Pergamon

Tetrahedron Letters 40 (1999) 4183–4186

TETRAHEDRON LETTERS

Synthesis of Hydroindolenones and Hydroquinolenones by Hypervalent Iodine Oxidation of Mono or Bicyclic Phenols

Omar Karam, Agnès Martin, Marie-Paule Jouannetaud, Jean-Claude Jacquesy*

Laboratoire de Chimie XII associé au CNRS
Faculté des Sciences - 40, Avenue du Recteur Pineau 86022 Poitiers (France)

Received 2 March 1999; accepted 7 April 1999

Abstract : Methoxy or fluoro hydroindolenones and hydroquinolenones can be obtained by oxidation of the corresponding 4-substituted open-chain phenols with C_6H_5-I-$(OCOCF_3)_2$ with methanol or pyridinium polyhydrogen fluoride followed by an intramolecular conjugate addition. The corresponding cyclo 2,5- hexadienones can be obtained directly by a similar oxidation of the bicyclic phenols. © 1999 Elsevier Science Ltd. All rights reserved.

Since the first synthesis of (dichloroiodo)benzene, $PhICl_2$ more than one hundred years ago, many hypervalent iodine reagents have been synthesized. Many of them appear as versatile oxidants of exceptional interest in organic chemistry, especially in heterocyclic synthesis.[1,2]

Syntheses of reduced indole derivatives have been described by oxidation of tyramine or tyrosine derivatives by treatment with phenyliodine bis(trifluoroacetate) (PIFA) or phenyliodine diacetate (PIDA), respectively.[3,4] Formation of the hexahydroindol-6-ones can be rationalized by intramolecular Michael-type reaction of the nitrogen group to the double bond of the intermediate dienone.

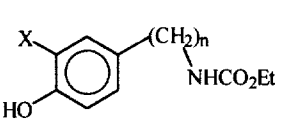
In this paper we report the synthesis of methoxy and of fluoro hydroindol-6-ones and of hydroquinolin-7-ones under the action of PIFA-MeOH or PIFA-pyridinium polyhydrogen fluoride (PPHF), respectively, on monocyclic phenols, followed by cyclization of the resulting open–chain dienones, or directly using the corresponding bicyclic phenols.

Oxidative methoxylation of phenols was carried out by addition of a slight excess (1.2mmol) of PIFA to a solution of the substrate (1 mmol) in methanol (5mL). After stirring the reaction mixture at room temperature for 15 minutes, excess of $NaHCO_3$ was added. After usual work-up, the product was flash-chromatographed over SiO_2.

Fluorination of phenols was carried out using methodology previously reported by our laboratory, pyridinium polyhydrogen fluoride then $C_6H_5I(OCOCF_3)_2$ being added to a solution of the phenol in dichloromethane.[5,6]

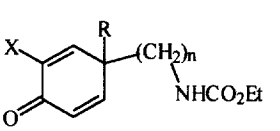
Cyclization of dienones **2a-d** and **3d** into the corresponding enones was performed by treatment with Na_2CO_3 in methanol, or with HCl in tetrahydrofuran or with PPHF for dienone **2a** (entry 2). Reaction of phenol **1a** with PIFA-PPHF lead directly to enone **5a** (entry 6), the intermediate dienone isomerizing spontaneously in the reaction conditions (Table 1.).

PII: S0040-4039(99)00718-2



1

a n = 2, X = H
b n = 2, X = Br
c n = 2, X = Cl
d n = 3, X = H
e n = 3, X = Br



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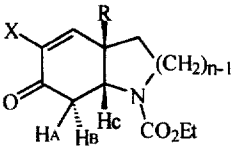
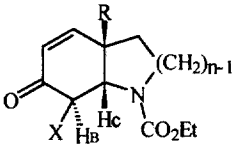
3 R = F



4 R = OCH_3
5 R = F



6 R = OCH_3
7 R = F

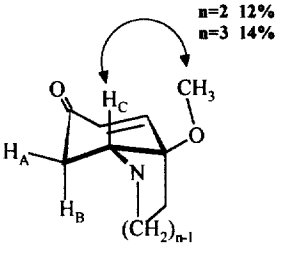
Table 1.

