Reactions of Podocarpic Acid Derivatives with Thallium(III) Nitrate

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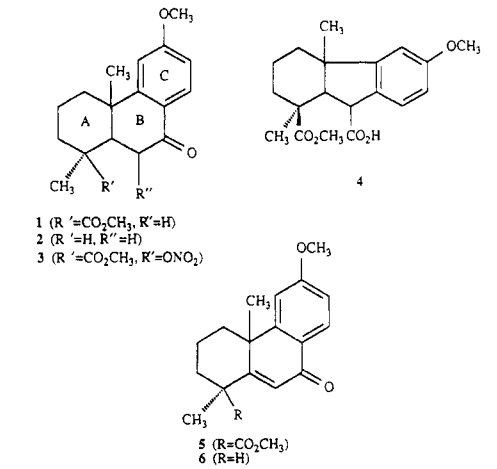
The reaction of methyl *O*-methyl-7-ketopodocarpate (**3**) with thallium(III) nitrate in acetic acid was performed in attempt to synthesize compound **4**, an intermediate in the total synthesis of the plant growth hormone gibberellic acid. The reaction unexpectedly resulted in new methodology for the one-step formation of methyl *O*-methyl-$\Delta^{5,6}$-7-ketopodocarpate from the keto ester **3**. Four model compounds, having similar skeletons to the keto ester **3**, were reacted with TTN under the same conditions to establish a general method for the formation of α,β-unsaturated ketones. These models yielded either the α-nitrato ketone and/or the decomposition product benzoic acid. Reaction of the hindered tricyclic ketone **11** with TTN yielded the expected α,β-unsaturated ketone **12**. Thus this methodology is selective for hindered tricyclic ketone systems.

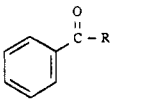
The most common reagents which have been employed in oxythallation reactions are $Tl(OCOCH_3)_3$,[1] $Tl(OCOCF_3)_3$,[2] $Tl(ClO_4)_3$,[3] $Tl(BF_4)_3$, $Tl_2(SO_4)_3$, and $Tl(ONO_2)_3$.[4] Thallium(III) nitrate (TTN) is the most versatile reagent for the oxidation of many types of organic substrates. TTN can easily be obtained as the stable, crystalline trihydrate [$Tl(ONO_2)_3 \cdot 3H_2O$]. Moreover, TTN is freely soluble in a wide range of solvents such as alcohols, glyme, acetonitrile, and organic acids. In this paper, we report the reaction of TTN with the podocarpic acid derivative, methyl *O*-methyl-7-ketopodocarpate.

The preparation of methyl *O*-methyl-7-ketopodocarpate (**1**) was carried out by methylation of podocarpic acid and subsequent benzylic oxidation.[5] The reaction of keto ester **1** with TTN in acetic acid was initiated in an attempt to synthesize the ring-contracted product compound **4**. However, this reaction unexpectedly resulted in the formation of the α,β-unsaturated keto ester **5**. This result provided a new one-step formation of the α,β-unsaturated keto ester **5** from the keto ester **1**. The α,β-unsaturated keto ester **5** has previously been reported to be formed from the keto ester **1** in two steps.[5-7]

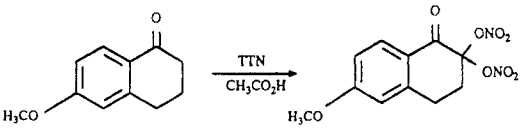
In order to investigate the possibility of this reaction as a general method for the formation of α,β-unsaturated ketones, four model compounds were selected for investigation, all of which have skeletons similar to the keto ester **1**. The model compounds are propiophenone (**7**), *n*-propyl phenyl ketone (**8**), isovalerophenone (**9**), and 6-methoxy-1-tetralone (**10**). Compounds **7-9** contain the basic skeleton of the B/C ring system (C_5-C_6-C_7-(O)Ar) found in the keto ester **1**; however, they have different substituents at the β-position (C_5). Compound **10** has the same skeleton as the B and C rings in the keto ester **1**.

