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Journal of Molecular Catalysis A: Chemical 230 (2005) 107–111
JOURNAL OF MOLECULAR CATALYSIS A: CHEMICAL
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Niobium(V) chloride: an efficient catalyst for selective acetylation of alcohols and phenols

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Received 9 December 2004; accepted 9 December 2004

Abstract

Acetylation of various alcohols, were carryout successfully, while using acetic anhydride and catalytic amount of niobium(V) chloride at room temperature. The method is very mild towards other functional groups and the yields were in excellent.

Keywords: Alcohols; Acetylation; Niobium(V) chloride; Methylenedichloride

In the post-genomic age, a premium is placed on versatile, complexity-generating reactions, where in a multitude of natural product, drug and lead-like compounds can be rapidly assembled and funneled into biological screening programmes [1]. Furthermore, the ability of chemists to optimize newly discovered lead compounds, as well as to produce analogues or mimics of biologically active natural products, relies upon the advancement of synthetic technologies. During endeavors in total synthesis, which involves the protection and deprotection of a variety of functional groups (Scheme 1).

Among the various functional groups, hydroxyl is very familiar and their protection as acetyl ester is the most frequently used one. It can be carried out by using either basic or acid conditions. The most common and cheap regent used in order to perform the acetylation is activated carboxylic acid derivative acetic anhydride [2] in presence of amine bases like triethylamine, pyridine, 4-diaminopyridine (DMAP) and 4-pyrrolidinopyridine (PPY) [3], etc. The other catalysts used for this transformation such as Bu_3P [4a], $COCl_2$ [4b], $TaCl_5$ [4c], $RuCl_2$ [4d], iodine [4e], montmorillonite K-10 [4f], K-SF [4g], MgBr–R_3N [4j], aminophosphine super base [4k], metal triflates [5], PS lipase and zeolites HZSM-360 [6] The main drawback of the reagents is that in addition to their lack of generality, they have to be applied in stoichiometric amounts or even in large excess to effect complete conversion of the substrate. Contemporary organic synthesis is constantly striving for discovery and design of reagents, which provides beneficial levels of efficiency and mildness towards other protecting groups.

As part of our continuing interest in the development of new synthetic methodologies [7], herein, we wish to report an efficient method for the selective acetylation of various alcohols. For instance the treatment of 4-methoxy benezylalcohol (entry **b**, Table 1), with acetic anhydride in the presence of niobium(V) chloride (10 mol%) in methylene dichloride at room temperature, afforded the acetylated compound in 96% yield. The reaction time is very short (2.0 h) and the obtained product is also very clean and further purification is not required. In a similar manner, 4-methyl phenol (entry **a**), phenyl ethanol (entry **c**) and phenylpropanol (entry **d**) were reacted very smoothly. Accordingly, cinnamylalcohol (entry **g**) and furfurylalcohol (entry **e**) were underwent acetylation without forming side products. Interestingly, the Baylis-Hillmann alcohol (entry **f**), which was very sensitive towards Lewis acids, was also acetylated in excellent yields. Aryl carbinols (entry **m**), reacted very well in short period but sterically hindered alcohols (entry **r**) required little more time when compared with others but yields were very good in all the cases. In all the cases, reactions were carried out at

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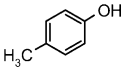
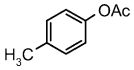
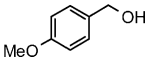
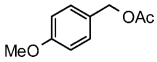
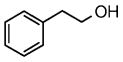
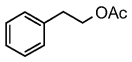
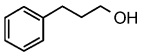
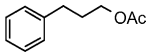
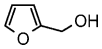
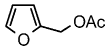
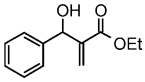
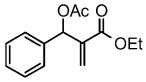
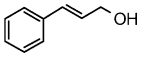
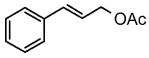
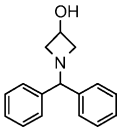
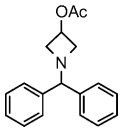
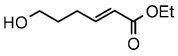
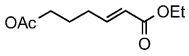
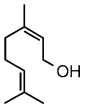
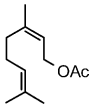
doi:10.1016/j.molcata.2004.12.012

