Heptafluoro-*p*-tolyl and Tetrafluoro-4-pyridyl as Novel and Selective Protecting Groups for Phenolic and Alcoholic Functions: Synthesis and Cleavage of Perfluoroaryl Ethers of Steroids

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The easily prepared heptafluoro-*p*-tolyl and tetrafluoro-4-pyridyl ethers of a variety of steroids react with sodium methoxide in dimethylformamide to regenerate the parent steroid by a mechanism involving an aryl–oxygen cleavage.

Perfluoroarenes react readily with a variety of nucleophiles and thus have potential as reagents for protecting reactive functional groups, but their use for this purpose has been little explored. Hexafluorobenzene has been used to protect carboxy functions as pentafluorophenyl esters during the synthesis of peptides.[1] Pentafluorophenyl ethers of carbohydrates have been described, but attempts to cleave them were unsuccessful.[2] We have investigated the much more reactive[3,4] but also readily available octafluorotoluene and pentafluoropyridine as reagents for protecting alcohols and phenols as perfluoroaryl ethers and have demonstrated their versatility for the selective protection and deprotection of these hydroxy functions. Although the reactions are exemplified using steroids as model compounds, they are clearly more generally applicable.

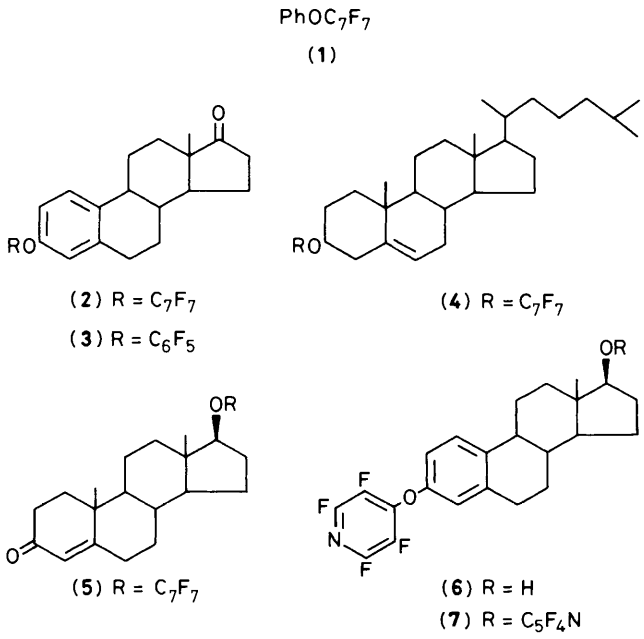
The derivatives† (Table 1) were conveniently formed under phase transfer conditions.[5] The phenolic derivatives [e.g. (**1**), (**2**), (**8**)] formed much more rapidly than did the derivatives of alcohols [*e.g.* (**4**), (**5**)]. Thus, and typically, oestradiol (9.2 mmol) and octafluorotoluene (9.4 mmol) reacted at room temperature in a two-phase system of dichloromethane and 1M-NaOH (30 ml each) containing tetra-n-butylammonium hydrogen sulphate (4.8 mmol) during 1 h to

† Satisfactory analytical data were obtained for all new compounds.

Table 1. Preparation of perfluoroaryl ethers.

Reagents		Reaction time	Product[a] (% yield)	M.p. (*t*/°C)
Octafluorotoluene	Phenol	20 min	(**1**) (96)	42—43[b]
Octafluorotoluene	Oestradiol	1 h	(**8**) (95)	93—94
Octafluorotoluene	Oestrone	1 h	(**2**) (95)	86—87
Octafluorotoluene	Cholesterol	6 days	(**4**) (63)	98—99
Octafluorotoluene	Testosterone	3 days	(**5**) (72)	115—116
Octafluorotoluene	Oestradiol	16 h[c]	(**10**) (76)	73—75
Pentafluoropyridine	Oestradiol	10 min	(**6**) (86)	115—116
Pentafluoropyridine	Oestradiol	1 h	(**7**) (92)	145—147
Hexafluorobenzene	Oestrone	16 h	(**3**) (12)	128—129

