BiCl₃-catalyzed Friedel–Crafts acylation reactions: bismuth(III) oxychloride as a water insensitive and recyclable procatalyst

Sigrid Répichet,[a] Christophe Le Roux,[a,*] Nicolas Roques[b] and Jacques Dubac[a]

[a]*Hétérochimie Fondamentale et Appliquée, Université Paul-Sabatier, 118 route de Narbonne, 31062 Toulouse Cedex 04, France*
[b]*Rhodia Organique Fine, Centre de Recherche de Lyon, 85 avenue des Frères Perret, 69192 Saint-Fons Cedex, France*

Abstract—The Friedel–Crafts acylation of activated and polycyclic aromatics is efficiently catalyzed by bismuth(III) chloride which is generated in situ from bismuth(III) oxychloride, a water insensitive and eco-friendly material. Bismuth(III) oxychloride is easily recovered in near quantitative yields after an aqueous work-up. © 2003 Elsevier Science Ltd. All rights reserved.
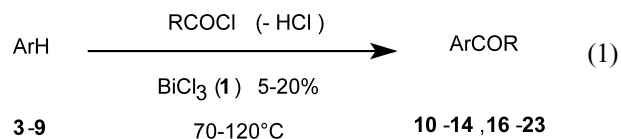
The applications of organobismuth(V)[1] and, more recently, of bismuth(III)[2] compounds in organic reactions are well known. Among the latter, the use of Bi(III) derivatives in catalytic transformations appears to be versatile and promising in their large-scale development. Bismuth compounds are attractive since many of them are commercially available, at a low cost, and have little or no toxicity.[3]

Bi(III) derivatives are mainly involved: (i) in oxido–reduction reactions;[4] (ii) in Lewis acid activated reactions,[2] due to the availability of valence shell unoccupied orbitals (or Bi–X σ*);[5] (iii) in ligand exchange reactions which, if they are reversible, take place in the catalytic cycle;[2f] and by a characteristic property, the softness of bismuth compared with the hardness of small size electronegative elements,[6] leading to labile acid–base interactions. This avoids the trapping of the Bi-based catalyst by *O*- or *N*-containing products (self-blocking reactions), for example in Mukaiyama-aldol, Michael,[7] carbonyl- and aza-Diels–Alder reactions,[8] or Friedel–Crafts acylation and sulfonylation.[2f]

Among these reactions, the FC acylation and related reactions require classically at least stoichiometric quantities of strong oxophilic Lewis acids, such as metal chlorides (AlCl₃, TiCl₄, FeCl₃),[9] which are non-recoverable materials after aqueous work-up. Consequently, the large scale development of these processes leads to corrosion and environmental problems due to large amounts of acidic effluents and solid wastes.

* Corresponding author. Fax: +33-5-6155-8204; e-mail: leroux@chimie.ups-tlse.fr

Bismuth(III) chloride (**1**) is the Bi-derivative for which the Lewis acid activity has been the most studied,[2] but it is moisture sensitive and non-recoverable from aqueous solutions. On the contrary, bismuth(III) oxychloride (**2**) is a water insensitive material which, in addition, exhibits an extremely low toxicity (LD₅₀ ORL (rat): 22 g/kg), as a result of its almost complete insolubility in aqueous solutions such as biological fluids.[3] Moreover, its transformation into BiCl₃ is possible.[10] Thus BiOCl could be regarded as a procatalyst for reactions involving BiCl₃ as catalyst, and/or allowing the recovery of the Bi-based catalyst after hydrolytic work-up. We investigate here some Friedel–Crafts acylation reactions with activated and polycyclic aromatics (Eq. (1)) in the presence of **1** or **2**, and the possibility of recovery and recycling the Bi-based catalyst.

$$\text{ArH} \xrightarrow[\substack{\text{BiCl}_3\ (\mathbf{1})\ \ 5\text{-}20\% \\ 70\text{-}120°C}]{\text{RCOCl}\ \ (\text{- HCl})} \text{ArCOR} \qquad (1)$$

