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Friedel–Crafts reactions in ionic liquids: the counter-ion effect on the dealkylation and acylation of methyl dehydroabietate

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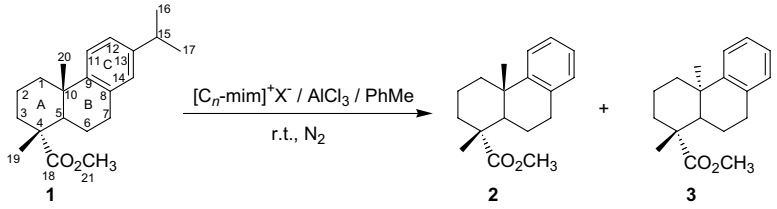
Abstract—Ionic liquids with different counter-ion and alkyl substitutes were tested as solvents in the dealkylation and acylation of methyl dehydroabietate, a useful and inexpensive building block for the synthesis of higher diterpenes derivatives. Ionic liquids with halogen counter-ions are very active in both reactions with high rate constant and conversion, avoiding the use of the conventional solvents (benzene and carbon disulfide) in these reactions. In the dealkylation reaction, the change of counter-ion from halogens to tetrafluoroborate had a dramatic effect on the stereoselectivity, showing the importance of the counter-ion in the course of the reactions.

The use of ionic liquids (IL) as alternative green solvents in organic synthesis has been the focus of a large volume of work.[1–3] The ultra-low volatibility of IL provides an obvious advantage over volatile organic solvents and their almost infinite flexibility in structure and anionic character enables to adjust their properties to suit the requirements of a particular process. Since the pioneering work of Wilkes and co-workers,[4,5] reporting IL based on dialkylimidazolium cations, Friedel–Crafts alkylations or acylations have been the most studied reactions.[6,7]

Our interest in the search for environmental friendly procedures[8–12] lead us to use appropriate new methodologies for the synthesis of higher diterpenes derivatives from resin acids,[13–15] in this particular case on the study of the dealkylation concerted with epimerizing/nonepimerizing conditions of methyl dehydroabietate (**1**) using those new solvents (Scheme 1). The effect of different lengths of the alkyl chains and counter-ions on reaction rate, conversion and selectivity was investigated. The study was extended to the acylation reaction (Scheme 2) and its performance compared with similar reactions in 'conventional' organic solvents.

Dealkylation of methyl dehydroabietate **1**[16] has been carried out with $AlCl_3$ in benzene or toluene at room temperature to give a mixture of isomers, methyl *trans*-deisopropyldehydroabietate **2** (ca. 30%) and methyl *cis*-deisopropyldehydroabietate **3** (ca. 70%). The deisopropylation process consists of two reverse Friedel–Crafts reactions, one a hydrogen replacement of the isopropyl



Scheme 1.

Keywords: Ionic liquids; Friedel–Crafts; Counter-ion effect; Methyl dehydroabietate.
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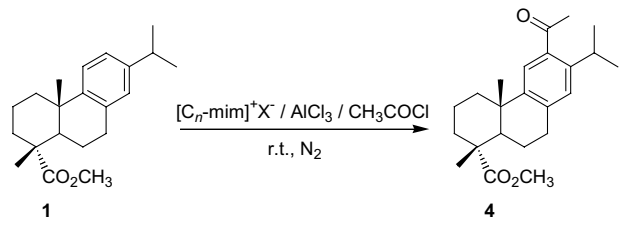
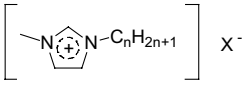


Scheme 2.

group and the other the cleavage of ring B, and one standard Friedel–Crafts reaction for the reformation of ring B. During the latter reaction, the intermediate carbonium ion has two steric modes of interaction with the benzene ring, so it is not surprising that bond formation occurs on the other side of ring A, thus creating the isomer **3**. Thus, using a bulkier and constrained solid catalyst (HY zeolite), in toluene at reflux, **2** (ca. 90%) was selectively produced.[8] In this later case no isomer **3** was formed, since no cleavage of ring B occurs.

As steric hindrance plays an important role in Friedel–Crafts reactions,[17] the dealkylation of **1** was carried out with a solvent/catalyst acidic complex ionic liquid, 1-alkyl-3-methylimidazolium heptahalodialuminate (III) $[C_nmim]Al_2Cl_6X$ with different counter ions and/or different 1-alkyl chain lengths ($n = 3, 5, 7$), in the presence of an excess of toluene (twice the mole fraction of **1**) as isopropyl acceptor.[8]



$X^- = Cl^-, Br^-, I^-, BF_4^-, PF_6^-$
$[Cn\text{-mim}]^+$, $n = 3,5,7$

The results obtained (Table 1) showed that no significant difference was introduced by the alkyl chain length used. All heptahalodialuminate complexes are highly active at room temperature with high conversion (90–98%), either with bromide or chloride as counter-ion, giving a proportion of isomers as described in the literature[16] for the traditional reaction with aluminium chloride in benzene, but in shorter reactions times. The marked difference in the stereoselectivity observed for $[C_5mim]I$ can be interpreted as due to the difficulty of this halogenoaluminate complex to promote the cleavage/reformation of ring B due to steric hindrance. In the case of halogen counter-ions, the increase in acidity introduced by the halogens (Cl < Br < I) is opposed by the size of the halogen ions.

