Stepwise Aldol Addition and Cyanhydrin Formation with Acetone and Thallous Cyanide

Qutaiba Abu-Salem[a], Norbert Kuhn[a], Eyad Mallah[a], H.-Jürgen Meyer[a], Markus Ströbele[a], and Klaus-Peter Zeller[b]

[a] Institut für Anorganische Chemie der Universität Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen
[b] Institut für Organische Chemie der Universität Tübingen, Auf der Morgenstelle 18, D-72076 Tübingen

Reprint requests to Prof. Dr. N. Kuhn. E-mail: norbert.kuhn@uni-tuebingen.de or
Prof. Dr. H.-J. Meyer. E-mail: juergen.meyer@uni-tuebingen.de or
Prof. Dr. K.-P. Zeller. E-mail: kpz@uni-tuebingen.de

The dithallous salt of 2,4-dihydroxy-2,4-dimethylpentanoic acid (**1**), formed by slow diffusion of acetone into an aqueous thallous cyanide solution, is transformed into 2,4-dihydroxy-2,4-dimethyl-pentanoic acid (**2**) by reaction with ammonium iodide. 2-Hydroxy-2,4,4-trimethylbutyrolactone (**3**) is obtained by treatment of **2** with catalytic amounts of benzenesulfonic acid. The sequence of the reactions and the crystal structure of **1** are discussed.

Key words: Reaction Mechanisms, Aldol Reactions, Cyanhydrines, Thallium, Crystal Structure

Introduction

The formation of aldols from aldehydes and ketones with acidic α-hydrogen atoms [1] is one of the classical reactions in organic chemistry [2]. Similarly, the combined addition of cyanide and a proton to the carbonyl group of aldehydes and ketones with formation of α-hydroxynitriles (cyanhydrins) [3, 4] belongs to the standard repertoire of organic synthesis [4]. The stepwise occurrence of both, aldol addition and cyanhydrin formation, could be a fruitful method for the construction of organic scaffolds. To the best of our knowledge, the reaction of excess acetone with sodium cyanide in the presence of $(\eta\text{-}C_5H_5)_2TiCl_2$ as Lewis acid catalyst is the only reported example [5] realizing this sequence in a "one pot" reaction.

As part of our investigations into the chemistry of thallous cyanide, we report in this communication on the TlCN-mediated transformation of acetone into 2,4-dihydroxy-2,4-dimethylpentanoic acid.

Results and Discussion

Formation of 2,4-dihydroxy-2,4-dimethylpentanoic acid (2) from acetone

When acetone was allowed to diffuse into aqueous thallous cyanide *via* the gas phase, the precipitation of cubic colorless crystals of the composition $Tl_2C_7H_{12}$-O_4 (**1**) was noted. In contrast, slow addition of liquid acetone to an aqueous TlCN solution results in immediate precipitation of thallous cyanide, rather than in the formation of the new thallium complex.

Structure analysis by X-ray single crystal diffraction indicated the formation of a thallium complex with the dianion of 2,4-dihydroxy-2,4-dimethylpentanoic acid (see below). The identity of the complex ligand has been proved further by the reaction of the thallium complex with ammonium iodide yielding 2,4-dihydroxy-2,4-dimethylpentanoic acid (**2**). The product showed a [M–H]⁻ peak in the FAB mass spectrum (negative mode) at $m/z = 161$, and the ^{1}H and ^{13}C NMR spectra are in accordance with the structure. Addition of catalytic amounts of benzenesulfonic acid to a solution of the α,γ-dihydroxy acid in D_2O results in a smooth transformation into 2-hydroxy-2,4,4-tri-methylbutyrolactone (**3**).

Obviously, the acetone penetrating into the aqueous thallous cyanide solution becomes involved in a multi-step reaction sequence consisting of a base-catalyzed aldol addition, followed by a cyanhydrin reaction. Finally, the cyano group is hydrolyzed to a carboxylate group. The smooth hydrolysis of the cyano function under mild conditions may be facilitated by
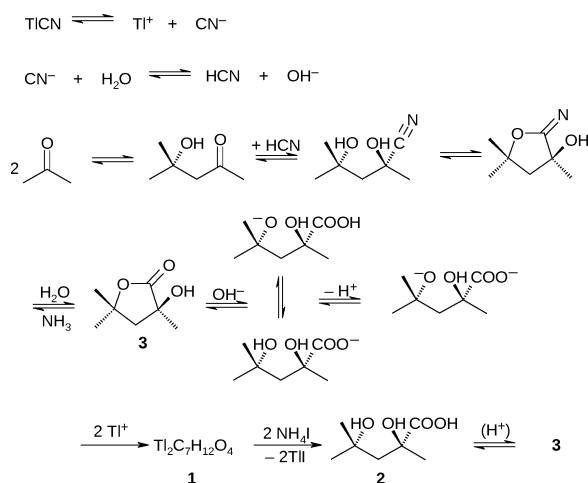
Scheme 1. Formation of $Tl_2C_7H_{12}O_4$ (**1**) on exposure of aqueous TlCN to acetone vapor and subsequent reaction to $C_7H_{14}O_4$ (**2**) and $C_7H_{12}O_3$ (**3**); racemic intermediates and products are represented by one enantiomeric structure only.
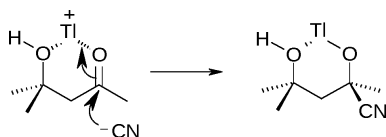
Scheme 2. Thallous ion-promoted cyanhydrin formation.

