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A New Method of Regioselective Protection of Primary Alcoholic Function with Rare Earths Salts.

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Abstract: *Regioselective acetylation of primary alcoholic functions, in the presence of secondary ones, was performed in very high yield with methyl ortoacetate, by means of catalysis with rare earths salts on silica gel.*

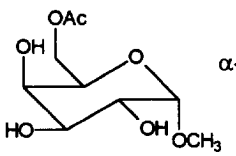
The regioselective protection of primary alcoholic functions, in the presence of secondary ones, is a typical problem of the organic synthesis. In particular regioselective acetylation is a goal which has been achieved by different methodologies, particularly chemical and enzymatic ones.

The simplest approach is to carry out the well-known acetylation with Ac_2O/Py at low temperature [(1)]. This methodology allows selection between the primary and secondary hydroxyls, but the regioselectivity is not complete and the reaction temperature is a key-point, strictly correlated to the nature of substrate. Another approach requires the use of AcOEt in the presence of a solid support, such as Al_2O_3 [(2)] or SiO_2.$NaHSO_4$ [(3)]. This methodology is limited by the relatively low yields (45-69%).

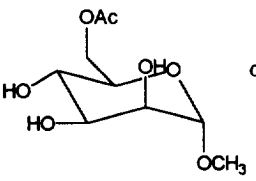
The enzymatic approach for the selective acetylation of primary hydroxyls requires the use of $AcOCH_2CF_3$ [(4)] or $AcOCH_2CCl_3$ [(5)] in the presence of porcine pancreatic lipase. The yields are moderately high (77-85%), but this methodology has been applied essentially to the carbohydrate field.

We wish to report a new very simple procedure for the regioselective acetylation of primary hydroxyls, performed by using methyl orthoacetate and the chloride of rare earths, dispersed on silica, as catalysts.

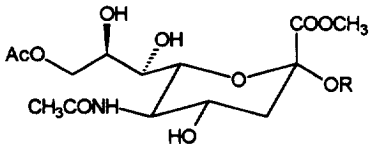
The described methodology was tested on different polyhydroxylated substrates (see figure), in particular on sugars and related substances. In all cases the results were very satisfactory, obtaining the regioselective protection of primary alcoholic functions in very high yields and in relatively short time.



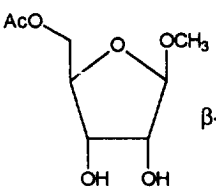
α-methyl galactoside



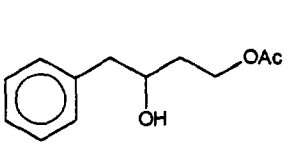
α-methyl mannoside

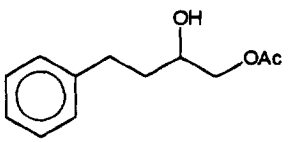


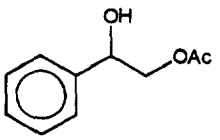
methyl sialoside
R=H, OCH_3



β-methyl riboside







The adopted experimental procedure is here described. The chloride of the rare earth, erbium, lanthanum, europium or neodymium, was dissolved in dry methanol and the solution adsorbed on suitable quantities of silica gel, to obtain a concentration of salt on silica of 2% w/w. Solvent was eliminated under reduced pressure at 40 °C and the catalyst stored in dry conditions.

Substrates (0.25-5.0 mmol) were dissolved in methanol (0.5-10 ml) and methyl-orthoacetate (0.5-10 ml), then 0.1-2.0 g of catalyst was added under stirring. The reaction is complete after 2-4 hr. The catalyst was removed by filtration, volatile materials evaporated in vacuo and the residue purified by silica gel chromatography in a suitable solvent, generally $CHCl_3$/MeOH 9:1. The esterification yields after purification were: α-methyl-mannoside, 90%; α-methyl-galactoside, 92%; methyl sialoside (methyl ester of N-acetylneuraminic acid) , 98%; α-methoxy methyl sialoside (methyl ester of N-acetylneuraminic acid α-methoxy), 90%; β-methyl-riboside, 94%; 1,3-hydroxy-4-phenyl-butane, 90%; 1,2-hydroxy-4-phenyl-butane, 91%; 1,2-hydroxy-3-phenyl-propane, 93%. Regioselectivity of esterification was checked by ^{1}H-NMR spectroscopy; selected data are reported in notes 6-7. We have noted an increasing in the catalytic effect (shorter reaction time) with the increase of atomic number of lanthanoid used and therefore with the decrease of ionic radius.

