

Indium Promoted-Convenient Method for Acylation of Alcohols with Acyl Chlorides

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Even though various reagents for coupling of alcohols with carboxylic acids and transesterification of esters have been developed,¹ there is still a great demand for a process by using acyl chlorides for the acylation of alcohols in the case of substrates having steric hindrance or low reactivity. The acylation of alcohols with acyl chlorides is commonly carried out in the presence of tertiary amines such as 4-(methylamino) pyridine or 4-pyrrolidinopyridine.² Many methods for the acylation of alcohols with acyl chlorides have been developed using a variety of reagents.³ Most recently, benzylation of alcohols with lithium perchlorate has been reported.⁴ However, these methods have their own disadvantages such as long reaction times, high reaction temperatures or difficult work-up process. And some of them are not applicable to the acylation of sterically hindered alcohols.

Recently, indium metal has drawn attention due to its unique properties such as low toxicity and stability in water and air compared with other metals.⁵ Herein we are reporting a simple and convenient procedure for the acylation of alcohols with acyl chlorides in the presence of indium metal.

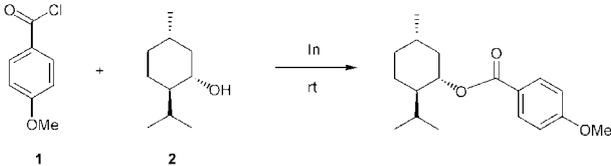
We chose *p*-anisoyl chloride (**1**) and (+)-menthol (**2**) as model compounds to examine the optimal reaction condi-

tions for the acylation of alcohols with acyl chlorides in the presence of indium. The results are summarized in Table 1. Reaction of **2** (1 equiv) with **1** (1 equiv) in the presence of indium (1 equiv) in CH₃CN at room temperature produced the corresponding ester in only 21% yield and the starting acyl chloride and alcohol were recovered. The optimal yield of the ester was attained with 3 equiv of **1** or **2** in the presence of 3 equiv of indium. The solvent effect of acylation of **2** with **1** in the presence of indium was studied. The reaction proceeded efficiently in common organic solvents such as DMF, Et₂O, THF or CH₂Cl₂ whereas non-polar solvents such as *n*-hexane or benzene gave poor yields of the ester.

The reactivity of acyl halides was studied. The results are presented in Table 2. The results show that aromatic acyl chlorides with electron-withdrawing groups including the non-substituted led to higher yield than those with electron-donating groups. The acylation of alcohol with aliphatic acyl chlorides also proceeded smoothly affording high yields of the ester. It is noteworthy that carbon-carbon double bonds remained intact under the present reaction conditions while the reaction performed under basic reaction conditions led to a double bond isomerized product.⁶

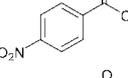
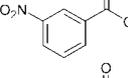
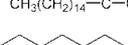
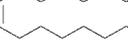
A variety of sterically different alcohols was employed for acylation to examine the scope and limitations of this process (Table 3). Indium metal is capable of the acylation of primary, secondary and tertiary alcohols although sterically

Table 1. Reaction of (+)-Menthol (**2**) with *p*-Anisoyl Chlorides (**1**) in the Presence of Indium under Various Reaction Conditions



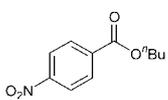
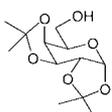
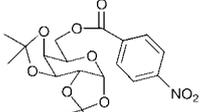
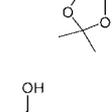
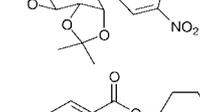
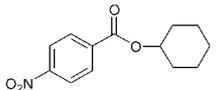
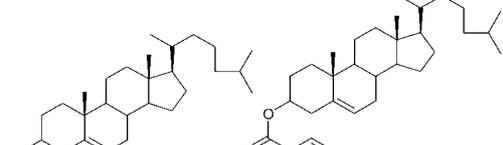
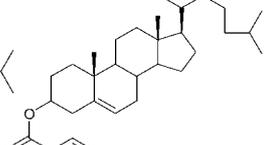
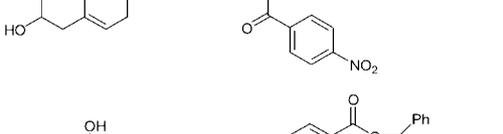
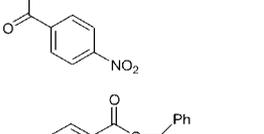
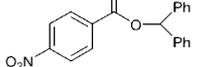
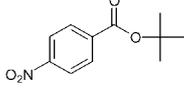
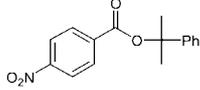
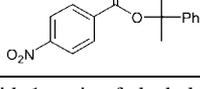
Entry	1 (equiv)	2 (equiv)	In (equiv)	Solvent	Time (h)	Yield (%)
1	1	1	1	CH ₃ CN	12	21
2	1	1	3	CH ₃ CN	12	43
3	1	3	3	CH ₃ CN	3	80
4	3	1	3	CH ₃ CN	2	86
5	1	3	3	DMF	3	84
6	1	3	3	Et ₂ O	3	79
7	1	3	3	THF	3	78
8	1	3	3	CH ₂ Cl ₂	3	77
9	1	3	3	Acetone	3	57
10	1	3	3	Benzene	3	35
11	1	3	3	<i>n</i> -Hexane	3	29

Table 2. Indium Promoted Acylation of (+)-Menthol with Acyl Chlorides

Entry	Acyl chloride	Product	Time (h)	Yield (%)
1			2.5	91
2			2.5	89
3			12 ^a	49
4			2.5	85
5			2	94
6			2	88

^aThe reaction was carried out with 1 equiv of acyl chloride.

Table 3. Indium Promoted Acylation of Alcohols with *p*-Nitrobenzoyl Chloride

Entry	Alcohol	Product	Time (h)	Yield (%)
1	<i>n</i> -Butanol		2	95
2			4	70
3			6	72 ^a
4			3	84
5			6	81 ^b
6			6	73 ^a
7			6	66
8			7	67
9			12	0
10			1	86 ^c

^aThe reaction was carried out with 1 equiv of alcohol and 3 equiv of *p*-nitrobenzoyl chloride. ^bIn THF. ^cAt 80 °C.

hindered secondary and tertiary alcohols gave relatively

lower yields. In the case of more sterically hindered tertiary alcohols, higher reaction temperature was required to accomplish the reaction.

In conclusion, we have demonstrated that indium metal, which is commercially available, without pre-treatment, is a mild and convenient promoter for the acylation of alcohols with acyl chlorides.

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