REVIEW PAPER

PERFLUOROARENES AS NOVEL AND SELECTIVE PROTECTING REAGENTS; APPLICATIONS IN ANTICANCER DRUG DEVELOPMENT

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NEW USES FOR PERFLUOROARENES

This review describes the work published from this laboratory since 1984 on the use of octafluorotoluene as a novel derivatizing reagent for the analysis of steroids by gas chromatography-mass spectrometry, the subsequent development of the perfluorotolyl group as a novel protecting group in synthesis, and preliminary studies of the potential of other perfluoroarenes in this context.

This story begins in 1983 with an analytical problem. We required a method for the analysis, using gas chromatography-mass spectrometry (GCMS), of 4-hydroxyandrostenedione (1), a novel agent recently introduced into the clinic for the treatment of hormone-dependent breast cancer. This required the hydroxyl function to be suitably protected to give a volatile, stable derivative. Conventional protection of this enolic hydroxyl function with groups such as trimethylsilyl and perfluoroacyl gave labile derivatives, and protection as methyl or pentafluorobenzyl esters also failed, in our hands, to give derivatives which satisfied our analytical requirements. Prompted by a speculation [1] that hexafluorobenzene might be a useful reagent for derivatizing hydroxyl functions as pentafluorophenyl ethers, we next considered this and other perfluoroarenes as derivatizing reagents. Phase-transfer catalysis [2] proved a convenient method for forming perfluoroaryl ethers, and was chosen because the desirability that the leaving group should be hard in the HSAB nomenclature [3] to avoid poisoning the catalyst is especially well satisfied when fluoride is the nucleofuge

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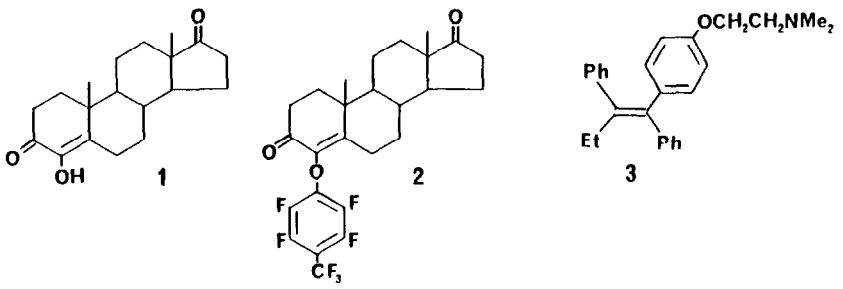
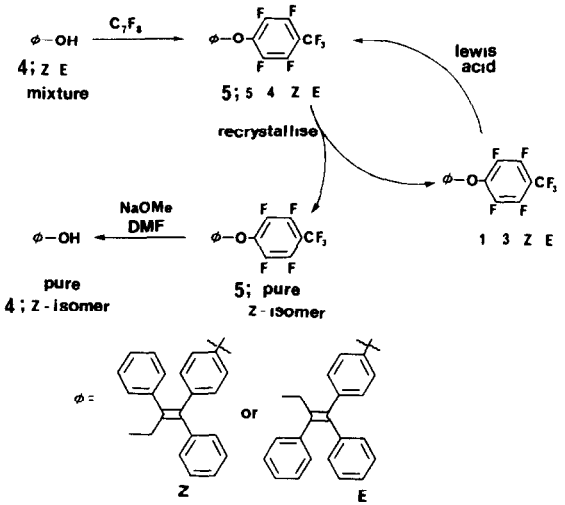
However, after preliminary (unpublished) experiments with hexafluorobenzene, which reacted sluggishly, we soon turned our attention to the more reactive [4] octafluorotoluene. This reacted with 1 to form the 4-O-perfluorotolyl ether (2) in good yield [5]. Moreover, 2 had good GCMS properties and proved a useful derivative for the quantification of the O-glucuronide of (1), the major metabolite in urine of patients given the drug, after its hydrolysis to 1 [6].



