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TRANSFORMATION OF ACYLOIN *O*-ACYL DERIVATIVES TO KETONES USING TETRABUTYLAMMONIUM FLUORIDE-THIOL SYSTEM

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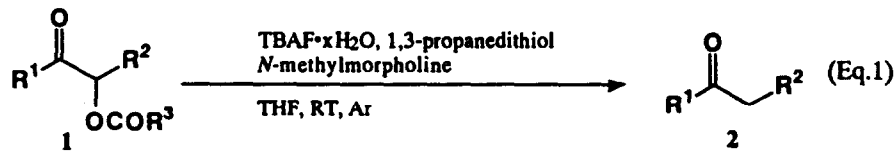
Abstract: The treatment of acyloin (α-hydroxyketone) *O*-acyl derivatives with tetrabutylammonium fluoride hydrate (TBAF•xH_2O)-1,3-propanedithiol system gave the corresponding ketones. Further, it was found that *N*-methylmorpholine added could prevent the concomitant of unidentified compounds to give the pure products in high yields.

The reductive transformation of acyloins to ketones is one of the important processes in the synthesis of natural products [1] and reactions utilizing various reagents have been investigated.[2]

Recently we reported that a TBAF•xH_2O-thiol system could remove phenacyl (Pac) ester groups selectively from amino acid derivative containing benzyl or 4-nitrobenzyl ester.[3] Since TBAF•xH_2O itself could remove 4-nitrobenzyl group [4,5] as well as Pac[4], the addition of the thiol had the important role in acquiring this selectivity. Contrary to the base-catalyzed hydrolysis without thiol,[5] oxidation (thiol) and reduction (OPac) occurred in the presence of thiol.[3] This reaction would be useful as method for the reductive transformation of acyloin derivatives to ketones. In this communication, we wish to report the treatment of various kinds of acyloin *O*-acyl derivatives (**1**) with TBAF•xH_2O-thiol system that affords the corresponding ketones (**2**) under mild conditions as illustrated in the following equation (Eq. 1).



(Eq.1)

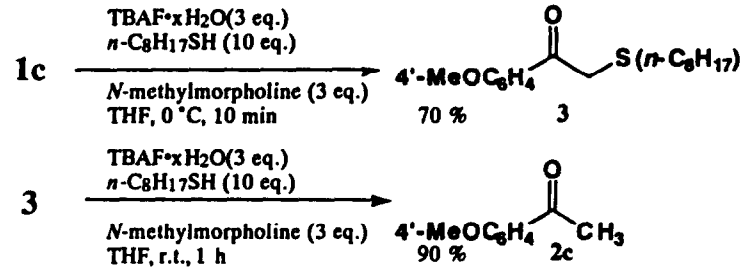
First, we examined the treatment of benzoin benzoate (**1a**) with 5 equivalents of TBAF•xH_2O and 5 equivalents of 1-octanethiol in tetrahydrofuran (THF) at room temperature, which gave the corresponding ketone (deoxybenzoin, **2a**) (Table 1, Run 1). Unfortunately, it was found that TLC of **2a**, which was purified by preparative TLC, was complicated. Further, it was difficult to purify the ketone (**2a**) from a small amount of unidentified compounds. The situation was same with 1,3-propanedithiol. In the detailed

study of conditions for the Pac removal we already found that 2-3 equivalents of TBAF•xH_2O were necessary for practical use.[4] The fact can be understood by assuming intermediate formation of hydrogen fluoride which is captured by the excess TBAF forming the corresponding hydrogen difluoride salt. Contamination of **2a** would be attributed to the incompleteness of hydrogen fluoride capture. Then, addition of some tertiary amines was examined. Among them, *N*-methylmorpholine could suppress the unidentified compounds formation most effectively (Runs 2, 3, and 4). While the reasons are uncertain, the reaction rate has decreased after addition of *N*-methylmorpholine. The highest yield of pure **2a** was obtained when 3 equivalents of TBAF•xH_2O, 10 equivalents of 1,3-propanedithiol, and 3 equivalents of *N*-methylmorpholine were employed (Run 4).

