Monatsh Chem (2013) 144:1351–1354
DOI 10.1007/s00706-013-1019-2

ORIGINAL PAPER

# Selective acylation of the phenolic hydroxyl of (hydroxyalkyl)phenols by using vinyl carboxylates as acyl donors in the presence of rubidium fluoride

**Toshifumi Miyazawa · Masato Yamamoto · Hiroshi Danjo**

Received: 2 April 2013 / Accepted: 11 May 2013 / Published online: 7 June 2013


**Abstract** Highly selective acylation of the phenolic hydroxy group can be achieved with (hydroxyalkyl)phenols carrying both alcoholic and phenolic hydroxyls by the use of vinyl carboxylates as acyl donors in the presence of rubidium fluoride.

**Keywords** (Hydroxyalkyl)phenols · Phenolic hydroxyls · Rubidium fluoride · Selective acylation · Vinyl carboxylates

## Introduction

Acylation of hydroxy functionalities is one of the most frequently employed processes in synthetic organic chemistry [1]. In the most conventional manner, acylation is carried out by treatment of alcohols with acyl halides or acid anhydrides. When using these reactive acylating agents, however, it is generally difficult to conduct selective acylation of compounds bearing multiple hydroxyls. Therefore, a wide variety of reagents and auxiliaries have been developed for such transformation [2–11], which is still a fundamental but important topic in synthetic organic chemistry. It is usually easy to selectively acylate an alcoholic hydroxyl in the presence of a phenolic one, while the reverse is much more difficult, because the latter hydroxyl is less nucleophilic than the former. Thus, the acylation of phenolic hydroxy groups is ordinarily performed under basic conditions where the phenolate is produced [5, 6]. Undoubtedly, a method for acylation of phenolic hydroxyls under nearly neutral conditions is more desirable [12], especially in cases in which labile functional groups exist together in the molecule. We report herein that a novel method composed of a combination of vinyl carboxylates and rubidium fluoride can acylate in a highly selective manner the phenolic hydroxy group of (hydroxyalkyl)phenols carrying both alcoholic and phenolic hydroxyls.

T. Miyazawa (✉) · M. Yamamoto · H. Danjo
Department of Chemistry, Faculty of Science and Engineering, Konan University, Kobe 658-8501, Japan
e-mail: miyazawa@konan-u.ac.jp

## Results and discussion

The fluoride ion has long been recognized as an efficient base for promotion of various types of base-assisted reactions in organic synthesis [13–19]. Concerning acylation of hydroxyls, a few examples have been reported employing specially devised acylating agents in the presence of cesium fluoride. For example, the combination of 2,2′-bipyridyl-6-yl carboxylates and CsF [2] and that of acylthiazolylidine-2-thiones and CsF [6] were applied to selective acylation of alcohols. We presumed that selective acylation of the phenolic hydroxyl of (hydroxyalkyl)phenols (Fig. 1) could be achieved by choosing an acylating agent of appropriate electrophilicity among more conventional compounds instead of specially developed ones in the presence of a suitable metal fluoride. Initially, 2-(4-hydroxyphenyl)ethanol (**1a**) was chosen as a model compound, and its acylation was examined using various acyl donors (2 mol equiv.) in the presence of CsF in acetonitrile at 80 °C (Table 1). No reaction took place with ethyl acetate even after 1 day. The reaction with 2,2,2-trifluoroethyl acetate was very slow in the presence of 0.1 mol equiv. CsF, with a slight deviation in selectivity toward the alcoholic hydroxyl. The reaction was accelerated with increase of the amount of CsF, the alkyl ester alone being quantitatively obtained with 5 mol equiv. CsF in 24 h. The

