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Nitroketene dithioacetal chemistry. Part 2: Synthesis of novel 4-(alkylsulfanyl)-2-[1-nitromethylidene]-1,3-dithioles from the dipotassium salt of 2-nitro-1,1-ethylenedithiol

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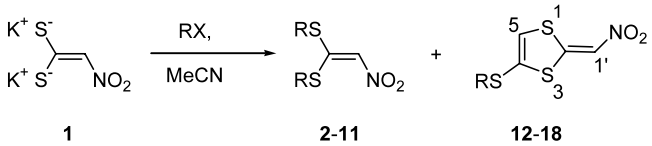
Abstract—The reaction of the dipotassium salt of 2-nitro-1,1-ethylenedithiol with long chain alkyl halides in acetonitrile medium furnished the novel heterocyclic, 4-(alkylsulfanyl)-2-[1-nitromethylidene]-1,3-dithioles. © 2003 Published by Elsevier Science Ltd.

The nitro ketene dithioacetal functional group is well known in synthetic organic sulfur chemistry as a two-carbon push–pull system.[1] While the nitro group acts as a powerful electron-withdrawing group, the two alkylated sulfurs readily donate their lone-pair of electrons to make the entire atomic framework highly polarized. Furthermore, the α,β-unsaturated nitro group is an excellent Michael acceptor; subsequent to the attack of a nucleophile at the β-carbon, an alkylsulfanyl group acts as a leaving group. There are several reports in the literature utilizing these aspects of nitro ketene dithioacetal chemistry for the synthesis of a variety of heterocycles.[2] In spite of the popularity of nitro ketene dithioacetal as a two-carbon synthon, a surprisingly small number of their *S*,*S*-dialkylated derivatives have been synthesized.[3] It has been claimed that some of the sulfoxide derivatives of *S*,*S*-dialkylated nitro ketene dithioacetals show potent antimicrobial properties.[4]

We became interested in the synthesis of a variety of alkylated derivatives of this synthon in order to study their physico-chemical and aggregation properties. We have recently reported the synthesis of several alkyl derivatives of nitroethylenedithiolate from the reaction of the dipotassium salt of 2-nitro-1,1-ethylenedithiol **1** with a series of simple alkyl halides in 50% aqueous methanol medium.[5] In this communication we report that, when the same reaction was conducted in acetonitrile as solvent and on slow addition of alkyl halide the reaction can be engineered towards the formation of the novel heterocyclic, 4-(alkylsulfanyl)-2-[1-nitromethylidene]-1,3-dithioles (**12**–**18**) along with the anticipated *S*,*S*-dialkylated derivatives (**2**–**11**) (Scheme 1). The results obtained in this study are presented in Table 1. Even though a few 2-[1-nitromethylidene]-1,3-dithiole derivatives are known,[6] 4-alkylsulfanyl 2-[1-nitromethylidene]-1,3-dithiole derivatives are being reported here for the first time.

The reaction of the dipotassium salt of 2-nitro-1,1-ethylenedithiol **1** with 2 equiv. of simple short-chain alkyl iodides such as methyl, ethyl and propyl iodide in 50% aqueous methanol resulted only in the expected *S*,*S*-dialkylated products **2**–**4**.[7] However, when the reaction was conducted with isopropyl iodide, in addition to the bis-alkylated product **5** (43%), a new compound, 4-(isopropylsulfanyl)-2-[1-nitromethylidene]-1,3-dithiole (**12**; $C_7H_9NO_2S_3$; MS: molecular ion $m/z=235$) was obtained in low yield (8%). When **1** was treated with isopropyl iodide in acetonitrile (slow addition of the alkylating agent to the reaction medium) 1,3-dithole **12** was obtained in 31% yield as a mixture of geometrical isomers in which the *E*-isomer predominated. For short-chain alkyl halides the dithiole product did not



1 **2-11** **12-18**

2: R = CH_3; **3**: R = CH_2CH_3; **4**: R = $CH_2CH_2CH_3$; **5**,**12**: R = $CH(CH_3)_2$; **6**,**13**: R = $CH_2(CH_2)_2CH_3$; **7**,**14**: $CH_2(CH_2)_3CH_3$; **8**,**15**: $CH_2(CH_2)_4CH_3$; **9**,**16**: $CH_2(CH_2)_5CH_3$; **10**,**17**: $CH_2(CH_2)_6CH_3$; **11**,**18**: $CH_2(CH_2)_8CH_3$.

Scheme 1.

