Indium(III) chloride as a new, highly efficient, and versatile catalyst for acylation of phenols, thiols, alcohols, and amines

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Abstract—Indium(III) chloride efficiently catalyses the acylation of structurally diverse phenols, alcohols, thiols, and amines under solvent free conditions. Acid sensitive alcohols are smoothly acylated without competitive side reactions. Acylation of 2-hydroxynaphthalene is carried out with carboxylic acids adopting the mixed anhydride protocol using trifluoroacetic anhydride. © 2003 Elsevier Ltd. All rights reserved.

Protection of phenols, thiols, alcohols and amines is an unavoidable exercise in organic synthesis and is frequently achieved through acylation with anhydrides[1] due to the ease of deprotection.[1,2] The various catalysts developed for the activation of anhydrides include nucleophilic agents such as DMAP[3] and Bu$_3$P[4] and Lewis acids such as CoCl$_2$,[5] Sc(OTf)$_3$,[6] Sc(NTf$_2$)$_3$,[7] TMSOTf,[8] Bi(OTf)$_3$,[9] Cu(OTf)$_2$,[10] TaCl$_5$,[11] zeolites,[12] clays,[13] Nafion-H,[14] yttria-zirconia,[15] and LiClO$_4$.[16] However, DMAP is highly toxic and Bu$_3$P is flammable and undergoes aerial oxidation. Triflates are costly and moisture sensitive. Special efforts are required to prepare Sc(NTf$_2$)$_3$, Bi(OTf)$_3$, Nafion-H, and yttria-zirconia. Other major disadvantages of the existing protocols are the requirement of long reaction times, stringent conditions, halogenated solvents and excess acylating agents. In most of the cases the reported methods are applicable to alcohols only and are not applicable to acid-sensitive substrates due to potential side reactions (e.g. dehydration and rearrangement). Thus, there is a necessity to develop a better acylation method. Since the introduction of Sc(OTf)$_3$ in 1995, there has been an upsurge of the uses of triflates as acylation catalysts,[6–10] and Bi(OTf)$_3$ has recently been introduced as a highly powerful acylation catalyst.[9] Apart from the high cost, the susceptibility to aqueous medium of triflates becomes a major concern for their industrial applications. The pK_h (negative log of hydrolysis constant) values of 1.58 and 3.70, respectively, of Bi^{+3} and In^{+3} suggest that indium derived catalysts should be more tolerable to aqueous condi-

tions.[17] This is reflected by the use of indium derivatives in catalysing organic reactions in aqueous media.[18] We were attracted by a recent report of the use of In(OTf)$_3$ as catalyst for the acetylation of alcohols and a few phenols.[19] The larger negative H_0 value of −14.1 of triflic acid[20] suggests that metal triflates should be very strong Lewis acids and thus might lead to competitive side reactions (e.g. rearrangement, dehydration, etc.) for acid sensitive substrates. This is reflected in the observations that TMSOTf, Sc(OTf)$_3$, and Bi(OTf)$_3$-catalyzed acetylation of tertiary alcohols necessitates the use of a large excess of Ac$_2$O and a low reaction temperature (e.g. −50 to −10°C) to minimise the potential side reactions. We reasoned that the use of an In(III) salt derived from a weaker protic acid should make the catalyst less susceptible to moisture and circumvent the problem of side reactions for acid-sensitive substrates. We disclose herein our findings on the catalytic effects of InCl$_3$ for acylation of phenols, thiols, alcohols and amines.

