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Selective Pivaloylation of Hydroxyl Groups by 3-Pivaloyl-1,3-thiazolidine-2-thione Under Neutral Conditions

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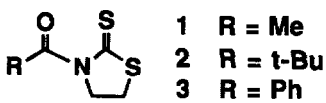
Abstract: Under neutral conditions, 3-pivaloyl-1,3-thiazolidine-2-thione (PTT) was found to act as a selective pivaloylating reagent for hydroxyl groups. The primary hydroxyl groups of diols containing primary and secondary hydroxyl groups, and the phenolic hydroxyl groups of the diols having alcoholic and phenolic hydroxyl groups were selectively pivaloylated by PTT.

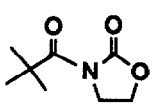
Since selective acylation of hydroxyl groups is important for various stages in organic synthesis, a number of methods have been developed[1]. Recently, the author has also reported a new method for the highly selective acylation of the primary hydroxyl groups of polyhydroxyl compounds by 3-acyl-1,3-thiazolidine-2-thiones[2]. In this reaction an equimolar amount of sodium hydride is required to activate the primary hydroxyl groups. Most the other methods are also conducted under basic or acidic conditions except for a few methods[3]. However, the acylation must be conducted under neutral conditions for the compounds which are labile to acids or bases.

In this paper, the author wishes to report a new method for the selective neutral pivaloylation of a variety of diols by 3-pivaloyl-1,3-thiazolidine-2-thione[2] (2)(PTT). The reagent PTT is readily prepared by the reaction of commercially available 1,3-thiazolidine-2-thione and pivaloyl chloride[4], and is stable in the open atmosphere at room temperature.

To examine the acylating ability of 3-acyl-1,3-thiazolidine-2-thiones[5] (Fig 1) under neutral conditions, the acylations of hexanol as the model compound were studied. A mixture of hexanol (0.8 mmol) and 3-acyl-1,3-thiazolidine-2-thiones (**1-3**) (0.88 mmol) in dry toluene (6 ml) was heated at 80 °C for 18 h (Table 1). From the



1 R = Me
2 R = t-Bu
3 R = Ph

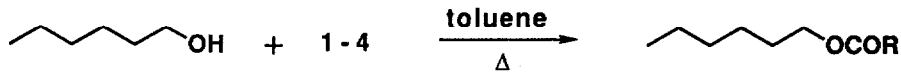


4

Fig. 1.

results, it was found that only PTT, which has the bulkiest group among these reagents, quantitatively gave hexylpivalate, while the other reagents did not react. 3-Pivaloyloxazolin-2-one[6] (**4**) (Fig 1), which has a structure analogous to PTT, was also entirely unreactive to hexanol.

Table 1. Acylation of Hexanol by 3-Acyl-1,3-thiazolidine-2-thiones Under Neutral Conditions



Reagent	Solvent	Temp.(°C)	Time (h)	Yield (%)[a]
1	toluene	80	18	2
2	,,	,,	,,	97
3	,,	,,	,,	1
4	,,	,,	,,	<1

a) Determined by GLC analysis.

The high reactivity of PTT was supported by the IR and ^{13}C NMR spectral studies of **1-3** (Table 2)[7]. Thus, the IR stretching frequency for the carbonyl group of PTT is significantly higher than that of **1** or **3**. Moreover, the chemical shift of the carbonyl carbon in PTT is 16.5 ppm higher than in **1** and **3**. Even if the substituent effect of the t-butyl group[8] of PTT was considered, the difference in their chemical shifts is larger than 10 ppm. These results suggest that the carbonyl group of PTT is more electrophilic than those of **1** or **3**. This high electrophilicity of PTT seems to arise from the high distortion[9] between the plane of the carbonyl group and that of the 1,3-thiazolidine-2-thione group.

Table 2. IR and ^{13}C NMR Spectral Data of **1-3**

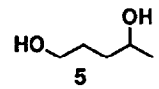
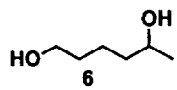
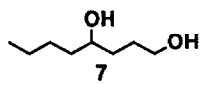
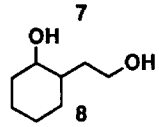
Compound	IR (cm^{-1})[a]	^{13}C NMR (ppm)[b]	
	ν (C = O)	δ (C = O)	δ (C = S)
1	1697	171.3	202.0
2	1726	187.8	200.6
3	1682	171.3	202.0

a) KBr disc. b) 400 MHz in $CDCl_3$

In order to explore the usefulness of this compound as a pivaloylating reagent for hydroxyl groups, the selective pivaloylation of diols containing primary and secondary hydroxyl groups under neutral conditions was examined. As can be seen from Table 3, the primary hydroxyl groups of the diols were selectively acylated in comparison with the acylation by pivaloyl chloride or pivalic anhydride. A typical procedure for the selective pivaloylation by the present method is as follows: A mixture of 1,4-octanediol (**7**)(102 mg, 0.7 mmol) and 1.1 eq. of PTT (156 mg, 0.77 mmol) in toluene (6 ml) was stirred at 80 °C for 40 h. The reaction mixture was concentrated and purified by preparative TLC to yield the pure primary monoalkyl ester (146 mg).

