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On the preparation of *ortho*-trifluoromethyl phenyl triflate

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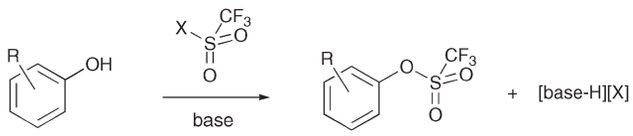
In contrast to an earlier report advocating a copper-mediated trifluoromethylation of *ortho*-iodophenyl triflate, *ortho*-trifluoromethyl phenyl triflate may be prepared simply by reacting the corresponding phenol with triflic anhydride in the presence of a nucleophilic catalyst and stoichiometric base.

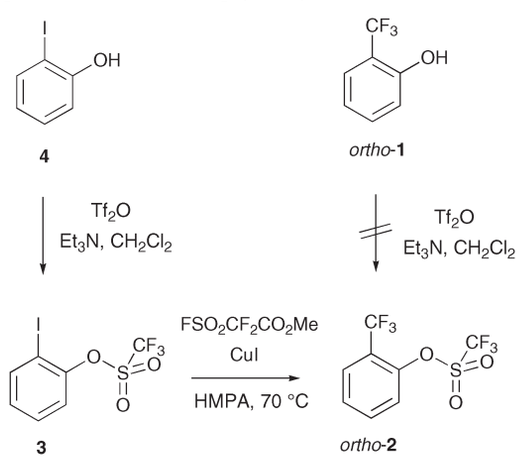
Organic triflates have long been of great interest and utility in organic synthesis. Aryl and vinyl triflates[1] in particular are notable for their application in cross-coupling reactions where the triflate acts as a pseudo halogen.[2] Both the synthesis and reactivity of aryl triflates may be viewed as complementary to the analogous halides: the triflate is readily prepared from the appropriate phenol and with the correct choice of palladium catalyst can be selectively cross-coupled in the presence of the aryl bromide and *vice versa*.[3]

We have an ongoing interest in the anionic thia-Fries rearrangement of aryl triflates[4] and recently had reason to prepare *ortho*-, *meta*- and *para*-trifluoromethyl phenyl triflates.[5] Aryl triflates are almost always prepared by reaction of the corresponding phenol with a triflating agent, CF_3SO_2X, where X = halide, triflate,[6] *N*-phenyl triflamide, *etc.*, in the presence of a base, Scheme 1.



Scheme 1 Conventional conditions for the preparation of aryl triflates.

We were thus somewhat surprised by a report from Qing *et al.*[7] that *ortho*-trifluoromethyl phenol (*ortho*-**1**) does not yield *ortho*-trifluoromethyl phenyl triflate (*ortho*-**2**) on reaction with Tf_2O and Et_3N in CH_2Cl_2. Instead, they describe that *ortho*-**1** is unstable under these reaction conditions and that the sole isolable product is *ortho*-hydroxybenzoic acid. On the basis of this result, Qing *et al.* advocate the use of a copper-mediated trifluoromethylation, Scheme 2. Although this procedure yields *ortho*-trifluoromethyl phenyl triflate (*ortho*-**2**) in 84% yield, the requisite *ortho*-iodophenyl triflate (**3**) must be prepared from *ortho*-iodophenol (**4**) and moreover, 5 equivalents of both $FSO_2CF_2CO_2Me$ and HMPA are required in the second step (**3** to **2**).

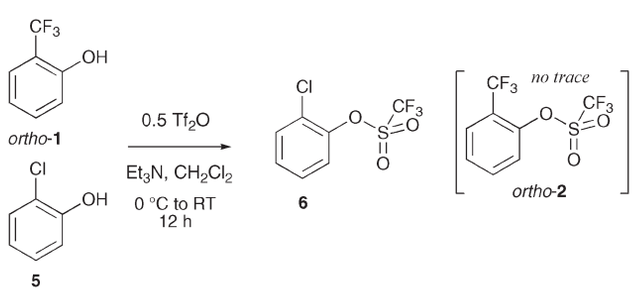


Scheme 2 The procedure of Qing *et al.*[7] for the preparation of *ortho*-**2**.

