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Note

# $InCl_3$ as a powerful catalyst for the acetylation of carbohydrate alcohols under microwave irradiation☆

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**Abstract**—Indium(III) chloride catalyzed microwave assisted acetylation of different carbohydrates is an efficient synthesis of per-*O*-acetyl derivatives and provides the products in good to excellent yields.


*Keywords:* Indium(III) chloride; Acetylation; Carbohydrate; Alcohol; Microwave irradiation

The protection of alcohols with an acetyl group is one of the most common transformations in organic synthesis. The process is sluggish in the absence of an appropriate catalyst and although in general, there are a number of methods available for this conversion, their use in the carbohydrate field has limitations. One of the widely used protocols for protecting carbohydrate alcohols with acetic anhydride requires pyridine[1] as both the solvent and activator, despite its known toxicity and unpleasant odor.[2] Further addition of pyridine derivatives, such as, 4-(*N*,*N*)-dimethylaminopyridine and 4-(1-pyrrolidino)pyridine as a co-catalyst speeds up this transformation. Wolfrom's anhydrous sodium acetate method[3] is still the choice for the stereoselective preparation of β-glycosyl acetates. Other acetylation methods use $Sc(OTf)_3$,[4] $Et_3N$-DMAP,[5] $I_2$,[6] $CoCl_2$,[7] $Cu(OTf)_2$,[8] and perchloric acid[9] as the catalyst. Recently, $ZnCl_2$, potassium acetate, or sodium acetate in combination with acetic anhydrate under microwave irradiation[10] has also been reported. Very recently the use of ionic liquids[11] both as solvent as well as the catalyst for per-*O*-acetylation has been disclosed. However, most of these procedures have their own disadvantages viz., the use of excess of acetic anhydride causing tedious work up in the neutralization process, the use of pyridine is restricted due to health hazards;[2] the use of heavy metal salts is also restricted for health reasons as well as environmental pollution. Apart from these issues, the use of $ZnCl_2$ or perchloric acid cannot be done when acid-labile protecting groups are present in the carbohydrate ring. Above all, longer reaction times, compatibility with functional groups present, the catalyst and the reagents used, the amounts and especially the cost of the reagents used are of great concern. Recently, Chakraborti and co-workers have reported[12] the use of $InCl_3$ for the acetylation of different alcohols at room temperature. Among the alcohols investigated only one carbohydrate was included, D-glucose. In our hands, when attempting to apply this method to the preparation of carbohydrate acetates, we could not achieve high yields using stoichiometric amounts of acetic anhydride. Therefore, there is still a need for general user-friendly procedure for the acetylation of carbohydrate alcohols.

Organic synthesis via microwave irradiation is becoming more and more popular because of substantially

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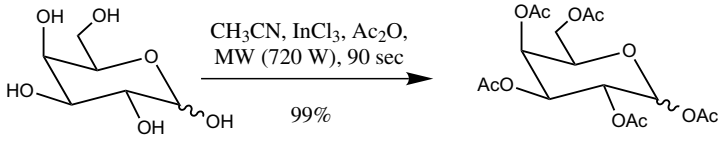
shorter reaction times that are required and the ease of use of the method. However, while microwave-assisted reactions are widely used in other areas of organic synthesis, their application in the carbohydrate area has not been as widespread. Accordingly, as a part of our ongoing programme[13] to develop an efficient, mild, rapid, and environmentally friendly procedure for the acetylation of carbohydrate alcohols, we have explored the use of microwave irradiation. When selecting a catalyst for these reactions, we chose indium(III) chloride, an increasingly popular Lewis acid in organic synthesis. Indium(III) chloride has a number of unique features among Lewis acids, which include ease of use in both organic as well as in aqueous media, low catalyst loading, moisture compatibility, and easy removal from reaction mixture. We now report that indium(III) chloride can act as a powerful catalyst for the acetylation of carbohydrate alcohols by acetic anhydride when the reaction is carried out under microwave irradiation.