At the time we were faced with the foregoing analytical problem, we were also engaged on the synthesis of analogues of the ICI drug Nolvadex (3, tamoxifen, *trans*-(Z)-1-[4-(2-dimethylamino)ethoxy]phenyl-1,2-diphenyl-1-butene), widely used to treat hormone-dependent breast cancer One route [7] proceeds *via* a hydroxylated precursor (4), obtained as a

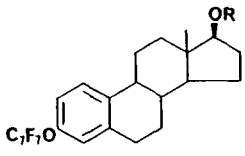


Scheme 1. Route to a precursor of the anti-cancer drug tamoxifen.

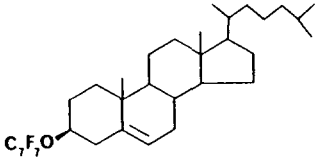
mixture of geometrical isomers. Since only the Z-isomer 3 has the required biological activity it is important to segregate the isomers, preferably at the precursor stage, since then analogues with varying side chains could readily be made. The requirement was for a derivative of 4 which would be formed in high yield, would be easily separable from the unwanted isomer, either by crystallization or by chromatography and from which 4 could be regenerated without isomerism to the unwanted isomer. The perfluorotolyl derivative (5) alone among a large number of derivatives evaluated, satisfied all these conditions, and readily regenerated 4 on treatment with sodium methoxide in dimethylformamide [8] Moreover, the residual mixture of 4 and its isomer, enriched in the latter, could be re-equilibrated using a Lewis acid and more 4 recovered, affording an efficient and high yielding synthesis of tamoxifen having commercial potential [9] (Scheme 1).

Reactions of various hydroxyl functions with octafluorotoluene

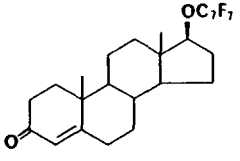
The foregoing successes in finding both an analytical and a synthetic use for octafluorotoluene prompted a wider exploration of its uses in both contexts. The natural steroids provided [5,10] ideal model compounds for such studies (*e.g.* Fig. 1). They contain a variety of hydroxyl functions, the phenolic 3-hydroxyl group in oestrone and oestradiol, the primary 21-hydroxyl in the corticosteroids, various



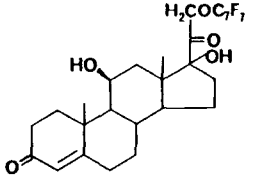
from oestradiol R = H
R = C_7F_7



from cholesterol



from testosterone

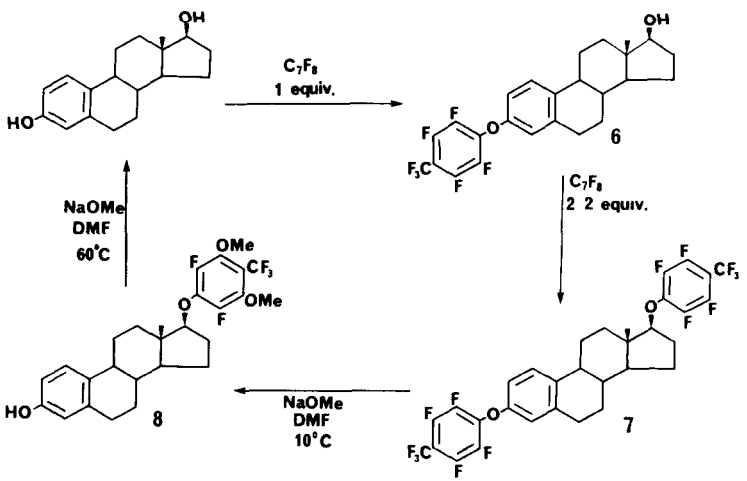


from cortisol

Fig. 1. Perfluorotolyl ethers which are formed from some common steroids by reaction with octafluorotoluene under phase-transfer catalysis.

secondary hydroxyl functions *e g.* 17-hydroxyl in oestradiol and testosterone, 3-hydroxyl in cholesterol and 11-hydroxyl as well as a tertiary, 17-hydroxyl function in cortisol. Only the hindered secondary 11β-hydroxyl and tertiary 17α-hydroxyl functions in cortisol failed to react.

