An Extremely Simple, Convenient, and Selective Method for Acetylating Primary Alcohols in the Presence of Secondary Alcohols

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Summary: Reaction of primary–secondary diols with acetyl chloride in dichloromethane in the presence of 2,4,6-collidine, *N,N*-diisopropylethylamine, or 1,2,2,6,6-pentamethylpiperidine (PMP) leads to the corresponding primary monoacetates simply, conveniently, and in good yields. In this way, other acyl chlorides, sulfonyl chlorides, and silyl chlorides in place of acetyl chloride also react with primary hydroxyl group selectively.

Acylation of alcohols is one of the most fundamental transformations in organic chemistry. Often selective acylation of the primary hydroxyl group of a primary–secondary diol is required, in particular, selective acetylation of hydroxyl groups in carbohydrates, in addition to being of theoretical interest, has great practical utility. Several sophisticated and relatively expensive reagents have been developed for this purpose; some of the most useful examples include triphenylphosphine–diethyl azodicarboxylate,[1] 2,2′-bipyridyl-6-yl carboxylates–cesium fluoride,[2] *N*-acetylimidazole,[3] ethyl acetate–alumina,[4] and enzymatic acetylation.[5] In another approach, for the introduction of an acetyl group particularly at the primary hydroxyl group, the sugar alcohol is per(trimethylsilyl)ated[6] to get the fully protected trimethylsilyl derivative which, on treatment with pyridine–acetic anhydride–acetic acid[7] followed by removal of trimethylsilyl groups at the secondary positions, provides the corresponding monoacetate.

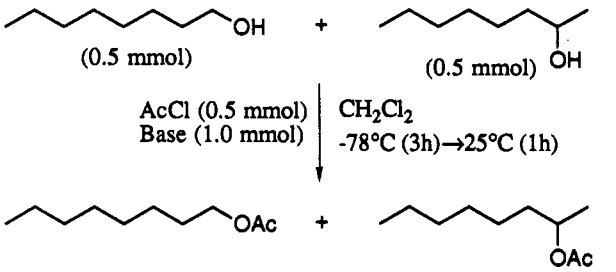
In this paper we wish to describe an extremely simple but powerful procedure for selective acetylation of the primary hydroxyl group in a series of structurally diverse primary–secondary diols, occurring with the use of acetyl chloride in the presence of sterically hindered amine.

The substantial difference of reaction rates between primary and secondary alcohols prompted us to examine selective acetylation of a primary–secondary alcohol. At first, we chose to investigate the selectivity in the acetylation of a 1:1 mixture of 1-octanol and 2-octanol with acetyl chloride in the presence of a variety of amines. Some of our results, summarized in Table I, strongly suggest a crucial role for the steric hindrance of amine on the selectivity of the reaction. The use of 2,4,6-collidine, *N,N*-diisopropylethylamine, or 1,2,2,6,6-pentamethylpiperidine (PMP) gave 1-octyl acetate highly selectively and in good yield.

In order to explore the generality and scope of the above selective acetylation by sterically hindered amine, the acetylation was examined with various structurally diverse primary–secondary diols and polyhydroxyl compounds. Several features of the results shown in Table II deserve comment, as follows: (1) 1,2-, 1,3-, and 1,4-diols were acetylated selectively. (2) Although both 2,4,6-collidine and *N,N*-diisopropylethylamine can be employed successfully as bases in all cases, the former generally affords superior results. For instance, cis diols were also acetylated selectively in the presence of 2,4,6-collidine, but the use of *i*-Pr_2EtN created some secondary monoacetate and diacetate (entry 5). In this case, the selectivity of acetylation was lost probably because internal proton transfer took place between primary alkoxide and secondary alkoxide by such a strong base as *i*-Pr_2EtN.[8] (3) Although the intrinsic polarity of most polyhydroxyl compounds greatly narrows the choice of the solvent, 2,4,6-collidine can dissolve most of these compounds and give high selectivity (entries 6 and 7).

