# A New Acylation Catalyst

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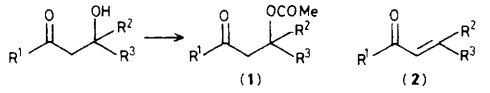
Cobalt(II) chloride catalyses the acylation of alcohols and amines with anhydrides in excellent yields.

4-Dimethylaminopyridine (DMAP) has emerged as a versatile reagent for effecting acylation,[1,2] and its role as an efficient acyl transfer catalyst[3] during the acylation of tertiary alcohols is particularly noteworthy. However, when we attempted to acetylate a β-hydroxycarbonyl compound using the protocol followed in the DMAP method,[3] a mixture of the acetate and the α,β-unsaturated carbonyl compound was obtained (see Table 1). This may be owing to the basic medium of this reaction being strong enough to cause elimination of the resulting acetate. To circumvent this problem, the acylation under non-basic conditions seemed an attractive alternative, although this has received little attention[4] in the past. This prompted us to look for a catalyst which can mediate acyl transfer under neutral or slightly acidic conditions and we now give a preliminary account of our findings.

Recently we have shown[5] that cobalt(II) chloride in acetonitrile efficiently catalyses the coupling of thiols with anhydrides to give thiol esters in very good yield. Similarly, here we observed that when an alcohol and an anhydride in acetonitrile are treated with a catalytic amount of cobalt(II)[6] chloride, excellent yields of esters were obtained. The reaction proceeded readily with primary alcohols at ambient temperature whereas some secondary and tertiary alcohols required heating to 80 °C for a few hours (Table 2). Typically, anhydrous cobalt(II) chloride (5 mol%) was dissolved in dry acetonitrile and a mixture of anhydride (1.5 equiv.) and alcohol (1 equiv.) in dry acetonitrile added slowly over a period of 5 min at room temperature. The resulting mixture

**Table 1.** Cobalt(II) chloride catalysed acetylation of β-hydroxycarbonyl compounds compared with the DMAP method.




| Entry | $R^1$ | $R^2$ | $R^3$ | Reaction conditions[b] | % Yield[a] of product(s) |
|---|---|---|---|---|---|
| 1 | Me | H | H | $CoCl_2$, room temp., 2 h | 89 (**1**) |
| 2 | Me | H | H | DMAP[c]–$Et_3N$, room temp., 2 h | 21 (**2**) + 67 (**1**) |
| 3 | Me | Me | H | $CoCl_2$, room temp., 2 h | 87 (**1**) |
| 4 | Me | Me | H | DMAP–$Et_3N$, room temp., 2 h | 28 (**2**) + 53 (**1**) |
| 5 | Me | Me | Me | $CoCl_2$, room temp., 2 h | 89 (**1**) |
| 6 | Me | Me | Me | DMAP–$Et_3N$, room temp., 2 h | 33 (**2**) + 45 (**1**) |
| 7 | EtO | Ph | H | $CoCl_2$, 80 °C, 2 h | 72 (**1**) |
| 8 | EtO | Ph | H | DMAP–$Et_3N$, room temp., 2 h | 18 (**2**) + 52 (**1**) |

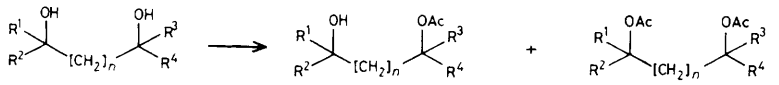
[a] Isolated yield of acetylated products. [b] All the reactions were carried out using 1.2 equiv. of acetic anhydride. [c] The acetylation using DMAP was carried out as described in ref. 3.

**Table 2.** Cobalt(II) chloride catalysed acylation of alcohols and amines.

| Entry | Alcohol/amine | Reaction conditions | % Yield[a] |
|---|---|---|---|
| 1 | Butan-1-ol | $(MeCO)_2O$, room temp., 2 h | 92 |
| 2 | Butan-1-ol | $(n\text{-}C_3H_7CO)_2O$, room temp., 2 h | 89 |
| 3 | But-2-en-1-ol | $(MeCO)_2O$, room temp., 2 h | 90 |
| 4 | Cyclohexan-1-ol | $(MeCO)_2O$, room temp., 3 h | 88 |
| 5 | (−)-Menthol | $(MeCO)_2O$, 80 °C, 2 h | 89 |
| 6 | Cholesterol | $(MeCO)_2O$, 80 °C, 2.5 h | 72 |
| 7 | D-Glucose | $(MeCO)_2O$ (10 equiv.), 80 °C, 4 h | 95 |
| 8 | Catechol | $(MeCO)_2O$ (2 equiv.), room temp., 3 h | 92 |
| 9 | t-Butyl alcohol | $(MeCO)_2O$, room temp., 3 h | 91 |
| 10 | t-Butyl alcohol | $(n\text{-}C_3H_7CO)_2O$, room temp., 4 h | 87 |
| 11 | t-Butyl alcohol | $\overline{OC(:O)\text{–}C_6H_4\text{–}C(:O)}$, 80 °C, 3 h | 73 |
| 12 | 1-Methylcyclohexan-1-ol | $(MeCO)_2O$, room temp., 5 h | 85 |
| 13 | 1-Methylcyclohexan-1-ol | $(n\text{-}C_3H_7CO)_2O$, room temp., 6 h | 81 |
| 14 | 1-Methyl-1-phenylethan-1-ol | $(MeCO)_2O$, room temp., 5 h | 83 |
| 15 | 1-Methyl-1-phenylethan-1-ol | $(n\text{-}C_3H_7CO)_2O$, room temp., 5 h | 80 |
| 16 | 1-Ethynyl-cyclohexan-1-ol | $(MeCO)_2O$, 80 °C, 2 h | 93 |
| 17 | Linalool | $(MeCO)_2O$, 80 °C, 1.5 h | 70 |
| 18 | β-Naphthylamine | $(MeCO)_2O$, 80 °C, 2 h | 94[b] |
| 19 | 2-Aminopyrimidine | $(MeCO)_2O$, room temp., 3 h | 91[b] |
| 20 | *p*-Aminophenol | $(MeCO)_2O$ (1 equiv.), room temp., 2 h | 83[b,c] |
| 21 | *p*-Aminophenol | $(MeCO)_2O$ (2.5 equiv.), room temp., 3 h | 87 |
| 22 | *p*-Nitroaniline | $(MeCO)_2O$, room temp., 0.5 h | 93[b] |
| 23 | 1-Aminoanthraquinone | $(MeCO)_2O$, 80 °C, 2 h | 79[b] |

