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Titanium Chelation in Regioselective Michael Additions to Conjugated Dienones and Trienones.

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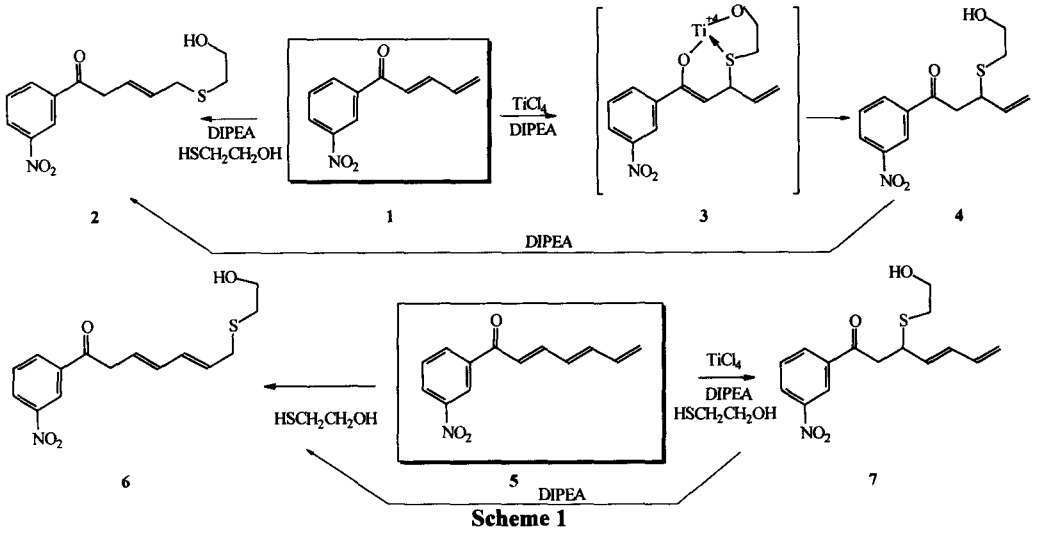
Abstract: The site of Michael addition of β-hetero atom substituted thiols (such as mercaptoethanol) to unsubstituted 2, 4-dienone and 2, 4, 6-trienones is at the terminal (ω) position. This site preference is transferred to the β site when the addition is accomplished using Ti^{+4} complexation. These β site addition products rapidly rearrange to the ω position on base treatment. © 1997 Elsevier Science Ltd.

Unsubstituted, dien– and trienones undergo Michael type[1] addition of thiols predominately at their terminal position [ω site]. Just on the basis of the relative steric effects at the available attachment sites [β, δ, ω, *etc.*], this mode of bonding would be anticipated. Nevertheless, the interplay of kinetic, electronic, resonance and steric effects is complex and subtle variations modify the result. Metal atom chelation can markedly determine the site of Michael addition in such systems. Mercaptoethanol addition to dienone **1**[2] in methanol/THF using diisopropylethylamine [DIPEA] catalyst, at 45°C, yields 5-(2-hydroxyethylthio)-*m*-nitro-3(E)-penteneophenone **2**[3] contaminated with only trace amounts of the isomeric β addition product 3-(2-hydroxyethylthio)-*m*-nitro-4-penteneophenone [**4**][4] (observed by both TLC [hexane/EtOAc, 3:1] and NMR). As the temperature of the reaction is lowered and the rate of reaction decreases, the amount of the β addition product **4** increases (NMR of crude after isolation). The maximum β isomer/δ isomer ratio occurs at about a



Scheme 1

1/1.5 distribution (β isomer **1**/ δ isomer **4**) at -40°C. This temperature is somewhat of a practical limit because of the slow addition rate below that temperature. These events suggested a classic, fast (lower transition path) equilibrium addition/elimination to the β site competitive with slower addition to the δ site (giving the thermodynamically more stable compound).

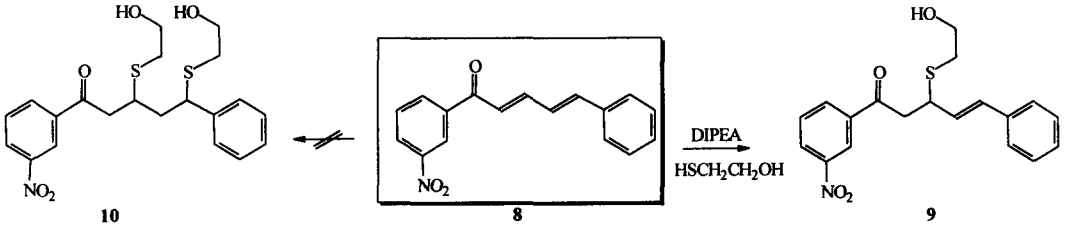
These findings were made during studies related to the synthesis of "molecular yardsticks" using titanium complexes of ketones with a β-thioethanol "chelating arm" in the aldol/dehydration synthesis.[5] The above observation implied that by using Ti^{+4}, we might be able to "capture" the less stable β adduct **4** through the complex **3** and drive the equilibrium to give exclusively β isomer **4**. Yardstick ETAC reagents[6] are of interest in the study of sequential alkylation through consecutive Michael reactions[7] used in the equilibrium cross-linking of enzyme and antibody proteins.[8]

