General Synthesis of 1-Ethylthio-2-nitroolefins

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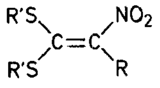
The synthetic potential of nitroolefins has been disclosed by Corey and Estreicher[1] and the synthetic utility of 2-nitroketene dithioacetals[2] (**1**) and 1-nitro-1-(phenylthio)-propene[3,4,5] (**2**) has been well documented. Although nitroolefins such as **3** should be potentially versatile as synthetic intermediates it is surprising that they have never appeared in the literature. We describe here a general synthesis of 1-ethylthio-2-nitroolefins (**3**).



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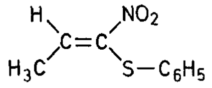

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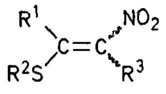

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We recently reported[6] the reductive replacement of the nitro group in nitromethyl ketones by hydrogen using the system aluminum chloride/ethanethiol, for example, the conversion of ω-nitroacetophenone (**4a**) into acetophenone diethyl dithioacetal (**5a**). The use of the less hard Lewis acid such as zinc chloride or boron trifluoride does not affect the nitro group; under these conditions, the actophenone (**4a, b, c**) is only converted into its *S,S*-diethyl acetal (**6a, b, c**). Treatment of these compounds with aluminum chloride in dichloromethane leads to elimination of one molecule of ethanethiol to give the corresponding 1-ethylthio-2-nitro-1-arylethylene (**7a, b, c**).

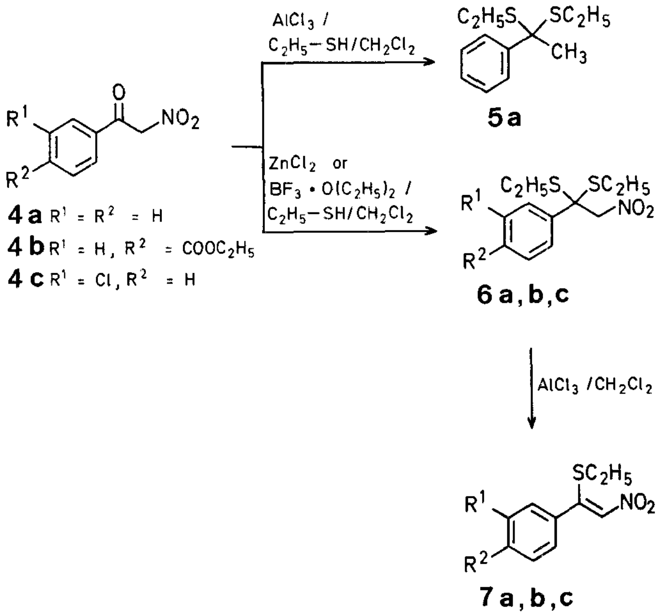
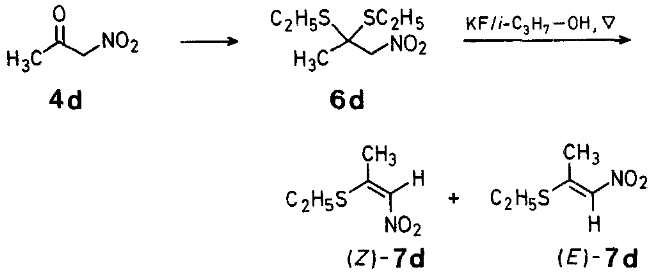


Table. Reaction Conditions of the Synthesis of 1-Ethylthio-2-nitroolefins (**7**) from α-Nitroketones (**4**)

