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Ring contraction/transannular cyclization of chiral bicyclo[3.3.1]nonanediones mediated by thallium(III) nitrate

Rytis Kubilius, Gintautas Bagdžiūnas, Eugenijus Butkus *

Department of Organic Chemistry, Vilnius University, Naugarduko 24, 03225 Vilnius, Lithuania

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ABSTRACT

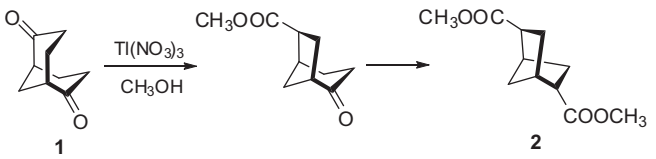
The reaction of several chiral bicyclo[3.3.1]nonane ketones mediated by thallium(III) nitrate to afford ring contraction products is investigated. The effect of solvent on the oxidation is discussed, and the use of thallium(III) nitrate for the oxidative rearrangement of regioisomers of bicyclononanones is outlined. In compounds with proximately located carbonyl groups in the bicyclic framework, unexpected transannular ring closure was observed.

The functionalization of various cyclic frameworks with high stereoselectivity is a challenging aspect of organic synthesis. The use of thallium(III) nitrate (TTN) as an oxidant for the transformation of bicyclic ketones is used to introduce carboxylate functions selectively.[1] The reaction proceeds via initial enolization of the ketone according to a pathway proposed by McKillop,[2] however, the final stage is still not clear.[3]

Herein a study on the oxidation of several bicyclo[3.3.1]nonanones mediated by TTN is presented. This framework and structurally related bicyclic skeletons have been shown to be intermediates for the synthesis of many natural and biologically active products or their metabolites.[4] Moreover, biosynthetic pathways for numerous sesquiterpenoids and other naturally occurring materials involve the formation and transformations of bicyclo[3.3.1]nonanones. We have studied the interconversion of this skeleton via ring closure/opening during chemical transformations which introduce the appropriate functional groups into a molecule via appropriate synthetic methods.[5] Thus access to stereochemically defined compounds of various ring size from this bicyclononane system via ring contraction has synthetic value. The effect of the solvent on TTN oxidations is discussed, and the use of TTN for the oxidative rearrangement of bicyclononanones outlined.

Reaction of easily accessible enantiomerically pure (+)-(1*S*,5*S*)-2,6-diketone **1** (ee >99%)[6] with TTN (molar ratio 1: 2) in methanol proceeded via subsequent oxidative rearrangement to afford exclusively, methyl (+)-*exo*,*exo*-bicyclo[2.2.1]heptane-2,5-dicarboxylate (**2**) in good yield (85%) (Scheme 1). Analysis of the ^{1}H and ^{13}C NMR spectra of (+)-**2** proved the stereochemistry of the ring contraction product. The spin–spin coupling constants $^{3}J_{H2endo-H3endo}$ and $^{3}J_{H2endo-H3exo}$ were 9.0 and 5.5 Hz, respectively, and corresponded well with the calculated values (Karplus equation) of 10.8 and 6.1 Hz. Five carbon signals at 33.5, 34.2, 40.2, 45.2, and 51.3 ppm were assigned to C-3(6), C-7, C-1(4), C-2(5), and the CH_3 groups, respectively. The high stereoselectivity of this conversion is in accordance with earlier observations on the stereoselectivities of bicyclo[3.2.1]octan-2-one[7] and other ring contraction reactions of bicyclic ketones,[8] and agree with the general reaction mechanism proposed by McKillop.[9]

Reaction of (+)-(1*S*,5*R*)-bicyclo[3.3.1]nonane-2,9-dione[10] (**3**) with an equimolar amount of TTN was carried out in methanol at room temperature giving a mixture of products. GC-MS analysis[11] indicated the presence of isomeric bicyclic structures [M^{+} = 244 (12%); 228 (22%); 214 (16%)] and minor quantities of the mono oxidation product **4**. The ^{1}H NMR spectrum showed signals at δ 3.57 and δ 3.66 indicating the presence of ester and/or acetal CH_3O groups. During the oxidation with thallium(III) nitrate, free nitric acid is evolved. It has been documented that the diketone **3**



Scheme 1.

* Corresponding author.
E-mail address: eugenijus.butkus@chf.vu.lt (E. Butkus).

