Reaction of dimethyl *N*-(2,2-diethoxyethyl)-iminodithiocarbamate with primary amines: a new general approach for the synthesis of 1-substituted-2-methylthioimidazoles

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Dedicated to Prof. T. R Govindachari on his 85th birth anniversary
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Abstract
Dimethyl *N*-(2,2-diethoxyethyl)-iminodithiocarbamate **3** is shown to react with primary amines in boiling acetic acid to afford 1-substituted-2-methylthioimidazoles in 81-87% overall yields.

Keywords: Dimethyl *N*-(2,2-diethoxyethyl)-iminodithiocarbamate, 2methylthioimidazoles

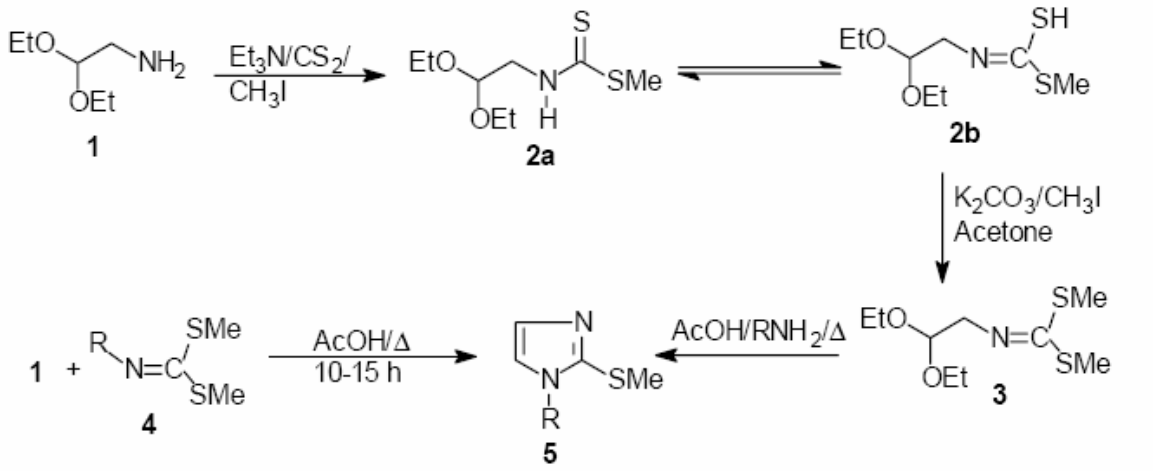
Introduction

We recently developed a number of synthetic approaches for constructing substituted imidazole derivatives.[1-4] One of these methods involves nitrosation of α-oxoketene S, N-acetals followed by cyclocondensation to yield the corresponding imidazoles in good yields.[1-3] In another approach we had shown that the dimethyl N-aryl/alkyl iminodithiocarbamates[5-7] react with amino acetaldehyde diethylacetal in boiling acetic acid to afford the corresponding N-substituted 2-methylthioimidazoles[4] in moderate to good yields. We required a large number of 2-methylthio N-substituted imidazoles having no substituents at 4 and 5 positions, to prepare a number of antiamoebic drugs through nitration to afford the corresponding 5-nitroimidazoles. The 1-N-side chain modification in our earlier method was associated with the conversion of both alkyl and aryl amines into the corresponding carbonimidodithioates **4** (Scheme-1) which were then reacted with aminoacetaldehyde acetal **1** to afford the corresponding imidazoles **5** in good yields. However this method required the tedious process of conversion of all the amines into the corresponding carbonimidodithioates **4**. Instead we considered an alternative approach involving the conversion of aminoacetaldehyde diethylacetal with the corresponding carbonimidodithioate

3 as a key intermediate, which is shown to react with various alkyl and aryl amines in the presence of boiling acetic acid, to afford the corresponding 2-methyl-thio N-substituted imidazoles **5** in good to excellent yields. We now report these results in this communication.

