Synthesis of 2-Dithioacetalmethylene-3-oxobutyronitrile from 2-Dithioacetalmethylene-3-oxobutyramide

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Nitriles are important building blocks in the construction of amines, amides, ketones, carboxylic acids, and esters. For example, 1,2-diarylimidazoles as the potent anti-inflammatory agent,[1] thiazole analogues as the inhibitor of superoxide,[2] benzamidines with activity of fibrinogen antagonist,[3] (*R*)-amides and (*S*)-acids as the enzyme,[4] and glutarimides with pharmacological effects[5] were all prepared from nitriles.

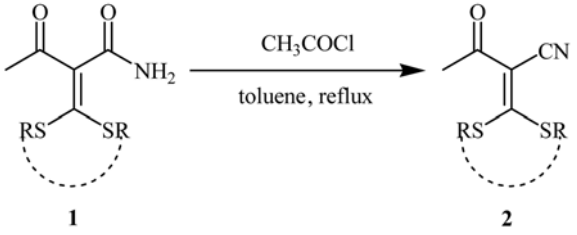
Occasionally, nitriles have been synthesized from aldehyde. For example, catalytic dehydration of aldoximes provided various types of cyano compounds.[6-9] *O*-Substituted aldoximes, formed by the reaction between aldehydes and 2,4-dinitrophenylhydroxylamine, underwent 1,2-elimination in the presence of a base to give the corresponding nitriles.[10] Bose and Narsaiah synthesized nitriles in one-pot from aldehydes in a solid state, using peroxymonosulfate on alumina.[11-15] Kaneda *et al.* reported one-pot synthesis of α-alkylated nitriles with carbonyl compounds, *via* aldol reaction-hydrogenation, using hydrotalcite-supported palladium nanoparticles as multifunctional catayst.[16] However, most of these methods suffer from the limited availability of starting materials, low reaction yields, drastic reaction conditions, or tedious work-up procedures.

Herein, we report a synthetic route to 2-dithioacetalmethylene-3-oxobutyronitriles from 2-dithioacetalmethylene-3-oxobutyramides, as shown in Scheme 1. The resulting nitriles contain an unstable α-acetoketene dithioacetal moiety, belonging to a class of α-oxoketene dithioacetals which are well-known for organic syntheses,[17-19] and thus can be employed as new intermediates for the syntheses of more complicated organic compounds. In fact, it was reported that 1-acetyl cyclopropane carboxamide was converted to 1-acetyl cyclopropane carbonitrile, using methanesulfonyl chloride in the presence of pyridine.[20] In comparison to acetyl chloride, however, methanesulfonyl chloride is more expensive and corrosive.

Results and Discussion

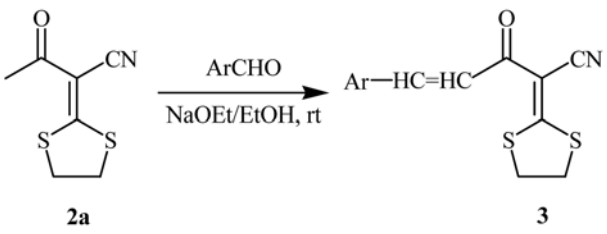
As shown in Scheme 1, we successfully converted 2-dithioacetalmethylene-3-oxobutyramide (**1**) to 2-dithioacetalmethylene-3-oxobutyronitrile (**2**) using acetyl chloride. Briefly, **1** was refluxed with acetyl chloride (0.5 equiv) in toluene for about 7-10 h to give 2-dithioacetalmethylene-3-oxobutyronitrile **2** in 85-90% yields (Table 1) along with a small amount of byproduct resulted from the removal of the alkylthio groups. **2a**, containing a 5-membered ring of dithioacetal moiety (R = CH_2CH_2), was obtained as a solid, after chromatographic separation of the reaction residue. The FT-IR spectrum of **2a** showed a characteristic absorption peak of cyano group at 2200 cm^{-1}. The ^{13}C-NMR spectrum showed a carbon resonance peak of cyano group at 117.8 ppm. The combined two spectral data confirmed the expected chemical structure of the isolated **2a**.

