Preparation of 5-Substituted 2-Mercapto-1-methylimidazoles. Direct Metalation of 2-Mercapto-1-methylimidazole

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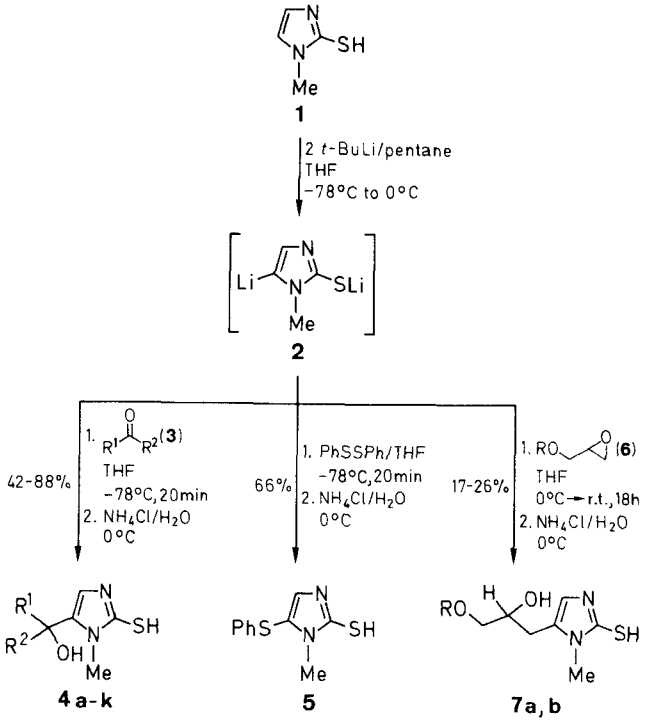
2-Mercapto-1-methylimidazole (**1**) is directly metalated with *tert*-butyllithium in tetrahydrofuran to give the 5, *S*-dianion **2**. Reaction of the dianion **2** with a series of electrophiles gives regioselectively 5-substituted 2-mercapto-1-methylimidazoles **4**, **5** and **7**.

As part of a program on a novel class of enzyme inactivators, it was necessary to prepare a series of 5-substituted 2-mercapto-1-methylimidazoles. A convenient route to these compounds was envisioned via direct, regioselective alkylation of commercially available 2-mercapto-1-methylimidazole (**1**).

Metalation of imidazoles has been studied for many years.[1] Suitable 1,2-disubstituted imidazoles react with butyllithium or with lithium diisopropylamide to give 5-lithioimidazoles. Although there are examples containing 2-aryl- and 2-alkylmercapto groups,[2-5] there are no reports of formation of dianions such as **2** derived from 2-mercapto-1-methylimidazole (**1**). We report here a simple method for direct metalation of **1** and the subsequent reaction of dianion **2** with a series of electrophiles.



3, 4	R^1	R^2	3, 4	R^1	R^2
a	4-$CH_3C_6H_4$	H	**g**	2-$PhOC_6H_4$	H
b	3-$CH_3C_6H_4$	H	**h**	*c*-C_6H_{11}	H
c	2-$CH_3C_6H_4$	H	**i**	Ph	Ph
d	*t*-Bu	H	**j**	$-(CH_2)_5-$	
e	4-PhC_6H_4	H	**k**	Ph	H
f	4-$PhOC_6H_4$	H			

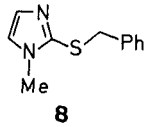
6, 7	R
a	Ph
b	2-PhC_6H_4

When the starting 2-mercapto-1-methylimidazole (**1**) in tetrahydrofuran was treated with two equivalents of *tert*-butyllithium at −78 °C and the resulting yellow solution warmed to 0 °C, a yellow precipitate presumed to be the dianion **2**, was obtained. Subsequent treatment of the dianion at −78 °C with various aldehydes and ketones **3** gave in good yield products **4a–k** listed in Table 1; no *S*-alkylation or 4-substitution was detected. Similar reaction of **2** with diphenyl disulfide gave exclusively compound **5**.