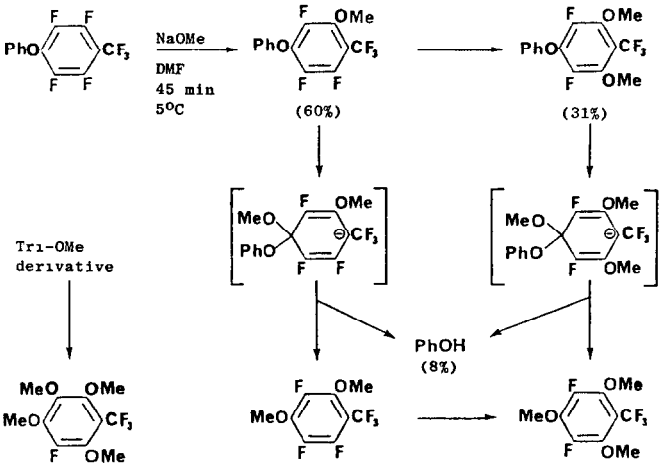
Our studies [5, 10] with oestradiol exemplify selective protection of either an aromatic or an aliphatic hydroxyl function in the presence of the other Thus brief (1 h) reaction with 1.1 mol equiv of octafluorotoluene under phase transfer conditions afforded the 3-O-perfluorotolyl ether (**6**) in 95% yield (Scheme 2) with 2 2 mol equiv., with a longer (16 h) reaction time the 17-hydroxyl function also reacts to give the *bis*-O-perfluorotolyl ether (**7**) in 76% yield. Treatment of **7** with sodium methoxide in dimethylformamide at 10°C regenerated the 3-hydroxyl function, and gave the 17-O-protected derivative (**8**), whereas further reaction at 60°C regenerated oestradiol.



Scheme 2 Selective protection and deprotection of oestradiol using octafluorotoluene.

It will be noted that the initial product from **7** is not the 17-O-perfluorotolyl ether but a *bis*-methoxy derivative, in which the fluoro-substituents flanking the trifluoromethyl group, and therefore activated to S_NAr substitution, are also displaced. This observation prompted an investigation [5] of the mechanism of removal of the perfluoroaryl substituent using the phenyl ether (**9**, Scheme 3) as a model compound

Brief treatment below ambient temperature afforded a monomethoxy-derivative as the principal product, together with the *bis*-derivative Either of these derivatives could be degraded to phenol via an S_NAr displacement *para* to the CF_3 substituent, as evidenced by the additional identification of both 3,5,6-trifluoro-2,4-dimethoxy-1-trifluoromethyl - benzene and 3,5-difluoro-2,4,6-trimethoxy-1-trifluoromethylbenzene by GCMS



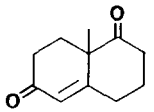
Scheme 3. Routes for the regeneration of phenol from its perfluorotolyl ether.

Further studies on model compounds defined the scope and limitations of octafluorotoluene in protecting aliphatic hydroxyl functions [5]. Thus 3-phenylpropanol and 1-phenylethanol were readily regenerated by sodium methoxide from their perfluorotolyl ethers, but the 2-phenylethyl ether gave mainly styrene, β-elimination being preferred in this case. The compatibility of perfluorotolyl with oxidizing and reducing agents was exemplified by the oxidation of the 17-hydroxyl function in **6** to give the oestrone derivative using pyridinium chlorochromate and the reverse reaction using sodium borohydride.

