4,5-Dihydroimidazoles from Dithiocarboxylic Esters, Thiocarboxamides, or Nitriles

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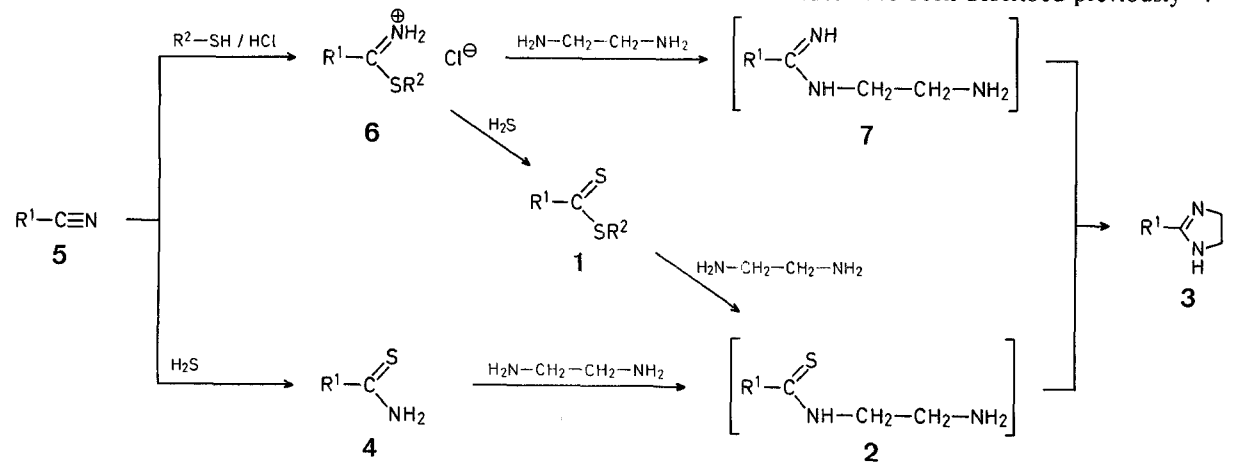
The synthesis of thiocarboxamides from dithiocarboxylic esters and aliphatic amines is a well-known reaction[1]. We recently used this reaction to obtain poly-thioamides from diamines and aliphatic or aromatic bis-dithiocarboxylates[2] and noticed that the poly-thioamides prepared from 1,2-diaminoethane exhibit a weak but unusual I.R. band near $\nu = 1600$ cm^{-1} which is absent in the spectra of all other poly-thioamides. We therefore attempted to prepare some model compounds for these polymers by reacting mono-dithioesters **1** with varying amounts of diaminoethane; however, in no case could the expected aminothioamide **2** be obtained, the 2-substituted 4,5-dihydroimidazole **3** always being the only isolable product. Since 4,5-dihydroimidazoles (2-imidazolines) exhibit a sharp I.R. band at $\nu = 1610$–1580 cm^{-1} (C=N), the occurrence of 2-imidazolines as end groups seems very likely in the diaminoethane-derived poly-thiocarboxamides. We report here the utilization of the observed reaction for the synthesis of 2-substituted 4,5-dihydroimidazoles (**3, 12**) (Method A).

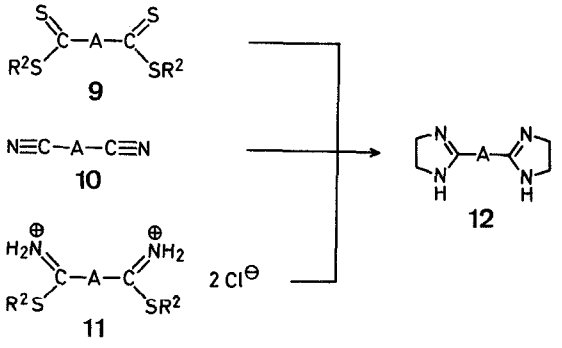
Primary thiocarboxamides (**4**) may be readily obtained by the base-catalyzed addition of hydrogen sulfide to nitriles (**5**). On the other hand, hydrogen sulfide is eliminated in the transamidation-cyclization of thiocarboxamides (**4**) with diamines so that both reactions might be combined to a catalytic process in which hydrogen sulfide functions as the catalyst. Patents have claimed such reactions at elevated temperatures and we have found that 2-substituted 4,5-dihydroimidazoles (**3, 12**) can be prepared from nitriles (**5, 10**) and 1,2-diaminoethane in the presence of hydrogen sulfide at room temperature (Method C).

2-Substituted 4,5-dihydroimidazoles (**3**) may also be prepared by the reaction of alkyl carboximidothioate hydrochlorides (**6**; obtained from nitriles, alkanethiols, and hydrogen chloride) with 1,2-diaminoethane (Method D). We assume that the *N*-(2-aminoethyl)-amidine **7** is an intermediate in this reaction since *N*-substituted amidines are obtained from compounds **6** and primary amines[6]. It should be mentioned that *N*-(2-aminoethyl)-amidines (**7**) might also be intermediates in the formation of 2-substituted 4,5-dihydroimidazoles (**3**) from nitriles (**5**) according to method C; however, when excess hydrogen sulfide is used in this reaction, the intermediacy of *N*-(2-aminoethyl)-thiocarboxamides (**2**) is more likely[7].