To assess the potential of $InCl_3$ for these transformations, a series of preliminary experiments were carried out by irradiating a carbohydrate (100 mg) with acetic anhydride (1.5 equiv per OH group) in acetonitrile (1 mL) containing $InCl_3$ at a range of concentrations, in the microwave. Under these conditions, 0.1 equiv of $InCl_3$ was found to be sufficient for complete conversion. Increasing in amount of catalyst only reduced the time by few seconds and the gain in yield was also insignificant (5–10%). When the same reaction conditions were applied without $InCl_3$, no product was formed, even after doubling the reaction time (Table 1, entry 4). It is pertinent to note that the use of nitromethane, dichloroethane, DMSO, or neat acetic anhydride was unsuitable. There was either no product formation or poor yields of the product were obtained even after 5 min of irradiation. A representative example is shown in Scheme 1.

After these preliminary experiments, the methodology was applied to a range of carbohydrate moieties. In all cases, the substrate was dissolved or suspended in acetonitrile, acetic anhydride, and $InCl_3$ were added, and the mixture was irradiated in a microwave oven in an open vessel. The reactions, which were completed in 10–210 s, afforded the acetylated compounds in good to excellent yield (Table 1).

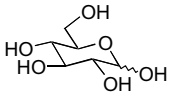
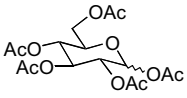
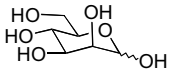
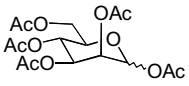
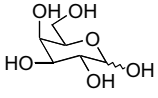
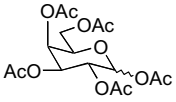
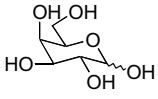
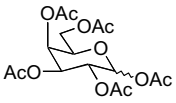
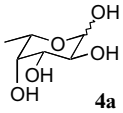
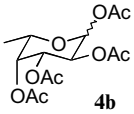
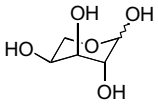
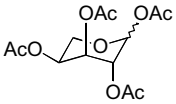
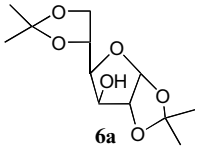
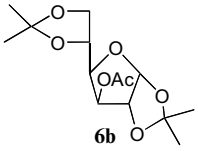
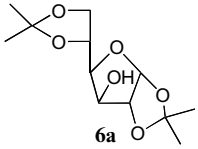
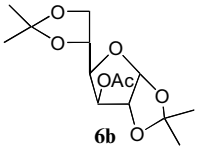
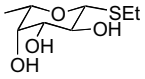
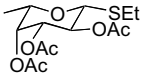
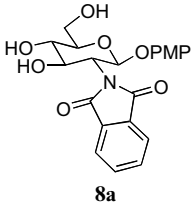
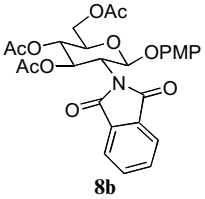
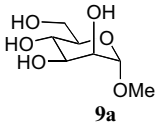
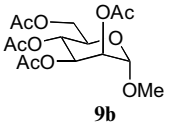
It was observed that the time required for full protection of completely unprotected carbohydrates (e.g., glucose, galactose, fucose, and mannose) was much more than the partially protected derivatives. This could be attributed to the lower solubility of the parent carbohydrate molecules, which contain a large number of free hydroxyl groups, in acetonitrile. Diacetone glucose failed to deliver the desired product (entry 7) under these conditions mainly due to the formation of acetic acid during the reaction, which caused the cleavage of the isopropylidene groups. Instead, the per-*O*-acetylated product was obtained. This problem was overcome by the addition of a base ($Et_3N$), which allowed the reaction to proceed smoothly (entry 8). This modification was extended to benzylidene protected carbohydrate moieties (entries 14–16); however, this did not provide better yields of the desired product (entry 14). Surprisingly, when we irradiated **13a** with acetic anhydride (3.0 equiv) in the presence of $Et_3N$ (6.0 equiv) and 0.1 equiv of $InCl_3$ for 60 s, a selectively 3-*O*-acetylated product (**13b**) (entry 15), was obtained, although in low yield, together with the recovery of starting material. When the same reaction was continued for another 60 s with the addition of excess acetic anhydride (2 equiv) and $Et_3N$ (4 equiv) the desired 2,3-di-*O*-acetyl product (**14**) was obtained in 70% yield (entry 16). The phthalimido group was well tolerated under these conditions (entry 10). It is interesting to note that the acetylation of **7a** afforded **7b** along with the formation of 1,2,3,4-tetra-*O*-acetyl-α-L-fucopyranose (10%). This side product was a result of apparent $S_N2$ attack of an acetyl group on the anomeric carbon atom. As outlined in Table 1, in general, the yields of these reactions are high.