intramolecular nucleophilic attack of the 4-hydroxy group yielding the intermediate five-membered imino-lactone which subsequently is hydrolyzed to the lactone **3**. The sequence is completed by base-mediated ring opening (Scheme 1).

Under identical conditions a similar process is not observed when thallous cyanide is replaced by potassium cyanide. It is therefore concluded that the formation of the precipitating thallium complex which shifts the solution equilibria to the dianion of 2,4-dihydroxy-2,4-dimethylpentanoic acid is essential for the overall reaction. The precipitated thallium salt is composed of the dianion of 2,4-dihydroxy-2,4-dimethylpentanioc acid (**2**) and two thallous ions per structural unit. Therefore, its formation requires an additional deprotonation step. This detail may also be important for the overall reaction scenario because in the second reaction step (cyanhydrin reaction) the protonation of the former carbonyl oxygen atom of the intermediate aldol is essential for shifting this equilibrium towards the cyanhydrin [6].

In a mechanistic variant the specific role of the thallous ion could be explained by its coordination with the aldol to give a chelate complex. In comparison

Table 1. Crystal structure data for **1**.

Formula	$C_7H_{12}O_4Tl_2$
M_r	568.91
Cryst. size, mm^3	$0.45 \times 0.4 \times 0.38$
Crystal system	monoclinic
Space group	$P2_1/n$
a, pm	680.4(1)
b, pm	1027.2(1)
c, pm	15.28.4(3)
β, deg	101.39(2)
V, pm^3	$1047.1(3) \times 10^6$
Z	4
D_{calcd}, g cm^{-3}	3.609
$\mu(MoK_\alpha)$, cm^{-1}	307.19
$F(000)$, e	992
hkl range	$\pm 9, \pm 13, \pm 20$
$((\sin\theta)/\lambda)_{max}$, Å^{-1}	0.6665
Refl. measured	14351
Refl. unique	2595
R_{int}	0.1217
Param. refined	122
$R1 / wR2^a$ (all refl.)	0.0400 / 0.0741
GooF (F^2)^a	1.015
$\Delta\rho_{fin}$ (max/min), e Å^{-3}	2.18 / −1.39

^{a} $R1 = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$; $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$, where P is $[2F_c^2 + \max(F_o^2, 0)]/3$; GooF $= \{\Sigma[w(F_o^2 - F_c^2)^2]/(n - p)\}^{1/2}$.

to the uncomplexed aldol, the thallous aldol complex should show enhanced reactivity towards the cyanide attack and thus accelerate the cyanhydrin formation (Scheme 2).

*The crystal structure of dithallium 2,4-dihydroxy-2,4-dimethyl-pentanoate (1)*

Structures of organic thallous salts [7] containing bonding Tl–O contacts have been reported in a limited number including carboxylates [8], alcoholates [9], diketonates [10], and crown ether complexes [11]. Salts of common inorganic oxoacids [12] have also been characterized by diffraction methods.

Compound **1** crystallizes in the monoclinic space group $P2_1/n$, Z = 4, with two racemic pairs of the chiral molecule in the unit cell (Table 1). Fig. 1 reveals the mode of connectivity in the polymeric arrangement in which every metal atom is linked to four oxygen atoms while each oxygen atom bridges two thallium atoms.

