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Regiocontrolled Ring Opening of 2-Methyltetrahydrofuran with Acid Chlorides and Iodides

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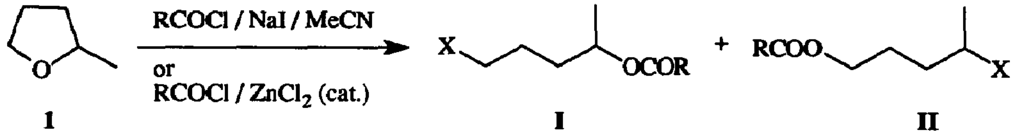
Abstract : Regioselective cleavage of 2-methyltetrahydrofuran with bulky acid iodides RCOI gives predominantly the primary iodides, while acid chlorides RCOCl lead to secondary chlorides almost exclusively, regardless of the nature of R.

The regioselective ring opening of unsymmetrical substituted heterocycles is a very interesting route to bifunctional molecules useful in organic synthesis [1]. This kind of reaction can be carried out with reagents which are a combination of an electrophile and a nucleophile [2]. 2-methyltetrahydrofuran, which is a customary model for regioselectivity studies, has been cleaved by a variety of reagents including BBr_3 [3], Me_2BBr [4], $Ac_2O/MgBr_2$ [5], MeCOCl/NaI [6], $AlCl_3$/NaI [7], Me_3SiCl/NaI [8], tBuCOCl/NaI [6]. Among these reagents, only the last three show a high regioselectivity leading predominantly to the primary iodides (>97/3). Moreover, none of the common reagents gives the secondary halides with a regioselectivity acceptable for synthetic applications, except acid chlorides in the presence of Pd^{II} [9] or Pt^{II} [10] complexes.

In order to direct the reaction towards a particular regioisomer, we studied the ring cleavage of 2-methyltetrahydrofuran with acid halides (RCOX). These reagents allow variations of some parameters which influence the regioselectivity like steric hindrance and/or electronic effect of the R group, and also the nature of X (scheme 1).



Scheme 1

First, 2-methyltetrahydrofuran was reacted with different acid iodides in MeCN at room temperature [11]. Acid iodides were formed *in-situ* from the corresponding chlorides and sodium iodide. The tetrahydrofuran ring opening reactions afforded iodoesters in good yields with the regioselectivity (primary/secondary iodides ratios I/II) reported in table 1.

Table 1 : Ring opening of the 2-methyltetrahydrofuran with RCOCl/NaI in MeCN (24 hrs, r.t.)

Runs	R	I / II [a]	yield %
1	Me	38 / 62[b]	85
2	Et	44 / 56	82
3	iPr	62 / 38	65
4	tBu	98 / 2	95
5	$ClCH_2$	10 / 90	56
6	Cl_3C	98 / 2	62
7	C_3F_7	99 / 1	70

a) Proportions determined by ^1H nmr spectroscopy and GC analysis
b) See ref 12

These results show an increase in the proportion of primary iodides with the steric hindrance of the acid halides from 38% with MeCOI (run 1) to 98% with tBuCOI (run 4). After complexation of the electrophile (RCOX) with the oxygen atom of the ether, the secondary halides arise from an attack of the halide ion on the most positive carbon atom (S_N1 type reaction) and primary halides from an attack on the less substituted carbon atom (S_N2 type reaction). In this context, the ability of RCOI to develop a positive charge on the heterocycle is crucial to control the regioselectivity. Thus, the increase in the proportion of primary halides from MeCOI to tBuCOI could be the consequence of a decrease in the electrophilic character of the reagent owing to steric hindrance and/or the electron-donating effect of the alkyl groups R.

In order to increase the selectivity towards the secondary halides and to estimate the relative importance of steric and electronic factors, we used chloroacetyl iodide ($ClCH_2COI$, run 5). The electron-withdrawing ability of the chlorine atom should enhance the electrophilicity of acid halide and thus favour the secondary iodide. This was effectively the case as shown by comparison with EtCOI (run 2) which has a similar bulkiness. To enhance this effect still further, the ring opening reaction was performed with trichloroacetyl iodide (Cl_3CCOI, run 6). Contrary to our expectations, the primary iodide was obtained almost exclusively, similarly to the result with tBuCOI in spite of an opposite electronic effect. We observed the same effect with heptafluoropropanoyl iodide (C_3F_7COI, run 7). Therefore it turns out that the steric hindrance of the reagent, when it is important, overcomes the electronic factor.