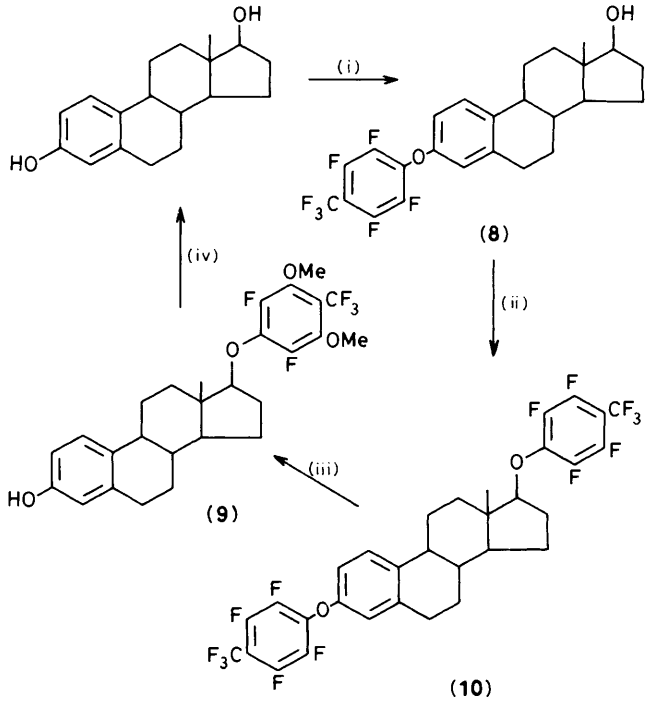
[a] Eluted from silicic acid with dichloromethane or chloroform (mono-derivatives) or with light petroleum (bis-derivatives) and crystallised from light petroleum. [b] Eluted with dichloromethane–light petroleum: lit.,[8] b.p. 90—120 °C at 2 mmHg. [c] 2M-NaOH was used to accelerate this reaction.



afford, after chromatography, a 95% yield of (**8**)‡ with only a trace (2%) of the bis-derivative (**10**) which was abundantly formed (76%) on prolonged reaction with 2.2 mol. equiv. of octafluorotoluene [Scheme 1, reactions (i)—(ii)].

Treatment of the perfluorotolyl ethers with sodium methoxide in dimethylformamide regenerated the phenolic or alcoholic function by a stepwise reaction involving successive displacement of the fluorine atoms adjacent to the CF_3 group followed by nucleophilic displacement of the aryloxy or alkoxy group. In the final step, electron release from the two methoxy groups in the intermediate presumably prevents displacement of the two remaining fluorine atoms and directs displacement

‡ The expected substitution *para* to the CF_3 substituent was established by ^{19}F n.m.r. spectroscopy (*cf.* refs. 6, 7): δ ($CDCl_3$; p.p.m. upfield from $CFCl_3$) for (**8**) 152.5 (2F, A_2X_2, F-2,6), 141.8 (2F, m, F-3,5), and 56.3 (3F, t, *J* 21.5 Hz, CF_3); for (**5**) 155.3 (2F, A_2X_2, F-2,6), 142.4 (2F, m, F-3,5), and 56.2 (3F, t, *J* 21.5 Hz, CF_3).



Scheme 1

of the aryloxy group. The phenolic ethers were cleaved faster than were the aliphatic ethers. Thus treatment of the bis-derivative (**10**) (0.18 mmol) with sodium methoxide (0.3 g) in dimethylformamide (0.5 ml) for 16 h at 60 °C afforded after column chromatography oestradiol in 90% yield, but briefer (1 h) reaction at 10 °C afforded the intermediate (**9**) [m.p. 76—78 °C, 78%] [Scheme 1, (iii)—(iv)]. Hence selective protection either of the phenol or of the alcohol functions, as well as protection of both, is exemplified in the sequence of reactions in Scheme 1. The conditions for removal of the perfluorotolyl group were compatible with an isolated ketone function, since oestrone was obtained from (**2**) in 87% yield, but the testosterone derivative (**5**), an unsaturated ketone, was unstable to the conditions required for deprotection.

The perfluorotolyl group was not cleaved or modified by a variety of acidic and basic reagents used to remove other protecting groups, and was compatible with Grignard reagents [*e.g.* (**1**) was unaffected by MeMgI] and some Lewis acids (*e.g.* $SnCl_4$). Compatibility with oxidising and reducing agents is exemplified by the conversions at 23 °C of (**8**) into (**2**) by pyridinium chlorochromate in dichloromethane (2 h) in 90% yield and of (**2**) into (**8**) in 88% yield by $NaBH_4$ in ethanol (15 min).

Pentafluoropyridine similarly afforded perfluoropyridyl ethers, exemplified by the mono- (**6**) and bis- (**7**) 2,3,5,6-tetrafluoro-4-pyridyl derivatives of oestradiol. The derivatives formed much faster than did the perfluorotolyl ethers but were cleaved at a similar rate. In contrast, perfluorophenyl ethers [*e.g.* the oestrone derivative (**3**)] were formed only slowly using hexafluorobenzene under the phase-transfer conditions described here. They gave only poor yields of the parent steroid on treatment with sodium methoxide and would appear to have little synthetic potential.

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