CHEMISTRY LETTERS, pp. 563-566, 1980.

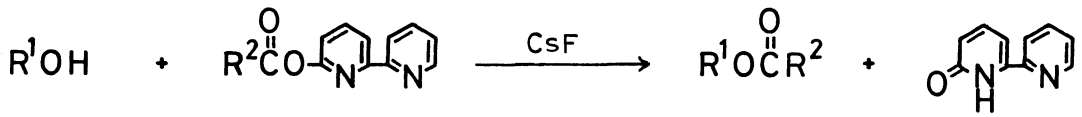
A USEFUL METHOD FOR SELECTIVE ACYLATION OF ALCOHOLS USING 2,2'-BIPYRIDYL-6-YL CARBOXYLATE AND CESIUM FLUORIDE

Teruaki MUKAIYAMA, Fong-Chang PAI, Makoto ONAKA, and Koichi NARASAKA
Department of Chemistry, Faculty of Science
The University of Tokyo, Hongo, Bunkyo-ku, Tokyo 113

Primary and secondary alcohols are acylated under mild conditions by the use of 2,2'-bipyridyl-6-yl carboxylates and cesium fluoride. Furthermore, the reaction is successfully applied to selective acylation of a primary carbinol group of diols containing primary and secondary carbinol groups or exclusive O-acylation of aromatic amino alcohols.

Acylation of alcohols is one of the most fundamental reactions in synthetic organic chemistry, and a wide variety of methods have been developed. In general, acylations of alcohols are carried out using hyper-reactive acylating reagents such as acyl chlorides or acid anhydrides. However, it is considerably difficult to conduct chemoselective acylation of alcohols containing polyfunctional groups by use of such reactive acylating reagents. After our examination of acylation reactions using various acylating reagents such as p-nitrophenyl carboxylate, 2-pyridyl carboxylate, 2,2'-bipyridyl-6-yl carboxylate and S-(2-pyridyl) thioate, it was found that 2,2'-bipyridyl-6-yl carboxylate is preferable as a selective acylating reagent.

In this communication, we wish to describe a useful method for selective acylation of hydroxyl groups which proceeds under almost neutral conditions employing 2,2'-bipyridyl-6-yl carboxylates(1) and cesium fluoride.



1 2

The acylating reagents(1) are readily prepared by the reaction of acyl chlorides with 6-(2-pyridyl)-2-pyridone(2)[1] and triethylamine or by the treatment of carboxylic acids and 2 with 2-chloro-1-ethylpyridinium tetrafluoroborate[2] and triethylamine. The esters (1) are moderately stable and easily purified by silica gel chromatography, and it is expected that 2,2'-bipyridyl-6-yloxyl group would be readily eliminated to form stable pyridone(2) by the attack of some nucleophiles.

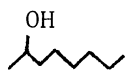
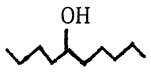
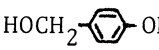
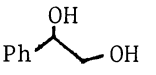
At first, we tried acylations of various alcohols using 2,2'-bipyridyl-6-yl carboxylates(1). No reaction took place when a mixture of the ester(1) and alcohol

Table 1 Reactions of alcohols with 2,2'-bipyridyl-6-yl carboxylates

R^1OH[a)]	R^2	Solv.	Conditions		Yield(%)
			Temp.	Time	
$PhCH_2OH$	n-C_5H_{11}	CH_2Cl_2	r.t.	1 d	54
		CH_3CN	r.t.	1 d	90
$PhCH_2OH$	$PhCH_2$	CH_2Cl_2	r.t.	3 d	83
Geraniol	CH_3	CH_3CN	r.t.	3 d	77
Geraniol	n-C_5H_{11}	CH_3CN	r.t.	2 d	81
		CH_3CN	refl.	7 h	88
Geraniol	$PhCH_2$	CH_2Cl_2	r.t.	2 d	85
i-C_3H_7OH	$PhCH_2$	CH_2Cl_2	r.t.	5 d	85
$Ph(CH_2)_2CH(CH_3)OH$	CH_3	CH_3CN	r.t.	10 d	40
$Ph(CH_2)_2CH(CH_3)OH$	n-C_5H_{11}	CH_3CN	r.t.	12 d	27
		CH_3CN	refl.	8 h	66
β-Cholesterol	$PhCH_2$	CH_2Cl_2	r.t.	3 d	68

a) The molar ratio of alcohol to 2,2'-bipyridyl-6-yl carboxylate is 1.2:1.

