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The Binary Reagent PhI(OAc)$_2$-Mg(ClO$_4$)$_2$:a SET Induced Ring Enlargement of Furan Derivatives into Pyranones

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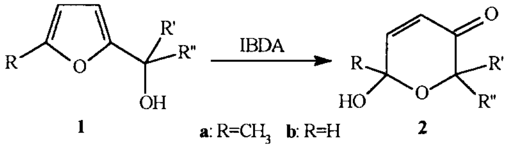
Abstract: *The binary reagent PhI(OAc)$_2$-Mg(ClO$_4$)$_2$ is very efficient for a high conversion of (2-furyl)-1-alcohols into pyranones. The reaction mechanism can be explained in terms of a SET process, with the generation of a cation radical as key intermediate.*

During our studies on the reactivity of hypervalent iodine reagents as oxidants in organic synthesis, we observed that pyranones **2a** can be easily obtained by an oxidative ring enlargement of [(5-methyl)-2-furyl]-1-alcohols **1a** with iodobenzenediacetate (IBDA) in a pH 7 buffered solution of 1/1 CH$_3$CN-water (Scheme 1).[1]

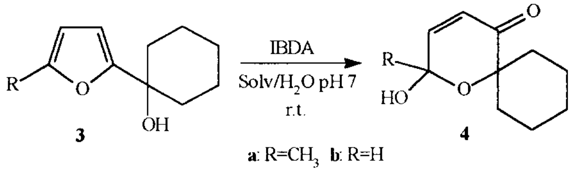


Scheme 1

(2-Furyl)-1-alcohols **1b** were found to be less reactive, giving lower yields of the corresponding pyranones **2b**. However, in terms of easiness, efficiency, and commercial availability, the IBDA oxidations represent one of the most attractive and environmentally less-hazardous procedures. The reactions are clean and the products can be easily obtained by column chromatography, since they only need to be separated from iodobenzene and eventually unreacted starting product.

Our results pointed out the crucial role played by the presence of a nucleophile, such as water, in the ring enlargement oxidation, showing clearly that the reactions proceed *via* some reactive intermediate which is electrophilic in nature. In keeping with this assumption, we carried out studies and experiments aimed both at optimising the efficiency and the generality of the reaction and elucidating its mechanistic pathway.

Solvent role. The effect of the solvents was examined by reaction of **3a** with IBDA. The yields of **4a** strongly depend upon the used solvent. The oxidative ring enlargement of **3a** (1 mmol) with IBDA (1 mmol) proceeds cleanly and quantitatively in poorly nucleophilic polar solvents, such as 1,1,1,3,3,3-hexafluoro-2-propanol (10 ml, 1/1 water ratio). Other polar solvents, such as acetonitrile, gave **4a**, but in lower yields and longer reaction times (Scheme 2 and Table 1).



Scheme 2

Table 1: Solvent role (1/1 water ratio).

Solvent	time	Yield (%)	Select (%)
CH_3CN	3h	76	90
CH_3OH	3h	80	80
$(CF_3)_2CHOH$	10min	99	99

(2-Furyl)-1-alcohols as Electron Donors. Recent reports[2,3] pointed out that IBDA generally acts as inner-sphere one electron-transfer oxidant. The reagent showed a redox potential E=-1.1 V (Ag/AgCl).

Preliminary electrochemical measurements on [5-methyl-(2-furyl)]-1-alcohols, such as **3a**, and on (2-furyl)-1-alcohols, such as **3b**, showed irreversible cyclic voltammograms (CV) at scan rate ν=10.0 mVs^{-1} with redox potential E=1.0 V and E=1.6 V (Ag/AgCl) respectively (c=0.1M in CH_3CN, $TBNBF_4$ c=0.1M as support electrolyte). These different values indicate that the electron donor strength decreased significantly on proceeding from **3a** to **3b**, and that compounds, such as **3a**, can be more easily oxidised by IBDA, giving some electrophilic species as key-intermediate.

Salt effect. As well known, the addition of salts is expected to promote the reaction involving radical species. Salts co-ordination with the radical pair enhances the formation rate of free radical species and increases reaction yields. As expected, the addition of salts, such as $Mg(ClO_4)_2$, KBF_4 and methyl-viologen, to a pH 7 buffered solution of 1/1 acetonitrile-water considerably enhanced the efficiency of the oxidative ring enlargement of **3a** to pyranone **4a** (Scheme 2). The best results were obtained by using $Mg(ClO_4)_2$, considering its low cost as well (Tables 2, 3).