Fig. 2 shows the monomeric unit of the dianion and the thallium atoms attached thereon in detail. As expected, the remaining O–H hydrogen atom of the dianion is bound to the oxygen atom of highest basicity and forms a hydrogen bond to the neighboring alcoholate oxygen atom [O(3) $\cdots$ H(8) 190(10), O(3)$\cdots$O(4) = 250.4(6) pm; O(3)–H(8)–O(4) 121(9)°].
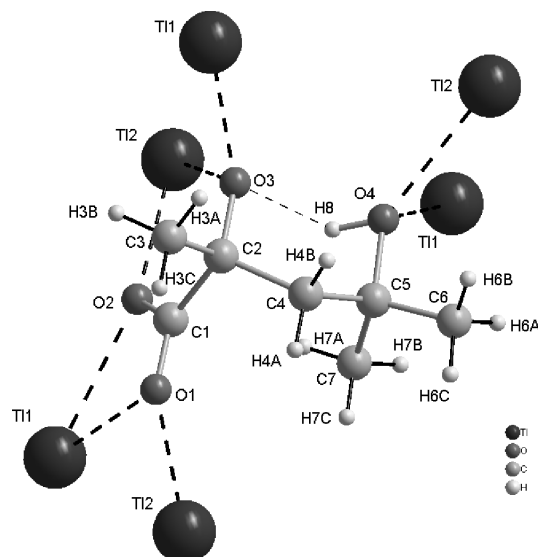
Table 2. Selected bond lengths (pm) and angles (deg) for **1** with estimated standard deviations in parentheses.

Tl(1)–O(1)	255.0(5)	Tl(1)–O(2)	287.4(6)
Tl(1)–O(3)	249.7(4)	Tl(1)–O(4)	267.6(4)
Tl(2)–O(1)	264.5(5)	Tl(2)–O(2)	252.6(5)
Tl(2)–O(3)	244.3(4)	Tl(2)–O(4)	284.3(5)
Tl(1)–Tl(2)	374.70(6)	O(1)–C(1)	126.1(8)
O(2)–C(1)	126.0(8)	C(1)–C(2)	154(1)
C(2)–O(3)	140.0(7)	C(2)–C(3)	153.2(8)
C(2)–C(4)	156.0(9)	C(4)–C(5)	150.3(8)
C(5)–O(4)	145.7(7)	C(5)–C(6)	148(1)
C(5)–C(7)	152(1)		
O(1)–C(1)–O(2)	120.3(7)		
O(1)–C(1)–C(2)	118.9(6)	O(2)–C(1)–C(2)	120.4(6)
C(1)–C(2)–C(3)	106.2(6)	C(1)–C(2)–O(3)	112.2(5)
C(1)–C(2)–C(4)	110.5(5)	C(3)–C(2)–O(3)	109.8(5)
C(3)–C(2)–C(4)	108.3(5)	O(3)–C(2)–C(4)	109.8(5)
C(2)–C(4)–C(5)	117.3(5)	C(4)–C(5)–C(6)	110.8(6)
C(4)–C(5)–C(7)	113.0(6)	C(4)–C(5)–O(4)	108.5(5)
C(6)–C(5)–C(7)	109.5(6)	C(6)–C(5)–O(4)	107.0(6)
C(7)–C(5)–O(4)	107.8(5)		
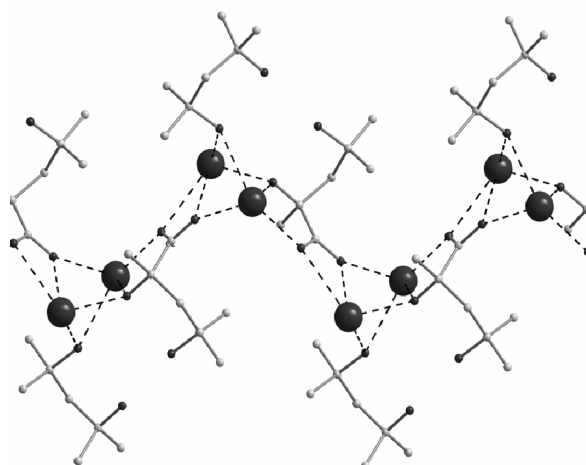
Fig. 1. Section of the structure of **1** with $[C_7H_{12}O_4]^{2-}$ anions being interconnected by Tl^+ (large atoms) *via* Tl–O interactions.

Fig. 2. Structure of the $[C_7H_{12}O_4]^{2-}$ anion surround by Tl^+ ions.

This arrangement may contribute to the orientation of the dianion in the solid state. Interestingly, all C–C bond lengths including that to the carboxylic group are in the same range (148 to 156 pm), the shortest one being C(5)–C(6) [148.3(10) pm]. The longest C–O bond [C(5)–O(4) = 145.7(7) pm] is found in the hydroxy group. Over all, the structural parameters of the dianion are in the expected range (for details see Table 2).

