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Access to new 4-fluorocyclohexa-2,5-dienimines using hypervalent iodine and pyridinium polyhydrogen fluoride

Lynda Basset, Agnès Martin-Mingot, Marie-Paule Jouannetaud *, Jean-Claude Jacquesy

Université de Poitiers, UMR 6514 'Synthèse et réactivité des Substances Naturelles', 40, Avenue du Recteur Pineau, F-86022 Poitiers Cedex, France

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Abstract

Nucleophilic *para*-fluorination of substituted anilines to afford 4-fluorocyclohexadieneimine derivatives is achieved in the presence of hypervalent iodine and pyridinium polyhydrogen fluoride.

Keywords: Hypervalent iodine; Fluorination; Anilines; Cyclohexadienimines

The introduction of fluorine in organic molecules strongly modifies their physical, chemical and biological properties.[1] The mild and selective introduction of a fluorine atom has been largely investigated over the past three decades and remains a great field of investigation.

With this aim we previously reported a novel synthesis of 4-fluorocyclohexa-2,5-dienones from 4-alkylphenols using pyridinium polyhydrogen fluoride (PPHF) in combination with hypervalent iodine(III) reagents.[2] It had previously been shown that hypervalent iodine reagent could also be an efficient reagent to access 4-alkoxy-4-alkylcyclohexa-2,5-dienimines from the corresponding substituted anilines, such new compounds being efficiently used in the synthesis of more complex structures.[3]

In our research for the synthesis of new fluorinated building blocks we now wish to report the synthesis of 4-fluoro-4-substituted cyclohexa-2,5-dieneimines from anilines with phenyliodine-(diacetate) (PIDA) and PPHF.

A typical experimental procedure for the reaction is as follows: To a stirred solution of aniline derivatives (1 mmol) in dry methylene chloride (20 mL) was added first PPHF (HF/pyridine 70/30 w:w, 0.1 mL), then PIDA (1.2 equiv) at room temperature. The mixture was stirred for 15 min. The Na_2CO_3 is added until neutralization of the mixture. After filtration, the organic layer is concentrated under vacuum and the residue is quickly purified by chromatography. The results are summarized in Table 1.

Products gave satisfactory spectral data (MS, ^1H, ^{13}C, ^{19}F NMR) and expected analytical results (HRMS).[4] The ^{19}F NMR spectra showed expected signals at $-150\ \text{ppm} < \delta < -140\ \text{ppm}$ for the ipso fluorinated alkylated compounds, at -106 ppm for the chlorofluorinated one and at -97 ppm for the difluorinated dieneimine. The ^1H NMR showed typical signals for vinylic hydrogen. It should be pointed out that the shielding of the hydrogen in α position of the imine function is approximately 1.3 ppm, due to the shielding zone of the π electron system of the tosyl group (Scheme 1).

Structures were also supported by the presence in ^{13}C NMR of the characteristic coupling between fluorine and carbon, $160\ \text{Hz} < {}^1J_{CF} < 170\ \text{Hz}$ for monofluorinated products and the typical triplet at 109.4 ppm with a 225 Hz coupling constant for the difluorinated imine.

The reported results in Table 1 deserve several comments.

It appears that the protecting group on the aniline nitrogen atom and the substitution of the aromatic moiety play a crucial role.

* Corresponding author. Tel.: +33 05 49 45 38 93; fax: +33 05 49 45 35 01.
E-mail address: marie.paule.jouannetaud@univ-poitiers.fr (M.-P. Jouannetaud).

