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ADDITION OF A SILYL KETENE ACETAL TO α,β -UNSATURATED CYCLIC ANHYDRIDES

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Addition of [1-methoxy-2 methyl-1-propenyl)-oxy] trimethylsilane (MTS) to unsymmetrical α , β -unsaturated cyclic anhydrides (namely, itaconic anhydride and citraconic anhydride) as well as symmetrical anhydrides (namely, maleic anhydride and 2,3dimethylmaleic anhydride) was investigated. Itaconic anhydride isomerizes to citraconic anhydride in the presence of MTS. In the presence of Lewis acid catalysts (Yb(OTf)₃] CH₂Cl₂), MTS adds to itaconic anhydride at room temperature in a 1,4-fashion. 1,2-Addition is the preferred pathway with both 2,3-dimethyl maleic anhydride and citraconic anhydride.

Keywords: 1,2-Addition; 1,4-addition; cyclic anhydrides; Lewis acid; silyl ketene acetal

Silyl ketene acetals have been widely investigated as a nucleophilic reagent in the Mukaiyama–Michael addition^[1] with α,β -unsaturated ketones,^[1a,1b] α,β -unsaturated esters,^[1c-e] Mukaiyama aldol,^[2–4] aldehydes,^[2,3] and ketones^[4] in a three-component Mannich-type reaction^[5] with aldehydes and amines, and in an imino aldol reaction^[5f-g,6] with imines with respect to diastereoselective and enantioselective synthesis.^[7] Silyl ketene acetals also react with acetals,^[7a,d] epoxides,^[8a] and acryloyl and monosubstituted acryloyl chlorides,^[8b] and they also can act as effective silylating agents for alcohols, carboxylic acids, mercaptans, and amides.^[8c]

The relative selectivity of 1,2- and 1,4-addition depends on the natures of the α , β -unsaturated carbonyl compound, silyl ketene acetal, and the catalyst. Reaction of β , β -dimethyl-substituted silyl ketene acetal [Me₂C=C (OMe)OSiMe₃] with cinna-maldehyde gives both 1,4- and 1,2-adducts 1:1 in 90% yield using 5% SmI₂/CH₂Cl₂ at $-20 \,^{\circ}C$,^[9a] whereas the 1,2-adduct is exclusively formed (90%) when the same reaction was carried out using 5 M lithium perchlorate in nitromethane^[9b] at room temperature. Silyl ketene acetals have electron-rich C=C double bonds and thus react with many electrophiles under moderate conditions. Their π -nucleophilicity in C–C bond-forming reactions was reported recently.^[10]

Recently, Mermerian and Fu reported that in the presence of an appropriate nucleophilic chiral catalyst, an E/Z isomeric mixture of acyclic and lactone-derived

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Scheme 1. Reaction between itaconic anhydride and MTS without catalyst.

silyl ketene acetals reacted with acyclic anhydrides,^[11] resulting in 1,3-dicarbonyl compounds that generate all-carbon quaternary stereocenters in good yields and enantioselectivity. In the absence of a catalyst, there is no reaction between the silyl ketene acetal and acyclic anhydride (acetic anhydride) at room temperature. Reactions of nucleophiles such as carbanions, Grignard reagents, Wittig reagents, nitrogen nucleophiles, and oxygen nucleophiles with cyclic anhydrides are known in the literature.^[12] However, there is no prior report on the reaction of silyl-protected ester enolates with α , β -unsaturated cyclic anhydrides. In the course of a study aimed at exploring the chain-end functionalization of poly(methyl methacrylate)s synthesized using group transfer polymerization (GTP),^[13] we became interested in the reaction of silyl ketene acetals with cyclic anhydrides as electrophiles. This article reports the results of this study.

It has been reported that itaconic anhydride reacts with alcohol,^[14a-d] amines,^[14e-f] and hydroxylamine derivatives^[14e] with preferred addition at the unconjugated carbonyl group, resulting in a regioselective ring opening of itaconic anhydride. Itaconic anhydride **1** was found to undergo facile isomerization to citraconic anhydride **2** upon addition of MTS **3**, both in tetrahydrofuran (THF) and in methylene chloride in the absence of catalyst (Scheme 1). The isomerization is complete in about 1 h. The ¹H NMR spectrum of the isomerized product shows peaks at 2.18 ppm and 6.63 ppm corresponding to $-CH_3$ and -CH, respectively, of citraconic anhydride (entry 1, Table 1).