As a logical extension of this methology, we further investigated the effect of sterically hindered amines for acylation of primary–secondary alcohols with other acyl chlorides with the exception of acetyl chloride and similar applications for sulfonylation and silylation. The results are shown in Table III. The use of acyl chloride, sulfonyl chlorides, and silyl chlorides in the presence of 2,4,6-collidine or *i*-Pr_2EtN permitted highly selective reaction at the primary position in preference to the secondary one

Table I. Selective Acetylation of 1-Octanol



base	yield[a] (%) prim. acetate + sec acetate	ratio[b] prim. acetate:sec acetate
pyridine	89	87.5:12.5
collidine	91	99.1:0.9
DABCO	91	90.0:10.0
quinuclidine	66	97.2:2.8
Et_3N	58[c]	97.0:3.0
i-Pr_2EtN	90	99.6:0.4
PMP	71	99.6:0.4

[a] Yield of isolated, purified product. [b] GLC analysis. [c] Some byproducts were produced.

(1) Mitsunobu, O. *Synthesis* **1981**, 1 and references cited therein.
(2) Mikaiyama, T.; Pai, F.-C.; Onaka, M.; Narasaka, N. *Chem. Lett.* **1980**, 563.
(3) (a) Staab, H. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 351. (b) Lemieux, R. U.; Driguez, H. *J. Am. Chem. Soc.* **1975**, *97*, 4063. (c) Vernon, J.; Roseman, S.; Lee, Y. C. *Carbohydr. Res.* **1980**, *82*, 59.
(4) (a) Posner, G. H.; Oda, M. *Tetrahedron Lett.* **1981**, *22*, 5003. (b) Rana, S. S.; Barlow, J. J.; Matta, K. L. *Ibid.* **1981**, *22*, 5007.
(5) (a) Faber, K.; Riva, S. *Synthesis* **1992**, 895 and references cited therein. (b) Moris, F.; Gotor, V. *J. Org. Chem.* **1993**, *58*, 653.
(6) Loewus, F.; Shah, R. H. *Methods Carbohydr. Chem.* **1972**, *6*, 14.
(7) (a) Fucjs, E. F.; Lehmann, J. *Chem. Ber.* **1974**, *107*, 721. (b) Horton, D.; Lehmann, J. *Carbohydr. Res.* **1978**, *61*, 553.

(8) It was proved by control experiments that an internal acetyl transfer between primary hydroxyl group and secondary hydroxyl group did not occur in the acetylation of 1,2-*O*-isopropylidene-D-xylofuranose in the presence of *i*-Pr_2EtN, as follows: the treatment of the primary monoacetate of 1,2-*O*-isopropylidene-D-xylofuranose with *i*-Pr_2EtN at −78 °C for 4 h had no reaction, and acetylation of the primary monoacetate with acetyl chloride in the presence of *i*-Pr_2EtN gave only a mixture of the primary monoacetate and the diacetate.

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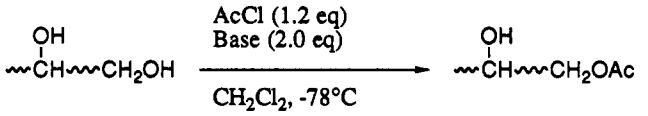
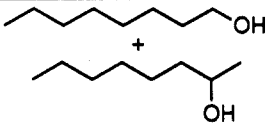
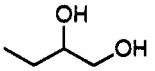
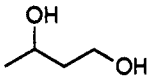
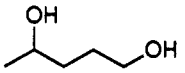
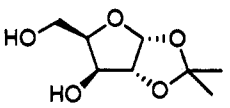
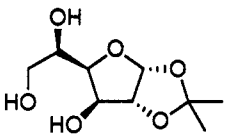
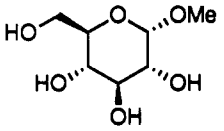
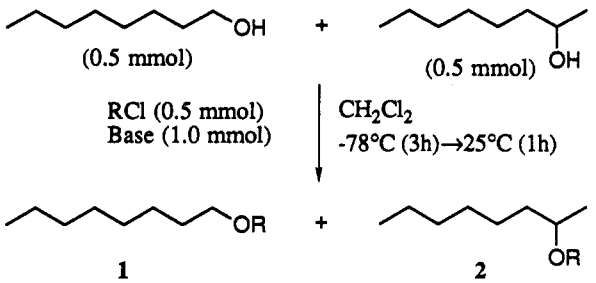
Table II. Selective Acetylation of the Primary Hydroxyl Group of Primary-Secondary Alcohols