It is interesting to note that in the two-step procedure of Qing *et al.*,[7] Scheme 2, the reaction of *ortho*-iodophenol (**4**) with Tf_2O/Et_3N in CH_2Cl_2 proceeds smoothly (84% yield), as indeed do most *ortho*-substituted phenols. It is thus curious that *ortho*-trifluoromethyl phenol (*ortho*-**1**) does not react in the manner desired. The combination of an activated aromatic nucleus with the strongly electron withdrawing trifluoromethyl group is known to induce high reactivity. For example, both *para*-trifluoromethyl phenol (*para*-**1**) and *para*-trifluoromethyl aniline readily polymerise on mild thermolysis.[8] Trifluoromethyl phenols are also photosensitive, forming hydroxybenzoic acids in water *via* radical intermediates of the type $ArCF_2$.[9] Furthermore, *ortho*-**1** and *para*-**1**, but not *meta*-**1**, are base labile, forming hydroxybenzoic acids in strong aqueous base, but undergoing polymerisation in dilute base.[8] This behaviour might thus appear to account for the failure of the reaction of *ortho*-**1** with Tf_2O and Et_3N in CH_2Cl_2 to yield *ortho*-**2** as reported by Qing *et al.*[7]

In our hands, *ortho*-trifluoromethyl phenol (*ortho*-**1**) is stable for long periods in Et_3N/CH_2Cl_2 solution, in the presence or absence of Tf_2O, as evidenced by $^{19}F\{^1H\}$ NMR monitoring with *o*-$C_6H_4F_2$ as an internal standard. On quenching such mixtures with water, we obtained no evidence for the generation of *ortho*-hydroxybenzoic acid and the bulk of the phenol (*ortho*-**1**) remains.† This then suggests that the failed reaction of Qing *et al.*[7] is a result not of the instability of *ortho*-**1** but rather its lack of reactivity towards Tf_2O.

An experiment in which *ortho*-**1** and *ortho*-chloro phenol (**5**) competed for a limiting quantity of Tf_2O demonstrated that the trifluoromethyl group significantly reduces the nucleophilicity of the phenol as compared to a chloro group, Scheme 3. Indeed, extensive conversion of phenol **5** to triflate **6** occurred within a period of 12 h at which point there was no *ortho*-**2** detectable. This result strongly supports the concept that neither *ortho*-**1** nor its corresponding triethylammonium phenolate[10] are sufficiently nucleophilic to react with Tf_2O.[5] However, even with *ortho*-chloro phenol (**5**) these reaction conditions (Et_3N, TF_2O, CH_2Cl_2, 0 to RT o/n) are not ideal as pure **6** was isolated in only 30% yield after chromatography of the crude product which contains numerous side-products.



Scheme 3 Competition experiment between *ortho*-chloro-(**5**) and *ortho*-trifluoromethyl (*ortho*-**1**) phenols for triflic anhydride.

By direct analogy with nucleophilic catalysis of acylation reactions, we reasoned that an *N*-triflyl 4-*N*′,*N*′-dimethylaminopyridinium intermediate would be substantially more reactive towards phenols/triethylammonium phenolates than the neutral anhydride Tf_2O.[11] Accordingly, 5 mol% DMAP[12] was found to catalyse the

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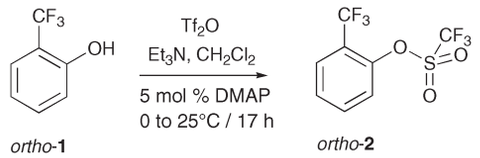
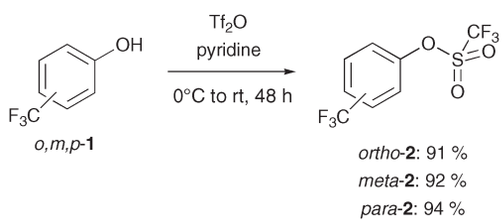
reaction of *ortho*-**1** with Tf_2O to afford the desired triflate *ortho*-**2** as the major product identifiable in the NMR spectrum of the crude product after work-up, Scheme 4.



