Oxidation of Aromatic Aldehyde and Ketone Alkylthiothiocarbonylhydrazones with Dimethyl Sulfoxide and Acetic Anhydride: A New Synthesis of Disulfides

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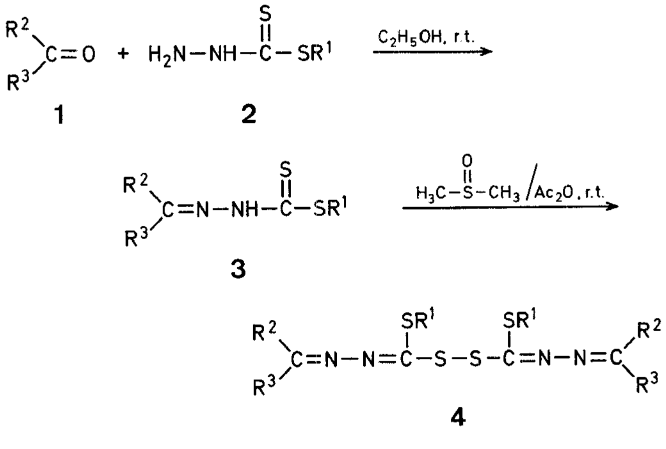
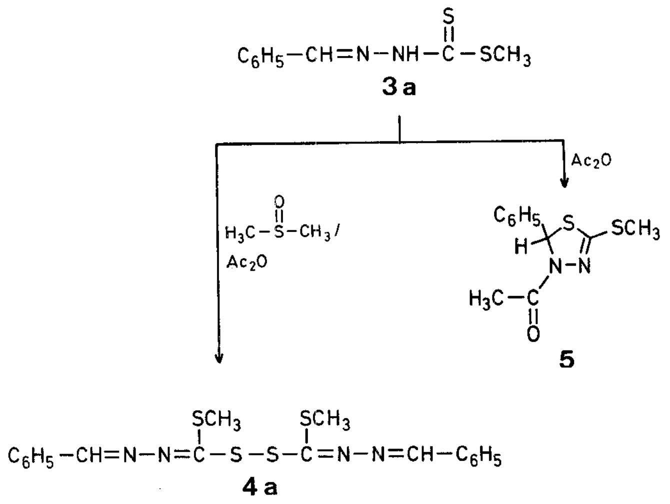
The dimethyl sulfoxide/acetic anhydride reagent has been used to oxidize various functionalized alcohols to the corresponding carbonyl compounds under mild conditions[1,2]. Dimethyl sulfoxide can, for example, also be used as a reagent for the oxidative *S*—*S* coupling of thiols to disulfides[3,4] but, as we have found, no reaction takes place when aldehyde or ketone alkylthiothiocarbonylhydrazones are heated with dimethyl sulfoxide at 100 °C for several hours.

We report here a new convenient method for the synthesis of bis[(alkylthio)-(1-arylalkylidenehydrazono)-methyl] disulfides (**4a–i**) by the oxidation of various aromatic aldehyde and ketone alkylthiothiocarbonylhydrazones (**3a–i**) with the dimethyl sulfoxide/acetic anhydride reagent at room temperature.



Whereas the reaction of benzaldehyde methylthiothiocarbonyl hydrazone (**3a**) with acetic anhydride gives 3-acetyl-5-methylthio-2-phenyl-2,3-dihydro-1,3,4-thiadiazole (**5**; structure supported by mass-, I.R.-, and ^{1}H-N.M.R.-spectrometric data) in analogy to the cyclocondensation of semicarbazones with acetic anhydride[5], the reaction of **3a** with the dimethyl sulfoxide/acetic anhydride system affords only the open-chain bis[(benzylidenehydrazono)-(methylthio)-methyl] disulfide (**4a**).



