Introduction of Perfluoroalkyl Substituents into Heteroarenes *via* Nucleophilic Substitution of Hydrogen

Mieczysław Mąkosza and Rafał Loska

Institute of Organic Chemistry, Polish Academy of Sciences,
Kasprzaka 44/52, 01-224 Warsaw 42, Poland

Reprint requests to Prof. Dr. Mieczysław Mąkosza. Fax: (+48) 226326681.
E-mail: icho-s@icho.edu.pl

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Dedicated to Professor Klaus Hafner on the occasion of his 80th birthday

A summary of research in the area of fluoroalkylation of electron-deficient aromatic compounds is presented. The reaction of dinitro- and cyanonitroarenes with trifluoromethyl-trimethylsilane (Me_3SiCF_3) and tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF) and subsequently with DMD provides trifluoromethylated cyano- and nitrophenols *via* oxidative nucleophilic substitution of hydrogen. Addition of fluorinated carbanions, generated either by addition of F^- anions to hexafluoropropene or by activation of Me_3SiCF_3, to *N*-alkylazinium salts leads to dihydropyridines, dihydroquinolines *etc.*, oxidation of which affords the respective fluoroalkylated heterocycles.

1,3-Dipolar cycloaddition of azine *N*-oxides to hexafluoropropene gives 2-heteroaryl-2,3,3,3-tetrafluoropropionic acid fluorides, which react with various protic nucleophiles to give esters and amides of 2-heteroarylperfluoropropionic acids, whereas reaction with water and decarboxylation of the free acids gives azines with a 1,2,2,2-tetrafluoroethyl group at C-2.

Key words: Nucleophilic Substitution, Azinium Salts, Fluoroalkylation, Oxidation, Reaction Mechanisms

Nucleophilic substitution of hydrogen is presently a well developed way to introduce substituents into electron-deficient arenes [1, 2]. The key common step of many variants of this process is the addition of nucleophilic agents to the electron-deficient aromatic ring in a position occupied with hydrogen to form intermediate σ^H adducts. Further conversion of the σ^H adducts can proceed in many ways [3], of which the most important are: (i) oxidation with an external oxidant – so the overall process is oxidative nucleophilic substitution of hydrogen (ONSH) [4] and (ii) base-induced β-elimination of HX when the nucleophile contains a leaving group X at the nucleophilic center, known as vicarious nucleophilic substitution (VNS; Scheme 1) [5]. Typical examples of such processes are the reaction of the carbanion of 2-phenylpropionitrile with nitrobenzene followed by oxidation of the formed σ^H adducts with potassium permanganate [6], and the reaction of chloromethyl phenyl sulfone with nitroarenes [7]. Being involved for many years in studies of these reactions we have attempted to use the concept of nucleophilic substitution of hydrogen for the introduction of perfluorinated substituents into electron-deficient aromatic rings.

Aromatic compounds that contain fluorinated substituents at the ring found numerous applications as novel pharmaceuticals, crop protection agents and liquid crystalline compounds [8, 9]. They owe their unique properties to the special character of perfluoroalkyl groups – low polarizability, high lipophilicity and electronegativity. From the viewpoint of medicinal chemistry, it is also the similar "physiological" size of fluorine and hydrogen [10] and the much greater C–F bond energy as compared to C–H that make partial fluorination an attractive way of modifying the structure of biologically active compounds in search for new pharmaceuticals exhibiting increased activity and metabolic stability. Considering that many fluorinated reagents are still relatively expensive, synthetic methods that allow to introduce a fluoroalkyl group into the functionalized molecule at a possibly late stage of synthesis of the target compound would be particularly valuable [9]. This prompted us to investigate the possibility of performing oxidative or vicarious nucleophilic substitution of hydrogen with fluorine-

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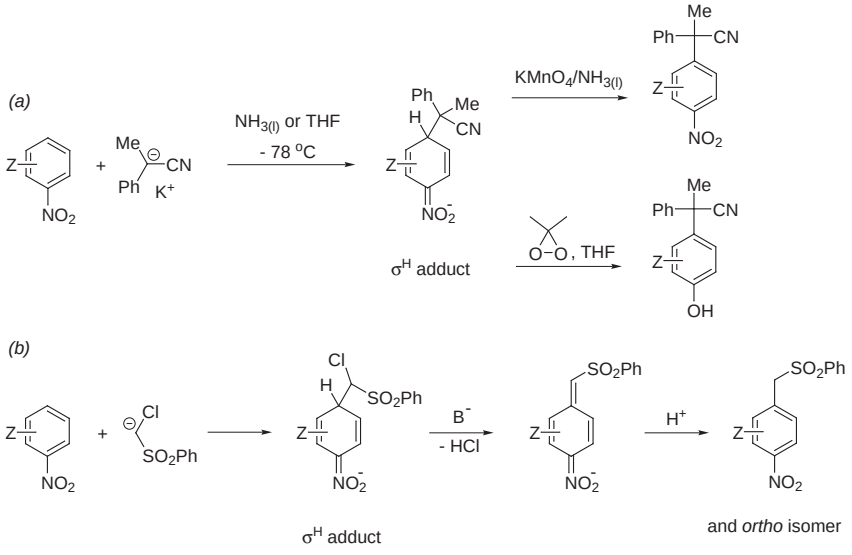
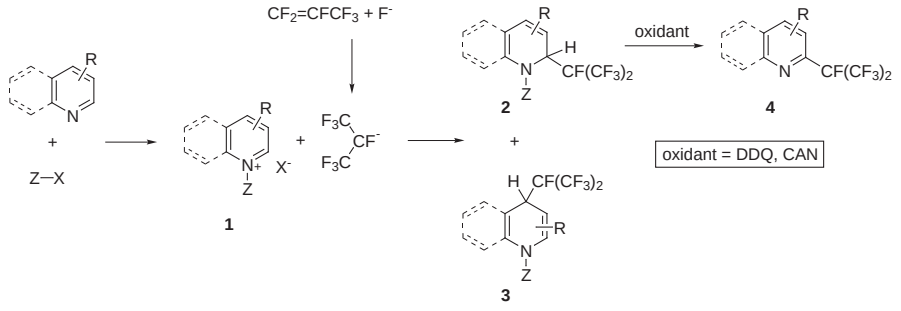


Scheme 1. Examples of oxidative (a) and vicarious (b) nucleophilic substitution of hydrogen in electrophilic arenes.