In a model reaction of 2-hydroxynaphthalene (1.0 mol) with Ac$_2$O (1 equiv.), the acetylation was complete in 2 min under neat conditions at room temperature affording a 95% yield in the presence of InCl$_3$ (0.1 mol%). The InCl$_3$ was recovered and further used without significant loss of its catalytic activity. To evaluate the catalytic efficiency of InCl$_3$ with other acylating agents, 2-hydroxynaphthalene was treated with different acid anhydrides. Acylation with propionic, *iso*-butyric, and pivalic anhydrides resulted in 90–95% yields at room temperature in 10 min in the absence of solvent. Acylation with benzoic anhydride could be carried out either in DCM at room temperature (2 h, 85% yield) or

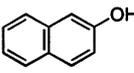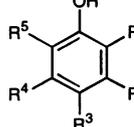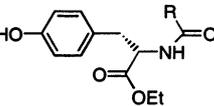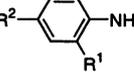* Corresponding author. E-mail: akchakraborti@niper.ac.in

at 80°C under neat conditions (15 min, 90% yield). However, no appreciable amount of trifluoroacetylation was observed with trifluoroacetic anhydride.

While testing the effectiveness of InCl$_3$ in the acylation of amines, we planned to treat various amines with Ac$_2$O under solvent free conditions in the absence of catalyst, as amines possess better nucleophilic properties compared to phenols, and were surprised to observe that diisopropylamine, aniline, 3-nitroaniline, and 4-nitroaniline afforded quantitative yields in 2–5 min at room temperature although various reports[10a,13b,15,19] claimed the need to use catalysts for the acetylation of these amines. However, the treatment of 2-nitroaniline with an equimolar amount of Ac$_2$O at room temperature for 60 min afforded 2-nitroacetanilide in only 9% yield. Anticipating that the *ortho*-nitro group offers steric hindrance, we planned to test the efficiency of InCl$_3$ for the acetylation of 2-nitroaniline and observed that the use of an equivalent amount of Ac$_2$O afforded an 80% yield, in 60 min, at room temperature.

To explore the generality and scope, structurally diverse phenols, thiols, and amines were subjected to acetylation catalysed by InCl$_3$ (Table 1). The reaction could be carried out with one equivalent of Ac$_2$O at room temperature in 2–60 min. Di- and tri-hydroxy aromatic compounds afforded the di- and tri-acetates in excellent yields (entries 15–19). Sterically hindered substrates (entries 5 and 6) require 1.5 equivalents of Ac$_2$O. Excellent chemoselectivity was observed for substrates bearing ketone, ester, and cyano functionalities, and no competitive Fries rearrangements were observed. The mildness of the acylation process allowed us to carry out the reaction with optically active substrates without any detrimental effect on the optical purity (entries 20 and 21).

Although recently metal triflates have been claimed to be the most effective acylation catalysts, the high cost, susceptibility to moisture and commercial non-availability (in some cases) do not make the metal triflates popular for use in large scale synthesis. Therefore, despite the observation that InCl$_3$ catalysed acetylation of a diverse series of phenols resulted in excellent yields, in short periods under solvent free conditions, we felt it necessary to compare the advantages of InCl$_3$ over metal triflates using a few common substrates. Thus, 2-hydroxynaphthalene was acetylated with 1 equiv. of Ac$_2$O in the presence of InCl$_3$ in 2 min under solvent free conditions but the In(OTf)$_3$ catalysed reaction requires 1.5 equiv. of Ac$_2$O in MeCN to afford comparable yields in 15 min. The superiority of InCl$_3$ over Cu(OTf)$_2$ may be demonstrated by the fact that the InCl$_3$-catalysed acetylation of electron-deficient phenols such as 4-bromophenol and 4-hydroxyacetophenone could be carried out with 1 equiv. of Ac$_2$O under neat conditions in 0.5 h, whereas the corresponding acetylation reactions using Cu(OTf)$_2$ required 2 equiv. of Ac$_2$O in DCM to afford comparable results in 2 h. The efficiency of InCl$_3$ may be compared with that of Bi(OTf)$_3$ during the acetylation of 2,4,6-trimethylphenol, a representative sterically hindered phenol. The Bi(OTf)$_3$ catalysed reaction requires 10

Table 1. InCl$_3$-catalysed acylation of phenols, thiols, and amines[a]

