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Preparation of Ketene Thioacetals from Dithioic Acid Dianions

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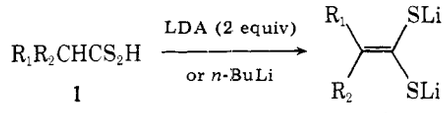
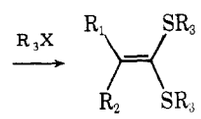
Ketene thioacetals have received considerable attention in recent years as important synthetic intermediates.[2] Although a host of ingenious methods exists for their synthesis,[3] we sought a method which would make them available from intermediates which are easily accessible. To this end, we have investigated the generation and alkylation of dithioic acid dianions.[4]

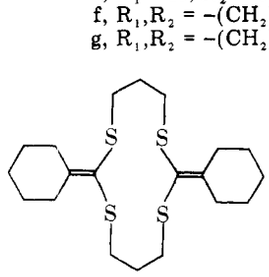


1 2

a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = CH_3$
c, $R_1, R_2 = -(CH_2)_5-$



3a, $R_1 = R_2 = H$; $R_3 = C_2H_5$
b, $R_1 = R_2 = H$; $R_3 = -(CH_2)_3-$
c, $R_1 = H$; $R_2 = R_3 = CH_3$
d, $R_1 = H$; $R_2 = CH_3$; $R_3 = C_2H_5$
e, $R_1 = H$; $R_2 = CH_3$; $R_3 = -(CH_2)_3-$
f, $R_1, R_2 = -(CH_2)_5-$; $R_3 = C_2H_5$
g, $R_1, R_2 = -(CH_2)_5-$; $R_3 = -(CH_2)_3$



4

The dithioic acids are conveniently prepared by quenching the appropriate Grignard reagent with carbon disulfide.[5] By this procedure the dithioic acids can be obtained in yields of 40–70%, except in the case of **1a** which is prepared in 20% yield. In spite of the diminished yield in the latter case, the ready availability of the starting reagents overcomes this difficulty.

Dianion formation is readily accomplished by the addition of the acid to 2 equiv of lithium diisopropylamide (LDA) in THF containing 3 equiv of hexamethylphosphoramide (HMPA) in THF (0 → 25 °C). The HMPA serves to solubilize the precipitated dianion, which is too viscous to permit stirring. Alternatively, *n*-butyllithium effects dianion formation at −78 °C. Although precipitation occurs in this instance as well, stirring is possible and the addition of HMPA is not necessary. The generation of the dianion of the branched acid **1c** is not readily achieved with *n*-BuLi at −78 °C unless 4 equiv of tetramethylethylenediamine (TMEDA) is present.

Table I

Entry	Dithioic acid	Method	Alkyl halide	Ketene thioacetal[a] (yield, %)
1	**1a**	A[b]	C_2H_5I	**3a** (97)[d]
2	**1a**	B[c]	C_2H_5I	**3a** (81)[d]
3	**1a**	A	$BrCH_2CH_2CH_2Cl$	**3b** (45)[d]
4	**1b**	A	C_2H_5I	**3d** (86)[e]
5	**1b**	B	C_2H_5I	**3d** (91)[e]
6	**1b**	A	CH_3I	**3c** (75)[e]
7	**1b**	B	CH_3I	**3c** (71)[e]
8	**1b**	A	$BrCH_2CH_2CH_2Cl$	**3e** (54)[e]
9	**1b**	B	$BrCH_2CH_2CH_2Cl$	**3d** (31)[e]
10	**1c**	A	C_2H_5I	**3f** (87)[e]
11	**1c**	C[f]	C_2H_5I	**3f** (71)[d]
12	**1c**	D[g]	$BrCH_2CH_2CH_2Cl$	**3g** (51)[h]

[a] All new compounds are in full accord with their NMR spectrum, combustion analysis, and/or mass spectrum. [b] LDA (2 equiv), HMPA (3 equiv), THF, 0 → 25 °C, 1 h; 2 equiv of RX, −78 °C → room temperature. [c] *n*-BuLi (2 equiv), THF, −78 °C, 1 h; 2 equiv of RX, −78 °C → room temperature. [d] VPC. [e] Distilled. [f] *n*-BuLi (2 equiv), TMEDA (4 equiv), THF, −78 °C, 4 h; 2 equiv of RX, −78 °C → room temperature. [g] Reagents of method A added simultaneously and slowly at room temperature to THF. [h] Sublimed and recrystallized.

The yields for cycloalkylation employing 1-bromo-3-chloropropane are less than in the cases using methyl or ethyl iodide. No substantial improvement in yield was obtained when 1,3-diiodopropane was used. The major difficulty to be overcome in the cycloalkylation was that of polymerization. Alkylation of **1c** by the LDA method gave dimer **4** in 28.5% yield. This difficulty was overcome by employing dilution techniques (entry 12, Table I).