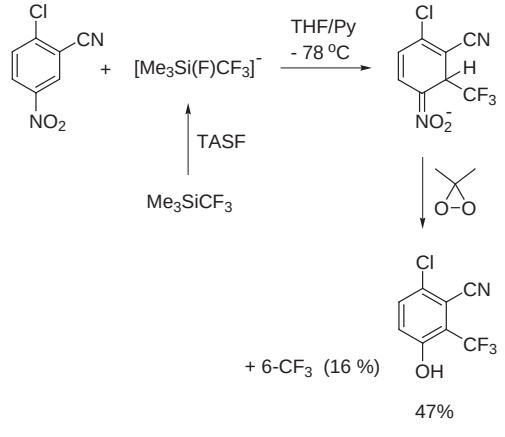
stabilized carbanions, with the aim of developing new reactions that introduce fluorinated substituents into electrophilic aromatic rings selectively and under mild conditions.

Before we began our research in this area only few examples of nucleophilic substitution of hydrogen or even halogens or other leaving groups in aromatic rings (*via* S_NAr mechanism) by fluorinated carbanions were known, and they were of limited practical value. Attempts to replace halogens or a nitro group in halodinitrobenzenes or halocyanonitrobenzenes with CF_3^-, generated from the Ruppert reagent (Me_3SiCF_3) without a metal catalyst, gave mixtures of the expected trifluoromethylnitroarenes only in low yields [11]. Oxidative nucleophilic replacement of hydrogen in trinitrobenzene by the trifluoromethyl carbanion was reported by Stahly [12]. Uno, Suzuki and co-workers described the addition of *n*-perfluoroalkyl lithium reagents to BF_3-complexed azaarenes leading to 1,2-dihydro-2-*n*-perfluoroalkylquinolines and diazines (but to pyridines only in very low yields), followed by spontaneous air oxidation to the corresponding perfluoroalkyl-containing heteroaromatic derivatives [13]. Chambers and co-workers described the nucleophilic perfluoroalkylation of heteroaromatic compounds *via* S_NAr substitution of fluorine in perfluorinated aromatics (mainly pyridines) in the reactions with carbanions formed by addition of fluoride anions to fluoroalkenes [14].

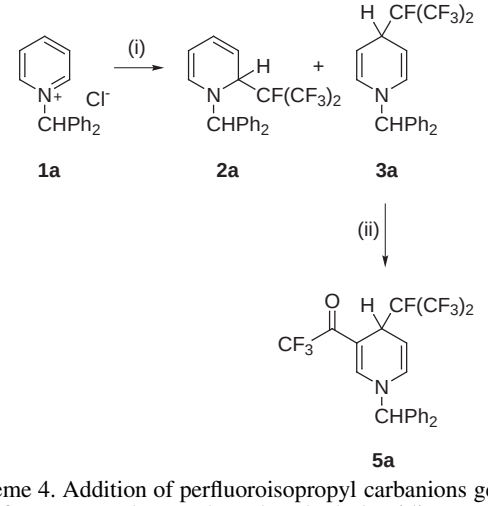
The simplest case seemed to be a reaction of nitroarenes with trifluoromethyl carbanions generated from the Ruppert compound, Me_3SiCF_3, which is a well known nucleophilic trifluoromethylation reagent [15]. One could expect that σ^H adducts of this carbanion to nitroarenes would undergo base induced β-elimination of HF, similarly to the reaction of trichloromethyl carbanions investigated by us previously [16]. Unfortunately, treatment of nitrobenzene and chloronitrobenzenes with the Ruppert reagent and *t*-BuOK resulted in recovery of the arenes whereas difluoromethylated nitroarenes were not detected in the reaction mixtures. Also attempts to afford oxidative substitution of hydrogen by the CF_3^- anion initially gave negative results. Treatment of the Ruppert reagent with tris(dimethylamino)sulfonium difluorotrimethylsilicate ($[(Me_2N)_3S]^+[Me_3SiF_2]^-$, TASF) in the presence of mononitroarenes followed by oxidation failed to produce trifluoromethylated nitroarenes. Perhaps due to the low nucleophilicity of a CF_3 group bound to the hypervalent silicon center, its addition to these nitroarenes proceeded only to a negligible degree. On the other hand, addition of this nucleophile to highly electron-deficient *m*-dinitro- and *m*-cyanonitrobenzenes did proceed, but the expected trifluoromethylated products were not formed, apparently due to the inefficient oxidation of the intermediate σ^H adducts with potassium permanganate or dichlorodicyanobenzoquinone (DDQ). These adducts could be efficiently oxidized with dimethyl dioxirane (DMD) giving trifluoromethylated nitro- and cyanophenols in which one of the nitro groups present in the substrate was replaced by a hydroxy group (Scheme 2) [17]. We have



Scheme 3. The concept of oxidative nucleophilic substitution of hydrogen in *N*-alkylazinium salts by perfluoroisopropyl carbanions, generated *in situ* from HFP and $KF_{(s)}$; Z–X = alkylating or acylating reagent.



Scheme 2. Oxidative substitution of hydrogen in 4-chloro-3-cyanonitrobenzene with the CF_3^- carbanion generated from Me_3SiCF_3.