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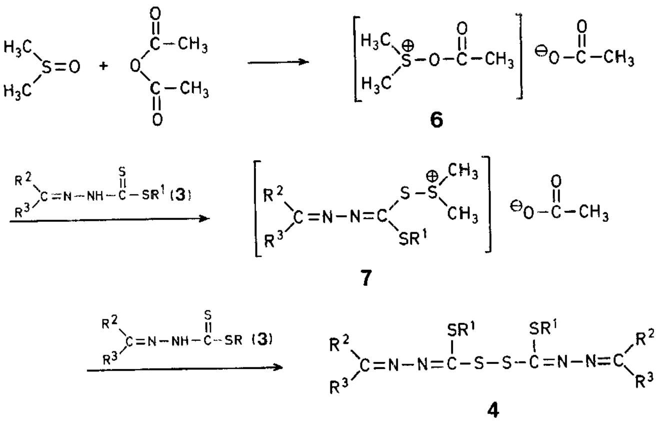
The structural assignment of compounds **4a-i** is based on microanalyses, mass-, and ^{1}H-N.M.R.-spectral data. The disulfide **4a** is used here as a representative example. The mass spectrum (C.I., NH_3) of **4a** shows a M+1 peak at *m/e*=419 and a prominent 1/2 M^{+} peak at *m/e*=209 resulting from *S*—*S* cleavage. The ^{1}H-N.M.R. spectrum of disulfide **4a** showed methine protons at $\delta = 8.44$ ppm (2H) and two multiplets of aromatic protons centered at $\delta = 7.8$ (4H) and $\delta = 7.40$ ppm (6H), due to the effect of the adjacent azomethine group. A similar type of disulfide (**4**; $R^1 = C_2H_5$, $R^2 = C_6H_5$, $R^3 = H$) has been prepared by oxidation of benzaldehyde ethyl-dithiocarbohydrazone with iodine[6]. Oxidation of compound **3a** with iodine by the reported procedure[6] gave the disulfide **4a** which was found identical with the compound obtained by oxidation of **3a** with dimethyl sulfoxide/acetic anhydride.

The formation of the disulfides **4a-i** may be rationalized as follows. Acetic anhydride reacts with dimethyl sulfoxide to give acetoxydimethylsulfonium acetate (**6**) as an intermediate[7]. The reaction of this intermediate with compound **3** gives the substituted thiodimethylsulfonium acetate **7**, which is converted into disulfide **4** by the action of another molecule of compound **3**.

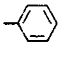
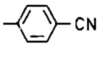
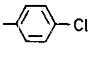
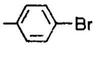
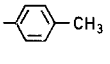
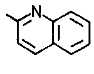
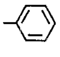
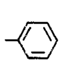


The method described here affords high yields and is applicable to a wide variety of aromatic and heteroaromatic alkyl-dithiocarbohydrazones.

Aldehyde and Ketone Alkylthiothiocarbonylhydrazones (3):

Compounds **3a-i** are prepared from aldehydes or ketones (**1**) and alkyl hydrazinedithiocarboxylates (**2**) according to known methods[5,8,9].

Table. Bis[(alkylthio)-(1-arylalkylidenehydrazono)-methyl] Disulfides (**4**) prepared