Scheme 4 The use of DMAP to catalyse the triflation of *ortho*-**1**. There is no reaction in the absence of catalyst.

However, the isolated yield of *ortho*-**2** was not good (30%) and this suggested that polymerisation of *ortho*-**1** may be a significantly competing side reaction. A better procedure emerged to be the use of pyridine as solvent, base and catalyst, Scheme 5, which gave *ortho*-**2** in 91% yield.‡ Using an analogous procedure, the *meta*- and *para*-isomers of **2** were also prepared in excellent yield.



Scheme 5 The ready preparation of trifluoromethyl phenyl triflates (*o*-,*m*-,*p*-**2**) using pyridine as nucleophilic catalyst, solvent and base.

In summary, the previously reported difficulties in the preparation of *ortho*-trifluoromethyl phenyl triflate (*ortho*-**2**) from the corresponding *ortho*-trifluoromethyl phenol (*ortho*-**1**) by base-mediated reaction with Tf_2O stem predominantly from low nucleophilicity rather than instability of **1** and its conjugate base.[7] Pyridine is commonly employed as a solvent for triflation[1] of phenols and the results presented herein suggest that the solvent may also participate as a nucleophilic catalyst under standard conditions.

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Notes and references

† Although we did not isolate any *ortho*-hydroxybenzoic acid, we do not dispute that Qing *et al.* may have done so, *after aqueous work-up*, as the phenol is known to be sensitive to aqueous base and to light, *vide supra*. The salient point is that $^{19}F\{^1H\}$ NMR analysis indicates that under the triflation conditions (Tf_2O, CH_2Cl_2, Et_3N, RT) the phenol is relatively inert.

‡ ***ortho*-Trifluoromethyl phenyl triflate**[7] (*ortho*-**2**): to a stirred solution of *ortho*-trifluoromethyl phenol (*ortho*-**1**) (3.45 g, 21 mmol) in anhydrous pyridine (10 cm^3) at 0 °C was added trifluoromethanesulfonic anhydride (3.8 ml, 23 mmol) dropwise over 5 min. The clear colourless solution changed to a dark orange colour and was allowed to return slowly to room temperature. After 48 h the reaction was quenched with water, extracted into CH_2Cl_2 (5 × 15 cm^3) and the organic phase washed with 1 M hydrochloric acid (20 cm^3), water (20 cm^3) and brine (10 cm^3). The organic phase was dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo* to give a pale yellow liquid. After purification by flash chromatography, eluting with 10% ethyl acetate in hexanes, *ortho*-trifluoromethyl phenyl triflate (*ortho*-**2**) (5.62 g, 91% yield) was obtained as a clear colourless liquid. (Found: N, 0.1; C, 32.8; H, 1.3%; $C_8H_4F_3O_3S$ requires N, 0; C, 32.7; H, 1.4%); ν_{max} (film)/cm^{-1} 1616w (benzene), 1318s (SO_2), 1211s, 1184s (SO_2O), 1132s (SO_2), 1115s, 882s, 765s (*ortho*-disubstituted benzene); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.74 (1H, d, J = 7.7 Hz, 3-H), 7.65 (1H, dd, J = 8.2, 7.9 Hz, 5-H), 7.50 (1H, d, J = 8.2 Hz, 6-H), 7.49 (1H, dd, J = 7.9, 7.7 Hz, 4-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 146.08 (s, 1-C), 133.95 (s, 5-C), 128.19 (s, 6-C), 128.00 (q, J_{CF} = 4.9 Hz, 3-C), 123.17 (q, J_{CF} = 32.7 Hz, 2-C), 122.33 (s, 4-C), 122.03 (q, J_{CF} = 272.9 Hz, Ar–CF_3), 118.41 (q, J_{CF} = 320.2 Hz, SO_2–CF_3); δ_F (376 MHz; $CDCl_3$) −61.5 (s, Ar–CF_3), −74.3 (s, SO_2–CF_3);[13] *m*/*z* (EI) 294 (M^+, 58%), 230 (33), 142 (97), 133 (48), 114 (100).