Compound **9** was selected for investigation since it is similar to keto ester **1** in respect to the location of a teritary hydrogen at the β-position. Hence, reaction of compound **9** with TTN was expected to produce the corresponding α,β-unsaturated ketone. Compound **7** has a primary hydrogen at the β-position and was expected to react with TTN to give the normal rearrangement product in a fashion similar to acetophenone.[8-10] Compounds **8** and **10** contain a secondary hydrogen at the β-position and were expected to result in a mixture of the α,β-unsaturated ketones and the normal rearrangement product. The reactions of these model compounds resulted in the formation of the corresponding α-nitrato ketones and/or the decomposition product benzoic acid.[11,12] Of interest was the reaction of 6-methoxy-1-tetralone (**10**) to yield the new white crystalline compound 2,2-dinitrato-6-methoxy-1-tetralone (**11**) (10%), mp 132-133 °C. To our knowledge, no organic compound with two nitrato groups on one carbon has been reported.





7 (R=CH_2CH_3)
8 (R=CH_2-CH_2-CH_3)
9 (R=CH_2-CH-$(CH_3)_2$)



10 **11**

Since α,β-unsaturated ketones were not observed from the reactions of compounds **7-10** with TTN in acetic acid, another attempt was made to demonstrate the applications of this new method. The decarbomethoxylated ketone **2** was selected as another example of a tricyclic ketone.

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Ketone **2** is less hindered than compound **1** since the ester group on the A ring has been removed. Compound **2** was prepared[7] from the α,β-unsaturated keto ester **5** via decarbomethoxylation and subsequent hydrogenation.

Treatment of the ketone **2** with TTN in acetic acid gave the α,β-unsaturated ketone **6** in good yield (80%). This result, in combination with the product obtained from the reaction of ketone **1**, suggests that this method has applicability only in the preparation of α,β-unsaturated ketones from hindered tricyclic ketones.

In an attempt to improve the yield of the α,β-unsaturated ketone, these reactions were performed in another solvent system, trimethyl orthoformate (TMOF)/MeOH. This solvent system was reported to show a remarkable effectiveness for TTN-mediated oxidations.[13,14] Treatment of the ketones **1** and **2** with TTN in TMOF/MeOH gave rise to ketones **5** (86%) and **6** (87%) in excellent yields.

The formation of α,β-unsaturated keto ester **5** with TTN in acetic acid may proceed by formation of the α-nitrato ketone **3**, followed by bimolecular elimination either in the boat conformation (E_2) or with the nitrato group in a pseudoequatorial position (E_i).

Experimental Section

Melting points were determined on a Fisher-Johns apparatus and are uncorrected. ^{1}H NMR spectra were recorded in $CDCl_3$ on Varian EM-360A or a General Electric/Nicolet NT-200 spectrometer and were referenced to TMS as an internal standard. IR spectra were recorded on a Perkin-Elmer Model 283B spectrophotometer. Merck silica gel 60 was used for column chromatography, and TLC data were obtained with precoated Merck (Darmstadt) silica gel G and GF-254. High-resolution MS EI was obtained at the Massachusetts Institute of Technology and at the chemical instrumentation center of Yale University. Analytical GC–MS was determined on a Finnigan 4510 quadropole mass spectrometer interfaced with a Finnigan gas chromatograph.

Methyl *O*-Methyl-$\Delta^{5,6}$-7-ketopodocarpate (5). A mixture of methyl *O*-methyl-6-bromo-7-ketopodocarpate (20 g, 0.05 mol), DBU (9.6 g, 0.06 mol), and *o*-xylene (60.4 mL) was stirred at 165 °C for 15 min. The ether extract of the acidified (5% HCl) reaction mixture was washed twice with 5% aqueous $NaHCO_3$ and H_2O and then dried with Na_2SO_4. Crystallization from aqueous MeOH yielded 14.4 g (90.5%) of **5** as a white crystalline solid: mp 175–177 °C (lit.[15] mp 173–175 °C); IR (KBr) 1735, 1685, and 1575 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, s, C-CH_3), 1.45 (3 H, s, C-CH_3), 3.62 (3 H, s, OCH_3), 3.88 (3 H, s, C-CH_3), 6.60 (1 H, s, vinylic), 7.00 (2 H, m, Ar), and 8.20 (1 H, d, Ar).