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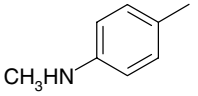
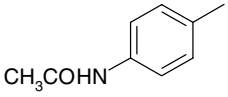
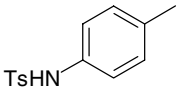
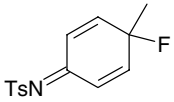
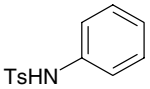
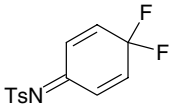
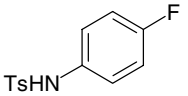
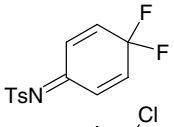
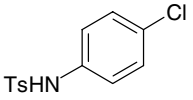
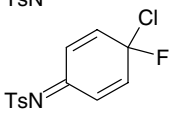
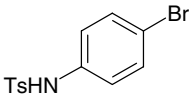
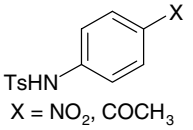
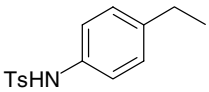
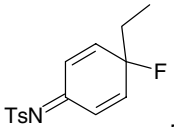
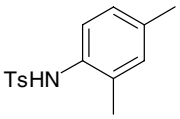
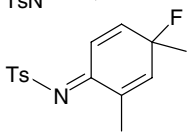
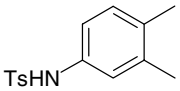
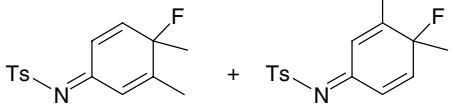
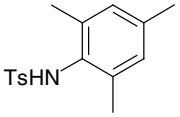
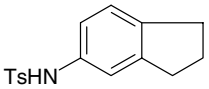
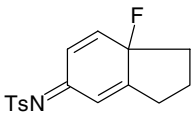
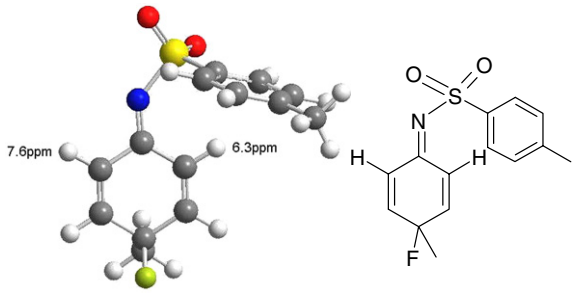
Table 1

Entry	Substrate	Products	Yield (%)
1		No reaction	
2		Complex mixture	
3			75[a]
4			18
5			47
6			51
7		Complex mixture	
8		No reaction	
9			61
10			57
11			77 (58/42)
12		No reaction	
13			24

[a] The use of PIFA (phenyliodine-(ditrifluoracetate)) instead of PIDA lowered the yield of the reaction.

Under our reaction conditions (PIDA, PPHF), *N*-methyl-*para*-toluidine did not react (entry 1) and *para*-methyl acetanilide led to complex mixture (entry 2). This is in agreement with the previously reported results. It was reported that *N*-methyl derivatives of aniline did not react with PIDA in methanol.[6] The behaviour of acetanilide in the presence of hypervalent iodine depends on the reaction conditions: in acetic acid they led to *meta*-acetoxy derivatives,[6] in toluene only complex mixtures were obtained[7] and in a mixture of $CHCl_3$ and TFA, hydrolyla-



Scheme 1.[5]

tion to N-*para* position and/or *N*-iodophenylation of acetanilides was observed.[8] Furthermore, no reaction occurred with 4-*tert*-butylacetanilide in the presence of PIFA and $Et_3N{\cdot}3HF$ in CH_2Cl_2 at room temperature and only 4-fluoroacetaniline was obtained in a modest yield after one day at reflux.[9]

The presence of a more electron withdrawing group such as tosyl makes sulfonamides weak organic acids, with a pK_a in the region of that of phenols.[10] As a result the following mechanism could be proposed: (Scheme 2).

It implies the reaction of the hypervalent iodine derivative with nitrogen atom, the resulting intermediate being trapped by the nucleophilic fluoride ion.

However, we cannot exclude the mechanism proposed by Langlois co-workers[9] in which the initial binding of the hypervalent iodine compound occurred on an oxygen atom of the sulfonamide moiety.

Substitution on the *para* position of the aromatic moiety was also studied. The presence of an electron withdrawing substituent prevented from any reaction (entry 8) whereas substitution with an electron donating group (except with the more oxidizable and bulkiest bromine atom) made this reaction easier (entries 3–7).

It must be also noticed that substitution at the *ortho* position of tosylated anilines clearly disfavoured the reaction yield probably due to steric effect, which was confirmed by the absence of reaction starting from di-*ortho*-substituted aniline (entry 12).

