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Applications of Dithioacetals in Ester Synthesis

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Abstract: The α-oxoketene dithioacetals are simple synthetic intermediates widely utilized and implicated for the synthesis of a variety of heterocyclic compounds other than alicyclic and aromatic compounds. They act as 1,3-electrophilic three-carbon synthons. The α-oxoketene dithioacetal of pyrazolone derivatives can be efficiently converted through a base-catalyzed alcoholysis into the corresponding ester in a single one-step reaction with good yield of pure products. In this article, we summarize recent direct conversion of α-oxoketene dithioacetals to highly desirable esters. The overall process is an example of intramolecular rearrangement of bonds. Characterization and identification of all synthesized compounds were assigned through ^{1}H NMR and mass spectroscopy.

Keywords: S,O-Acetal, alcoholysis, cyclocondensation, α-oxoketene dithioacetal, synthons, thiomethyl

The α-oxoketene dithioacetals[1–3] can be considered masked β-ketoesters that have ambient electrophilicity at 1,3-carbon centers as a result of the presence of bisalkylthio groups, which can be converted into ester functionality when desired.[1a]

Conversion of α-oxoketene dithioacetals into the corresponding α,β-unsaturated ester involves reduction of ketones with $NaBH_4$ followed by $BF_3 \cdot OEt_2$-mediated alcoholysis. As a part of our interest in the chemistry[4] of α-oxoketene dithioacetals, we developed a one-pot method for synthesis of ester using α-oxoketene dithioacetals as intermediates.[5–8] (See Fig. 1)

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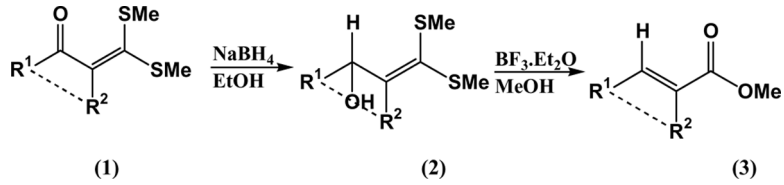
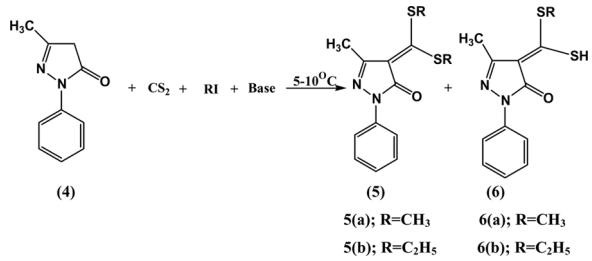


Figure 1. Conversion of α-oxoketene dithioacetals into the corresponding α,β-unsaturated ester.



Scheme 1. One-pot synthesis of ester using α-oxoketene dithioacetals.

Compound **4** was converted into 4-(bis-methylsulfanylmethylene)-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one **5a**[9] and 4-(bis-ethylsulfanyl-methylene)-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one **5b** by the route shown in Scheme 1. Thus, **4** was treated with carbon disulfide and methyl iodide to give a mixture of **5a** and **5b** in the presence of Sodium hydroxide (NaOH)/Potassium hydroxide (KOH). (See Scheme 1)

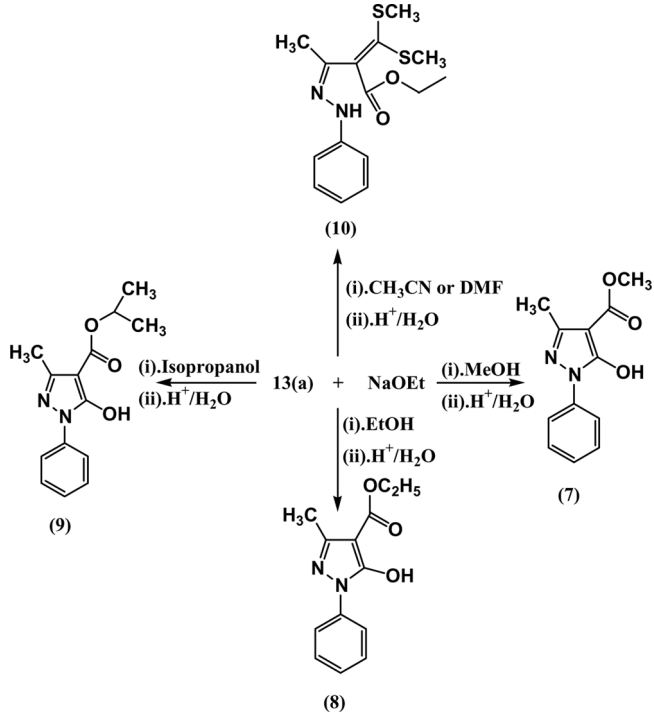
Compound **5a** was reacted with sodium ethoxide with overall yield of 70–90% in the presence of suitable alcohols to give **7**, **8**, and **9**. (Scheme 2)