Entry	Substrate	Time (min)	Yield (%)[b,c]
1	naphthalene-OH structure	2	95
2	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OMe$	20	90
3	$R^1 = OMe$; $R^2 = R^4 = R^5 = H$; $R^3 = HC{:}CHMe$	15	95
4	$R^1 = OMe$; $R^2 = R^4 = R^5 = H$; $R^3 = H_2CCH{:}CH_2$	15	95
5	$R^1 = R^3 = {}^tBu$; $R^2 = R^4 = R^5 = H$	15	90[c]
6	$R^1 = R^5 = {}^tBu$; $R^2 = R^4 = H$; $R^3 = Me$	60	86[c]
7	$R^1 = R^2 = R^5 = Me$; $R^3 = R^4 = H$	15	90
8	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = Br$	30	91
9	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = COMe$	30	92
10	$R^1 = R^3 = R^4 = R^5 = H$; $R^2 = COMe$	15	90
11	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CO_2Me$	15	91
12	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = CN$	15	91
13	$R^1 = R^3 = R^4 = R^5 = H$; $R^2 = NO_2$	20	90
14	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = NO_2$	30	98
15	$R^1 = R^2 = R^4 = R^5 = H$; $R^3 = OH$	5	91[d]
16	$R^1 = OH$; $R^2 = R^3 = R^4 = R^5 = H$	15	98[d]
17	$R^1 = R^3 = R^4 = R^5 = H$; $R^2 = OH$	10	95[d]
18	$R^1 = OH$; $R^2 = R^4 = R^5 = H$; $R^3 = {}^tBu$	15	91[d]
19	$R^1 = R^2 = OH$; $R^3 = R^4 = R^5 = H$	5	84[e]
20	$R = Me$	30	100
21	$R = Ph$	30	100
23	$R = Me$	10	95
24	$R = OMe$	15	100
25	$R^1 = NO_2$; $R^2 = H$	60	80
26	$R^1 = R^2 = NO_2$	30	98

[a] The substrate was treated with Ac$_2$O (1 equiv per OH/SH/NH$_2$ group except for entries 5 and 6) in the presence of InCl$_3$ (0.1 mol%) under neat conditions at room temperature. [b] Isolated yield of the corresponding acetylated product. [c] The substrate was treated with Ac$_2$O (1.5 equiv per OH group) in the presence of InCl$_3$ (0.1 mol%) under neat conditions at room temperature. [d] Isolated yield of the di-acetate. [e] Isolated yield of the tri-acetate.

equiv. of Ac$_2$O in DCM to afford a 95% yield in 2.5 h, whereas the InCl$_3$ catalysed reaction affords comparable yields with stoichiometric amounts of Ac$_2$O in 1 h under neat conditions. The presence of the adjacent carbonyl group in benzoin makes the hydroxyl group less nucleophilic and this is reflected in the fact that acylation of benzoin requires 3 h to afford an 85% yield using 1.5 equiv. of Ac$_2$O in MeCN during the Bi(OTf)$_3$ catalysed reaction. Contrary to this, a 92% yield is obtained in 0.25 h with 1 equiv. of Ac$_2$O in the presence of InCl$_3$ under solvent free conditions.

We planned to use InCl$_3$ for further exploration of the scope of the acetylation reaction with various alcohols (Table 2). Excellent chemoselectivity was observed. Secondary and tertiary alcohols did not undergo any competitive dehydration (entries 2, 4, 5–11, 13–16) and no rearrangement took place for allylic and propargylic substrates (entries 9–15). Optically active substrates were efficiently acetylated without any detrimental effect on the optical purity (entries 6–8) demonstrating the mildness of the acetylation process. However, a sterically hindered alcohol required a longer reaction time (entry 8).

