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LETTERS

$LiClO_4$–acyl anhydrides complexes as powerful acylating reagents of aromatic compounds in solvent free conditions

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Abstract—The Friedel–Crafts acylation of various activated benzenes is smoothly carried out with acyl anhydrides in the presence of 2 equiv. of $LiClO_4$, as reaction promoter, under solventless conditions. © 2002 Elsevier Science Ltd. All rights reserved.

The Friedel–Crafts acylation is among the most fundamental transformations in organic chemistry and it is widely applied in industrial production of useful intermediates. In its classical formulation, the reaction requires more than 1 equiv. of a Lewis acid as the promoter ($AlCl_3$) which can not be recovered and reused, owing to its instability in aqueous media.[1] To obviate this problem, several approaches based on the employment of catalytic amounts of metal triflates have been recently developed.[2] In many of them, the addition of $LiClO_4$ as promoter accelerates the acylation process and increases the yields.[3] However, the action of $LiClO_4$ seems to be limited to enhance the efficiency of the metal triflate catalyst, in fact it has been reported that the reaction does not work in the presence of $LiClO_4$ alone,[3a,4] in spite of its well-known Lewis acid character.[5]

We wish to report now that $LiClO_4$ itself can act as a very efficient promoter if the reaction is carried out in solventless conditions.[6]

Ac_2O (1.05 equiv.) is added to $LiClO_4$ (2 equiv.) and warmed to 60°C under stirring until the salt is completely dissolved. When 1 equiv. of anisole is added to this solution, a smooth Friedel–Crafts acylation occurs within 1 h leading to 4-methoxyacetophenone **2** in quantitative yields (Scheme 1).

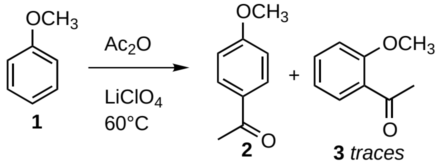
The reason of this unexpected activation is ascribed to the formation of a complex with a strong electrophilic character between $LiClO_4$ and Ac_2O in neat Ac_2O.

The reaction is highly regioselective, the product of *o*-acetylation **3** being obtained only in traces (<1%).[7] The observed regioselectivity has been reasonably interpreted in terms of the high steric requirement of the $LiClO_4$–Ac_2O complex.

If the reaction is carried out with less than 2 equiv. of $LiClO_4$, the process becomes slower; moreover, the conversion of anisole is not complete even for prolonged reaction times when the perchlorate proportion is below 1 equiv.

This is not surprising if we consider that both the reaction product **2** and AcOH can coordinate to $LiClO_4$ so destabilizing the $LiClO_4$–Ac_2O complex. In order to verify this hypothesis, some experiments were carried out in the presence of AcOH. Data reported in Table 1 indicate that the addition of AcOH at the beginning of the reaction slows the process and then a larger amount of $LiClO_4$ is necessary to restore the normal reactivity.

An analogous decrease in reactivity is noted when increasing amounts of $MeNO_2$ are initially added to the



Scheme 1. Acetylation of anisole at 60°C in the presence of $LiClO_4$.

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reaction mixture, since $MeNO_2$ can compete with Ac_2O in complexing the $LiClO_4$. These findings account for the previously reported opinion that $LiClO_4$ alone is not able to promote the acylation reaction,[3a,4] since these experiments were carried out in $MeNO_2$ solvent. We found that if the reaction is carried out with $MeNO_2$ as solvent (1 ml/mmol of anisole, Table 1, entry 12) after 8 h the conversion is only 70%.

The addition of more than 2 equiv. of $LiClO_4$ in solvent free conditions does not produce an appreciable increase in the reaction rate, but the mixture becomes extremely viscous and difficult to stir. Therefore a 2:1 ratio between $LiClO_4$ and anisole has been chosen as the most convenient condition (standard procedure).

Results reported in Table 2 show that it is possible to introduce various acyl groups into the *para*-position of anisole under the standard conditions. Only in the case of the solid benzoic anhydride it has been necessary to carry out the reaction in the presence of 4 equiv. of $MeNO_2$ at higher temperature. In all cases yields are almost quantitative.

Table 1. Acetylation of anisole (1 equiv.) with acetic anhydride (1.05 equiv.) at 60°C in the presence of $LiClO_4$ under various conditions

Entry	$LiClO_4$ (equiv.)	Solvent (equiv.)	Time	Yield (%)[a]
1	0.5	–	7 h	75
2	1	–	5 h	85
3	1.5	–	2.5 h	>99
4	2	–	50 min	>99
5	3	–	45 min	>99
6	2	AcOH (1.)	3 h	>99
7	3	AcOH (1)	3 h	>99
8	2	AcOH (2)	7 h	95
9	3	AcOH (2)	2 h	>99
10	2	$MeNO_2$ (2)	2 h	>99
11	3	$MeNO_2$ (2)	1.5 h	>99
12	2	$MeNO_2$ (19)	8 h	70

[a] Yields of 4-methoxyacetophenone **2**; in all cases 2-methoxyacetophenone **3** was detected by GLC only in traces.