It is interesting to note that reaction of **5a** with NaOEt in dimethyl formamide (DMF) or CH_3CN as a solvent gave compound **10**.

In conclusion, we have developed an efficient one-step method to prepare different 4-substituted pyrazole-esters under simple reaction conditions. This method features a short reaction time and good yields of pure products.

EXPERIMENTAL

Unless otherwise noted, all materials were used as received from a commercial supplier without further purification. All anhydrous reactions were performed using oven-dried glassware, and all solvents were dried before



Scheme 2. Role of α-oxoketene dithioacetals in ester synthesis.

preceding with the reactions. Reactions were monitored using silica-gel G thin-layer chromatography (TLC) plates and their spots were visualized under an ultraviolet (UV) lamp or by iodine vapors. Melting points were taken in an electrically heated instrument and are uncorrected.

Synthesis of 4(Bis-methylsulfanyl-methylene)-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one (5a)

A mixture of 3-methyl-1-phenyl pyrazol-5-one (172.4 mmol, 30 g) and CS_2 (172.4 mmol, 10.40 ml) was dissolved in anhydrous DMF and slowly added to a mixture of anhydrous K_2CO_3 (431.0 mmol, 59.48 g), DMF (20 ml), and C_6H_6 (40 ml) at 0°C. After 5 h, CH_3I (344.8 mmol, 21.46 ml) in 10 ml C_6H_6 was added dropwise. After 6 h, the solvent was removed, and the residue was dissolved in $CHCl_3$ (800 ml), washed with water (2 × 100 ml), and dried over anhydrous sodium sulfate. The mixture was concentrated to give a dark orange-red viscous solution, which was purified on silica gel using ethyl acetate and hexane as an eluent to give **5a** in 40.54 g (84.58%). Mp = 46–48°C;

^{1}H NMR [300 MHz, $CDCl_3$, 25°C, $Si(CH_3)_4$]: δ 2.51 (s, 3H, CH_3); δ 2.689 (s, 3H, SCH_3); δ 2.751 (s, 3H, SCH_3); δ 7.122–7.985 (m, 5H, Ar-H) ($J_a = 8.4$; $J_b = 7.5$, 7.8; $J_c = 6.9$, 7.2 Hz).

Synthesis of 4(Bis-ethylsulfanyl-methylene)-5-methyl-2-phenyl-2,4-dihydropyrazol-3-one (5b)

A mixture of 3-methyl-1-phenyl pyrazol-5-one (5.7 mmol, 1 g) and CS_2 (5.7 mmol, 0.34 ml) were dissolved in anhydrous DMF and slowly added to a mixture of anhydrous K_2CO_3 (14.2 mmol, 1.95 g), DMF (20 ml), and C_6H_6 (40 ml) at 0°C. After 5 h, C_2H_5I (11.4 mmol, 0.91 ml) in 10 ml C_6H_6 was added dropwise. After 6 h, solvent was removed, and the residue was dissolved in $CHCl_3$ (800 ml), washed with water (2 × 100 ml), and dried over anhydrous sodium sulfate. The mixture was concentrated to give a dark orange-red viscous solution, which was purified on silica gel using ethyl acetate and hexane as an eluent to give **13b** in 1.32 g (75.42%). Mp = 40–42°C; ^{1}H NMR [300 MHz, $CDCl_3$, 25°C, $Si(CH_3)_4$]: δ 2.52 (s, 3H, CH_3); δ 1.31–1.44 (double t, 3H, $CH_2\underline{CH_3} \times 2$) ($J = 7.5$, 7.2, 8.1, 7.5, 7.5 Hz); δ 3.17–3.34 (double q, 4H, $\underline{CH_2}CH_3 \times 2$) ($J = 7.5$, 7.5, 7.2, 7.5, 7.2, 7.2 Hz); δ 7.12–7.98 (m, 5H, Ar-$\underline{H}$) ($J_a = 7.8$; $J_b = 7.8$; $J_c = 7.2$, 7.2 Hz).