The regiochemistry of the products was confirmed by NMR experiments on compound **4k**. The benzylic and the imidazole ring protons of **4k** have similar chemical shifts and, therefore, could not be assigned unequivocally. Two carbons, each bearing a single proton, were observed by ^{13}C-NMR spectroscopy at $\delta = 65.8$ and 112.3. The chemical shifts of these resonances clearly assign them to the benzylic and imidazole ring carbons, respectively. A HETCOR (carbon–proton correlation) experiment was used to relate the proton at $\delta = 5.7$ to the benzylic carbon at $\delta = 65.8$. NOE experiments showed that the order of groups around the ring is methyl, the proton at $\delta = 5.7$, and then the proton at $\delta = 6.3$. Thus, the benzylic substituent is attached to the 5-position of the imidazole.

However, reaction of **2** with epoxides proceeded less regioselectively. Treatment of dianion **2** at −78 °C with epoxides **6** gave no reaction. The reaction was therefore carried out at 0 °C giving the products listed in Table 2 but in modest yield. This may result from competing *S*-alkylation of the 5-alkylated products, which have greater solubility than the starting dianion. The derived products **7a–b** crystallized cleanly from the crude product mixture. Attempts to alkylate **1**, protected prior to metalation as the 2-methoxy-2-propyl sulfides or as the triphenylmethyl sulfides, were unsuccessful. Decomposition occurred prior to alkylation due to the instability of the anion formed.

A failure of the regioselective 5-alkylation was discovered when dianion **2** was treated with benzyl bromide. Only the *S*-alkylated product **8**[6] was isolated; the yield was modest even by using 0.5 equivalents of benzyl bromide. The identity of **8** was confirmed by comparison of its ^{1}H-NMR spectrum to that of the product reported from reaction of **1** with benzyl iodide.[7]



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All reagents were of commercial quality. Aldehydes, ketones, epoxides, 2-mercapto-1-methylimidazole (**1**) and diphenyl disulfide were purchased from Aldrich Chemical Company. THF was dried by distillation from benzophenone/sodium under argon. Melting points were taken using a Thomas-Hoover capillary melting point apparatus and are uncorrected. Microanalyses were obtained using a Control Equipment Model 240XA elemental analyzer. IR spectra were obtained using a Perkin-Elmer 1420 spectrophotometer. ^{1}H-NMR spectra were obtained using a Varian XL 300 MHz or a Nicolet NT-360 MHz spectrometer.

5-(1-Hydroxyalkyl)-2-mercapto-1-methylimidazoles 4; General Procedure:

In a dried, three-necked round-bottom flask equipped with an addition funnel, stirrer, and a rubber septum is placed a solution of 2-mercapto-1-methylimidazole (**1**; 0.57 g, 5 mmol) in THF (30 mL). The solution is cooled to −78 °C and a solution of *t*-BuLi in pentane (6.2 mL, 10.5 mmol) is added dropwise by syringe over 2 min. The yellow solution is warmed to 0 °C with rapid stirring to give a yellow precipitate, then re-cooled to −78 °C. A solution of the electrophile **3** (6 mmol) in THF (2 mL) is added dropwise over 1