Table 2 Selective acylation of dihydroxyl compounds[a)]

R^1OH[b)]	R^2	Conditions		Yield(%)	
		Temp.	Time	mono-Ac	di-Ac
	CH_3	r.t.	5 d	81[c)]	10
	CH_3	r.t.	7 d	69[c)]	8
	CH_3	r.t.	2.5 h	71[d)]	3
	CH_3	r.t.	2 d	17[c)]	39

a) CH_3CN was used as solvent.
b) The molar ratio of alcohol to 2,2'-bipyridyl-6-yl acetate is 1:1.
c) Primary alkyl ester.
d) Phenyl ester.

Table 3 Selective acylation of amino alcohols[a)]

R^1OH	R^2	Conditions		Yield(%)		
		Temp.	Time	O-Ac	N-Ac	O,N-diAc
H_2N-C$_6$H$_4$-OH	CH_3	r.t.	20 min	84	—	5
H_2N-C$_6$H$_4$-$(CH_2)_2OH$	CH_3	r.t.	10 h	70	—	15
$H_2N(CH_2)_6OH$	CH_3	r.t.	10 min	—	60	—
H_2N-$(CH_2)_2$-C$_6$H$_4$-OH	CH_3	r.t.	10 min	—	55	—

a) DMF was used as solvent.

in acetonitrile was stirred at room temperature. However, it was found that, in the presence of cesium fluoride, the reaction proceeded smoothly to give the corresponding ester(3) and 6-(2-pyridyl)-2-pyridone(2). It has been known that the nucleophilicity of protic organic compounds is increased by the formation of a strong hydrogen bond between an active hydrogen and a fluoride anion, and several fluorides such as cesium fluoride, potassium fluoride and tetraalkylammonium fluoride are generally used for this purpose.[3)] Among these fluorides, cesium fluoride was chosen in the present reaction because cesium fluoride is more soluble in polar solvents than potassium fluoride, and tetraalkylammonium fluoride has its difficulty in removing trace amounts of water. When a mixture of 2,2'-bipyridyl-6-yl hexanoate (0.5 mmol), benzyl alcohol (0.6 mmol) and cesium fluoride (2-2.5 mmol, dried well at 140°C for 3 h in vacuo before use) in acetonitrile was stirred for 1 d at room temperature, benzyl hexanoate was isolated in 90% yield after work-up and purification. The results of reactions of various alcohols with 1 are summarized in Table 1. The effect of the solvent is significant and polar aprotic solvents such as acetonitrile and dimethylformamide are suitable.

The substantial difference of reaction rates between primary and secondary alcohols prompted us to examine selective acetylation of the following dihydroxyl compounds such as 1,6-heptanediol(4), 1,5-nonanediol(5), 1-phenyl-1,2-ethanediol (6), and p-hydroxybenzyl alcohol(7) employing 2,2'-bipyridyl-6-yl acetate(1a). The treatment of 4(0.5 mmol) with 1a(0.5 mmol) and cesium fluoride (2.5 mmol) in acetonitrile at room temperature produced 6-hydroxyheptyl acetate(8) in 81% yield and 1-methylhexamethylene diacetate(9) in 10% yield. In contrast with this result, when acetylation was conducted by the reaction of equimolecular amounts of 4 and acetic anhydride in pyridine at room temperature according to a conventional method, a 3:1 mixture of 8 and 9 was obtained. The results of the reactions of various dihydroxyl compounds with 1a are listed in table 2. It was made clear that a primary carbinol group is acetylated in preference to a secondary one, and acetylation of a phenolic hydroxyl group predominates over that of an aliphatic one. This selectivity arises from a small difference of reactivity of hydroxyl groups toward the ester(1a) owing to a difference of their steric factors or strength of a hydrogen bond with a fluoride anion. The strength of a hydrogen bond depends on acidity of an active hydrogen. In the case of a 1,2-dihydroxyl compound

such as 6, the selectivity of acetylation was lost since internal acyl transfer took place easily.