Results and Discussion

The required hitherto unreported dimethyl N-(2,2,diethoxyethyl)-iminodithiocarbamate **3** was prepared from aminoacetaldehyde acetal **1** with carbon disulphide in the presence of triethylamine followed by *in situ* alkylation with methyl iodide in 87% yield as a viscous oil in one pot reaction. The carbonimidodithioate **3** was then reacted with equimolar quantities of amines in refluxing acetic acid for six hours and the reaction mixtures after work up yielded the corresponding crude products which were purified by column chromatography on silica gel using ethyl acetate:hexane as an eluent to afford the corresponding 1-substituted-2-methylthioimidazoles **5a-l** in 81-87% overall yields.



5a, R = C_6H_5
b, R = Me
c, R = Et
d, R = Bu
e, R = $CH_2C_6H_5$
f, R = Cyclohexyl
g, R = $CH_2(CH_2)_6CH_3$
h, R = $CH_2(CH_2)_{10}CH_3$
i, R = $CH_2(CH_2)_{14}CH_3$
j, R = $CH_2CH_2C_6H_5$
k, R = -CH_2-furyl
l, R =

Scheme 1

In conclusion it is apparent that the present method is more efficient since it involves the preparation of a lone key intermediate **3** which is obtained in high yield and can be used for the synthesis of imidazoles by reacting with various amines.

Experimental Section

General Procedures. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer-297 spectrophotometer and frequencies are expressed in cm^{-1}. The ^1H NMR spectra were recorded on Varian EM-390 (90 MHz) spectrometer using tetramethyl silane as internal standard and the chemical shifts are expressed as δ (ppm) down field from TMS. The mass spectra were recorded on Jeol D-300 spectrometer and relative intensities are expressed in percentage. Elemental analysis were carried out on a Heraeus CHN-O Rapid analyzer.

Starting materials. The commercial samples of various amines and other chemicals were purified before use. Commercially available anhydrous potassium carbonate, acetic acid and methyl iodide were used as such.

Dimethyl *N*-(2,2-Diethoxyethyl)-iminodithiocarbamate (3) (Scheme 1). To a mixture of aminoacetaldehyde diethylacetal (133 gms, 1.0 mole) and triethylamine (182 gms, 2.0 moles) in hexane (500 ml) carbon disulphide (114 gms, 1.5 mole) was added dropwise and the reaction mixture was kept stirring for 3 hours and then methyl iodide (143 gms, 1.0 mole) was added in portion and stirring was continued further 3 hours. Excess hexane was removed under reduced pressure, and the residue was diluted with a mixture of chloroform (150 ml) and acetone (500 ml) followed by addition of anhydrous potassium carbonate (280 gms, 2 moles). To the above reaction mixture methyl iodide (143 gms, 1.0 mole) was added dropwise over a period of 2-3 hours, and refluxed on a water bath for 5 hours. The reaction mixture was cooled, filtered, washed with acetone (200 ml) and the combined solution was dried (Na_2SO_4) and concentrated under reduced pressure to yield the crude N-(2,2-diethoxyethyl)-iminodithiocarbamate **3** as viscous brown liquid. It was purified by passing through silica gel column using hexane: ethyl acetate (9:1) as eluent to afford pure **3** in 87% yield as viscous oil; IR (Neat); ν_{max} 2914, 1579 cm^{-1}; ^1H NMR (90 MHz, CCl_4); δ 1.19 (t, *J* = 7 Hz, 6H, CH_2CH_3), 2.36 (s, 3H, SCH_3), 2.56 (s, 3H, SCH_3), 3.36-3.72 (m, 6H, $-CH_2$), 4.72 (t, *J* = 7 Hz, 1H, CH). Anal calcd for $C_9H_{19}NO_2S_2$ (237.3): C, 45.54; H, 8.06; N, 5.90%. Found: C, 45.32; H, 7.9; N, 6.13%.

General method for the preparation of 1-aryl/alkyl-2-methylthioimidazoles (5a-l)

A mixture of dimethyl N-(2,2-diethoxyethyl)-iminodithiocarbamate **3** (2.37 gms, 0.01 mole) and

an appropriate amine (0.012 mole) in acetic acid (20 ml) was refluxed for 8 hours. The acetic acid was removed under reduced pressure and the residue was diluted with water (20 ml) and extracted with chloroform (3 x 50 ml). The extract was washed with water (2 x 50 ml), dried (Na_2SO_4) and evaporated to yield the crude 1-substituted-2-methylthioimidazoles **5**, which were purified by passing through silica gel column using hexane:ethyl acetate (98:2) as eluent to afford the corresponding pure imidazoles in 81-87% overall yields.