Steric influence of the substitution was also demonstrated after the submission of the *ortho* and *meta* methyl substituted anilines on reaction conditions: while mono-*ortho*-substituted aniline yielded only one conformer (methyl and tosyl groups in *anti* conformation),[4] *meta*-substituted aniline yielded *syn* and *anti* conformers in almost the same ratio (entries 10 and 11).

The fluorination of *N*-tosyl-5-aminoindan (entry 13) confirmed the ability to use such a technology to access polycyclic fluorinated building blocks.

In summary, the reaction of *N*-tosyl-*para*-substituted anilines in the presence of PIDA and PPHF was studied and afforded an easy access to new 4-fluorinated cyclohexa-2,5-dienimines.

This reaction is a novel example of the great scope of the hypervalent iodine compounds in organic synthesis. Furthermore, this investigation sets the stage for the application to more elaborated substrates and makes this technology an attractive route to synthetic, highly valued fluorinated building blocks.

References and notes

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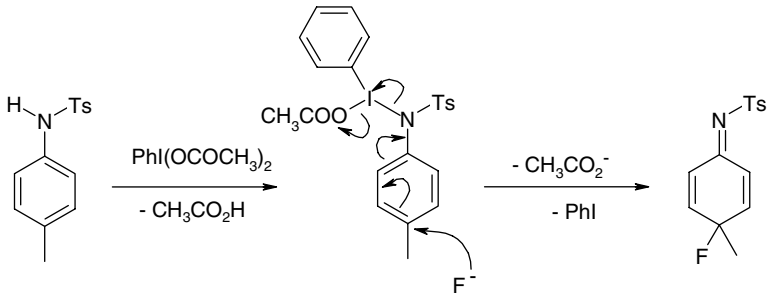
4. Selected spectral data: *Product entry 5*: ^{1}H NMR (300 MHz, $CDCl_3$, TMS as an internal standard): δ 6.44 (dd, $J = 10.1$ Hz, $J = 2.3$ Hz, 1H), 6.70–6.78 (m, 2H), 7.26 (s, 3H), 7.37 (d, $J = 8.0$ Hz, 2H), 7.74 (dd, $J = 10.1$ Hz, $J = 2.3$ Hz, 1H), 7.88 (d, $J = 8.3$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 21.6, 109.4 (t, $J = 225$ Hz), 124.6 (t, $J = 9$ Hz), 127.5, 132.9, 133.1 (t, $J = 9$ Hz), 135.7 (t, $J = 25$ Hz), 136.1 (t, $J = 25$ Hz), 136.9, 144.7, 160.9 (t, $J = 5$ Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$ external standard C_6F_6 (δF—162.90)): δ −97.1.



Scheme 2.

MS (EI) *m*/*z*: 283 (M^+). HRMS Calcd: 283.04783. Found: 283.0475 (1 ppm).

Product entry 10: ^{1}H NMR (300 MHz, $CDCl_3$,TMS as an internal standard): δ 1.58 (d, $J = 21.0$ Hz, 3H), 1.88 (d, $J = 2.5$ Hz, 3H), 2.44 (s, 3H), 6.72 (dm, $J = 7.8$ Hz, 1H), 6.77–6.84 (m,1H), 7.33 (d, $J = 8.0$ Hz, 2H), 7.51 (d, $J = 10.2$ Hz, 1H), 7.88 (d, $J = 8.2$ Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 17.3, 21.6, 25.5 (d, $J = 27$ Hz), 86.7 (d, $J = 160$ Hz), 122.1 (d, $J = 8$ Hz), 127.1, 129.58, 135.1 (d, $J = 9$ Hz), 138.4, 141.9 (d, $J = 20.5$ Hz), 143.7, 146.0 (d, $J = 21$ Hz), 164 (d, $J = 6$ Hz). ^{19}F {H} NMR (282 MHz, $CDCl_3$, external standard C_6F_6 (δF—162.90)): δ −145.0. MS (EI) *m*/*z*: 293(M^+). HRMS Calcd: 293.08858. Found: 293.071 (4 ppm).

5. Geometry optimization was executed with Chem 3D by applying the PM3 semi-empirical methods in MOPAC.
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