Table 1. Compounds **4a–k** Prepared

Product	Yield (%)	mp (°C) (solvent)	Molecular Formula[a]	IR (Nujol) ν(cm^{-1})	^{1}H-NMR (solvent/TMS) δ, J(Hz)
4a	67	196–197 (EtOAc)	$C_{12}H_{14}N_2OS$ (234.3)	1460, 1380, 1080	($CDCl_3$): 2.2 (br s, 1H, OH), 2.37 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 5.69 (s, 1H, CH), 6.32 (s, 1H, H-4), 7.23 (d, 2H$_{arom}$, J = 12), 7.26 (d, 2H$_{arom}$ obscured by $CHCl_3$), 9.9 (br s, 1H, SH)
4b	79	192–194 (EtOAc/Et_2O)	$C_{12}H_{14}N_2OS$ (234.3)	1460, 1380, 1090	($CDCl_3$): 2.2 (br s, 1H, OH), 2.37 (s, 3H, CH_3), 3.56 (s, 3H, CH_3), 5.69 (s, 1H, CH), 6.33 (d, 1H, H-4, J = 2), 7.18 (m, 3H$_{arom}$), 7.26 (m, 1H$_{arom}$), 9.9 (br s, 1H, SH)
4c	76	205–207 (EtOAc/Et_2O)	$C_{12}H_{14}N_2OS$ (234.3)	1460, 1380, 1080	($CDCl_3$): 2.20 (d, 1H, OH, J = 6), 2.26 (s, 3H, CH_3), 3.68 (s, 3H, CH_3), 5.87 (d, 1H, CH, J = 6), 6.08 (d, 1H, H-4, J = 2), 7.19 (m, 1H$_{arom}$), 7.27 (m, 2H$_{arom}$), 7.49 (m, 1H$_{arom}$), 9.45 (br s, 1H, SH)
4d	80	211–213 (EtOAc/Et_2O)	$C_9H_{16}N_2OS$ (200.3)	1480, 1350, 1080, 1050	($CDCl_3$): 1.00 (s, 9H, *t*-C_4H_9), 1.90 (br s, 1H, OH), 4.37 (s, 1H, CH), 6.65 (d, 1H, H-4, J = 2), 9.50 (br s, 1H, SH)
4e	59	220–221 (EtOAc)	$C_{17}H_{16}N_2OS$ (296.4)	1460, 1380, 1040	(DMSO-d_6): 3.30 (s, 3H, CH_3), 5.75 (d, 1H, CH, J = 6), 6.12 (d, 1H, OH, J = 6), 6.41 (d, 1H, H-4, J = 2), 7.37 (m, 1H$_{arom}$), 7.47 (m, 4H$_{arom}$), 7.68 (d, 4H$_{arom}$, J = 8), 12.05 (br s, 1H, SH)
4f	76	218–219 (EtOAc)	$C_{17}H_{16}N_2O_2S$ (312.4)	1460, 1380, 1260, 1090, 1000	(DMSO-d_6): 3.39 (s, 3H, CH_3), 5.69 (d, 1H, CH, J = 6), 6.09 (d, 1H, OH, J = 6), 6.37 (d, 1H, H-4, J = 2), 7.02 (m, 4H$_{arom}$), 7.37 (m, 1H$_{arom}$), 7.39 (m, 4H$_{arom}$), 12.02 (br s, 1H, SH)
4g	65	186–188 (EtOAc)	$C_{17}H_{16}N_2O_2S$ (312.4)	1460, 1380, 1240, 1090, 990	(DMSO-d_6): 3.37 (s, 3H, CH_3), 5.69 (d, 1H, CH, J = 6), 6.13 (d, 1H, OH, J = 6), 6.37 (s, 1H, H-4), 6.95 (d, 1H$_{arom}$, J = 8), 7.03 (m, 3H$_{arom}$), 7.14 (m, 2H$_{arom}$), 7.38 (m, 2H$_{arom}$), 12.02 (br s, 1H, SH)
4h	42	203–204 (EtOAc)	$C_{11}H_{18}N_2OS$ (226.3)	1460, 1380, 1080	($CHCl_3$): 1.0 (m, 2H), 1.22 (m, 3H), 1.49 (d, 1H, J = 15), 1.75 (m, 4H), 2.05 (d, 1H, J = 15), 2.10 (br s, 1H, OH), 3.66 (s, 3H, CH_3), 4.28 (d, 1H, CHOH, J = 9), 6.58 (d, 1H, H-4, J = 2), 10.48 (br s, 1H, SH)
4i	88	214–216 (EtOAc)	$C_{17}H_{16}N_2OS$ (296.4)	1440, 1370, 1090, 1010	(DMSO-d_6): 3.18 (s, 3H, CH_3), 5.80 (d, 1H, H-4, J = 2), 6.82 (s, 1H, OH), 7.33 (m, 10H$_{arom}$), 12.05 (br s, 1H, SH)
4j	45	171–172 (EtOAc/Et_2O)	$C_{10}H_{16}N_2OS$ (212.3)	1480, 1380, 1090	(DMSO-d_6): 1.20 (m, 1H), 1.45 (m, 2H), 1.60 (m, 5H), 1.86 (d, 2H, J = 15), 3.62 (s, 3H, CH_3), 4.95 (br s, 1H, OH), 6.68 (d, 1H, H-4, J = 2), 12.05 (br s, 1H, SH)
4k	63	209–211 (EtOAc)	$C_{11}H_{12}N_2OS$ (220.3)	1480, 1450, 1370, 1080, 1000	(DMSO-d_6): 3.36 (s, 3H, CH_3), 5.70 (s, 1H, CH), 6.10 (br s, 1H, OH), 6.33 (s, 1H, H-4), 7.35 (m, 5H$_{arom}$), 12.00 (br s, 1H, SH)

[a] Satisfactory microanalyses obtained: C ±0.37, H ±0.37, N ±0.24.