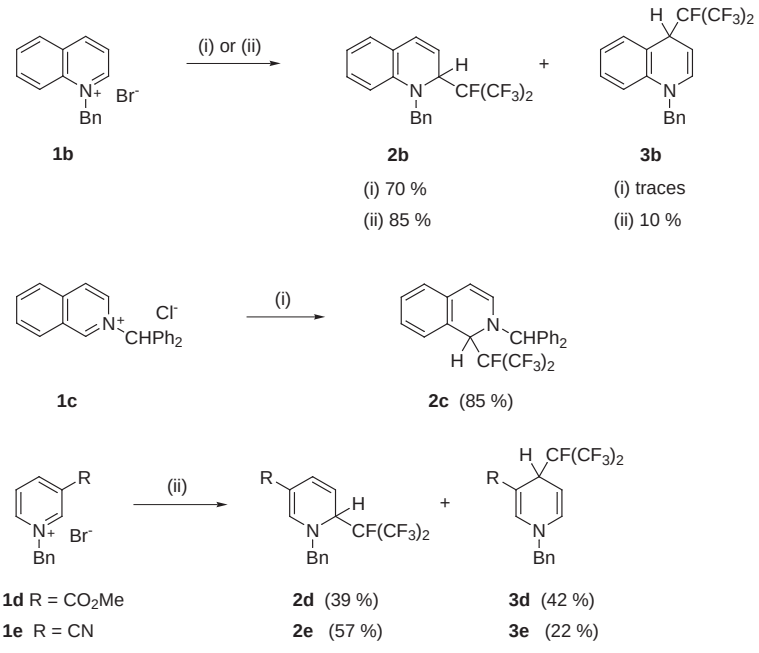


Scheme 4. Addition of perfluoroisopropyl carbanions generated from HFP and F^- to the *N*-benzhydrylpyridinum salt **1a** and subsequent trifluoroacetylation of the 1,4-dihydropyridine derivative **3a**; (i) 5.0 equiv. $KF_{(s)}$, ~ 4 equiv. HFP, r. t., CH_2Cl_2, 24 h; (ii) TFAA, *i*-Pr_2NEt, 0 °C, 30 min.

reported earlier that in ONSH reactions DMD acted *via* oxidation of the negatively charged nitro group rather than the sp^3 carbon center in the ring of the anionic σ^H adduct [18].

The possibility to afford oxidative substitution of hydrogen by perfluoroisopropyl carbanions generated *via* addition of fluoride anions to inexpensive hexafluoropropene (HFP) was of great interest, particularly if solid potassium fluoride could serve as the source of F^- anions in the reaction mixture. A precedent for this assumption was already provided by the research of Chambers and co-workers [14] and also by others in the case of electrophiles other than arenes [19]. Unfortunately, many attempts to react mono- and dinitroarenes with HFP in the presence of powdered, "spray-dried" KF and subsequent oxidation gave negative results. It seems that in this case the addition to nitroarenes does not proceed due to the low nucleophilicity of perfluoroisopropyl carbanions and their bulkiness. We therefore turned our attention to the reaction of these carbanions with azinium salts that exhibit much higher electrophilicity than nitroarenes. Moreover, in this case the products of the carbanion addition would be neutral dihydroazines. Their formation would provide us a proof that at least the first step of the nucleophilic substitution of hydrogen, that is the addition of $[CF(CF_3)_2]^-$ carbanions, formed in the two- or even three-phase reaction mixture (solid KF and one or two liquid phases), is a feasible process. Further oxidation of these dihydroazines should then produce the desired substituted azines (Scheme 3).

Attempts of such reactions with *N*-acylpyridinium salts were unsuccessful – only acyl fluorides, perfluoroisopropyl ketones and unreacted pyridines were recovered. Positive results could be obtained with the much more stable *N*-alkylazinium salts **1**. Indeed, when a suspension of *N*-benzhydrylpyridinium chloride and $KF_{(s)}$ in CH_2Cl_2 was treated with HFP, smooth formation of a mixture of *N*-benzhydryl 2- and

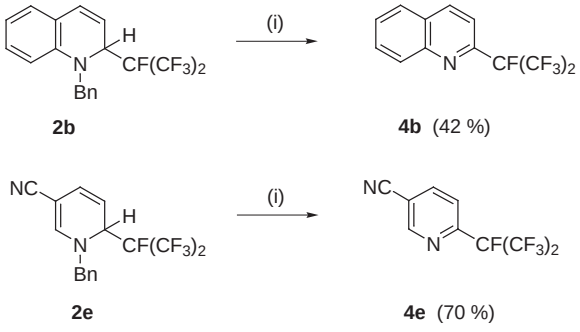


Scheme 5. Reactions of *N*-benzhydryl- and *N*-benzylazinium salts with perfluoroisopropyl carbanions; (i) HFP, $KF_{(s)}$, CH_2Cl_2, r. t., 24 h; (ii) HFP, $KF_{(s)}$, DMF, r. t., 2 h.

4-perfluoroisopropyl 1,2- and 1,4- dihydropyridines (**2a** and **3a**) took place (Scheme 4) [20]. These compounds were of moderate stability, nevertheless they could be isolated, analyzed and identified. Since it is known that dihydropyridines containing electron withdrawing substituents in the position 3- and/or 5- of the ring are reasonably stable compounds [21], in another experiment we acylated a crude mixture of **2a** and **3a** with trifluoroacetic anhydride (TFAA) directly after the reaction with HFP and KF which allowed us to obtain **5a** in good yield as a stable and easy to handle substance. Neither the other isomer, **2a**, nor its acylation products could be detected in this case.

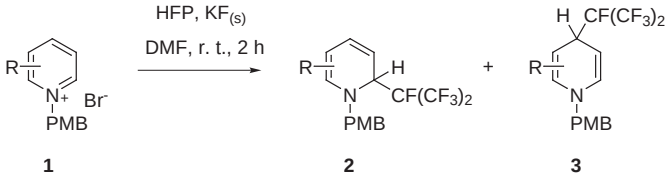
We then performed the addition of *in situ* generated perfluoroisopropyl carbanions to a series of substituted *N*-benzylpyridinium, quinolinium and isoquinolinium salts and obtained the expected dihydroazines containing a perfluoroisopropyl group at the sp^3 ring carbon atom usually in very good yields (Scheme 5). As expected, the yields and stability of the products obtained from the pyridine series were particularly high when electron withdrawing substituents were already present in the ring, especially in the 3 position. The stability of these products is also increased by the bulky and electron-withdrawing perfluoroisopropyl substituent.