To further probe the utility of this method, we compared $InCl_3$ to some other well-established catalysts used in 'standard' acetylation methods, under microwave irradiation (Table 2). All the reactions were irradiated for 90 s in appropriate solvent or neat (following 'standard' conditions). Surprisingly, using acetic anhydride and pyridine, D-galactose did not yield any pentaacetate and D-glucose yielded only 33% of the pentaacetate under microwave condition. Interestingly, in the $Cu(OTf)_2$ mediated reactions, there are differences in yields between the reactions performed neat or in solvent. Those done in solvent provide better yields for both D-glucose and D-galactose. Acetylation failed on both the carbohydrate moieties when using $CoCl_2$ as the catalyst. This comparative study shows that when using microwave irradiation, $InCl_3$ is a better choice than the 'standard' methods and the yields under these



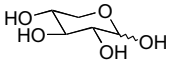
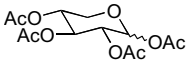
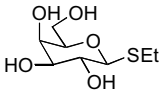
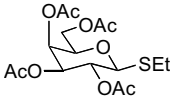
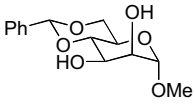
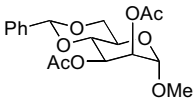
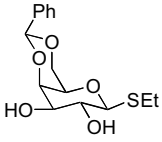
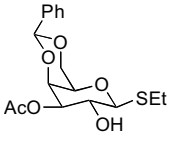
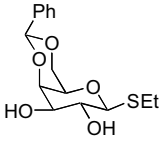
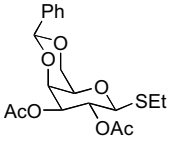
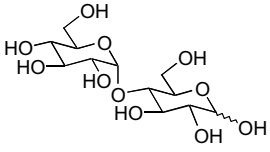
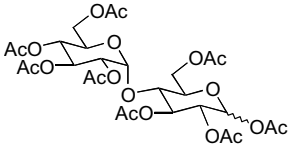
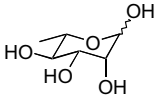
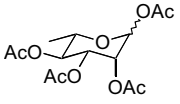

**Scheme 1.**

**Table 1.** $InCl_3$ catalyzed microwave-assisted acetylation of carbohydrates moieties

| Entry | Substrate | Product | $InCl_3$ (equiv) | Time (s) | Yield[a] | Ratio (α/β) | Ref. |
|---|---|---|---|---|---|---|---|
| 1 |  **1a** |  **1b** | 0.1 | 90 | 94% | 4/1 | 14a |
| 2 |  **2a** |  **2b** | 0.1 | 210 | 97% | 4.5/1 | 14b |
| 3 |  **3a** |  **3b** | 0.1 | 90 | 99% | 9/1 | 14c |
| 4 |  **3a** |  **3b** | 0 | 210 | No reaction | — | |
| 5 |  **4a** |  **4b** | 0.1 | 40 | 99% | 9/1 | 14d |
| 6 |  **5a** |  **5b** | 0.1 | 40 | 91% | 2.6/1 | 14e |
| 7 |  **6a** |  **6b** | 0.1 | 20 | No desired product | — | |
| 8 |  **6a** |  **6b** | 0.1[b] | 10 | 72% | — | 14f |
| 9 |  **7a** |  **7b** | 0.1 | 40 | 50% | — | 14g |
| 10 |  **8a** |  **8b** | 0.1 | 40 | 77% | — | |
| 11 |  **9a** |  **9b** | 0.1 | 210 | 97% | — | 14h |