The Fourier transform–infrared (FT-IR) spectrum of the crude product (entry 1, Table 1) shows absorbance at 2958 cm^{-1} (due to methyl group) and 3114 cm^{-1} (due to =CH), which is characteristic of citraconic anhydride. Itaconic anhydride is known to isomerize to citraconic anhydride upon heating

Entry	Catalyst (10 mol%)	Solvent	Temp. (°C)	Time (min)	Isolated yield of 5 (%)
1	No catalyst	THF	30	40	Nil ^c
2	No catalyst	CH ₂ Cl ₂	30	120	Nil^{c}
3	Yb(OTf) ₃	THF	30	30	80
4	Yb(OTf) ₃	THF	10	30	76
5	Yb(OTf) ₃	CH ₂ Cl ₂	30	20	90
6	Yb(OTf) ₃	Toluene	30	20	89

Table 1. Reaction between itaconic anhydride^a 1 and MTS^b 3

Note. Order of addition: itaconic anhydride + Lewis acid + solvent + MTS (1.2 equivalents). ${}^{a}2.46$ mmol.

^b1.2 equivalents.

^cThe isolated product was citraconic anhydride.



Scheme 2. Reaction between itaconic anhydride and MTS using Yb(OTf)₃ as catalyst.

 $(\geq 100 \,^{\circ}\text{C})^{[15]}$ or in the presence of a base.^[16] The precise mechanism of isomerization is not clear. It is postulated that a small concentration of ester enolate anion present in the equilibrium with the silvl ketene acetal in a polar solvent is enough to abstract a proton α to the carbonyl, resulting in the generation of the more stable isomer. Michael-type addition of MTS **3** to itaconic anhydride **1** (Scheme 2), however, could be accomplished using Lewis acid Yb(OTf)₃ as catalyst (entries 3–6, Table 1).

The reaction between MTS **3** and itaconic anhydride **1** is exothermic at room temperature. Upon column chromatography on silica (ethyl acetate + petroleum ether), desilylation of **4** occurred, and the dicarboxylic acid **5** was formed in ~90% yield. The ¹H NMR spectrum of diacid **5** (entry 6, Table 1) shows a peak at 2.46 ppm as multiplet (5H) of $-2CH_2$ and -CH peaks apart from other peaks, which is in accordance with the proposed structure. The reaction takes place in both polar and nonpolar solvents. The 1,4-addition of MTS **3** with itaconic anhydride **1** competes to the exclusion of isomerization of itaconic anhydride into citraconic anhydride in the presence of Yb(OTf)₃. This is attributed to the effective coordination of Lewis acid with the α , β -unsaturated carbonyl group.

The reaction of citraconic anhydride with Grignard reagent (or with $Ph_3P=CHCO_2Bu$ -t) is reported to give a mixture of isomeric butenlides that display poor regiochemical preferences in reactivities of the two-carbonyl carbons in citraconic anhydride.^[12] Also, the reaction of a variety of thiols, including hydrogen sulfide, with α , β -unsaturated cyclic anhydrides (maleic, citraconic anhydride) in the presence of a basic catalyst (triethylenediamine) under anhydrous conditions produced alkylthio and arylthio anhydrides rapidly and in high yields.^[17] No reaction was observed between MTS **3** and citraconic anhydride **2** in THF at room temperature without a catalyst (entry 1, Table 2). However, citraconic anhydride **2** adds to MTS **3** in a 1,2-fashion (Scheme 3) in the presence of a Lewis acid, Yb(OTf)₃ (10 mol%), in dichloromethane (DCM) at room temperature (entry 2, Table 2), giving **7** in 80% isolated yield.

1,2-Silyl adduct of citraconic anhydride 6 in $CDCl_3$ shows the peaks corresponding to =C-H and $=C-CH_3$ slightly shifted due to 1,2-addition of MTS 3

Entry	Citraconic anhydride (mmol)	Catalyst	Solvent (mL)	Time (h)	Isolated yield of 7 (%)
1	2.46		THF, 10	2	No reaction
2	5.0	Yb (OTf) ₃ (10 mol%)	CH ₂ Cl ₂ , 20	2	80

Table 2. Reaction between MTS^a 3 and citraconic anhydride 2 at room temperature

^a1.2 equivalents.