***meta*-Trifluoromethyl phenyl triflate**[7] (*meta*-**2**): obtained as a clear colourless liquid in 92% yield using an identical procedure to that described above, but starting with *meta*-**1**; (Found: N, 0.1; C, 32.4; H, 1.2%; $C_8H_4F_3O_3S$ requires N, 0; C, 32.7; H, 1.4%); ν_{max} (film)/cm^{-1} 1594w (benzene), 1324s (SO_2), 1211s, 1174s (SO_2O), 1128s (SO_2), 909s (*meta*-disubstituted benzene), 810s (*meta*-disubstituted benzene); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.68 (d, J = 7.7 Hz, 4-H), 7.61 (dd, J = 8.0, 7.7 Hz, 5-H), 7.55 (s, 2-H), 7.50 (d, J = 8.0 Hz, 6-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 149.35 (s, 1-C), 133.01 (q, J_{CF} = 33.8 Hz, 3-C), 131.03 (s, 5-C), 125.26 (q, J_{CF} = 3.8 Hz, 4-C) 124.86 (s, 6-C) 122.82 (q, J_{CF} = 272.9 Hz, Ar–CF_3), 118.73 (q, J_{CF} = 3.8 Hz, 2-C), 118.68 (q, J_{CF} = 320.5 Hz, SO_2–CF_3); δ_F (376 MHz; $CDCl_3$) −63.7 (s, Ar–CF_3), −73.6 (s, SO_2–CF_3);[13] *m*/*z* (EI) 294 (M^+, 70%), 275 (30), 230 (65), 161 (21), 145 (26), 133 (63), 113 (39), 69 (100)

***para*-Trifluoromethyl phenyl triflate**[7] (*para*-**2**): obtained as a clear colourless liquid in 94% yield using an identical procedure to that described above, but starting with *para*-**1**; (Found: N, 0.0; C, 32.4; H, 1.2%; $C_8H_4F_3O_3S$ requires N, 0; C, 32.7; H, 1.4%); ν_{max} (film)/cm^{-1} 1610w (benzene), 1323s (SO_2), 1211s, 1172s (SO_2O), 1127s (SO_2), 979s (Ar–H), 846s (*para*-disubstituted benzene); δ_H (400 MHz; $CDCl_3$; Me_4Si) 7.75 (2H *app.* d, J = 8.5 Hz, 3-H and 5-H), 7.42 (2H, *app.* d, J = 8.5 Hz, 2-H and 6-H); δ_C (100 MHz; $CDCl_3$; Me_4Si) 151.5 (s, 1-C), 130.8 (q, J_{CF} = 33.5 Hz, 4-C), 127.7 (q, J_{CF} = 3.6 Hz, 3-C and 5-C), 123.2 (q, J_{CF} = 272.4 Hz, Ar–CF_3) 121.9 (s, 2-C and 6-C) 118.7 (q, J_{CF} = 320.7 Hz, SO_2–CF_3);[13] δ_F (376 MHz; $CDCl_3$;) −63.3 (s, Ar–CF_3), −73.4 (s, SO_2–CF_3); *m*/*z* (EI) 294 (M^+, 69%), 275 (17), 230 (59), 161 (14), 145 (27), 133 (60), 113 (34), 69 (100).