The strong Lewis acid character of metal triflates makes them unsuitable in dealing with acid-sensitive substrates such as 1-methyl-1-cyclohexanol, 1-ethynyl-1-cyclohexanol, 3-methyl-1-pentyn-3-ol, and linalool necessitating the requirement of the use of a large excess of Ac$_2$O and/or low temperature (0 to −20°C) to suppress the competitive side reactions. Therefore, distinct advantages of InCl$_3$ over the metal triflates may be best demonstrated through comparison of the results of a few representative examples of acid-sensitive substrates. Thus, 1-methyl-1-cyclohexanol was acetylated in 91% yield[9a,b] in the presence of Sc(OTf)$_3$ with 5 equiv. of Ac$_2$O at −20°C in 5 h and the TMSOTf catalysed acetylation was carried out at −10°C in Ac$_2$O as solvent, whereas a quantitative yield was obtained in 0.25 h using a stoichiometric amount of Ac$_2$O at room temperature in the presence of InCl$_3$. Acetylation of 1-ethynylcyclohexanol catalysed by Sc(OTf)$_3$, Bi(OTf)$_3$ and TMSOTf require 10 equiv. of Ac$_2$O and MeCN/ DCM as co-solvent affording 94, 88, and 68% yields, respectively, in 2–4 h while a quantitative yield of the product was obtained with 1 equivalent of Ac$_2$O in 0.5 h in the absence of solvent. A quantitative yield was obtained in 0.5 h during the acetylation of 3-methyl-1-pentyn-3-ol with a stoichiometric amount of Ac$_2$O in the absence of solvent at room temperature under the catalytic influence of InCl$_3$ but the TMSOTf-catalysed reaction affords an 80% yield in 1 h with 2 equiv. of Ac$_2$O in DCM at 0°C. Acetylation of linalool is found to be highly sensitive to the nature of the catalyst and therefore provides a suitable example for comparison of the catalytic activities of the catalysts with varying Lewis acid character. The Sc(OTf)$_3$ catalysed acetylation of linalool uses Ac$_2$O as the solvent at −20°C providing a 68% yield of the expected product along with an 8% yield of a rearranged product in 2.5 h.[6] Treatment with 3 equiv. of Ac$_2$O at −25°C for 5 h under neat conditions in the presence of Cu(OTf)$_2$

Table 2. InCl$_3$-catalysed acylation of alcohols[a]

Entry	Substrate	Time (min)	Yield (%)[b]
	R^1, R^2, R^3—C—OH		
1	$R^1 = R^2 = H; R^3 = H_2CPh$	30	85
2	$R^1 = H; R^2 = Me; R^3 = Ph$	30	90[c]
3	$R^1 = Ph; R^2 = H; R^3 = COPh$	15	92
4	$R^1 = Et; R^2 = H; R^3 = Ph$	60	100
5	$R^1 = Me; R^2,R^3 = (H_2C)_5$	15	100[c]
6		5	82[d]
7		45	70[e]
8		120	90
9		30	85[c]
	R^1, R^1, R^2—C—OH R^2		
10	$R^1 = Me; R^2 = H$	30	100[c]
11	$R^1 = H; R^2 = Me$	30	100[c]
	R^2, R^1—C≡C—R^3 HO		
12	$R^1 = R^2 = R^3 = H$	30	100
13	$R^1 = R^2 = Me; R^3 = H$	30	100
14	$R^1 = Me; R^2 = Et; R^3 = H$	30	100
15	$R^1,R^2 = (CH_2)_5; R^3 = H$	30	100[c]
16		15	90

[a] The substrate was treated with Ac$_2$O (1 equiv per OH group) in the presence of InCl$_3$ (0.1 mol%) under neat conditions (except entries 2,5,9-11,15) at room temperature. [b] Isolated yield of the corresponding acetylated product. [c] The reaction was carried out in MeCN at room temperature. [d] Isolated yield of the pentaacetate. [e] Reactions carried out in MeCN and MeNO$_2$ for 15 min afforded 87 and 100% yields, respectively.

