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Ipso-Chlorination of 4-Alkylphenols Ethers A Novel Route to 4-Chlorocyclohexa-2,5-dienones.

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Abstract : *Selective chlorination of 4-alkylphenols ethers with* SbF_5/CH_2Cl_2 ($CHCl_3$, CCl_4) *yields 4-chlorocyclohexa-2,5-dienones; no α-chlorination to a carbonyl group is observed in the reaction conditions.*

Aromatic electrophilic substitution of phenolic derivatives can yield unexpected products such as 2,4 and/or 2,5-dienones as a result of *ipso* attack *ortho* or *para* to the functional group.

4-Halo-2,5-dienones are of special interest[1,2], as substrates for dienone-phenol rearrangement and potential intermediates for the synthesis of complex molecules[3-5].

4-Chlorocyclohexadienones were prepared by chlorination of *para* alkylated phenols with chlorine[6-14], alkyl hypochlorites[9,15,16], sulfuryl chloride[11], antimony pentachloride[17], N-chlorosuccinimide[4,18], trichloroisocyanuric acid[18,19]. These studies are only relative to monocyclic or to estradiol derivatives and except for *para* cresol[17], yields are low or unspecified, polychlorinated dienones being the major products.

We report here a convenient synthesis of mono and polycyclic 4-chloro-2,5-cyclohexadienones by ionic chlorination of methyl ethers of *para* substituted phenols using SbF_5/CH_2Cl_2($CHCl_3$, CCl_4) at low temperature[20].

In a typical experiment, CH_2Cl_2 (5mL) at -55°C is slowly added under magnetic stirring to SbF_5 (2.1g; 10 mmol) maintained at -55°C in a Teflon flask. Ether **3** (324 mg : 2 mmol) in CH_2Cl_2 (5 mL) was slowly added. The resulting mixture was stirred for 10 min at -55°C, then was poured over H_2O-ice-Na_2CO_3. After usual work-up, the crude product was flash chromatographed.

The results reported in Tables 1 and 2 show that monochlorocyclohexadienones were obtained in fair yields[21].

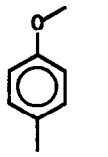
Table 1

Substrate / Reagent	1	2	3
	Products (%) Yield		
SbF_5-CH_2Cl_2	**4**(49)+**5b**(13)+**6**(a+b)(10)[i]		**9**(52)+**10**(a+b)(11)[i]
SbF_5-$CHCl_3$	**4**(51)+**5b**(22)+**6**(a+b)(10)[ii]	**7**(47) + **8**(8)[iiii]	**9**(50)+**10**(a+b)(16)[ii]
SbF_5-CCl_4	**5a**(23) + **5b**(42)[iii]		**9**(39)+**10a**(15)[iii]

i : -55°C, 10 min; ii : - 40°C, 10 min; iii : 0°C, 90 min; iiii : -55°C, 90 sec.

Table 2
Chlorination of Methylestrone 11

Reagent	Product (%)	Reaction Conditions
SbF_5-CH_2Cl_2	**11**(9)+**12a**(40)+**12b**(10)+**12c**(6)+**13**(10)+**14**(7)	-40°C, 90 min
SbF_5-$CHCl_3$	**11**(7)+**12a**(49)+**12b**(17) +**12c**(4)	0°C, 90 min
SbF_5-CCl_4	**11**(24) + **12a**(40) + **12b**(15)	20°C, 5h



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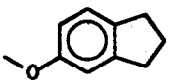

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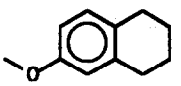

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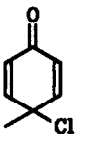

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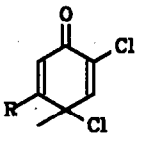
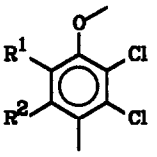
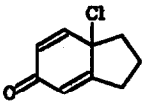


5 a R=H
5 b R=Cl



6 a R^1=H, R^2=Cl
6 b R^1=Cl, R^2=H



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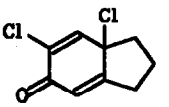

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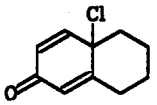

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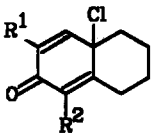
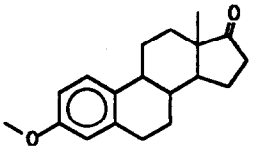


10 a R^1=Cl, R^2=H
10 b R^1=H, R^2=Cl



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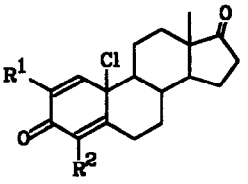
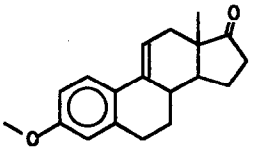


