Pergamon

Tetrahedron Letters, Vol. 35, No. 16, pp. 2541-2544, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 \$6.00+0.00

0040-4039(94)E0327-T

Nucleophilic *Para*-Fluorination of 4-Alkylphenols by Hypervalent Iodine Reagent and Pyridinium Polyhydrogen Fluoride (PPHF) A Novel Route to 4-Fluorocyclohexa-2,5-dienones

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Abstract : *Ipso-fluorination of 4-alkylphenols with* C_6H_5*-I(OCOCF*$_3$*)*$_2$*-pyridinium polyhydrogen fluoride (PPHF) yields 4--fluorocyclohexa-2,5-dienones.*

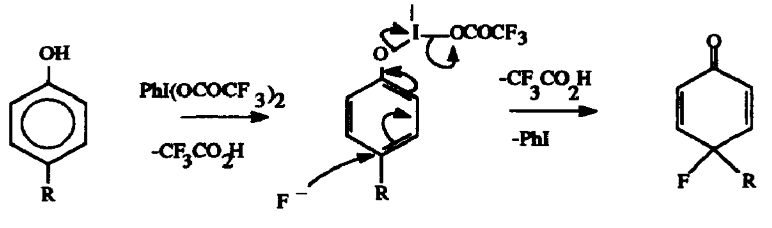
The use of hypervalent iodine reagents such as phenyliodine bis(trifluoroacetate) (PIFA) or phenyliodine diacetate (PIDA) in now well documented. These electrophilic oxidants have been used for the synthesis of many 4,4-disubstituted cyclohexa-2,5-dienones from phenols by intermolecular or intramolecular trapping of the intermediates by aromatic rings, oximes, alcohols, acids, amides[1-8].

We now wish to report on account of the importance of the selective incorporation of fluorine into organic compounds[9], a novel and general synthesis of 4-fluorocyclohexa-2,5 dienones from 4-substituted phenols using hypervalent iodine reagent PIFA with pyridinium polyhydrogen fluoride (PPHF).

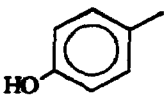
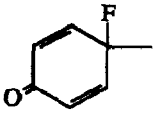
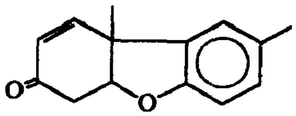
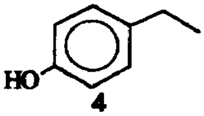
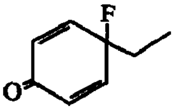
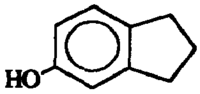
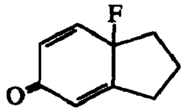
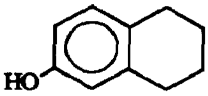
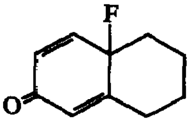
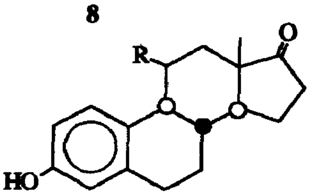
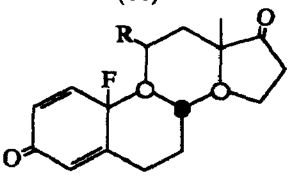
A typical experimental procedure for the reaction of tetrahydronaphthol **8** is as follows. To a stirred solution of phenol **8** (300 mg, 2 mmol) in methylene chloride (40 mL) was added at first pyridinium polyhydrogen fluoride (30% py : 70% HF w/w, 0.5 mL) then PhI(OCOCF$_3$)$_2$ (1.1g, 2.56 mmol) at room temperature. The mixture was stirred at room temperature for 30 min. Excess of solid K_2CO_3 was added and the resulting mixture was stirred in the same conditions for 5 minutes. After filtration, the organic filtrate was evaporated and the residue was flash chromatographed over SiO_2 to yield dienone **9** (220 mg, 66%).

The results reported in the table show that mono and polycyclic 4-fluorocyclohexa-2,5-dienones were obtained in fair yields from the corresponding phenols.