4	R^1	R^2	R^3	Reaction time [h][a]	Yield[b] [%]	m.p. [°C] (solvent)	Molecular formula[c]	M.S.[d] *m/e* (M+1)	^{1}H-N.M.R. ($CDCl_3/TMS_{int}$)[e] δ [ppm]
a	CH_3	H		23	90	165° (acetone)	$C_{18}H_{18}N_4S_4$ (418.6)	419	2.50 (s, 6H, SCH_3); 7.50-7.35 (m, 6H_{arom}); 7.84-7.77 (m, 4H_{arom}); 8.44 (s, 2H, CH=)
b	CH_3	H		23	89	202-203° (chloroform)	$C_{20}H_{16}N_6S_4$ (468.6)	469	2.51 (s, 6H, SCH_3); 7.76-7.04 (m, 4H_{arom}); 7.96-7.84 (m, 4H_{arom}); 8.44 (s, 2H, CH=)
c	CH_3	H		22	79	204° (benzene)	$C_{18}H_{16}Cl_2N_4S_4$ (487.5)	488	2.48 (s, 6H, SCH_3); 7.44-7.30 (m, 4H_{arom}); 7.80-7.67 (m, 4H_{arom}); 8.37 (s, 2H, CH=)
d	CH_3	H		26	81	200° (benzene)	$C_{18}H_{16}Br_2N_4S_4$ (576.4)	577	2.50 (s, 6H, SCH_3); 7.60-7.48 (m, 4H_{arom}); 7.73-7.63 (m, 4H_{arom}); 8.37 (s, 2H, CH=)
e	CH_3	H		28	70	176-177° (benzene)	$C_{20}H_{22}N_4S_4$ (446.6)	447	2.83 (s, 6H, CH_3); 2.50 (s, 6H, SCH_3); 7.34-7.20 (m, 4H_{arom}); 7.76-7.63 (m, 4H_{arom}); 8.38 (s, 2H, CH=)
f	CH_3	H		21	93	186° (chloroform)	$C_{24}H_{20}N_6S_4$ (520.7)	521	2.56 (s, 6H, SCH_3); 8.33-7.48 (m, 12$H_{quinoline}$); 8.67 (s, 2H, CH=)
g	n-C_3H_7	H		23	89	106-107° (ethanol)	$C_{22}H_{26}N_4S_4$ (474.7)	475	1.04 (t, 6H, CH_3); 1.92-1.60 (m, 4H, $C\underline{H}_2$—CH_3); 3.08 (t, 4H, $SC\underline{H}_2$); 7.48-7.35 (m, 6H_{arom}); 7.88-7.72 (m, 4 H_{arom}); 8.40 (s, 2H, CH=)
h	i-C_3H_7	H		16	85	160° (chloroform)	$C_{22}H_{26}N_4S_4$ (474.7)	475	1.40 (d, 12H, CH_3); 4.00-3.72 (m, 2H, —CH); 7.50-7.32 (m, 6H_{arom}); 7.88-7.76 (m, 4H_{arom}); 8.41 (s, 2H, CH=)
i	CH_3	CH_3		22	89	169-170° (acetone)	$C_{20}H_{22}N_4S_4$ (446.6)	447	2.48 (s, 6H, SCH_3); 2.52 (s, 6H, CH_3); 7.50-7.34 (m, 6H_{arom}); 8.00-7.84 (m, 4 H_{arom})

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[a] Stirring at room temperature.

[b] Yield of pure isolated product after crystallization.

[c] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.30; H, ±0.30; N, ±0.30.

[d] Obtained on a JEOL JMS-D300 spectrometer. All mass spectra were taken in ammonia gas for chemical ionization.

[e] Obtained on a JEOL PS-100 spectrometer.

Bis[(alkylthio)-(1-arylalkylidenehydrazono)-methyl] Disulfides (4a-i); General Procedure:

A mixture of dimethyl sulfoxide (3 ml) and acetic anhydride (2 ml) is stirred at room temperature for 1 h. Then, the aldehyde or ketone alkylthiothiocarbonylhydrazone (**3**; 1 mmol) is added and stirring is continued for 1 h. The separated yellow crystalline product **4** is isolated by suction and recrystallized from a suitable solvent (see Table).

3-Acetyl-5-methylthio-2-phenyl-2,3-dihydro-1,3,4-thiadiazole (5):

A mixture of benzaldehyde methylthiothiocarbonylhydrazone (**3a**; 3.15 g, 0.015 mol) and acetic anhydride (20 ml) is heated at 100 °C for 1 h, and then concentrated under reduced pressure. The resultant solid is crystallized from methanol to give colorless crystalline **5**: yield: 3.47 g (92%); m.p. 75–76 °C.

$C_{11}H_{12}N_2OS_2$	calc.	C 52.36	H 4.79	N 11.10
(252.3)	found	52.47	4.81	10.96

M.S. (70 eV): $m/e = 252$ (M^+); 209 ($M^+ - CO{-}CH_3$).

I.R. (KBr): $\nu = 1660\ cm^{-1}$ ($C{=}O$).

^{1}H-N.M.R. ($CDCl_3/TMS_{int}$): $\delta = 2.30$ (s, 3H, $CO{-}CH_3$); 2.56 (s, 3H, SCH_3); 7.06 (s, 1H, 5-H); 7.30 ppm (s, 5H_{arom}).

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