 mol% BuLi to give **1**/**2** in a 90/10 ratio.

‖ Whether aryne generation proceeds *via ortho*-metallation (E_{1cb}-like) or direct elimination (E_2-like) is the subject of ongoing study.

** In DMF solution, careful heating to 235–240 °C by microwave resulted in *o*-chlorophenol. In all cases heating above 250 °C resulted in decomposition to an uncharacterisable tar.

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