Reaction of Dimethyl *N*-Aryl- and *N*-Alkylcarbonimidodithioates with Aminoacetaldehyde Diethyl Acetal: A Direct Synthesis of 1-Aryl- and 1-Alkyl-2-methylthioimidazoles

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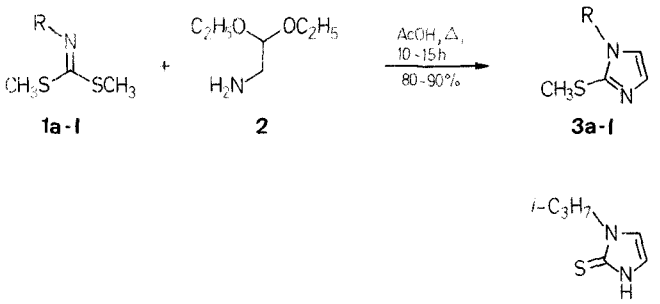
The reaction of dimethyl *N*-aryl- or *N*-alkylcarbonimidodithioates with aminoacetaldehyde diethyl acetal in refluxing acetic acid affords 1-aryl or 1-alkyl-2-methylthioimidazoles in good yields. Dimethyl *N*-isopropylcarbonimidodithioate gave 1-isopropylimidazole-2(3*H*)-thione under similar conditions.

Dimethyl *N*-aryl- and *N*-alkylcarbonimidodithioates are known for a long time.[1,2] However, their synthetic application has hitherto been relatively limited despite their easy access

from a large number of aromatic and aliphatic amines.[2] Some of their recent applications include the synthesis of cyclic guanidine derivatives,[3] β-lactams,[4] dihydro-1,3,5-oxadiazines,[5] as well as lithiation reactions leading to 2-arylimino- and 2-alkylimino-1,3-oxathiolanes[6] and α-branched amino acids.[7] We now report the application of these compounds to the synthesis of 1-aryl- and 1-alkyl-2-methylthioimidazoles by reaction with aminoacetaldehyde acetals.

The reaction of dimethyl *N*-phenyliminocarbonimidodithioate (**1a**) with aminoacetaldehyde diethyl acetal (**2**) in boiling acetic acid afforded, after work-up, 1-phenyl-2-methylthioimidazole (**3a**) in 80% yield. The reaction was found to be general for other *N*-arylcarbonimidodithioates (**1b–i**) under similar conditions, the corresponding imidazoles **3b–i** being obtained in 80–90% overall yields (Table). When the reaction was extended to the synthesis of 1-alkyl-2-methylthioimidazoles, the 1-methyl (**3j**), 1-ethyl (**3k**), and 1-benzyl (**3l**) derivatives could be obtained in good yields. However, the analogous reaction with the *N*-isopropyl derivative **1m** afforded only 1-isopropylimidazole-2(3*H*)-thione (**4**). The desired imidazole **3m** (R = *i*-C_3H_7) which was formed in low yield during the initial period (1 h) of the



1a–l **2** **3a–l**

4 (75% from **1m**)

1, 3	R	1, 3	R
a	C_6H_5	**h**	3-ClC_6H_4
b	4-$CH_3C_6H_4$	**i**	2,4,5-$(CH_3O)_3C_6H_2$
c	4-$CH_3OC_6H_4$	**j**	CH_3
d	4-ClC_6H_4	**k**	C_2H_5
e	4-BrC_6H_4	**l**	$C_6H_5CH_2$
f	2-$CH_3C_6H_4$	**1m**	*i*-C_3H_7
g	2-ClC_6H_4		