1-Phenyl-2-methylthioimidazole[4] (5a). Colorless crystals, reaction time 6 hrs; Yield 83**%**; m.p. 54-55 C; (lit. m.p. 53-54 C[4]); identical with that reported in the literature.[4]

1-Methyl-2-methylthioimidazole[4,8] (5b). Viscous oil; reaction time 7 hrs; Yield, 82%; IR (Neat): *νmax* 3100, 3051, 1487, 1425 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ 2.49 (s, 3H, SCH_3), 3.26 (s, 3H, NCH_3), 6.88 (brs, 2H, H-4 and H-5). Anal calcd for $C_5H_8N_2S$ (128.1): C, 46.87; H, 6.29; N, 21.87%. Found: C, 46.63; H, 6.07; N, 22.09%.

1-Ethyl-2-methylthioimidazole[4] (5c). Viscous oil; reaction time 2 hrs; Yield, 82%; IR (Neat): ν_{max} 3109, 3024, 1490, 1450 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ 1.16 (t, *J* = 7 Hz, 3H, -CH_2 CH_3), 2.5 (s, 3H, SCH_3), 3.19-3.66 (m, 2H, -CH_2CH_3), 7.00 (brs, 2H, H-4 and H-5). Anal calcd for $C_6H_{10}N_2S$ (142.2): C, 50.67; H, 7.08; N, 19.70%. Found: C, 50.43; H, 7.31; N, 19.46%.

1-Butyl-2-methylthioimidazole[8] (5d). Viscous oil, reaction time 8 hrs; Yield 85%; IR (Neat): ν_{max} 3102, 3049,1509,1490 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ 1.00 (t, *J* = 7 Hz, 3H, -CH_2CH_3), 1.13-1.89 (m, 4H, CH_2CH_2-), 2.59 (s, 3H, SCH_3), 3.82 (t, *J* = 7 Hz, 2H, -C*H*$_2(CH_2)_2CH_3$), 6.82 (s, 1H, H-4), 6.89 (s, 1H, H-5). Anal calcd for $C_8H_{14}N_2S$ (170.2): C, 56.45; H, 8.29; N, 16.46%. Found: C, 56.19; H, 8.07; N, 16.73%.

1-Benzyl-2-methylthioimidazole[4] (5e). Viscous oil; reaction time 11 hrs; Yield, 86%. Spectral and analytical data are identical with that reported in the literature.[4]

1-Cyclohexyl-2-methylthioimidazole (5f). Viscous oil; reaction time 8 hrs; Yield, 86%; IR (Neat):ν_{max} 3058, 2925, 1481, 1440 cm^{-1}; ^1H NMR. (90 MHz, CCl_4): δ 1.03 – 2.1 (m, 10H, ring CH_2), 2.59 (s, 3H, SCH_3), 3.8 (brs, 1H, CH), 6.85 (brs, 2H, H-4 and H-5); m/z: 196 (M^+, 8%), 127 (100%), 114 (28%). Anal calcd for $C_{10}H_{16}N_2S$ (196.3); C, 61.18; H, 8.21; N, 14.27%. Found: C, 60.94; H, 8.03; N, 14.48%.

1-Octyl-2-methylthioimidazole (5g). Viscous oil; reaction time 7 hrs; Yield 84%; IR (Neat): ν_{max} 3047, 2900, 1487, 1444 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ 0.89 (brs, 3H, -CH_2 $(CH_2)_6CH_3$), 1.30 (brs, 12H, -$CH_2(CH_2)_6CH_3$), 2.62 (s, 3H, SCH_3), 3.89 (t, *J*= 7 Hz, 2H, -$CH_2(CH_2)_6CH_3$), 6.95 (s, 1H, H-4), 7.06 (s, 1H, H-5). Anal calcd for $C_{12}H_{22}N_2S$ (226.3): C, 63.69; H, 9.80; N, 12.38%, found: C, 63.45; H, 9.59; N, 12.56%.