Scheme 3. Reaction between citraconic anhydride and MTS.

to citraconic anhydride **2**. Upon column chromatography over silica, desilylation occurred, resulting in hemiacetal **7** as the major product. The ¹H NMR spectrum of **7** is in agreement with the proposed structure, in which a peak at 6.26 ppm corresponding to -OH appeared. The peak at 6.26 ppm corresponding to the hydroxyl proton disappeared upon D₂O exchange. In the ¹H NMR spectrum of compound **6**, the characteristic alkene proton (=C-H) was identified at 5.75 ppm as a singlet, which is further confirmed by the resonance at 109.56 ppm (=C-H) in the ¹³C NMR spectrum. This novel observation, in contrast to the more favorable less sterically hindered 1,2-addition, could be due to the methyl group directed hyperconjugative electronic factors preventing the attack of nucleophile (MTS) at *C=O and thereby giving the observed product **6** exclusively. Also, ¹³C NMR spectrum of **7** in CDCl₃ is in agreement with the proposed structure.

When maleic anhydride was reacted with MTS **3** in THF at 30 °C in the absence of a catalyst, an immediate exotherm is observed. The reaction temperature increases to 40 °C and stays at 40 °C for about 5–10 min. A brown liquid is obtained, which appears to be a complex mixture of products as evidenced by thin-layer chromatography (TLC). The NMR spectrum is also quite complex. In spite of several attempts, no single clean product could be isolated from this reaction. We suspect that maleic anhydride, being a strong electron acceptor, undergoes oligomerization (with side reactions) in the presence of a weak nucleophile such as ester enolate.

In the absence of a catalyst, 2,3-dimethylmaleic anhydride **8** did not react with MTS **3**. In the presence of a nucleophilic catalyst, tetra-n-butyl ammonium bibenzoate (TBABB) or Lewis acid catalyst Yb(OTf)₃, 2,3-dimethylmaleic anhydride **8** reacts with MTS **3** (Scheme 4), resulting in a 1,2-adduct (entries 2–5, Table 3). The reaction was found to be clean and quantitative as evidenced by TLC.

TBABB (0.1 mol%) was sufficient to catalyze the 1,2-addition reaction between 2,3-dimethylmaleic anhydride 8 and MTS 3 (entry 5, Table 3). In ¹³C NMR of the product 9 (entry 4, Table 3), the C attached to OSiMe₃ appeared at 109 ppm, and the spectrum confirms the proposed structure.



Scheme 4. Reaction between 2,3-dimethylmaleic anhydride and MTS.

Entry	Catalyst	Solvent (mL)	Time (h)	Isolated yield of 9 (%)
1	Nil	THF, 10	12	No reaction
2	Yb(OTf) ₃ (10 mol%)	CH ₂ Cl ₂ , 10	2	96
3	TBABB (0.5 mol%)	THF, 10	1	95
4	TBABB (1 mol%)	THF, 20	2	98
5	TBABB (0.1 mol%)	THF, 20	2	96

Table 3. Reaction between 2,3-dimethylmaleic anhydride^{*a*} 8 and MTS^{*b*} 3 at 30 $^{\circ}$ C

^a2.46 mmol.

^b1.2 equivalents.

The silyloxy derivative, **9**, was desilylated using TBAF/MeOH at 30 °C for 1 h. The silyl peaks disappeared completely. Column chromatography of the mixture gave a viscous yellow liquid in 80–85% yield. Based on ¹H and ¹³C NMR, the structure of the product was confirmed as hemiacetal **10**. The peak at 108.41 ppm of C attached to OH indicates that addition of MTS **3** to 2,3-dimethylmaleic anhydride **8** occurs in 1,2-fashion. β , β -Dimethyl-substituted silyl ketene acetal **3** (MTS), which is a hindered ketene acetal, in the presence of TBABB generates^[1b,18] a very potent carbon nucleophile, which in reactivity is equivalent to an ester enolate. The addition to 2,3-dimethylmaleic anhydride **8** occurs efficiently in an exclusive 1,2-fashion to give the hemiacetal **10** on desilylation in excellent yields.

In conclusion, we have studied the reactions of MTS with various cyclic anhydrides, summarized in Scheme 5. Itaconic anhydride isomerizes to citraconic anhydride in the presence of MTS in THF and CH_2Cl_2 . However, in the presence of a Lewis acid catalyst (Yb(OTf)₃, 10 mol%), MTS adds to itaconic anhydride in a 1,4-fashion. The 1,2-addition is the preferred pathway with both citraconic anhydride and 2,3-dimethyl maleic anhydride. Both nucleophilic catalysts, namely, TBABB (0.1 mol%) and the Lewis acid Yb(OTf)₃ (10 mol%), are effective in 1,2-addition of MTS to 2,3-dimethyl maleic anhydride.



