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Tartaric acid and its *O*-acyl derivatives. Part 14: Nucleophilic ring-opening reaction of nonsymmetrically substituted tartaric acid anhydride as a tool for the synthesis of totally differentiated tartaric acid derivatives

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ABSTRACT

The ring-opening reaction of nonsymmetrically substituted tartaric acid anhydride was used to synthesize monoamides and monoesters of *O*-benzoyltartaric acid, type **I** (**a**) and **II** (**b**) building blocks with all four functional groups differentiated. The correct structure of the regioisomers, which had earlier been misassigned, was established. The type **I**–type **II** regioisomer rearrangement, which proceeded via acyl migration, was examined. Moreover, it was shown that acyl migration induced by selective crystallization may yield one of the regioisomers quantitatively.

1. Introduction

Tartaric acid (**1**) plays an important role in all areas of chemistry involving chirality.[1,2] This four-carbon molecule possesses two chiral centers and two pairs of functional groups—hydroxylic and carboxylic—arranged in such a way that the compound has C_2 symmetry. This unique structure makes tartaric acid a valuable starting material but also complicates its desymmetrization.[3–5] Regioselective modifications of the hydroxy and carboxy groups, especially those leading to totally differentiated tartaric acid derivatives with all four groups functionalized, remains a challenge.

A literature search for evidence of type **I** and type **II** building blocks revealed that tartaric acid derivatives bearing four distinct substituents are very scarce.[5–8] Bell obtained a few *O*-acyltartaric monoamides via the aminolysis of the corresponding diacyltartaric anhydride or amide followed by the deprotection of one hydroxy group; however, the structure of the resulting compounds was misassigned.[7,8] Alternatively, one acyl function was cleaved by rapid basic methanolysis.[7] Recently, a strategy involving the use of hexafluoroacetone (HFA) to enable the formation of *O*-protected monotartrates was described.[5] Although HFA allows for the independent modification of the carboxy and the hydroxy group, its high toxicity limits its use.

While working on the synthesis of compounds applicable as biopolymers, we required a simple, scalable and ecologically viable process for the preparation of totally differentiated tartaric acid derivatives. Because the distinction between carboxylic groups can be directly accomplished by the ring opening of diacyltartaric[1,9a,b] or succinic anhydrides,[10] a strategy involving the use of a five-membered cyclic anhydride for both 2,3- and 1,4-desymmetrization, similar to the application of *O*-acylmalic anhydride,[11a–e] was very promising. Thus, we chose an *O*-benzoyltartaric acid anhydride (**3**) with differentiated 2,3-hydroxy groups as a starting material[12,13] to achieve further 1,4-desymmetrization of the tartaric unit, providing the desired tartaric acid derivatives with four distinct substituents (**4**–**9**) (Fig. 1).[14]

2. Results and discussion

We examined the regioselectivity of the ring-opening of anhydride **3** by nitrogen and oxygen nucleophiles (Scheme 1, Table 1). We found that *O*-protected tartaric anhydride **3** reacted in a non-regioselective manner. The reaction proceeded with the formation of the corresponding *O*-benzoyltartaric monoamides (**4**–**6**) and monoesters (**7**–**9**) wherein two regioisomers, types **I** (**a**) and **II** (**b**), were formed, depending on the carbonyl center attacked by the nucleophile (Scheme 1). We also observed that, in contrast to the

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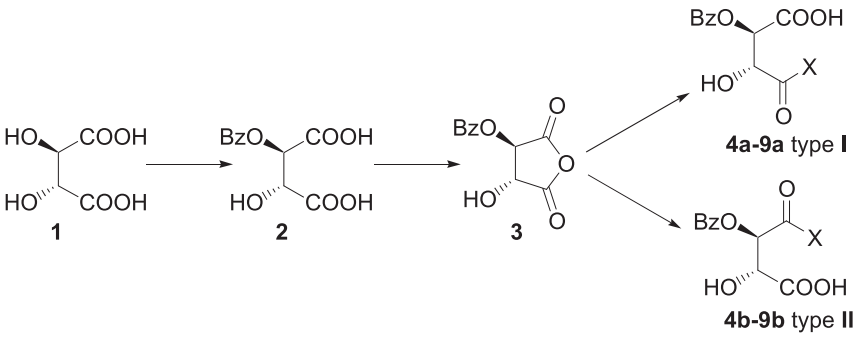
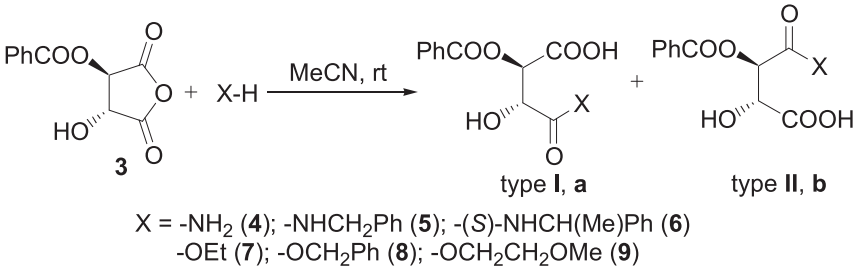


Fig. 1. An approach to the totally differentiated tartaric acid derivatives, monoamides (**4**–**6**) and monoesters (**7**–**9**) of *O*-acyltartaric acid.