Keywords: nitroketene dithioacetals; 2-nitromethylidene-1,3-dithioles; domino reaction.

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Table 1. Reaction of the dipotassium salt of 2-nitro-1,1-ethylenedithiol **1** with alkyl halides in acetonitrile medium

Entry	Alkyl halide (RX)	Bis-alkylated product; yield (%)	1,3-Dithiole; yield (%)
1	CH_3I	**2**; 60	–
2	CH_3CH_2I	**3**; 51	–
3	$CH_3CH_2CH_2I$	**4**; 42	–
4	$(CH_3)_2CHI$	**5**; 6	**12**; 31
5	$CH_3(CH_2)_2CH_2Br$	**6**; 24	**13**; 7
6	$CH_3(CH_2)_3CH_2I$	**7**; 20	**14**; 8
7	$CH_3(CH_2)_4CH_2Br$	**8**; 7	**15**; 21
8	$CH_3(CH_2)_5CH_2I$	**9**; 3	**16**; 28
9	$CH_3(CH_2)_6CH_2I$	**10**; 3	**17**; 21
10	$CH_3(CH_2)_8CH_2I$	**11**; 3	**18**; 21

form even in acetonitrile and only the bis-alkylated products **2**–**4** were isolated. The UV spectrum of **12** showed an intense absorption at 416 nm ($\log \varepsilon = 4.02$) indicating extensive conjugation in the molecule. Its ^1H NMR spectrum showed a characteristic singlet at 6.93 ppm arising from the C-5-H located on the 1,3-dithiole ring and a singlet at 7.7 ppm corresponding to the nitromethylidene hydrogen (C-1′-H). The stereochemistry of the major olefin was assigned as *E* by comparison with data on similar compounds.[6a] In agreement with the proposed structure, the proton-decoupled ^{13}C NMR spectrum of **12** showed six signals.[8]

Previously, based on the X-ray crystal structure analysis, Komarova and co-workers proposed an interesting resonance stabilization for some 1,3-dithiole derivatives involving the lone pair of electrons on both the sulfur atoms.[6a] 1,3-Dithioles can potentially exhibit characteristics of an aromatic ring as shown in Figure 1 (structures **A** and **B**). In such cases the signal for the C-5-H is expected to appear more downfield since it is next to a partially positively charged sulfur. Similarly, the methylidene hydrogen, C-1′-H, is expected to resonate at a higher field since it resides in a shielded environment created by the electron rich carbon. Initially the 2D NOESY spectrum of octylsulfanyl derivative **17** was recorded to determine the steric proximity of C-5-H of the heterocycle and C-1″-H of the side-chain and thus assign the chemical shift for C-5-H. Unfortunately, the spectrum did not reveal the anticipated cross-peaks, possibly because the side chain does not adopt favorable conformation required for observing NOE connections. The HMBC spectrum of **17** was recorded to ascertain the chemical shifts of C-5-H and C-1′-H through ^1H–^{13}C long range couplings. The 2D NMR spectrum revealed a long range coupling between C-5-H ($\delta = 6.89$ ppm) and quaternary carbon C-4 ($\delta = 134.14$ ppm) and coupling between C-1′-H ($\delta = 7.69$ ppm) and C-2 ($\delta = 165.56$ ppm) in the heterocycle. Furthermore, and in agreement with the assignment, the C-1″-H ($\delta = 2.89$ ppm) of the alkylsulfanyl side chain revealed connectivity to C-4. Since C-5-H appeared upfield in comparison to C-1′-H, in contrast to expectations from the structures **A** and **B** as shown in Figure 1, we believe that the 1,3-dithiole heterocyclic rings in **12**–**18** do not exhibit aromatic resonance stabilization.

When longer chain alkyl halides were employed in the reaction in acetonitrile, 1,3-dithiole products **13**–**18** (7–28%) along with bis-alkylated products **6**–**11** were formed (Table 1).[8] Interestingly, the ratio of 1,3-dithiole to bis-alkylated product increased with chain length, indicating that increased steric bulk in the alkyl halide favors the formation of the heterocyclic product. For example, the reaction of **1** with decyl iodide resulted in 1,3-dithiole **18** and bis-alkylated product **11** in a 7:1 ratio, whereas the reaction of **1** with butyl bromide resulted in 1,3-dithiole **13** and bis-alkylated product **6** in the ratio of 1:3.5. A possible mechanism involving domino pathways for the formation of the 1,3-dithiole moiety is given in Scheme 2. Conjugate addition of the monoalkylated product **20** to protonated species **19** and subsequent loss of hydrogen sulfide leads to intermediate **21**. Intramolecular cyclization followed by elimination of the nitro group results in 1,3-dithiole products **12**–**18**.