Reaction of keto functions with octafluorotoluene

The failure of keto functions to react with octafluorotoluene under phase-transfer conditions prompted us to explore alternative conditions

which might promote their reaction and expand the scope of perfluorotolyl as a protecting group. Whilst a variety of strong bases can generate enolate ions from ketones, potential reactivity towards perfluoroarenes narrows the choice. Fluoride in a dipolar aprotic solvent was deemed the ideal base since octafluorotoluene remains unaltered by it. The Wieland-Miescher ketone (10), chosen as a model compound, reacted at ambient temperature at either keto function, depending on the choice of base (caesium fluoride in dimethylformamide or tetra-n-butylammonium fluoride in tetrahydrofuran) [11]. However, it appeared that these functions were mutually activating, since the steroidal ketones androstenedione and testosterone required elevated temperatures to generate perfluorotolyl enol ethers 11 (Scheme 4) and 12 using caesium fluoride and the 17-keto function in androstenedione did not react. That the failure of the 17-keto function in testosterone to react was due to steric hindrance by the 18-methyl substituent, and was not an intrinsic property of unactivated saturated keto functions was shown [11] by derivatizing the 3-keto function in the ring A-saturated steroid 5α-dihydrotestosterone to give the derivative 13. The direction of enolization, contrary to that in androstenedione, was again established by ^1H n.m.r. spectroscopy. The absence of C-perfluoroaryl derivatives from the products of all the foregoing reactions shows that perfluorotolyl is acting as a hard electrophile.



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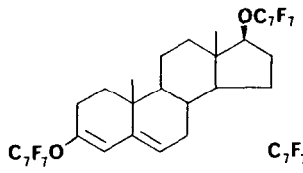

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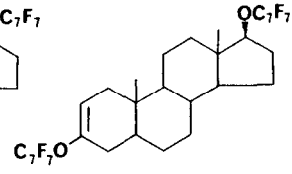
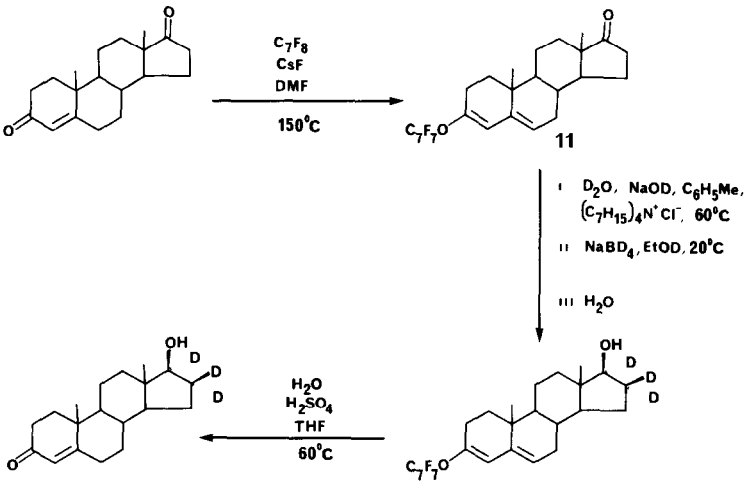


13

Derivatives 11 - 13 are enol ethers, and as such proved labile to acid hydrolysis which regenerated the parent steroids. The ether 13, but not 11 or 12, could be similarly degraded by sodium methoxide in dimethyl formamide. Thus certain keto-functions can be successfully protected with octafluorotoluene as exemplified in a synthesis [11, 12] of a trideuterated analogue of testosterone (Scheme 4), needed for an assay of this steroid in human plasma using GCMS. A base-catalysed exchange introduced deuterium at C-16 into 11 and subsequent reduction with sodium borodeuteride introduced a third deuterium atom. The perfluorotolyl group protected the base-sensitive enone function during the exchange reaction and prevented its reduction by borodeuteride.