Decarbomethoxylated Methyl *O*-Methyl-$\Delta^{5,6}$-7-ketopodocarpate (6). A mixture of 2.5 g (0.013 mol) methyl *O*-methyl-6-bromo-7-ketopodocarpate and 3.9 g (0.026 mol) of DBU in 15.1 mL of *o*-xylene was refluxed at 165 °C for 10 h. The ether extract of the acidified (5% HCl) reaction mixture was washed twice with 5% Na_2CO_3 and water and then dried with $MgSO_4$. The residue was crystallized using CH_2Cl_2–MeOH to give 2.99 g (92%) of **6**. An analytical sample had the following characteristics: mp 122–124 °C (lit.[16,17] mp 120–121 °C); IR (KBr) 1650 and 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.15 (3 H, d, C-CH_3), 1.42 (3 H, s, C-CH_3), 3.88 (3 H, s, O-CH_3), 6.30 (1 H, s, vinylic), 7.00 (2 H, m, Ar), and 8.21 (1 H, d, Ar).

Decarbomethoxylated Methyl *O*-Methyl-7-ketopodocarpate (2). A solution of 1.10 g of decarbomethoxylated methyl *O*-methyl-$\Delta^{5,6}$-7-ketopodocarpate in 100 mL of *o*-xylene containing a catalytic amount of 5% Pd/C was hydrogenated at 20 psi for 1 h. After filtration and solvent removal, 0.75 g of a colorless oil was obtained. GLC and HPLC indicated a mixture of cis and trans isomers: IR (KBr) 1650 and 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.11 (3 H, s, C-CH_3), 1.30 (3 H, s, C-CH_3), 3.80 (3 H, s, O-CH_3), 6.86 (2 H, m, Ar), and 8.00 (1 H, d, Ar); HRMS calcd for $C_{17}H_{22}O_2$ 258.1602, found 258.1629. The dissappearance of the NMR signal for the vinylic proton of compound **12** indicates the hydrogenation reaction was complete.

Methyl *O*-Methyl-$\Delta^{5,6}$-7-ketopodocarpate (5). A mixture of 4.44 g (0.01 mol) of TTN and 3.16 g (0.01 mol) of methyl *O*-methyl-7-ketopodocarpate in 20 mL of CH_3COOH was stirred for 8 h at 65 °C. The acetic acid was then removed by distillation under reduced pressure. The residue was diluted with H_2O, extracted with $CHCl_3$, dried with $MgSO_4$, and filtered. The product obtained on concentration of the extract was recrystallized from MeOH to yield 2.23 g (71%) of **5** as a white crystalline solid: mp 174–176 °C.

Oxidation of Propiophenone (7). A solution of 4.44 g (0.01 mol) of TTN and 1.34 g (0.01 mol) of propiophenone in 20 mL of CH_3COOH was refluxed for 8 h. Thallium(I) nitrate, which precipitated, was removed by filtration, and the filtrate was neutralized with 5% aqueous $NaHCO_3$. The solution was extracted with $CHCl_3$, dried with $MgSO_4$, and filtered. After recrystallization from hexane, a white crystalline solid was obtained as α-nitratopropiophenone (1.40 g, 72%): mp 47–49 °C (lit.[11] mp 47–49 °C); IR (KBr) 1675, 1620, and 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.60 (3 H, d, C-CH_3), 6.20 (1 H, q, α-H), 7.46 (2 H, t, Ar), 7.61 (1 H, s, Ar), and 8.00 (2 H, d, Ar). Anal. Calcd for $C_9H_9O_4N$: C, 55.38; H, 4.61; N, 7.18. Found: 55.27; H, 4.69; N, 7.16.