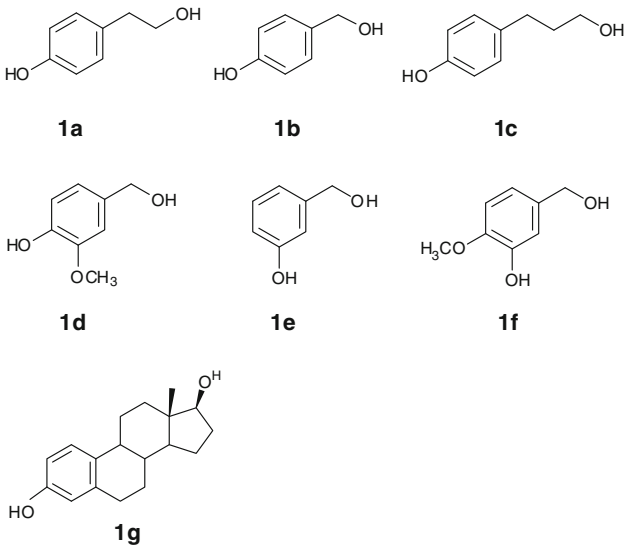


**Fig. 1** (Hydroxyalkyl)phenols examined in this study

**Table 1** Acylation of 2-(4-hydroxyphenyl)ethanol (**1a**) using various acyl donors in the presence of CsF

| Acyl donor | Mol equiv. CsF | Time | Yield/% | | |
|---|---|---|---|---|---|
| | | | Phenyl ester | Alkyl ester | Diester |
| $CH_3CO_2CH_2CH_3$ | 5 | 24 h | 0 | 0 | 0 |
| $CH_3CO_2CH_2CF_3$ | 0.1 | 24 h | 8.5 | 13.8 | 1.5 |
| | 1 | 24 h | 2.8 | 54.8 | 2.4 |
| | 5 | 24 h | 0 | 100 | 0 |
| $CH_3COCl$ | 0 | 30 min | 0 | 96.2 | 0 |
| | 0.1 | 30 min | 5.4 | 59.9 | 9.0 |
| $(CH_3CO)_2O$ | 0 | 30 min | 0 | 0 | 0 |
| | 0.1 | 30 min | 58.0 | 6.0 | 5.7 |
| | 0.5 | 30 min | 9.7 | 58.4 | 8.4 |
| | 1 | 30 min | 0 | 86.4 | 0 |
| $CH_3CO_2CH{=}CH_2$ | 0 | 2 h | 0 | 0 | 0 |
| | 0.1 | 13 min | 78.2 | 0 | 21.8 |
| | 1 | 15 min | 70.4 | 0 | 29.6 |

Reactions were conducted in acetonitrile at 80 °C using 2 mol equiv. of an acyl donor

acylation with acetyl chloride proceeded smoothly in the absence of CsF, only the alkyl ester being obtained in 96 % yield in 30 min. The coexistence of CsF (0.1 mol equiv.) even decelerated the reaction and resulted in concomitant formation of a small amount of the phenyl ester and the diester. On the other hand, the acylation with acetic anhydride did not proceed in the absence of CsF. When 0.1 mol equiv. CsF was present, the phenyl ester was obtained as the major product, though the conversion was not very high (70 %) after 30 min. Interestingly, the selectivity was inversed when the amount of CsF was increased to 0.5 mol equiv. or above, the alkyl ester alone being obtained in 86 % yield with 1 mol equiv. CsF. Enol esters such as vinyl acetate have been employed as beneficial acyl donors in lipase-catalyzed acyl-transfer reactions, because their use makes the reactions completely irreversible [20]. We tried vinyl acetate as an acylating agent in the presence of CsF. The reaction did not proceed in the absence of CsF. When 0.1 mol equiv. CsF was employed, the acylation proceeded rather smoothly: the parent diol was completely consumed in 13 min. Moreover, the phenyl ester was produced as the major product, though accompanied by a considerable amount of the diester. The proportion of the diester increased when the amount of CsF was augmented to 1 mol equiv.

As vinyl acetate proved to be an appropriate acyl donor for the acylation of the phenolic hydroxyl in the presence of CsF, we examined next the effect of alkaline metals composing metal fluorides. LiF and NaF were totally ineffective: no reaction took place even after several hours. With KF (0.1 mol equiv.) only the phenyl ester was produced in 42.2 % yield in 2 h. As shown in Table 2, when RbF (0.1 mol equiv.) was employed, the yield of the phenyl ester exceeded 90 %, while the diester was reduced to ca. 8 %, though more time (35 min) was required for complete consumption of the parent diol. Thus, the combination of vinyl acetate and RbF was found to be the method of choice for preparation of the phenyl ester as the main product. When the amount of RbF was increased to 1 mol equiv., the yield of the phenyl ester was improved to some extent, while reduction of the fluoride to 0.05 mol equiv. resulted in a remarkable decrease in the yield of the phenyl ester. Acylations of **1a** with vinyl esters of other carboxylic acids were also examined in the presence of RbF (0.1 mol equiv.). Acylations with vinyl esters of propanoic, butanoic, and benzoic acids proceeded in almost the same manner,