Table 1
Niobium(V) chloride: an efficient catalyst for acetylation of alcohols

S. no.	Substrate	Product[a]	Reaction time (h)	Yield[b] (%)
a			3.0	94
b			2.0	96
c			2.5	90
d			2.0	93
e			2.5	90
f			2.0	94
g			2.0	88
h			2.5	92
I			3.0	90
j			2.0	89
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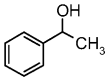
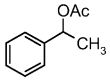
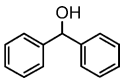
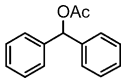
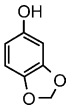
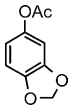
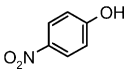
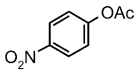
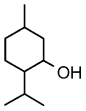
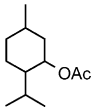
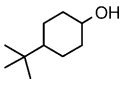
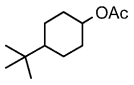
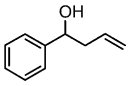
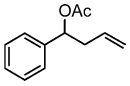
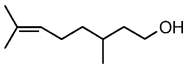
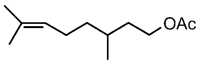
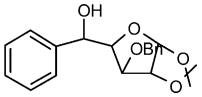
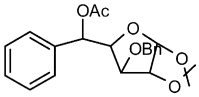
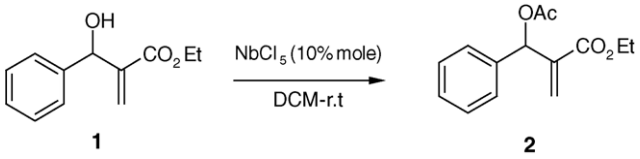
l			2.5	95
m			3.0	96
n			2.5	90
o			3.0	86
p			2.5	90
q			2.0	93

Table 1 (*Continued*)