Oxidation of *n*-Propyl Phenyl Ketone (8). A mixture of 8.88 g (0.02 mol) of TTN and 2.56 g (0.02 mol) of *n*-propyl phenyl ketone in 40 mL of CH_3COOH was refluxed for 8 h. Inorganic salt of thallium(I) nitrate was removed by filtration. The filtrate was neutralized with 5% aqueous $NaHCO_3$ and extracted with ether. The aqueous layer was reacidified with 5% HCl, extracted with $CHCl_3$, and dried with $MgSO_4$. Recrystallization from hexane yielded benzoic acid (0.55 g, 33%); mp 122–123 °C. The ether extract was dried ($MgSO_4$), filtered, concentrated in vacuo, and chromatographed on silica gel (hexane–benzene) to yield 1.88 g (45%) of α-nitrato *n*-propyl phenyl ketone as a yellow liquid: bp 88–90 °C (0.05 mm) [lit.[13] bp 105–106 °C (0.2 mm)]; IR (KBr) 1680, 1625, and 1275 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09 (3 H, t, C-CH_3), 2.18 (2 H, m, β-H), 6.05 (1 H, t, α-H), 7.48 (2 H, t, Ar), 7.62 (1 H, d, Ar), and 8.02 (2 H, d, Ar). Anal. Calcd for $C_{10}H_{11}O_4N$: C, 57.41; H, 5.26; N, 6.69. Found: C, 57.21; H, 5.24; N, 6.44.

Oxidation of Isovalerophenone (9). A mixture of 9.0 g (0.02 mol) of TTN and 3.24 g (0.02 mol) of isovalerophenone in 20 mL of CH_3COOH was stirred for 8 h at 65 °C and filtered to remove thallium(I) nitrate. Most of the CH_3COOH was removed by distillation under reduced pressure. The material was neutralized with 5% aqueous $NaHCO_3$ and extracted twice with ether. The aqueous layer was reacidified with 5% HCl, extracted twice with $CHCl_3$, dried with $MgSO_4$, filtered, concentrated in vacuo, and recrystallized from hexane to yield benzoic acid (1.64 g, 71%) mp 122–123 °C.

Oxidation of 6-Methoxy-1-tetralone (10). A mixture of 8.88 g (0.02 mol) of TTN and 3.52 g (0.02 mol) of 6-methoxy-1-tetralone in 40 mL of CH_3COOH was reacted for 8 h at 60 °C and filtered to remove the inorganic salts. The filtrate was neutralized with 5% aqueous $NaHCO_3$, extracted with $CHCl_3$, dried with $MgSO_4$, and recrystallized with hexane–benzene to yield 2,2-dinitrato-6-methoxy-1-tetralone (**11**) as a white chrystalline solid: mp 132–133 °C; IR (KBr) 1680, 1595, 1260, and 1230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.20 (C_3-2H, t), 3.42 (C_4-2H, t), 4.46 (3 H, s, OCH_3), 7.00 (1 H, s, Ar), 7.60 (1 H, d, Ar), and 8.08 (1 H, d, Ar); HRMS calcd for $C_{11}H_{10}O_8N_2$ 298.0437, found 298.0446. Anal. Calcd for $C_{11}H_{10}O_8N_2$: C, 44.29; H, 3.35; N, 9.39. Found: C, 45.08; H, 3.84; N, 10.07.

Methyl *O*-Methyl-$\Delta^{5,6}$-7-ketopodocarpate (5). A 4.44-g (0.01-mol) portion of TTN was added to a solution of 3.16 g (0.01 mol) of methyl *O*-methyl-7-ketopodocarpate (3.16 g, 0.01 mol) in 25 mL of a 1:1 mixture of MeOH and trimethyl orthoformate. The reaction mixture was refluxed for 8 h, concentrated in vacuo, and diluted with 25 mL of $CHCl_3$. After filtration, the filtrate was washed successively with 2 × 50-mL portions of water and 5% aqueous $NaHCO_3$ and then dried with $MgSO_4$. Concentration of the filtrate gave a reddish liquid, which was then recrystallized

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from acetone to yield 2.51 g (86%) of methyl *O*-methyl-$\Delta^{5,6}$-7-5 (2.51 g, 86%) as a white crystalline solid: mp 174-176 °C.