The Tl–O distances in **1** are in the range between 244 and 267 pm. The closest one [Tl(2)–O(3) = 244.3(4) pm] is significantly shorter than that found in thallous trinitrophenolate (263.4 pm [13]) or in or-

ganic Tl(III) salts like bis(pentafluorophenyl)thallium hydroxide (251.4 pm [14]) and even in the trigonal structure of Tl_2O (251.6 pm [15]). The coordination geometries around the thallous and oxygen centers do not obey classical polyhedral models which indicates the bonds to be dominated by electrostatic interactions. In addition, the coordination geometry of thallium(I) may be influenced by its stereochemically active lone pair.

The closest intermetallic distance in **1** [Tl(1)···Tl(2) = 374.70(6) pm] is clearly inside the van der Waals range of *ca.* 400 pm [16], but significantly elongated in comparison with the structure of Tl_2O (351.6 pm [15]) or with bonding distances found *e. g.* in metallic thallium (341.6 pm [17]), $\{Tl[C(SiMe_3)_3]\}_4$ (332.3 pm [18]), Cs_6Tl_6 (302.6 pm [19]), or $(Me_3Si)_3SiTl–Tl(Si(SiMe_3)_3$ (291.4 pm [20]). Nevertheless, the structure of **1** may also be regarded as a reference for closed-shell interactions as discussed in [21, 22].

Experimental Section

2,4-Dihydroxy-2,4-dimethylpentanoic acid, dithallium salt (1)

A beaker filled with a solution of 2.00 g (8.69 mmol) thallous cyanide in 10 mL of water was placed in a chamber containing acetone. Over 4 d at r. t., acetone was allowed to diffuse into the aqueous solution. The crystalline product was filtered off, washed with acetone and dried under argon. Yield: 1.48 g (60 %) of **1** as colorless crystals. – ^{1}H NMR (400.16 MHz, D$_2$O): δ = 1.16, 1.19 (2s, 6 H, 4-Me$_2$), 1.23 (s, 3 H, 2-Me), 1.73 and 2.19 (AB type, 2 H, CH$_2$, ^2J = 15.0 Hz). – ^{13}C NMR (100.62 MHz, D$_2$O): δ = 30.2 (2-Me), 32.3, 32.7 (4-Me$_2$), 52.4 (C^3), 74.8 (C^2), 78.8 (C^4), 187.2 (C^1). – ^{13}C NMR (MAS): δ = 33.2 (Me), 53.1 (C^3), 75.3 (C^2), 81.5 (C^4), 192.6 (C^1). – C$_7$H$_{12}$O$_4$Tl$_2$ (568.94): calcd. C 14.78, H 2.13; found C 14.00, H 2.11.

2,4-Dihydroxy-2,4-dimethylpentanoic acid (2)

To a solution of 0.167 g (1.15 mmol) of ammonium iodide in 4 mL of methanol, 0.326 g (0.574 mmol) of compound **1** was added. After stirring for 1 h at r. t., the filtered solution was evaporated *in vacuo* to dryness. The resulting solid was washed with diethyl ether and dried *in vacuo*. Yield 0.05 g of **2** (44 %), colorless solid. – ^{1}H NMR (400.16 MHz, D$_2$O): δ = 11, 1.15 (2s, 6 H, 4-Me$_2$), 1.24 (s, 3 H, 2-Me), 2.22 and 2.28 (AB type, 2 H, CH$_2$, ^2J = 14.0 Hz). – ^{13}C NMR (100.62 MHz, D$_2$O): δ = 27.4 (2-Me), 29.4, 30.0 (4-Me$_2$), 49.6 (C^3), 72.3 (C^2), 76.0 (C^4), 183.7 (C^1). – FAB-MS (3-nitrobenzylic alcohol): *m/z* = 161 ([M–H]$^-$). – C$_7$H$_{14}$O$_4$ (162.19): calcd. C 51.84, H 8.70; found C 51.32, H 8.84.

2-Hydroxy-2,4,4-trimethylbutyrolactone (3)

To an NMR sample of **2** in D$_2$O, catalytic amounts of benzenesulfonic acid were added, and the lactone **3** was identified by NMR spectroscopy. – ^{1}H NMR (400.16 MHz, D$_2$O): δ = 1.11, 1.15 (2s, 6 H, 4-Me$_2$), 1.24 (s, 3 H, 2-Me), 1.94 (m, 2 H, CH$_2$). – ^{13}C NMR (100.62 MHz, D$_2$O): δ = 27.4 (2-Me), 29.4, 30.0 (4-Me$_2$), 49.6 (C^3), 72.3 (C^2), 76.0 (C^4), 183.7 (C^1).

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