

INTRAMOLECULAR SELECTIVITY IN THE SIDE-CHAIN OXIDATION OF ALKYLBENZENES UNDER Gif^{IV} CONDITIONS.

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Summary : The intramolecular selectivity in the side-chain oxidation of alkylbenzenes, under the Gif^{IV} conditions, has been determined. The 1^o-C: 2^o-C: 3^o-C reactivity ratios are 1: 5: 9.3 and little difference in reactivity is exhibited by methyl groups *para* and *meta* to a chloro substituent. It has also been found that these selectivities result from the operation of two competing oxidations pathways, one of which not requiring catalysis by Fe^{III}. The catalyzed pathway is particularly effective towards secondary positions, as expected in Gif^{IV}-promoted oxidations.

The Gif-type oxidation systems, developed by Prof. Barton and his group, certainly represent a novel and powerful means to perform an efficient and selective functionalization of unactivated alkanes, under mild conditions.^{1,2}

Recently, one of these systems and namely that indicated as Gif^{IV} (Fe^{III} as the catalyst, pyridine + AcOH, Zn and O₂) has proved to be effective also in the side-chain oxidation of alkylaromatic compounds, the process resulting unaffected by competitive ring hydroxylation.³

Since we have long used selectivity data as mechanistic probe for the side-chain reactions of alkylbenzenes⁴, we have felt that the extension of this approach to the Gif^{IV}-promoted benzylic oxidation could be worthwhile, providing us with further information on the scope of this oxidizing system as well as on the reaction mechanism. Thus, in this note we report on a product study of the side-chain oxidation of *para*-ethyltoluene (1), *ortho*-ethyltoluene (2), *para*-cymene (3) and 1-chloro-3,4-dimethylbenzene (4), under the Gif^{IV} experimental conditions.

Following the instructions of Barton and coworkers, to a stirred solution of the substrate (2 mmol) in pyridine (28 ml), FeCl₂·4H₂O (0.25 mmol), 2.3 ml of AcOH and 1.5 g of Zn-powder were added. The suspension was vigorously stirred in an open vessel for 16 h and after work-up the distribution of the isomeric oxidation products was determined by GC (comparison with authentic specimens). The side-chain oxidation products were obtained in overall yields comparable to those observed by the Barton group with similar substrates³ and, where tested, the mass balance was very good (> 90%). All results are in Table 1.

Table I. Distribution of the isomeric oxidation products in the reactions of the substrates **1 - 4** under Gif^{IV} conditions^a.

Substrate	Products (yields, %) ^b	Overall yield, %
<i>p</i> -ethyltoluene (1)	<i>p</i> -methylacetophenone (10.3) <i>p</i> -ethylbenzaldehyde (3.1)	13.4
<i>o</i> -ethyltoluene (2)	<i>o</i> -methylacetophenone (7.6) <i>o</i> -ethylbenzaldehyde (2.8)	10.4
<i>p</i> -cymene (3)	2-hydroxy-2-(<i>p</i> -tolyl)propane (6.2) <i>p</i> -isopropylbenzaldehyde (2.0)	8.2
1-chloro-3,4-dimethylbenzene (4)	4-chloro-2-methylbenzaldehyde (2.0) ^c 5-chloro-2-methylbenzaldehyde (1.4) ^c	3.4

^a) For the conditions of the experiments see text.

^b) Average of at least two determinations. Yields determined by GC (substrates **1, 3, 4**: capillary column 25m x 0.32mm OV-17, t: 100-190 °C; substrate **2**: capillary column 25m x 0.2mm methylsilicon gum, t: 75-105 °C) using ethyl benzoate as the internal standard and based on the amount of initial substrate. The error is $\pm 10\%$.

^c) Determined as the corresponding alcohols after reduction of the reaction product with LiAlH_4 . The two isomeric aldehydes were not separable under the conditions of our GC analysis.

From the isomeric distribution in the oxidation of **1** and **3** the relative reactivity of primary, secondary and tertiary benzylic position ($1^\circ\text{-C} : 2^\circ\text{-C} : 3^\circ\text{-C}$) can be evaluated, after statistical correction, to be 1 : 5 : 9.3. From the data for compound **2** the $2^\circ\text{-C} : 1^\circ\text{-C}$ reactivity ratio is 4 : 1, not significantly different from that calculated from the results of compound **1**. From the isomeric distribution for the oxidation of **4** a very low positional selectivity results, since attack at the CH_3 group *para* to the chloro substituent is only 1.4 times faster than that at the *meta* CH_3 group. The latter observation clearly excludes any involvement of an electron transfer pathway in these oxidations.⁴

The $1^\circ\text{-C} > 2^\circ\text{-C} > 3^\circ\text{-C}$ reactivity order is of interest since it would seem that in the benzylic oxidation Gif^{IV} does not exhibit that significant enhancement of the reactivity of the secondary position, which is the most peculiar behaviour of this system in the oxidation of unactivated alkanes. Accordingly, in the latter

reactions the intramolecular selectivity is $2^\circ\text{-C} > 3^\circ\text{-C} > 1^\circ\text{-C}$.