Decarbomethoxylated Methyl *O*-Methyl-$\Delta^{5,6}$-7-ketopodocarpate (6). A mixture of 0.44 g (0.001 mol) of TTN and 0.26 g (0.001 mol) of ketone **2** in 2.5 mL of a 1:1 mixture of MeOH and trimethyl orthoformate was refluxed for 8 h, concentrated in vacuo, and diluted with $CHCl_3$. Thallium(I) nitrate was removed by filtration. The filtrate was washed successively with 2 × 50-mL portions of water and 5% aqueous $NaHCO_3$ and then dried with $MgSO_4$. Concentration of the extract and repetitive recrystallization from a 50:1 CH_2Cl_2-MeOH gave the α,β-unsaturated ketone **6** (87%): mp 122-124 °C.

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Nonconventional Friedel-Crafts Chemistry. 1. Reaction of α-Tetralone and Anthrone with Arenes under Friedel-Crafts Conditions

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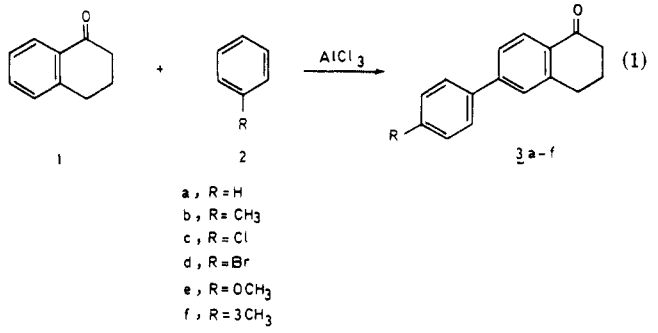
α-Tetralone and anthrone were reacted with arenes in the presence of aluminum chloride to give 6-aryl-1-tetralone and 10-arylanthrone, respectively. The mechanisms of these reactions are discussed.

Introduction

In previous reports[1], the condensation of phenols and naphthols with arenes in the presence of Lewis and Brønsted acids was investigated. The results of these investigations in addition to our interest in Friedel-Crafts chemistry[2-8] led us to consider the possibility of analogous reactions of α-tetralone and anthrone with arenes, with the aim of shedding more light on the mechanistic aspects of these reactions.

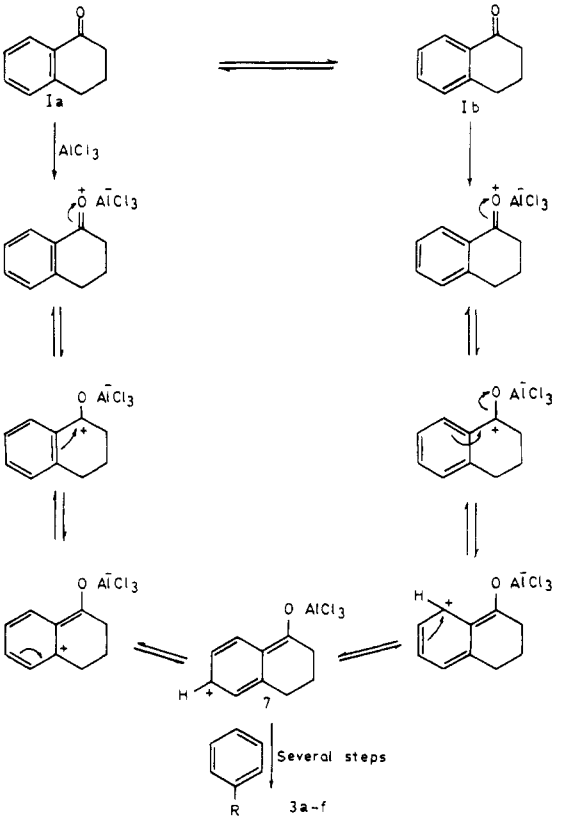
Results and Discussion

Surveying the results of Table I showed that, in the presence of $AlCl_3$ catalyst, α-tetralone reacted with arenes to yield 6-aryl-1-tetralone (eq 1) in fairly good yields (45-68%).



(1)

Scheme I



For instance, in the case of benzene (Table I, entry 1), 6-phenyl-1-tetralone (**3a**; 56%) was formed in addition to biphenyl (10%), terphenyl (7%), and quarterphenyl (5%). The formation of biphenyl, terphenyl, and quaterphenyl under these reaction conditions could be explained via dimerization, trimerization, and tetramerization of benzene under prevailing reaction conditions.[9-11] The reaction of

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