The next goal of our research was to achieve removal of the *N*-alkyl group combined with rearomatization of the azine ring (see Scheme 3). It is well

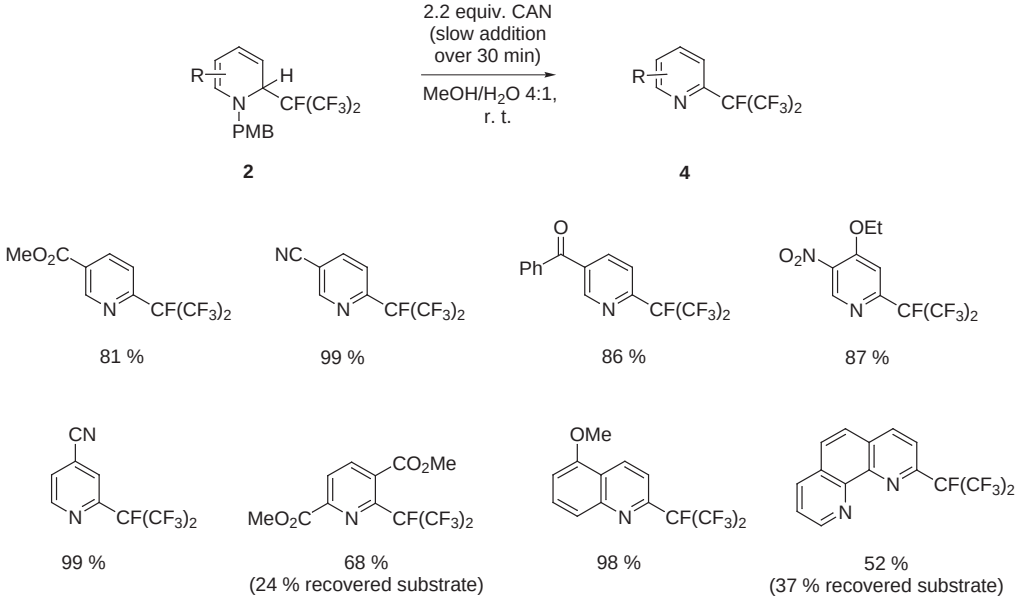


Scheme 6. Preliminary experiments of oxidative deprotection/aromatization of *N*-benzyl-1,2-dihydroazines in the presence of DDQ; (i) 4.0 equiv. DDQ, CH_2Cl_2, 0 °C to r. t., 24 h.

known that *N*-alkylated dihydroazines undergo oxidation to give the corresponding *N*-alkyl-substituted azinium salts [21]. On the other hand, oxidants like DDQ or cerium(IV) ammonium nitrate (CAN) are commonly applied for debenzylation of benzylic ethers and amines [22]. However, prior to our work there were no reports of oxidation of *N*-alkyl-dihydroazines with concomitant oxidative C–N bond cleavage. We were therefore pleased to observe that already in the first experiment dihydroquinoline **2b** upon treatment with DDQ underwent a clean transformation into the respective 2-perfluoroisopropyl derivative **4b** (Scheme 6). The success of this reaction was



Scheme 7. Reactions of *N*-*p*-methoxybenzylazinium bromides with $[CF(CF_3)_2]^-$ carbanions.

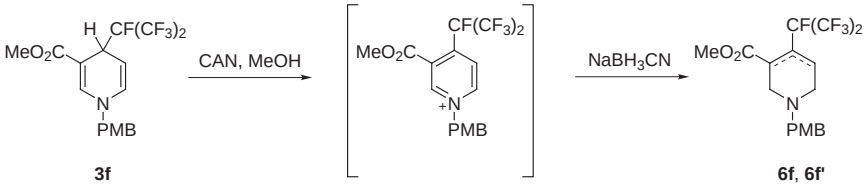


Scheme 8. Preparation of perfluoroisopropyl-substituted azines *via* CAN oxidation of 1,2-dihydroazines.

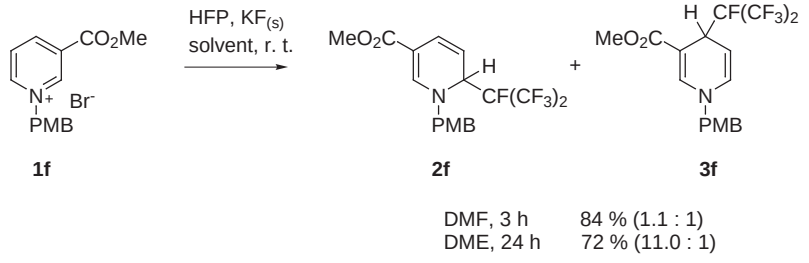
surprising in the view of the only relevant precedence we could find in the literature: according to Lau and co-workers an attempt to oxidize 1-*p*-methoxybenzyl-2-phenyl-1,2-dihydroquinoline with DDQ failed; they observed no reaction even after 24 h under forcing conditions [23]. In the case of our perfluoroalkyl-substituted dihydroazines the reaction proved to be general for the 1,2-dihydro isomers: on treatment with DDQ or preferentially with CAN we observed that the expected perfluoroalkylated aromatic azines are produced, albeit the reaction was rather slow and yields of the desired products moderate.

Taking into account that oxidative cleavage of a C–N bond should proceed faster when the *N*-benzyl group contains electron donating substituents [22c], we then prepared a series of *N*-(*p*-methoxybenzyl)-azinium salts that reacted with perfluoroisopropyl carbanions and formed perfluoroalkylated dihydroazines when exposed to HFP and KF (Scheme 7). These dihydroazines when treated with CAN in aqueous methanol underwent rapid and often nearly quantitative oxidation to perfluoroalkylated aromatic azines (Scheme 8) [20].