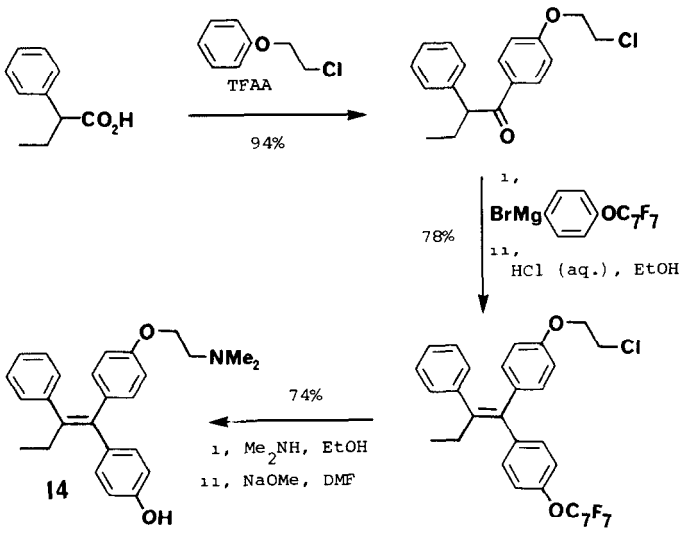
Scheme 4 Synthesis of a deuterated analogue of testosterone.

Applications of the perfluorotolyl group in the synthesis of analogues of tamoxifen. compatibility with other reagents

Compatibility with a wide variety of reagents is an essential feature of a protecting group if it is to be versatile. The resistance of perfluorotolyl to certain oxidizing and reducing agents, and to Lewis acids has already been exemplified The following applications in the synthesis of analogues of tamoxifen provide further examples of reaction conditions resisted by the perfluorotolyl substituent.

The McMurry reaction, in which two ketone molecules react in the presence of an appropriate titanium derivative is a rapid and convenient method of forming olefinic linkages, particularly where cross-coupling, i.e the reaction of two different ketones can be achieved. Thus the zinc and titanium tetrachloride promoted condensation of 4-hydroxypropiophenone with 4-perfluorotolyl phenyl ketone provided [13] a more rapid route to the tamoxifen precursor **5** than that previously described [8].

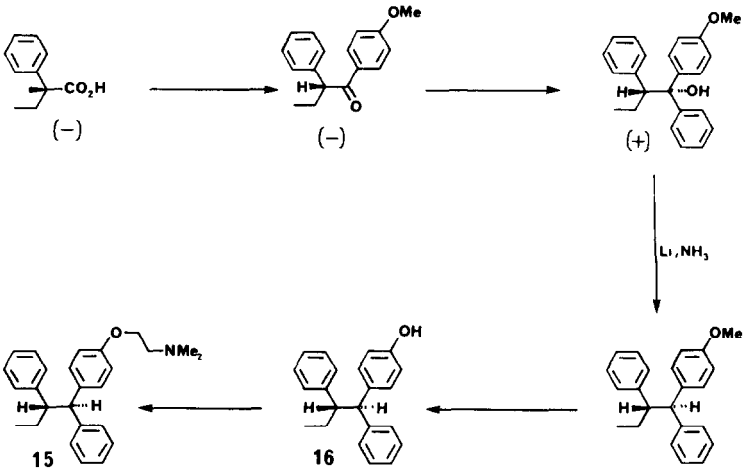
The 4-hydroxy-derivative (14) of tamoxifen is a highly biologically active metabolite and again only the corresponding geometrical isomer has



Scheme 5. Synthesis of 4-hydroxytamoxifen.

the required activity. A synthesis [14] (Scheme 5) illustrates the stability of the perfluorotolyl group to a Grignard reaction elsewhere in the molecule and again illustrates easy separation of geometrical isomers of perfluorotolyl derivatives.

Although the required isomer 14 is thereby obtained pure, under physiological conditions it isomerises to give an equilibrium mixture with the unwanted isomer. This problem has been overcome by preparing an



Scheme 6. Synthesis of dihydrotamoxifen.

analogue (15, Scheme 6) in which the olefinic bond system is saturated [15]. The resulting introduction of chirality gives further opportunities for studying the stereochemistry of the interaction between inhibitors of oestrogen-receptor binding and the receptor macromolecule The synthesis started from one enantiomer of 2-phenylbutanoic acid and introduced the second chiral centre with high diastereoselectivity

The perfluorotolyl group had two functions in this synthesis. First, conversion of the phenol (16) into its perfluorotolyl ether removed the minor proportion of the diastereoisomer since diastereoisomers of the ether, unlike those of 16 were separable by column chromatography Second, after reaction of the perfluorotolyl ether with (+)-1-phenylethanol, its enantiomeric purity could be established by comparing (Fig. 2) the ^1H n.m r. spectrum of the product with that obtained from a racemate.