After the synthesis of compound **2a**, we attempted to synthesize different analogs, containing a 6- or 7-membered ring of ketene dithioacetal moiety. **2b** and **2c** were synthesized under similar conditions in 90% and 85% yields, respectively. Finally, we also attempted to synthesize other analogs, containing acyclic ketene dithioacetal moieties. **2d** (R = CH_3) and **2e** (R = $C_6H_5CH_2$) were successfully synthesized in 86% and 89% yields, respectively. This result indicates that the chemical reaction of **1** with acetyl chloride



1 **2**

Scheme 1



2a **3**

Scheme 2

Table 1. Synthesis of 2-dithioacetalmethylene-3-oxobutyronitriles (**2a-e**) and α-cyano-α'-cinnamoyl dithioacetals (**3a-c**)

Intermediate	R	Ar	Product	Time (h)	Yield[a] (%)
1a	$(CH_2)_2$	–	2a	8	89
1b	$(CH_2)_3$	–	2b	10	90
1c	$(CH_2)_4$	–	2c	7	85
1d	CH_3	–	2d	7	86
1e	$C_6H_5CH_2$	–	2e	8	89
2a	$(CH_2)_2$	2-Pyridinyl	3a	1	82
2a	$(CH_2)_2$	4-$CH_3OC_6H_4$	3b	1	89
2a	$(CH_2)_2$	4-$NO_2OC_6H_4$	3c	0.5	77

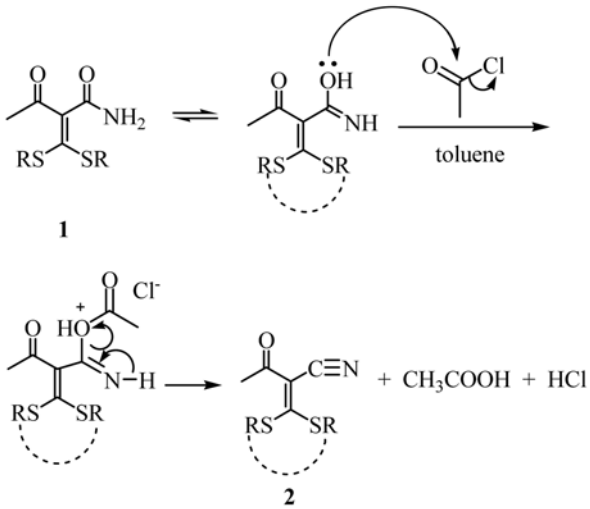
[a]Based on the isolated product

is not much affected by the structure (ring size, cyclic or acyclic) of ketene dithioacetal moiety.

In order to investigate any possibility of further functionalization of **2**, **2a** was reacted with various benzaldehydes (ArCHO), such as picolinaldehyde, 4-methoxybenzaldehyde and 4-nitrobenzaldehyde, as shown in Scheme 2. Briefly, **2a** (1.0 equiv) was reacted with ArCHO (1.1 equiv) in the presence of NaOEt (0.5 equiv) in ethanol at room temperature (Table 1). The isolation yields after column chromatographyic separation were moderate to high (77-89%). This result indicates that the reactions are not significantly affected either by the electron-releasing or electron-withdrawing effect of substituents in the ArCHO.

The α-cyano-α'-cinnamoyl dithioacetals **3a-c** have unique structural characteristics. They have five active carbons that are all conjugated (Ar**C**H=**C**H-**C**O-**C**(CN)=**C**S_2) (double Michael system), and thus can undergo the Michael addition in two different ways. In addition, the cyano group in these compounds can be converted to an amino group *via* hydrogenation. The resulting intermediates, containing the amino group, can then undergo intramolecular cycloaddition to form the corresponding aza-cyclic compounds.

For the preparation of nitriles from primary amides, Lewis acids have been often employed under a vigorous reaction condition.[21] In a recent example, Nakajima and co-workers



synthesized nitriles by reacting primary amides with $(COCl)_2$-activated dimethyl sulfoxide, in the presence of triethylamine at –78 °C.[22] We proposed a mechanism for the conversion of the amide group to cyano group with acetyl chloride as shown in Scheme 3. Acetyl chloride reacts with amino-carbonyl oxygen of 2-dithioacetalmethylene-3-oxobutyramide, to form the corresponding adduct salt. Subsequently, the salt undergoes elimination to give the corresponding nitrile product along with acetic acid and hydrochloride.

In conclusion, the reaction of 2-dithioacetalmethylene-3-oxobutyramides with acetyl chloride is an effective method for the synthesis of 2-dithioacetalmethylene-3-oxobutyronitriles. The nitriles were further converted to α-cyano-α'-cinnamoyl dithioacetals *via* crossed aldol reaction with benzaldehydes. The synthesized α-cyano-α'-cinnamoyl dithioacetals can be employed as new precursors for synthesis of more functionalized compounds.