**Table 2** Acylation of 2-(4-hydroxyphenyl)ethanol (**1a**) using various vinyl esters as acyl donors in the presence of RbF

| Acyl donor | Mol equiv. RbF | Time/min | Yield/% | | |
|---|---|---|---|---|---|
| | | | Phenyl ester | Alkyl ester | Diester |
| $CH_3CO_2CH{=}CH_2$ | 0.05 | 35 | 28.5 | 0 | 0 |
| | 0.1 | 35 | 91.8 | 0 | 8.2 |
| | 1 | 30 | 93.1 | 0 | 6.9 |
| $CH_3CH_2CO_2CH{=}CH_2$ | 0.1 | 55 | 91.0 | 0 | 9.0 |
| $CH_3(CH_2)_2CO_2CH{=}CH_2$ | 0.1 | 75 | 92.1 | 0 | 3.1 |
| $(CH_3)_3CCO_2CH{=}CH_2$ | 0.1 | 180 | 100 | 0 | 0 |
| $C_6H_5CO_2CH{=}CH_2$ | 0.1 | 60 | 87.6 | 0 | 3.1 |
| $CH_3CO_2C(CH_3){=}CH_2$ | 0.1 | 35 | 0 | 0 | 0 |

Reactions were conducted in acetonitrile at 80 °C using 2 mol equiv. of an acyl donor

affording results similar to that with vinyl acetate, though the times needed for complete consumption of the parent diol were different. The acylation with 2,2-dimethylpropanoic acid vinyl ester proceeded regiospecifically to give only the phenyl ester, though a longer reaction time was necessary for complete consumption of the parent diol. On the contrary, isopropenyl acetate did not work as an acyl donor in the presence of RbF.

The chlorides, bromides, and iodides of cesium and rubidium were completely ineffective for acylation. The occurrence of acylation in the presence of cesium and rubidium fluorides can be rationalized in terms of the "naked" fluoride anion from the corresponding salts facilitated by the electropositive character and large ionic radius of the cesium and rubidium ions [13, 14, 21]. Moreover, the fact that only vinyl esters can act as good acyl donors suggests that their carbonyl groups can effectively be activated by the cesium or rubidium ion in the presence of the vinyl group. The large activity of CsF compared with RbF ascribed to the larger ionic radius of the cesium ion would be responsible for the observed smaller selectivity when CsF was employed. Furthermore, it is quite interesting to know that the use of KF (0.1 mol equiv.) in the presence of 18-crown-6 (0.1 mol equiv.) resulted in the formation of the phenyl ester in 84.7 % yield, together with the diester (12.1 % yield), in 60 min, as compared with the aforementioned result obtained with KF alone.

Next, we set about examining the general applicability of this novel acylation method using vinyl carboxylates and RbF for selective acylation of the phenolic hydroxyl of (hydroxyalkyl)phenols. The results are compiled in Table 3. Quite a similar result was observed in the acetylation of 3-(4-hydroxyphenyl)propanol (**1c**) bearing a longer alkyl chain. Although the reaction of (4-hydroxyphenyl)methanol (**1b**) was rather slow in the presence of 0.1 mol equiv. RbF and 1 mol equiv. was necessary for complete consumption of the parent diol in 30 min, the selectivity observed was akin to that obtained with the diol **1a**. With the diol **1d** bearing a substituent *ortho* to the phenolic hydroxyl in **1b**, the reaction was rather slow and afforded the phenyl ester in 83 % yield in 2 h accompanied by a greater amount of the diester. With the diol **1e** having the *meta* reciprocal position between the phenolic hydroxyl and the alkyl chain or the diol **1f** bearing a substituent *ortho* to the phenolic hydroxyl in **1e**, the yield of the phenyl ester was around 80 %, though a fair amount of the diester was produced. With β-estradiol (**1g**) the reaction proceeded regiospecifically to afford the phenyl ester quantitatively in 60 min in the presence of 0.1 mol equiv. RbF.

**Table 3** Acylation of (hydroxyalkyl)phenols (**1**) with vinyl acetate in the presence of RbF

| Diol | Mol equiv. RbF | Time/min | Yield/% | | |
|---|---|---|---|---|---|
| | | | Phenyl ester | Alkyl ester | Diester |
| **1b** | 0.1 | 60 | 8.2 | 0 | 0 |
| | 1 | 30 | 92.7 | 0 | 7.3 |
| **1c** | 0.1 | 30 | 96.0 | 0 | 4.0 |
| **1d** | 1 | 120 | 83.3 | 0 | 11.6 |
| **1e** | 1 | 25 | 78.3 | 0 | 13.9 |
| **1f** | 1 | 30 | 78.8 | 0 | 19.6 |
| **1g** | 0.1 | 60 | 100 | 0 | 0 |

Reactions were conducted in acetonitrile at 80 °C using 2 mol equiv. vinyl acetate

**Table 4** Acylation of phenol (**2**) and 2-phenylethanol (**3**) with vinyl acetate in the presence of RbF

| Substrates | Time/min | Yields/% | |
|---|---|---|---|
| | | Phenyl ester | Alkyl ester |
| **2** | 45 | 100 | – |
| **3** | 60 | – | 10.4 |
| **2** + **3** | 45 | 82.8 | 3.8 |
| | 60 | 98.8 | 7.8 |

Reactions were conducted in acetonitrile at 80 °C using 1 mol equiv. each of the substrates and 2 mol equiv. vinyl acetate in the presence of RbF (0.1 mol equiv.)