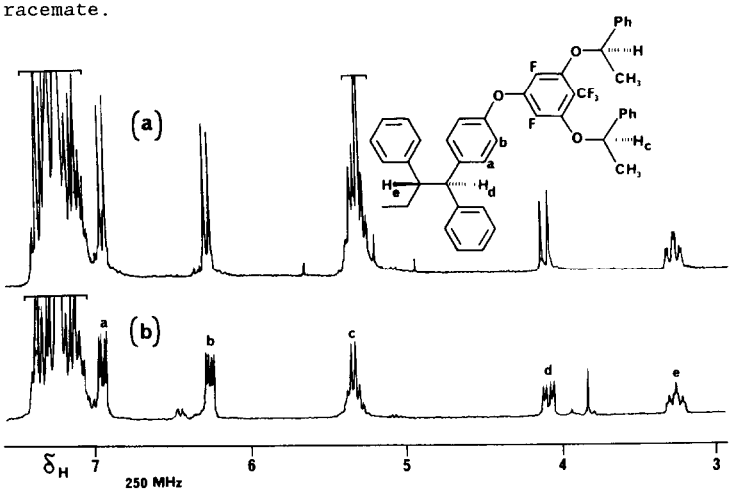


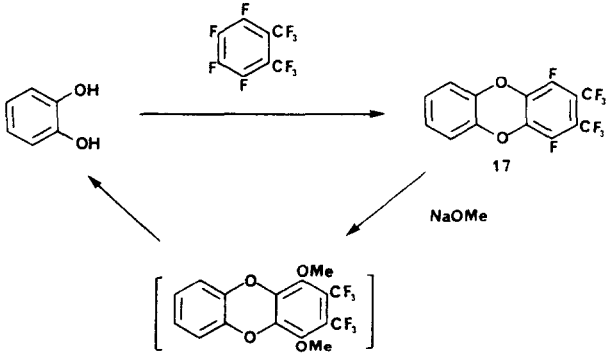
Fig 2. Part of the proton NMR spectrum of the product obtained by reaction of one diastereoisomer of the perfluorotolyl ether of the dihydrotamoxifen precursor **16** (Scheme 6) with (+)-1-phenylethanol (a) compared with the spectrum of the product obtained from racemic **16** (b).

Other perfluoroarenes as protective reagents

Pentafluoropyridine is the most studied reagent in this context It proved more reactive than octafluorotoluene towards both aromatic and aliphatic hydroxyl functions in steroids [5, 10] The 3-O-perfluoro-4-pyridyl derivative of oestradiol was obtained in 86% isolated

yield after only 10 min reaction at room temperature under phase-transfer catalysis and sequential further additions of the reagent gave a 92% yield of the 3,17-bis-O-perfluoropyridyl derivative in only 1 h The reagent therefore offers potential advantages over octafluorotoluene where molecules contain other functional groups which are partly labile under the conditions of derivatization. Removal of the tetrafluoro-4-pyridyl groups follows the same course as the removal of perfluorotolyl and a dimethoxylated intermediate can likewise be isolated Pentafluoropyridyl ethers analogous to the tamoxifen precursor 5 were also readily separable by chromatography or crystallization but here it was the E-isomer which was less soluble and crystallized preferentially. Other perfluoroarenes proved inapplicable in this synthetic approach, either because they formed derivatives too slowly and these were insufficiently labile (hexafluorobenzene, chloropentafluorobenzene) or because the geometrical isomers of the derivatives were not separable (cyanopentafluorobenzene, nitropentafluorobenzene) [8]. This last fact throws light on the essential properties of the perfluorotolyl and perfluoropyridyl group which makes their derivatives chromatographically separable, namely the combination of electron-withdrawing properties, masking polar functions and allowing the subtler differences in physicochemical properties produced by such factors as differing stereochemistry to emerge, whilst at the same time their lipophilicity introduces no new polar function into the molecule