It should be noted that only 2-perfluoroalkylated azines can be prepared *via* oxidation of 1,2-dihydroazines. Unfortunately, 1,4-dihydro isomers **3** failed to undergo a similar reaction although they were totally consumed in the presence of DDQ or CAN. In this case the final products were probably perfluoroalkylated azinium salts rather than products of decomposition. This view was supported by an experiment in which dihydroazine **3f** was successively treated with



Scheme 9. Oxidation of the *N*-*p*-methoxybenzyl-1,4-dihydropyridine derivative to a fluoroalkylated pyridinium salt and its reduction to two isomers of a tetrahydropyridine.



Scheme 10. Regioselectivity of the reaction of the 3-methoxycarbonylpyridinium salt **1f** with $[CF(CF_3)_2]^-$ perfluorocarbanions in solvents of different polarity.

CAN and $NaBH_3CN$. After aqueous workup the two isomeric tetrahydropyridines **6f**, **6f'** were obtained in good yield (Scheme 9). The reason for the different outcome of the reactions of 1,2- and 1,4-dihydroazines with oxidants is probably due to their different oxidation rates [24]. In the case of *N*-(*p*-methoxybenzyl)-1,2-dihydroazines, oxidative C–N bond breaking proceeds faster than oxidative aromatization of the starting dihydroazine. *N*-Unsubstituted 1,2-dihydroazines are subsequently oxidatively aromatized to aromatic azines. On the other hand, the 1,4-dihydro isomers undergo oxidative aromatization faster than debenzylation, and the produced perfluoroalkylated azinium salts are resistant towards oxidative debenzylation.

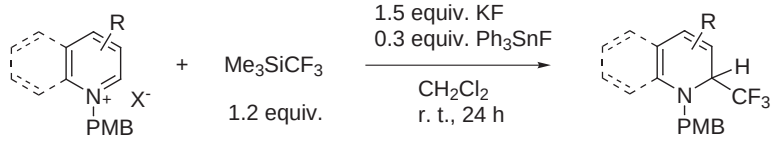
Dihydropyridines bearing an *N*-benzhydryl substituent were inert towards DDQ and CAN oxidation.

In general we observed that in the addition of perfluoroisopropyl carbanions to azinium salts the 1,2-dihydroazines are formed preferentially to 1,4-isomers, which indicates that the $[CF(CF_3)_2]^-$ carbanion belongs to the group of hard nucleophiles like trifluoromethyl [17] or difluoro(phenylsulfonyl)methyl carbanions [25]. Despite a significant stabilizing effect of the two CF_3 groups the addition is irreversible, as we have not observed any interconversion between 1,2- and 1,4-dihydropyridines even after several months of storage. Only in the case of pyridinium salts with no substituents or Cl or Me groups in the ring we observed highly regioselective formation of the 1,4-dihydro-4-perfluoroisopropylpyridines. In the first case, high regioselectivity may arise from the sterical bulkiness of the benzhydryl group at the nitrogen atom.

The regioselectivity of the addition to the 2-/6- *vs.* 4-position of the pyridinium ring is affected by the polarity of the reaction medium. From the synthetic point of view it was interesting to find that using 1,2-dimethoxyethane (DME), a solvent of moderate polarity and capable of dissolving some amount of potassium fluoride, allowed to obtain **2f** both in good yield and with much higher regioselectivity then in DMF or MeCN (Scheme 10).

Concluding this part of our work, we have established that a three step operation – formation of azinium salts, addition of perfluoroisopropyl carbanions generated *in situ via* addition of F^- anions to HFP and oxidation of the dihydroazines with CAN in aqueous methanol – is an efficient protocol for the introduction of the perfluoroisopropyl group into aromatic azines. The first two reactions can be performed as a one-pot operation. The whole process can be considered as an example of nucleophilic substitution of hydrogen in the heteroaromatic ring with a fluorinated carboanion.

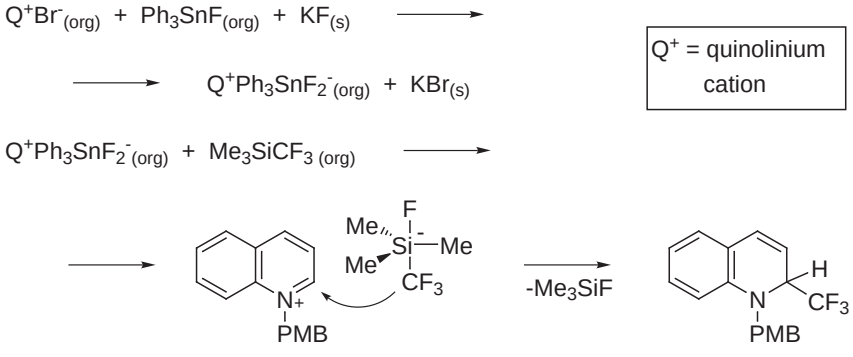
We then turned our attention to the problem of introducing a trifluoromethyl group into the heterocyclic ring [26]. This synthetic goal can be achieved *via* radical [27] or electrophilic trifluoromethylation [28], but probably the most synthetically useful of the existing methods is the reaction of aryl bromides or iodides with (trifluoromethyl)copper reagents [8, 29]. However, this process requires the preparation of the appropriate halogenated substrates; oxidative nucleophilic substitution of hydrogen by a CF_3^- carbanion could thus provide a valuable alternative.



1 **7** (41 - 88 %)

R = 3-Me, 3-CO_2Me, 3-CN, 3-COPh, quinoline, 5-methoxyquinoline, isoquinoline, phenanthroline

Scheme 11. Trifluoromethylation of azinium salts with Me_3SiCF_3.



Scheme 12. Operation of Ph_3SnF as phase-transfer co-catalyst for the addition of CF_3^- carbanions to azinium salts.