(*continued on next page*)

**Table 1** (*continued*)

| Entry | Substrate | Product | $InCl_3$ (equiv) | Time (s) | Yield[a] | Ratio (α/β) | Ref. |
|---|---|---|---|---|---|---|---|
| 12 |  **10a** |  **10b** | 0.1 | 40 | 95% | 9/1 | 14i |
| 13 |  **11a** |  **11b** | 0.1 | 60 | 65% | — | 14j |
| 14 |  **12a** |  **12b** | 0.1[b] | 30 | 46% | — | 14k |
| 15 |  **13a** |  **13b** | 0.1[b] | 60 | 40% | — | 14k |
| 16 |  **13a** |  **14** | 0.1[b] | 120 | 70%[c] | — | 14l |
| 17 |  **15a** |  **15b** | 0.1 | 90 | 97% | 1.2/1 | |
| 18 |  **16a** |  **16b** | 0.1 | 40 | 95% | >95%α | 14m |

[a] Isolated yields.
[b] This reaction was performed in the presence of $Et_3N$ (2.0 equiv per equiv of $Ac_2O$).
[c] In this reaction an excess amount of $Ac_2O$ (2 equiv) and $Et_3N$ (4 equiv) were added further.

conditions were higher when carried out without microwave irradiation (Table 2). We note, however, that the $I_2$-catalyzed reaction provides comparable yields for both D-glucose and D-galactose.

To conclude, the $InCl_3$ catalyzed acetylation of carbohydrates with acetic anhydride under microwave irradiation provides carbohydrate peracetates in good to excellent yield. The process is operationally simple and requires only 0.1 equiv of the catalyst. These features, combined with the short reaction times and easy work-up make this method an attractive alternative to existing methodologies for the acetylation of carbohydrate alcohols.

## 1. Experimental section

### 1.1. General methods

$^1H$ NMR spectra were recorded with tetramethylsilane (TMS, $\delta$ 0.00) as internal standard on a Varian Gemini 400 MHz FT NMR spectrometer. Mass spectra were measured on Hewllet Packard-5989A mass spectrometer (CI, 20 eV). IR spectra were recorded using Perkin–Elmer 1650 FT-IR spectrophotometer. Melting points were measured in a glass capillary on a digital melting point apparatus model No. Büchi-535, and are uncorrected. All the chromatography solvents were distilled

**Table 2.** Comparative study of acetylation under microwave irradiation

| Substrate | Method | $Ac_2O$ (equiv) | Solvent | Yield (%) (microwave) | Ratio (α/β) | Yield reported (%) (non-microwave) |
|---|---|---|---|---|---|---|
| Glucose | $Ac_2O$/py[1] | 7.5 | $CH_3CN$ | 33 | 3.7/1 | 95[1] |
| | $Ac_2O/I_2$[6] | 9.5 | — | 90 | 8.5/1 | >98[6] |
| | $Ac_2O/Cu(OTf)_2$[8] | 5.1 | — | 71 | 3.7/1 | 98[8] |
| | $Ac_2O/Cu(OTf)_2$ | 5.1 | $CH_3CN$ | 81 | 4.7/1 | — |
| | $Ac_2O/CoCl_2$[7] | 10 | $CH_3CN$ | No reaction | — | 95[7] |
| | $Ac_2O/InCl_3$ | 7.5 | $CH_3CN$ | 94 | 4/1 | — |
| Galactose | $Ac_2O$/py[1] | 7.5 | $CH_3CN$ | No pentaacetate | — | 98[1] |
| | $Ac_2O/I_2$[6] | 9.5 | — | 86 | 6/1 | >98[6] |
| | $Ac_2O/Cu(OTf)_2$[8] | 5.1 | — | 12 | >95%α | 90[8] |
| | $Ac_2O/Cu(OTf)_2$ | 5.1 | $CH_3CN$ | 79 | 4.7/1 | — |
| | $Ac_2O/CoCl_2$[7] | 10 | $CH_3CN$ | No reaction | — | — |
| | $Ac_2O/InCl_3$ | 7.5 | $CH_3CN$ | 99 | 9/1 | — |

before use. Silica gel (100–200 mesh, SRL, India) was used for column chromatography.