A few examples of the synthesis of imidazolines from thiocarboxamides have been described previously[6,7].



According to the literature[1] and to our own observations, the transamidation of thiocarboxamides may proceed more readily than that of carboxamides. We therefore tried to prepare the 2-substituted 4,5-dihydroimidazoles **3** from thiocarboxamides (**4**) and 1,2-diaminoethane. This reaction is rather slow at room temperature and it becomes nearly quantitative only after the reaction mixture has been allowed to stand for several days (Method B). We performed this transamidation-cyclization reaction also with *N*-ethoxycarbonyl-4-methyl-thiobenzamide (**8h**) prepared via Friedel-Crafts reaction from toluene and ethoxycarbonyl isothiocyanate[3].



2-Alkyl- and 2-Aryl-4,5-dihydroimidazoles (3); General and Typical Procedures:

Method A:

2-Alkyl- and 2-Aryl-4,5-dihydroimidazoles (**3b–g, 12c**): A solution of the dithiocarboxylic ester (**1**; 10 mmol) or the aliphatic bis-dithiocarboxylic ester[2] (**9c**; 5 mmol) in benzene (20 ml) is added with stirring to 1,2-diaminoethane (0.902 g, 15 mmol) at ~0°C. The yellow color of the dithioester disappears within a few minutes. The mixture is evaporated to dryness in vacuo and the residual product **3** or **12c** (quantitative yield) recrystallized from 2,2,4-trimethylpentane ("isooctane") or cyclohexane or (for **12c**) from water (with boiling water, ring cleavage may occur!).

2,2'-Phenylene-bis[4,5-dihydroimidazoles] (**12a, b**): The aromatic bis-dithiocarboxylic ester (**9**; 50 mmol) and 1,2-diaminoethane (9.015 g, 150 mmol) are refluxed in benzene (200 ml) for 1 h. The resultant pre-

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cipitate is collected by suction and dissolved in cold 10% hydrochloric acid. This solution is filtered and poured into excess aqueous 10% sodium hydroxide. The precipitated product **12** is isolated by suction, washed with water, and dried in vacuo.

Method B:

2-Alkyl- and 2-Aryl-4,5-dihydroimidazoles (e.g., **3a, h**): A solution or suspension of the thiocarboxamide (**4**; 5 mmol) or the *N*-ethoxycarbonylthiocarboxamide (**8**; 5 mmol) in 1,2-diaminoethane (0.902 g, 15 mmol) is stirred at room temperature for 3 days. Excess diamine is then evaporated and the residual product **3** recrystallized, for example, from 2,2,4-trimethylpentane.

Method C:

2-Alkyl- and 2-Aryl-4,5-dihydroimidazoles (e.g., **3a, f**): A solution of the nitrile **5** (100 mmol) in 1,2-diaminoethane (18.03 g, 300 mmol) is saturated with hydrogen sulfide at 0 °C and the mixture then allowed to stand at room temperature for 4 days. Excess 1,2-diaminoethane is evaporated in vacuo and the residual product **3** (nearly quantitative yield) recrystallized from 2,2,4-trimethylpentane.

2,2'-Phenylene-bis[4,5-dihydroimidazoles] **(12a, b):** A solution of 1,3- or 1,4-dicyanobenzene **(10a, b**; 5.205 g, 40 mmol) in dimethylformamide (20 ml) + 1,2-diaminoethane (10 ml) is saturated with anhydrous hydrogen sulfide at room temperature. The mixture is allowed to stand for 24 h, then heated to reflux for 1 h, cooled, and poured into water (100 ml). The precipitate is collected by suction and dissolved in cold 10% hydrochloric acid. This solution is filtered and poured into excess aqueous 10% sodium hydroxide. The precipitated product **12** is isolated by suction, washed with water, and dried in vacuo.

Method D:

2-Heptyl-4,5-dihydroimidazole **(3c):** A mixture of ethyl octanimidothioate hydrochloride (**6c**; 2.24 g, 10 mmol), 1,2-diaminoethane (1.202 g, 20 mmol), and dimethylformamide (20 ml) is heated at 80 °C for 1 h. After cooling, the mixture is poured into water (200 ml) and the aqueous mixture extracted with dichloromethane (2 × 50 ml). The organic extract is dried with magnesium sulfate and evaporated to dryness in vacuo. The residual product **3c** is recrystallized from 2,2,4-trimethylpentane; yield: 0.76 g (45%); m.p. 61 °C.