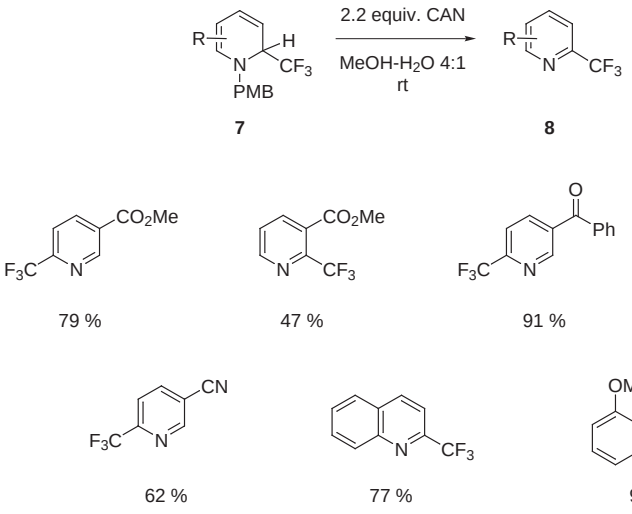
Adopting an approach similar to the one described above, we subjected *N*-*p*-methoxybenzyl azinium salts to the reaction with Me_3SiCF_3 and a suitable fluoride anion source to observe smooth addition of CF_3^- carbanions selectively in the position 2- (6-) of the heterocyclic ring. The resulting dihydroazines **7** were formed in good yields and exhibited similar properties to their counterparts with a $CF(CF_3)_2$ group [26] (Scheme 11). The fluoride anion source that is necessary for the formation of the $[Me_3Si(F)CF_3]^-$ anions can be provided either by TASF, which is soluble in the organic solvents, or simply by solid KF as shown in the examples in Scheme 11. In the latter case the reaction is possible since the azinium salt itself acts as a solid-liquid phase transfer catalyst (Scheme 12). However, to obtain a good yield of the adducts it is necessary to use Ph_3SnF as a phase transfer co-catalyst [30]. Its role is to form hypervalent $[Ph_3SnF_2]^-$ anions on the surface of the solid phase. These anions are then transported into the bulk of the organic solvent as highly lipophilic ion pairs with the azinium cations and transfer the F^- anions to Me_3SiCF_3 to form the active trifluoromethylating agent. This process enables the use of $KF_{(s)}$ as an effective and inexpensive source of F^- despite its high lattice energy and negligible solubility in solvents like CH_2Cl_2.

The complete regioselectivity of the addition of CF_3^- to the azinium ring suggests that this carbanion in the form of a hypervalent $[Me_3Si(F)CF_3]^-$ anion acts as a harder nucleophile [21] than a $[CF(CF_3)_2]^-$ carbanion in which the two CF_3 groups strongly delocalize the negative charge. This observation is in agreement with the fact that nucleophilic trifluoromethylation with Me_3SiCF_3 of α,β-unsaturated carbonyl compounds proceeds exclusively as 1,2-addition [31].

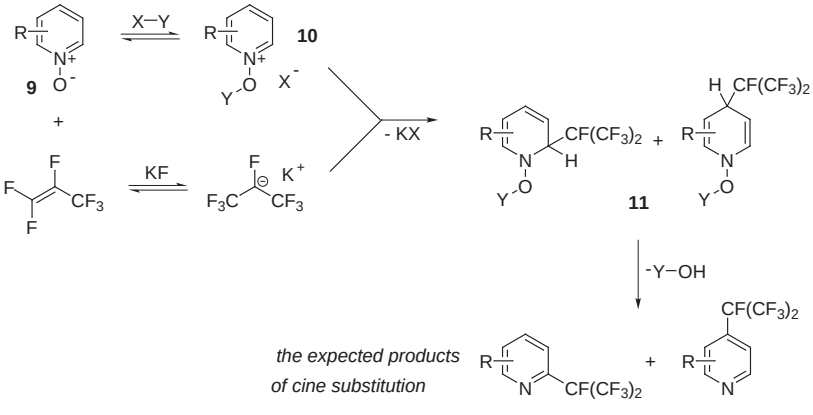
The trifluoromethylated 1,2-dihydroazines are readily converted into 2-trifluoromethylazines when oxidized with CAN in aqueous methanol (Scheme 13) [26].

The two reactions, nucleophilic trifluoromethylation of the azinium salt and deprotection/aromatization, can be performed in one reaction vessel, without isolating the intermediate dihydroazine. It can be achieved by simply evaporating the solvent after the addition step (CH_2Cl_2) and then adding MeOH and aqueous CAN. For example, 2-trifluoromethyl-5-methoxyquinoline was obtained in this way in an overall yield of 87 %.

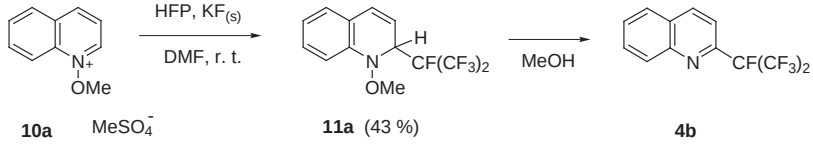
Anionic σ^H adducts of nucleophiles to electron-deficient arenes can be converted into products of nucleophilic replacement of hydrogen *via* elimination of a leaving group located in the ring in vicinity of the



Scheme 13. Oxidative *N*-deprotection/aromatization of 2-trifluoromethyl-1,2-dihydroazines.



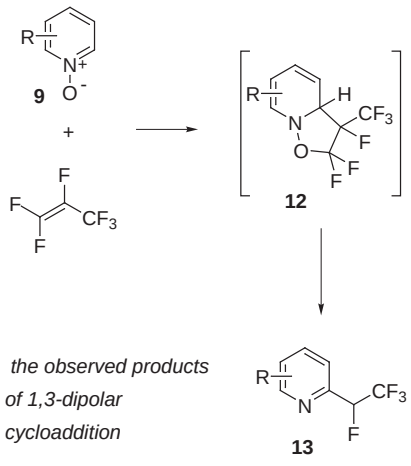
Scheme 14. Fluoroalkylation of azines *via cine* substitution by perfluorocarbanions generated from HFP and KF; X–Y = alkylating or acylating reagent.



Scheme 15. Addition of perfluoroisopropyl carbanions to the *N*-methoxyquinolinium salt **10a**.

addition site. This process, known as *cine* substitution, offers interesting synthetic possibilities [32]. This type of reaction was widely used in the synthesis of substituted azines *via* azine *N*-oxides [33]. In particular, Uno, Suzuki and co-workers described the addition of the *n*-perfluorohexyllithium reagent to BF_3-complexed pyridine *N*-oxide to obtain 2-*n*-C_6F_{13}-pyridine albeit in very low yield [13].