S. no.	Substrate	Product[a]	Reaction time (h)	Yield[b] (%)
r			3.0	90
s			2.5	91
t			2.5	92
u			3.0	86
v			2.0	88

[a] All the products were characterised by ^{1}H NMR, IR and mass spectroscopy. The spectral data for selected products; **2f**: IR (neat); 3083, 2961, 2857, 1714, 1605, 1478, 1369, 1157, 1032, 865, 759 cm^{-1}; ^{1}H NMR (CDCl3); 1.24 (t, 3H, J = 6.6 Hz), 2.10 (s, 3H), 4.15 (q, 2H, J = 6.6 Hz), 5.80 (s, 1H), 6.35 (s, 1H), 6.63 (s, 1H), 7.15–7.40 (m, 5H); **2i**; IR (neat); 1726, 1601, 1563, 1471, 1395, 1213, 1104, 1042, 951, 837, 727 cm^{-1}; ^{1}H NMR (CDCl3); 1.22 (t, 3H, J = 6.8 Hz), 1.72–1.82 (m, 2H), 2.00 (s.3H), 2.20–2.40 (m, 2H), 4.00–4.20 (m, 4H), 5.80 (d, 1H, J = 17.0 Hz), 6.80–7.00 (m, 1H); **2k**; IR (neat); 2816, 1694, 1404, 1249, 1173, 1119, 999, 755, 704 cm^{-1}; ^{1}H NMR (CDCl3); 1.40 (s, 9H), 1.60–1.80 (m, 4H), 2.00 (s, 3H), 3.20–3.35 (m, 2H), 3.45 (d, 2H, J = 6.5 Hz), 3.60–3.75 (m, 1H); EIMS *m/z* (%); 229 (m + 10), 184 (12), 145 (15), 127 (35), 83 (29), 57 (100), 43 (38); **2p**; IR (neat); 2863, 1714, 1598, 1504, 1437, 1269, 1052, 872, 736 cm^{-1}; ^{1}H NMR (CDCl3); 0.76 (d, 3H, J = 6.90 Hz), 0.87 (d, 3H, J = 6.9 Hz), 0.90 (d, 3H, J = 6.6 Hz), 0.95–1.13 (m, 3H), 1.30–1.60 (m, 2H), 1.80–1.90 (m, 2H), 1.94–2.04 (m, 2H), 2.08 (s, 3H), 4.60–4.70 (m, 1H); **2q**; IR (neat); 2826, 1720, 1608, 1542, 1453, 1317, 1252, 1107, 1054, 906, 831, 764 cm^{-1}; ^{1}H NMR (CDCl3); 0.86 (s, 9H), 0.93–1.36 (m, 5H), 1.80–1.86 (m, 2H), 1.92–1.98 (m, 2H), 2.05 (s, 3H), 4.56–4.66 (m, 1H); EIMS *m/z* (%); 198 (m + 38), 155 (21), 139 (100), 112 (57), 84 (21), 57 (34); **2r**; IR (neat); 2841, 1706, 1611, 1549, 1378, 1196, 952, 752 cm−1; H NMR (CDCl3); 1.25–1.50 (m, 8H), 1.57 (s, 3H), 2.00 (s, 3H), 2.08–2.16 (m, 2H); **2t**; IR (neat); 3079, 2934, 2861, 1719, 1598, 1426, 1297, 1056, 853, 769 cm^{-1}; ^{1}H NMR (CDCl3); 2.05 (s, 3H), 2.55–2.70 (m, 2H), 5.08 (t, 2H, J = 9.5 Hz), 5.58–5.88 (m, 2H), 7.20–7.40 (m, 5H); **2u**;. IR (neat); 1708, 1627, 1568, 1409, 1387, 1247, 1108, 1053, 886, 808, 765 cm^{-1}; ^{1}H NMR (CDCl3); 0.94 (d, 3H, J = 6.5 Hz), 1.10–1.25 (m, 1H), 1.60 (s, 3H), 1.62 (s, 3H), 1.65–1.72 (m, 1H), 1.82–2.00 (m, 2H), 2.08 (s, 3H), 4.08–4.18 (m, 2H), 5.12 (t, 1H, J = 6.9 Hz), EIMS; *m/z* (%): 198 (M + 32), 155 (61), 139 (1 0 0), 111 (34), 83 (19), 69 (28), 55 (21).

[b] Isolated and unoptimized yields.



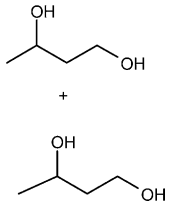
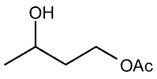
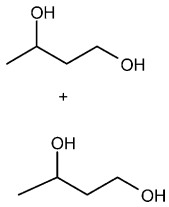
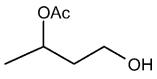
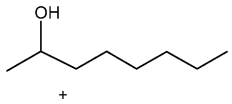
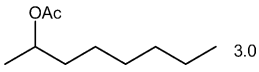
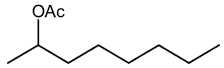
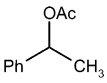
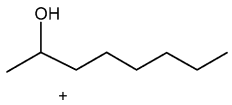
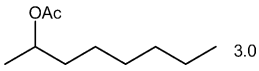
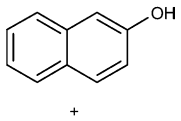
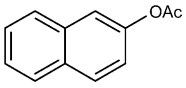
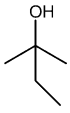
Scheme 1.