Next, we examined selective O-acetylation of amino alcohols such as p-aminophenol(10), 2-(p-aminophenyl)ethanol(11), 6-aminohexanol(12), and p-(2-aminoethyl)-phenol(13) utilizing 2,2'-bipyridyl-6-yl acetate(1a). Amino groups of these amino alcohols are usually acetylated by use of such a reactive acylating reagent as acetyl chloride in preference to hydroxyl groups because amino groups have stronger nucleophilicity than hydroxyl groups. In the case of the reaction of 10 or 11 with 1a and cesium fluoride, O-acetylation proceeded predominantly, whereas, in the case of 12 and 13, N-acetylation took place exclusively. It was also found that selectivity of O-acetylation vs. N-acetylation decreased in the reaction of 1a with 10 when 2-pyridyl acetate or S-(2-pyridyl) thioacetate was employed as an acylating reagent in place of 1a, or when 1,5-diazabicyclo[5.4.0]undec-5-ene(DBU) was used as a base instead of cesium fluoride. From these results, it is apparent that the combined use of 2,2'-bipyridyl-6-yl carboxylate (1) and cesium fluoride is necessary for selective O-acylation of aromatic amino alcohols. A hydroxyl group activated by cesium fluoride is acylated by 1 in preference to an aromatic amino group because 1 is relatively inert to an aromatic amino group, but an aliphatic amino group which has much stronger nucleophilicity than an aromatic one undergoes N-acylation even by use of the ester (1).

It is noted that 2,2'-bipyridyl-6-yl carboxylates are mild acylating reagents and hence are able to acylate alcohols with a high degree of selectivity in combination with cesium fluoride under almost neutral conditions. Therefore, the present acylation is useful for the selective protection of various hydroxyl compounds.

References and Note

1) A mixture of 2,2'-bipyridyl-1-oxide (5 g) and acetic anhydride (50 ml) was heated in a sealed tube at 180°C for 4 h. After removal of acetic anhydride, the residue was dissolved in methanol and basified with conc. aqueous NaOH. The solution was stirred overnight and evaporated. The residual solids were purified by silica gel column chromatography and recrystallized with ethyl acetate to give 2.6 g (52% yield) of 6-(2-pyridyl)-2-pyridone; mp 121.5-122.5°C. IR(KBr): 3300, 3050, 2950, 1645, 1600, 1580, 1480, 1000, 790 cm^{-1}. ^{1}HNMR(KBr): δ 6.4-6.9(m, 2H), 7.1-7.8(m, 4H), 8.5(m, 1H). Found: C, 70.03; H, 4.56; N, 16.16%. Calcd for $C_{10}H_8N_2O$: C, 69.75; H, 4.68; N, 16.27%. 2,2'-Bipyridyl-1-oxide was prepared according to the method in the literature: I. Murase, Nippon Kagaku Zasshi, 77, 682 (1956). (Chem. Abstr., 52, 9100a (1958))

2) K. Saigo, M. Usui, K. Kikuchi, E. Shimada, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 50, 1963 (1977).

3) J. H. Clark and J. M. Miller, J. Am. Chem. Soc., 99, 498 (1977); S. L. Beaucage and K. K. Ogilvie, Tetrahedron Lett., 1977, 1691; K. K. Ogilvie, S. L. Beaucage, and M. F. Gillen, ibid., 1978, 1663, 3203.

(Received February 28, 1980)