We supposed that *N*-alkoxyazinium salts **10** available *via O*-alkylation of azine *N*-oxides **9** would add perfluorocarbanions as readily as their *N*-alkyl analogs (Scheme 14). The *N*-alkoxydihydroazines should then be able to eliminate alcohol to produce substituted azines. *O*-Methylation of quinoline *N*-oxide with dimethyl sulfate gave the expected *N*-methoxypyridinium salt **10a** that when exposed to the system generating perfluoroisopropyl carbanions (HFP and potassium fluoride) gave the expected perfluoroalkylated *N*-methoxy dihydroazine **11a** albeit only in moderate yield (Scheme 15). Elimination of methanol from this intermediate occurred spontaneously, but it was a very slow process. Attempts to induce elimination and re-aromatization for example by the addition of a base failed – weak bases, like Et_3N, were ineffective and strong ones (*t*-BuOK) caused decomposition of the dihydroquinoline. The overall efficiency of this two-step

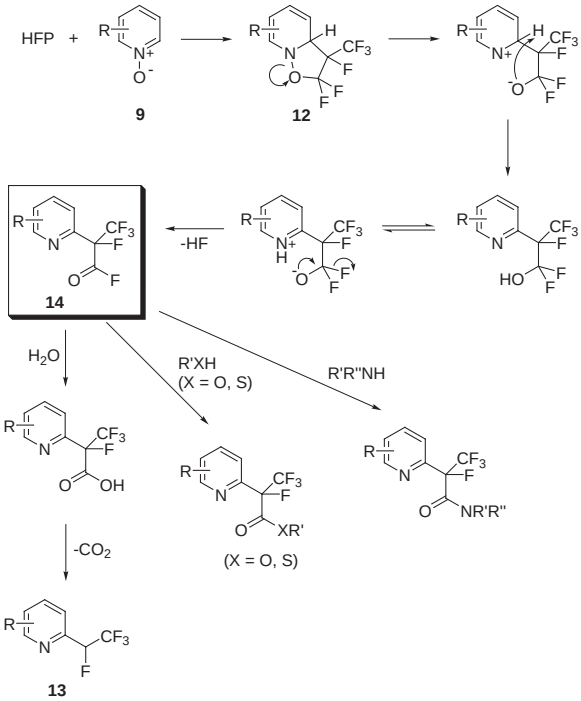


Scheme 16. 1,3-Dipolar cycloaddition of azine *N*-oxides to HFP.

process as a method of fluoroalkylation of azines was thus rather low. Reactions of analogous *N*-methoxy salts from the pyridine series were completely unsuccessful due to rapid decomposition of the substrates in the presence of HF and HFP to unidentified tarry materials; only traces of the expected fluoroalkylpyridines were detected.

We therefore attempted a similar reaction with *N*-acyloxy and *N*-sulfonyloxy azinium salts that should be more electrophilic, whereas elimination of an acyloxy anion should be more facile. Since *O*-acylation and *O*-sulfonylation of azine *N*-oxides are very fast and reversible processes [34], these experiments were carried out by mixing *N*-oxides, acyl or sulfonyl chlorides, KF and HFP in solvents like DMF, MeCN, CH_2Cl_2 *etc*.

Unfortunately, in spite of many attempts with various azine *N*-oxides we have not observed formation of azines substituted with the perfluoroisopropyl group. On the other hand, unexpected products (**13**) containing a 1,2,2,2-tetrafluoroethyl group were formed. Among the products of the reaction of quinoline *N*-oxide **9a** a small quantity of 4,5,5-trifluoro-4-trifluoromethylisoxazolidine **12a** was detected, indicating the direct 1,3-dipolar cycloaddition of the *N*-oxide to HFP. We supposed that this is the actual reaction pathway whereas the initial isoxazolidine adduct decomposes rapidly to give the tetrafluoroethyl derivative as the final product (Scheme 16). Indeed treatment of azine *N*-oxides with HFP under moderate pressure (glass pressure tube) resulted in the formation of tetrafluoroethyl derivatives of azines in good yields [35]. This type of reaction was already reported

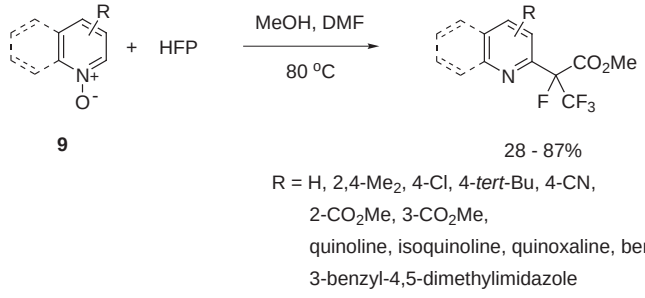


Scheme 17. General mechanism of the reaction of azine *N*-oxides with HFP and various nucleophiles proceeding *via* the key intermediate **14** [38].