entry	alcohol	base	yield of prim. monoacetate[a] (%)	ratio[b] prim. monoacetate:diacetate
1		*i*-Pr_2EtN	99	99.5:0.5[c]
		collidine	90[d]	99.1:0.9
2		*i*-Pr_2EtN	72	98.7:1.3
		collidine	92	99.2:0.8
3		*i*-Pr_2EtN	88[d]	99.4:0.6
		collidine	97	98.9:1.1
4		*i*-Pr_2EtN	86[d]	95.7:4.3
		collidine	92	98.5:1.5
5		*i*-Pr_2EtN	29	47.2:52.8[e]
		collidine	91	>99:1
6		collidine[f]	88	*g*
7		collidine[f]	75	*g*

[a] Yield of isolated, purified product. [b] GLC analysis. [c] Secondary monoacetate. [d] 1.0 equiv of AcCl was added. [e] Secondary monoacetate was formed in 20% yield. [f] The reaction was run in collidine as a solvent at −40 °C for 3 h and at 25 °C for 1 h. [g] No secondary acetates were formed in a detectable amount.

Table III. Selective Reactions of 1-Octanol



	Pyridine		collidine		*i*-Pr_2EtN		PMP	
RCl R	yield[a] (%) 1 + 2	selectivity[b] (%) 1	yield[a] (%) 1 + 2	selectivity[b] (%) 1	yield[a] (%) 1 + 2	selectivity[b] (%) 1	yield[a] (%) 1 + 2	selectivity[b] 1
PhCO	87	88.2	64	98.2	30	95.4		
MeCO	89	87.5	90	99.1	90	99.6	71	99.6
PrCO	98	81.6	99	93.5	36	88.8		
Cl_3CCO	>99	52.3[c]	95	75.6[c]	94	91.5[c]	93	92.8[c]
$MeSO_2$	64[d]	82.4[c]	75[d]	91.2[c]	94[d]	94.6[c]	>99[d]	94.9[c]
Ts	87[d]	81.3[e]	47[d]	97.4[e]	10[d]	97.8[e]		
TMS	67	58.5	81	63.8	>99	70.5	85	81.1
TBDMS	52	97.3	50	98.6	13	95.8		

[a] Yield of isolated, purified product. [b] GLC analysis. [c] ^1H NMR analysis. [d] The reactions were run at −78 °C for 3 h and at 25 °C for 1 day. [e] HPLC analysis.

in all cases. The use of PMP was most effective for the selective reaction with Cl_3CCOCl and sterically unhindered chlorides like AcCl, MsCl, and TMSCl. Although the selectivities of acylation and sulfonylation, respectively, were not influenced by alkyl moieties of acyl chloride and sulfonyl chloride in the presence of pyridine, silylation by *tert*-butyldimethylsilyl chloride (TBDMSCl) in the presence of pyridine was much more selective than that by trimethylsilyl chloride (TMSCl).

For an understanding of the mechanism of selective

acylation reactions with sterically hindered bases, the role of bases in acyl-transfer reaction has to be discussed in detail: As Brönsted bases R_3N, they can produce an anion R^1O^- from a substrate R^1OH. This anion is a better nucleophile than R^1OH and therefore reacts more rapidly with the electrophilic acylating reagent R^2COCl. The extent of general base catalysis depends upon the relative basicities of R_3N and R^1O^- upon the position of the acid–base equilibrium. In the case of sterically hindered tertiary amines like *i*-Pr_2EtN and PMP, primary alkoxide R^1O^- can be selectively produced in this initial process. Even in the case of the acyl chloride/2,4,6-collidine system the same mechanism is supported.[9,10]

It is noted that 2,4,6-collidine is a mild and sterically hindered base, and hence acetyl chlorides are able to acetylate various alcohols including polyhydroxyl compounds with a high degree of selectivity at low temperature without the need of added 4-(dimethylamino)pyridine (DMAP).[10] This makes the present esterification useful for the selective protection of various hydroxyl compounds.

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Supplementary Material Available: Full experimental details and compound characterization (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm addition of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) Appreciable quantities of *N*-acetylcollidinium chloride could not be detected in a 1:1 mixture of acetyl chloride and 2,4,6-collidine in CD_2Cl_2 by ^1H and ^{13}C NMR analyses.

(10) Höfle, G.; Steglich, W.; Vorbrüggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569.