Perfluoro-o-xylene has potential as a novel protecting reagent for catechol and other suitably orientated vicinal diol functions [5] Thus

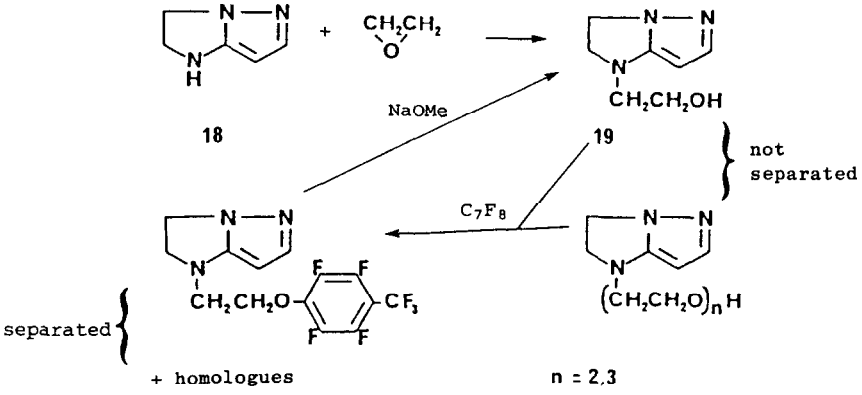


Scheme 7. Protection and deprotection of catechol using perfluoro-o-xylene

in reacting with catechol under phase-transfer catalysis (Scheme 7) displacement of fluorine *para* to one of the trifluoromethyl substituents leaves another which is activated and a second displacement gives mainly the substituted dioxin (17). Regeneration of catechol occurs readily by successive displacements of the remaining fluorine substituents by methoxide followed by cleavage of two aryl-oxygen linkages. Because only one fluorine substituent (that para to CF_3) is significantly activated in octafluorotoluene, the yield of the corresponding cyclic derivative from catechol is low and its reaction with methoxide ion does not regenerate catechol. However, a moderate yield of the *bis*-perfluorotolyl ether can be obtained, so that catechols could be protected in the conventional manner using octafluorotoluene.

Future Prospects

The studies reported here, though limited in the types of compound studied, point to a wider potential application of the perfluoroarenes in general, and of octafluorotoluene in particular, in synthesis.



Scheme 8. Synthesis of a N-hydroxyethyl derivative of the antitumour drug IMPY

Compatibility of the perfluoroaryl group with a wide variety of reagents, the selective reactivity of perfluoroarenes with different types of hydroxyl and keto-functions, and the striking ability of the less polar

perfluoroarenes to give derivatives of closely related compounds which are readily separable are features highlighted in this review. This last-mentioned property has been further exploited in this laboratory [16] in the synthesis (Scheme 8) of a derivative of the anti-cancer agent IMPY (18; 2,3-dihydro-1-H-imidazo[1,2-b]pyrazole), namely the 2-hydroxyethyl derivative (19) Reaction of IMPY with ethylene oxide formed an inseparable mixture of **19** with the products of its further reaction with this reagent. However, the perfluorotolyl ethers proved readily separable by chromatography, and **19** was readily regenerated in the usual manner.

The rather harsh conditions presently used to cleave perfluoroaryl derivatives of alcohols and phenols might discourage their wider application in synthesis and this aspect requires further study. Also some perfluoroarenes which might have useful specialist applications, e g perfluoro-o-xylene, are not commercially available. Here there is potential for collaboration between chemists interested in the application in synthesis of perfluoroarenes and those who have the specialised knowledge and technology required to produce them.

Finally, octafluorotoluene has potential in the analysis of steroids using GCMS or gas chromatography with an electron-capture detector since the steroid perfluoroaryl derivatives have excellent chromatographic properties and give abundant molecular ions (aryl or enol ethers) or characteristic fragment ions (aliphatic derivatives) A preliminary report of the derivatization of the common natural steroids and a procedure for derivatizing keto steroids extracted from human plasma has appeared [18].

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