Scheme 1. Regioselectivity of the ring-opening of anhydride **3** by nitrogen and oxygen nucleophiles.

Table 1
Regioselectivity in the ring opening of *O*-benzoyltartaric anhydride (**3**) by nucleophiles

Compound[a]	Nucleophiles X–H	Regioisomer I, **a**	Regioisomer II, **b**
	X	(%) HPLC[b]	
4	NH_2	73	27
5	$NHCH_2Ph$	60	40
6	(*S*)-NHCHMePh	39	61
7	OEt	60	40
8	OCH_2Ph	90	10
9	OCH_2CH_2OMe	70	30

[a] Conditions: anhydride **3** was dissolved in MeCN at rt followed by the addition of 1 equiv of the nucleophile, reaction was stopped rapidly by the acidification with MeCOOH.
[b] The regioisomer ratio was determined by the dissolution of the reaction mixture in a water/MeCN/MeCOOH system and HPLC analysis.

Table 2
The ratio of regioisomers (type **I**/type **II**)[a] of monobenzoyl monoamides (**4**–**6**) and monoesters (**7**–**9**) formed in the ring opening of **3** by nucleophiles according to reaction conditions *i*[b] or *ii*[c]

Compound	X	Procedure *i*[b]		Procedure *ii*[c]	
		Type I, **a** (%)	Type II, **b** (%)	Type I, **a** (%)	Type II, **b** (%)
4	NH_2	73	27	97	3
5	$NHCH_2Ph$	60	40	100[d]	—
6	(*S*)-NHCH(Me)Ph	39	61	94	6
7	OEt	60	40	40	60
8	OCH_2Ph	90	10	48	52
9	$OCH_2CH_2OCH_3$	70	30	49	51

[a] The regioisomer ratio was determined by the dissolution of the reaction mixture in a water/MeCN/MeCOOH system and HPLC analysis.
[b] Conditions: 1 equiv of amine X–H, rt, 5 s or 1 equiv of alcohol X–H, rt, 1 day.
[c] Conditions: 3 equiv of amine X–H, rt, 7 days or 1 equiv of alcohol, addition of 10 mol % of benzylamine, 50 °C, 2–4 days.
[d] Crystallization occurred.

nucleophilic ring opening of malic anhydride,[11a–f] the major regioisomer formed was usually the product of the reaction at the C-3 site of tartaric anhydride **3** (type **I** regioisomer, (**a**)).

Despite a lack of regioselectivity we found that the compound crystallizing from the reaction mixture in each case was the regioisomer of type **I**. Thus, we synthesized several monoamides (**4a**–**6a**) and monoesters (**7a**–**9a**) of monobenzoyl-L-tartaric acid (type **I**, yield 22–65%) utilizing **3** as a starting material in a very simple procedure.

It was much more difficult to obtain type **II** building blocks with both hydroxy and carboxy functionalities attached to the same C3 carbon. Despite considerable efforts to isolate high-purity type **II** regioisomers, we only succeeded with derivatives of (*S*)-2-phenylethylamine (**6b**) and 2-methoxyethanol (**9b**). For other substituents, both multiple recrystallizations and column chromatography failed, most likely due to the higher polarity of the type **II** building blocks compared to those of type **I**.

During attempts to produce monoamide **5b**, we noticed that the ratio of regioisomers formed after the reaction of **3** with benzylamine was dependent on the reaction conditions. To explain this behavior, we decided to perform the nucleophilic ring opening of benzoyltartaric anhydride (**3**) using two procedures (Table 2).

The first procedure was rapid (Table 2, Procedure *i*) and entailed the use of stoichiometric amounts of the nucleophile and subsequent acidification; therefore, the results revealed the initially formed product ratio obtained just after the ring-opening reaction reached completion. The second method (*ii*) (Table 2, Procedure *ii*) involved the use of an excess of amine or the addition of catalytic amine in the case of monoesters (**7**–**9**) and prolonged reaction times or heating. We observed that the product ratio differed between that measured directly after ring opening and those obtained after extended reaction, namely an excess of amine-mediator. We assumed that it was a result of interconversion between type **I** and type **II** regioisomers due to the intramolecular acyl migration, which most likely occurs via a five-membered transition state (Scheme 2). This acyl migration phenomenon is encountered in carbohydrate chemistry and may significantly disturb the selected synthetic route.[15a–d]