Confirmation of dianion formation was obtained by quenching the alleged dianion **2b** (method B) with 3 equiv of methanol-d_1 followed by acidification and exchange of the carboxyl proton. The NMR spectrum revealed a deuterium coupled doublet [δ 1.35 (3 H, $J_{H,H}$ = 7 Hz, CH_3CHD–)] and a deuterium coupled quartet [δ 3.00 (1 H, $J_{H,H}$ = 7 Hz, CH_3CHD–)]. That the α deuterium was not introduced as a consequence of methoxide exchange was confirmed by noting the lack of deuterium incorporation when the lithium salt of **1b** was exposed to 1 equiv of $LiOCH_3$ and 2 equiv of CH_3OD in THF under the reaction conditions.

Experimental Section

Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. Diisopropylamine and hexamethylphosphoramide were distilled from calcium hydride and stored over molecular sieves. Tetramethylethylenediamine (TMEDA) was distilled from potassium hydroxide and stored over molecular sieves. Alkyl halides were distilled prior to use. Gas chromatograms were obtained using a Varian Aerograph Model 90-P instrument with a 6 ft × 0.25 in, 5% SE 30 on Anakrom 60–70 mesh SD column (TC corrected; **3d** internal standard). NMR spectra were obtained on Perkin-Elmer R32, Bruker HX-270, or Varian CFT-20 instruments using Me_4Si as an internal standard. Elemental analyses were performed by Atlantic Microlabs (Atlanta). Standardization of *n*-butylithium in hexane was effected by the diphenylacetic acid technique.[6]

2-Ethylidene-1,3-dithiane (3e) (Entry 8). To a solution of LDA (prepared at 0 °C from 18.0 mL (128 mmol) of diisopropylamine and 46 mL (2.4 M, 110 mmol) of *n*-BuLi/hexane in 240 mL of THF at 0 °C) maintained under an atmosphere of N_2 was added at 0 °C 27.0 mL (150 mmol) of HMPA, followed by a solution of 5.3 mL (50 mmol) of propanedithioic acid (**1b**) in 5 mL of THF over a period of 10 min.

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After stirring the golden yellow solution at 25 °C for 2h, it was cooled to −78 °C followed by the dropwise addition (5 min) of a solution of 5.4 mL (50 mmol) of 1-bromo-3-chloropropane in 5 mL of THF. The solution was allowed to warm to 25 °C overnight. The reaction mixture was poured into hexane and washed with 5% aqueous $NaHCO_3$ solution and twice with water, and the combined washes were backwashed with hexane. The combined hexane extracts were washed with saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was distilled to yield 3.89 g (54%) of **3e** as a colorless liquid (GLC pure): bp 51–53 °C (0.2 mm) [lit.[3k] bp 43–44 °C (0.1 mm)]; NMR ($CDCl_3$) δ 1.76 (3 H, d, J = 7 Hz), 2.87 (4 H, m), and 6.00 (1 H, q, J = 7 Hz).

α,α-Bis(thioethyl)methylidenecyclohexane (3f) (Entry 11). To a solution of 1.87 mL (2.3 M, 4.3 mmol) of n-BuLi in 5 mL of THF at −78 °C maintained under an atmosphere of N_2 was added 1.2 mL (8.0 mmol) of N,N,N',N'-tetramethylethylenediamine followed by a solution of 0.32 g (2 mmol) of cyclohexanecarbodithioic acid (**1c**) in 1 mL of THF. The reaction mixture was maintained at −78 °C for 4 h, after which time 0.35 mL (4.3 mmol) of ethyl iodide was added to the orange solution, giving an immediate yellow-white suspension. After warming to 25 °C over 7 h, water was added and the mixture was thoroughly extracted with ether and backwashed with 5% aqueous $NaHCO_3$, water, and brine. The ethereal extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo, affording 0.48 g of crude yellow liquid: GLC, 71% yield (internal standard); NMR ($CDCl_3$) δ 1.16 (6 H, t, J = 6 Hz), 1.36–1.68 (6 H, m), and 2.49–2.87 (8 H, m).[7]

2,8-Bis(cyclohexylidene)-1,3,7,9-tetrathiacyclododecane (4). To a solution of 6.6 mmol of LDA (vide supra) in 8 mL of dry THF maintained under N_2 at 0 °C was added dropwise 1.56 mL (9.0 mmol) of dry HMPA followed by the dropwise addition of a solution of 0.48 g (3.0 mmol) of cyclohexanecarbodithioic acid (**1c**) in 1 mL of THF. The ice bath was removed, and the reaction mixture was allowed to warm to 25 °C over 1.5 h. The orange suspension was cooled to −78 °C (acetone–CO_2) followed by the dropwise addition of 0.34 mL (3.3 mmol) of freshly distilled 1-bromo-3-chloropropane. The reaction mixture was allowed to warm to 25 °C over a period of 6 h by allowing the CO_2 to evaporate. The reaction mixture was taken up in 50% benzene–hexane, washed successively with water, 5% aqueous sodium bicarbonate, water, and saturated brine, dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to give an orange-brown solid. The residue was chromatographed on SiO_2 (25 g), providing (15% benzene–hexane) 171 mg (28.5% yield) of white crystals of dimer **4** (mp 128 °C). Recrystallization from absolute ethanol provided 101.2 mg of **4**: mp 129.5 °C; ^1H NMR ($CDCl_3$, 270 MHz) δ 1.57 (12 H, m), 1.94 (4 H, quintet, J = 6.6 Hz), 2.62 (8 H, m), 3.01 (8 H, t, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 20 MHz) δ (relative intensity) 26.48 (45), 28.03 (100)[8] 32.92 (91), 34.20 (90), 121.21 (23), 154.00 (22); mass spectrum (70 eV), m/e 400 (M^+).