3-9   **10**-14 , **16**-23

In the case of aromatic ethers, strongly activated substrates, BiCl₃ (**1**) was able to catalyze their acylation efficiently at about 80–85°C, using an acid chloride as reagent, and at higher temperatures (140°C), using an acid anhydride.[11] Many Lewis acids are efficient for such a reaction.[9] In the case of toluene **3**, the aromatic ring is much less activated than in anisole (σ^+_p(Me) = −0.31, (σ^+_p(OMe) = −0.78),[12] and its acylation is more difficult to achieve. Numerous metal chlorides,[9] and even some metal triflates,[13a,b] are inefficient in the catalytic acylation of toluene, while some other catalytic

systems containing triflic acid[13c,d] or the potentially explosive lithium perchlorate,[13e,f] have been reported for such reaction. The catalytic activity of **1** for the acetylation of **3** was previously reported as very low.[14] However, we examined the benzoylation of **3**, and we observed that the activity of **1**, which is both triflate- and perchlorate-free, is rather remarkable: an isolated yield of 40–70% of methylbenzophenone (**10**) was obtained using 10–20 mol% of **1**, after 5 h of heating at reflux (Table 1, entries 1 and 2). The benzoylation yield became high with xylenes (**4a–c**) (entries 3, 4, 6), and specially with mesitylene (**5**) (entries 9 and 10).

Polycyclic aromatics are sensitive to strong Lewis acids (AlCl$_3$, FeCl$_3$, TiCl$_4$) commonly used for their acylation, and this reaction is not regioselective.[9a,15,16] A milder activator has been described, but it requires a large excess of the (RCO)$_2$O/Me$_2$S/BF$_3$ system and strictly anhydrous conditions.[16] Interestingly, **1** appeared as an efficient catalyst for the benzoylation of three polycyclic aromatics, naphthalene (**6**), anthracene (**7**) and pyrene (**8**), and the reactions were regioselective (Table 1, entries 11–13).

The recovery and the recycling of a FC acylation catalyst is seldom possible after aqueous work-up. However, the recovery of some metal triflates (rare earths, Bi) has been reported.[13a,b,f] Another alternative consists in the use of supported catalysts, which avoids or strongly reduces the effect of leaching.[17] Since **1** is freely soluble in an HCl-containing solution, the recov-ery of 'bismuth' from the crude **1**-catalyzed acylation reaction, after aqueous work-up, simply required the neutralization of the aqueous layer with NaOH. This method allows for quantitative precipitation of BiOCl (**2**).

*Typical procedure for the benzoylation of mesitylene (**5**).* A 100 mL flask equipped with a condenser and a stirring bar was charged with mesitylene (**5**) (12 g; 0.10 mol), benzoyl chloride (7.03 g; 0.05 mol) and bismuth chloride (**1**) (1.58 g; 5 mmol). The flask was heated in a thermostated oil bath at 120°C for 4 h. After cooling, GC analysis of crude product using tetradecane as internal standard indicated that 2,4,6-trimethylben-zophenone (**16**) had been formed in quantitative yield (with respect to benzoyl chloride). Dichloromethane (80 mL) and 6% aqueous HCl (80 mL) were added to the red–brown crude mixture. The acidic layer was sub-jected to another extraction with dichloromethane (80 mL). The combined organic phases were dried over sodium sulfate and concentrated under reduced pres-sure. The product was purified by flash chromatogra-phy (silica gel; eluent: pentane/dichloromethane = 1:1) to give 10.10 g (90% yield) of ketone **16** [*954-16-5*], identified from an authentic sample.[18] ^{1}H NMR (CDCl$_3$): δ 2.10 (s, 6 H, 2- and 6-Me), 2.34 (s, 3 H, 4-Me), 6.91 (s, 2 H, aromatic protons of mesityl group); other aromatic protons: 7.44 (m, 2 H), 7.57 (m, 1 H) and 7.82 (m, 2 H). GC–MS, *m/z* %: 224 (M$^+$, 88), 223 (96), 209 (42), 208 (38), 147 (57), 119 (36), 105 (27), 91 (48), 77 (*100*), 51 (51).