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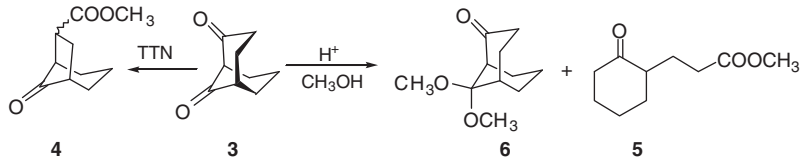
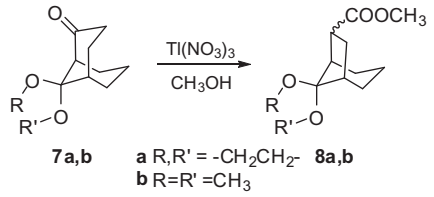
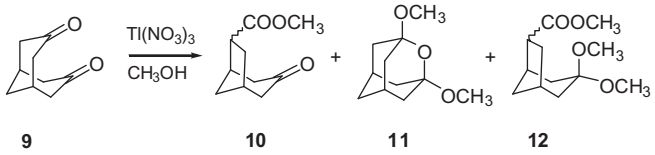


Scheme 2.



Scheme 3.



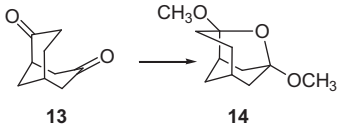
Scheme 4.

undergoes ring-opening in acidic aqueous solution, by way of carbon–carbon bond cleavage between atoms C-1 and C-2 leading to the formation of 3-(2-oxocyclohexyl)propanoic acid.[12] Indeed, the reaction mixture of **3** and TTN in methanol contained methyl 3-(2-oxocyclohexyl)propanoate (**5**, 20%). In addition, the spectra of this compound were identical to those of **5** prepared as follows. A methanol solution of **3** was acidified with concentrated aqueous hydrochloric acid and kept overnight at room temperature. The main component in the mixture (59%) was acetal **6** (Scheme 2). The synthesis of analogous ethanediol acetal **7** illustrates the tendency of **3** to form acetals at the C-9 carbonyl instead of the C-2 carbonyl.

Acetals of diketone **3** may impede the ring-opening of the bicyclic skeleton. In order to verify this observation, oxidative rearrangement of *spiro*[1,3-dioxolane-2,9′-bicyclo[3.3.1]nonan]-2′-one[13] (**7a**) was carried out. Treatment of **7a** with TTN in methanol afforded the rearrangement products, diastereomeric esters **8a** (38%) (Scheme 3). Since traces of water are present originating from $Tl(NO_3)_3{\cdot}3H_2O$, minor amounts of the deprotected diketone **3** (hydrolysis product) and the subsequently rearranged ketoester **4** (3%), respectively, were also present. Since ethanediol acetal **7a** undergoes oxidative rearrangement, analogous behavior of dimethyl acetal **7b** would be expected and diastereomers of acetal **8b** were the main products in the reaction mixture. The products of acetal hydrolysis and Favorskii-like rearrangement were also identified in this reaction mixture.

The reaction of bicyclo[3.3.1]nonane-3,7-dione (**9**) with an equimolar amount of TTN was carried out in methanol. The diketone **9** showed lower reactivity compared to the 2,6- and 2,9-isomers **1** and **3** under the same reaction conditions.[14] The starting material was still present in the mixture after 24 h at room temperature. Three compounds were formed during this reaction: the oxidative rearrangement product **10**, tricyclic acetal **11**, and the rearranged acetal 1**2** (Scheme 4). The first two compounds were separated by flash chromatography.

In order to prove the structure of **11**, a methanolic solution of **9** was acidified with a catalytic amount of *p*-toluenesulfonic acid and stored overnight at room temperature over molecular sieves. Analysis of the IR, ^{1}H NMR, and mass spectra proved the formation of tricyclic acetal **11**. Thus formation of **11** occurs with indirect participation of thallium(III) nitrate. The unexpected formation of **11** could be accounted for by the proximity of the carbonyl groups in **9**, and transannular cyclization takes place before oxidation. In addition, the 2,7-diketone **13** with proximate carbonyl groups gives an analogous cyclic acetal **14** under similar reaction conditions which support the above conclusion.



In conclusion, reaction of enantiomerically pure (+)-2,6-diketone **1** with TTN (molar ratio 1: 2) in methanol proceeds via oxidative rearrangement, exclusively affording methyl (+)-*exo*,*exo*-bicyclo[2.2.1]heptane-2,5-dicarboxylate **2** in good yield. Analogous transformations of (+)-2,9-dione, 2,7- and 3,7-diketones led not only to oxidative rearrangement but also to transannular ring closure into tricyclic products due to the proximity of the carbonyl groups in the bicyclononane skeleton.