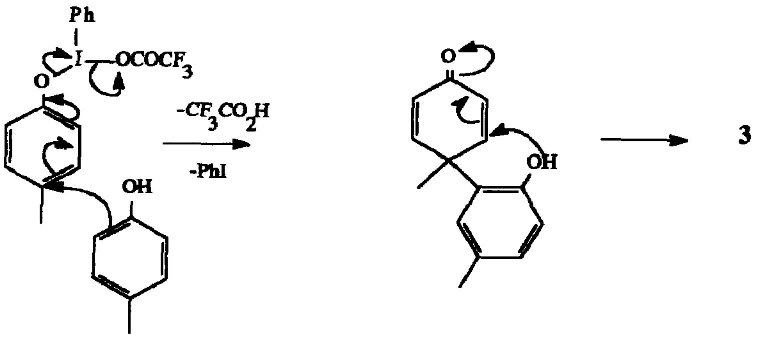
The postulated mechanism implies reaction of the reagent PIFA on the phenolic group and trapping of the resulting intermediate by a nucleophilic fluoride.



Fluorination of phenols with $PhI(OCOCF_3)_2$ and PPHF

Starting phenol	Products (%yied)[15]
 1	 2(68) +  3(8)
 4	 5 (61)
 6	 7 (42)
 8	 9(66)
 10 :a R=H b R=OH	 11 :a R=H (77) b R=OH (58)

Formation of the known Pummerer ketone 3 as a by-product was observed when starting from *para*cresol 1[10]. This oxidative dimerization can be accounted for by a similar process :



The synthesis of 4-fluorocyclohexa-2,5-dienones previously reported in the litterature have been carried out using **electrophilic fluorinating agents** : fluorine[11], trifluoromethylhypofluorite CF_3OF[12], perchloryl fluoride ClO_3F[13], N-fluoroperfluoroalkylsulfonylimides[14]. All these reagents require special equipment due to their unstability and toxicity. The **nucleophilic fluorination** of phenols with $PhI(OCOCF_3)_2$ and pyridinium polyhydrogenfluoride is much easier to handle and extremely simplifies workup.

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15. a) : Yields are for isolated products after chromatography. New products (**5**, **7**, **9**, **11b**) gave satisfactory spectral data (MS, ^{1}H and ^{13}C NMR).and the expected analytical (HRMS and/or microanalysis) results, except dienone **7** which is unstable.

    b) : Selected spectral data of the new products :

    5 : ^{1}H NMR (200 MHz, CDCl$_3$) : 0.92 (3H, t), 1.91 (2H, m), 6.25 (d, J = 10), 6.85 (dd, J = 10 and 7). ^{13}C NMR : (50.13 MHz, CDCl$_3$) : 7.4 (d, J = 7), 31.8 (d, J = 24), 89, 5 (d, J = 163), 129.5 (d, J = 8), 145 (d, J = 22), 185.

    7 : ^{1}H NMR : 6.1 (1H, s), 6.22 (1H, dd, J = 10 and 2), 6.98 (1H, dd, J = 10 and 5). ^{13}C NMR : 21.4, 28.2, 92.5 (d, J = 161), 123.8 (d, J = 4), 131 (d, J = 7), 140.5 (d, J = 19), 162.5 (d, J = 13), 185.7.

    9 : ^{1}H NMR : 6.06 (1H, s), 6.20 (1H, dd, J = 10 and 2), 6.82 (1H, dd, J = 10 and 6). ^{13}C NMR : 20.5, 27.4, 32.0, 38.3 (d, J = 25), 87.5 (d, J = 163), 123.9 (d, J = 5), 129.3 (d, J = 8), 145.8 (d, J = 23), 158.7 (d, J = 19), 185.5.

    11b : ^{1}H NMR : 1.20 (3H, s,), 3 (1H, d, J = 16), 4.51 (1H, m), 6.06 (1H, s), 6.30 (1H, d, J = 10), 7.30 (1H, dd, J = 10 and 7). ^{13}C NMR : 15.8, 21.7, 30.8, 31.2, 31.8, 34.9, 38.6, 47, 51.5, 57.5, 69.2, 90.5 (d, J = 164), 123.5 (d, J = 4), 130.6 (d, J = 7), 143.2 (d, J = 22), 158.5 (d, J = 18), 184.5, 217.8.

(*Received in France* 27 *January* 1994; *accepted* 14 *February* 1994)