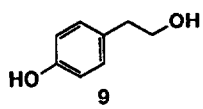
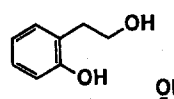
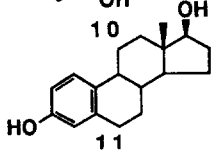
In the case of the diols having phenolic and alcoholic hydroxyl groups such as *p*-hydroxyphenethyl alcohol (**9**), *o*-hydroxyphenethyl alcohol (**10**), and estradiol (**11**), it was clarified that the alcoholic hydroxyl groups are preferentially acylated (Table 4). Especially, the alcoholic hydroxyl group of **10** was selectively acylated to yield almost a single product. In contrast with these results, when these pivaloylations were carried

Table 3. Selective Pivaloylation of Diols by PTT Under Neutral Conditions

Diol	Reagent[a)]	Temp. (°C)	Time (h)	Yield and Recovery [b)] (%) 1° Pivalate	2° Pivalate	Dipivalate	Diol
 5	PTT[c)]	65	65	81	3	8	8
	Me_3CCOCl/Et_3N[d)]	r.t.	10	61	20	5	15
	$(Me_3CCO)_2O/Et_3N$[c)]	65	15	67	8	17	8
 6	PTT[c)]	65	65	78	4	8	10
	Me_3CCOCl/Et_3N[d)]	r.t.	10	68	10	12	10
 7	PTT[c)]	80	40	87	2	6	5
	Me_3CCOCl/Et_3N[d)]	r.t.	10	71	18	6	5
 8	PTT[c)]	80	22	82	3	8	7

a) 1.1 eq. of reagent was used. b) Determined by GLC and/or ^1H NMR. c) Toluene was used as a solvent.
d) Dichloromethane was used as a solvent.

Table 4. Selective Pivaloylation of Diols Containing Alcoholic and Phenolic Hydroxyl Groups

Diol	Reagent[a)]	Solv.	Temp. (°C)	Time (h)	Yield[b)] (%)	Ratio[c)] (Alcoholic : Phenolic)
 9	PTT	toluene	65	48	53	4 : 1
	PTT/Et_3N	toluene	65	48	69	1 : 40
	Me_3CCOCl/Et_3N	CH_2Cl_2	r.t.	10	92	1 : 21
 10	PTT	toluene	65	48	91	>100 : 1
	PTT/Et_3N	toluene	65	24	85	1 : 1.5
	Me_3CCOCl/Et_3N	CH_2Cl_2	r.t.	10	86	1.2 : 1
 11	PTT	toluene	60	90	61	2 : 1
	Me_3CCOCl/Et_3N	CH_2Cl_2	r.t.	10	85	1 : 23

a) 1.1 eq. of reagent was used. b) Yield of monoesters. GLC yield. c) Determined by GLC and/or ^1H NMR.

out in the presence of triethylamine, phenyl esters were selectively produced, similar to the pivaloylation by pivaloyl chloride. That is to say, it was found that the ratio of the products could be reversed whether triethylamine was present or not in the reaction. The difference in these selectivities is attributed to the difference in the nucleophilicities and steric hindrance between the phenolic and alcoholic hydroxyl groups. Thus, the nucleophilicity of the phenolic hydroxyl group is less than that of the alcoholic hydroxyl group under neutral

conditions, while under basic conditions, the nucleophilicity of the latter is less than that of the former because the phenolate is easily produced in basic media. Furthermore, the steric hindrance of the primary hydroxyl groups is less than that of phenolic hydroxyl groups.

The present method, which can be conducted under neutral conditions, is applicable to compounds which are labile to acids and bases. Studies of the relationship between the structure and the reactivity of PTT, and the further extension of the scope of this method are in progress.

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2. Yamada, S. *J. Org. Chem.*, in press.
3. For an example see ref. 1d), 1k). Enzyme-catalyzed acylations have also been developed. For example, Margolin, A. L.; Delinck, D. L.; Whalon, M. R. *J. Am. Chem. Soc.*, **1990**, *112*, 2849, and references therein.
4. **2** was prepared as follows: To a solution of 1,3-thiazolidine-2-thione (12.0 g) and triethylamine (13.0 g) in CH_2Cl_2 (50 ml) at 0 °C was added dropwise a solution of pivaloyl chloride (14.0 g) in CH_2Cl_2 (20 ml). The solution was stirred for 10 h at room temperature and was worked up as usual manner to give a crude product. This was recrystallized from ether-hexane to yield a pure specimen (15.8 g): m.p. 58.0 ~ 59.5 °C. IR (KBr) 1726 (C=O), 1388, 1280, 1245, 1209, 1149, 1045, 1003, 873 cm^{-1}; ^1H NMR ($CDCl_3$, TMS) d 1.41 (9 H, s, t-Bu), 3.48 (2 H, t, J=7.25 Hz, 5-H), 4.19 (2 H, t, J=7.25 Hz, 4-H).
5. a) Compound **1**: Chung-shi, L.; Yuen-hwa, Y.; Yao, L.; Yong-jun, L.; Ai-hsueh, L.; Chi-yi, H. *Tetrahedron Lett.*, **1981**, *22*, 3467. b) Compound **2**: see ref. 4. c) Compound **3**: Izawa, T.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.*, **1979**, *53*, 555.
6. An oil. b.p. 91-93 °C (0.5 mmHg), IR (neat) 1780, 1686, 1386, 1289, 1200, 940 (cm^{-1}), ^1H NMR ($CDCl_3$, TMS) d 1.38 (s, 9 H), 4.04 (t, J=7.81 Hz, 2 H), 4.40 (t, J=7.81 Hz, 2 H), MS m/z 172 (M^++1, 2.1), 156 (3.2), 128 (6.4), 116 (41.8), 100 (8.3), 88 (34.4), 57 (100), high-resolution MS calcd for $C_8H_{14}O_3N$ (M^++1) m/z 172.0974, found m/z 172.1001.
7. Fujita et al. have discussed (*J. Chem. Soc., Perkin I*, **1981**, 914) a method of distinguishing between Δ^2-1,3-thiazolidine-2-thiol ester and 3-acyl-1,3-thiazolidine-2-thione by ^{13}C NMR. The structure of **2** was determined according to their method. The X-ray analysis of **2** is now in progress and will be reported.
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