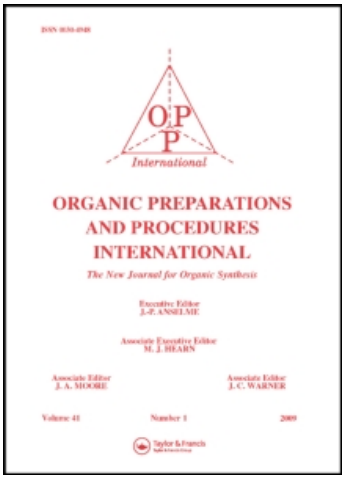

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AN ALTERNATIVE SYNTHESIS OF ARYL AND HETEROARYL BROMIDES FROM ACTIVATED ARYL HYDROXY COMPOUNDS

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Aryl triflates, prepared from the corresponding aryl hydroxy compounds and trifluoromethanesulfonic anhydride, have recently been identified as versatile intermediates for the conversion of phenols into a wide range of functionalized aromatic compounds.[1] The most common application of aryl triflates is in organometallic coupling reactions for activated as well as non-activated aryl triflates.[2] Palladium or nickel catalysts are frequently utilized for the conversion of aryl triflates by the action of dichlorobis(triphenylphosphine)palladium into styrenes (the Heck reaction),[3] to benzamides in the presence of carbon monoxide and an amine,[4] or alternatively to aryl nitriles using potassium cyanide.[5,6] The palladium-catalyzed reactions of aryl or heteroaryl triflates with (a) organostannanes,[7] (b) arylboron compounds,[8a,b] (c) alkenyl difluoromethylsilanes[9] and (d) ketene trimethylsilyl acetals[10] give arenes and biaryls. Treatment of aryl triflates with reactive high order mixed cuprates yields the corresponding alkylarenes.[11] Aryl triflates can also be reduced by catalytic hydrogenation over 10% palladium on carbon[12] or with formic acid[13] to afford the parent arenes.

By comparison, nucleophilic substitution reactions of activated aryl triflates, albeit intuitively more facile, have received scant attention. The displacements of triflate by the dimethyl malonate anion for the synthesis of nitrophenylmalonates,[14] and by reaction with amines at elevated pressures as a route to arylamines[1] have been described. The displacement of the triflate moiety with bromide, however, has not been reported previously. We now show that activated aryl and heteroaryl triflates readily undergo nucleophilic substitution on treatment with tetra-*n*-butylammonium bromide (TBAB, **4**) to yield conveniently the corresponding aryl bromides.

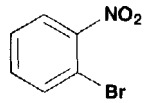
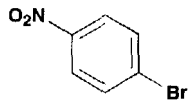
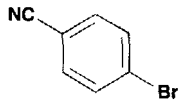
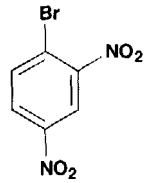
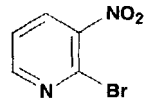
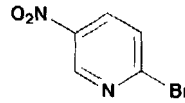
The triflates **3**, were prepared from the corresponding aryl hydroxy compounds **1** by treatment with 1.1 equivalents of trifluoromethanesulfonic anhydride **2** in the presence of triethylamine.[1]

Compounds **3** were then treated with TBAB (**4**) in refluxing toluene to introduce the bromide ion and complete the displacement. The elevated reaction temperature served a dual purpose in that reaction times were conveniently short and permitted the sufficient solubility of TBAB. The use of TBAB as a source of bromide is quite convenient compared to literature procedures which generally require the handling of hazardous reagents. The overall success of the reaction was found to be strongly

$$\underset{\mathbf{1}}{\mathrm{ArOH}} + \underset{\mathbf{2}}{(\mathrm{CF_3SO_2})_2\mathrm{O}} \xrightarrow{\mathrm{Et_3N}} \underset{\mathbf{3}}{\mathrm{Ar{-}OSO_2CF_3}} \xrightarrow[\text{toluene, }\Delta]{n\text{-}\mathrm{Bu_4N^+\,Br^-}\ (\mathbf{4})} \underset{\mathbf{5}}{\mathrm{Ar{-}Br}} \qquad (1)$$

dependant upon the activation of the initial aryl triflates. Since the substitution takes place *via* an addition-elimination process, aryl triflates bearing strong electron-withdrawing groups greatly enhance the rate of the reaction. As shown in Table 1, 2-(trifluoromethanesulfonyloxy)-5-nitropyridine (**3f**) reacted