Scheme 5. Summary of reactions between MTS and various anhydrides.

EXPERIMENTAL

Materials

Calcium hydride (Aldrich) was used as received. THF (S.D. Fine Chemicals, Mumbai) was distilled from sodium and benzophenone adduct and flash distilled over polystyryl lithium immediately prior to use. DCM was fractionally distilled over CaH₂, under vacuum, and stored under nitrogen. MTS (95% Aldrich, USA) was distilled under vacuum ($35 \degree C/15 mm$ Hg) and stored under nitrogen. TBABB was prepared according to the reported procedure^[18] and recrystallized as white crystals from diethylether. Yb(OTf)₃(99%, Aldrich, USA) was dried under dynamic vacuum for several hours before use. Itaconic anhydride (95%, Aldrich, USA) was recrystallized from dry diethylethter. Maleic anhydride (S.D. Fine Chemicals, Mumbai) was recrystallized from dry benzene. Citraconic anhydride (98%, Aldrich, USA) was distilled under vacuum (bp 93–94 °C/10 mmHg). 2,3-Dimethylmaleic anhydride (97% Fluka, Switzerland) was recrystallized from dry chloroform.

All reactions, unless stated otherwise, were performed in a dry N_2 atmosphere. ¹H and ¹³C spectra were recorded using a 200-MHz or 500-MHz spectrometer in CDCl₃(unless stated otherwise). IR spectra were recorded on an FT-IR spectrophotometer. Microanalyses were performed using a CHNS analyzer.

Reaction Between Itaconic Anhydride and MTS

A flame-dried, 50-mL, round-bottom flask was charged with 0.1525 g (0.246 mmol, 10 mol%) of Yb(OTf)₃ catalyst and 0.275 g (2.46 mmol) of itaconic anhydride. Dry CH₂Cl₂ or toluene (10 mL) was transferred using a canula under nitrogen and stirred for 5 min. Subsequently, 0.5 mL (2.46 mmol) of MTS was added, and the reaction continued at 30 °C. The progress of reaction was monitoring by TLC.

The desilylation reaction was carried out using 1 N HCl/THF (1:9) for 1 h at 30 °C. The formed diacid was (Scheme 2) extracted into ethyl acetate, washed well with water, and dried over Na₂SO₄. After concentration of the organic layer, column chromatography (60- to 120-mesh silica gel, EtOAc/*n*-hexane as eluent) afforded diacid **5** in excellent yields (Table 1).

FT-IR (neat) of diacid **5** showed peaks at 1730 cm^{-1} due to carboxylic acids C=O stretching and peak at 3196 cm^{-1} due to O–H stretching. The acid value of the diacid **5** was found to be 511 mg KOH/g of sample (95% of theory, acid value of theory = 538 mg KOH/g of sample). ¹H NMR (200 MHz, CDCl₃ + acetone-d₆): $\delta = 1.11$ (s, 6H, 2 CH₃), 2–3 (m, 5H, 2CH₂ and –CH), 3.54 (s, 3H, –OCH₃). Anal. calcd. for diacid **5** (C₁₀H₁₆O₆): C, 51.72; H, 6.94. Found: C, 51.80; H, 7.0.

Reaction Between Citraconic Anhydride and MTS

A flame-dried, 50-mL, round-bottom flask was charged with 0.3101 g (0.5 mmol, 10 mol%) of Yb(OTf)₃ catalyst and 0.5 mL (5.0 mmol) of citraconic anhydride. Dry CH₂Cl₂ (20 mL) was transferred using a canula under nitrogen and stirred for 5 min. Subsequently, 1.0 mL (5.0 mmol) of MTS was added, and the reaction continued at $30 \,^{\circ}$ C. The progress of reaction was monitored by TLC.

Yb(OTf)₃ was filtered, and DCM was removed under reduced pressure. The product was dissolved in 20 mL THF. Water (2 mL) was added, and THF solution was stirred for 1 h at 30 °C. The 1,2-adduct formed (Scheme 3) was dried over Na₂SO₄. After concentration of the organic layer, column chromatography (60- to 120-mesh silica gel, EtOAc/*n*-hexane as eluent) afforded a 1,2-adduct (7) in 80% yield (0.856 g) (Table 2).

