Selective acylation of aliphatic alcohols in the presence of phenolic hydroxyl groups†

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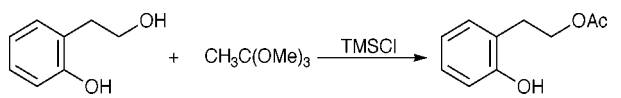
A new and efficient method for the selective acylation of aliphatic hydroxyl groups in the presence of phenolic groups using a mixture of trimethyl orthoacetate and trimethylsilyl chloride at room temperature is reported. The reactions are selective, high yielding and complete within 3–6 h.

Performing chemoselective transformations is a challenging problem in organic synthesis, especially when identical functional groups in similar chemical environments are present. Selective acylation of aliphatic hydroxyl groups in the presence of aromatic hydroxyl groups is an important process.[1] In the case of phenols it has been previously carried out using metal sulfates supported on silica gel,[2a] the Ac_2O-catalytic $BF_3 \cdot Et_2O$ reagent system[2b] or over an alumina surface[2c] in ethyl acetate solvent. In recent years orthoesters were successfully used for the conversion of carbonyl compounds to their acetals,[3] for the esterification of acids,[4a] for the etherification of alcohols[4b] and also used for the alkylation of amines[4c] and active methylene compounds.[4d] In a further effort to conceive new methods for the selective acylation of aliphatic hydroxyl groups in the presence of phenolic hydroxyl groups we explored the applicability of orthoesters as acylating agents. We have found that the trimethyl orthoacetate–TMSCl system is especially effective for the selective acylation of aliphatic hydroxyl groups.

A number of substrates, bearing both aliphatic and aromatic hydroxyl groups, were selectively acylated at the aliphatic hydroxyl groups by using 1 equiv. trimethylsilyl chloride and 1 equiv. trimethyl orthoacetate in dichloromethane at room temperature (see Scheme 1). The selectivity may be attributed to the *in situ* generation of anhydrous HCl from TMSCl[5] and aliphatic alcohols.

The alkyl hydroxyl groups, including primary and secondary alcohols, were selectively acylated in the presence of phenolic hydroxyl groups in good yields (Table 1). Chemoselectivity was achieved under these reaction conditions due to the greater nucleophilicity of aliphatic hydroxyl groups compared to phenolic groups. When we tried to acylate benzyl alcohol it gave only the dimerised product (benzyl ether); likewise, in the case of cinnamyl alcohols, Claisen-rearranged product formation was observed by ^{1}H NMR spectroscopy.



Scheme 1

In conclusion, this method provides higher selectivity for alkyl hydroxyl groups in the presence of phenolic groups and affords better yields than conventional acylation methods. As the method is mild and highly selective, it is an attractive addition to the existing methods.

Experimental

A mixture of alcohol (10 mmol), trimethyl orthoacetate (10 mmol) and trimethylsilyl chloride (10 mmol) was stirred in dichloromethane under a nitrogen atmosphere for the time given in the table. After complete conversion, as monitored by TLC, the reaction mass was diluted with water and extracted with dichloromethane (20 ml). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to afford crude product, which was further purified by column chromatography on silica gel (100–200 mesh) using ethyl acetate and hexane (3 : 7) to yield pure monoacylated product.

Entry b. ^{1}H NMR ($CDCl_3$): δ 1.96 (2H, m, $-CH_2CH_2CH_2-$), 2.01 (3H, S, $-COCH_3$), 2.57 (2H, t, $J = 8.0$ Hz, $ArCH_2CH_2-$), 4.04 (2H, t, $J = 6.0$ Hz, $-CH_2OAc$), 5.56 (br s, OH), 6.58–6.91 (4H, AB type, J = 8 Hz, aromatic).

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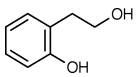
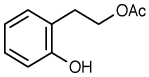
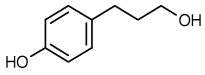
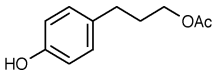
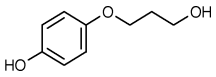
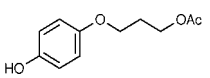
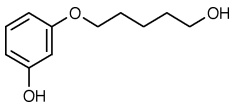
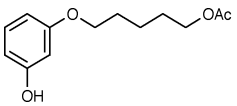
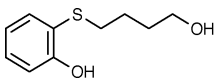
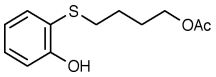
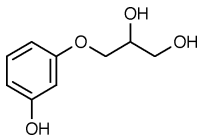
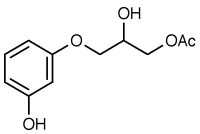
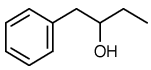
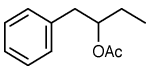
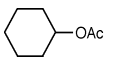
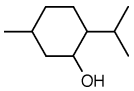
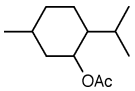
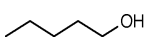
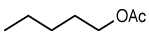
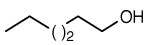
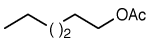
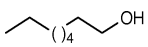
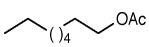
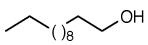
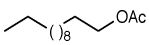
Table 1 Selective acylation of aliphatic hydroxyl groups over phenolic groups

Entry	Alcohols	Product1[a]	Reaction time/h	Yield[b] (%)
a			3	85
b			4	88
c			4	87
d			5	83
e			4	81
f			3	70
g			4	78
h			5	70
i			6	73
j			5	85
k			5	83
l			6	81
m			6	78

[a] All products were characterised by ^{1}H NMR and IR spectra. [b] Isolated yields after column chromatography.