In the same manner, the reductive transformation of various kinds of acyloin *O*-acyl derivatives (**1**) to ketones (**2**) was performed (Table 2). The transformation of acetate (**1 b**) also proceeded to give **2a** in high yield (Run 1). When 4'-nitrophenacyl type derivative (**1 g**) was used as substrate, 4'-octylthioacetophenone (**2 g**) was obtained as the result of an additional nucleophilic substitution of 4'-nitro group (Run 6). In the case of tertiary ester (**1 h**) no desired product was obtained, but the starting material was recovered in 83 % yield (Run 7).

A typical experimental is as follows: To a THF (10ml) solution of benzoin acetate (**1 b**, 73.5mg, 0.289mmol), 1,3-propanedithiol (0.143ml, 1.45mmol), and *N*-methylmorpholine (0.0953ml, 0.867mmol) was added a THF solution of TBAF•xH_2O (274mg, 0.867mmol) at room temperature under argon, and the mixture was stirred for 3 h. Then the reaction was quenched by addition of $CuSO_4$ solution, and organic material was extracted with ethyl acetate (EtOAc). The extract was washed with 1M HCl aq., 5% $NaHCO_3$ aq., and water, dried (Na_2SO_4) and condensed under reduced pressure. The residue was purified by preparative TLC (*n*-hexane : EtOAc = 3 : 1) to give deoxybenzoin (**2a**, 56.5mg, 99 %).

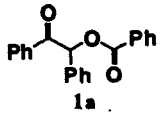
When **1 c** was treated with 3 equivalents of TBAF•xH_2O, 10 equivalents of 1-octanethiol, and 3 equivalents of *N*-methylmorpholine at 0 °C for 10 min, α-(octylthio)ketone (**3**)[6] was obtained in 70 % yield (Eq. 2). Further, 4'-methoxyacetophenone (**2 c**, 90 % yield) was obtained when treatment of **3** with the same conditions at room temperature for 1 h. This fact strongly suggests the initial formation of α-(alkylthio)ketone.



(Eq. 2)

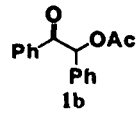
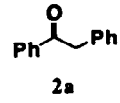
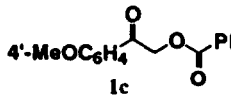
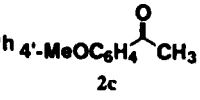
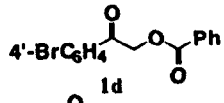
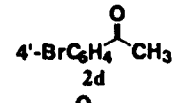
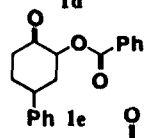
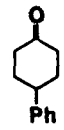
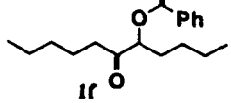
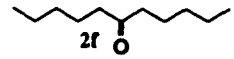
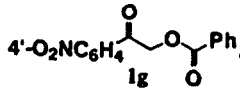
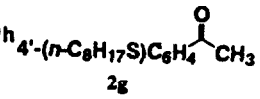
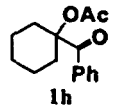
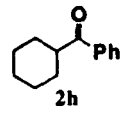
From these facts, although the details of the reaction process are uncertain at present, we would like to propose the following reaction mechanism (Eq. 3). *N*-Methylmorpholine is useful to capture hydrogen fluoride. Finally, protonation of enolate anion (**5**) gave the corresponding ketones (**2**).

Table 1. The transformation of benzoin benzoate (**1a**) to the corresponding ketone (**2a**) with TBAF•xH_2O-thiol[a)]