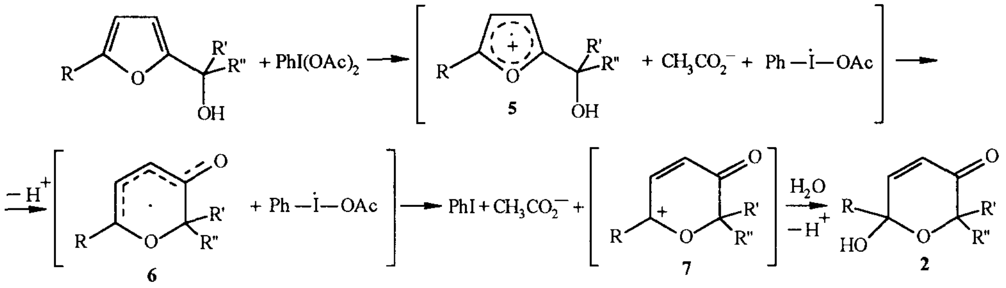
Table 2. Salt effect in the conversion **3a**→**4a**.

Salt	Molar ratio	time, rt	Yield (%)	Conv (%)
none	-	3h	76	85
$Mg(ClO_4)_2$	0.5	1h	95	99
$Mg(ClO_4)_2$	1	30min	95	99
$Mg(ClO_4)_2$	2	10min	95	99
KBF_4	2	24h	50	50
KBF_4	4	1h	95	99
Met-Viol	0.25	24h	50	50
Met-Viol	0.5	1h	95	99
Met-Viol	1	10min	95	99

ESR Spectra of Reaction Intermediates. The reaction of 2-furyl-1-alcohols, such as **3a**, with IBDA in $(CF_3)_2CHOH$ (c=2.2 10^{-1}M) at rt, produced stable radical species, which were detected in the ESR spectrum (Figure 1). The ESR spectra were time-dependent. In fact, the intensity of signal at g=2.006 increased during the reaction of **3a** and disappeared upon its end. Furthermore, identical radical species were observed performing the reaction of **3a** with IBDA and $Mg(ClO_4)_2$ in CH_3CN. Studies about the hyperfine coupling constants and the structure of radical intermediates are in course.

Kita's research group recently described the hypervalent iodine-induced nucleophilic substitution of *para*-substituted phenol ethers. The study of the reaction mechanism pointed out the generation of cation radicals as reactive intermediates through a SET process.[4]

The weight of the collected evidences seems to favour a SET mechanism for IBDA oxidation of (2-furyl)-1-alcohols **1** into pyranones **2**, presumably *via* a cation radical intermediate, such as **5**, in 1,1,1,3,3,3-hexafluoro-2-propanol (Scheme 3).[5]



Scheme 3

Table 3. Oxidation results.

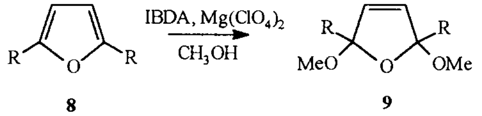
R	**R'**	**R''**	**Temp(°C)**	**time(h)**	**Yield(%)**	**d.e.**
H	H	H	50	2	50	-
H	H	Me	50	2	55	2:1
Me	H	Me	rt	1	72	4.1
Me	H	Et	rt	1	80	6:1
H	H	*n*Bu	50	2	55	2:1
Me	H	*n*Bu	rt	1	90	10:1
H	Cyclohexyl		50	2	75	-
Me	Cyclohexyl		rt	1	95	-
Me	H	$nC_{10}H_{21}$	rt	1	85	10:1
H	Ph	Ph	rt	2	80	-

a) Molar ratio $PhI(OAc)_2/Mg(ClO_4)_2$ 1:2 .

b) The reported yields refer to isolated, chromatographically pure compounds. All the structures have been confirmed by IR, ^1H-NMR and ^{13}C-NMR. GC-MS analysis were in agreement with previously described data.[1]

Moreover, an analogue mechanism is described for the electrochemical oxidation in alcohols of furans to 2,5-dialkoxy-2,5-dihydroderivatives.[6]

The key-role played by the formation of cations **5** and **7** was witnessed by a parallel experiment which was carried out using furan derivatives **8a,b** (Scheme 4).



a: $R=CH_3$ **b**: R=H

Scheme 4

In this case, the oxidation of **8a,b** with $IBDA/Mg(ClO_4)_2$ (molar ratio 1/2) at rt for 2h in methanol led to the formation of 2,5-dimethoxy-furan derivatives **9a,b**, clearly in agreement with the above mechanistic pathway.

In summary, our studies have demonstrated , beside the mechanism of the reaction, that the binary reagent $PhI(OAc)_2/Mg(ClO_4)_2$ is very efficient and that our procedure constitutes one of the most convenient and flexible methods for the synthesis of pyranones from furans (Table 3).[1]

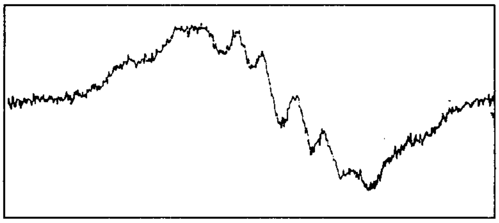


Figure 1. ESR spectrum of **3a**.

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