Synthesis of 5-Hydroxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid Methyl Ester (7)

Compound **5a** (3.5 mmol, 1 g) was added to a solution of $NaOC_2H_5$ (7.0 mmol, 0.47 g) in 10 ml dry methanol, followed by heating under reflux for 2 h. Concentrated HCl was added until it became acidic, followed by water. Then the precipitate was filtered and washed with water. Mp = 138–140°C; yield = 0.8 g (95.86%); ^{1}H NMR [300 MHz, $CDCl_3$, 25°C, $Si(CH_3)_4$]: δ 2.40 (s, 3H, CH_3); δ 3.92 (s, 3H, OCH_3); δ 7.26–7.79 (m, 5H, Ar-H) ($J_a = 8.1$; $J_b = 7.2$; $J_c = 7.5$, 9.3 Hz); δ 9.99 (broad s, 1H, O-H); MS (m/z) M^+ 233.

Synthesis of 5-Hydroxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid Ethyl Ester (8)

Compound **5a** (3.5 mmol, 1 g) was added to a solution of $NaOC_2H_5$ (7.0 mmol, 0.47 g) in 10 ml dry ethanol, followed by heating under reflux for 2 h. Concentrated HCl was added until it became acidic, followed by water. Then the precipitate was filtered and washed with water. Mp = 95–97°C; yield = 0.74 g (83.63%); ^{1}H NMR [300 MHz, $CDCl_3$, 25°C,

$Si(CH_3)_4$]: δ 1.383–1.425 (t, 3H, $CH_2\underline{CH_3}$) ($J = 5.7$, 6.9 Hz); δ 2.412 (s, 3H, CH_3); δ 4.351–4.417 (q, 2H, $C\underline{H_2}CH_3$) ($J = 6.9$, 5.7, 7.2 Hz); δ 7.265–7.796 (m, 5H, Ar-H) ($J_a = 7.8$; $J_b = 6.9$; $J_c = 6.9$, 8.4 Hz); δ 10.081 (broad s, 1H, O-H); MS (m/z) M^+ 247.

Synthesis of 5-Hydroxy-3-methyl-1-phenyl-1H-pyrazole-4-carboxylic Acid Isopropyl Ester (9)

Compound **5a** (3.5 mmol, 1 g) was added to a solution of $NaOC_2H_5$ (7.0 mmol, 0.47 g) in 10 ml dry ethanol, followed by heating under reflux for 2 h. Concentrated HCl was added until the mixture became acidic, followed by water. Then the precipitate was filtered and washed with water. Mp = 58–60°C; yield = 0.70 g (74.85%); ^{1}H NMR [300 MHz, $CDCl_3$, 25°C, $Si(CH_3)_4$]: δ 1.370–1.391 (d, 6H, $CH_3 \times 2$) ($J = 6.3$ Hz); δ 2.405 (s, 3H, CH_3); δ 5.217–5.300 (p, 1H, CH) ($J = 6.0$, 6.6, 6.0, 6.3 Hz); δ 7.261–7.787 (m, 5H, Ar-H) ($J_a = 7.5$; $J_b = 5.4$; $J_c = 7.2$, 8.1 Hz); δ 10.132 (broad s, 1H, O-H); MS (m/z) M^+ 261.

Synthesis of 3,3-Bis-methylsulfanyl-2-[1-(phenyl-hydrazono)-ethyl]-acrylic Acid Ethyl Ester (10)

Compound **5a** (0.5 g, 7.0 mmol) was added to a solution of anhydrous $NaOC_2H_5$ (0.24 g, 1.4 mmol) in 10 ml acetonitrile or 20 ml DMF, followed by heating under reflux for 6 h or stirring at room temperature for 24 h. Concentrated HCl was added until the mixture became acidic, followed by water. The precipitate was filtered and washed with water. Mp = 98–100°C; yield = 3.3 g (56.70%); ^{1}H NMR [300 MHz, $CDCl_3$, 25°C, $Si(CH_3)_4$]: δ 1.40 (s, 3H, CH_3); δ 2.41 (s, 3H, CH_3); δ 2.52 (s, 3H, SCH_3); δ 4.34–4.41 (q, 2H, $OC\underline{H_2}CH_3$); δ 7.25–7.79 (m, 5H, Ar-H); δ 10.08 (broad s, 1H, NH).

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