room temperature with high efficiency and the solvent used was methylene dichloride.[1] This method is very mild and compatible with a wide range of functional groups such as methoxy (entry **b**), methylenedioxy (entry **n**), ethoxy (entry **i**), carbomates (entry **k**) and acetonides (entry **v**) present in the substrate. In view of the emerging importance of the catalyst, we have studied the role of catalyst by using in different quantities. When the catalyst was used one equivalent, the reaction completes with in 1 h. If the catalyst was used in 10 mol%, the reaction completion takes place more than 1 h. From the above observation, it is very clear that catalytic amount of catalyst is enough for complete conversion instead of stiochiometric, in terms of economic point of view. In order to increase the scope of the present method further, a comparative study on selective acetylation of various alcohols was carried out (Table 2).[2] Initially, butane-1,3-diol was reacted with acetic anhydride with niobium(V) chloride at room temperature for 3 h, primary hydroxyl group was acetylated in 80% and secondary hydroxy was acetylated 20% yield, respectively, no diol-acetylayted product observed. In the case of octan-2-ol and 1-phenyl ethanol, the hydroxy group of 1-phenyl ethanol was acetylated 75%,

[1] General procedure: To a stirred mixture of substrate (2 mmol) in methylene dichloride (10 mL) was added acetic anhydride (4 mmol) and followed by addition of catalyst Niobium pentachloride (0.2 mmol) at room temperature. The progress of the reaction was monitored by TLC. After complete conversation of starting material, as indicated by TLC, the reaction mixture was diluted by adding methylene dichloride (20 mL) and washed with water twice followed by brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain the pure products.

[2] General procedure comparative study: To a stirred mixture of 2-Octanol (1 mmol) and 1-phenyl ethanol (1 mmol) in methylene dichloride (10 mL) was added acetic anhydride (1 mmol) and followed by addition of catalyst Niobium pentachloride (0.1 mmol) at room temperature and stirred for 3 h. The progress of the reaction was monitored by TLC. The reaction mixture was diluted by adding methylene dichloride (20 mL) and washed with water twice followed by brine. The organic layer was dried over sodium sulfate and concentrated under reduced pressure to obtain crude product, further purified by column chromatography.

Table 2
Niobium(V) chloride: an efficient catalyst for acetylation of alcohols

Entry	Alcohols	Reagent	Product[a]	Time (h)	Yield (%)[b]
1		$NbCl_5$ (10 mol%) Ac_2O/DCM		3.0	80
					20
2		$NbCl_5$ (10 mol%) Ac_2O/DCM	 3.0	3.0	25
					75
3		$NbCl_5$ (10 mol%) Ac_2O/DCM	 3.0	3.0	100
					NO
4		$NbCl_5$ (10 mol%) Ac_2O/DCM		3.0	100
					NO

[a] All the products were characterised by ^1H NMR, IR and mass spectroscopy.
[b] Isolated and unoptimized yields.

whereas octan-2-ol hydroxy group acetylated only 25%. In the third experiment secondary hydroxy of octan-2-ol and tertiary hydroxy of 2-methyl-buten-2-ol was subjected to acetylation, secondary hydroxy of octane-2-ol acetylated completely whereas and tertiary hydroxy of 2-methyl-buten-2-ol not acetylated. In the fourth experiment 1-naphthol and 2-methyl-buten-2-ol treated with acetylation only 1-naphthol was acetylated, whereas 2-methyl-buten-2-ol not acetylated, when we used tertiary alcohol alone, the acetylated takes place very smoothly. Therefore, niobium(V) chloride is useful for electron withdrawing hydroxy group more effectively than electron donating hydroxy group. From the, above study, the reactivity order, towards acetylation with acetic anhydride–niobium(V) chloride reagent system was as follows: phenolic > benzylic > aliphatic primary > aliphatic secondary > tertiary.

In conclusion, the niobium(V) chloride is proved to be a useful and novel catalyst for selective acetylation of a wide range of alcohol functional groups such as primary, secondary, tertiary, benzylic and phenolic. The experimental procedure is very simple, mild reaction conditions, high conversion, enhanced reaction rates, cleaner products, high yields and avoiding the tedious workup procedure for the isolation of products.

Acknowledgment

AKB thanks to U.G.C. New Delhi for fellowship.

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