Entry	Phenol	Conditions	Dienone (%)	Bicyclic Enone (%)
1	**1a**	PIFA - MeOH	**2a** (63)	**4a** (70)
2	**1a**	1)PIFA - MeOH 2)PPHF		**4a** (54)
3	**1b**	PIFA - MeOH	**2b** (54)	**4b** (54) + **6b** (20)
4	**1c**	PIFA - MeOH	**2c** (47)	**4c** (70) + **6c** (10)
5	**1d**	PIFA - MeOH	**2d** (67)	**4d** (60)
6	**1a**	PIFA - PPHF		**5a** (35)
7	**1d**	PIFA - PPHF	**3d** (43)	**5d** (50)

Products gave satisfactory spectral data (MS, ^1H, ^{13}C NMR) and the expected analytical (HRMS) results.[8]

In enones **4a-d**, **5a** and **5d**, **6b** and **6c** the ring junction was expected to be *cis* for steric reasons.[3,4] This was confirmed by NMR experiments complicated by the presence of two carbamate bond rotamers in approximately 1:1 ratio:

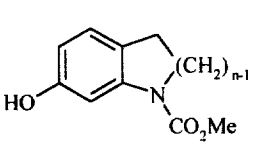
- in the methoxylated series, $^3J_{HH}$ coupling constants in ketone **4a**, which could be measured at room temperature in $CDCl_3$ have the expected values ($J_{H_AH_C}$=6Hz, $J_{H_BH_C}$=10Hz) for such a system.[4,7] Similar coupling constants were observed in quinolinone **4d** ($J_{H_AH_C}$=5Hz, $J_{H_BH_C}$=13Hz) the NMR experiment being performed at 70°C in DMSO to observe complete coalescence. Furthermore, NOE studies confirmed the assigned configuration : with ketones **4a** and **4d**, NOE's measured at the H_C proton when the methyl group of the methoxy moiety is saturated are 12% and 14%, respectively.



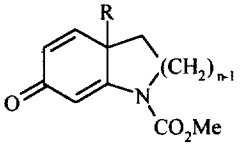
- in fluoroketone **5a** the $^3J_{HH}$ coupling constants ($J_{H_AH_C}$=6.4Hz, $J_{H_BH_C}$=11.3Hz) are very close to those observed with the analogous ketone **4a**, implying that hydrogen H_C is axial in the ketonic ring. Moreover, the observed $^3J_{H_C\text{-}F}$ coupling constant (J=20Hz) is in agreement with a *cis* ring junction, higher values being expected for a *trans* one.[9] In ^1H NMR experiments, coupling constants could not be measured with ketone **5d**,

even at high temperature on account of the carbamate rotamers. This problem could be circumvented by synthesizing the bromo analog **7e** by reaction of phenyltrimethymammonium tribromide on ketone **5d** in THF.[10] In the resulting ketone **7e** (40% yield) coupling constants $J_{H_BH_C}$=12Hz, $J_{H_C\text{-}F}$=12Hz confirm the *cis* ring junction.

We previously reported the *ipso*-fluorination of polycyclic phenols with PIFA-PPHF to yield 4-fluorocyclohexadienones.[5,6] We have discovered that the analogous fluorination or methoxylation, as previously described (*vide supra*), can be performed on the nitrogen analogs **8** and **9** to give the corresponding dienones (Table 2.). The presence of the carbamate moiety, *meta* to the aromatic ring, does not modify the reactivity of the aromatic ring. This novel oxidative dearomatization of nitrogen-substituted polycyclic phenols should find applications in natural product chemistry.



8 n=2
9 n=3



10 n=2 **a** R=F
11 n=3 **b** R=OCH_3

Table 2.

Phenol	Conditions	Dienone (%)
8	PIFA - PPHF	**10a** (39)
8	PIFA - MeOH	**10b** (48)
9	PIFA - PPHF	**11a** (29)
9	PIFA - MeOH	**11b** (67)

These new dienones gave satisfactory spectral and analytical data.[11]

In summary, this study demonstrates the synthetic interest of hypervalent iodine reagents in heterocyclization chemistry, especially to prepare angular substituted (methoxy or fluoro) cyclohexenones.