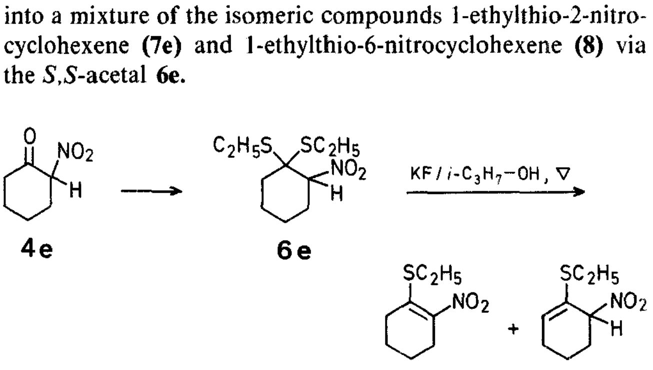
4 (mmol)	Dithio-acetalization[a]	Elimination of Ethanethiol	Products Yield [%][d]
a (4.9)	$ZnCl_2$ (5.0 equiv), 0°C - r.t., 4 h	$AlCl_3$ (1.1 equiv), 0°C, 5 min[b]	**7a**: 57
b (2.5)	$ZnCl_2$ (5.0 equiv), 0°C - r.t., 3 h	$AlCl_3$ (1.8 equiv), 0°C - r.t., 2.7 h[b]	**7b**: 79
c (1.6)	$BF_3 \cdot O(C_2H_5)_2$ (4.9 equiv), 0°C, 4 h	$AlCl_3$ (1.1 equiv), 0°C, 10 min[b]	**7c**: 57
d (76)	$BF_3 \cdot O(C_2H_5)_2$ (1.5 equiv), 0°C, 45 min	$AlCl_3$ (1.2 equiv), 0°C, 15 min[b]	(*Z*)-**7d**: 38, (*E*)-**7d**: 17
		KF (1.18 equiv), reflux, 50 min[c]	(*Z*)-**7d**: 56, (*E*)-**7d**: 39
e (27)	$BF_3 \cdot O(C_2H_5)_2$ (1.5 equiv), 0°C, 30 min	$AlCl_3$ (1.1 equiv), 0°C, 5 min[b]	**7e**: 19, **8**: 47
		KF (1.18 equiv), reflux, 50 min[c]	**7e**: 18, **8**: 81[e]

[a] Reactions carried out in dichloromethane.
[b] Reactions with $AlCl_3$ carried out in dichloromethane.
[c] Reactions with KF carried out in 2-propanol.
[d] Overall yield from **4**.
[e] Product **8** can be isomerized to **7e** (see procedure).

Performance of a similar sequence with nitroacetone (**4d**) affords the *S,S*-diethyl acetal **6d** which, on elimination of ethanethiol using aluminum chloride in dichloromethane or potassium fluoride in 2-propanol, is converted into a mixture of the two stereoisomeric 2-ethylthio-1-nitropropenes (*Z*)-**7d** and (*E*)-**7d**.



In the same manner, 2-nitrocyclohexanone (**4e**) is converted into a mixture of the isomeric compounds 1-ethylthio-2-nitrocyclohexene (**7e**) and 1-ethylthio-6-nitrocyclohexene (**8**) via the *S,S*-acetal **6e**.



In the elimination of ethanethiol from the *S,S*-diethyl acetals **6d** and **6e** derived from aliphatic nitromethyl ketones, the use of potassium fluoride in 2-propanol leads to a better yield than the use of aluminum chloride in dichloromethane.

The isolated undesired product **8** can in part be isomerized to compound **7e** by treatment with potassium fluoride in 2-propanol. From the mixture of compounds **7e** and **8** thus obtained, compound **7e** can be easily isolated by crystallization. The same treatment of the filtrate gives another crop of the desired crystalline product **7e**. Repetition of the procedure finally furnished the desired olefin **7e** in 82% yield.

The structure of (*Z*)-2-ethylthio-1-nitropropene [(*Z*)-**7d**] was determined by nuclear Overhauser enhancement (N.O.E.) (12%) of the signal at $\delta = 7.23$ ppm (vinyl-H) on irradiation at $\delta = 2.27$ ppm (C—CH$_3$). In the case of (*E*)-**7d**, the N.O.E. value (11%) observed for the signal at $\delta = 6.85$ ppm (vinyl-H) on irradiation at $\delta = 2.85$ ppm (S—$\underline{\mathrm{CH_2}}$—CH$_3$) confirmed the assigned structure.

4-Ethoxycarbonyl-ω-nitroacetophenone (4b):

Ethyl 4-formylbenzoate is condensed with nitromethane by the reported method[10]. Jones oxidation then affords **4b** in 43% overall yield; m.p. 103–105 °C (methanol).

$C_{11}H_{11}NO_5$	calc.	C 55.69	H 4.67	N 5.91
(237.2)	found	55.47	4.59	5.80

I.R. (KBr): $\nu = 2965$, 1720, 1695, 1555, 1380, 1265 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): $\delta = 1.42$ (t, $J = 7$ Hz, 3H); 4.41 (q, $J = 7$ Hz, 2H); 5.92 (s, 2H); 7.90 (d, $J = 8$ Hz, 2H); 8.17 ppm (d, $J = 8$ Hz, 2H).

Nitroketones **4a**[7], **4c**[8], **4d**[7,8], and **4e**[9] are known.