As shown in Table 4, when phenol (**2**) and 2-phenylethanol (**3**) were allowed to react with vinyl acetate in the presence of RbF (0.1 mol equiv.), **2** was acetylated quantitatively in 45 min, while the yield of the acylated product of **3** was only 10 % after 60 min. When a mixture of equimolar amounts of **2** and **3** was treated in the same manner as above, **2** was acetylated in more than 80 % yield in 45 min and almost quantitatively in 60 min, while the yield of the acylated product of **3** was less than 8 %. Thus, the results of this competition reaction resemble those obtained with the diol **2a**.

## Conclusion

With (hydroxyalkyl)phenols carrying both an alcoholic and a phenolic hydroxyl, highly selective acylation of the phenolic hydroxyl can be achieved without resorting to specially devised reagents, but by using the more conventional acyl donors, vinyl carboxylates, with the assistance of RbF. Therefore, the present method should be an attractive alternative to the existing methods.

## Experimental

Typical acylation procedure is as follows: a mixture of a (hydroxyalkyl)phenol (0.4 mmol) and vinyl acetate

(0.8 mmol) in 7 $cm^3$ acetonitrile was heated in the presence of RbF (0.04 mmol or 0.4 mmol) at 80 °C for the specified time. RbF was filtered off and the solvent was removed under reduced pressure. The residual oil was dissolved in dimethyl sulfoxide (DMSO)-$d_6$ and subjected to $^1$H nuclear magnetic resonance (NMR, 500 MHz) analysis for quantification of the reaction products. The methylene protons attached to the benzene ring were mainly employed for this purpose. The whole content of the reaction mixture was used up for one analysis, and several discrete reaction mixtures were used for different reaction times.

## References


1. Wuts PGM, Greene TW (2007) Greene's protective groups in organic synthesis, 4th edn. Wiley, New York
2. Mukaiyama T, Pai F-C, Onaka M, Narasaka K (1980) Chem Lett 563
3. Nagao Y, Fujita E, Kohno T, Yagi M (1981) Chem Pharm Bull 29:3202
4. Kunieda T, Mori T, Higuchi T, Hirobe M (1985) Tetrahedron Lett 26:1977
5. Paradisi MP, Zecchini GP, Torrini I (1986) Tetrahedron Lett 27:5029
6. Yamada S, Sugaki T, Matsuzaki K (1996) J Org Chem 61:5932
7. Breton GW (1997) J Org Chem 62:8952
8. Orita A, Mitsutome A, Otera J (1998) J Org Chem 63:2420
9. Sabitha G, Subba Reddy BV, Kiran Kumar Reddy GS, Yadav JS (2000) New J Chem 24:63
10. Ranu BC, Dutta P, Sarkar A (2000) J Chem Soc Perkin Trans 1:2223
11. Caddick S, McCarroll AJ, Sandham DA (2001) Tetrahedron 57:6305
12. Orazi OO, Corral RA (1969) J Am Chem Soc 91:2162
13. Clark JH, Miller JM (1977) J Am Chem Soc 99:498
14. Clark JH (1978) J Chem Soc Chem Commun 466
15. Yakobson GG, Akhmetova NE (1983) Synthesis 169
16. Hayat S, Atta-ur-Rahman, Choudhary MI, Khan KM, Schumann W, Bayer E (2001) Tetrahedron 57:9951
17. Shoda S, Moteki M, Izumi R, Noguchi M (2004) Tetrahedron Lett 45:8847
18. Patil R, Li W, Ross CR, Kraka E, Cremer D, Mohler ML, Dalton JT, Miller DD (2006) Tetrahedron Lett 47:3941
19. Inahashi N, Fujiwara T, Sato T (2008) Synlett 605
20. Faber K (2011) Biotransformations in organic chemistry, 6th edn. Springer, Berlin, p 328
21. Kruizinga WH, Kellogg RM (1981) J Am Chem Soc 103:5183