Table 2. Compounds **7a, b** Prepared

Product	Yield (%)	mp (°C)	Molecular Formula[a]	IR (Nujol) ν(cm^{-1})	^{1}H-NMR ($CDCl_3$/TMS) δ, J(Hz)
7a	17	141–143	$C_{13}H_{16}N_2O_2S$ (264.3)	1460, 1380, 1240, 1150, 1040	2.60 (br s, 1H, OH), 2.84 (m, 2H, CH_2), 3.60 (s, 3H, CH_3), 3.97 (m, 2H, CH_2), 4.20 (m, 1H, CH), 6.61 (s, 1H, H-4), 6.90 (d, 2H$_{arom}$, J = 8), 6.99 (t, 1H$_{arom}$, J = 8), 7.29 (m, 2H$_{arom}$), 10.2 (br s, 1H, SH)
7b	26	190–191	$C_{19}H_{20}N_2O_2S$ (340.4)	1450, 1370, 1260, 1230, 1120, 1020	2.30 (br s, 1H, OH), 2.64 (m, 2H, CH_2), 3.41 (s, 3H, CH_3), 3.96 (m, 2H, CH_2), 4.01 (m, 1H, CH), 6.44 (d, 1H, H-4, J = 2), 6.97 (d, 2H$_{arom}$, J = 8), 7.09 (t, 1H$_{arom}$, J = 8), 7.3–7.5 (m, 7H$_{arom}$), 10.25 (br s, 1H, SH)

[a] Satisfactory microanalyses obtained: C ±0.12, H ±0.05, N ±0.14.

min. The mixture is stirred at −78 °C for 20 min, warmed to 0 °C, hydrolyzed with sat. NH_4Cl solution (15 mL), diluted with H_2O (10 mL), and extracted with EtOAc (60 mL). The extract is washed with H_2O (10 mL) and brine (10 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The crude product is taken up in Et_2O (25 mL) and filtered to give the pure product as a white solid. The product can be further purified by crystallization from EtOAc (Table 1).

2-Mercapto-1-methyl-5-(phenylthio)imidazole (5):
Obtained from 2-mercapto-1-methylimidazole (**1**; 0.57 g, 5.0 mmol) and diphenyl disulfide (1.1 g, 5.0 mmol) according to the general procedure above; yield: 66%; mp 213–214 °C.

$C_{10}H_{10}N_2S_2$	calc.	C 54.02	H 4.53	N 12.60
(222.3)	found	53.92	4.25	12.67

IR (Nujol): ν = 1470, 1320, 1080, 740

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.49 (s, 3 H, CH_3); 7.14 (m, 2 H_{arom}), 7.14 (s, 1 H, H-4), 7.30 (m, 3 H_{arom}).

5-[(3-Aryloxy-2-hydroxy)propyl]-2-mercapto-1-methylimidazoles 7; General Procedure:
In a dried three-necked round-bottom flask equipped with an addition funnel, stirrer, and a rubber septum is placed a solution of 2-mercapto-1-methylimidazole (**1**; 2.28 g, 20 mmol) in THF (50 mL). The solution is cooled to −78 °C and a solution of *t*-BuLi in pentane (24.7 mL, 42.0 mmol) is added dropwise by syringe over 3 min. The yellow solution is warmed to 0 °C with rapid stirring to give a yellow precipitate. A solution of the epoxide **6** (20 mmol) 1.0 equiv in THF (10 mL) is added dropwise over 5 min. The mixture is stirred 18 h while warming to r.t. The mixture is cooled to 0 °C, hydrolyzed with H_2O (75 mL) and sat. NH_4Cl solution (50 mL) and diluted with CH_2Cl_2 (200 mL). The layers are separated and the organic layer is washed with H_2O (20 mL), and then extracted with 5% NaOH solution (4 × 50 mL). The aqueous extract is neutralized to pH 6–7 using conc HCl, then extracted with CH_2Cl_2 (3 × 100 mL). The organic extract is washed with H_2O (30 mL) and brine (30 mL), dried (Na_2SO_4), and concentrated at reduced pressure. The crude product is recrystallized from EtOAc (Table 2).

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