¹H NMR (200 MHz, CDCl₃) of **6**: $\delta = 0.12$ (s, 9H, -OSiMe₃), 1.27 (s, 3H, CH₃), 1.33 (s, 3H, CH₃), 2.08 (s, 3H, =C-CH₃), 3.62 (s, 3H, -OCH₃), 5.75 (s, 1H, =C-H). ¹³C NMR (50 MHz, CDCl₃) of **6**: $\delta = 1.11$ (1 s, Si (CH₃)₃), 14.80, 21.17, 21.67, 51.43, 52.30, 109.56, 119.05, 169.14, 169.85, 174.44. ¹H NMR (200 MHz, CDCl₃) of **7**: $\delta = 1.16$ (s, 3H, CH₃), 1.37 (s, 3H, CH₃), 2.08 (s, 3H, =C-CH₃), 3.78 (s, 3H, -OCH₃), 5.85 (s, 1H, =C-H), 6.26 (s, 1H, OH). ¹³C NMR (25 MHz, CDCl₃) of **7**: $\delta = 14.49$, 19.88, 21.89, 47.92, 52.97, 109.57, 120.51, 165.02, 169.95, 176.86. Anal. calcd. for **7** (C₁₀H₁₄O₅): C, 56.07; H, 6.59. Found: C, 56.10; H, 6.65.

Reaction Between Maleic Anhydride and MTS

A flame-dried, 50-mL, round-bottom flask was charged with 0.0505 g $(8.15 \times 10^{-5} \text{ mol}, 10 \text{ mol}\%)$ of Yb(OTf)₃ catalyst and 0.0799 g $(8.15 \times 10^{-4} \text{ mol})$ of maleic anhydride. Dry CH₂Cl₂ (10 mL) was transferred using a canula under nitrogen and stirred for 5 min. Subsequently, 0.2 mL ($8.15 \times 10^{-4} \text{ mol}$) of MTS was added, and the reaction continued at 30 °C. The progress of the reaction was monitored by TLC.

Reaction Between 2,3-Dimethylmaleic Anhydride and MTS

A flame-dried, 50-mL, round-bottom flask was charged with 0.0119 g $(2.46 \times 10^{-2} \text{ mmol}, 1 \text{ mol}\%$ based on MTS) of TBABB catalyst. Dry THF (10 mL) was transferred using a canula under nitrogen followed by 0.5 mL (2.46 mmol) of MTS. The mixture was stirred for 5 min. Subsequently, 0.3102 g (2.46 mmol) of 2,3-dimethylmaleic anhydride in 5 mL of THF was added, and the reaction continued at 30 °C (Scheme 4). The progress of the reaction was monitored by TLC. The 1,2-adduct **9** was formed in quantitative yield (0.739 g, 100%) (Table 3). The silyloxy derivative, **9**, was desilylated using TBAF/MeOH at 30 °C for 1 h. The silyl peaks disappeared completely. Column chromatography of the mixture gave a viscous yellow liquid in 85% yield.

¹H NMR (500 MHz, CDCl₃) of **9**: $\delta = 0.07$ (s, 9H, -OSiMe₃), 1.25 (s, 3H, CH₃), 1.31 (s, 3H, CH₃), 1.75 (s, 3H, =C-CH₃), 1.94 (s, 3H, =C-CH₃), 3.59 (s, 3H, -OCH₃). ¹³C NMR (125 MHz, CDCl₃) of **9**: $\delta = 0.65$ [1 s, Si (CH₃)₃], 8.10, 12.38, 21.34, 51.16, 51.73, 108.40, 125.75, 158.96, 171.02, 177.36. ¹H NMR (500 MHz, CDCl₃) of **10**: $\delta = 1.15$ (s, 3H, CH₃), 1.38 (s, 3H, CH₃), 1.81 (s, 3H, =C-CH₃), 1.96 (s, 3H, =C-CH₃), 3.78 (s, 3H, -OCH₃), 6.26 (s, 1H, OH). ¹³C NMR (125 MHz, CDCl₃) of **10**: $\delta = 8.27$, 12.39, 19.69, 21.92, 47.97, 52.73, 108.41, 127.37, 155.62, 171.48, 176.90. Anal. calcd. for **10** (C₁₁H₁₆O₅): C, 57.88; H, 7.07. Found: C, 57.90 H, 7.05.

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