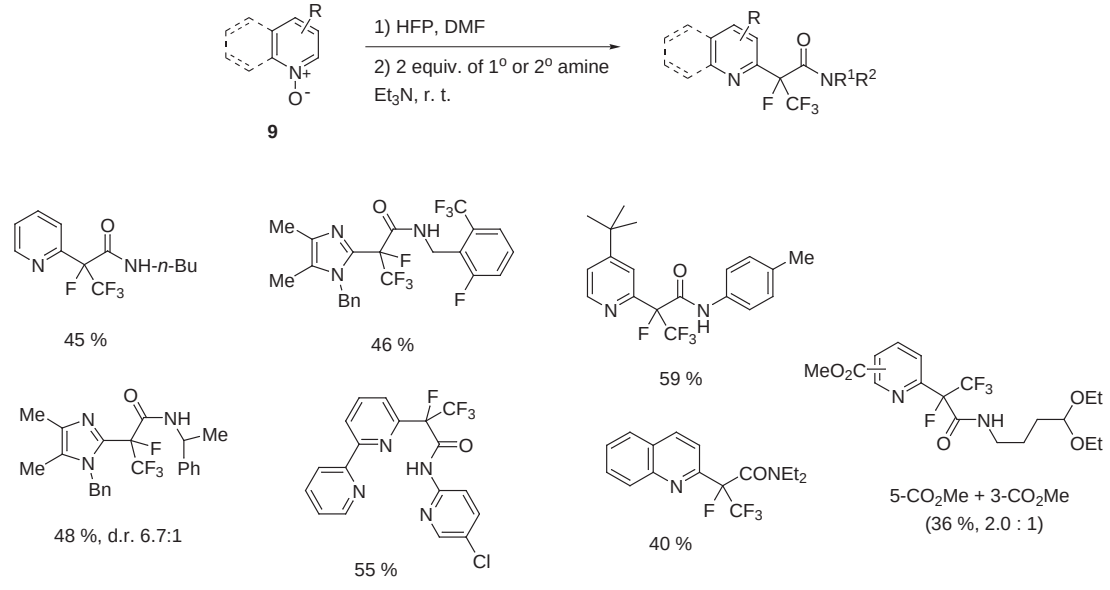
in two early papers [36, 37], but it was carried out under elevated temperature and pressure in an autoclave. Our investigation revealed that this process can be performed under much milder conditions using a wide variety of *N*-oxides of five- and six-membered heterocycles [35].

According to early reports on dipolar cycloaddition of HFP to *N*-oxides formation of the fluorinated isoxazoline derivative was followed by N–O bond breaking with concomitant aromatization of the ring and subsequent retro aldol-type splitting that liberates difluorophosgene and the tetrafluoroethyl azine derivative [36, 37]. Our detailed studies revealed that indeed the initially formed isoxazolidines undergo ring opening *via* N–O bond splitting, but the produced intermediate aldol-type anions do not dissociate *via* C–C bond cleavage (retro-aldol type), but *via* departure of a fluoride anion and formation of the respective acyl fluorides (Scheme 17) [38].

Acyl fluorides of 2-heteroarylperfluoropropionic acids of type **14** are highly electrophilic species. Aqueous treatment of the reaction mixture after the reaction of HFP with *N*-oxide results in rapid hydrolysis of **14** to form carboxylic acids that undergo rapid de-



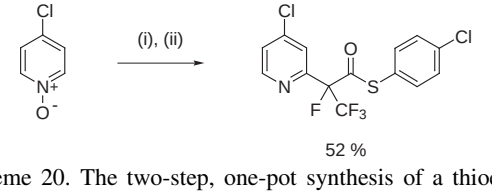
Scheme 18. Synthesis of methyl 2-heteroarylperfluoropropionates from *N*-oxides, HFP and methanol.



Scheme 19. The two-step, one-pot synthesis of amides of 2-heteroarylperfluoropropionic acids.

carboxylation to 2-tetrafluoroethyl compounds **13** described above. However, treatment of fluorides **14** with other protic nucleophiles allows the isolation of a variety of derivatives of 2-heteroarylperfluoropropionic acids, which are potentially interesting from the medicinal chemistry point of view [39]. When, instead of using water, the reaction mixture is quenched with alcohols, or when the reaction is carried out in the presence of alcohols, then esters of 2,3,3,3-tetrafluoro-2-heteroarylpropionic acids are obtained in good yields (Scheme 18). According to expectation, hydrolysis of such esters leads again to the tetrafluoroethyl derivatives **13**.

Thanks to the fact that acid fluorides **14** are stable in the reaction mixture, they can be used for acylation of nucleophiles that react directly with HFP, like thiols and primary and secondary amines, and the respective thioesters and amides of 2-heteroarylperfluoropropionic acids can be readily synthesized (Schemes 19 and 20). We also found that other fluoroalkenes like 2*H*-pentafluoropropene and chlorotrifluoroethylene undergo similar reactions with *N*-oxides and protic nucleophiles [38].



Scheme 20. The two-step, one-pot synthesis of a thioester of 2-heteroarylperfluoropropionic acid; (i) HFP, DMF, 80 °C, 5 h; (ii) 2 equiv. of *p*-ClC_6H_4SH, DMF, r. t., 14 h.

In conclusion, two efficient synthetic methodologies for introducing fluoroalkyl substituents into electron-deficient heteroaromatic rings have been developed. The first of them relays upon the process of oxida-

tive nucleophilic substitution of hydrogen. The reaction of dinitro- and cyanonitroarenes with Me_3SiCF_3 and TASF and subsequently with DMD provides trifluoromethylated cyano- and nitrophenols. Fluorinated carbanions, generated either by addition of F^- anions to HFP or by activation of the Ruppert reagent, add to azinium salts to provide fluoroalkylated dihydroazines, often with good regioselectivity and in high yields. The oxidative deprotection and aromatization of these intermediates, previously unknown for *N*-alkyldihydroazines, gives access to azine derivatives containing a perfluoroisopropyl or trifluoromethyl group in the position originally occupied by hydrogen.

In the second approach, hexafluoropropene reacts with azine *N*-oxides along the 1,3-dipolar cycloaddition pathway to form unstable isoxazolidines that undergo rapid aromatization by N–O bond scission, followed by elimination of HF to give 2-heteroaryl-2,3,3,3-tetrafluoropropionic acid fluorides as the final stable intermediates. These intermediates can react with a variety of protic nucleophiles. Hydrolysis and decarboxylation provides heterocycles containing a 1,2,2,2-tetrafluoroethyl substituent in the C-2 position of the ring. Reaction of the acid fluorides with alcohols, amines and thioles provides esters, amides and thioesters of 2-heteroaryl-2,3,3,3-tetrafluoropropionic acids. The reaction is of a general character, and by changing the *N*-oxide, fluoroalkene and nucleophile it can be applied to the synthesis of various nitrogen heterocycles with only partially fluorinated side chains, which in turn may be suitable for further functionalization.

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