Table 2. Acylation of anisole with various anhydrides under standard conditions unless otherwise mentioned

Entry	$(RCO)_2O$	Solvent (equiv.)	Time (h)	Yield (%)[c]
1	$(EtCO)_2O$[a]	–	1	>99
2	$(i\text{-}PrCO)_2O$[a]	–	1.5	>99
3	$(C_5H_{11}CO)_2O$[a]	–	1.5	92
4	$(PhCO)_2O$[b]	–	6	78
5	$(PhCO)_2O$[b]	$MeNO_2$ (4)	4	97

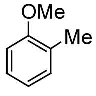
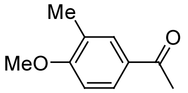
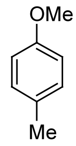
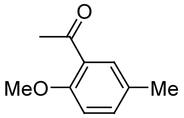
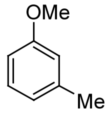
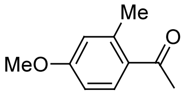
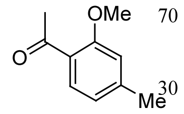
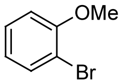
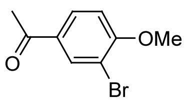
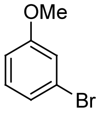
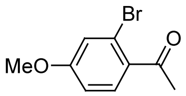
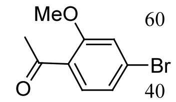
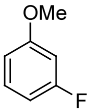
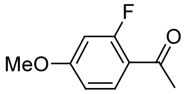
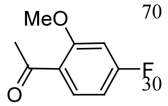
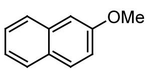
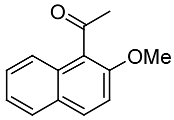
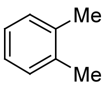
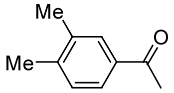
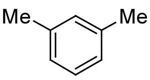
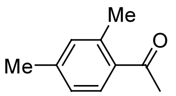
[a] Reaction carried out at 60°C.

[b] Reaction carried out at 100°C.

[c] Yields of 4-acylanisole; in all cases 2-acylanisole was detected by GLC only in traces.

The standard method was applied to the acetylation of various activated aromatic compounds. Data and reaction conditions are reported in Table 3. The results confirm the high regioselectivity of the reaction: the 4-substituted acylated products are exlusively obtained from *ortho*-substitued substrates (Table 3, entries 1, 4, and 8).

Table 3. Acetylation of activated benzenes with standard procedure under various reaction conditions (R. C.)

entry	substrate	R. C.	product	yield (%)[a]
1		1.5h at 60°C		>99
2		3h at 100°C		>99
3		2h at 60°C	 	94
4		5h at 100°C		>99
5		5h at 100°C	 	94
6		1h at 100°C	 	>99
7		1.5h at 60°C		85
8		15h at 100°C		65
9		15h at 100°C		75

a) Yields in pure isolated products

Prolonged reaction times and higher temperatures are required when acetylation can occur only at the sterically hindered *ortho*-position (Table 3, entry 2).

Higher temperatures are obviously required when the substrate is deactivated with respect to anisole (Table 3, entries 4, 5, 6, 8, and 9). Again steric interactions can account for the formation of two acetylated derivatives in the reactions of *meta*-substituted anisoles (Table 3, entries 3, 5, and 6). In all cases yields are almost quantitative, with the exception of xylenes, but it was reported[2a] that these compounds suffer from decomposition phenomena when kept at high temperatures for long times.

The present method appears to be competitive and in some cases superior to recently reported catalytic procedures, in which $LiClO_4$ is used as additive in quantities ranging from 1 to 10 equiv. to enhance the effectiveness of the catalyst; in fact, our reaction proceeds smoothly in solvent free conditions, an increasingly important feature for the development of green chemistry; moreover, $LiClO_4$ is not expensive and it is stable to moisture. In addition, although it has to be employed in more than stoichiometric amounts, it can be quantitatively recovered and reused after activation. The recovery procedure and recycling are very simple: after the reaction is complete and cooled to room temperature, CH_2Cl_2 is added under stirring; $LiClO_4$ precipitates and can be quantitatively separated by filtration or centrifugation. The precipitate can be reactivated by heating in vacuum at 140°C and reused. We repeated this procedure four times for the acetylation of anisole without any loss of activity. This simple work up also allows facile recovery of the reaction products.

Typical procedure: 2 equiv. of commercial anhydrous $LiClO_4$ were dried in vacuo (0.1 Torr) at 140°C for 2 h. After cooling, the anhydride (1.05 equiv.) was added to $LiClO_4$ and the mixture was heated at the desired temperature until $LiClO_4$ was dissolved. Then the substrate (1 equiv.) was added dropwise and the reaction was monitored by GLC. After the reaction was complete, it was cooled and CH_2Cl_2 was added. The precipitated $LiClO_4$ was recovered by centrifugation and reutilized. The organic layer was treated with aqueous $NaHCO_3$ and dried over $MgSO_4$. The reaction product was recovered by simple removal of the solvent and purified by column chromatography when necessary.

CAUTION: Lithium perchlorate and oxidizable materials could lead to devastating explosions and must be handled with care. While we have never experienced any problem even when reactivating it by heating, we urge users to protect themselves and to take appropriate safety measures.[8]

Acknowledgements

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