These results and our interest in obtaining either one or the other of the isomers, led us to study the effect of the bulkier air and moisture stable tetrafluoroborate $[BF_4]$ or hexafluorophosphate $[PF_6]$ 3-methyl-1-pentylimidazolium ionic liquids, that were used, up to now in Friedel–Crafts reactions with metal trifluoromethanesulfonates.[18]

In the present study, for these two ionic liquids, no reaction was observed when the proportion of reagents was the same as with the heptahalodialuminate (III) systems. However, increasing the amount of solvent/catalyst complex ionic liquid a higher conversion (90%) and selectivity for **2** (85%) were obtained with tetrafluoroborate 3-methyl-1-pentylimidazolium ionic liquid in longer reaction time (15 h).

These systems were also applied to the Friedel–Crafts acetylation of methyl dehydroabietate **1** (Scheme 2). No carbon disulfide[19] was used and the reactions were very fast, resulting in short reaction times (15 min) and high conversions (>80%) and regioselectivities (>95 %) in the case of methyl 12-acetyl-dehydroabietate **4** using different halogenoaluminate (III) ionic liquids, except when the counter ion was chloride. As for the dealkylation reaction, the complexes air and moisture stable tetrafluoroborate $[BF_4]$ and hexafluorophosphate $[PF_6]$ 3-methyl-1-pentylimidazolium ionic liquids also proved to be inactive except when the catalytic complex $[C_5mim]BF_4/AlCl_3$ (1:2) was used in a larger amount (7-fold).

In conclusion, the results obtained (Tables 1 and 2) show that both dealkylation and acetylation of methyl dehydroabietate **1** can be improved in terms of reaction rate by the use of appropriate ionic liquids as solvents, and thus avoiding the conventional organic solvents usually employed in these reactions (benzene and carbon disulfide). In the case of dealkylation, it is possible to direct the cleavage/reformation of ring B to high yields

Table 1. Dealkylation of methyl dehydroabietate **1** using $AlCl_3$ as catalyst and toluene with different ionic liquids as solvents[a]

Entry	Solvent	Time (h)	Conversion (%)	**2**:**3** (%)
1	Benzene[b]	3	100	27:73
2	$[C_3mim]Br$	0.5	98	28:72
3	$[C_5mim]Br$	0.5	98	29:71
4	$[C_7mim]Br$	0.5	96	28:72
5	$[C_5mim]Cl$	0.5	90	27:73
6	$[C_5mim]I$	0.5	87	52:48
7	$[C_5mim]PF_6$	48	0	—
8	$[C_5mim]BF_4$	48	0	—
9	$[C_5mim]PF_6$[c]	48	0	—
10	$[C_5mim]BF_4$[c]	15	90	85:15

[a] The reaction as carried out in the presence of $AlCl_3$ and toluene. **1**/ionic liquid/$AlCl_3$/toluene = 1/2/4/4.
[b] Ref. 16; **1**/benzene/$AlCl_3$ = 1/352/5.
[c] **1**/ionic liquid/$AlCl_3$/toluene = 1/7/14/4.

Table 2. Acylation of methyl dehydroabietate **1** with acetyl chloride using $AlCl_3$ as catalyst with different ionic liquids as solvents[a]

Entry	Solvent	Time (h)	Conversion (%)	**4** (%)
1	CS_2[b]	4	100	86
2	[C_3mim]Br	0.25	95	96
3	[C_5mim]Br	0.25	96	97
4	[C_7mim]Br	0.25	90	95
5	[C_5mim]Cl	0.25	80	98
6	[C_5mim]I	0.25	97	98
7	[C_5mim]PF_6	48	0	—
8	[C_5mim]BF_4	48	0	—
9	[C_5mim]PF_6[c]	48	0	—
10	[C_5mim]BF_4[c]	0.5	87	94

[a] The reaction as carried out in the presence of acetyl chloride and $AlCl_3$. **1**/ionic liquid/$AlCl_3$/acetyl chloride = 1/2/4/4.
[b] Ref. 19; **1**/CS_2/$AlCl_3$/acetyl chloride = 1/52/3/3.
[c] **1**/ionic liquid/$AlCl_3$/acetyl chloride = 1/7/14/4.

of stereoisomers, **2** or **3**, which can be obtained as main products using either [mpim]BF4 or [mpim]halogen, respectively.

1. Experimental

1.1. General procedure for dealkylation of methyl dehydroabietate 1

A 10 mL round bottomed flask was charged with the ionic liquid (0.64 mmol), toluene (136 μL, 1.28 mmol) and $AlCl_3$ (171 mg, 1.28 mmol). Once the mixture was homogeneous, **1** (100 mg, 0.32 mmol) was added. The reaction mixture was stirred at room temperature and monitored by GLC (Fisons 8000 equipped with a BP-1 column SGE, 12 m, 0.25 μm film thickness) using standards obtained in accordance with the literature.[16] Aliquots were quenched with water, extracted with diethyl ether and dried over anhydrous $MgSO_4$ before analysis. In reactions where no aliquots were removed, the product was extracted with a high mass balance (>80%) and the compounds were isolated by crystallization from diethyl ether/methanol to yield methyl *trans*-deisopropyldehydroabietate **2** (15–62%) or methyl *cis*-deisopropyldehydroabietate **3** (10–68%).

1.2. General procedure for acylation of 1

To the homogeneous mixture of the ionic liquid (0.64 mmol) and $AlCl_3$ (171 mg, 1.28 mmol), **1** (100 mg, 0.32 mmol) and acetyl chloride (91.3 μL, 1.28 mmol) were added and left stirring at room temperature. Aliquots were quenched with water, extracted with diethyl ether and dried over anhydrous $MgSO_4$ before analysis by GLC using standards previously obtained.[19] In a reaction where no aliquots were removed, **4** was extracted with diethyl ether with high mass balance (>90%). Recrystallization from methanol afforded methyl 12-acetyldehydroabietate **4** (98 mg, 85%).

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