Experimental Section

All reagents were purchased from the Aldrich Chemical Co., and used without further purification unless otherwise noted. A solution of 0.1N NaOEt in EtOH was prepared immediately prior to use. The products were purified by column chromatography over silica gel purchased from the Qingdao Ocean Chemical Co. **1** was prepared according to a known method.[17-19] Melting points were not corrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance-600, 400 NMR spectrometer, using $CDCl_3$ and TMS as solvent and internal standard, respectively. IR spectra were recorded on a Magna-560 FT-IR spectrophotometer in the range of 400-4000 cm^{-1}, using KBr pellets. Mass spectra (MS) were recorded on a Gas Chromatography/Mass Spectrometer (HP6890/5973). Elemental analyses were measured on a Vario EL analyzer.

General Procedure for the Synthesis of 2. A 100-mL three-necked flask was equipped with a reflux condenser, a sealed stirrer unit and a thermometer. Toluene (98%, 20 mL), acetyl chloride (785 mg, 10 mmol) and 2-dithioacetalmethylene-3-oxobutyramide **1** (0.4 g, 2.0 mmol) were transferred into the flask. The solution was refluxed for 7-10 h. The solvent was removed under reduced pressure to obtain crude product, which was then column chromatographed over silica gel to give compound **2** (hexane-EtOAc, 85/15).

2-(1,3-Dithiolan-2-ylidene)-3-oxobutyronitrile (**2a**): yellow crystal; mp 145-147 °C (recrystallization from hexane-methane, 5/3); R_f = 0.3 (hexane–EtOAc, 3/2); IR (KBr): 2200, 1662, 1441, 1274 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 3.54 (m, 2H, SCH_2), 3.59 (m, 2H, SCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9, 37.3, 40.5, 97.8, 117.8, 183.9, 189.9; MS: m/z (%), 185 (M, 100%); Anal. calcd for $C_7H_7NOS_2$: C, 45.38; H, 3.81; N, 7.56. Found: C, 48.07; H, 4.54; N, 7.04.

2-(1,3-Dithian-2-ylidene)-3-oxobutyronitrile (**2b**): mp 110-112 °C (recrystallization from hexane-methane, 5/3); R_f = 0.5 (hexane-EtOAc, 1/1); IR (KBr): 2197, 1647, 1416,

1263 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.30-2.37 (m, 2H, $SCCH_2CS$), 2.42 (s, 3H, CH_3), 2.99 (t, 2H, J = 8.0 Hz, SCH_2), 3.13 (t, 2H, J = 8.0 Hz, SCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 29.7 (2 C), 29.8, 105.1, 117.3, 181.1, 190.4; MS: m/z (%), 199 (M, 100%); Anal. calcd for $C_8H_9NOS_2$: C, 48.21; H, 4.55; N, 7.03. Found: C, 47.07; H, 3.34; N, 7.04.

2-(1,3-Dithiepan-2-ylidene)-3-oxobutyronitrile (**2c**): mp 87-89 °C (recrystallization from hexane-methane, 5/3); R_f = 0.6 (hexane-EtOAc, 3/2); IR (KBr): 2237, 1607, 1416, 1253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 2.28-2.35 (m, 4H, $SCCH_2CCH_2CS$), 2.38 (m, 2H, CH_2), 2.40 (s, 3H, CH_3), 3.10 (t, 2H, J = 7.8 Hz, SCH_2), 3.15 (t, 2H, J = 7.8 Hz, SCH_2); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 29.8, 29.8, 29.9, 30.1, 103.1, 117.5, 180.6, 188.4; MS: m/z (%), 476 (M, 90%); Anal. calcd for $C_9H_{11}NOS_2$: C, 50.67; H, 5.20; N, 6.57. Found: C, 50.53; H, 5.20; N, 6.53.

2-(Bis(methylthio)methylene)-3-oxobutyronitrile (**2d**): mp 56-58 °C (recrystallization from hexane-methane, 5/3); R_f = 0.3 (hexane-EtOAc, 6/1); IR (KBr): 2201, 1666, 1419, 1250 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H, CH_3), 2.59 (s, 3H, CH_3), 2.78 (s, 3H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.9, 29.8, 29.9, 103.1, 117.5, 180.6, 188.4; MS: m/z (%), 187 (M, 25%); Anal. calcd for $C_7H_9NOS_2$: C, 44.89; H, 4.84; N, 7.48. Found: C, 43.98; H, 4.84; N, 7.50.