12 a R^1=R^2=H
12 b R^1=Cl, R^2=H
12 c R^1=H, R^2=Cl



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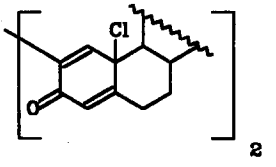
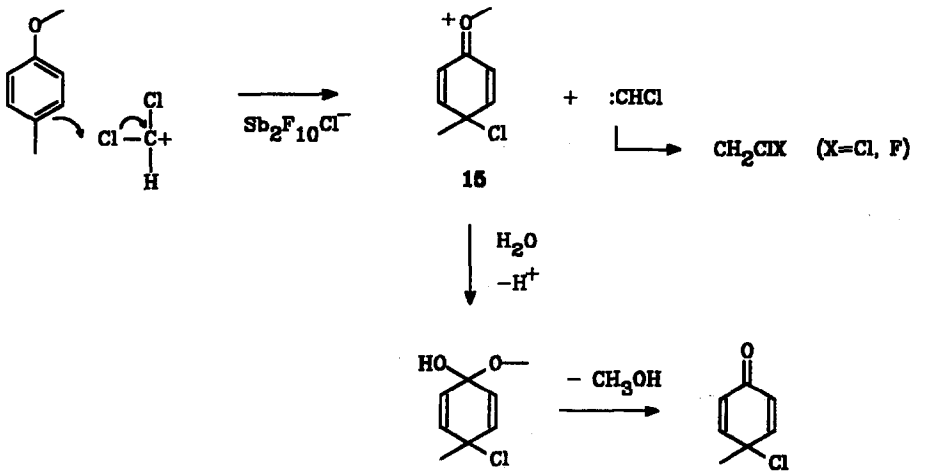


14

Mono and bicyclic ethers are very reactive substrates especially ether **2** which exhibits a surprising high reactivity. In the steroid series, 10β-chloro derivatives useful for the detection and diagnosis of hormone-dependent tumors are obtained in higher yields than previously reported[18,19].

According to the results reported in Tables 1 and 2 reactivity order of the halogenating reagents is SbF_5-CH_2Cl_2 > SbF_5-$CHCl_3$ > SbF_5-CCl_4 reflecting that of the corresponding electrophilic chloromethylcations $(ClCH_2)_2Cl^+$, $CHCl_2^+$ and CCl_3^+[22-24].

The postulated mechanism implies that the chloromethylcations liberate "Cl^+" and leave a carbene (:CH_2, :CHCl or :CCl_2, from $(ClCH_2)_2Cl^+$, $CHCl_2^+$ or CCl_3^+, respectively) which is trapped in the acidic conditions.



The mechanism is substantiated by the formation of ion **15** when ether **1** was reacted with SbF_5-$CDCl_3$. This ion, and the analogous ions obtained from ethers **3** and **11** have been fully caracterized by ^{1}HNMR. Precursors of the monochlorodienones (and dienones themselves) being stable in the reaction conditions, formation of dichloro derivatives (**5a**, **10a** or **b**, **12b** or **c**) implies initial *ortho* chlorination.

Our results suggest that an electrophilic chlorination of a C-H bond might be operative in the reaction of alkanes R-H with SbF_5-CH_2Cl_2 to yield R-Cl, preferably to a nucleophilic chlorination of the intermediate carbocation proposed by the authors[25].

It is worth noting that when the reaction is carried out on ketone **11**, no α-chlorination to the carbonyl group is observed. Even the easily enolizable 6-methoxy-1-tetralone yields only a mixture of 5-chloro (91%) and 7-chloro (4%) derivatives with SbF_5-CH_2Cl_2. This implies that enolization does not proceed in the reaction conditions, the carbonyl groups giving stable complexes with the Lewis acid[26]. A similar selective chlorination of tetralones has been reported by Guetté when using hexachloro-2,4-cyclohexadienone[27].

Our results suggest that the chloromethylcations might have a wider range of applicability for the selective chlorination of aromatics with respect to other halogenizable functions.

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20. Lower yields are observed with the corresponding phenols.
21. Yields are for isolated products after chromatography. New compounds gave satisfactory spectral data (MS, ^1H, and ^{13}C NMR) and the expected analytical (HRMS and/or microanalysis) results, except dienone **7** which is unstable. Selected spectral data **7** : ^1H NMR (200 MHz, $CDCl_3$), 7.13 (d, J = 10, 1H), 6.21 (dd, J = 10 and 1.4, 1H), 6.08 (d, J = 1.4, 1H). MS m/e (%) : 170(10), 168(30), 133(97), 105(100). **9** : ^1H NMR (200 MHz, $CDCl_3$) : 6.90 (d, J = 10, 1H), 6.19 (dd, J = 10 and 1.5, 1H), 6.06 (s, 1H). MS m/e (%) : 184(27), 182(80), 147(85), 91(100). **12a** : ^1H NMR (200 MHz, $CDCl_3$) : 7.13 (d, J = 10, 1H), 6.19 (dd, J = 10 and 1.4), 6.09 (d, J = 1.4, 1H), 0.98 (s, 3H). MS m/e (%) : 306(6), 304(18), 270(100). **14** : ^1H NMR (200 MHz, $CDCl_3$) : 7.25 (s, 2H), 6.13 (s, 2H), 0.98 (s, 6H). MS m/e (%) : 610(4), 608(21), 606(32), 574(100), 572(37), 538(45).
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