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2 (*a*) *Transition Metals for Organic Synthesis*, M. Beller and C. Bolm, ed., Wiley-VCH, Weinheim, 1998; (*b*) J. Tsuji, *Palladium Reagents and Catalysts*, John Wiley, Chichester, 1995.
3 T. Kamikawa and T. Hayashi, *Tetrahedron Lett.*, 1997, **38**, 7087.
4 J. P. H. Charmant, A. M. Dyke and G. C. Lloyd-Jones, *Chem. Commun.*, 2003, 380.
5 A survey of the literature revealed that these compounds (*ortho*-, *meta*- and *para*-**2**) were first prepared by Qing *et al.* in 1997 (see ref. 7) using the method shown in Scheme 2. Wu *et al.* have reported the use of *ortho*-trifluoromethyl phenyl triflate (*ortho*-**2**) in cross-coupling reactions (J. Wu, J.-F. Marcoux, I. W. Davies and P. J. Reider, *Tetrahedron Lett.*, 2001, **42**, 159). The compound (*ortho*-**2**) was prepared by reacting phenol (*ortho*-**1**) with trifluoromethylsulfonyl chloride in CH_2Cl_2/Et_3N at 0 °C. The (unoptimised) yields were less than 50%: J. Wu and J. Marcoux, personal communication. The fact that the reaction proceeds with the chloride (CF_3SO_2Cl) in CH_2Cl_2/Et_3N but not the anhydride (Tf_2O) is consistent with the low nucleophilicity of the phenol (*ortho*-**1**) described herein.
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7 F.-L. Qing, J. Fan, H.-B. Sun and X.-J. Yue, *J. Chem. Soc., Perkin Trans 1*, 1997, 3053.
8 R. G. Jones, *J. Am. Chem. Soc.*, 1947, **69**, 2346.
9 P. Seiler and J. Wirz, *Helv. Chim. Acta*, 1972, **55**, 2693.
10 Titration experiments with Et_3N (followed by $^{19}F\{^1H\}$ NMR in CD_2Cl_2) showed no evidence for deprotonation of *ortho*-**1** to give the phenolate.
11 To the best of our knowledge, nucleophilic catalysis of phenol triflation employing triflic anhydride has not previously been noted. However, the nucleophilic catalysis of sulfonation has been studied in depth. For leading references, see: I. M. Gordon, H. Maskill and M.-F. Ruasse, *Chem. Soc. Rev.*, 1989, **18**, 123; . A super-stoichiometric combination of DMAP and Tf_2O has been reported by Banwell *et al.* as an efficient system for promoting Bischler–Naperialski cyclisation under mild conditions, see: M. G. Banwell, B. D. Bissett, S. Busato, C. J. Cowden, D. C. R. Hockless, J. W. Holman, R. W. Read and A. W. Wu, *J. Chem. Soc., Chem. Commun.*, 1995, 2551.
12 For leading references, see: M. R. Heinrich, H. S. Klisa, H. Mayr, W. Steglich and H. Zipse, *Angew. Chem., Int. Ed.*, 2003, **42**, 4826.
13 Qing *et al.* (see ref. 7) assign ^{19}F shifts of −93.2, −91.5 and −91.9 ppm for the Ar–CF_3 groups and −80.3, −81.7 and −81.8 ppm for the $ArOSO_2CF_3$ groups in *ortho*-, *meta*- and *para*-**2**, respectively. Similar shifts are assigned to a range of analogous aryl triflates and aryl trifluromethanes. In our hands, Ar–OSO_2CF_3 compounds have ^{19}F shifts in the range −73 to −75 ppm (δ_F CCl_3F = 0 ppm), see, for example: J. P. H. Charmant, I. A. Fallis, N. J. Hunt, G. C. Lloyd-Jones, M. Murray and T. Nowak, *J. Chem. Soc., Dalton Trans.*, 2000, 1723–1732; The ^{19}F shift of Ph–CF_3 is −64 ppm (M. Hesse, H. Meier and B. Zeeh, translated by A. Linden and M. Murray, *Spectroscopic Methods in Organic Chemistry*, George Thieme, Stuttgart, 1997). Our assignment of −61.5, −63.7 and −63.3 ppm for the Ar–CF_3 groups and −74.3, −73.6 and −73.4 ppm for the $ArOSO_2CF_3$ groups in *ortho*-, *meta*- and *para*-**2**, respectively, is thus consistent with both sets of chemical shifts. We suggest that all of the ^{19}F spectra of Qing *et al.* in ref. 7 have been mis-referenced.