TABLE 1. Nucleophilic Substitution of Aryl Triflates (**3a-f**) with TBAB (**4**)

ArOTf	Product	Structure	Ratio of **3**:**4**	Time (hrs)	Yield (%)	mp. (°C)	mp. (lit.) (°C)
3a	**5a**		1:2	48	48	40-41	40-41.5[16]
3b	**5b**		1:3	48	60	124-126	126-127[16]
3c	**5c**		1:3	72	32	112-113	113[17]
3d	**5d**		1:2	20	87	73-74	72.5-73[18]
3e	**5e**		1:2	24	86	124-125	125[19]
3f	**5f**		1:1	6	98	139-141	139-141[19]

with tetra-*n*-butylammonium bromide much faster than 4-nitrophenyl triflate (**3b**) and that an excess of TBAB was necessary for less reactive aryl triflates. For example, the weak electron withdrawing

effect of the cyano group in 2-(trifluoromethanesulfonyl)oxy-4-cyanobenzene (**3c**), led to a yield of only 32% of the corresponding bromo derivative, even after a 72 hrs period of reflux. Similar reactivity trends have been observed for the reactions of unactivated triflates with amines.[1]

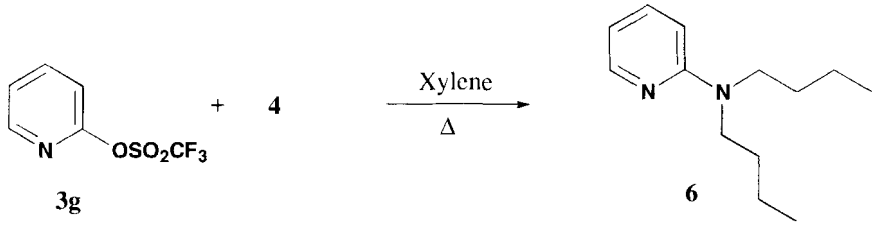
The bromides **5** were obtained after evaporation of the solvent and purification by column chromatography (see Experimental section) and were identified by ^{1}H, ^{13}C NMR spectroscopy (Table 2) and by comparison with literature data.

Table 2. Spectroscopic Data of Aryl and Heteroaryl Bromides **5**

Cmpd	^{1}H NMR ($CDCl_3$)												^{13}C NMR ($CDCl_3$)
No.	δ	H	m	J(Hz)	δ	H	m	J(Hz)	δ	H	m	J(Hz)	δ (ppm)
5a	7.83	1	m	–	7.73	1	m	–	7.46	2	m	–	114.3, 125.5, 128.2, 133.2, 135.0[a]
5b	8.11	2	d	8.7	7.70	2	d	8.7					124.9, 129.9, 132.6, 146.9
5c	7.64	2	d	8.3	7.53	2	d	8.3					111.1, 117.9, 127.9, 132.5, 133.3
5d	8.70	1	s	–	8.33	1	m	–	8.03	1	d	8.7	120.8, 121.8, 127.1, 136.4[a]
5e[b]	8.65	1	d	4.7	8.38	1	d	8.0	7.68	1	dd	8.0 4.7	123.6, 132.2, 133.8, 146.7, 152.5
5f	9.19	1	d	2.9	8.48	1	dd	8.8 2.9	7.90	1	d	8.8	128.7, 133.6, 143.5, 145.1, 147.2

a) Quaternary carbon atoms attached to nitro groups could not be observed. b) Spectrum was run in a mixture of $CDCl_3$ and DMSO.

In the case of 2-trifluoromethanesulfonyloxypyridine (**3g**), the bromide ion could not be introduced under the conditions described. To make the reaction conditions more favourable, **3g** was treated with TBAB in refluxing xylene rather than toluene. However, this led to the dibutylamino derivative **6**. It would appear that at higher temperatures the ammonium salt acts in a nucleophilic manner (Figure 2), presumably *via* a Meisenheimer complex to afford **6**. Related transformations are known for nucleophilic substitution of heteroaromatic halides by acyclic tertiary amines.[15]



(2)

It has been estimated that the leaving ability of the triflate anion is 10^7 times greater than for bromide or chloride ions.[20] Therefore, the nucleophilic displacement of aryl triflates with TBAB

occurs readily. However, refluxing 4-nitrophenyl triflate with benzyltriethylammonium chloride or potassium chloride in the presence of 18-crown-6 ether in toluene for 3 days yielded only trace amounts of the corresponding 4-nitrophenyl chloride. Obviously, less mild reaction conditions may be required because of the weaker nucleophilicity of the chloride ion compared to that of bromide.