In the event, when mercaptoethanol addition was carried out on a complex of the dienone **1**[2] and titanium tetrachloride in THF at -40°C using N-methylmorpholine (1 equiv.), after quenching the mixture with citric acid solution, only the β adduct **4** was observed. Accomplished on a preparative scale, pure β adduct **4** was isolated in excellent yield. This β adduct **4** was completely transformed to the δ isomer **2** within seconds upon treatment with a trace of DIPEA in methanol at room temperature. This isomerization undoubtedly occurs through a retro-Michael/ Michael addition equilibrium. The δ isomer forms a Ti^{+4} complex that fragments on treatment with DIPEA at room temperature to give dienone. Other chelating functions on the mercaptan chain (—$N(C_2H_5)_2$, —OCH_3) also serve to realize the same β site trapping process with Ti^{+4} but the chelation trapping does not appear as efficient without some attached function. Trienone **5**[9] behaves in an exactly related fashion producing ω addition product **6**[10] in the absence of Ti^{+4} and β site addition [**7**[11]]in the presence of Ti^{+4}. Neither simple isomerization of the β, γ double bond of **2** to the α, β position nor *bis*-Michael additions of thiols (through isomerization of the double bond [β,γ ➛ α,β] followed by a second Michael addition to the now conjugated double bond) were observed even with excess thiol or with Ti^{+4}.

The starting diene and trienones [**1**[2] & **5**[9]] were prepared by addition of titanium tetrachloride to *m*-nitroacetophenone at -60°C in THF, warming the inhomogeneous yellow mixture to 0°C, recooling to -40°C and then adding 3 equivalents of DIPEA. This sequence resulted in the formation of a brilliant red complex which is soluble in THF at -40°C. Rapid addition of acrolein or pentadienal at 0°C to this complex gave 55-60% yields of the corresponding dienone **1**[2] or trienone **5**[9] Substituted unsaturated aldehydes (cinnimaldehyde, sorbaldehyde and crotonaldehyde) and a variety of acetophenones behave in an exactly similar fashion. Reaction of unsaturated aldehydes using *m*-nitropropiophenone and Ti^{+4} was unsuccessful. This result is revealing when compared with the almost quantitative yield in the aldol/dehydration synthesis of extended ETAC reagent 2-(2-hydroxyethylthiomethyl)-*m*-nitro-2(Z),4-pentadienophenone from acrolein, $TiCl_4$ and 3-(2-hydroxyethylthio)-*m*-nitropropiophenone.[5] The synthetic path is an extension of the Ti^{+4} aldol/dehydration

sequence first introduced in simple Knoevnagel condensations by Lehnert[12] and by Harrison[13] and adapted by us for the synthesis of "molecular yardsticks".[5]

β Adduct **4** was produced exclusively in the presence of titanium tetrachloride either because of capture of the β site addition product as a chelated complex by the thioethanol side chain or because concurrent titanium association with the carbonyl of the α, γ-dienone system and with mercaptoethanol directs the thiol to the β site. The accomplishment of the above sequence [**Scheme 1**] lends documentation for the reality of the Ti^{+4} complexing effect proposed in the synthesis of molecular yardsticks.[5] The adducts **4** or **7** as their Ti^{+4} complex can also be condensed with unsaturated aldehydes to produce extended ETAC type systems with two arms.[14] Aldol reaction occurs at the position α to the carbonyl followed by elimination of the aldol β—OH.



Scheme 2

As documented in the work of Posner[1,15] and of Ruhemann[16] over 90 years ago, alkyl and aryl substitution at the terminal position of the dienone or trienone dramatically alters the site of addition and the product distribution in the Michael addition equilibrium. In contrast to **1** and **5**, DIPEA catalyzed addition of mercaptoethanol to cinnimylidene-*m*-nitroacetophenone [**8**[17], Scheme 2] yields only the product of addition at the β site [**9**][18]. No δ site addition could be recognized and attempts to identify it's intermediacy using excess mercaptoethanol to capture a second conjugate addition at the β site after isomerization [giving 5-phenyl-2,5-bis(2-hydroxyethylthio)-*m*-nitrovalerophenone, **10**] failed. $TiCl_4$ does not effect these processes.

Evans has pioneered the studies of stereoselective aldol and Michael reactions with chlorotitanium enolates of chiral acyloxyazolidinones.[19,20] While there are numerous examples of stereoselectivity and asymmetric induction in the Michael reaction, there are few reports of Michael reactions regioseletivity affected and controlled by metal atom chelation.[21]

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2 **1**:*m*-Nitro-2(E),4(E)-pentadienophenone, mp 86-88.5°, ^{1}H-NMR(acetone-d6) δ 5.68(d, 1 H, J=9.94Hz), 5.86(d, 1 H, J=16.83Hz), 6.71-6.81(m, 1 H), 7.32-7.49(m, 2 H), 7.86(t, 1 H), J=7.90Hz), 8.43(d. 1 H, J=7.73Hz), 8.47(d, 1 H, J=8.19Hz), 8.75(s, 1 H). ^{13}C-NMR(acetone-d6) δ 188.5, 149.5, 146.3, 140.0, 136.4, 134.9, 131.2, 128.0, 127.8, 126.3, 123.6.