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Table. 2-Substituted 4,5-Dihydroimidazoles **(3, 12)**

Educt[a]	R^1 or A	R^2	Method	Product	Yield [%]	m.p. [°C]	Molecular formula[b] or m.p. [°C] reported	I.R. (KBr) ν_{NH}	I.R. (KBr) $\nu_{C=N}$ [cm^{-1}]	^{1}H-N.M.R. δ [ppm] (**3**: $CDCl_3/TMS_{int}$; **12**: $D_2O/HCl/TMS_{ext}$) CH_2 (ring)	N—H[c]	2-alkyl	others
4a	CH_3	—	B	**3a**	80	104°	105°, 107°[12]	3120	1585	3.48	4.9	1.83 (s, 3H)	
5a	CH_3	—	C	**3a**	75								
1b	t-C_4H_9	C_2H_5	A	**3b**	63	116°	$C_7H_{14}N_2$ (126.2)	3185	1603	3.54	4.5	1.20 (9H)	
1c	n-C_7H_{15}	C_2H_5	A	**3c**	65	61°	64-65°[13]	3184	1605	3.60	4.4	2.24 (2H, α-CH_2)	
6c	n-C_7H_{15}	C_2H_5	D	**3c**	45								
1d	n-C_9H_{19}	C_2H_5	A	**3d**	77	71°	71°[14]	3185	1602	3.58	4.4	2.21 (t, 2H, α-CH_2)	0.8-1.9
1e	n-$C_{11}H_{23}$	C_2H_5	A	**3e**	63	82°	81-83°[15]	3185	1604	3.55	4.3	2.22 (t, 2H, α-CH_2)	0.8-1.9
1f	C_6H_5	C_2H_5	A	**3f**	62	101°	101°[12,16]	3190	1603, 1592	3.68	5.1	—	7.35 (3H); 7.75 (2H)
5f	C_6H_5	—	C	**3f**	82								
1g	c-C_6H_{11}	C_2H_5	A	**3g**	72	134°	120°[17]	3190	1605	3.55	4.7	2.3 (m, $1H_{tert}$)	1-2
8h	4-H_3C—C_6H_4—	—	B	**3h**	48	181°	175-176°[11]	3120	1588	3.77	4.5	—	2.38 (3H); 7.2 (2H); 7.6 (2H)
4i	4-i-C_3H_7—C_6H_4—	—	B	**3i**	63	115°	$C_{12}H_{16}N_2$ (188.3)	3100	1588	3.78	4.7	—	1.23 (6H); 2.95 (1H); 7.3 (3H); 7.7 (2H)
9a	1,3-C_6H_4	CH_3	A	**12a**	35	~244°	[d]	3150	1608, 1593	4.3	3.5	—	7-8.5
9b	1,4-C_6H_4	CH_3	A	**12b**	43	~318°	[d]	3175	1598	4.3	3.5	—	8.2
10b	1,4-C_6H_4	—	C	**12b**	65								
9c	—$(CH_2)_{10}$—	C_2H_5	A	**12c**	84	176°	$C_{16}H_{30}N_4$ (288.4)	3170	1604	3.95	3.6	2.58 (t, 4H, $2CH_2$)	1.65 (4H); 1.3 (12H)

[a] The aliphatic dithioesters **1b, c, e, g** and **9c** were obtained from the nitriles[2,8], the aromatic dithioester **1f** from phenylmagnesium chloride[9]. *N*-Ethoxycarbonyl-4-methyl-thiobenzamide **(8h)** and 4-isopropyl-thiobenzamide **(4i)** were obtained from the isothiocyanates[3]. Dimethyl benzene-1,3- and dimethyl benzene-1,4-bis[dithiocarboxylate] **(9a, b)** were prepared from the dinitriles[10]; it should be noted that in Ref.[10] the 1,4-isomer (**9b**, m.p. 150-154 °C) is obtained in only 1% yield by sulfurization of dimethyl terephthalate with phosphorus(V) sulfide. We prepared **9b** in 80% yield following the method reported for the 1,3-isomer **9a** in Ref.[10]; however, in the first step of the reaction (Pinner reaction), the use of hydrogen chloride-saturated methanol is required and the process must be repeated in order to obtain pure dimethyl benzene-1,4-bis[carboximidothioate] dihydrochloride **(11b)**; reaction of **11b** with hydrogen sulfide/pyridine according to Ref.[2] affords **9b** in 80% yield [based on terephthalodinitrile **(10b)**]; m.p. 157 °C (chloroform)[18].

[b] The microanalyses were in satisfactory agreement with the calculated values: C, ±0.21; H, ±0.25; N, ±0.23.

[c] Position and intensity of this signal largely depend on the water content of compounds **3**; the reported signals were found with samples dried over phosphorus pentoxide. The spectra of compounds **12** were recorded in water in the presence of sufficient hydrochloric acid to dissolve compounds **12**: only residual N—H protons appear in the region noted; the signals of the $\overset{\oplus}{N}$—H protons are found at $\delta \approx 8.3$ ppm.

[d] Corrected m.p.s, determined using differential scanning calorimetry (DuPont 900). Compounds **12a** and **12b** have been reported in numerous patents; an m.p. has hitherto not been given, however.

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