A Mild and Efficient Method of Aromatic Fluorination

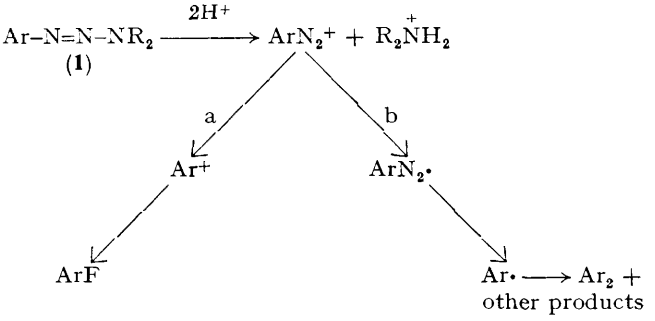
By MOSHE N. ROSENFELD and DAVID A. WIDDOWSON*
(*Department of Chemistry, Imperial College, London* SW7 2AY)

Summary Aromatic fluorides are prepared in high yield by treatment of aryltriazenes with 70% hydrogen fluoride in pyridine at 0—80 °C.

As a part of our studies on the synthesis of fluoro-compounds of medicinal interest, we required a method of introduction of fluorine into the aromatic ring which was rapid, efficient, and operable under mild conditions in

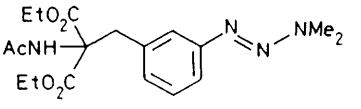
order that fluorine-18 ($t_{\frac{1}{2}}$ 2 h) labelled compounds could be produced. Conventionally, aromatic fluorination is achieved by the Balz–Schiemann reaction,[1] or *via* electrophilic fluorination with one of the newer reagents.[2] In respect of fluorine-18 work, these latter reagents are not feasible and the Balz–Schiemann reaction, thus far, is the only method successfully used.[3] We report now a simple and mild procedure which is applicable to a wide range of aromatic substrates.

Fluorination *via* diazotisation of aromatic amines in hydrogen fluoride either aqueous,[4] pure,[5] or 70% in pyridine[6] gives poor yields or is of limited utility. Commonly, the unwanted products are those resulting from homolysis of the aryl–nitrogen bond in the diazonium ion. As this is a reductive process,[7] we sought to generate diazonium ions in the absence of nitrogen oxides, the main potential reductants in the system. Aryl triazenes (**1**) which can be prepared in high yield[8] are a potential source of aryldiazonium ion[9] under controlled, mild acid conditions (Scheme, route a). In particular, the system can be largely free of initiators of radical decomposition (simplified as Scheme, route b)[7] and the generation of aryl cation can be maximised.



SCHEME

Thus, aryltriazenes (**1**, R_2 = Me_2 or $[CH_2]_5$) were treated with 70% hydrogen fluoride in pyridine[10] to give good to high yields of aryl fluorides (see Table). A range of simple aryl residues was examined in order to determine the functional group compatibility. Aryl rings containing electron donating or mildly electron withdrawing groups (runs 1—8) were all efficiently fluorinated, with the exception of the *o*-anisyl analogue (run 9), which gave only 2,2′-bianisyl. That this results specifically from the *ortho*-oxygen function, rather than a bulk effect, is shown by the successful fluorination of the *o*-tosyloxyphenyltriazene (run 10). The *p*-halogenophenyltriazenes gave anomalous results. Only *p*-chlorophenyltriazene (run 11) gave significant amounts of aryl fluoride. The bromo- and iodo-analogues gave up to 50% of *p*-dibromo- or *p*-di-iodo-benzene, respectively.†



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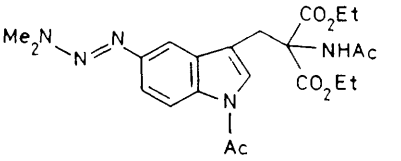

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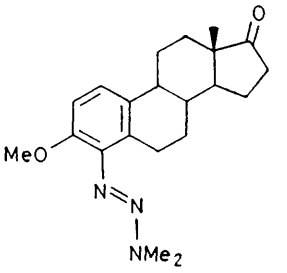

(4)

The aryl residues substituted with strongly electron withdrawing groups were not fluorinated under these mild conditions (*e.g.* run 12) but these are the aryl fluorides which are most readily prepared by conventional nucleophilic substitution.[11]

TABLE. Conversion of aryl triazenes ($ArN{=}NNR_2$)[a] into aryl fluorides

Run	Ar	R_2	Co-solvent	Temp. /°C	Time /h	Yield %
1	Ph	$-[CH_2]_5-$	AcOH	18	0·25	97
2	4-$MeOC_6H_4-$	$-[CH_2]_5-$	AcOH	18	1	75
3	2-$HO_2CC_6H_4-$	Me_2	AcOH	45	0·33	89
4	3-$HO_2CC_6H_4-$	$-[CH_2]_5-$	—	45	1	96
5	4-$HO_2CC_6H_4-$	$-[CH_2]_5-$	—	18	0·5	95
6	4-$EtO_2CC_6H_4-$	Me_2	AcOH–Et_2O	18	0·33	90
7	2,4,6-$Me_3C_6H_2-$	Me_2	—	30	1	97
8	2,4-$Me_2C_6H_3-$	$-[CH_2]_5-$	1,2-Dimethoxyethane	60	2	20
9	2-$MeOC_6H_4-$	$-[CH_2]_5-$	AcOH	18	0·25	0[c]
10	2-$TsOC_6H_4-$[b]	Me_2	—	18	1	79
11	4-ClC_6H_4-	$-[CH_2]_5-$	—	50	1	35
12	4-$O_2NC_6H_4-$	Me_2	—	18	2	0[d]
13	(**2**)	—	AcOH	18	1	76
14	(**3**)	—	AcOH	18	0·5	20[e]
15	(**4**)	—	AcOH	18	0·33	85

[a] All new compounds were fully characterised by micro- and spectral analysis. [b] Ts = $MeC_6H_4SO_2$-*p*. [c] The main product was 2,2′-bianisyl. [d] No reaction. When heated, 4,4′-dinitrodiphenyl was produced. [e] The principal by-product was the corresponding phenol.

† A more detailed explanation of these results will be given in the full paper.

A number of more complex substrates (**2**—**4**) were successfully fluorinated (runs 13—15). Of particular note is the fluorination of the 4-triazenoestrone methyl ether (**4**) (run **15**), despite the adjacent methoxy group. These examples indicate the general applicability of the method and further work is aimed at producing compounds of medicinal interest. Of importance for fluorine-18 labelling is the observation that the fluorination can be run with stoicheiometric quantities of hydrogen fluoride.

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