Table. 1-Aryl- and 1-Alkyl-2-methylthioimidazoles **3a–l** Prepared

Product	Reaction time (h)	Yield[a] (%)	m.p. (°C)[b]	Molecular Formula[c] or Lit. m.p. (°C)	MS (70 eV)[d] *m/e* (M^+) (%)	IR (KBr/neat)[e] ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS)[f] δ
3a	10	80	55[g]	53–54[9]			
3b	10	89	75	$C_{11}H_{12}N_2S$ (204.2)	204 (61)	3160, 3010, 1510, 1440	2.39 (s, 3H, CH_3); 2.54 (s, 3H, SCH_3); 7.00 (s, 1H, H-4); 7.03 (s, 1H, H-5); 7.31 (s, $4H_{arom}$)[h]
3c	11	85	100	$C_{11}H_{12}N_2OS$ (220.2)	220 (60)	3120, 3000, 1510, 1442	2.45 (s, 3H, SCH_3); 3.76 (s, 3H, OCH_3); 6.70–7.29 (m, 6H, H-4, H-5, $4H_{arom}$)
3d	10	81	110–112	$C_{10}H_9ClN_2S$ (224.6)	224 (100); 226 (96)	3120, 2900, 1480, 1435	2.50 (s, 3H, SCH_3); 6.98 (s, 1H, H-4); 7.07 (s, 1H, H-5); 7.32 (m, $4H_{arom}$)[h]
3e	10	90	97	$C_{10}H_9BrN_2S$ (269.1)	268 (35); 270 (10)	3095, 2925, 1481, 1440	2.50 (s, 3H, SCH_3); 7.00 (s, 1H, H-4); 7.05 (s, 1H, H-5); 7.00–7.65 (m, $4H_{arom}$)[h]
3f	15	82	oil	$C_{11}H_{12}N_2S$ (204.2)	204 (38)	3102, 3024, 1490, 1458	2.05 (s, 3H, CH_3); 2.51 (s, 3H, SCH_3); 6.81 (s, 1H, H-4); 6.96 (s, 1H, H-5); 7.05–7.40 (m, $4H_{arom}$)[h]
3g	16	83	oil	$C_{10}H_9ClN_2S$ (224.6)	224 (80); 226 (35)	3100, 3051, 1590, 1480, 1435	2.50 (s, 3H, SCH_3); 6.84 (s, 1H, H-4); 6.94 (s, 1H, H-5); 7.0–7.55 (m, $4H_{arom}$)[h]
3h	10	80	45	$C_{10}H_9ClN_2S$ (224.6)	224 (81); 226 (79)	3108, 3092, 1590, 1482, 1473	2.51 (s, 3H, SCH_3); 6.90 (s, 2H, H-4 and H-5); 7.0–7.35 (m, $4H_{arom}$)[h]
3i	10	81	120	$C_{13}H_{16}N_2O_3S$ (280.1)	280 (93)	3110, 3095, 1595, 1509, 1443	2.51 (s, 3H, SCH_3); 3.71 (s, 3H, OCH_3); 3.73 (s, 6H, OCH_3); 6.50 (s, 2H, H-4 and H-5); 6.90 (s, $2H_{arom}$)[h]
3j	11	80	oil[g]	oil[9]			
3k	12	81	oil[g]	oil[9]			
3l	15	85	oil	oil[13]	204 (100)	3100, 3058, 1492, 1450, 1425	2.52 (s, 3H, SCH_3); 5.00 (s, 2H, $C_6H_5CH_2$); 6.72 (s, 1H, H-4); 6.90 (s, 1H, H-5); 6.90–7.30 (m, $5H_{arom}$)[h]

[a] Yield of pure isolated product.
[b] Uncorrected, measuted with a Thomas Hoover Capillary melting-point apparatus.
[c] *Satisfactory microanalyses obtained*: C ±0.29, H ±0.33, N ±0.35.
[d] Recorded on Jeol JMS-D 300 spectrometer.
[e] Recorded on a Perkin-Elmer 297 Infrared spectrophotometer.
[f] Recorded on Varian EM-390 NMR spectrometer.
[g] The products **3a**, **3j**, and **3k** were characterized by comparison of their IR and ^{1}H-NMR spectral data with reported values[9] as well as by mass spectra and microanalyses.
[h] $J_{4,5}$ is not clearly resolved.

reaction was found to undergo rapid demethylation to the thione **4** (as monitored by TLC), probably due to steric hindrance.[8] This was further confirmed by refluxing **3m** (prepard by a known procedure[9]) in acetic acid for 1 h, the thione **4** being obtained in nearly quantitative yield (95%).

In summary, dimethyl *N*-aryl- and *N*-alkylcarbonimidodithioates (**1**) are useful precursors of 1-aryl-, 1-methyl-, 1-ethyl-, and 1-aralkyl-2-methylthioimidazoles which (**3a, j, k, l**) were earlier obtained by a two-step procedure involving synthesis of the corresponding imidazole-2(3*H*)thiones and their methylation.[9-14] The starting materials **1a–l** were prepared according to the reported procedure.[2]

1-Aryl-and alkyl-2-methylthioimidazoles (3a–l); General Procedure:
A solution of the dimethyl *N*-aryl- or *N*-alkylcarbonimidodithioate **1** (10 mmol) and aminoacetaldehyde diethyl acetal (**2**; 2.0 g, 15 mmol) in AcOH (10 mL) is heated to boiling for 10–15 h. Then, AcOH is removed under vacuum and the residue is dissolved in $CHCl_3$ (50 mL). This solution is washed with H_2O (3 × 30 mL), dried (Na_2SO_4), and evaporated to give the crude product **3** which is purified by column chromatography on silica gel using EtOAc/hexane (1:4) as eluent, and crystallized from CH_2Cl_2.

1-Isopropylimidazole-2(3*H*)-thione (4):

From **1m**: A solution of dimethyl *N*-isopropylcarbonimidodithioate (**1m**; 1.50 g, 10 mmol) and aminoacetaldehyde diethyl acetal (**2**; 2.0 g, 15 mmol)in AcOH (10 mL) is heated to boiling for 20 h until compound **1m** has been consumed completely (TLC, EtOAc/benzene 1:4). Work-up as in the General Procedure gives the thione **4** as pale-colored crystals (from CH_2Cl_2); yield: 1.00 g (75%); m.p. 169–70°C (Lit.[11] m.p. 168–9°C, superimposable IR and NMR spectra).

From **3m**: A solution of 1-isopropyl-2-methylthioimidazole[9] (**3m**; AcOH (10 mL) is refluxed for 1 h. Work-up of the (mixture as described gives **4**; yield: 0.43 g (95%) mixture m.p., superimposable IR and NMR spectra).

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