### 1.2. General procedure for acetylation

To a solution of the carbohydrate (100 mg) and $Ac_2O$ (1.5 equiv per OH) in acetonitrile (1 mL) $InCl_3$ (0.1 equiv) was added and the mixture was irradiated at 720 W in a microwave oven (LG model: MC-804AAR) for the appropriate time (see Table 1). The reaction mixture was then diluted with ethyl acetate and washed with sodium bicarbonate and water, dried ($Na_2SO_4$) and evaporated to dryness. The residue was purified on silica gel to afford the desired products in the yields listed in Table 1. All the products were characterized by 1D $^1H$ NMR spectroscopy, 2D $^1H$–$^1H$ correlation spectroscopy, IR spectroscopy, and mass spectrometry. Spectroscopic data and combustion analysis data are presented only for previously unreported compounds.

### 1.3. *p*-Methoxyphenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranoside (8b)

Mp 70–72 °C; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta_H$ 1.89, 2.04 and 2.10 (3s, 9H, 3 C(O)C$H_3$), 3.73 (s, 3H, C$H_3$), 3.93–3.98 (m, 1H, H-5), 4.16–4.37 (m, 2H, H-6), 4.57 (dd, 1H, $J$ = 10.8, 8.6 Hz, H-2), 5.24 (dd, 1H, $J$ = 10.2, 9.1 Hz, H-4), 5.85 (d, 1H, $J$ = 8.6 Hz, H-1), 5.852 (dd, 1H, $J$ = 10.8, 9.1 Hz, H-3), 6.73 (d, 2H, $J$ = 9.1 Hz, Ph), 6.85 (d, 2H, $J$ = 9.1 Hz, Ph), 7.71–7.76 (m, 2H, Ph), 7.84–7.88 (m, 2H, Ph); IR (KBr): 1750, 1719, 1508, 1386, 1219, 1039 $cm^{-1}$. Anal Calcd for $C_{27}H_{27}O_{11}N$: C, 59.89; H, 5.03; N, 2.59. Found: C, 61.18; H, 5.05; N, 2.80.

### 1.4. 1,2,3,6-Tetra-*O*-acetyl-4-*O*-(2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranosyl)-D-glucopyranose (15b)

(α:β mixture; 1.2:1): $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.99, 2.00, 2.014, 2.018, 2.024, 2.027, 2.031, 2.051, 2.075, 2.10, 2.102, 2.139, 2.144, 2.17, 2.225 (15s, 48H, 16C(O)C$H_3$), 3.82–3.97 (m, 3H, H-5, H-4′ (2)), 4.01–4.12 (m, 7H, H-4 (2), H-6 (4), H-6′), 4.20–4.27 (m, 4H, H-5, H-5′ (2), H-6′), 4.46 (dd, 2H, $J$ = 12.3 and 2.5 Hz, H-6′ (2)), 4.84–4.9 (m, 2H, H-1′), 4.95–5.00 (m, 2H, H-2), 5.04 and 5.09 (2d, 2H, $J$ = 10.7 Hz, H-3′), 5.29 (t, 1H, $J$ = 8.9 Hz, H-3), 5.33–5.44 (m, 2H, H-2′), 5.51 (dd, 1H, $J$ = 10.2 and 8.6 Hz, H-3), 5.74 (d, 1H, $J$ = 8.3 Hz, H-1α), 6.24 (d, 1H, $J$ = 2.8 Hz, H-1β). IR (KBr): 1754, 1373, 1225, 1035 $cm^{-1}$. Anal Calcd for $C_{28}H_{38}O_{19}$: C, 49.56; H, 5.64. Found: C, 49.90; H, 5.35.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