1-Dodecyl-2-methylthioimidazole (5h). Viscous oil; reaction time 9 hrs; Yield, 87%; IR (Neat)*:* ν_{max} 2900, 1441, cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ 0.89 (brs, 3H, -$CH_2(CH_2)_{10}CH_3$); 1.30 (brs, 20H, -$CH_2(CH_2)_{10}CH_3$), 2.60 (s, 3H, SCH_3, 3.85 (t, *J* = 7 Hz, 2H, -$CH_2(CH_2)_{10}CH_3$), 6.89 (s, 1H, H-4), 6.95 (s, 1H, H-5), MS (m/z, %): 282 (M^+, 100); 235 (M^+-47,88). Anal calcd for $C_{16}H_{30}N_2S$

(282.4): C, 68.04; H, 10.70; N, 9.92%. Found: C, 68.29; H, 10.47; N, 10.18%.

1-Cetyl-2-methylthioimidazole (5i). Viscous oil; reaction time 9 hrs; Yield 87%; IR (Neat)*:* ν_{max} 2900, 1441 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ 0.89 (brs, 3H, $-CH_2(CH_2)_{14}CH_3$), 1.30 (brs, 28H, $-CH_2(CH_2)_{14}CH_3$), 2.92 (s, 3H, SCH_3), 3.82 (t, *J* = 7 Hz, 2H, $-CH_2(CH_2)_{14}CH_3$), 6.82 (s, 1H H-4), 6.92 (s, 1H, H-5). MS (m/z, %): 338 (M^+, 98.8); 291 (M^+-47, 44.8). Anal cald for $C_{20}H_{38}N_2S$ (338.5): C, 70.96; H, 11.31; N, 8.27%. Found: C, 71.21; H, 11.07; N, 8.51%.

1(2-Phenylethyl)-2-methylthioimidazole (5j). Viscous oil; reaction time, 8 hrs; yield: 83%; IR (Neat)*:*ν_{max} 3120, 1447, cm^{-1}; ^1H NMR. (90 MHz, CCl_4): δ 2.46 (s, 3H, SCH_3), 2.89 (t, *J* = 7 Hz, 2H, $-CH_2CH_2C_6H_5$), 4.03 (t, *J* = 7Hz, 2H, $-CH_2CH_2C_6H_5$), 6.69 (s, 1H, H-4), 6.89 (s, 1H, H-5), 6.95-7.33 (m, $5H_{ArH}$). MS (m/z, %): 218 (M^+ 91.2). Found: C, 66.2; H, 6.2; N, 12.59. Anal calcd for $C_{12}H_{14}N_2S$ (218.3): C, 66.01; H, 6.46; N, 12.83%.

1(2-Furylmethyl)-2-methylthioimidazole (5k). Viscous oil; reaction time 6 hrs; Yield: 81%; IR (Neat)*:* ν_{max} 3160, 1440 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ 2.52 (s, 3H, SCH_3), 5.00 (s, 2H, $-CH_2$), 6.30 (brs, 2H, H-4 and H-5), 6.95 (brs, 2H, 3,4 furyl), 7.42 (brs, 1H, furyl). MS (m/z, %): 194 (M^+, 81.6), 81(100). Anal calcd for $C_9H_{10}N_2OS$ (194.2): C, 55.65; H, 5.19; N, 14.42%. Found: C, 55.49; H, 5.02; N, 14.17%.

1-Cyclopropyl-2-methylthioimidazole (5l). Viscous oil; reaction time 6 hrs; Yield: 81%; IR (Neat):ν_{max} 3150, 1492, 1425 cm^{-1}; ^1H NMR (90 MHz, CCl_4): δ 0.89 (brs, 4H, cyclopropyl CH_2); 2.56 (s, 3H, SCH_3), 3.09 (m, 1H, CH), 6.82 (brs, 2H, H-4 and H-5). MS (m/z, %): 154 (M^+, 100). Anal cald for $C_7H_{10}N_2S$ (154.2): C, 54.46; H, 6.53; N, 18.17%. Found: C 54.71; H, 6.29; N, 18.41%.

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