Our methodology presents, in comparison with the above described procedures, a series of advantages. The reagent and the solvent used seem to be suitable for a very broad variety of substrates. The procedure is very simple and the reaction time relatively short. The yields are always more than 90% and the work-up is very simple, being catalyst, reagent and the solvent easily eliminated by filtration and evaporation.

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References and Notes

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6. ^{1}H-NMR (D_2O, 300 MHz). α -methyl-mannopiranoside: δ: 2.10 (3H, s, $COCH_3$), 3.35 (3H, s, OCH_3), 4.85 (2H, m, $\underline{CH_2}OAc$), 4.70 (1H, d, 6.5 Hz, H-1); α-methyl-ribofuranoside: δ: 2.06 (3H, s, $COCH_3$), 4.25 (2H, m, $\underline{CH_2}OAc$), 4.92 (1H, d, 7.0 Hz, H-1), 3.38 (3H, s, OCH_3); α -methyl-galactopiranoside: δ: 2.10 (3H, s, $COCH_3$), 3.35 (3H, s, OCH_3), 4.85 (2H, m, $\underline{CH_2}OAc$), 5.27 (1H, d, 6.5 Hz, H-1); methyl-sialoside: δ : 1.87 (1H, dd, J=11.0 and 12.0 Hz, H-3 $_{ax}$), 2.00 (3H, $NHCOO\underline{CH_3}$), 2.05 (3H, s, $COCH_3$), 2.20 (1H, dd, J=5.0 and 11.0 Hz, H-3 $_{eq}$), 3.76 (3H, s, $COOCH_3$), 4.22 (1 H, dd, J=5.0, 11.0 Hz, H-9 $_a$), 4.40 (1 H, dd, J=2.0, 11.0, H-9 $_b$); α-methoxy methyl-sialoside: δ : 1.70 (1H, dd, J=11.0 and 12.0 Hz, H-3 $_{ax}$), 2.02 (3H, $NHCOO\underline{CH_3}$), 2.05 (3H, s, $COCH_3$), 2.52 (1H, dd, J=5.0 and 11.0 Hz, H-3 $_{eq}$), 3.25 (3 H, s, OCH_3), 3.74 (3H, s, $COOCH_3$), 4.25 (1 H, dd, J=5.0, 11.0 Hz, H-9 $_a$), 4.45 (1 H, dd, J=2.0, 11.0, H-9 $_b$).
7. ^{1}H-NMR ($CDCl_3$, 300 MHz). 1,3-hydroxy-4-phenyl-butane: δ: 2.15 (3H, s, $COCH_3$), 4.35 (2H, m, 2H-1), 3.70 (1H, m, H-3) 1.95 (2H, m, 2H-2), 2.80 (2H, m, 2H-4), 7.05 (5H, Ph); 1,2-hydroxy-4-phenyl-butane: δ: 2.15 (3H, s, $COCH_3$), 4.55 (2H, m, 2H-1), 3.80 (1H, m, H-2), 2.55 (2H, m, 2H-3) 2.01 (2H, m, 2H-4), 7.05 (5H, Ph); 1,2-hydroxy-2-phenyl-ethane: δ: 2.08 (3H, s, $COCH_3$), 4.20 (2H, ABX system, J_{AB}=10.0, J_1=8.0, J_2=3.0, 2H-1), 4.94 (1H, ABX system, J_1=8.0, J_2=3.0, H-2), 7.35 (5H, Ph), 2.50 (1H, bs, OH).

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