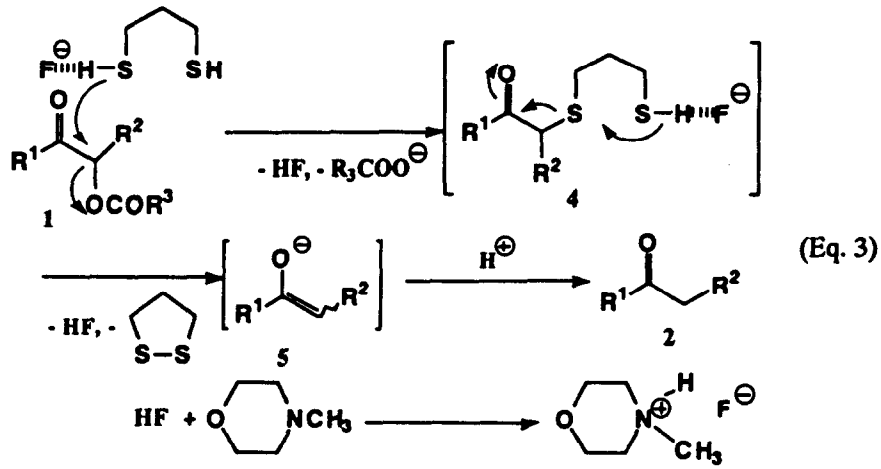
Run	1	TBAF•xH_2O(eq.)	Thiol(eq.)[b)]	Amine(eq.)[c)]	Time(h)	Yield(%)[d)]
1	 **1a**	5	5[e)]	-	1/12	<81[f)]
2		2	10	3	5.5	79
3		3	5	3	1.1	84
4		3	10	3	1	91

a) All the reactions were performed with the same procedure as described in the text, unless otherwise noted. b) 1,3-Propanedithiol was used, unless otherwise noted. c) *N*-Methylmorpholine was used. d) Isolated yield. e) 1-Octanethiol was used. f) It was difficult to purify **2a** from unidentified compounds.

Table 2. The reaction of various acyloin *O*-acyl derivatives (**1**) with TBAF•xH_2O-thiol-amine[a)]

Run	1	2	Time(h)	Yield(%)
1	 **1b**	 **2a**	3	99
2	 **1c**	 **2c**	1/12	84
3	 **1d**	 **2d**	1/12	74
4	 **1e**	 **2e**	4	74
5	 **1f**	 **2f**	3	62
6[b)]	 **1g**	 **2g**	1/12	82
7	 **1h**	 **2h**	5	-[c)]

a) All the reactions were performed with the same procedure as described in the text, unless otherwise noted. b) 1-Octanethiol (10 eq.) was used. c) **1h** (83 %) was recovered.



(Eq. 3)

It should be noted that the present reaction provides a convenient method for the reductive transformation of acyloin *O*-acyl derivatives to ketones using commercially available reagents. Further study including the application of TBAP×H_2O-thiol system to the reductive transformation of various organic compounds is now in progress.

REFERENCES AND NOTES

1) For example: Paquette, L. A.; Ross, R. J.; Shi, Y.-J. *J. Org. Chem.*, **1990**, 55, 1589; Marshall, J. A.; Greene, A. E. *J. Org. Chem.*, **1971**, 36, 2035; Maruyama, S.; Chan, D.; Brown, M. *Tetrahedron Lett.*, **1968**, 34, 3715.

2) Recent example; Inokuchi, T.; Kawafuchi, H.; and Torii, S. *Chem. Lett.*, **1992**, 1895, and references therein.

3) Ueki, M.; Aoki, H.; Katoh T. *Tetrahedron Lett.*, **1993**, 34, 2783.

4) Ueki, M.; *Proc. 2nd Akabori Conference (S. Sakakibara, ed., Protein Research Foundation, Osaka, 1988)*, pp.5; Ueki, M.; Kai, K.; Amemiya, M.; Horino, H; Oyamada, H. *J. Chem. Soc., Chem. Commun.*, **1988**, 414..

5) Namiki, M.; Kundu, B.; Rinehart, K.L. *J. Org. Chem.*, **1991**, 56, 5464, and references therein.

6) ^{1}H NMR(60MHz) TMS($CDCl_3$) δ=0.6-2.0 (m, 15H), 2.53 (t, *J*=7Hz, 1H), 3.70 (s, 2H), 3.83 (s, 3H), 6.83 (d, *J*=9Hz, 2H), 7.87 (d, *J*=9Hz, 2H).

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