The bis-alkylated product, 1,1-di(methylsulfanyl)-2-nitroethylene **2** was subjected to treatment with the strong base, sodium methoxide (hard nucleophile) with the expectation that the intermediate anion of the type **20** (Scheme 2) would be generated in the medium which in the absence of alkyl halide may produce a dithiole product.[9] However, this reaction furnished only the known[10] 1,1,1-trimethoxy-2-nitroethane **22** (Scheme 3). The bis-alkylated product **2** did not show any reactivity with DBU, a non-nuclophilic base, even under reflux in benzene. The reaction of **2** with sodium benzenethiolate (soft nucleophile) furnished a mixture of geometrical

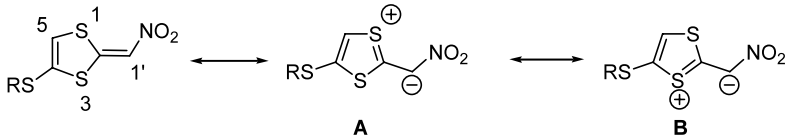
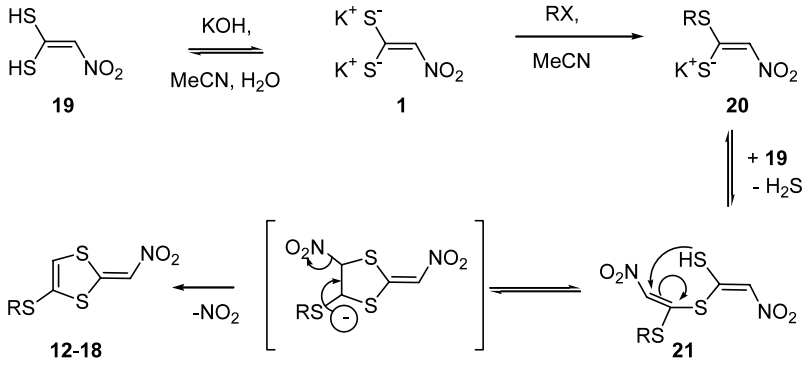
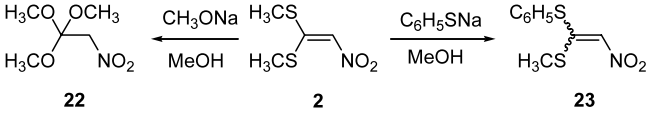


Figure 1.



Scheme 2.



Scheme 3.

isomers of 1-[1-(methylsulfanyl)-2-nitro-1-ethenyl]-sulfanylbenzene **23** (Scheme 3) generated by conjugate addition of the benzenethiolate anion followed by elimination of methanethiolate anion. On the other hand, the reaction of **2** with TMSCl in the presence of NaI in THF at reflux resulted in a polymeric product. Thus, it is clear from these studies that bis-alkylated products could not be induced to undergo transformation to dithiole derivative possibly due to the fact that the nitro ethylene moiety behaves as a good Michael acceptor.

In this report we have shown that the simple reaction of the dipotassium salt of 2-nitro-1,1-ethylenedithiol **1** with long chain or sterically hindered alkyl halides leads to interesting 4-alkylsulfanyl 2-nitromethylidene-1,3-dithioles along with bis-alkylated products. As heterocyclic systems with more than one sulfur atom show impressive physico-chemical properties, e.g. enhanced electrical conductivity,[11] our findings should be of general interest.