References and notes

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8. Selected spectral data of : **4d** (mixture of rotamers) : **^{1}H NMR** (DMSO – 70°C) : δ 2.27 (dd, J=5 and 16Hz, 1H, H_A), 3.04 (dd, J=13 and 16Hz, 1H, H_B), 3.15 (s, 3H, OCH_3), 4.72 (dd, J=5 and 13Hz, 1H, H_C), 6.00 (d, J=10Hz, H-6), 6.94 (d, J=10Hz, 1H, H-5) ; **^{13}C NMR** ($CDCl_3$) : δ 37.68 and 37.70, 37.7 and 38.0 (C-2 and C-8), 73.8 (C-4a), 130.8 (C-6), 155.1 (N-CO), 156.5 (very small, C-5), 197.4 (C-7) ; **EI MS** m/z (%) : 253(2), 221(15), 123(100) ; **HR-MS** : calcd : 253.1314, found : 253.1312. **5d** (mixture of rotamers) : **^{1}H NMR** ($CDCl_3$) : δ 2.65 (m, 2H, H-8), 4.85 (m, 1H, H_C), 5.97 (d, 1H, J=10.3Hz, H-6), 6.86 (dd, 1H, J=10.3 and 10.3 Hz, H-5) ; **^{13}C NMR** ($CDCl_3$) : δ 29.6 (d, J=25Hz, C-4), 37.8 and 37.9 (C-2 and C-8), 61.8 (CH_2-CH_3 and C-8a), 90.2 (d, J=173Hz, C-F), 129.0 (d, J=8.5 Hz, C-6), 150.2 (d, J=28Hz, C-5), 155 (N-CO), 196.5 (C-7) ; **EI MS** m/z (%) : 241(22), 221(90), 56(100); **HR-MS** : calcd : 241.1114, found : 241,1100. **7e** (mixture of rotamers) : **^{1}H NMR** ($CDCl_3$) : δ 4.87 and 4.98 (t, 1H, J=12 Hz and 12Hz, H_C), 5.48 and 5.53 (d, 1H, J=12 Hz, H_B), 6.23 (d, 1H, J=10.3Hz, H-6), 7.15 and 7.17 (dd, 1H, J= 10.3 and 10.5Hz, H-5) ; **^{13}C NMR** ($CDCl_3$) : δ 52.7 and 52.9 (2d, J=10Hz, C-8), 59.4 and 60.2 (2d, J=23Hz, C-8a), 90.2 and 90.3 (2d, J=179Hz, C-F), 127.5 and 127.6 (2d, J=9Hz, C-6), 149.9 and 150.0 (2d, J=26Hz, C-5), 155.4 and 155.7 (N-CO), 189.2 (C-7); **EI MS** m/z (%) : 321(10), 319(10), 301(5), 299(5), 240(60), 220(75), 192(90), 56(100).
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10. Jacquesy, J. C.; Jouannetaud, M. P. *Bull. Soc. Chim. Fr.* **1977**, *II*, 202-208.
11. Selected spectral data of : **11a** : **^{1}H NMR** ($CDCl_3$) : δ 3.81 (s, 3H, CH_3OCO), 6.25 (m, 1H, H-6), 6.37 (m, 1H, H-8), 6.75 (m, 1H, H-5); **^{13}C NMR** ($CDCl_3$) : δ 33.8 (d, J=25.5Hz, C-4), 53.6 (CH_3OCO), 85.1 (d, J=166.5Hz, C-4a), 119.8 (d, J=4Hz, C-8), 128.9 (d, J=7Hz, C-6), 142.4 (d, J=20 Hz, C-5), 150.6 (d, J=18 Hz, C-8a), 154.7 (N-CO), 186.1 (C-7); **EI MS** m/z (%) : 225(96), 197(40), 59(100); **HR-MS** : calcd : 225.0796, found : 225.0801. **11b** : **^{1}H NMR** ($CDCl_3$) : δ 3.10 (s, 3H, OCH_3), 3.79 (s, 3H, CH_3OCO), 6.32 (d, J=9Hz, 1H, H-6), 6.43 (s, 1H, H-8), 6.55 (d, J=9Hz, 1H, H-5); **^{13}C NMR** ($CDCl_3$) : δ 52.0 and 53.2 (2 OCH_3), 71.6 (C-4a), 122.8 (C-8), 129.9 (C-6), 147.2 (C-5), 154.2 and 154.7 (N-CO and C-8a), 186.8 (C-7); **EI MS** m/z (%) : 237(8), 207(79), 179(35), 59(100); **HR-MS** : calcd : 237.1005, found : 237.1001.