Table 1. Bismuth(III) chloride (**1**)-catalyzed or bismuth(III) oxychloride (**2**)-procatalyzed acylation of aromatics

Entry	ArH	Acylating reagent (ArH/RCOCl/**1**)[a,b]	Conditions[c]	Product[d] and yield (%)[e]
1	Toluene (**3**)	PhCOCl (2:1:0.1)	120°C; 5 h	**10**[f]; 40
2	Toluene (**3**)	PhCOCl (2:1:0.2)	120°C; 5 h	**10**[f]; 70
3	*o*-Xylene (**4a**)	PhCOCl (2:1:0.1)	120°C; 12 h	**11a**; 93
4	*m*-Xylene (**4b**)	Me(CH$_2$)$_4$COCl (30:1:0.1)	100°C; 24 h	**12**; 88
5	*m*-Xylene (**4b**)	PhCOCl (2:1:0.1)	120°C; 5 h	**11b**; 80
6	*p*-Xylene (**4c**)	PhCOCl (2:1:0.1)	120°C; 12 h	**11c**; 90
7	Mesitylene (**5**)	MeCOCl (2:1:0.1)	70°C; 8 h	**13**; 89
8	Mesitylene (**5**)	Me$_2$CHCOCl (2:1:0.1)	80°C; 2 h	**14**; trace, **15**; 62
9	Mesitylene (**5**)	PhCOCl (2:1:0.1)	120°C; 4 h	**16**; 90
10	Mesitylene (**5**)	*p*-NO$_2$C$_6$H$_4$COCl (2:1:0.05)	120°C; 4 h	**17**; 97
11	Naphthalene (**6**)	PhCOCl[g] (1:1:0.2)	120°C; 5 h	**18**; 80
12	Anthracene (**7**)	PhCOCl[g] (1:1:0.2)	110°C; 2 h	**19**; 84
13	Pyrene (**8**)	PhCOCl[g] (1:1:0.2)	110°C; 5 h	**20**; 72
14	Anisole (**9**)	Me$_2$CHCOCl (2:1:0.1)	80°C; 2 h	**21**; 71
15	Anisole (**9**)	Me$_3$CCOCl (2:1:0.1)	100°C; 3 h	**22**; 94
16	Anisole (**9**)	PhCOCl (2:1:0.1)	110°C; 6 h	**23**; 96

[a] Molar ratios.

[b] For RCOCl/**1** = 1/0.1 (resp. 1/0.2) the equivalent reaction has been carried out using RCOCl/**2** = 1.2/0.1 (resp. 1.4/0.2) and gave identical result under similar conditions since the reaction of **2** with acyl chlorides (Eq. (2)) occurs quasi-spontaneously (entries 2, 4, 5, 9, 11–16).

[c] Temperature of the oil bath.

[d] Acylation product and major isomer (≥95%): methylbenzophenone (**10**), 3,4-(**11a**), 2,4-(**11b**), 2,5-dimethylbenzophenone (**11c**), 2,4-dimethyl-caprophenone (**12**), 2,4,6-trimethylacetophenone (**13**), 2,4,6-trimethylisobutyrophenone (**14**), 2-methyl-1-mesityl-1-chloropropene (**15**), 2,4,6-trimethylbenzophenone (**16**), 2,4,6-trimethyl-*p*-nitrobenzophenone (**17**), 1-benzoylnaphthalene (**18**), 9-benzoylanthracene (**19**), 1-benzoylpyrene (**20**), *p*-methoxyisobutyrophenone (**21**), *p*-pivalophenone (**22**), *p*-benzophenone (**23**).

[e] Isolated yield after work-up, with respect to the minor reagent.

[f] *o*-**10**/*m*-**10**/*p*-**10** = 18/2/80.

[g] Reactions carried out in chlorobenzene as solvent.

Dichloromethane was substituted by a more eco-friendly solvent, methyl tert-butyl ether (MTBE), without notable change of yield.

The aqueous solution was neutralized by cautious addition of aqueous NaOH (2 M). The solid formed was filtered off, and washed with 20 mL of distilled water, 20 mL of acetone (or ethanol) and oven-dried at 100°C for 5 h. This product was identified as BiOCl (2) using an X-ray powder pattern technique.[19] Mass obtained: 1.30 g (99.7% recovery of bismuth).