Anal. Calcd for $C_{20}H_{32}S_4$: C, 59.94; H, 8.05; S, 32.00. Found: C, 59.75; H, 8.07; S, 31.88.

The monomer **3g,** prepared by the modified method of adding the dianion and the dihalide simultaneously and slowly to THF at 25 °C (51% yield), had the following physical and spectral properties: mp 93.5 °C (lit. mp 92–93[3k] and 93.6–94 °C[3m]); ^1H NMR ($CDCl_3$, 90 MHz) δ 1.45–1.70 (6 H, m), 2.05–2.30 (2 H, m), 2.38–2.60 (4 H, m), 2.82–2.96 (4 H, m); ^{13}C NMR ($CDCl_3$, 20 MHz) δ (relative intensity) 25.16 (46), 26.38 (32), 27.40 (87), 30.25 (77), 31.99 (100), 115.59 (10), 144.87 (14); mass spectrum (70 eV), m/e 200 (M^+).

Anal. Calcd for $C_{10}H_{16}S_2$: C, 59.94; H, 8.05; S, 32.00. Found: C, 59.94; H, 8.06; S, 31.99.

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Registry No.—**1a,** 594-03-6; **1b,** 1892-30-4; **1c,** 35329-08-9; **3a,** 4992-59-0; **3b,** 21777-31-1; **3c,** 6251-15-6; **3d,** 13879-93-1; **3e,** 51102-62-6; **3f,** 66483-12-3; **3g,** 37891-71-7; **4,** 66483-11-2.

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(7) Identical with the product of entry 10. Anal. Calcd for $C_{11}H_{20}S_2$: C, 61.05; H, 9.32; S, 29.63. Found: C, 60.79; H, 9.29; S, 29.47.
(8) A ^{13}C spectrum at 68 MHz resolved this signal into two peaks: δ 28.12 (97) and 27.92 (60).

Synthesis and Oxidation of Substituted *N*-Phenyl-2-[(phenylamino)sulfinyl]acetamides

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N-Phenyl-2-[(phenylamino)sulfinyl]acetamide (**4a**) was first prepared in our laboratory by the reaction of aniline with the adduct formed from ketene and sulfur dioxide.[1] We also reported the cycloaddition of ketene (**1**) and *N*-sulfinylaniline (**2**) to give *N*-phenyl-1,2-thiazetidin-3-one 1-oxide (**3**) and described the reactions of **3** with aniline and *p*-toluidine to afford the corresponding *N*-phenyl-2-[(phenylamino)sulfinyl]acetamides, **4a** and **4b,** respectively.[2]

The present communication describes a more convenient synthesis of **3** and provides experimental details regarding the facile cleavage of **3** with substituted anilines and the oxidation of the resultant sulfinamides **4** to the corresponding sulfonamides **5.**

Treatment of approximately 1.5 mol equiv of gaseous ketene **1** with 1 equiv of *N*-sulfinylaniline (**2**) in acetone at −78 °C for 2 h was found to give *N*-phenyl-1,2-thiazetidin-3-one 1-oxide (**3**) in quantitative yields. Unreacted ketene and ketene dimer were removed in vacuo. A precooled solution of 2.1–2.5 equiv of the aniline in acetone was then added slowly to the residue in a dropwise fashion. The mixture was stirred 1.5 h longer and stored at −78 °C overnight to complete the reaction. Recrystallization of the crude solid from methanol or ethanol afforded pure **4** in yields of 50–71%.

Sulfinamides **4** show typical infrared absorption (KBr) at 3050–3200 cm^{-1} (vs, amide NH), 1650–1670 cm^{-1} (vs, amide C=O), and 1050–1060 cm^{-1} (vs, S=O). Their ^1H NMR spectra in Me_2SO-d_6 exhibit a singlet at δ 4.08–4.16 attributable to the methylene protons and a multiplet at δ 7.15–7.45 indicative of the aromatic protons. In addition, the sulfinamide protons appear as sharp singlets at δ 9.02–9.07, and the amide protons appear as broad singlets at δ 10.2–10.65.

We next turned our attention to oxidation of the sulfi-

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