Acknowledgment

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13. *spiro*[1,3-Dioxolane-2,9′-bicyclo[3.3.1]nonan]-2′-one (**7a**). P_2O_5 (0.1 g) was added to a solution of **3** (0.41 g, 2.7 mmol) and ethanediol (0.17 g, 2.7 mmol) in dry toluene (10 mL). The mixture was refluxed with azeotropic removal of H_2O, cooled, and residual P_2O_5 was quenched with H_2O. The product was extracted with benzene (3 × 5 mL); the extracts were combined, washed with saturated $NaHCO_3$ (2 × 10 mL) solution and H_2O (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The product was distilled in vacuo to afford 0.19 g (37%) of an oily liquid, bp 112–115 °C/2 mmHg. IR, λ_{max}: 1715, 1112, 1100 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): 3.9 (m, 4H, $O(CH_2)_2O$), 2.54 (m, 2H), 2.32–1.77 (m, 8H), 1.74–1.6 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 212.2

(C2′), 116.2 (C9′), 64.6 (C4 and C5), 51.2 (C1′), 38.4 (C3′), 37.4 (C5′), 26.2 (C8′), 25.2 (C7′), 24.1 (C4′), 20.4 (C6′).

14. *General procedure for the reaction of bicyclo[3.3.1]nonane ketones with TTN*: A solution of thallium(III) nitrate (590 mg, 1.33 mmol) in MeOH (15 mL) was added gradually to a solution of the bicyclic ketone (200 mg, 1.31 mmol) in MeOH (15 mL) and the mixture was stirred for 3–9 h. $TlNO_3$ precipitated from the mixture. The majority of the MeOH was evaporated and the residue was treated with acidified H_2O (3 mL of HCl in 70 mL of H_2O). The resulting mixture was extracted with $CHCl_3$ (3 × 70 mL), washed with 5% $KHCO_3$ (50 mL), and then with H_2O (50 mL), dried over $CaCl_2$, and the solvent was evaporated to afford the products. Spectral data for selected compounds: methyl *exo*,*exo*-(1*R*,2*S*,4*R*,5*S*)-bicyclo[2.2.1]heptane-2,5-dicarboxylate (**2**): yield 85%, bp = 119–120 °C/4 mmHg, n_D^{20} = 1.4760; $[\alpha]_{546}^{17}$ +40.0 ($CHCl_3$, *c* 0.1); IR max/cm^{-1} 1728, 730; ^{1}H NMR (300 MHz, $CDCl_3$): 1.40 (2H, m, C7-H), 1.48 (2H, d, *J* = 9.0 Hz, C3(C6)-H_{endo}), 1.70–1.98 (2H, m, C3(C6)-H_{exo}), 2.20 (2H, dd, *J* = 5.5 and 9.0 Hz, C2(C5)-H), 2.45 (2H, d, *J* = 4.0 Hz, C1(C4)-H), 3.52 (6H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$): 33.5, 34.2, 40.2, 45.2, 51.3 (all skeletal C), 175.7 (C=O). MS (relative intensity), *m*/*z* 212 (M^+, 19), 180 (15), 152 (14), 120 (9), 86 (100). Anal. Calcd for $C_{11}H_{16}O_4$: C, 62.25; H, 7.59. Found: C, 62.65; H, 7.06. Methyl 3-oxobicyclo[3.2.1]octane-6-carboxylate (**10**): IR ν_{max}/cm^{-1} 1736, 1710. MS (EI) (relative intensity) *m*/*z*: 182 (17) [M^+], 167 (5) [M^+-CH_3], 152 (8), 125 (16), 122 (18), 109 (100), 93 (39), 79 (30), 67 (28), 55 (15), 41 (27). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.51; H, 7.87. 1,3-Dimethoxy-2-oxatricyclo[3.3.1.1^{3,7}]decane (**11**), purified by flash chromatography (silica gel, $CHCl_3$–acetone, 4:1): IR ν_{max}/cm^{-1} 1163, 1134. ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ: 3.09 (6H, s, $2CH_3O$), 2.38 (2H, dd, *J* = 4.5, 5.4, $C_{5,7}$-H), 1.74 (4H, d, *J* = 5.6, $C_{4,8,9,10}$-H_{eq}), 1.63 (2H, s, both C_6-H), 1.44 (4H, dd, *J* = 5.4, 4.5, $C_{4,8,9,10}$-H_{ax}). MS (EI) (relative intensity) *m*/*z*: 198 (12) [M^+], 183 (7) [M^+-CH_3], 170 (4), 157 (6), 138 (6), 125 (100), 109 (27), 97 (27), 72 (47), 41 (14).