We have also taken into account the nucleophilicity of the halide X as a parameter which could influence the regioselectivity. A weaker nucleophile than iodide (i.e. chloride) should disfavour an S_N2 cleavage reaction pathway. Therefore, the 2-methyltetrahydrofuran ring cleavage was performed with acid chlorides in the absence of NaI[13].

Table 2 : Ring opening of the 2-methyltetrahydrofuran with RCOCl and RCOCl/$ZnCl_2$ cat. (r.t.).

Runs	R	$ZnCl_2$ (mol %)	Reaction time [a]	Yields %	I / II
8	Me [b]	0	5 d	62	5 / 95
9	Me	0	1 h	53	3 / 97
10	Me	0	6 h	89	3 / 97
11	Me	5	1 h	95	3 / 97
12	tBu	0	24 h	6	2 / 98
13	tBu	0	7 d	62	4 / 96
14	tBu	5	24 h	92	2 / 98
15	$ClCH_2$	5	24 h	65	3 / 97
16	Cl_3C	5	24 h	5	4 / 96
17	C_3F_7	5	24 h	5	2 / 98

a) Reaction time in hours (h) or in days (d) ; b) This reaction was performed in MeCN and the others without any solvent

As shown in the table 2, these reactions give predominantly the secondary chlorides regardless of the structure of the acid chloride. When the reaction was carried out in MeCN (run 8), 5 days were necessary to obtain a 62% yield of chloroesters. In order to reduce the reaction time and improve the yield, we performed the other reactions without solvent and, in some cases, in the presence of a catalytic amount of $ZnCl_2$. We noted that these experimental conditions strongly accelerate the kinetics of the reaction without any change in the regioselectivity. For example, the reaction with acetyl chloride in the presence of 0.05 equivalents of $ZnCl_2$ gives the cleavage product in 95% yield in only one hour (run 11).

In conclusion, acid halides RCOX allow us to direct the ring cleavage reaction of the 2-methyltetrahydrofuran. With X = I, primary iodides are obtained predominantly when bulky R groups are used. However, with X = Cl, secondary chlorides are obtained independently of the nature of R.

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11. **Typical procedure with RCOCl/NaI** : To an acetonitrile (10 ml) solution of 0.86 g of 2-methyltetrahydrofuran (10 mmol) and 1.79 g of sodium iodide (12 mmol) was added an acetonitrile (5 ml) solution of 1.20 g of pivaloyl chloride (10 mmol) at 0°C. After 24 h of stirring, at ambient temperature, the reaction mixture was quenched by the addition of aqueous $NaHCO_3$ followed by discolouration by an aqueous solution of $Na_2S_2O_3$. After extraction with diethylether, followed by drying over Na_2SO_4, we obtained 2.83 g (95%) of a 97/3 mixture of the two regioisomers 4-pivaloyloxy-1-iodopentane and 1-pivaloyloxy-4-iodopentane.

12. We found a reproducible ratio of 38/62 instead of 49/51 previously reported by Oku *et al* [6]. This discrepancy is somewhat surprising since the experimental conditions are similar.

13. **Typical procedure with RCOCl in the presence of $ZnCl_2$** : To 0.86 g of 2-methyltetrahydrofuran (10 mmol) containing a catalytic amount of anhydrous $ZnCl_2$ (68 mg, 5 mol %) was added 0.78 g of acetyl chloride (10 mmol) at 0°C. After 1 h of stirring, at ambient temperature, the reaction mixture was quenched by the addition of aqueous $NaHCO_3$. The same workup as above was employed. We obtained 1.56 g (95%) of a 3/97 mixture of the two regioisomers 4-acetoxy-1-chloropentane and 1-acetoxy-4-chloropentane.

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