The Bi-catalyzed FC acylation would become particularly interesting if 2 could be reused. The transformation of 2 to 1 is easy, and can be achieved with various chlorinating agents,[10a] in particular with an acid chloride (Eq. (2)).[10b] Generally, it is carried out prior to the reaction of interest, but for the acylation reactions it can be realized in situ, using an excess of acid chloride.

$$BiOCl + 2 \ RCOCl \longrightarrow BiCl_3 + (RCO)_2O \quad (2)$$
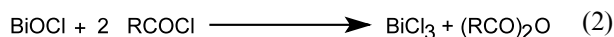
With this end in view, we carried out the acylation of aromatics 3–8 using 2 as procatalyst or 1. In both cases, the results were similar and are collected in Table 1 (entries 2, 4, 5, 9, 11–13). In the same way, the acylation of anisole (9) with $Me_2CHCOCl$, Me_3CCOCl and PhCOCl, in the presence of 2 (10% mol), gave the p-methoxyisobutyrophenone (21), -pivalophenone (22) and -benzophenone (23) in 71, 94 and 96% yields (entries 14–16), respectively.

In this last method, there is loss of a part of the acid chloride introduced. In the case of a rare and costly acid chloride, this disadvantage can be removed using another chlorinating agent, for example thionyl chloride (according to the $BiCl_3$ purification process previously reported),[20] to carry out the transformation of 2 to 1 prior to the acylation reaction. Moreover, since the reaction of 2 with the acid chloride leads to anhydride formation, it is possible that the latter intervenes as acylating agent, in addition to the acid chloride. In fact, in the presence of 1 and under the temperature conditions used (70–120°C), the reactivity of activated aromatics with respect to an acid anhydride is low (anisole),[11] or non-existent: 3 or 4b/(PhCO)$_2$O/1 = 2/1/0.1, 120°C, 5 h, no reaction. This observation is consistent with the acid chloride, rather than the anhydride, being the actual acylating agent.

In the FC acylation itself, these experimental conditions are too drastic to effect acylation of some aromatics (except anisole)[11] using an alkanoyl chloride. The simultaneous presence of a metal chloride and HCl induces the transformation of the enolizable ketone formed into an α-chlorostyrene.[21,22] Thus, the 1-catalyzed isobutyrylation of 5 gave 2-methyl-1-mesityl-1-chloropropene (15) as the main product (62%) and not the expected ketone 14 (Table 1, entry 8). Nevertheless, the acylation product was obtained using acetyl or hexanoyl chloride as reagent and mesitylene or m-xylene as aromatic substrate (entries 4 and 7). The yield

of ketone 12 was similar to that obtained, in the same experimental conditions, with antimony(III) triflate as catalyst.[23] However, the use of acetyl, pivaloyl or hexanoyl reagents and 3 or 4a,c, 6–8 led only to a tarry mixture of products.

As regards mechanistic considerations, we have already shown that 1 acts as a Lewis acid with activation of the acylating reagent by initial formation, from rt, of a coordination complex.[11] In the presence of an acid chloride, this complex is much more stable than the complex between 1 and a ketone, which explains the effective catalytic power of 1 in the FC acylation and related reactions.[2f] However, the complex between 1 and RCOCl is not electrophilic enough to achieve the acylation of benzene or deactivated chlorobenzene. For that another Bi-based catalyst (or procatalyst), bismuth(III) triflate, must be used.[2f,13b,24] Therefore, chlorobenzenes, such as o-dichlorobenzene, can be used as solvents for 1-catalyzed FC acylation reactions, specially for those involving solid aromatics (Table 1, entries 11–13). In other cases, working with liquid aromatics, solvent-free reactions are the most general.[2f,9,13b,24,25] These conditions have been used here with the liquid aromatics 3–5 and 9, using an excess of the aromatic substrate, necessary in the case of formation of a solid aryl ketone.

In conclusion, from $BiCl_3$ (1)-catalyzed FC acylation reactions, bismuth was recovered in near quantitative yields after an aqueous work-up, as BiOCl (2), a non-toxic and moisture insensitive material. Moreover, 2 was recycled by in situ transformation into 1 using the acylating agent, acid chloride, or before the acylation reaction using thionyl chloride. This recovery method of 1, through the medium of 2, seems applicable to most of the known 1-catalyzed organic reactions.

In spite of the limited catalytic power of 1, this method is a simple, cheap, safe and eco-friendly alternative to the classical processes of the FC acylation and related reactions.

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