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8. *Spectral data for selected compounds*:
Compound **12** ($C_7H_9NO_2S_3$): mp 88°C; UV (MeOH) λ_{max} 416 nm; IR (Nujol) ν 3111, 3058, 2922, 1524, 1462, 1376, 1289, 1256, 1189 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$:CCl_4, 1:1) δ 1.35 (d, 6H, $J=6.9$ Hz) 3.38 (heptet, 1H, $J=6.9$ Hz), 6.93 (s, 1H), 7.7 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$:CCl_4, 1:1) δ 23.25, 40.90, 121.41, 122.73, 133.09, 165.59 ppm.
Compound **15** ($C_{10}H_{15}NO_2S_3$): mp 90°C; UV (MeOH) λ_{max} 415 nm; IR (Nujol) ν 3111, 3076, 2924, 2855, 1475, 1398, 1294, 1240, 1201 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$:CCl_4, 1:1) δ 0.86 (t, 3H, $J=7.2$ Hz), 1.3–1.6 (m, 8H), 2.34 (t, 2H, $J=7.1$ Hz), 6.89 (s, 1H), 7.68 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$:CCl_4, 1:1) δ 14.1, 22.58, 28.14, 29.57, 31.32, 36.71, 120.34, 121.43, 134.15, 165.50 ppm.
Compound **16** ($C_{11}H_{17}NO_2S_3$): mp 101°C; UV (MeOH) λ_{max} 417 nm; IR (Nujol) ν 3112, 3085, 2935, 1481, 1292, 1242, 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$:CCl_4, 1:1) δ 0.87 (t, 3H, $J=6.9$ Hz), 1.28–1.50 (m, 8H), 1.60–1.68 (m, 2H,), 2.89 (t, 2H, $J=7.2$ Hz), 6.89 (s, 1H), 7.68 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$:CCl_4, 1:1) δ 14.15, 22.63, 28.41, 28.80, 29.58, 31.71, 36.69, 120.38, 121.39, 134.13, 165.57 ppm.
Compound **17** ($C_{12}H_{19}NO_2S_3$): mp 108°C; UV (MeOH) λ_{max} 418 nm; IR (Nujol) ν 3112, 3083, 2955, 2854, 1522, 1474, 1390, 1292, 1244, 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$:CCl_4, 1:1) δ 0.86 (t, 3H, $J=6.9$ Hz), 1.20–1.50 (m, 10H), 1.61–1.68 (m, 2H), 2.89 (t, 2H, $J=7.2$ Hz), 6.89 (s, 1H), 7.69, (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$:CCl_4,

1:1) δ 14.17, 22.68, 28.43, 28.80, 29.35, 29.57, 29.75, 31.80, 120.39, 121.39, 134.14, 165.56 ppm.

Compound **18** ($C_{14}H_{23}NO_2S_3$): mp 98°C; UV (MeOH) λ_{max} 418 nm; IR (Nujol) ν 3011, 3078, 2923, 2853, 1520, 1463, 1377, 1289, 1242, 1203 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$:CCl_4, 1:1) δ 0.88 (t, 3H, $J=7.2$ Hz), 1.20–1.50 (m, 14H), 1.60–1.67 (m, 2H), 2.89, (t, 2H, $J=7.2$ Hz), 6.85 (s, 1H), 7.69 (s, 1H) ppm; ^{13}C NMR (300 MHz, $CDCl_3$:CCl_4, 1:1) δ 14.25, 22.77, 28.47, 29.16, 29.38 (2C), 29.57, 29.61, 29.79, 31.69, 120.27, 121.46, 134.13, 164.37 ppm.

Compound **11** ($C_{22}H_{43}NO_2S_2$): UV (MeOH) λ_{max} 361, 304 nm; IR (neat) ν 3129, 2925, 2854, 1524, 1465, 1311, 931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$:CCl_4, 1:1) δ 0.84 (t, 3H, $J=7.2$ Hz), 0.87 (t, 3H, $J=7.2$ Hz), 1.20–1.50 (m, 28H), 1.61–1.69 (m, 4H), 2.91 (t, 2H, $J=7.5$ Hz), 2.98 (t, 2H, $J=7.8$ Hz), 7.01 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$:CCl_4, 1:1) δ 14.25 (2 C), 22.77 (2 C), 27.41, 28.62, 28.98, 29.01, 29.13, 29.23, 29.39, 29.49, 29.53, 29.59, 29.62, 31.10, 31.98, 34.68, 36.43, 36.81, 125.51, 162.21 ppm.

Typical experimental procedure: To the solution of the dipotassium salt of 2-nitro-1,1-ethylenedithiol (1 mmol) in dry acetonitrile (5 mL), alkyl halide (1 mmol) in acetonitrile (5 mL) was added dropwise over 3 h. The reaction mixture was stirred at rt until completion of the reaction (12–24 h, TLC and GC). The reaction mixture was then diluted with ice-cold water (25 mL) and extracted with dichloromethane (3×15 mL). The combined organic fractions were washed with water (10 mL), brine (10 mL) and dried (anhyd. Na_2SO_4). The crude product obtained after evaporation of the solvent was subjected to column chromatography on silica gel (100–200 mesh, ACME) using dichloromethane in hexanes (2:8) to give the *S*,*S*-bisalkylated and 1,3-dithiole products, in that order.

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