1,1-Bis[ethylthio]-2-nitro-1-phenylethane (6a):

Zinc chloride (3.29 g, 24 mmol) is added to a stirred, ice-cooled solution of ω-nitroacetophenone (**4a**; 1.05 g, 4.9 mmol) and ethanediol (5 ml, 67 mmol) under nitrogen. Stirring is continued for 1 h with ice-cooling and for 3 h at room temperature. The mixture is then poured into water (200 ml) and extracted with dichloromethane (3 × 100 ml). The extract is dried with sodium sulfate, filtered, and evaporated. The residue is column-chromatographed on silica gel using acetone/hexane (1/20) as eluent to give **6a** as a light yellow oil; yield: 0.96 g (73%).

$C_{12}H_{17}NO_2S_2$	calc.	C 53.10	H 6.31	N 5.16
(271.4)	found	53.66	6.49	5.27

High-resolution M.S.: calc. for $C_{12}H_{17}NO_2S_2(M^+)$: $m/e = 271.0700$; found: $m/e = 271.0671$.

I.R. (neat): $\nu = 2985$, 1555, 1440, 1370 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): $\delta = 1.22$ (t, $J = 7.5$ Hz, 6H); 2.61 (q, $J = 7$ Hz, 2H); 2.63 (q, $J = 8$ Hz, 2H); 4.95 (s, 2H); 7.2–7.8 ppm (m, 5H).

The reaction conditions for the preparation of the other dithioacetals **6** are listed in the Table. These compounds were directly used for the next step after a rough purification by short-column chromatography.

1-Ethylthio-2-nitro-1-phenylethylene (7a); Typical Procedure:

Aluminum chloride (230 mg, 1.7 mmol) is added to a solution of 1,1-bis[ethylthio]-2-nitroethylbenzene (**6a**; 430 mg, 1.6 mmol) in dichloromethane (5 ml) under nitrogen at 0 °C, the mixture is stirred for 5 min, poured into water (100 ml) and extracted with dichloromethane (3 × 50 ml). The organic layer is dried with sodium sulfate, filtered, and evaporated. The residue is purified by column chromatography on silica gel using ethyl acetate/hexane (1/10) as eluent to give **7a** as light yellow needles; yield: 258 mg (78%). An analytically pure sample may be obtained by recrystallization from 2-propanol; m.p. 54–54.5 °C.

$C_{10}H_{11}NO_2S$	calc.	C 57.39	H 5.30	N 6.69
(209.3)	found	56.98	5.23	6.66

High-resolution M.S.: calc. for $C_{10}H_{11}NO_2S$ (M^+): $m/e = 209.0511$, found: $m/e = 209.0511$.

I.R. (KBr): $\nu = 3080$, 1555, 1455, 1440, 1325 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): $\delta = 1.10$ (t, $J = 8$ Hz, 3H); 2.44 (q, $J = 8$ Hz, 2H); 7.23 (s, 1H); 7.1–7.5 ppm (m, 5H).

1-(4-Ethoxycarbonylphenyl)-1-ethylthio-2-nitroethylene (7b):

Yield: 79%; m.p. 47–47.5 °C (2-propanol).

$C_{13}H_{15}NO_4S$	calc.	C 55.50	H 5.37	N 4.98
(281.3)	found	55.61	5.43	5.00

High-resolution M.S.: calc. for $C_{13}H_{15}NO_4S$ (M^+): $m/e = 281.0721$, found: $m/e = 281.0714$.

I.R. (KBr): $\nu = 2980$, 1710, 1550, 1470, 1310, 1255 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): $\delta = 1.12$ (t, $J = 8$ Hz, 3H); 1.43 (t, $J = 7$ Hz, 3H); 2.43 (q, $J = 8$ Hz, 2H); 4.43 (q, $J = 7$ Hz, 2H); 7.20 (s, 1H); 7.38 (d, $J = 8$ Hz, 2H); 8.14 ppm (d, $J = 8$ Hz, 2H).

1-(3-Chlorophenyl)-1-ethylthio-2-nitroethylene (7c):

Yield: 57%; m.p. 99–99.5 °C (2-propanol).

$C_{10}H_{10}ClNO_2S$	calc.	C 49.28	H 4.14	N 5.75
(243.7)	found	49.23	4.18	5.70

I.R. (KBr): $\nu = 3080$, 1545, 1440, 1315 cm^{-1}.

^{1}H-N.M.R. (CDCl$_3$/TMS$_{int}$): $\delta = 1.13$ (t, $J = 8$ Hz, 3H); 2.44 (q, $J = 8$ Hz, 2H); 7.20 (s, 1H), 7.1–7.5 ppm (m, 4H).