3 **2**: oil, ^{1}H-NMR($CDCl_3$) δ 2.48(s, 1 H), 2.64(t, 2 H), 3.15(d, 2 H), 3.68(t, 2 H), 3.81(d, 2 H), 5.57-5.69(ddd(qu), 1 H), 5.62-5.72(ddd(qu), 1 H), 7.68(t, 1 H), 8.25(d, 1 H), 8.39(d, 1 H), 8.70(s, 1 H).

4 **4**: oil. ^{1}H-NMR($CDCl_3$) δ 2.63-2.78(m, 2 H), 3.33(ddd, 2 H), 3.75(t, 2 H), 3.93(ddd as a q, 1 H), 5.13(dd as a t, 2 H), 5.68-5.78(ddd, 1 H), 7.68(t, 1 H, J=8.14Hz), 8.26(d 1 H, J=6.98Hz), 8.40(d, 1 H), 8.73(s, 1 H). All proton relationships identified through COSEY and NOSEY NMR study.

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9 **5**:*m*-Nitro-2(E),4(E),6 heptatrienophenone, mp 109-110.5°. ^{1}H-NMR($CDCl_3$) δ 5.40(d, 1 H), 5.50(d, 1 H), 6.41-6.55(m, 2 H), 6.68-6.78(m, 1 H), 6.98(m, 1 H), 7.45-7.56(m, 1 H), 7.68(t, 1 H), 8.25(d, 1 H), 8.46(d, 1 H), 8.72(s, 1 H). ^{13}C-NMR(acetone-d6) δ 188.2, 149.5, 146.0, 144.0, 140.3, 137.5, 134.8, 132.1, 131.2, 127.7, 125.7, 123.5, 122.8.

10 **6**:oil; ^{1}H-NMR($CDCl_3$) δ 2.71(t, 2H), 3.2(d, 2H), 3.70(t, 2H), 3.82(d, 2H), 5.68(m, 2H), 6.05(q, 1H), 6.32(q, 1H), 7.65(t, 1H), 8.22(d, 1H), 8.44(d, 1H), 8.75(s, 1H).

11 **7**:oil; ^{1}H-NMR($CDCl_3$) δ 2.75(m, 2H), 3.38(t, 2H), 3.80(t, 2H), 4.96(q, 1H), 5.63(m, 1H) imposed on 5.66(d, 1H), 5.90(m, 1H), 6.10(m, 1H), 6.33(m, 1H), 7.65(t, 1H), 8.22(d, 1H), 8.42(d, 1H), 8.78(s, 1H).

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14 To a THF solution of **3** with $TiCl_4$ at -70°C warmed to 0°C, recooled to -70°C was added DIPEA, warmed to 0°C yields a dark purple solution. This was cooled to -40°C and crotonaldehyde added.. Work-up with aqueous citric acid and chromatography yielded 35% 2-(3-(2-hydroxyethylthio)-1-propenyl)-*m*-nitro-2, 4-hexadienophenone as an oil. ^{1}H-NMR($CDCl_3$) δ 1.94 (d, 3H), 2.14(t, 1H), 2.68(t, 2H) 3.28(d, 2H), 3.75(q, 2H) 5.94(q, 1H), 6.14(sex, 1H) 6.40-6.68(m, 3H), 7.65(t, 1H), 8.09(d, 1H), 8.39(d, 1H), 8.53(s, 1H). Sulfone by mCPBA oxidation, mp 109-115°C.

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17 **8:** mp 134-135°C; ^{1}H-NMR($CDCl_3$) δ 7.07(m, 3H), 7.38(m, 3H), 7.52(q, 2H), 7.67 (m,1H), 7.68(t,1H), 8.31(d,1H), 8.42(d,1H), 8.78(s,1H). ^{13}C-NMR(acetone-d6) δ 187.9, 148.4, 146.6, 143.5, 139.5, 135.8, 133.9, 129.9, 129.6, 128.9, 127.5, 126.9, 126.5, 123.9, 123.2.

18 **9:** oil; ^{1}H-NMR($CDCl_3$) δ 2.75(bm, 2H), 3.37(m, 2H), 3.80(m, 2H), 4.16(q, 1H), 6.12(dd, 1H), 6.52(d, 1 H), 7.25-7.45(m, 5H), 7.72(t, 1H), 8.33(d, 1H), 8.44(d, 1H), 8.83(s, 1H). ^{13}C-NMR(acetone-d6) δ 196.1, 148.5, 137.9, 133.5, 129.9, 129.4, 128.7, 128.6, 128.1, 127.8, 127.4, 126.4, 122.8, 61.0, 43.4, 42.8, 31.1.

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