[a] Isolated yields. All the acylated products were satisfactorily characterized by $^1H$ n.m.r. and i.r., spectroscopy. [b] The acylation of these amines was found to be very slow without cobalt(II) chloride. [c] Only *p*-amino-*O*-acetylphenol was obtained.

**Table 3.** Cobalt(II) chloride catalysed selective acylation of dihydroxy compounds.



(3) (4)

| Entry | $R^1$ | $R^2$ | $R^3$ | $R^4$ | Reaction conditions | % Yield[a] of product(s) |
|---|---|---|---|---|---|---|
| 1 $n=2$ | Me | Me | H | H | $(MeCO)_2O$ (1 equiv.), room temp., 6 h | 78 (**3**) |
| 2 $n=2$ | Me | Me | H | H | $(MeCO)_2O$ (2.5 equiv.), 80 °C, 2.5 h | 81 (**4**) |
| 3 $n=1$ | Me | Me | Me | H | $(MeCO)_2O$ (1 equiv.), room temp., 5 h | 72 (**3**) |
| 4 $n=1$ | Me | Me | Me | H | $(MeCO)_2O$ (2.5 equiv.), 80 °C, 3 h | 79 (**4**) |
| 5 $n=1$ | H | H | H | Me | $(MeCO)_2O$ (1 equiv.), 80 °C, 2 h | 21 (**3**) + 23 (**4**) |
| 6 $n=1$ | H | H | H | Me | $(MeCO)_2O$ (2.5 equiv.), 80 °C, 2.5 h | 76 (**4**) |

[a] Isolated yield.

was stirred at ambient temperature under an atmosphere of nitrogen or heated to 80 °C (for some secondary and tertiary alcohols) for the time indicated in Table 2. Usual workup and column chromatography gave esters in excellent yields. Thus a variety of alcohols were acylated with acetic, butyric, and phthalic anhydrides under these conditions and the results are given in Tables 1—3. It is noteworthy, though not particularly surprising, that the β-hydroxycarbonyl compounds can be acetylated in very high yields under these conditions without any trace of α,β-unsaturated carbonyl compounds, which are obtained in substantial amounts when acetylation is carried out by the DMAP method (see Table 1). This method as also suitable for the selective acetylation of a primary or secondary hydroxy group in the presence of a tertiary one as evidenced by the formation of monoacetate by employing 1 equiv. of acetic anhydride (entries 1 and 3 in Table 3). In contrast, no selectivity was observed between a primary and a secondary hydroxy group of butane-1,3-diol (entry 5 in Table 3) when the reaction was carried out at 80 °C.† Similarly D-glucose underwent smooth penta-acetylation (entry 7, Table 2) but was not subject to the selective monoacetylation of the primary hydroxy group; instead a mixture of di- and tri-acetates was obtained.

Amino groups were also acetylated satisfactorily by this method and a phenolic group was shown to be acetylated in preference to an amino group in *p*-aminophenol (entry 20 in Table 2). However, the limitation of this method is evident as no acylation of t-butyl alcohol with isobutyric or pivalic anhydrides was observed even on prolonged heating at 80 °C.

In conclusion, cobalt(II) chloride catalysed acylation is a good alternative to the DMAP method and advantageous with respect to the acylation of β-hydroxycarbonyl compounds and the selective acylation of a primary and secondary hydroxy group in the presence of a tertiary one. Mechanistically this reaction seems to be interesting and we are investigating the role of cobalt(II) chloride which may involve electron transfer.

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## References

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6 For other catalytic reactions of cobalt(II) chloride see: J. Marquet and M. Moreno-Manas, *Chem. Lett.*, 1981, 173; H. Matsuda and H. Kanai, *ibid.*, 1981, 395.

† No acetylation was observed when the reaction of butane-1,3-diol or D-glucose were carried out at room temperature and therefore, when the reactions were conducted at 80 °C using 1 equiv. of acetic anhydride, indiscriminate acetylation took place. A careful monitoring of these reactions revealed that the secondary hydroxy group has a propensity to acetylate at the same rate as the primary one. Although at present we do not have sufficient examples to say this with any conviction, a detailed account of this observation will be communicated later.

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