However, this discrepancy is probably only apparent since we have discovered that substantial oxidation of our substrates also occurs in the absence of the iron^{III} catalyst (Table 2). This finding clearly indicates

Table 2. Isomeric distribution in the uncatalyzed autoxidation of substrates 1-4^a.

Substrate	Products (yields, %) ^b	Overall yield, %
<i>p</i> -ethyltoluene (1)	<i>p</i> -methylacetophenone (2.1) <i>p</i> -ethylbenzaldehyde (4.4)	6.5
<i>o</i> -ethyltoluene (2)	<i>o</i> -methylacetophenone (3.9) <i>o</i> -ethylbenzaldehyde (1.7)	5.6
<i>p</i> -cymene (3)	2-hydroxy-2-(<i>p</i> -tolyl)propane (4.5) <i>p</i> -isopropylbenzaldehyde (1.5) <i>p</i> -isopropylbenzyl alcohol (0.5)	6.5
1-chloro-3,4-dimethylbenzene (4)	4-chloro-2-methylbenzaldehyde (0.3) ^c 4-chloro-2-methylbenzyl alcohol (0.7) 5-chloro-2-methylbenzaldehyde (0.2) ^c 5-chloro-2-methylbenzyl alcohol (0.6)	1.8

a) The conditions are exactly those for the experiments in Table 1, but without the iron^{III} catalyst.

b) Determined by GC. (See footnote b in Table 1).

c) Determined after reduction to alcohol.

that under the conditions of Gif^{IV} oxidation another oxidative process takes place in addition to that catalyzed by the Fe^V oxenoid intermediate suggested to be the active species in the Gif-promoted reactions².

Thus, the above reported $1^\circ\text{-C} : 2^\circ\text{-C} : 3^\circ\text{-C}$ reactivity ratios are certainly determined in the simultaneous operation of the two competitive processes, which makes impossible any meaningful discussion of these values with respect to the actual behaviours of the Gif^{IV} promoted benzylic oxidation. However, the knowledge of these selectivity data can still be of some utility to the synthetic chemist.

Interestingly, a valuable information can instead be obtained when the data of Table 2 are compared with those of Table 1. From this comparison we note that a significant effect of the iron^{III} catalyst is

observed only for what concerns attack at the secondary position (substrates **1** and **2**, especially the former).

Surprisingly, for compounds **3** and **4** there is little difference in the extent of the oxidation between the catalyzed and the uncatalyzed process.

This observation is very important since it fully confirms Barton conclusion that the Gif systems are indeed especially reactive towards a secondary position, whereas their effectiveness towards primary and tertiary positions is much lower. Accordingly, with substrates **3** and **4**, which lack of secondary positions, the reactivity of the Gif system may be so low as to allow the uncatalyzed reaction to become a substantial part of the oxidative process. In contrast, when substrates with secondary positions are involved, the reactivity of the Gif^{IV} system becomes sufficiently high to clearly overcome that of the uncatalyzed autoxidation.

The uncatalyzed reaction is certainly of interest and deserves further attention. Particularly remarkable is the preferential oxidation of the methyl group in *para*-ethyltoluene. Preliminary experiments have indicated that both Zn and pyridine are essential components of the system. When one of these two species is lacking, especially Zn, autoxidation becomes almost negligible. Additional investigation is however necessary before some reasonable hypothesis on the mechanism of this reaction and on the actual role of Zn and pyridine becomes possible.

Acknowledgements. This work has been carried out into the framework of the Progetto Finalizzato CNR Chimica Fine.

References

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3. Barton D.H.R., Halley F., Ozbalik N., Mehl W., *Tetrahedron Letters* **1989**, 30, 6615.
4. Baciocchi E., Crescenzi M., Lanzalunga O., *J. Chem. Soc. Chem. Commun.* **1990**, 687 and references therein.
5. The correction of the data of the Gif-promoted reaction for the uncatalyzed autoxidation is of doubtful significance in view of the small yields of products and the relatively large experimental errors.

(Received in UK 8 March 1991)