(*Z*)- and (*E*)-2-Ethylthio-1-nitropropene [(*Z*)-7d and (*E*)-7d]:

To a stirred solution of 2,2-bis[ethylthio]-1-nitropropane (**6d**; 114 mg, 0.55 mmol) [prepared from nitroacetone (**4d**; 68 mg, 0.66 mmol)] in 2-propanol (2 ml) is added potassium fluoride (38 mg, 0.65 mmol). The mixture is refluxed for 50 min with continuous removal of the formed ethanethiol by controlling the temperature of the condenser. After cooling, the mixture is poured into aqueous ammonium chloride and extracted with dichloromethane (3 × 50 ml). The organic layer is washed with saturated sodium chloride solution (50 ml), dried with sodium sulfate, filtered, and evaporated. The residue is subjected to preparative T.L.C. on silica gel using dichloromethane/hexane (1/1) as solvent.

Crystalline (Z)-*2-ethylthio-1-nitropropene* [(*Z*)-**7d**] is obtained from the more polar fraction; yield: 45 mg (56%); m.p. 38–39 °C (2-propanol).

$C_5H_9NO_2S$	calc.	C 40.80	H 6.16	N 9.52
(147.2)	found	40.64	6.30	9.56

I.R. ($CHCl_3$): $\nu = 2990, 1560, 1480, 1320\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.36$ (t, $J = 8$ Hz, 3 H); 2.27 (d, $J = 1$ Hz, 3 H); 2.95 (q, $J = 8$ Hz, 2 H); 7.23 ppm (q, $J = 1$ Hz, 1 H).

(E)-*2-Ethylthio-1-nitropropene* [(*E*)-**7d**] is obtained as a light yellow oil from the less polar fraction; yield: 31 mg (39%).

$C_5H_9NO_2S$	calc.	C 40.80	H 6.16	N 9.52
(147.2)	found	41.20	6.37	9.88

High-resolution M.S.: calc. for $C_5H_9NO_2S$ (M^+): $m/e = 147.0355$, found: $m/e = 147.0371$.

I.R. (neat): $\nu = 2980, 1580, 1510, 1315\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.37$ (t, $J = 8$ Hz, 3 H); 2.50 (d, $J = 1$ Hz, 3 H); 2.85 (q, $J = 8$ Hz, 2 H); 6.85 ppm (s, 1 H).

1-Ethylthio-2-nitrocyclohexene (7e) and 1-Ethylthio-6-nitrocyclohexene (8):

Application of the above procedure (**4d** → **7d**) to 2-nitrocyclohexanone (**4e**; 3.87 g, 27 mmol) affords a mixture of products **7e** and **8** which is separated by column chromatography on silica gel. Elution with chloroform/hexane (1/1) affords *1-ethylthio-6-nitrocyclohexene* (**8**) as a light yellow oil; overall yield from **4e**: 1.28 g (81%).

$C_8H_{13}NO_2S$	calc.	C 51.31	H 7.00	N 7.48
(187.3)	found	51.69	7.19	7.74

I.R. (KBr): $\nu = 2940, 1555, 1450, 1370\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.20$ (t, $J = 7$ Hz, 3 H); 1.5–2.5 (m, 6 H); 2.71 (q, d, $J = 7, 2.5$ Hz, 2 H); 5.08 (m, 1 H); 6.32 ppm (t, $J = 4$ Hz, 1 H).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 14.2$ (q), 17.1 (t), 26.3 (t), 26.9 (t), 29.2 (t), 85.0 (d), 125.6 (s), 137.3 ppm (d).

Further elution gives *1-ethylthio-2-nitrocyclohexene* (**7a**); overall yield from **4e**: 0.29 g (18%); m.p. 118–119 °C (2-propanol).

$C_5H_{13}NO_2S$	calc.	C 51.31	H 7.00	N 7.48
(187.3)	found	51.33	7.22	7.52

I.R. (KBr): $\nu = 2945, 1565, 1450, 1270\ cm^{-1}$.

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 1.33$ (t, $J = 8$ Hz, 3 H); 1.5–1.9 (m, 4 H); 2.4–2.9 (m, 4 H); 2.90 ppm (q, $J = 8$ Hz, 2 H).

^{13}C-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 13.3$ (q); 21.7 (t); 22.5 (t); 25.2 (t); 27.0 (t); 30.5 (t); 140.2 (s); 153.7 ppm (s).

Isomerization of 8 to 7e:

A mixture of **8** (9.5 g, 51 mmol) and potassium fluoride (3.5 g, 60 mmol) in 2-propanol is refluxed for 2 h. Cooling the solution yields a crop of **7e**. The filtrate is treated in the same manner for several times to increase the yield of **7e** up to 6.6 g (69%). The final residue is separated by column chromatography on silica gel to afford **7e** (1.2 g, 13%) and **8** (0.57 g, 6%); total yield of **7e**: 82%.

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