In conclusion, an alternative method for the conversion of activated phenols and heteroaryl hydroxy compounds into the corresponding aryl bromides *via* their intermediate aryl triflates has been provided in a two step procedure. The present method for the conversion of heteroaryl hydroxy compounds is convenient and practical compared to the literature procedures which involve the use of (a) phosphorus tribromide,[21] (b) phosphorus oxybromide or phosphorus pentabromide,[22-24] or (c) a tertiary phosphine dibromide (prepared in situ from triphenylphosphine and bromine).[25] The use of acetyl bromide or mesyl chloride/lithium bromide has limited applications.[26,27] The options for the conversion of activated phenols into their corresponding aryl bromides are even more limited and only the use of triphenylphosphine dibromide is reported to be of practical value.[28,29] Therefore, the described procedure using TBAB as bromide source proves to be a valuable extension of the triflate methodology.

EXPERIMENTAL SECTION

Melting points were determined with a hot stage apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a Varian-300 (300 MHz) spectrometer using TMS as an internal standard. The phenols **1a-d** and heteroaryl hydroxy compounds **1e-f** are commercial products. Aryl triflate **3** were prepared from the corresponding phenols and trifluoromethanesulfonic anhydride according to the literature procedure in 78 - 98% yields.[1] Triflate **3a**: yield: 89% (oil)[30], **3b**: yield: 98% (mp. 52°, lit.[7] mp. 53°), **3c**: yield: 95% (oil)[30] and **3d**: yield: 78% (mp. 50°, lit.[31] mp. 50-51°) are known compounds and their structures were confirmed by comparison of their physical and NMR data with the reported values.

2-(Trifluoromethanesulfonyl)oxy-3-nitropyridine **3e** : yield: 89%, colorless oil; ^{1}H NMR: δ 8.67 (1H, dd, J= 4.7 and 1.8 Hz), 8.60 (1H, dd, J= 8.1 and 1.8 Hz), 7.68 (1H, dd, J= 8.1 and 4.7 Hz); ^{13}C NMR: δ (ppm) 111.9, 116.2 (CF_3), 120.4 (CF_3), 125.0, 136.7, 147.0, 152.4.

Anal. Calcd. for $C_5H_3F_3N_2O_5S$: C 26.48, H 1.11, N 10.29; Found C 26.46, H 1.06, N 10.31

2-(Trifluoromethanesulfonyl)oxy-5-nitropyridine **3f** : yield: 86%, pale yellow solid; mp. 82 - 83°); ^{1}H NMR: δ 9.26 (1H, d, J= 2.7 Hz), 8.72 (1H, dd, J= 8.8 and 2.7 Hz), 7.40 (1H, d, J= 8.8 Hz); ^{13}C NMR: δ (ppm) 115.5, 116.3 (CF_3), 120.6 (CF_3), 136.6, 144.0, 145.0, 158.3.

Anal. Calcd. for $C_5H_3F_3N_2O_5S$: C 26.48, H 1.11, N 10.29; Found C 26.46, H 1.08, N 10.29

General Procedure for the Preparation of Aryl Bromides 5.- A mixture of aryl triflate **3** (5 mmol) and tetra-n-butylammonium bromide **4** in toluene (30 mL) was heated under reflux for the time indicated in Table 1. The solvent was removed at reduced pressure and the residue dissolved in diethyl ether (50 mL), washed with water (3 x 50 mL) and dried ($MgSO_4$). The diethyl ether was evaporated in vacuo and the crude product purified by column chromatography [silica gel (230-400 mesh)] using a mixture of hexane and methylene chloride (ratio : 1/1) as the eluent to afford the corresponding aryl

bromide **5**. Ethyl acetate was used as the eluent for the purification of **5f**.

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