afforded an 83% yield of the acetylated product which contained 9% of the rearranged product.[10b] The use of TMSOTf as the catalyst failed to produce any of the expected product.[8b] The InCl$_3$-catalysed reaction resulted in an 85% yield of the desired product using 1 equiv. of Ac$_2$O in 0.5 h at room temperature without any concomitant formation of the rearranged product. The use of InCl$_3$ was further found to be advantageous compared to metal triflates for acylation of sterically hindered alcohols. Thus, while the InCl$_3$ catalysed

acetylation of *endo*-borneol was carried out with 1 equiv. of Ac$_2$O for 2 h at room temperature in the absence of solvent, 10 equiv. of Ac$_2$O in THF was required in the presence of Bi(OTf)$_3$ to afford a comparable yield in 7 h. Acetylation of 1-adamantanol was carried out with 1 equiv. of Ac$_2$O in 0.25 h in the absence of solvent whereas the Bi(OTf)$_3$, Sc(OTf)$_3$, and TMSOTf-catalysed acetylations required 10 equiv. of Ac$_2$O in MeCN/DCM to afford comparable results in 3.5–8.5 h.[9b]

Further, studies were carried out during the InCl$_3$-catalysed acylations of 2-hydroxynaphthalene with equimolar mixtures of (a) Ac$_2$O and (EtCO)$_2$O; (b) Ac$_2$O and (^{i}PrCO)$_2$O; (c) Ac$_2$O and (^{t}BuCO)$_2$O; (d) Ac$_2$O and (PhCO)$_2$O and (e) Ac$_2$O and (F$_3$CCO)$_2$O. Formation of 2-naphthyl acetate with 72, 87, 96, 100, and 100% selectivity, respectively, demonstrated the influence of the steric and electronic effects of R in (RCO)$_2$O on chemoselectivity.

To make the acylation generalised with respect to the carboxylic acid, we planned to adopt a mixed anhydride protocol. Thus, 2-hydroxynaphthalene was treated separately with acetic acid, benzoic acid, phenyl acetic acid, dihydrocinnamic acid, cinnamic acid, 4-methoxycinnamic acid, 1-naphthoic acid, and thiophene-2-carboxylic acid in the presence of an equimolar amount of (F$_3$CCO)$_2$O under the catalytic influence of InCl$_3$ affording the corresponding acylated products in 100, 98, 81, 100, 98, 90, 90, and 100% yields, respectively, in 10–60 min at room temperature under neat conditions. The exothermicity of the reaction proved to be detrimental for the use of a stronger Lewis acid such as In(OTf)$_3$ or Sc(OTf)$_3$, and in most of the cases an intractable product mixture was obtained. The advantage of InCl$_3$ over In(OTf)$_3$ and Sc(OTf)$_3$ was demonstrated by the fact that the reaction of 2-hydroxynaphthalene with an equimolar mixture of (F$_3$CCO)$_2$O and thiophene-2-carboxylic acid resulted in 65 and 74% yields, respectively, with In(OTf)$_3$ and Sc(OTf)$_3$.

In conclusion, InCl$_3$ is a new and highly efficient catalyst for acylation of phenols, thiols, alcohols and amines. The advantages include low cost, ease of handling; and with increasing environmental concern,[21] the solvent-free conditions employed in the present method will make it 'environment friendly' and useful for industrial applications.

Typical procedure for acylation. 4-Nitrophenol (347.5 mg, 2.5 mmol) was treated with Ac$_2$O (0.24 mL, 2.5 mmol) at room temperature for 30 min under magnetic stirring in the presence of InCl$_3$ (0.55 mg, 0.0025 mmol, 0.1 mol%). The reaction mixture was extracted with Et$_2$O to afford 4-nitrophenyl acetate (444 mg, 98%), which was in full agreement with the spectral data (mp, IR, ^{1}H NMR and EIMS) of an authentic sample.

Typical procedure for acylation with carboxylic acids following the mixed anhydride protocol. 2-Thiophenecarboxylic acid (320 mg, 2.5 mmol) was treated with

(F$_3$CCO)$_2$O (0.35 mL, 2.5 mmol) at room temperature for 30 min under magnetic stirring in the presence of InCl$_3$ (5.5 mg, 0.025 mmol, 1 mol%) followed by 2-hydroxynaphthalene (360 mg, 2.5 mmol) for an additional 10 min. The reaction mixture was extracted with Et$_2$O to afford 2'-naphthyl thiophene-2-carboxylate (635 mg, 100%).

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