2-(Bis(benzylthio)methylene)-3-oxobutyronitrile (**2e**): mp 58-60 °C (recrystallization from hexane-methane, 5/3); R_f = 0.3 (hexane-EtOAc, 3/2); IR (KBr): 2201, 1668, 1439, 1249 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.44 (s, 3H, CH_3), 4.20 (s, 2H, SCH_2), 4.39 (s, 2H, SCH_2), 7.20-7.36 (m, 10H, ArH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.2, 40.8 (2 C), 42.9 (2 C), 109.5, 118.3, 128.0-134.9 (10 C), 176.2, 191.1; MS: m/z (%), 339 (M, 80%); Anal. calcd for $C_{19}H_{17}NOS_2$: C, 67.22; H, 5.05; N, 4.13. Found: C, 67.81; H, 4.85; N, 4.24.

General Procedure for the Synthesis of 3 from 2a. To a stirred suspension of 2-(1,3-dithiolan-2-ylidene)-3-oxobutyronitrile (**2a**) (2.0 mmol) in ethanol (15 mL), various arylaldehydes (2.2 mmol) and a fresh solution of 0.1 N NaOEt in EtOH (10 mL) were added. The mixture was stirred at room temperature for about 1 h. The solvent was removed under reduced pressure, when the starting material, **2a** disappeared (checked by TLC). The residue was washed with water (3 × 15 mL) and then dried. The crude product was column chromatographed on silica gel (hexane-EtOAc, 90/10), and recrystallized from hexane-EtOAc (3/2) to give **3**.

2-(1,3-Dithiolan-2-ylidene)-3-oxo-5-(pyridin-2-yl)pent-4-enenitrile (**3a**): mp 168-170 °C (recrystallization from hexane-methane, 2/1); R_f = 0.3 (hexane-EtOAc, 1/2); IR (KBr): 2202, 1648, 1430, 1330, 1221 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.56-3.65 (m, 4H, SCH_2), 7.28 (m, 1H, ArH), 7.50 (d, 1H, J = 8.0, ArH), 7.70 (m, 1H, ArH), 7.77 (d, 1H, J = 12.0 Hz, =CH), 7.85 (d, 1H, J = 12.0 Hz, =CH), 7.67 (d, 1H, J = 4.0 Hz, ArH); MS: m/z (%), 274 (M, 15%); Anal. calcd for $C_{13}H_{10}N_2OS_2$: C, 56.91; H, 3.67; N, 10.21. Found: C, 56.32; H, 3.57; N, 10.50.

2-(1,3-Dithiolan-2-ylidene)-5-(4-methoxyphenyl)-3-oxo-pent-4-enenitrile (**3b**): mp 205-207 °C (recrystallization from hexane-methane, 2/1); R_f = 0.3 (hexane-EtOAc, 1/2); IR (KBr): 2197, 1645, 1434, 1510, 1256 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 3.54-3.62 (m, 4H, SCH_2), 3.86 (s, 3H, OCH_3), 6.91 (d, 1H, J = 12.0 Hz, =CH), 7.25 (d, 1H, J = 6.0, ArH), 7.58 (d, 1H, J = 6.0, ArH), 7.76 (d, 1H, J = 12.0 Hz, =CH); MS: m/z (%), 291 (M, 18%); Anal. calcd for $C_{15}H_{13}NO_2S_2$: C, 59.38; H, 4.32; N, 4.62. Found: C, 57.61; H, 4.25; N, 4.50.

2-(1,3-Dithiolan-2-ylidene)-5-(4-nitrophenyl)-3-oxo-pent-4-enenitrile (**3c**): mp 256-258 °C (recrystallization from hexane-methane, 2/1); R_f = 0.3 (hexane-EtOAc, 1/3); IR (KBr): 2207, 1635, 1335, 1210, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.72 (m, 4H, SCH_2), 7.41 (d, 1H, J = 15.6 Hz, =CH), 7.43 (d, 1H, J = 15.6 Hz, =CH), 7.97 (d, 1H, J = 8.7 Hz, ArH), 8.25 (d, 1H, J = 8.7 Hz, ArH); MS: m/z (%), 306 (M, 21%); Anal. calcd for $C_{14}H_{10}N_2O_3S_2$: C, 52.82; H, 3.17; N, 8.08. Found: C, 52.80; H, 3.15; N, 8.44.

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